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The HBM4EU chromates study – Outcomes and impacts on EU policies and occupational health practices

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ABSTRACT

Within the EU human biomonitoring initiative (HBM4EU), a targeted, multi-national study on occupational exposure to hexavalent chromium (Cr(VI)) was performed. Cr(VI) is currently regulated in EU under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and under occupational safety and health (OSH) legislation. It has recently been subject to regulatory actions to improve its risk management in European workplaces. Analysis of the data obtained within the HBM4EU chromates study provides support both for the implementation of these regulatory actions and for national enforcement programs and may also contribute to the updating of occupational limit values (OELs) and biological limit values for Cr(VI). It also provides useful insights on the contribution of different risk management measures (RMMs) to further reduce the exposure to Cr(VI) and may support the evaluation of applications for authorisation under REACH. Findings on chrome platers' additional per- and polyfluoroalkyl substances (PFAS) exposure highlight the need to also pay attention to this substance group in the metals sector. A survey performed to evaluate the policy relevance of the HBM4EU chromates study findings supports the usefulness of the study results. According to the responses received from the survey, the HBM4EU chromates study was able to demonstrate the added value of the human biomonitoring (HBM) approach in assessment and management of occupational exposure to Cr(VI). For future occupational studies, we emphasise the need for engagement of policy makers and regulators throughout the whole research process to ensure awareness, relevance and uptake of the results in future policies.

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1. Introduction

The recently completed EU human biomonitoring initiative (HBM4EU, www.hbm4eu.eu/about-hbm4eu/), was a European Joint Programme that aimed to harmonise the collection and use of biomonitoring data to better understand human exposure to chemicals in the environment, in occupational settings and through the use of consumer products to improve chemical risk assessment and management efforts, and to support policy making (Ganzleben et al., 2017). Within the context of the HBM4EU project several priority substances were selected for investigation based on the most important needs of policy makers and risk assessors, as well as common needs of participating countries and a broad range of other stakeholders including trade unions (Ougier et al., 2021). Many of the priority substances, along with having an important economic role, also pose health risks for workers due to their occupational use. One of the priority substances was hexavalent chromium (Cr(VI)), which was the main focus of the first of a series of three different HBM4EU occupational studies (Santonen et al. 2019a, 2022), the other two being focussed on electronic waste (E-waste) and diisocyanates exposures (Jones et al., 2022; Scheepers et al., 2021). In addition to Cr(VI), it was recognised that in chrome plating activities there may also be exposure to another group of HBM4EU priority chemicals, per- and polyfluoroalkyl substances (PFASs). PFASs, including PFOS (perfluorooctane sulfonate), have been used as mist suppressants in chrome plating baths to prevent the evaporation of Cr (VI) vapours (Blepp et al., 2017; Gluge et al., 2020). Although PFOS has now been largely replaced in the EU, many of its substitutes in chrome plating activities are also PFASs which may cause similar health and environmental concerns.

Occupational exposure to Cr(VI) has been associated with an increased risk of lung and sinonasal cancers and is suspected to lead to gastrointestinal tract cancers (den Braver-Sewradj et al., 2021; ECHA 2013; IARC 2012). In addition, it is a common cause of occupational asthma, allergic dermatitis and there is a concern for adverse effects on reproductive health (Sun and Costa 2022). Exposure to Cr(VI) may occur in several occupational activities, e.g., in welding, Cr(VI) electroplating and other surface treatment processes such as paint application and removal of old paint containing Cr(VI) (SCOEL 2017). In order to limit the workers' exposure to Cr(VI) in the EU, Cr(VI) is currently regulated under both the European regulation (EC 1907/2006) on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and the EU Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD) (EU 2004). The current binding Occupational Exposure Limit (OEL) set under the EU Directive 2004/37/EC is 10 μg/m^3 (8-h time-weighted average (8-h TWA)) until January 17, 2025. After that period, the OEL (8-h TWA) will be reduced to 5 μg/m^3. For welding, plasma-cutting processes and similar work processes that generate fumes, there is a derogation with an OEL of 25 μg/m^3 (8-h TWA) until January 2025; after that date the OEL (8-h TWA) of 5 μg/m^3 will be applicable. France, the Netherlands and Denmark already have stricter limits, with an OEL of 1 μg/m^3 (8-h TWA) for Cr(VI) in all uses (Beskæftigelsesministeriet 2020; Ministère du travail, 2012; MinSZW 2016). In the US, the American Conference of Governmental Industrial Hygienists (ACGIH) has published, for inhalable Cr(VI) compounds, a threshold limit value (TLV) of 0.2 μg/m^3 (8-h TWA) and a TLV Short-Term Exposure Limit (STEL) of 0.5 μg/m^3 (ACGIH 2021). No EU-wide biological limit values (BLVs) for Cr(VI) are available, however some Member States have set BLVs for occupational exposure to Cr(VI), measured as urinary chromium (U–Cr). For example, France and Finland have derived BLVs of 2.5 μg/L and 10 μg/L corresponding to their respective OELs of 1 μg/m^3 and 5 μg/m^3 for Cr(VI) (ANSES 2017; STM 2020). The German Research Foundation (DFG 2020) has established biological exposure equivalents for carcinogenic substances (EKA values), ranging from 12 to 40 μg/L for U–Cr. These correspond to exposures ranging between 30 and 100 μg/m^3 soluble alkaline chromate and/or Cr(VI) containing welding fumes over an 8-h work shift (Bolt and Lewalter 2012). Since these current national BLVs are mainly based on studies from plating workers, they include uncertainties especially concerning their applicability to workplaces other than the electroplating industry. One of the main aims of the HBM4EU chromates study was to provide EU relevant data on the current occupational Cr(VI) exposure to support the regulatory risk assessment and decision-making process. In addition, exposure to PFASs was evaluated in a subset of workers performing chrome plating activities.

