1 Prioritised substance group: Cadmium (Cd) and Hexavalent Chromium (Cr VI)

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1.1 Background Information

1.1.1 Hazardous properties

Cadmium

Cadmium is a potentially toxic metal that ranks 7th on the priority list of hazardous substances of US Agency for Toxic Substances and Disease Registry's (ATSDR). 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).

Kidneys, as a major location of Cd accumulation, are primary organ of adverse metal effects that occur at general population after lifelong exposure resulting in urine concentrations of 4 µg Cd/g creatinine. The same level of exposure in more sensitive groups (pregnant and postmenopausal women, elderly) can also lead to bone effects such as osteoporosis and increased risk of fractures. The existence of Cd adverse effects at lower environmental exposures (<1 µg Cd/g creatinine) - related to bone diseases, effects on kidney functions, effects on endocrine system, reproduction and development ect. - has been recently seriously questioned (Åkesson et al., 2014; Nordberg et al., 2015; Apostoli and Catalani 2015; Bernard, 2016).

However, Cd co-exposure and effects in mixtures of chemicals has not been addressed sufficiently. Most experimental and human studies are dealing with exposure to a single element while real environmental exposure is generally characterised by many substances in unpredictive combinations or exposure conditions and by essential metal status (Apostoli and Catalani 2015, Nordberg 2015).

Hexavalent Chromium

Chromium can exist in oxidation states ranging from -2 to +6, but is most frequently found in the environment in the trivalent (+3) and hexavalent (+6) oxidation states. The +3 and +6 forms are the most important as the +2, +4, and +5 forms are unstable and are rapidly converted to +3, which in turn is oxidised to +6 (Towill et al. 1978). Hexavalent form - Cr(VI) - is more toxic than trivalent form.

- Cr(III) for its high oxidising potential - and easily penetrates biological membranes.

Hexavalent chromium was classified by IARC as a human carcinogen (Group 1) associated with increased lung cancer risk among workers in certain industries and also cancer of the nose and nasal sinuses.

In EU the estimated number of Cr(VI)-exposed workers in 2012 was ~786,000, with the largest numbers exposed to welding (IARC, 2012). In the EU CLP Regulation (EC) No 1272/2008 they are classified as genotoxic (Muta. 1B) and as carcinogen (Carc. 1B or 1A).

Also the dermal exposure to Cr(VI) compounds can cause skin irritation, ulceration, sensitization, and allergic contact dermatitis (NIOSH, 2002). The toxicity of Cr(VI) in humans has been reviewed extensively (ATSDR, 2012; Costa and Klein, 2006; U.S. EPA 1998). After absorption, mainly via inahalation for workers and/or via ingestion for the general population, Cr(VI) readily penetrates cell membranes. The details of Cr(VI) toxic activity assumed that genotoxicity, including a wide variety of effects such as DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation, and dominant lethal mutations, may be due to the reduced forms of intracellular origin, formed by the reduction of Cr(VI) to Cr(III) (Stearns et al., 1995). The main protection mechanism against Cr(VI) activity in the lungs and the stomach is the extracellular reduction of Cr(VI) to Cr(III) by a NADPH-dependent mechanism involving ascorbate (De Flora et al., 2000). Animal trials show that glutathion plays an important role in Cr(VI) reduction in erythrocytes, also showing certain reduction activity in the lungs (Suzuki and Fukuda, 1990).

1.1.2 Exposure characteristics:

Natural and anthropogenic sources of Cd (European Chemical Agency, 2013; Nordberg et al., 2015):

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 : plastics as colour pigment and stabilizer, automobile radiators, alkaline batteries, mining activities, fertilizers, sewage sludge, inappropriate waste disposal; 50-90%). During the twentieth century the world consumption of Cd has increased continuously to a global supply of 22,000 metric tons (International Cadmium Association, 2002) and it has remained at this level since 2000. Cadmium is normally transported between the three main environmental compartments:

Air: Levels of Cd in the ambient air are usually low, whereas indoor air levels can be higher due to cigarette smoking (1 - 2 µg of Cd/ cigarette) and poor ventilation. The document of air quality criteria by World Health Organisation (WHO, 2000) indicates levels of Cd in Europe of 1-10 ngCd/m^3 for urban areas and 0.1 – 0.5 ngCd/m^3 for rural areas. In more remote areas values of 10 – 100 times lower have been reported and around some Cd-emitting industries the levels could approached 200-600 ngCd/m^3.

