Substance report

June 2022

Cadmium

HBM4EU science and policy for a healthy future

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Authors and Acknowledgements

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First version (December 2019) by RPA consultants, based on scoping documents produced by the chemical group leader (CGL) and colleagues. The EEA has since updated this document to reflect the work developed before the conclusion of HBM4EU, with the support of the CGL and other colleagues.

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Glossary

Abbreviations	
ATSDR	Agency for Toxic Substances and Disease Registry
C&L	Classification and Labelling
CLP	The 'Classification, Labelling, Packaging' Regulation Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
HBM	Human Biomonitoring
HBM4EU	European Human Biomonitoring Initiative
IARC	International Agency for Research on Cancer
OEL	Occupational Exposure Limits
REACH	The 'Registration, Evaluation, Authorisation and Restriction of Chemicals' Regulation Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
STOT RE	Specific target organ toxicity - repeated exposure
SVHC	Substances of Very High Concern
WP	Work package
WPL	Work package leader

1 Key messages

- New HBM4EU data from human biomonitoring studies carried out over Europe supports the recommendation by EFSA to reduce Cd exposure as also the estimated mean dietary exposure of adults in the EU is close or slightly exceeding the tolerable weekly intake (TWI) (EFSA, 2009; EFSA, 2012).

- Based on HBM4EU findings from the aligned studies[1] (2014 – 2021), the risk of adverse health effects on the kidney cannot be excluded: In the majority of the sampling sites, 5% of the study participants (non-smoking) overlap with (and possibly exceed) age-dependent alert values for adverse effects on kidney functioning.
- Findings from HBM4EU suggests geographical variations in human internal cadmium with median values varying up to a factor 3 between the EU-sampling sites.
- Long-term formal EU-wide human biomonitoring activities are required to provide regular assessment of the risks posed by pollutants such as cadmium to our health.
- In terms of health effects, cadmium particularly affects the kidneys but HBM4EU data also identifies that Cd exposure contributes to the risk of osteoporosis. In women above 55 years old, 23 % of the cases were attribute to Cd exposure. Cd is also classified as a human carcinogen.

2 Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until 2022. It generates knowledge to inform about the safe management of chemicals, and hence protect human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts to build upon existing evidence bases and improve chemical risk assessment. HBM4EU compares data from across Europe which allows an understanding of regional differences and can help to identify vulnerable groups in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This document provides a summary of the known and suspected adverse human health effects of cadmium and describes the main exposure pathways for humans. It also indicates where HBM could be of value in the support and development of EU policy, along with the remaining challenges in determining human cadmium exposure. This substance report is intended to inform scientists, relevant stakeholders, and policy makers on the value of HBM to establish the EU population's exposure to cadmium.

This document based largely on the HBM4EU scoping document for cadmium, first draft produced in 2019 and updated regularly, as well as the accompanying reports on legislative mapping and policy questions. Where necessary, additional information has been used from the European Chemical Agency (ECHA) documents including the Classification and Labelling (C&L) Inventory, and legislative text for relevant EU policy areas, have also been used for this report.

2.2 Overview of cadmium

Metallic cadmium is a white silvery metal with a low melting point (321°C). Cadmium levels in the environment vary widely and are a consequence of both natural (erosion of parent rocks, volcanic eruptions, forest fires; 10-50 %) and anthropogenic sources (used in, for example, plastics as colour pigment and stabiliser, automobile radiators, alkaline batteries, mining activities, fertilisers, sewage sludge, inappropriate waste disposal; 50-90%). During the twentieth century the world

[1] The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonised as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

consumption of Cd has increased continuously to a global supply of 22,000 metric tonnes (International Cadmium Association, 2002) and it has remained at this level since 2000.

Cadmium is a potentially toxic metal that ranks 7th on the priority list of hazardous substances of the US Agency for Toxic Substances and Disease Registry's (ATSDR). The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as human carcinogens (Group 1). Chronic occupational exposures (~45 years) to Cd in the air at concentrations of 5-10 µgCd/m^3 could lead to renal tubular damage in some of exposed workers and exposure to higher levels of 100 µgCd/m^3 may result in obstructive lung disease (Nordberg et al., 2015). Experimental studies showed that Cd can induce lung and prostate cancer in laboratory animals and some epidemiological studies have also found increased rates of cancer in the same and some other organs (Nordberg et al., 2015). After prolonged exposure, Cd can cause adverse effects on kidneys and contribute to increased risk of osteoporosis (Nordberg et al., 2018).

3 Human exposure to cadmium

Cadmium is present in the natural environment but there is additional exposure from industry and agriculture (Strumylaite et al., 2019). Natural sources (such as volcanic eruptions and forest fires) account for 10-50% of Cd levels, but anthropogenic sources (e.g.plastics, alkaline batteries, mining and waste disposal) can contribute 50-90% of the total level in some areas. Annual global production of cadmium from refineries is in the range of 24,000 tonnes per annum (US Geological Survey, 2022).

