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HBM4EU chromates study - Overall results and recommendations for the biomonitoring of occupational exposure to hexavalent chromium

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ABSTRACT

Exposure to hexavalent chromium [Cr(VI)] may occur in several occupational activities, e.g., welding, Cr(VI) electroplating and other surface treatment processes. The aim of this study was to provide EU relevant data on occupational Cr(VI) exposure to support the regulatory risk assessment and decision-making. In addition, the capability and validity of different biomarkers for the assessment of Cr(VI) exposure were evaluated.

The study involved nine European countries and involved 399 workers in different industry sectors with exposures to Cr(VI) such as welding, bath plating, applying or removing paint and other tasks. We also studied 203 controls to establish a background in workers with no direct exposure to Cr(VI). We applied a cross-sectional study design and used chromium in urine as the primary biomonitoring method for Cr(VI) exposure. Additionally, we studied the use of red blood cells (RBC) and exhaled breath condensate (EBC) for biomonitoring of exposure to Cr(VI). Personal measurements were used to study exposure to inhalable and respirable Cr(VI) by personal air sampling. Dermal exposure was studied by taking hand wipe samples.

The highest internal exposures were observed in the use of Cr(VI) in electrolytic bath plating. In stainless steel welding the internal Cr exposure was clearly lower when compared to plating activities. We observed a high correlation between chromium urinary levels and air Cr(VI) or dermal total Cr exposure. Urinary chromium showed its value as a first approach for the assessment of total, internal exposure. Correlations between urinary

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chromium and Cr(VI) in EBC and Cr in RBC were low, probably due to differences in kinetics and indicating that these biomonitoring approaches may not be interchangeable but rather complementary.

This study showed that occupational biomonitoring studies can be conducted successfully by multi-national collaboration and provide relevant information to support policy actions aiming to reduce occupational exposure to chemicals.

1. Introduction

Hexavalent chromium (Cr(VI)) is an occupational carcinogen that may cause lung cancer in humans (IARC, 2012). Positive associations have been observed between Cr(VI) exposure and cancers of the nose and nasal sinuses (IARC, 2012) and there are also concerns related to other respiratory tract cancers and to gastrointestinal track cancers (Deng et al., 2019; ECHA, 2013). In addition, occupational exposure to Cr(VI) is a common cause of asthma, allergic dermatitis and there is a concern of reproductive effects. Exposure to Cr(VI) may occur in several occupational activities, i.e. welding, Cr(VI) electroplating and other surface treatment processes such as paint application and removal of old paint containing Cr(VI) (SCOEL, 2017). Soluble hexavalent compounds, like chromium trioxide, sodium or potassium dichromate are used in chrome plating in baths (electroplating) but can be used also in surface treatment by spraying, brush or pen applications or in passivation processes. Sparingly soluble strontium chromate and zinc chromate hydroxide are used in chromate paints for example in the aviation sector (ECHA, 2021). Welding and flame cutting of stainless steel leads to ultra-fine and nano-sized chromium oxide particles in both trivalent and hexavalent form. Composition of welding fumes is determined to a great extent by the technique used, with manual metal arc (MMA) producing more Cr(VI) emissions than metal inert gas (MIG) or tungsten inert gas (TIG) techniques (IARC, 2012; Scheepers et al., 2008). Differences in the type of Cr(VI) emissions, including solubility of the Cr(VI) compounds and size of the particles, affect the probability of exposure, the exposure routes, and the toxicokinetics of Cr (Wilbur et al., 2012).

Occupational exposure to Cr(VI) is currently regulated in EU under both the European regulation (EC, 1907/2006) on the Registration, Evaluation, Authorization 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 or mutagens at work (EU, 2004). The recent binding Occupational Exposure Limit (OEL) set under 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 limited at 5 μg/m^3. For welding, plasma-cutting processes and similar work processes that generate fumes, there is a derogation with an OEL value of 25 μg/m^3 (8-h TWA) until 5 years after the transposition date of 2017; after that period, the OEL (8-h TWA) of 5 μg/m^3 will also be applicable. France and the Netherlands have even stricter limits with an OEL of 1 μg/m^3 (8-h TWA) for Cr(VI) in all uses (Décret, 2012; MinSZW, 2016). From other European countries, Denmark has also implemented an OEL of 1 μg/m^3, which is planned to be lowered further to 0.25 μg/m^3 if technically and economically feasible (Beskæftigelsesministeriet, 2020). In US, ACGIH has proposed an updated threshold limit value (TLV) of 0.2 μg/m^3 (8-h TWA) for Cr(VI) based on the respiratory tract effects of Cr(VI) (ACGIH, 2021).