In this article, we have analysed the results of the HBM4EU chromate study from an EU policy perspective, highlighting the main findings that should be considered by regulators working in the field of REACH or occupational safety and health (OSH) regulations. In addition, to obtain further insight on the usability and potential policy uptake of the results, EU and national regulators and stakeholders' opinions on the potential policy implications of the results were obtained using a focused on-line survey. Information on the potential impact of the results on the risk management measures (RMMs) used in companies participating in the HBM4EU chromates study were also gathered. Reflecting on these initiatives, we present and discuss the main outputs of the HBM4EU chromates study from the policy perspective.

2. Materials and methods

To allow us to identify the main outputs of the HBM4EU chromates study from a policy perspective, three main activities were undertaken:

1. Detailed analysis of the policy relevant findings of the HBM4EU chromates study
2. Online webinar and research brief to distribute information on the results of the study
3. Survey to policy makers and other stakeholders as well as to participating companies to collect their views on the usefulness and potential implications of the HBM4EU chromate study results

These activities are discussed in detail in the following sections.

2.1. Analysis of the policy relevant findings of the HBM4EU chromates study

A detailed description of the HBM4EU chromates study has been published (Santonen et al. 2019a, 2022). Briefly, the HBM4EU chromates study involved nine EU countries, collecting samples from 399 exposed workers (mainly males) from three main industry sectors with potential exposure to Cr(VI): welding, bath plating, and other surface treatment (Santonen et al. 2019a, 2022). Samples were also collected from 203 control subjects, not occupationally exposed to Cr(VI), to establish background levels in workers with no direct exposure to Cr (VI). Detailed characteristics of the worker and control population are available in Santonen et al. (2022). A cross-sectional study design was applied and U–Cr was used as the primary biomonitoring method for exposure. Red blood cells (RBC), blood plasma and exhaled breath condensate (EBC) were also investigated to establish their usefulness and suitability as additional biological matrices for the biomonitoring of exposure to Cr(VI). To help understand the contribution of different routes of exposure, personal air samples (inhalable and respirable), hand wipes and relevant worker and workplace contextual information were also collected. The overall results have been described in (Santonen et al., 2022) and further analyses of the exposure data, and effectiveness of various RMMs on exposure are described in (Viegas et al., 2022). Publications by Tavares et al. (2022), Ndaw et al. (2022) and Leese et al. (submitted) describe detailed analyses on effect marker analyses and blood and EBC chromium analyses, respectively. In this paper we present the detailed analysis of the main policy relevant findings, which the project team consider as being the most important from a policy perspective.

2.2. Online webinar and research brief to inform stakeholders of the HBM4EU chromates study results

To support the dissemination of the results at the EU level, an online webinar was held on the January 21, 2021, prior to the scientific publication of the final results. The aims of the webinar were to:

i) inform stakeholders on the key results of the HBM4EU chromates study as early as possible;
ii) give recommendations to workplaces on the monitoring of Cr(VI) exposure;
iii) provide information for policy action and;
iv) support the science to policy interface.

In addition, the webinar was important for us to get feedback from regulators on the initial results and helped us to identify who to contact for later survey (see below). The primary target groups for the webinar were national and EU policy makers, regulatory agencies, as well as industry and worker representatives. Presentations included the objectives of the study and policy questions, main occupational hygiene and exposure biomarker results and recommendations to workplaces and occupational health professionals on the monitoring of exposure to Cr (VI). There was also a discussion session on the answers to the policy questions that the study had provided and the value of human biomonitoring (HBM) data in supporting policy action. The program for the webinar is provided as supplementary material 1. In addition, a research brief aimed at informing scientists and policymakers was published (www.hbm4eu.eu/wp-content/uploads/2018/12/Brief_Exposure_CRVI_EN.pdf). This research brief, made available in the end of 2020, summarised the first key findings of the HBM4EU chromates study, emphasised the role of biomonitoring in the management of occupational Cr(VI) exposure and discussed on the benefits of multi-national studies in the assessment of occupational exposure.

2.3. On-line policy survey and participating companies feedback survey

With the purpose of gathering information on the usefulness of the HBM4EU chromates study results from the policy perspective, a short survey (supplementary material 2) was developed specifically for policy makers. This was conducted in March 2022 using a web-based tool Webropol (www.webropol.com). Webinar participants working in the regulatory field and participants of the HBM4EU EU policy board (representatives of EC services and EU agencies dealing with chemicals) were contacted and received information and an invitation to participate in the online survey. The exact number of policy makers invited to participate in the survey is not available as participants were also asked to forward the invitation to those in their professional network (employing a snowballing process to maximise participation). The survey was completed anonymously with no individual or employer names being requested. The questions covered by the survey included the following topics: general usefulness of the results from the policy perspective, potential use of the results in the updating of national or EU OELs for Cr(VI), possible impact of the results on recommendations on improvement of workplace and work practice and whether the results have impacted their views on the usability of biomonitoring in the management of Cr(VI) exposures. The full survey question set is available in supplementary material 2 and was administered in English.