Water: Cadmium concentration of natural surface water and groundwater is usually <1µgCd/L. Drinking water in general does not exceed concentrations of 5 µgCd/ L, but could be contaminated in some occasions due to the Cd impurities of galvanised pipes, water heaters/coolers or by leakage of Cd into groundwater from dumped Cd oxide sludge.

Soil: In nonpolluted areas Cd concentrations are below 1mgCd/kg of soil. Levels in soil can be increased by either waterborne or airborne Cd. Most of agricultural soils contamination occurs by the use of phosphate fertilizers leading in elevated levels of Cd in crops. In Sweden, the levels of fertilizers have been regulated, but a small increase is still occurring, depending on the region and type of farming.

Natural and anthropogenic sources of Cr(VI) and Cr(VI) compounds

The occurrence of Cr(VI) is rare naturally. Most of Cr(VI) compounds are man-made (products or by-products) and human-caused Cr(VI) contamination is a result of large industrial emissions (mainly from metallurgical, chemical, and refractory brick industries). Major uses of Cr(VI) compounds include metal plating, manufacture of pigments and dyes, corrosion inhibitors, chemical synthesis, refractory production, leather tanning, and wood preservation (Blade et al., 2007). Due to a lack of internal supply and to demand from the steel industry, the EU has been an importer of Cr ores. The main sources for EU imports in 2006 were South Africa (approximately 80%). Within the EU, Finland was the main producer of Cr in 2006, producing over 99% of the total EU Cr production (219,500 tonnes). A report on a critical raw material profile by the European Commision in 2014 revealed that the forecast average annual demand for Cr growth of 3%-4.5% *per year* (EC Report, 2014, Report on Critical raw materials for the EU (http://ec.europa.eu/DocsRoom/documents/10010/attachments/1/translations).

Mobilisation of Cr occurs among the following environmental compartments:

Air: In rural areas air Cr concentration above 10 ng/m^3 was uncommon whereas in urban (released from anthropogenic point sources) it was 2-4 times higher than regional background concentrations (WHO, 2003). In particular, air Cr concentrations in urban European areas were found to span 4-70 ng/m^3, while in industrial European settings were in the range 5-200 ng/m^3 (WHO, 2000). Approximately one-third of the atmospheric releases of total Cr from anthropogenic sources are believed to be in the Cr(VI) form (ATSDR cap. 6). As a result of smoking, Cr concentrations in indoor air (≈ 1000 ng/m^3) may be 10-400 times greater than outdoor concentrations (WHO, 2003). In workplace air, on a national level, many countries experienced a level of exposure to Cr(VI) equal to 1 µg/m^3 (France) and 5 µg/m^3 (Sweden, Lithuania and Denmark).

Water: Surface runoff, deposition from air, and release of municipal and industrial waste waters are sources of Cr in surface waters. The Cr(VI) species can persist in aquatic media as water-soluble complexes, but in presence of organic matter (or other reducing agents) it undergoes reduction to Cr(III). Although total Cr may reach levels greater than 50 µg/L, in general it is detected at concentrations in the order of few tens of µg/L or lower. In rainwater, Cr concentrations on average fall in the range 0.2-1 µg/L, some part of which may be accounted for by Cr(VI). Total Cr concentrations in groundwater and water from drinking water sources/supplies may range from < 1 µg/L up to a few µg/L. The presence of Cr(VI) in drinking water and/or its precursors is often consequence of anthropogenic contamination by industrial activity, with levels up to 53 µg/L in the case of Thiva- Tanagra-Malakasa basin (Eastern Sterea Hellas, Greece). Finally, as water treatment facilities use strong oxidants to potabilise water, in drinking water Cr may easily be present in the form of Cr(VI) (WHO, 2003; EFSA 2104).