In occupational health, urinary total chromium (U–Cr) is currently the most often used biomarker for the assessment of exposure to Cr(VI). No EU-wide biological limit value (BLV) has been set for U–Cr in Europe, but some Member States have defined national BLVs for occupational exposure to Cr(VI) measured as 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 Spanish authorities have adopted the ACGIH BEI® level of 10 μg/l for U–Cr measured during a shift and 25 μg/l at the end of the last shift of the workweek as their BLV (INSHT, 2019). UK has adopted biological monitoring guidance value (BMGV) of 10 μmol/mol creatinine (ca. 6.3 μg/l) in post-shift urine (HSE, 2018). The German DFG (DFG, 2020) has established biological exposure equivalents for carcinogenic substances (EKA values), ranging from 12 to 40 μg/l for U–Cr at the end of shift and from 9 to 35 μg/l in the erythrocyte fraction of whole blood at the end of the shift in the end of the work week. These urinary values 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). The main limitation of U–Cr is that it is not specific for Cr(VI) since it reflects exposure to both Cr(III) and Cr(VI). Therefore, there has been a need to develop additional biomarkers that are more specific in quantifying Cr(VI) exposure, such as Cr in red blood cells (RBC) (Lewalter et al., 1985) and Cr(VI) in exhaled breath condensate (EBC), respectively (Goldoni et al., 2010; Leese et al., 2017).

The European human biomonitoring initiative (HBM4EU) (www.hbm4eu.eu/about-hbm4eu/) is a joint effort of 30 countries, the European Environment Agency and the European Commission which uses biomonitoring to assess human exposure to chemicals in Europe, so to better understand the associated health impacts and to improve chemical risk assessment (Ganzleben et al., 2017). Within HBM4EU, Cr(VI) was defined as one of the priority compounds at European level (Ormsby et al., 2017). The HBM4EU chromates study was designed to address the concerns related to the occupational exposure to hexavalent chromium. The main aim was to provide EU relevant data on occupational Cr(VI) exposure to support the regulatory risk assessment and decision-making. In addition, the capability and validity of different biomarkers for the assessment of Cr(VI) exposure were evaluated in a harmonized way and under quality assurance/quality control measures.

The present paper describes the overall results of the HBM4EU chromates study and the main recommendations regarding the monitoring of occupational exposure to Cr. Follow-up publications (in preparation) will describe specific data sets in more detail, regarding the applicability of different types of biomarkers and matrices, as well as the effectiveness of the different risk management measures (RMMs) available for different processes.

2. Materials and methods

The HBM4EU chromates study was designed as a multi-center cross-sectional survey, carried out originally in eight countries, i.e. Belgium, Finland, France, Italy, Poland, Portugal, the Netherlands and the United Kingdom. At a later stage, Luxembourg joined the study as a ninth participating country. Sampling protocol has been described in detail in (Santonen et al., 2019). Detailed Standard Operating Procedures (SOPs) (Santonen et al., 2019), providing information on the collection, handling, storage and transfer of the biological and occupational hygiene samples, were designed to allow the study team to perform data collection in a harmonized way, resulting in comparable data for the nine participating countries. All the samplings were performed between October 2018 and December 2020.

2.1. Study population

Exposed workers were recruited from companies with activities that are known to be associated with occupational exposure to Cr(VI), more specifically (i) chrome plating, (ii) surface treatment by sanding, spraying or painting, and (iii) stainless-steel welding. Unexposed workers were recruited either within the same company, but from activities that are known not be associated with Cr(VI) exposure (for example office staff) ("within company controls"), or from other companies with no activities associated with Cr(VI) exposure ("outwith company controls"). Recruitment of the companies and workers followed the dedicated SOP for the selection of participants, recruitment, informing participants and obtaining informed consent. Common information leaflets and informed consent forms were developed and translated in the national languages (English, Finnish, French, Polish, Italian, Portuguese, Dutch and German). Study protocols were submitted for approval by ethics review boards in each of the participating countries with the approvals being granted before recruiting the study participants (Santonen et al., 2019).

2.2. Questionnaires

Two questionnaires were used to collect relevant contextual information. The first questionnaire was completed by a company representative, prior to the sampling campaign, in order to collect general information on the workplace and operating conditions and RMMs adopted. The second questionnaire was completed by the researcher while interviewing the worker as close as possible to the end of work shift, and included detailed description of job activities, specific work tasks performed during the day, RMMs used in different tasks and work organization during the days of sampling. The questionnaire also included questions on the workers' background exposure to Cr(VI) from other sources due to e.g. air pollution related to the place of residence, living habits, smoking, implants, and food supplements.