The primary source of human exposure to cadmium is through food, as a result of uptake of cadmium from soil. The main foods associated with cadmium exposure include cereals and vegetables, but also meat and meat products (European Commission, n.d.) (EFSA, 2012). As a result of this vegetarians can have greater exposure to cadmium through diet (European Commission, n.d.). An assessment by the European Food Safety Authority indicates that the average lifetime exposure for the EU population is 2.04 µg/kg body weight per week (EFSA, 2012), compared to the reported tolerable weekly intake of 2.5 µg/kg body weight. However, this population average masks much higher average levels in certain groups such as toddlers (4.85 µg/kg body weight (EFSA, 2012)).

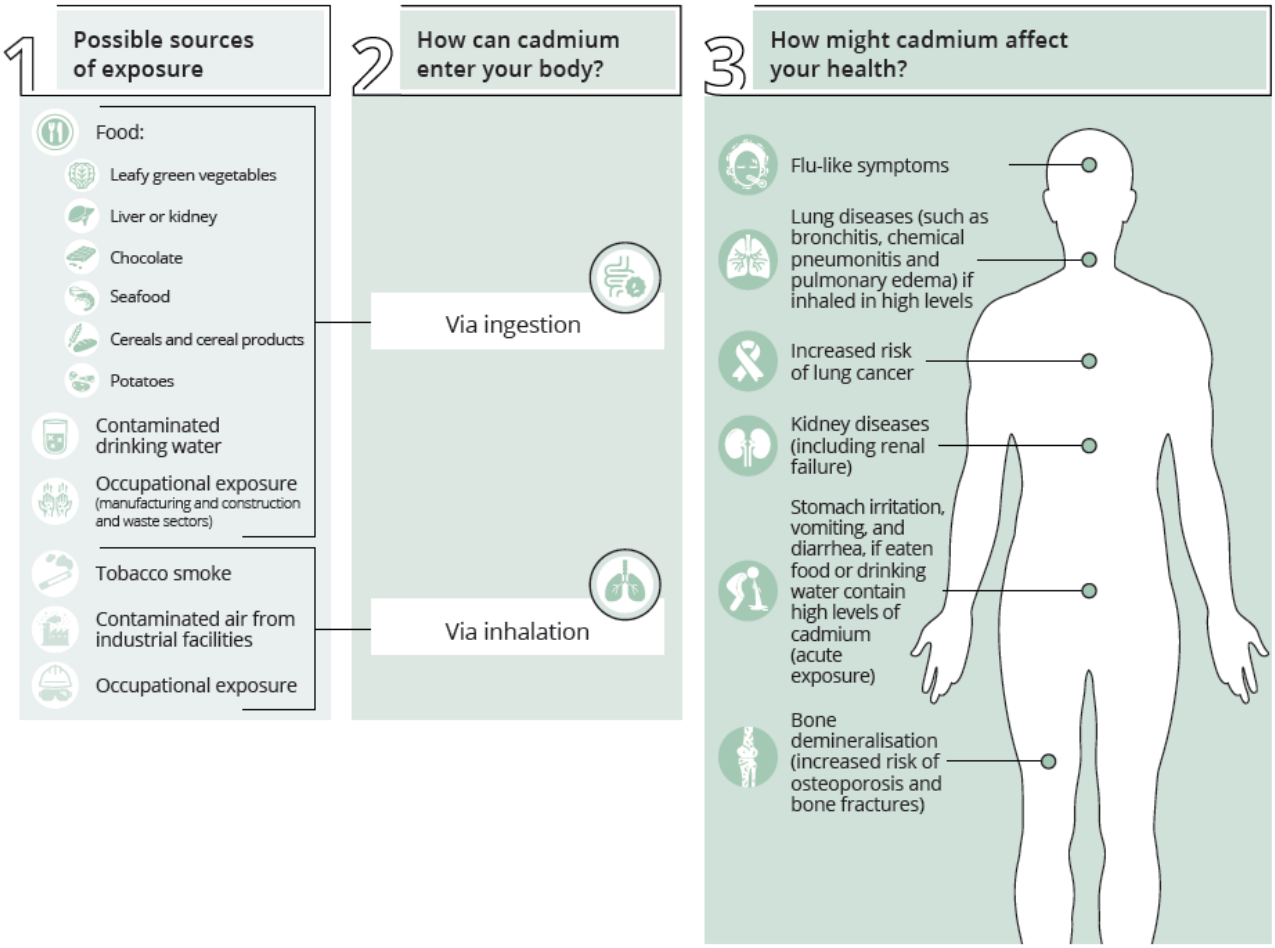

Figure 3.1 Overview of exposure routes, pathways and health effect of Cadmium

3.1 Environmental exposure

As mentioned above, for the general population the primary exposure route for cadmium is through diet, but exposure can also occur directly through cadmium present in the environment. The main environmental routes for human exposure to cadmium are air, soil and water (as summarised in Table 3.1).

Table 3.1 Environmental routes of human Cd exposure

Compartment	Concentrations	Note(s)
Air	European levels (WHO, 2000): 1-10 ng Cd/m^3 (urban areas) 0.1 – 0.5 ng Cd/m^3 (rural areas)	Levels of Cd in ambient air are low, however indoor levels can be higher due to cigarette smoking and poor ventilation.
Water	Surface water and groundwater: <1µg Cd/L Drinking water: 5µg Cd/L	Drinking water may be contaminated due to impurities in pipes, water heaters/coolers and

		leakage into groundwater from dumped Cd oxide sludge.
Soil	Non-polluted areas: <1 mg Cd/kg soil	Concentrations can increase due to waterborne or airborne Cd emissions. Phosphate fertilisers can increase Cd in soil and crops.