Soil: Chromium levels in soils can vary up to three orders of magnitude, reflecting the composition of the parent rock from which the soils were formed and/or local anthropogenic sources (WHO, 2000). Estimated total Cr concentrations in agricultural European soils found that total Cr is quite abundant.

From this study, 2.7% of soils were above the threshold value (100 mg/kg) and 1.1% above the guideline value (300 mg/kg) set by the Finnish Ministry of Environment and about 2 million ha of agricultural land - with special emphasis for Piemonte, Lorraine-Alsace, Western-Macedonia and Central Greece - were considered at an ecological and health risk (Toth et al., 2016).

Other sources of exposure to Cr(VI) need to be considered for general population, including the release Cr, with Cr(VI) as the predominant species, from orthopedic implants made from stainless steel and cobalt-chromium alloys. Dermal exposure through leather articles and cosmetics, and oral exposure of children through toys have been reported.

Human exposure route and Human Biomonitoring (HBM) data availability for Cd

General population is exposed to Cd primarily through diet and drinking water (5-10 % of ingested Cd is absorbed), and tobacco smoke (10-50 % of inhaled Cd is absorbed). The mean exposure of adults in Europe and North America through food is 10-20 µg Cd/day, which results in average urinary excretion of 0.5-1.0 µg Cd/day and blood concentrations of 0.5-1.0 µgCd/L for non-smokers (twice as high in smokers) (Nordberg et al., 2015).

At the European level the biomarkers are collected in national HBM programs (German Environmental Survey, GerES; The Flemish Environment and Health Study, FLEHS; French Nutrition and Health Survey, ENNS; Czech Republic HBM, CZ-HBM; Slovenian National HBM; etc.) and international projects (Public health impact of long-term, low-level mixed element exposure in susceptible population strata, PHIME and DEMOnstration of a study to COordinate and Perform Human Biomonitoring on a European Scale, COPHES/DEMOCOPHES).

Health-based reference values for cadmium in urine are 1 µg/L (µg/g creatinine; HBM I) and 4 µg/L (µg/g creatinine; HBM II) for adults, and 0.5 µg/L (µg/g creatinine; HBM I) and 2 µg/L (µg/g creatinine; HBM II) for children, as set by the German Human Biomonitoring Commission (Schulz et al., 2011). In blood, reference value is below 1 µg/L for adults (Wilhelm et al., 2004).

Human exposure route and Human Biomonitoring (HBM) data availability for Cr(VI)

Breathing contaminated workplace air is the main source in occupational setting. For the general population exposure to Cr occurs primarily by ingestion of Cr-contaminated soil, food, and water, but also through inhalation of ambient air. Cigarette smoking is another important source of Cr exposure, including the hexavalent state. When talking about total Cr, it is accepted that the contribution of drinking water to the total exposure is substantial only when levels are above 25 µg/L (WHO, 2003). However, the EFSA Panel on Contaminants in the Food Chain noted that the contribution of drinking water to total Cr refers to Cr(VI), whereas in food the trivalent form Cr(III) is the major form. Mean chronic exposure assessment for Cr(VI) across European dietary surveys through the consumption of drinking water ranged from 0.7 ng/kg b.w. per day to 159.1 ng/kg b.w. per day (EFSA, 2014).

Biological monitoring of exposure to Cr(VI) compounds is a practice in occupational settings. In workers, the distribution of inhaled Cr(VI) permits the biological monitoring of Cr in urine, whole blood, plasma, and blood cells. Relevant biological monitoring guidance values for occupational exposure to Cr have been reported on a national basis, but not at EU level. The Spanish authorities set a biological limit value (BLV) for total Cr concentration of10 µg/L in urine measured during a shift and 25 µg/L at the end of the workweek (INSHT, 2016). In the UK, a biological monitoring guidance value (BMGV) of 10 µmol/mol creatinine in post shift urine was established (HSE, 2011).