A second survey was developed (see supplementary material 3) which aimed to gather information on the main impacts of the HBM4EU chromates study on occupational health practices within the companies who had participated. Participating companies had previously received their aggregated results from their national research team. This survey consisted of 13 questions (11 multiple choice questions and two open text questions). The questions enabled, for example, the collection of information on how the company results were communicated to the OSH officers, occupational physicians and workers in the company and possible impacts of the results on follow-up exposure monitoring, risk assessment and risk management practices. The two open text questions aimed to collect information on the benefits and drawbacks of participating in the study. Anonymisation of the feedback survey was accomplished by the national research teams sending an invitation e-mail with a Webropol link to the companies who participated in the HBM4EU chromates study from their country. No individual or company names were asked to be disclosed. The survey was translated into national languages, if necessary, otherwise it was administered in English.

Summary statistics of the responses for both surveys were automatically generated from Webropol.

3. Results and discussion

In the HBM4EU chromates study, the highest internal exposures were observed in workers who used Cr(VI) in electrolytic bath plating. Higher exposure of bath plating workers was confirmed with the chromium-blood-based biomarkers and EBC Cr(VI) analyses (Leese et al. submitted; Ndaw et al., 2022). In stainless steel welding, the internal Cr exposure was significantly lower when compared to plating activities (Santonen et al., 2022). A high correlation was observed between U–Cr levels and air Cr(VI) or dermal total Cr exposure, also between Cr-blood-based biomarkers and air Cr(VI), especially in platers. U–Cr showed its value as exposure biomarker as a first step in the assessment of total, internal exposure and can be quantitatively correlated with inhalation exposure (Viegas et al., 2022), while Cr-blood-based biomarkers were shown useful to provide more specific information on systemic availability (Ndaw et al., 2022). In addition, our results from the effect biomarker analyses further suggested that there might still be a residual health risk in the studied industry sectors (Kozlowska et al., 2022; Tavares et al., 2022). Based on these results we have made several key observations relevant from a policy or regulatory risk management perspective (Table 1) and these are discussed in detail in the following sections. Furthermore, the results of the policy and participating companies surveys made for the policy makers and companies are presented and used to identify whether the policy makers shared our views on the potential policy implications, and whether the study resulted in improvements in risk management in the participating companies.

Table 1
Policy relevant key observations from the HBM4EU chromates study, as identified by study researchers.

No.	Policy observation
1.	For welding, air levels are achievable below the future EU Binding Occupational Exposure Limit Value (BOELV) of 5 μg/m^3. Use of local exhaust ventilation (LEV) and respiratory protective equipment (RPE) seemed to be effective in reducing exposure in welding, although it must be recognised that the use of RPE should be considered as the last resort in the hierarchy of controls.
2.	Although exposure levels below the BOELV of 5 μg/m^3 are achievable also in surface treatment activities, effective RMMs, including automation of Cr electroplating processes and improved use of RPE are needed to further reduce exposure.
3.	Biomonitoring is a valid method and can be a necessary tool to evaluate the effectiveness of the RMMs in place in Cr(VI) uses.
4.	Specific biological guidance values for Cr(VI) in welding do not currently exist. Our study provides the necessary data to set specific guidance values for welders and gives further confidence for the setting of guidance values for activities involving exposure to water-soluble chromates.
5.	Cr-related activities were associated with the induction of oxidative stress and genotoxic effects, thereby representing a potential risk for workers health. There is still a need to consider further lowering of OELs for Cr(VI) to reduce the identified risks.
6.	Exposure to PFASs (per- and polyfluoroalkyl substances) in the metal industry needs attention in occupational safety and health practice.

3.1. Policy observation 1: air levels below a BOELV of 5 μg/m^3 are achievable in welding

The HBM4EU chromates study included 399 Cr(VI) exposed workers, of which almost half (195) were stainless steel welders. The remaining workers were performing chrome plating, other surface treatment activities or other related tasks. Welder and electroplating data were available from eight and seven participating countries, respectively. Taking into account the number of workers and countries representing different parts of Europe, the welder data is considered to give a good overview of Cr(VI) exposure in stainless steel welding although some selection bias (i.e., poorly performing workplaces might not be well represented in the study) cannot be excluded. The BOELV of 25 μg/m^3 and, after January 2025, of 5 μg/m^3, applies to Cr(VI) generated during the welding of stainless steel. In the setting of these BOELVs, socioeconomic and feasibility factors have been considered. Although in the HBM4EU chromates study, the main focus was on biomonitoring data, we also collected air monitoring data. We observed that 95% of Cr(VI) personal measurements (inhalable and respirable combined) measured outside RPE being worn, were below a BOELV of 5 μg/m^3 and 75% of the measurements were below 1 μg/m^3 which is the 8-h TWA OEL currently enforced in France, Denmark and the Netherlands for Cr(VI) (Fig. 1). The TLV-TWA of 0.2 μg/m^3 adopted by ACGIH was, however, exceeded in 73% of cases (Fig. 1). Thus, our welding data suggest that the BOELV of 5 μg/m^3, and even lower exposure levels, are technically achievable in these welding activities. In our study, the most common welding processes reported were tungsten inert gas (39.5%) and shielded metal arc welding (17.4%) but no differences were observed in U–Cr levels between exposures of workers using these welding techniques (Viegas et al., 2022). Also, in studies by (Pesch et al., 2018) and (Meeker et al., 2010) only 16% and 18% of the samples collected from the welders' breathing zone exceeded 1 μg/m^3 concentration of Cr(VI). Air monitoring data is supported by our biomonitoring data showing that 95% of U–Cr measurements were below 3.4 μg/g creatinine (Fig. 2), which was estimated to correspond to inhalation exposure to average air levels of 5 μg/m^3 specifically in welding activities (Viegas et al., 2022). However, although exposures in welders remained mostly below the becoming BOELV of 5 μg/m^3, it needs to be noted that EU CMRD (2004/37/EC) requires minimisation of exposure to carcinogens in all activities. This might require further emphasis on technical measures to control the exposure. In our study, use of LEV and RPE correlated significantly with lower internal Cr exposure for the studied welders showing that when used properly these can be effective in reducing exposure. However, the use of RPE always needs to be considered as the last resort in the hierarchy of controls, other preventive and protective measures, such as LEV, should be prioritised. The use of RPE can only be acceptable as a temporary measure to manage residual risk where other means of control are not possible. As reported in Viegas et al. (2022) in our study about 70% of welders used some type of LEV and around half did not wear RPE.