3.2 Occupational exposure

Occupational exposure of workers in the non-ferrous smelting industry can be a significant exposure route. Soluble inorganic cadmium compounds are of greatest concern for occupational safety (WHO, 2010).

A binding occupational exposure limit value of 0.001 mg/m^3 is specified for cadmium (inhalable fraction) under the Carcinogens and Mutagens Directive (Directive (EU) 2019/983). Member States were required to implement the requirements of the Directive by 11 July 2021. A transition period is allowed until 11 July 2027, with the interim limit value for the inhalable fraction being 0.004 mg/m^3. In Member States with a national biomonitoring programme, a biological limit value of ≤0.002 mg Cadmium/g creatinine can be used.

3.3 Consumer exposure

Human activities (behaviour, life-style) also add to cadmium exposure. Diet and drinking water (5-10% of ingested Cd absorbed) and smoking tobacco (10-50% of inhaled Cd absorbed) are the main routes of exposure for the general population. The mean exposure of adults to Cd is 10-20 µg Cd/day (for Europe and North America) resulting in average urinary levels of 0.5-1.0 µg Cd/day and blood levels of 0.5-1.0 µg Cd/L (Nordberg et al., 2015) in non-smokers; values are twice as high in smokers.

4 Health impacts of cadmium

4.1 Overview of key health impacts from cadmium

Prolonged or repeated exposure to cadmium and cadmium containing chemicals poses multiple health concerns to humans irrespective of whether it arises from natural or anthropogenic sources. Due to its toxicity (Acute Tox. 2) and potential wider impacts on human health, cadmium ranks 7th in the priority list of hazardous substances of the US Agency for Toxic Substances and Disease Registry's (ATSDR). It has also been identified as a Substance of Very High Concern (SVHC) by ECHA due to its carcinogenic and STOT RE (specific target organ toxicity - repeated exposure) properties. Cadmium has the potential to cause genetic defects (Muta. 2), as well as organ specific toxicity (STOT RE 1), as well as being a human carcinogen (Carc. 1B, Carc 1, as classified by ECHA and IARC respectively) and a suspected human reproductive toxicant affecting fertility (Repr. 2) (ECHA, n.d.).

The current EU (extracted from the ECHA C&L Inventory) and IARC classifications for hazards to human health are summarised in Table 4.1, including the toxicity underlying the classifications.

Specific adverse health effects will vary depending on the level of exposure. For example, long-term inhalation exposure (~45 years) from occupational sources may lead to renal tubular damage

in exposed workers at concentrations levels of 5-10 µgCd/m^3. Obstructive lung disease is also a risk at cadmium concentrations of >100 µg Cd/m^3 (Nordberg et al., 2015) with one study showing increased rates of lung and prostate cancer in exposed workers (Nordberg et al., 2015). Cadmium accumulation occurs particularly in the kidneys, with lifetime exposures potentially leading to concentrations of up to 4 µg Cd/g creatinine in urine, a level that would pose a serious threat to the health in sensitive groups (e.g. pregnant women, postmenopausal women and the elderly) and that also associates with increased risk of osteoporosis. Epidemiological studies in general populations have also reported statistically significant associations with a number of adverse health effects at low exposures, but dose-response relationships have not been established (summarized by Nordberg et al., 2018).

Table 1.1 Overview of CLP classifications for cadmium as per ECHA data

Substance	Properties of concern				Category according to CLP criteria								ECHA info card
	Carcinogenicity	Mutagenic	Skin sensitising (SS)	Reproductive Toxicity	Carcinogenicity	Acute Toxicity	Specific target organ tox (repeated exposure)	Reproductive Toxicity	Mutagenic	Eye Damage/ Eye Irritation	Skin Sensitivity	Skin Corrosion/ Irritation	
Cadmium					1B*	2*	1*	2*	2*				Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.); ** Based on IARC classification. Blank cells denote a lack of classification.

4.2 Vulnerable target groups

Those considered to be most at risk from cadmium exposure includes smokers and those working in industries where individuals are using and/or are exposed to cadmium. Activities where occupational exposure may occur include those working in the metals industry, production and use of pigments and production/recycling of electronics and electrical items (NIOSH, 2019).

Pregnant and postmenopausal women and the elderly are identified as sensitive groups, particularly with regard to bone effects such as osteoporosis and increased risk of fractures. However, as Cd accumulates with age, exposure should be kept within the age-dependent safe limits for adverse effects throughout the lifetime, in order not to exceed them later in life.

4.3 Societal concerns

Societal concerns for Cd exposure include (European Chemical Agency, 2013; Nordberg et al., 2015; 2018):

- Despite improved regulations, no decrease in soil Cd concentrations and human background intakes has been seen, in fact there has been an increase in local regions, e.g. in Sweden;
- Continuous accumulation of Cd in the body has been found to cause adverse effects in susceptible populations;
- Uncertainties exist in the current health risk assessment; and
- High societal costs relating to health care and adverse implications to lifespan and quality of life are apparent.