In Germany, in order to help interpretation of occupational biomonitoring results, DFG did set a BAR (Biologischer Arbeitsstoff-Referenzwert) for the general not occupationally exposed population of working age of 0.6 µg/L urine for Cr(VI) compounds (inhalable fraction) (DFG, 2012). DFG further established the DFG-EKA values (biological exposure equivalents for carcinogenic substances) for Cr(VI) that set the range of total Cr in urine (form 10 µg/L to 40 µg/L) and in erythrocyte fraction of whole-blood (form 9 µg/L to 35 µg/L) if soluble alkaline chromate of a certain concentration and/or hexavalent welding fumes (only for urine) were inhaled over a work shift (DFG, 2015).

No HBM survey have been performed at EU level on Cr(VI) exposure of the general population. Few Human Biomonitoring data come from individuals accidentally or intentionally ingesting Cr(VI) compounds.

1.1.3 Policy relevance

Cadmium

Since cadmium is listed in Regulation (EC) No 1272/2008 as human carcinogen, (Carc. 1B) and due to its increasing evidence of toxicity, both national and international agencies have sought to regulate its exposure. The WHO (2004) guidelines for drinking water quality has been revised from 5 to 3µgCd/L and WHO (2000) guidelines for ambient air 5 ngCd/L. The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2012) has recommended a maximum intake from food of 25µg/kg bw/month (Nordberg et al., 2015). The main rational for action/inaction lies in Regulation (EC) No. 1881/2006 of 19 December 2006 that sets maximum levels for certain contaminants in foodstuffs and contains the most recent maximum levels for Cd in foodstuffs. Furthermore, use of Cd is restricted in certain products (Annex XVII of REACH), among them recycled PVC, the existing allowed limit of which is currently in review. There is also ongoing discussion as regards allowable maximum levels in phosphate fertilizers with a link to acceptable maximum levels in food. Overall, the levels in food, recycled PVC and fertilizers continue to be reviewed by the Commission. An updated scientific basis is therefore of great importance.

Hexavalent Chromium

In the case of Cr(VI) compounds an oral minimal risk level (MRL) of 0.005 mg/kg b.w. *per day* was derived for intermediate (15-364 days) exposure based on haematological effects in rats, while reported in a chronic drinking water study (> 1 year) an oral MRL of 0.001 mg/kg b.w. *per day* was derived selecting as critical effect non-neoplastic lesions of the duodenum (ATSDR, 2012). The WHO derived an oral tolerable daily intake (TDI) for non-cancer effects of 0.9 µg CrVI/kg b.w. *per day* taking into account the data relative to outcome observed in female mice after exposure to sodium dichromate dehydrate in drinking-water (WHO/IPCS, 2013). In a recent document, EFSA provided information on benchmark doses, margin of exposure (MOE) and TDI for the European population (EFSA, 2014).

To date no EU regulation regarding maximum levels of total Cr in food has been established.

A maximum value of 50 µg Cr/L for total Cr both in water intended for human consumption and in natural mineral waters are reported by the Council Directive 98/83/EC and the Commission Directive 2003/40/EC, but no level is available specifically for Cr(VI).

In air, the EU proposed an OEL (occupational Exposure Limit) for the hazardous Cr(VI) of 25 µg/m^3; the number of future cancer cases can be most substantially decreased through full compliance with the OEL(https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016SC0152&from=EN). In addition, the Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit (PEL) of 5 µg/m^3 and an action level (AL) of 2.5 µg/m^3; both for a 8-hour time-weighted average (TWA) exposure to Cr(VI) (OSHA, 2006). The National Institute for Occupational Safety and Health (NIOSH) has recommended a 10-hour TWA exposure limit for all Cr(VI) compounds of 1 µg Cr(VI)/m^3 (NIOSH, 2013).