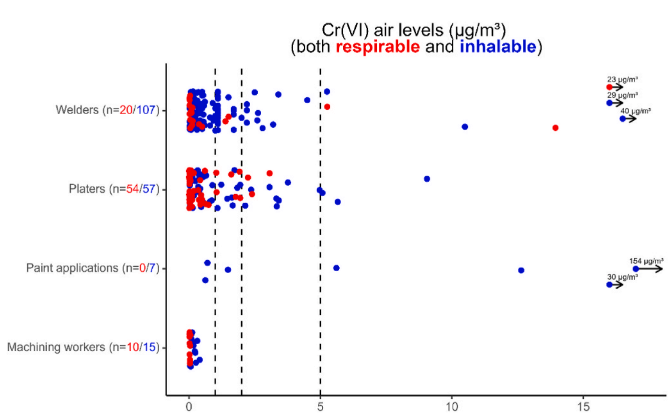

Fig. 1. Personal exposure to Cr(VI) in the breathing zone reflecting TWA concentrations for an 8-hr work shift for both inhalable and respirable particle size fractions stratified by industrial sector and illustrating the number of measurements exceeding the levels of 1, 2, or 5 μg/m^3.

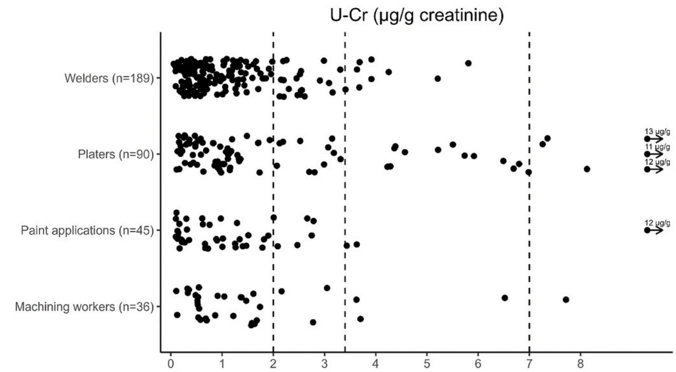

Fig. 2. Post-shift U–Cr excretion stratified by industrial sector illustrating the number of measurements exceeding the levels of 2, 3.4 and 7 μg/g creatinine. Values of 2 and 7 μg/g creatinine correspond to 8 h TWA inhalation exposure to 1 and 5 μg/m^3 in plating activities with exposure to soluble chromates. Value of 3.4 μg/g creatinine corresponds exposure to 5 μg/m3 in welding activities with exposure to poorly soluble Cr(VI) compounds. This value can be applied also in machining activities which also is likely to involve mostly exposure to poorly soluble Cr(VI).

3.2. Policy observation 2: In chromium surface treatment activities, effective RMMs, including automation and improved use of RPE are needed to further reduce exposure

Although in chrome plating and other surface treatment activities, workers' exposures were reported to be below the BOELV of 5 μg/m^3, there is still a need for further improvement to achieve both the EU CMRD and the EU REACH authorisation requirements on the minimisation of exposure to Cr(VI) following the hierarchy of control principles.

The Cr(VI) substances (chromium trioxide, dichromium tris(chromate) and some other Cr(VI) substances) are included in Annex XIV (Authorisation List) of the European REACH regulation (EC 1907/2006). According to this regulation, these substances cannot be used or placed on the market after a specified date, unless the use has been authorised by the EC or is exempt from authorisation. Manufacturers, importers or users of the Cr(VI) substances can apply for authorisation for their uses. Many more than 100 authorisations for different uses of chromates have already been requested, some of these covering hundreds of workers, which means that potentially thousands of workers are exposed to Cr(VI) compounds in these surface treatment activities (https://echa.europa.eu/applications-for-authorisation-previous-consultations).

Earlier within HBM4EU, we evaluated REACH applications for authorisation available in November/December 2018 (accessible at https://echa.europa.eu/applications-forauthorisation-previous-consultations) related to the use of chromates for surface treatment (essentially by plating, sanding and spraying). Workers' combined exposure estimates in these applications were always below 2 μg/m^3 (Santonen et al., 2019b). Often exposure models were used to provide these estimates, even when measurement data was available. In the cases where estimates were obtained through actual measurement data, further adjustments were made to account for the use of RPE and for the frequency of the tasks being considered. Our HBM4EU chromates air measurement and biomonitoring data from the chrome plating activities, and other surface treatment activities (including machining and spray applications) show that exposure levels were not always below 2 μg/m3. Although median air Cr(VI) levels in plating and machining tasks, and median U–Cr levels in all surface treatment activities suggested exposure levels below 1 $\mu g/m^3$ (as 8-h TWA, corresponding U–Cr levels ~ 2 μg/g creatinine (Viegas et al., 2022), there were still a significant number of measurements exceeding these levels (Fig. 2). For example, 13% of air measurements and 22% of U–Cr measurements in plating activities exceeded 2 $\mu g/m^3$, corresponding to U–Cr level of 3.2 μg/g creatinine in plating activities (with exposure to soluble chromates). Higher exposure levels correlated with a lack of process automation and also with the non-use of RPE (Viegas et al., 2022). This reiterates the need to place more emphasis on implementing appropriate technical solutions to help further reduce exposures. Examples include increasing the level of automation of the plating process e.g., during dipping/unloading of metal objects in the electroplating baths, the adjustment of bath Cr(VI) levels and how process quality control samples are collected for analysis. Following these identified needs, the ongoing REACH authorisations are already promoting this by requesting applicants to evaluate the feasibility of implementing automated systems to replace manual tasks where exposure to Cr(VI) is foreseen and would normally rely only on the use of personal protective equipment (PPE). However, the proper use of RPE in tasks with the highest exposure potential (such as the ones previously mentioned) and also during maintenance procedures should be considered as the last resort as long as other engineering, technical and administrative measures have shown to be ineffective to achieve the required level of control or when those measures cannot be implemented.