5 EU policies on cadmium

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as ECHA consultations. These are available in the HBM4EU Science to Policy section.

Table 2.1 provides a summary of some key legislative measures which have been put in place to control cadmium use and environmental releases and to protect citizens from the effects of elevated cadmium exposure.

Table 2.1 Overview of EU policies relating to cadmium

General chemical	• The manufacture, use and sale of cadmium and its compounds are restricted for certain applications under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). See conditions of restrictions here. • Cadmium is subject to EU **harmonized classification and labelling** under Regulation (EC) No 1272/2008 on classification, labelling and packaging (the CLP Regulation). • **Human biomonitoring (HBM) values** – the HBM4EU project has recommended a range of HBM-GV values for the general population and for workers (Lamkarkach et al., 2021).	• **Food Safety** – Regulation (EU) 2021/1323 issued in August 2021 set new limits for cadmium in certain foods including in fruits, vegetables, mushrooms, chocolate, seafood, meat and baby food. • **Cosmetic products** – Regulation (EC) No 1223/2009 on cosmetic products prohibits cadmium and its compounds in cosmetic products. • **Toys** – Directive 2009/48/EC on the safety of toys sets migration limits for mercury from different types of toys (0.3-17 mg/kg). • **Electrical equipment** – The Restriction of Hazardous Substances Directive (2002/95/EC) controls the use of cadmium in electrical equipment (limited to 0.01% by weight). • **Batteries** – The Batteries Directive limits the Cd content of batteries being placed on the market.	**Consumer**
Environmental	*Water* • Cadmium and its compounds are listed as priority hazardous substances under the Water Framework Directive 2000/60/EC. • Environmental Quality Standards for cadmium are specified. The limit value varies depending on the hardness of the water. • The Drinking Water Directive (Directive 2020/2184) limits the concentration of cadmium in water for public consumption to 5 µg/L. *Air* • The National Emissions reduction Commitments Directive (NEC) (2016/2284/EU) sets reporting requirements on emissions and projections of cadmium. *Industrial emissions* • Directive 2010/75/EU on industrial emissions and the associated Best Available Techniques (BAT) process require control on emissions of a range of pollutants including cadmium emissions from industrial installations/activities.	• An occupational exposure limit value for cadmium is specified under the Carcinogens and Mutagens Directive (2004/37/EC). The limit for an 8-hour exposure time is set at 0.001 mg/m^3 (inhalable fraction). This limit will take effect from 2027 and in the meantime an interim limit is set at 0.004 mg/m^3.	**Occupational**

6 Policy questions for cadmium

6.1 Introduction

For each of the HBM priority substances stakeholders were asked to identify policy related questions that HBM4EU should address in order to contribute to the strengthening of policy ambitions on cadmium. Further background detail on cadmium and how the policy questions were selected is available in the scoping document and the report on stakeholder consultation and mapping of needs.

The current situation for cadmium's policy questions is summarised in the next section and they were based on a document updated by the CGL and work package leader (WPL).

6.2 What is the current exposure of the EU population to cadmium?

The European HBM dashboard has 41 datasets with Cd exposure data integrated and in IPCHEM metadata for 74 datasets with Cd data are available.

Based on the concentration ranges reported for adults, the levels in urine span from below LOD to 3.15 µg/L and in blood from below LOD to 7.07 µg/L. In cord blood the levels are <LOD-5.31 µg/L, while in children <LOD-1.33 µg/L (blood) and <LOD-5.18 µg/L (urine) and in adolescents <LOD-22.9 µg/L (blood) and <LOD-0.154 µg/L (urine) The LODs ranged between 0.0001 and 0.06 µg/L in urine, between 0.02 and 0.2 µg/L in blood, and between 0.01 and 0.12 in cord blood.

New data for cadmium from the HBM4EU Aligned Studies included 2510 individuals. P50 and P95 of urinary cadmium concentrations are in the range of 0.10-0.37 µg/g crt and 0.26- 1.71 µg/g crt across studies in adults. For the subpopulation of non-smokers P50 and P95 of urinary cadmium concentrations are in the range of 0.09- 0.36 µg/g crt and 0.23- 1.56 µg/g crt across studies in adults.

6.3 Does the exposure to Cd differ significantly between countries and population groups? What are the main reasons for differences in exposure?

The HBM4EU Aligned Studies data revealed differences in internal exposure up to a factor 3 between the specific EU study sites.

When comparing the four regions, higher levels were observed in West and East than in North and South, but after accounting for the main influencing factors (age, sex, smoking status and sampling year), the differences between the regions were not statistically significant.

6.4 Is there a significant time trend of Cd levels in existing population studies?

No significant time trend was revealed from the existing and the HBM4EU aligned studies data. As described by Becker et al. (2013), no obvious trends of decreasing Cd concentrations have been observed in neither of the followed population groups in Germany. Similarly, also in Czech Republic, no significant trend was reported (Cerna et al., 2012).