Hexavalent Cr is included in the revised Annex XIV to the EU REACH Regulation; inclusion in this Annex means that in order to continue to use chromium trioxide and other hexavalent chromium compounds after 21 September 2017, an authorisation will be required.

In addition, since 1 May 2015 a restriction on Cr(VI) in leather is in place (EU Regulation 301/2014) and applicable at EU level (limit of 3 ppm). That threshold is expected to be 80 % effective in reducing the occurrence of new Cr(VI)-related allergic dermatitis cases due to Cr(VI) in leather articles.

Moreover, current migration limits for Cr(VI) are laid down in the Toy Safety Directive 2009/48/EC for ensuring the safety of toys. The current migration limits for Cr(VI) from toys are: 0.2 mg/kg toy for scraped-off toy materials, 0.02 mg/kg toy material for dry (powder-like or pliable) toy materials and 0.005 mg/kg toy material for liquid or sticky toy materials, respectively.

Regarding cosmetics, because of its allergenic character, the presence of Cr(VI) is prohibited in cosmetics by a German cosmetics regulation and also by the corresponding new EU Cosmetics Directive (EU) No 1223/2009; the only allowable green colorants are those based on the trivalent form of Cr (chromium hydroxide green ($Cr_2O(OH)_4$) and chromium oxide green (Cr_2O_3)).

1.1.4 Technical aspects

(Nordberg et al., 2015, Bernard et al 2016)

Biomarkers related to low environmental cadmium exposure that are currently commonly used are levels of:

- Cd in urine is usually accepted as biomarker of body burden reflecting long term accumulation, but such definition is limited to occupational or really excessive exposures. At low environmental situations urine Cd levels are influenced by several factors including physiological variations related to normal (age, circadian rhythm) and stress conditions (physical stress, smoking) or silent (undercurrent) pathophysiological conditions. All these factors are affecting kidney pathways and co-excretion patterns of renal functional biomarkers and Cd itself. Co-excretion of Cd and proteins adds uncertainty to the relationship between UCd and the body burden of Cd.
- Cd in blood /plasma (in most laboratories chemical analyses are not sensitive enough to permit the accurate measurement of plasma or serum). At low Cd levels blood represents recent and past exposure; they cannot be properly distinguished.
- Cd in placenta is used as indicator of Cd exposure during pregnancy
- Cd in cord blood is indicating Cd transfer from maternal blood to cord blood
- Cd in feces - at low doses comparable with urine excretion)
- Cd in kidney, liver or bone tissues is reflecting Cd accumulation.
- Renal function biomarkers in urine such as: albumin (Alb) and Imunoglobulin G (IgG) indicating glomerular kidney damage, and N-acetyl-beta-D-glucosaminidase (NAG), α1-microglobulin (A1M), β2 microglobulin (B2M), retinol-binding protein (RBP), Kidney Injury Molecule-1 (KIM-1), metallothioneins (MTs) indicating tubular kidney damage (Nordberg et al., 2015) – at low levels they rather function as indicators of normal physiological processes, so they are unrepresentative for Cd risk assessment at low levels.

The most common methods for Cd determination in human matrices are inductively coupled plasma mass spectrometry (ICP-MS), atomic absorption spectrophotometry (AAS) and atomic fluorescence spectrophotometry (AFS). For the *in vivo* determination of Cd in tissues, X-ray fluorescence is used. For the determination of renal function biomarkers in urine the standard nephelometric immunochemical method is used, which is less accurate than the measurement of Cd levels in urine or blood. Therefore, determination of renal function biomarkers in relation to Cd exposure and health risk assessment is more reliable at high Cd exposures (> 4 μgCd/ml).

Biomarkers related to Cr(VI) exposure are, currently, the followings:

An important consideration in biological testing for Cr(VI) is the reduction of Cr(VI) to Cr(III) throughout the body. Basically, inhalation is the primary route of concern for occupational Cr(VI) exposure. Inhaled Cr(VI) enters the respiratory system, where it may remain, be reduced, or enter the bloodstream. Cr(VI) may be reduced to Cr(III) in the lungs or plasma and excreted as Cr(III) in the urine. Cr(VI) that is not reduced in the plasma may enter erythrocytes and lymphocytes. This distribution of absorbed Cr(VI) permits the biological monitoring of Cr in urine, whole blood, plasma, and red blood cells (RBCs) in occupational settings.