3.3. Policy observation 3: biomonitoring is a valid and suitable tool to ensure the effectiveness of the risk management measures to control Cr(VI) exposures

Metals like Cr(VI) are not typically absorbed through the skin but dermal exposure may still contribute to the total exposure e.g., due to hand-to-mouth behaviour (Cherrie et al., 2006). This was shown in our HBM4EU chromates study where dermal contamination was found to be significantly correlated with Cr in blood and urine (Santonen et al., 2022; Viegas et al., 2022). In welding and surface treatment activities, RPE is often used to manage the residual risk in tasks where exposure is not sufficiently controlled by technical means. In spraying applications, risk management is often based on the use of PPE, including RPE. External exposure levels are generally high and workers' actual exposure has been (e.g., in applications for authorisation) typically adjusted to take into consideration to the Assigned Protection Factors (APFs) of respiratory protection being worn (assuming that it is used and maintained correctly) (ECHA 2016). Biomonitoring can be used to ensure the effectiveness of the PPE. In REACH applications for authorisation and previous publications, variable exposure levels have been estimated for spray applications based on modelling or external measured exposure data (ECHA 2016; Vincent et al., 2015). Our data suggests that total exposure in spray applications can be effectively controlled to levels even lower than those observed in bath plating through the use of RPE. However, there are often uncertainties related to the exposure if its control is based on PPE, e.g., RPE needs to be appropriate for the agent, well maintained and all tight fitting RPE must fit to the wearer's face. Biomonitoring is the only way to ensure that this is indeed the case, and its use should be promoted for this purpose. This has recently been done in some cases in the REACH authorisation context where biomonitoring has been recommended for the monitoring of exposure of workers where their protection depends primarily on the use of RPE (EC 2020). We expect that our results could further facilitate this application of HBM.

3.4. Policy observation 4: biological guidance values for Cr(VI) in welders need to be based on the welder specific data

One of the challenges related to the use of Cr biomonitoring data, both in the OSH field and in REACH authorisations, has been the uncertainty related to the interpretation of the biomonitoring data. Although there are existing correlations between air Cr(VI) and U–Cr levels available (Chen et al., 2002; Lindberg and Vesterberg 1983), those have shown considerable variability. As discussed in (Viegas et al., 2022), our regression analysis made for bath plating workers supports the analysis performed by (Chen et al., 2002). Using the regression equation based on the dataset of (Chen et al., 2002), an exposure level of 2 $\mu g/m^3$ (used as a reasonable exposure estimate in some REACH applications for authorisation for chrome plating) corresponds to a U–Cr level of 3.5 μg/g creatinine observed in chrome platers. This is close to the value of 3.2 μg/g creatinine obtained using our regression equation for platers (y (μg/g creatinine) = 0.742 + 1.235*x ($\mu g/m^3$), providing the required confidence for the use of these regression equations for the conversion of urinary levels as Cr(VI) air levels in surface treatment activities to enable the quantitative health risk and impact assessment. Similarly, these regression equations can be used to derive a HBM guidance value or BLV for Cr(VI) for activities in which soluble chromates are used.

However, in contrast to plating where exposure is to highly water-soluble chromates, in welding activities the exposure is to Cr(VI) oxides, encapsuled in the solid welding particle (Antonini et al., 2010). This is likely to affect the toxicokinetics of Cr and resulting urinary levels (Viegas et al., 2022). There are only a few existing BLVs for Cr(VI) and even fewer values which have specifically considered welding. In France, ANSES has derived a BLV of 2.5 μg/L corresponding to their respective OEL of 1 $\mu g/m^3$ (ANSES 2017). This limit value is based on the correlation between air Cr(VI) and U–Cr levels observed in chrome plating industry and is not considered to apply to welding. In Finland, a BLV of 10 μg/L, corresponding to Finnish OEL of 5 $\mu g/m^3$ is used (STM 2020). Although the value is based on the air Cr(VI) to U–Cr correlations observed in chrome plating, the value has been applied to all Cr(VI) exposures. The German DFG (DFG 2020) has established biological exposure equivalents for carcinogenic substances (EKA values), ranging from 12 to 40 μg/L (approximately 9–30 μg/g crea) for U–Cr specifically in welding. These urinary values correspond to exposures ranging between 30 and 100 $\mu g/m^3$ soluble alkaline chromate and/or Cr(VI) containing welding fumes over an 8-h work shift (Bolt and Lewalter 2012). Our regression analyses (Viegas et al., 2022) suggest that the use of these existing biological guidance values for welding fumes derived from correlations between air Cr(VI) and U–Cr levels from chrome plating activities result in an underestimation of the external exposure. Air Cr (VI) levels of 5 $\mu g/m^3$ in welding seem to result only in U–Cr levels of about 3.4 μg/g creatinine whereas in plating activities air Cr(VI) levels of 5 $\mu g/m^3$ correspond to about 7 μg/g creatinine (Viegas et al., 2022). This can be explained by the different Cr species in welding and plating. Although there are uncertainties related to these air-to-urine correlations (Viegas et al., 2022), this needs to be considered when setting biological limit/guidance values for Cr(VI).