The data from HBM4EU Aligned studies (2014-2021) and its comparison with the DEMOCOPHES data (2012-2014) confirmed that there is no obvious time trend in the last decade. The exposure levels in adults from the two time periods are similar.

6.5 Is there a link between high soil contamination with Cd and human exposure via dietary sources?

Linking HBM and „environmental data" revealed that there is a significant contribution of Cd exposure in humans from phosphorous fertilizers.

Meta-analysis of existing data, representing the period 2007-2018, showed inconsistent associations between HBM and soil cadmium concentrations across different countries, population groups or different types of matrices. At specific study sites, positive and statistically significant associations between Cd in soil and Cd in urine and/or blood were observed, suggesting a link between Cd in soil and exposure level through consumption of local food in those areas and/or population groups. This was further confirmed by positive associations between HBM data and percentage of agricultural and/or cropland, and phosphorous fertilizer consumption in the older HBM datasets as well as in the new datasets from the HBM4EU Aligned studies. Furthermore, association analysis with individual food consumption data available from participants' questionnaires in the Aligned studies showed an important contribution of vegetarian diet to the overall exposure, with approx. 35% higher levels in vegetarians as opposed to non-vegetarians.

6.6 Which population groups are most at risk?

The task 5.3 analysis indicated exceedance of the HBM guidance value for the higher percentile of exposure. These data, however, are not representative of the population at large and should be dealt with caution.

Osteoporosis cases attributable to Cd exposure was estimated in three European countries (Belgium, France and Spain), based on measured urinary Cd levels from HBM studies conducted in these countries. The targeted population was women over 55 years old. Around 23% of the cases were attributed to Cd exposure. In women aged under 55, it was estimated that between 6 and 34% of the considered populations under 55 years were at risk for osteoporosis.

6.7 Are the overall exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, TDI)?

The task 5.3 analysis indicated exceedance of the HBM guidance value for the higher percentile of exposure. These data, however, are not representative of the population at large and should be dealt with caution.

Also based on the EFSA evaluation of the dietary Cd exposure, mean exposure of adults across Europe is close to, or slightly exceeding the TWI of 2.5 µg/kg bw/week.

In the HBM4EU Aligned Studies, the share of individuals with exposure levels exceeding the HBM-GV value of 0.3 µg/g crt for adults (21-30 years) ranges from 2.13-56.39 %. The share of individuals with exposure levels exceeding the HBM-GV value of 0.5 µg/g crt for adults (31-40 years) ranges from 0-35.43%. For the subpopulation of non-smokers the share of individuals with exposure levels exceeding the HBM-GV value of 0.3 µg/g crt for adults (21-30 years) ranges from 0.96-51.22 %. The

share of individuals with exposure levels exceeding the HBM-GV value of 0.5 µg/g crt for adults (31-40 years) ranges from 0-33.88 %. Overall, there were 16.4% study participants who exceeded the age-dependent HBMGVs set by Lamkarkach et al. (2021).

So, at most study sites, there is a certain proportion of people that showed elevated exposure, with levels that cannot be considered safe.

6.8 Has regulation under REACH had a favourable impact, such as a reduction of GM/median concentrations?

Based on the very limited availability of the systematically repeated exposure data available (as explained under the time trends policy question activities), this question will be difficult to answer at this stage and will have to wait until repeated HBM exercises are performed in the future.

However, HBM4EU Aligned Studies data enabled comparison with the DEMOCOPHES study data collected in DK, SE, CZ, HU, PL, SK, ES, SI, BE, LU and DE in years 2011-2012.

The cadmium levels in the HBM4EU Aligned Studies are broadly similar to those of the previous DEMOCOPHES study that sampled children and their mothers between 2011 and 2012.

Based on the available datasets there seems not yet a clear trend for decreasing internal concentrations of Cd with time.

6.9 Are environmental quality standards for Cd in water sufficiently restrictive to protect human health from exposure to cadmium via the environment and via dietary sources?

Based on the available HBM data, mean daily intake of Cd is in the range of 0.1 to 0.7 µg/kgbw/day, with the highest levels observed in Poland, indicating that the highly exposed individuals might be close to the EFSA tolerable weekly intake (TWI) of 2.5 µg/kgbw/week.

This shows that the current cadmium regulations and measures are not protective enough and that further reduction of Cd exposure in the general population is needed.

7 HBM4EU outputs to date

7.1 Categorisation

Substances under HBM4EU have been categorised depending on availability of HBM data. The categorisation indicates the information gaps allowing the development of targeted activities to fill the knowledge gaps. Substances will pass from Category E over D, C, B towards Category A as more information becomes available. Fully characterised substances should end up as category A substances.

Table 3.1 HBM4EU categorisation for cadmium

Category		Priority substance(s)	Details
A	HBM data are sufficient to provide an overall picture of exposure levels across Europe	Cadmium	The exposure pathways are identified. Knowledge on health impacts is available.

7.2 Key outputs

In order to further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach to study HBM planning and conduct in Europe.

Inventory of studies holding Cd exposure data was obtained through WP7 (Task 7.1) with an online questionnaire which was distributed with an aim to identify existing HBM studies.