- Cr in urine

Urinary Cr levels are a measure of total Cr exposure as Cr(VI) is reduced within the body to Cr(III). The average urinary excretion half-life of Cr(VI) is about 39 h.

- Cr measurements in blood and plasma

Plasma or whole blood Cr levels are indicative of total Cr exposure because Cr(VI) may be reduced to Cr(III) in the plasma. Moreover many variables can affect Cr levels in the blood, including diet, varying rates in gastrointestinal absorption, and individual capacity to reduce Cr(VI).

- Cr measurements in red blood cells (RBCs)

Intracellular Cr levels are indicative of Cr(VI) exposure because Cr(VI) passes through cell membranes, while Cr(III) does not. The Cr concentration inside erythrocytes indicates exposure to Cr(VI) sometime during the approximate 120-day lifespan of the cells. There are two advantages to the monitoring of Cr levels in RBCs versus urine: i), the sampling time may be relatively independent of the time of exposure, and, ii), it permits the determination of Cr(VI), rather than only total chromium, absorption.

Thus, in principle, erythrocyte Cr concentration was recommended for its specificity but limited by its low sensitivity. Plasma Cr concentration was recommended as a sensitive parameter, limited by its lack of specificity.

- Cr measurements in exhaled breath condensate (EBC)

In the last years also the exhaled breath condensate (EBC) is depicted as a very good biomarker of occupational exposure. This could potential be a non-invasive alternative to measure exposure to Cr(VI) compounds long after exposure.

In any case, the above biomarkers of exposure are not sufficiently validated and great efforts could be made in this sense. In addition, while biomonitoring of occupationally exposed workers has been used to assess high-level inhalation exposures in the workplace, evaluating low-level environmental exposure to Cr(VI) has to be still addressed.

Moreover, the inter- and intrapersonal variability in background levels of Cr is known to be significant and influenced by food and beverage intake, smoking, exercise, habits. Thus, the role of each factor must be carefully understood.

Overview of the biomoritoring methods is available for total Cr in occupational setting. The DFG proposed two regulatory methods: the first for total Cr in urine, the second for total Cr in whole blood as well as in plasma and in erythrocytes. The analytical determination is done using a standard graphite or a pyrolytically coated graphite tube in combination with electrothermal atomic absorption spectroscopy (EAAS) (detection limit were 0.1 µg /L and 0.5 µg /L) (DFG, 1990). Other analytical techniques for total Cr determination in human matrices is inductively coupled plasma mass spectrometry (ICP-MS).

Because Cr(VI) is largely reduced to Cr(III) in the body, speciation of Cr could not be useful in HBM programmes. However, several methods aiming at direct or indirect measurement of Cr(VI) have been published in literature. They are usually based on some kind of separation of Cr(III) and Cr(VI) (i.e., micro liquid chromatography (µLC) system or ion chromatography), followed by ICP-MS quantification (detection limits ranging from 0.1 to 1.0 µg/L).

However, as far as know, none of these methods have obtained the status of regulatory method yet nor have they undergone a validation.

1.1.5 Societal concern:

The societal concerns regarding cadmium exposure is mostly due to (European Chemical Agency, 2013; Nordberg et al., 2015):

- no decrease in soil Cd concentrations and human background intakes in Europe during recent years in spite of improved regulations and guidelines; in local regions and farms even a slight increase has been observed, particularly in Sweden.
- possible occurrence of adverse effects in susceptible populations at present exposure levels due to continuous accumulation of cadmium in the body
- uncertainties in health risk assessment and therefore in deriving a safe exposure level,
- 'high societal costs in terms of health care and shortening of life time and a decreased quality of life' (European Chemical Agency, 2013; Nordberg et al., 2015).