3.5. Policy observation 5: further lowering of OELs for Cr(VI) is needed

Cr(VI) is a non-threshold carcinogen able to cause direct DNA damage. Therefore, it has not been possible to set a health-based limit value for Cr(VI) and it is of utmost importance to minimise occupational exposure as low as reasonable achievable (ALARA). Based on the assumption of the linear dose-response on the carcinogenicity of Cr(VI), Cr(VI) exposure has been estimated to result in an excess life-time cancer risk of 4×10^{-3} at 1 μg $Cr(VI)/m^3$ and 20×10^{-3} at 5 $\mu g/m^3$ in 40 years occupational exposure (AGS 2014; DECOS 2016; ECHA 2013; SCOEL 2017). Our data support the further lowering of Cr(VI) OELs, not only by showing that lower levels are achievable but also supporting the conclusion that the current levels are not sufficiently low regarding the genotoxic risk (Tavares et al., 2022).

In addition to direct DNA damage, events such as oxidative stress, inflammation, oxidative DNA damage and telomere damage have been implicated in the carcinogenicity process of Cr(VI) (Annangi et al., 2016; Santonen et al., 2019a). It is also recognised that Cr(VI) can also induce micronuclei through aneuploidic mechanisms (Fang et al., 2014). Such health effects of Cr(VI) can be assessed using effect biomarkers in human blood, urine or other biological samples providing evidence of early biological effects. They often reflect subclinical changes before the onset of disease, e.g., an elevated frequency of micronuclei in human peripheral blood lymphocytes has been shown to be predictive for cancer risk (Bonassi et al., 2007). Further, they encompass the aggregate exposure, revealing the exposure to the same chemical from multiple exposure routes, through different sources.

The results of the effect biomarker analysis in the HBM4EU chromates study contributed to the interpretation of exposure biomarkers data and went beyond by identifying groups at risk that had not been captured by exposure biomarkers analysis (Tavares et al., 2022). This was the case for welders who, despite displaying the lowest internal exposure assessed by U–Cr levels, revealed induction of genome damage (micronuclei in reticulocytes) in their blood cells compared to controls. These observed changes in the effect biomarkers can be explained not only by exposure to chromate species but also by co-exposure to other chemical species that contribute to the observed toxic effects. Being non-specific to the cause is a characteristic of most effect biomarkers (Zare Jeddi et al., 2021b).

Another example was the evidence that the control subjects recruited among administrative staff of the industries involved in the study displayed comparatively higher levels of genome damage in blood cells and oxidative damage biomarkers in urine than controls from other sectors, pointing at potential health risks and need for intervention measures (Tavares et al., 2022).

The results of effect biomarkers further suggested that there might still be measurable genotoxic risk in these industries, even though the exposures were mostly well below the current binding OEL in the EU. Thus, significantly increased genome damage and oxidative stress detected in the studied workers and, particularly in the subgroups of workers in painting applications and electrolytic bath platers who showed the highest level of genetic damage in blood lymphocytes, support the conclusion that these levels may still represent a relevant excess cancer risk.

The correlation found between the frequency of DNA and chromosomal damage (assessed by the comet assay and MN assay in blood cells) and the levels of Cr in plasma and in pre- and post-shift urine samples reinforces the value of these effect biomarkers, supported on mechanistic knowledge, to further clarify how exposure links to potential future health outcomes, e.g., increased cancer risk. As such, the inclusion of effect biomarkers in occupational studies may contribute to risk assessment and management, including the updating of OELs. Therefore, their inclusion should be considered when designing such studies as suggested by (Zare Jeddi et al., 2021a).

3.6. Policy observation 6: exposure to PFASs in the metals industry needs attention

In the HBM4EU chromates study, we measured PFAS exposure of a subset of chrome platers and some welders. So far, occupational exposure to PFASs have been described in a few occupational sectors e.g., in the manufacturing of fluoropolymers, firefighting and professional ski waxing (Langenbach and Wilson 2021). Occupational exposure to PFASs may, however, occur in the metal industry, especially in electroplating activities (Gluge et al., 2020; Langenbach and Wilson 2021). PFASs have been used as mist suppressants especially in chrome plating baths to prevent the release of Cr(VI) containing aerosols formed by hydrogen gas generated during the plating process that causes bubbles at the water surface (Gluge et al., 2020; Langenbach and Wilson 2021). PFOS was earlier the most important perfluorinated substance used in plating activities. Due to the restrictions of its manufacture and use, in the EU it has been largely replaced in other activities except in its use as a mist suppressant for non-decorative hard Cr(VI) plating in closed loop systems (EU, 2019). Our results from the HBM4EU chromates study suggest that workers performing chrome plating activities may have been exposed to PFASs including PFOS (Göen et al. in preparation). Some of the chrome platers showed clearly elevated PFOS levels (the 95 percentile for PFOS among platers being 192 μg/L). which may be related to the former application of PFOS in electroplating baths (Göen et al. in preparation). Based on these observations it is concluded that PFAS exposure in the metals sector is clearly an under-recognised hazard and deserves further investigation. In addition, currently the regulatory efforts on PFASs are focused on environmental protection and environmental health, and there appears to be insufficient awareness of worker's exposure and needs for RMMs including e.g., setting of OELs and BLVs for PFASs. Although the use of many PFASs (like PFOS and perfluorooctanoic acid (PFOA)) is currently heavily restricted, PFASs is a large group of chemicals, which warrants attention also in occupational health (Moore et al., 2022).

