Prioritised substance group: Cadmium (Cd)

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Short overview of results of the activities carried out within HBM4EU in 2020 to answer the policy questions with reference to corresponding deliverables.

Policy Question	Short Summary of Results
1. What is the current exposure of the European population to Cd?	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 the 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. From the datasets having information on Cd internal exposure, 37 datasets from 17 countries have so far confirmed sharing of individual or aggregated data (the majority is individual data, 33 datasets) to assess the exposure in Europe and its geographical variability. Based on the data available, we decided to look at the exposure data for the period between 2007-2017. However, the work is in progress (acquisition of individual or aggregated data from data providers) and the number of datasets is constantly being updated. Preliminary assessment of the data available from the above-mentioned datasets has been done. So far, we have 27 datasets having Cd measurements for adult general population from all 4 geographic regions (north, south, east, west). Although the preferred matrix for internal Cd assessment is Cd in blood, the majority of the datasets (23) have the measurements available for urine, while only 10 for whole blood. Additionally, we have 5 datasets for Cd in cord blood, 3 datasets for Cd in child's blood, 2 for Cd in adolescent's blood, and 10 for Cd in child's urine and 1 for Cd in adolescent's urine. Based on the concentration ranges reported for adults, the levels in urine span from below LOD to 5.34 µg/L and in blood from below LOD to 6.26 µg/L. In cord blood the levels are <LOD-2.5 µg/L, while in children/adolescents <LOD-22.9 µg/L and <LOD-0.144 µg/L in blood and urine, respectively. However, the mean values for all datasets that have this data available are all below the established HBM I value of 1 µg/L urine (adults) and 0.5 µg/L urine (children/adolescents). Further assessment as described in the research protocol is on-going. Additional exposure assessment will be performed based using harmonized methodology developed and agreed in task 8.1 (aligned studies) to obtain EU-wide coverage for recent exposure (2014-2018). Cadmium will be measured in samples of identified

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	on-going studies (200-300 participants per study). The studies selected include adults (20-39 years) from 8 countries distributed among 4 geographical areas of Europe: Denmark, Iceland, Czech Republic, Poland, Croatia, France, Switzerland, and Germany. Cadmium will be determined in urine (available in all 8 studies) or whole blood (available in 3 studies). Among others, results obtained in aligned studies will allow further evaluation of the proper use of biomarkers (urine vs. blood) at low level of exposure. The laboratories performing laboratory analysis have been tested through the QA/QC scheme, which has completed the third round of proficiency tests for the determination of Cd in urine and whole blood. The first list of approved laboratories is now available and includes 33 labs for urine samples and 22 labs for Cd in blood. The comparable results obtained from the aligned studies will also enable derivation of European Reference Values (ERVs) as part of task 10.3.
2. Does the exposure to Cd differ significantly between countries and population groups? What are the main reasons for differences in exposure?	This question will be answered once the work described in the substance-specific research protocol developed within task 10.4 is completed. The work is in progress as described above. Spatial analysis will be done according to the Statistical analysis plan (Deliverable 10.5, Section 7). Once the required data (individual or aggregated) from the available datasets will be acquired, the data will be compared statistically and visualized with respect to geographic regions (north, south, east, west), countries and the NUTS regions. In cases of individual data (which is the majority of the datasets), we'll be able to confound for the known and hypothetical determinants of Cd exposure (e.g. smoking) to reveal the geographical and/or environmental pattern(s). This will also allow as to identify the main reasons for possible differences.
3. Is there a significant time trend of Cd levels in existing population studies?	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. However, 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).
4. Is there a link between high soil contamination with Cd and human exposure via dietary sources?	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 5.5. The model enables to predict an oral intake via data on Cd concentrations in soil, phosphate fertilizers and food. Using HBM and food consumption data, the oral intake will be validated using the PBPK modelling (work in progress).
5. Which population groups are most at risk?	Dietary intake limit values are derived based on relationship between renal tubular impairments (proteinuria) and urinary Cd for women aged above 50 years (EFSA, JEFCA, ATSDR). Also, the HBM4EU HBM guidance value (HBM-GV) has been derived for the general population based on the increase in prevalence of elevated beta-2-microgloblin urinary levels as indicator of tubular proteinuria. The HBM-GV has been set at 1 ug/g crea, similar to the value of EFSA and the German HBM-I value. The kidney

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	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. The data indicated exceedance of the HBM guidance value for the higher percentile of exposure. 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. Variation in renal physiology is one of the main factors confounding the association at low exposure levels (co-excretion of low-molecular weight proteins and Cd). Moreover, normalization of Cd concentrations for diuresis is also a questionable issue, therefore the health risk assessment should rely on Cd measured in blood to compensate uncertainties related to Cd in urine (Stajnko et al., 2017).
6. Are the overall exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, TDI)?	We'll be able to answer this question once the complete data from the available datasets will be acquired (work within 10.4, described above). For the time being, we have concentration ranges available from the metadata of various studies, and from the literature. However, 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 ug/kg bw/week. 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). The data 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.
7. Has the regulation under REACH had the favourable impact like 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.

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8. 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?	Work in progress within WP10 and WP12 Following collection of HBM and dietary intake EU-wide data, and validation through the PBPK models, (drinking) water as a source of Cd will be included in exposure pathway to derive 'limit' value for Cd in water. In some of the countries (e.g. Slovenia) actual measurements in water and in population will allow direct links to be established.
9. What is the maximum acceptable level for Cd in food stuffs?	Work in progress within WP10 and WP12 (similarly as above)
10. Can input be given to the decision as to whether the exemption for Cd in quantum dots under the RoHS Directive can be scrapped?	In general, population such a relationship is difficult to establish as currently the level of exposure is rather low and the time trends not established. Moreover, at this stage studies on occupational exposure in production line are also not available.

References:

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