The societal concerns regarding Cr(VI) exposure are mostly related to:

- anthropogenic Cr(VI) occurrence in water, air and soils as a consequence of industrial activities despite the available limits provided by European regulations and guidelines;
- occurrence of Cr(VI) in many consumers' products such as leather, toys, cosmetics, despite the limits already in place at European level;
- some populations are at higher risk for exposure to Cr(VI), such as children (e.g., from toys) and occupationally exposed workers in many industries;
- possible occurrence of adverse effects with respect to cancer, reproductive and developmental toxicity, but also skin sensitisation and allergy, in exposed and general populations;
- the absence of harmonised HBM reference levels and toxicological derived guidance values for Cr(VI) at European level and the lack of validated analytical tools;
- uncertainties in health risk assessment considering also the inter- and intrapersonal variability of Cr(VI) levels and the influence by food and beverage intake, smoking, exercise, habits;
- high prevalence and incidence of Cr(VI) allergy in the general population and risks of carcinogenic effects, maximise the societal costs in terms of quality of life and health care.

1.2 Categorisation of substances

Table 10-1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A and B substances

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	Cd	cadmium	7440-43-9	Regulation (EC) No 1272/2008 as carcinogen Regulation (EC) No. 1881/2006 for food Restricted use of Cd: Regulation (EC) No. 1907/2006; Annex XVII of REACH (entry 23)
C	Cr(VI)	hexavalent chromium	18540-29-9	Revised Annex XIV to the EU REACH Regulation Directive (EU) No 1223/2009 on cosmetics CLP Regulation (EC) No 1272/2008 as genotoxic (Muta. 1B) and as carcinogen (Carc. 1B or 1A) REACH Regulation (EC) No 1907/2006 for inclusion of substances in the Authorisation List (Annex XIV) Regulation (EU) No 301/2014 in leather articles Directive (EC) No 2009/48 on toy safety

1.3 Objectives / Policy-related questions

Objectives:

1. Synthesise an overview of available biomonitoring and exposure data on Cd and Cr(VI) relevant to the European population.
2. Overview of toxicological data on Cd and Cr(VI) available for European population
3. Identify data and analytical gaps.
4. Identify the key groups at risk considering:
   - life-style, nutritional status and genetic background,
   - gender, age; postmenopausal women, elderly,
   - regions with elevated levels in the environment,
   - occupational settings,
   - co-exposure to chemical mixtures.
5. To assess EU exposure to Cd due to use of phosphate-based fertilizers.

Based on the information above, develop a plan for population-based cross-European and/or targeted HBM studies (demonstration studies) within 2-5 years HBM4EU program.

Policy questions related to Cd:

1. What is the current (last 10 years) exposure of the European population to Cd?
2. Does the exposure to Cd differ significantly between countries and population groups? What are the main reasons for differences in exposure?
3. Is there a significant time trend of Cd levels in existing population studies?
4. Is there a link between high soil contamination with Cd and human exposure via dietary sources?
5. Which populations are most at risk?
6. Are the overall exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, TDI)?
7. Has the regulation under REACH had the favourable impact like a reduction of GM/median concentrations?

8. Are environmental quality standards for Cd in water sufficiently restrictive to protect human health from exposure to Cd via the environment and via dietary sources?
9. Using EU food consumption data, are current Cd food maximum levels sufficiently health protective?
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?

Policy questions related to Cr(VI):

1. What is the level of exposure to Cr(VI) occupationally relevant in the EU population?
2. Does the exposure to Cr(VI) differ significantly between countries and population groups?
3. What are the groups at risk (e.g. by industrial sector)?
4. Are the exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, BLV, OEL)?
5. Have the newly collected HBM data on Cr(VI) an impact in risk assessment procedures (e.g. REACH)?
6. Which are the appropriate HBM matrices, methods and biomarkers for Cr(VI)?
7. Which are possible health effects resulting from exposure to Cr(VI)?
8. Which are possible mechanistic explanation and AOPs for Cr(VI)?
9. Which are the effects of metals mixtures?