3.7. Survey respondents' views on the usefulness of the HBM4EU chromates study results

We received 41 responses to the survey issued to policy makers on the potential policy impacts of the HBM4EU chromates study. Most respondents (71%) indicated that they were working in the OSH field, 54% were working with REACH legislation (40% of these indicated to work in both fields). Most of the respondents (76%) were representing national organizations, covering 17 different countries (14 EU countries, 3 outside EU) and 22% EU organizations.

Most of the respondents (66%) had heard about the HBM4EU chromates study. This high number is partly explained by the organization of the webinar (see Materials and methods) to disseminate the results of the chromates study and that the webinar attendees, working in the regulatory field were invited to participate in the survey. This webinar was attended by more than 100 online participants, number of registrants being 196. Of these 38% represented national or EU authorities or regulatory risk assessors (see Supplementary Table 1), who were invited to participate in the survey.

Most of the respondents considered the results to be useful either from the EU (85.4%) and/or the national policy (90%) perspective (Fig. 3). The results were considered especially useful in the light of future updates of either EU binding OELs or national limit values (65%). As discussed earlier, the EU binding limit value from year 2025 is 5 μg/m^3 for all uses whereas some countries have set national limit values at a significantly lower level of 1 μg/m^3. Considering that there might still be a residual genotoxicity and excess cancer risk at the measured exposure levels, it is extremely important that regulators consider the possibilities to further lower the OELs for Cr(VI). These results give confidence that one of our main messages – i.e. lower Cr(VI) levels are achievable using appropriate RMMs and should be aimed for in these activities – may contribute to future regulations.

Promotion of the substitution and EU/national enforcement programs were also considered important (Fig. 3). Authorisation of chromate uses is currently an important driver for companies to consider substitution (ECHA 2020). Trivalent chromium [Cr(III)] is the most often mentioned substitute of Cr(VI) in surface treatment activities (ECHA 2022). In companies' feedback questionnaires, at least one company mentioned that they are currently considering substituting Cr (VI) with Cr(III).

A drawback of the HBM4EU chromates study mentioned in the open text responses was related to limitations in the representativeness of the study with respect to its European country coverage. For example, although companies were included from nine different countries the fact that Germany, for example, did not participate was considered a limitation by some respondents. Although this can be considered as a limitation, in reality it is rather difficult to collect data covering all EU countries and even the coverage of nine countries representing different parts of Europe (southern, western, northern, eastern parts) in one research project is uncommon. In addition, the data gathered in this

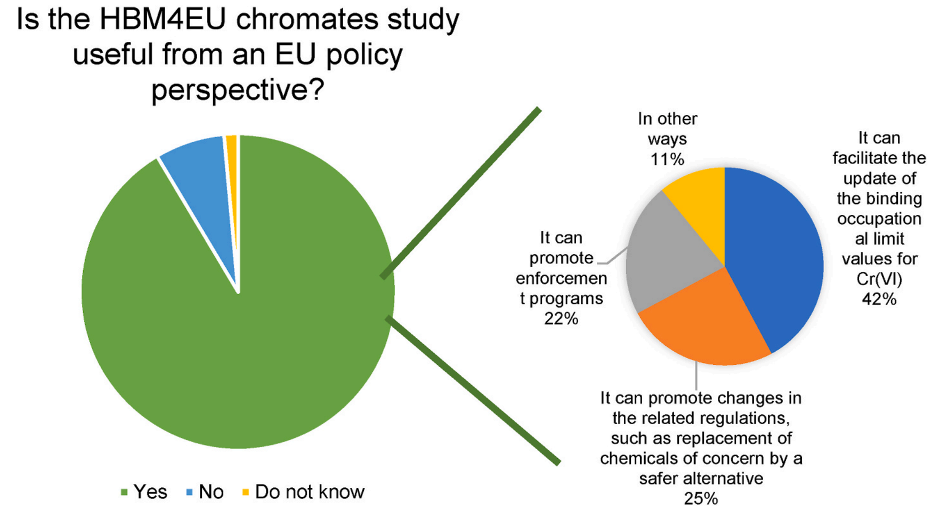

Fig. 3. Usefulness of the HBM4EU chromates study from the perspective of policy makers.

study can be complemented by further national studies performed using the same methodology and considering the lessons learned from this study discussed also by Galea et al. (2021).

More than half (53%) of the respondents stated that they planned to make new or update existing recommendations based on the findings of the HBM4EU chromates study; most commonly (30%) to the monitoring of occupational exposure to Cr(VI) (Fig. 4). Only 37% responded that they had recommended biomonitoring in their country or in their policy field for the occupational risk assessment for Cr(VI). When asked whether HBM4EU chromates study results have had an impact on their view on the usability of biomonitoring, 67% of the respondents considered that it did. Based also on the open responses, the usefulness of the biomonitoring in the management of occupational exposure to Cr (VI) was considered to be demonstrated in the HBM4EU chromates study (Supplementary Table 2). It was, for example, commented that the study "*indicates that biomonitoring is possible and provides helpful data*" or "*confirms the present strategy*". Some of those who answered that the study had not had an impact on their view, explained that the reason for this was that they already had a positive view on biomonitoring applicability. The results give confidence for the possibilities to further promote the use of HBM in the management of occupational exposure. Concerns related to the ethical and privacy issues have sometimes limited the use of HBM in occupational health, as noted in the survey by (Louro et al., 2019). This issue has been discussed earlier also by (Viegas et al., 2020) who described the potential of HBM as an exposure assessment tool, distinguishing the role of HBM in exposure assessment and health surveillance and clarify ethical and communication aspects to guarantee that general data protection regulations are followed. A study involving HBM also helps to identify actions and research needs particularly with reference to the European context.