Within WP10 (task 10.4) a substance-specific research protocol has been elaborated to exploit the available datasets with an aim to assess current Cd exposure of the European population and its geographical distribution. Individual data has been received for 32 studies from 15 countries in all 4 geographic regions, covering population groups of children, adolescents, adults, pregnant or lactating women and new-borns. The data refers to the time period 2007-2018. The existing data collection includes 22428 single measurement data, with the largest proportion of data for morning urine (n=7688), followed by whole blood (n=6740), spot random urine (n=3615) and cord blood (n=2717). The most represented groups are children and adults.

For Cd, questionnaires for adults, adolescents and children are available.

Questionnaires for the 2nd occupational study on e-waste (incl. total Cd as a biomarker) have also been developed.

The newly derived data from HBM4EU Aligned Studies includes data from 9 countries (10 studies) in urine of adults (20-39 years old) and represents the time-period 2014-2021. Biomarker data from 8 countries (9 studies) was assured by the HBM4EU QA/QC program. The participating studies are distributed among 4 geographical areas of Europe and include the following countries: Denmark, Iceland, Czech Republic, Poland, Croatia, Portugal, France, Luxembourg, and Germany.

Only 3 datasets have been identified that have repeated Cd measurements available: German ESB and GerES (from 1986), Czech Republic (from 1996) and Belgium with limited time points (3). Therefore, data is insufficient to evaluate time-trend on the EU-wide scale.

Within the work package WP5 (task 5.3) available data has been identified and applied into the mathematical models to describe the transfer from soil via fertilizers to plants (dietary source) and from plant to human via diet. Due to the scarcity of the external data available (soil, food, fertilizers, etc), the application was limited to the region-specific case study in Slovenia. The local case study is described in the Deliverable 5.8. The model enables to predict an oral intake via data on Cd concentrations in soil, phosphate fertilizers and food. Furthermore, European databases were exploited to obtain Cd concentrations in soil, percentages of agricultural areas and phosphorous fertilizer application for different countries and NUTS areas.

Dietary intake limit values are derived based on the relationship between renal tubular impairments (proteinuria) and urinary Cd for women aged above 50 years (EFSA, JEFCA, ATSDR). The kidney dysfunction is considered as the critical effect, but there is also evidence for low dose bone effects.

The EFSA evaluation (2009) of the dietary Cd exposure showed that exposure of some subgroups, such as vegetarians, children and smokers and people living in highly contaminated areas could exceed the TWI of 2.5 ug/kg bw/week by about 2-fold. However, the revised assessment (EFSA 2012) indicated that the actual risk of adverse effects for an individual at current dietary exposure in the EU was low for adults, because the TWI was established based on an early indicator of changes in kidney function suggesting possible kidney damage later in life.

Within task 5.3 (Deliverable 5.5), evaluation of fractions of urinary samples exceeding the threshold value of 1 µg/g creatinine has been assessed for the available HBM data for women >50 years.

Furthermore, attributable burden of disease related to Cd exposure was calculated in women aged > 50 years for chronic kidney disease, as a critical health effect, and osteoporosis at hip or spine. However, the estimations are preliminary and still premature for the use in policy recommendation.

The main uncertainty arises from the questionable causality between Cd exposure and bone/kidney effects at low doses of exposure (below 5 µg Cd/g creatinine) that are commonly observed in the general European population.

This has been outlined also in the Deliverables 13.4 and 13.5 elaborated within the task 13.2 with a purpose to establish exposure-health relationships.

The methodology agreed within the framework of the HBM4EU project was used to derive HBM-GVs of urinary cadmium for the general population (HBM-GV_{GenPop}) and for workers (HBM-GV_{Worker}) exposed to cadmium (Cd) and its compounds. Taken into account the accumulation of Cd in the human body throughout life, HBM4EU derived age-dependent alert values to prevent exceeding the guidance value of 1 µg/g creatinine for adults over 50 years and therefore prevent adverse kidney effects. These were set to 0.1 µg/g creatinine (crt) for children of 10 years of age or younger, 0.2 µg/g crt for 11-20 years, 0.3 µg/g crt for 21-30 years, 0.5 µg/g crt for 31-40 years, 0.8 µg/g crt for 41-50 years (Lamkarkach et al., 2021).

For occupational exposure, an 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-$GV_{Wworker}$ 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).

The work conducted within task 5.3 (Deliverable 5.5) included evaluation of fractions of urinary samples exceeding the threshold value of 1 µg/g creatinine (critical Cd urinary level established by EFSA; HBM-I value and HBM4EU HBM guidance value) from the available HBM data (urinary Cd in women >50 years from Spain and France – BIOAMBIENT_ES and ENNS studies; and urinary Cd in women 35-45 years from 17 EU countries - DEMOCOPHES).

Furthermore, HBM4EU Aligned Studies data was used to estimate the percentage of study population exceeding the age-dependant HBM-GVs.

The HBM4EU data (2014 – 2020) for the European adult population aged 20-39 years shows that at most sampling sites 5% of the study participants exceeded recommended alert values for urinary cadmium levels. Exceedances in the different studies and locations range from 1.42% up to 42.7%. The studies with most adults exceeding the guidance value were from Western and Eastern Europe.