1.4 Research activities to be undertaken

Table 10-2: Listing of research activities to be carried out to answer the policy questions summed up in 7.3

Policy question	Subst.	Available knowledge	Knowledge gaps and activities needed
What is the current (last 5 years) exposure of the European population to Cd?	Cd	Data of various HBM studies across EU	Collection and evaluation of existing data
Does the exposure to Cd differ significantly between countries and population groups? What are the main reasons for differences in exposure?	Cd	Data of various HBM studies across EU; geochemical maps, food consumption data, data on fertilizer use	Geospatial comparison of existing HBM data and its evaluation according to available environmental data (Cd in soil, crops, use of artificial fertilizers,…), and food consumption data.
Is there a significant time trend of Cd levels in existing population studies?	Cd	Data of various HBM studies across EU	Data collected in a defined population group(s) over a certain time period covering at least 3 points.
Is there a link between high soil contamination with Cd and human exposure via dietary sources?	Cd	Content of Cd in soil and various food stuffs in contaminated areas; limited data available on human exposure in contaminated areas.	Assess the link using available data; carry out focused survey(s) to obtained high quality concentration data (soil, food, HBM) and detailed food consumption data.

Policy question	Subst.	Available knowledge	Knowledge gaps and activities needed
Are the overall exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, TDI)?	Cd	Data of various HBM studies across EU	Comparison of HBM data with TDI values and HBM guidance values
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?	Cd	Content of Cd in water and food stuffs.	HBM data to be used for the reconstruction of exposure/intake dose.
Using EU food consumption data, are current Cd food maximum levels sufficiently health protective	Cd	Data on human exposure; content of Cd in relevant food stuffs.	Reconstruct the intake dose based on the HBM data using reverse dosimetry and estimate the acceptable concentration in relevant food stuffs.
Can input be given to the decision as to whether the exemption for Cd in quantum dots under the RoHS Directive can be scrapped?	Cd	Human exposure and effects data are limited.	Exposure using HBM to be tested in well-designed case studies.
What is the level of exposure to Cr(VI) occupationally relevant in the EU population?	Cr(VI)	Few data available on Cr(VI) levels at workplace in Europe	Implement studies on occupational exposure to Cr(VI) in the EU population
Does the exposure to Cr(VI) differ significantly between countries and population groups?	Cr(VI)	Few data available on Cr(VI) levels in population groups and across EU	Implement studies comparing EU countries and population groups (general population and workers)
What are the groups at risk (e.g. by industrial sector)?	Cr(VI)	Limited data available on Cr(VI) in industries	Investigate and identify groups at risk like heavily exposed workers
Are the exposure levels (in different population groups) above any health-relevant assessment levels (HBM guidance values, BLV, OEL)?	Cr(VI)	Absence of biological monitoring guidance values at EU level	Derive HBM guidance values for occupational Cr(VI) exposure
Have the newly collected HBM data on Cr(VI) an impact in risk assessment procedures (e.g. REACH)?	Cr(VI)	Few data available on Cr(VI) levels after authorisations/restrictions in Europe	Implement the risk assessment evaluation related to Cr(VI)
Which are the appropriate HBM matrices, methods and biomarkers for Cr(VI)?	Cr(VI)	Sensitive analytical methods and specific biomarkers for Cr(VI) are limited	Revise and harmonise/develop analytical methods and biomarkers for Cr(VI)
Which are possible health effects resulting from exposure to Cr(VI)?	Cr(VI)	Health effects data on Cr(VI) are limited	Implement the knowledge on effect biomarkers associated to Cr(VI)
Which are possible mechanistic explanation and AOPs for Cr(VI)?	Cr(VI)	Lack of knowledge on AOPs for Cr(VI)	Find known or suspected AOPs associated to Cr(VI)
Which are the effects of metals mixtures?	Cr(VI)	Mixtures data including Cr(VI) are limited	To be tested in case studies

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