Concerning the results of the survey dedicated to evaluating the impact on the companies, only nine out of 44 participating companies (20%) responded to the questionnaire (four companies from Italy, two from Finland and only one company from each of UK, France and Portugal). According to the results all the companies reported to evaluate their results together with their OSH officers and eight of the nine companies communicated their results to the company occupational physician and to their workers. When communicating the study results, five companies communicated the results individually to each worker and seven companies indicated that they had communicated the aggregated data (also) through the employee representatives (it is evident that some companies used both ways of communicating the results). In seven out of nine companies the study results triggered changes to the RMMs in place such as improvements in the LEV systems, hygiene facilities and in the PPE provided to workers. Seven of the companies had previously used biomonitoring for chemical risk assessment, with all nine responding companies stating that they were planning to use biomonitoring for the assessment of Cr(VI) exposure also in the future.

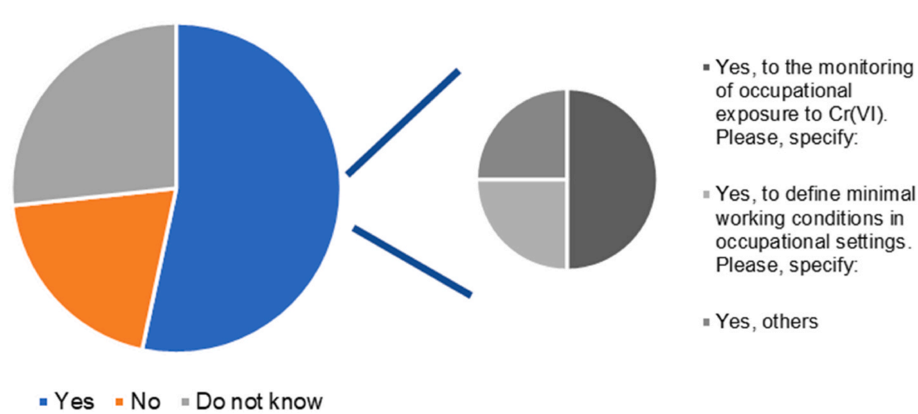

Fig. 4. Response to question: Planning to make new or update existing recommendations based on the findings of the HBM4EU chromates study.

4. Conclusions

Providing policy relevant data on chemical exposures for use in regulatory risk management was a major aim of HBM4EU (Ganzleben et al., 2017). To achieve this, active collaboration with policy makers is required. Cr(VI) was prioritised within HBM4EU, since it is a high concern for workers' exposure and there are new regulatory measures planned (or recently implemented) in EU under both chemicals regulation (REACH) and OSH legislation. Knowledge on the regulatory needs was used to target the HBM4EU chromates study at specific occupational activities. Based on the results of this study we were able to draw several policy relevant conclusions (summarised in Table 1), which in the future may contribute to the updating of workplace limit/guidance values and in the monitoring and risk management practises applied in industry. Although the policy makers' survey on the usefulness of the HBM4EU chromates study results were limited in size and can therefore only be considered indicative, it gives confidence on the policy relevance of the results and supports our own views on the policy implications of the results. For future studies, we would like to emphasise the importance of early and continued engagement of the policy makers to the project to ensure the usability of the results. It is also important at an early stage to convey the anticipated benefits of the work and to ensure the clear communication of the project and its outputs in a format that can be easily taken up by regulators. These aspects will be considered and improved when further occupational HBM surveys are planned under the new EU partnership PARC (Partnership for the risk assessment of chemicals, https://www.anses.fr/en/content/european-partnership-assessment-risks-chemicals-parc). In PARC the number of partners and countries involved in the planned occupational studies are higher than those in HBM4EU which might assure even bigger EU wide representativeness of the results.

Another aim of the HBM4EU project was to facilitate the use of HBM data in chemical risk assessment and management. Although in many countries there is a longstanding tradition in the use of biomonitoring in occupational health, there is still room for improvement in its use as an exposure assessment tool at workplaces (Viegas et al., 2020). The same applies to the use of HBM in the national or regional regulatory risk assessment and policy making (Louro et al., 2019). An effective communication and information exchange between scientists and regulatory risk assessors/policy makers is key to generate impact on the regulatory practices, and can be realized via, amongst others, Human Biomonitoring Global Registry Framework as proposed by Zare Jeddi and colleagues (Zare Jeddi et al., 2021b). Based on the feedback received from the surveys, the HBM4EU chromates study provides convincing evidence to facilitate the wider use and further development of HBM for exposure and risk assessment, risk management and evaluation of the effectiveness of the RMMs by demonstrating how it can be used successfully and in ethically sustainable and responsible ways.

Disclaimer

The contents, including any opinions and/or conclusions expressed of this manuscript, are those of the authors alone and do not necessarily reflect the opinions or policy of the organizations to which they are employed.

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Declarations of competing interest

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Appendix A. Supplementary data

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