The cadmium levels are broadly similar now compared to the previous DEMOCOPHES study that sampled children and their mothers between 2010 and 2012 in DK, SE, CZ, HU, PL, SK, ES, SI, BE, LU, DE). This indicates that current cadmium regulations and measures are not protective enough and that further reduction of Cd exposure in the general population is needed.

The implementation of the neurological effect marker (BDNF) linking cadmium to health effects in HBM4EU-related studies has shown promising results constituting an added value for human studies (Rodríguez-Carrillo et al., 2022).

Within WP 12, a PBPK model has been developed for cadmium, exposure reconstruction to estimate dietary intake was based on numerous studies on different geographic scales and

population sizes covering a large part of the EU Member States (including HBM4EU Aligned Studies data).

The level of exposure to Cd is rather low and the time trends not established. Moreover, at this stage studies on occupational exposure in production line are also not available. It is currently difficult to assess the risks of Cd in quantum dots for the general population as this requires specific modelling for Cd exposure for use of Cd-containing quantum dots in electronic equipment. No attempts have been made in WP12 to model quantum dot related exposure of workers to Cd.

Short summary of the deliverables from the HBM4EU project for cadmium:

- Deliverable 5.3 (Scoping paper on the development of an indicator on chemical exposure in the European population):
  - Available data have been identified and applied to models in order to describe the transfer of Cd from soil to plants (e.g. via fertilisers).;
  - Due to the scarcity of data, the model could not be used on an EU-wide scale and was limited to region-specific examples (see Slovenia case study in deliverable 5.5); and
  - The model will be used to predict an oral intake via data on Cd concentrations in soils, phosphate fertilizers and food. This currently applies to Slovenia as a region-specific study due to existing data gaps

- Deliverable 5.5 (Human biomonitoring in risk assessment: 2nd set of examples on the use of HBM in risk assessments of HBM4EU priority chemicals):
  - Kidney dysfunction is a critical effect (based on consideration of Cd dietary intake values and renal dose-response). Increasing evidence for bone effects at low dosages lead to bone effects being classed as another critical effect (ATSDR, 2012; Nordberg et al., 2018)
  - Following an evaluation of the fraction of urinary samples exceeding the threshold value of 1 µg/g creatinine for women over 50 years old, it was discovered that the Risk Characterisation Ration (RCR) was above 1 in the Spanish BIOAMBIENT.ES and French ENNS studies (1.82 and 1.15 respectively). This suggests these populations may be at increased risk of adverse health impacts already; and
  - Attributable burdens of chronic kidney disease and osteoporosis from Cd exposure has been calculated for women aged over 50 years. These estimations are indicative and preliminary for policy use, e.g. because of uncertainties in terms of causality and the response of bone/kidney effects at low exposure.

Figure 7.1 describes a case study on the link between Cd soil contamination and human Cd dietary exposure, based on the methods used in Task 5.3 (as set out in deliverable 5.5)

CASE STUDY: *Cd concentrations in soils and human Cd dietary exposure study in Slovenia*

- The link between Cd soil contamination and human exposure via dietary sources was assessed using a mathematical predictive model. The model was elaborated to estimate the contamination of Cd in plants for human consumption over a 99-year projection period;
- It was used to predict the evolution of Cd concentrations according to input fertilizer scenarios based on Slovenian specific data. This could then be used to assess the impact of variations of Cd in soils on the exposure of the Slovenian population through human internal Cd concentration; and
- There is local contamination due to phosphate-based fertilizer use in the North-East parts of Slovenia.

Figure 7.1: A case study on Cd concentrations and the human intake of Cd in Slovenia, using a mathamatical predictive model

- Deliverable 7.1 (Report on ongoing activities and existing data and data gaps for the 1st prioritised substances including a list of metadata that can be uploaded in IPCheM):
    - An inventory for studies including human biomonitoring data for cadmium exposure. A questionnaire was sent to the participating countries to obtain information and data on Cd biomarkers from population surveys and cohort studies; and
    - Cadmium substances were the most studied in the West and South of Europe (23% and 24% respectively of the total number of reported studies across the substances considered).

- Deliverable 8.1 (Description of the national programmes. A strategy to collect EU wide HBM data):
    - Additional exposure assessment using an 'aligned studies methodology' to obtain EU-wide coverage for recent HBM exposure data between 2014 and 2019; and
    - Cd will be measured in **adult** samples (19-40 years) of HBM studies across 9 countries in four geographic locations across Europe. Cd will be determined in urine or whole blood.

- Deliverable 9.2 (Prioritised list of biomarkers, matrices and analytical methods for the 1st prioritisation round of substances):
    - Deliverable 9.2 highlights whole blood (0.5 mL) and urine (1 mL) as the two matrices used for Cd analysis;
    - Urine is the preferable matrix because it requires only non-invasive sampling. Blood is an alternative biomarker used in HBM surveys dealing with low exposure. Blood levels also reflect exposure over more recent weeks while urine reflects accumulated exposure and
    - At low levels when using an ICP-MS, measures to correct interferences of tin and molybdenum in urinary levels of Cd should be in place.

- Work package 10 (Data management and analysis):

    - Metadata of 63 HBM data collections with data on cadmium exposure, covering 16 European countries, can be identified in IPCHEM.

    - In the HBM4EU repository, aggregated data from 39 and 1 HBM data collections on cadmium exposure are available in HBM4EU harmonized format and own format respectively.
    - Deliverable 10.6 (2nd annual list of exposure distributions and/or European reference values): exposure distributions have been established for the existing harmonised aggregated HBM data on Cd.
    - Deliverable D10.5 (Statistical analysis plan): besides the plan with regard to statistical issues common to all HBM data analysis, a substance specific statistical analysis plan is developed for Cadmium listing the exposure related policy questions and a list of variables needed to explore these questions.
    - On-going research protocol (task 10.4) to explore available datasets to assess current Cd exposure in Europe and the geographical distribution of the data.

- Deliverable 13.5 (Identified gaps for the establishment of AOPs and required studies):
    - Knowledge gaps in the data have been identified in Deliverable 13.5, along with methods to tackle them. These are described in Table 7.2.

7.3 Key data gaps

HBM4EU is a five-year project, that kicked off in 2017 and will run till June 2022. HBM4EU has helped to identify a number of specific data gaps that are needed to give policy makers relevant

and strategic data to establish appropriate regulations and improve chemical risk management. However, some gaps and needs for action will remain after the end of HBM4EU which should be addressed in the future:

The challenges facing the determination of Cd exposure and the adverse health effects include a lack of adequate data. Studies into the scale of existing Cd exposure are limited to regional-specific examples (such as the Slovenia case study) because of data gaps, making it difficult to evaluate at the EU-wide scale. Inaccuracies in the methods used to determine Cd exposure concentrations and effects (specifically the methods used for renal function biomarkers) means it is most reliable at higher exposures and raises issues regarding the nature of health effect associations at low exposures.

Some of the key challenges and gaps are summarised below:

- Insufficient data: not enough data to evaluate time- and spatial trends on an EU-wide scale, with studies being region-specific (Slovenia case study)
- Uncertainties: questionable causality between Cd exposure and bone/kidney effects at low exposure dosage;
- Knowledge gaps (identified in Task D13.5 and summarised above in Table 7.2
- Cd determination methodology inaccuracies: lack of consistency across all matrices (leading to uncertainties)

Table 7.2: Knowledge gaps identified in Deliverable 13.5

Gap(s) identified	Actions to tackle the gap
Low exposure levels and associations with both renal tubular dysfunction and effects on bones have been questioned	Health risk assessment should not rely only on Cd measured in urine? (due to renal physiology). A re-evaluation of the relationship in considering both blood and urine Cd concentrations is required
Lack of assessment of possible co-exposures, making it difficult to evaluate the association between Cd exposure and pulmonary disorders	Re-assessment of the exposure-health associations. Non-smoking individuals should be included in population-based studies. Account for other compounds from tobacco smoking believed to cause similar effects
Population-based studies estimating relationships of low-level Cd with kidney dysfunction are often not considering co-exposure to other nephrotoxic compounds	Epidemiologic/other population-based studies should address co-exposure to nephrotoxic elements to provide data for a refined risk assessment
Cd associations with kidney, prostate and breast cancer are not yet established	More studies are needed into the associations between Cd and these types of cancer. Effect biomarkers of Cd exposure and mechanisms of Cd action
Mechanisms have been proposed for the Cd impacts on bone. However, existing KEs (Key Event) in the AOP (Adverse Outcome Pathway) Wiki Database are not identified as part of the Cd toxicity pathways	Some of the listed mechanisms that are identified as KEs should be linked to Cd toxicity pathways. Work on AOP for kidney toxicity of metal mixtures including Cd is also of concern
Good supporting epidemiological evidence for Cd effects on endocrine disruption, abnormal	Predict molecular interactions theoretically, test experimentally potential targets corresponding

sperm and neurodevelopment/immunotoxic effects, but mechanisms of toxicity and relevant AOPs are unknown	to MIEs (Molecular Initiatives Event) of AOPs – consider relevant health outcomes if positive. Risk assessment in relation to the listen outcomes
Lack of information on the health effects of typical chronic lower level exposures in the general population	A chemical analysis of both external exposures and internal doses would be of use

8 Future recommendations

Due to the well-known limitation of normalization to urinary creatinine, especially in the case of Cd, the use of specific gravity to correct the dilution effect is strongly recommended in future HBM studies.

It is generally accepted that urinary Cd concentrations reflect long-term exposure, however, at lower exposure levels due to normal physiological variability in the kidney, urinary Cd is less reliable. Therefore it is recommended that the ratio of Cd in urine to renal markers / bone effects is re-assessed using SG-normalized urinary levels and blood Cd levels.

Re-assessment of the association between soil and HBM data on cadmium is needed, using more complete spatially resolved soil data, especially the use of phosphate based fertilizer and other ancillary data currently not available for all NUTS areas. In addition, further development and validation of the predictive model for estimating soil Cd transfer to plants is needed to better link external exposure scenarios in different EU regions

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