2.3. Air and dermal sample collection and Cr analysis

For electroplaters and surface treatment workers, simultaneous sampling of the inhalable and respirable fractions of Cr(VI) and total Cr was performed following specific guidance (CEN, 1993). Personal inhalable dust measurements were obtained using an IOM sampling head (flow rate 2 l/min), whereas for the respirable dust fraction measurements were obtained using the Higgins Dewell type (flow rate 2.2 l/min) or similar cyclone sampling heads. The sampling head cassettes were loaded with pre-weighed 25 mm PVC-filters (GLA-5000) or MCE-filters. These measurements were done outside the respiratory protective equipment (RPE), in the breathing zone of the workers.

For welders, alternatively the SKC Mini-sampler was used, loaded with a pre-weighed 13 mm MCE filter, at a flow rate of 0.75 l/min, with this being positioned under the welding visor. These SKC mini-samplers were used only by UK, Belgium and Luxembourg for the collection of total Cr. Also the few Cr(VI) samples collected under the RPE were collected using SKC mini-samplers. All the samples were collected for a representative period of the work shift.

The air samples were analysed gravimetrically for determination of the dust fraction and then analysed for total Cr using OSHA Method ID-125G (OSHA, 2002) and Cr(VI) using ISO 16740 Method (ISO, 2005) and NIOSH Method 7600 (NIOSH, 2015). Only the results of the Cr(VI) analysis are presented in this manuscript. The other results will be presented in subsequent manuscripts.

Dermal wipe samples were collected using SKC Ghost sampling wipes (or similar lead wipes) (NIOSH, 2003; OSHA, 2002). Samples were collected at set periods during the working shift (pre-shift, first break period, lunch and post-shift). At each sampling period, a standardized wiping procedure was applied. Using a separate wipe for each hand, five horizontal and five vertical wipes across the surface of the palm of the hand (including the fingers) were made, followed by a wipe in the clockwise direction. This procedure was repeated for the dorsal hand region, with each finger then being wiped. The wipes were analysed for total Cr using OSHA Method ID-125G (OSHA, 2002). Average hand areas of 535 cm^2 per male hand (total 1070 cm^2 for both hands) and 445 cm^2 per female hand (total 890 cm^2 for both hands) (EPA, 2011) were used in subsequent calculations.

2.4. Blood and urine sample collection and Cr analysis

All countries, except UK, collected blood samples for RBC-Cr analyses. Blood samplings were preferentially performed on the 3rd - 5th day of the working week. One blood sample was collected in a tube with potassium ethylenediamine tetra acetic acid (K-EDTA) appropriate for trace elements analyses from each (exposed or non-exposed) participant and was kept at +4 °C until analysis. To avoid haemolysis, plasma and RBC separation was conducted, preferably within 8 h (and maximum 24 h) from the specimen collection, following the method described by Devoy et al. (2016). Samples were centrifuged (10 min at 1000–2000×*g* or 5 min at 2700×*g*) and the supernatant containing the plasma and white blood cells was used for Cr analyses (storage at +4 °C up to 7 days or −20 °C for longer periods). The pellet underwent three washing steps with 0.9% NaCl solution (with a volume corresponding the initial volume of blood collected), in order to eliminate interfering plasma/Cr residues. The hematocrit (HT) values (measured before (HT1) and after the washing steps (HT2)) were measured to indicate RBC loss during washing steps and the final results were corrected for HT2. After the last washing step, the tube containing RBCs was filled up with 1% Triton X-100 in deionised water/0.2% HNO_3 (or 0.2% NH_4OH depending on the technique used) up to the initial volume. RBCs were then stored at room temperature up to 3 days or at −20 °C for up to 3 months.

Two spot urine samples were collected from the exposed workers, the first before the start of the shift at the beginning of the working week, and the second one at the end of the shift in the end of the working week (typically on Thursday or Friday). To avoid contamination of urine samples, participants were instructed to remove their work clothes and to thoroughly wash their hands before the urine collection. One spot urine sample was collected from the control individuals at any time of the working week. Urine samples were collected in previously decontaminated containers (e.g. pre-washed with 10% of nitric acid solution) to avoid background contamination. After collection, urine samples were homogenized and aliquoted in several pre-labeled tubes and stored at −20 °C. Urinary creatinine concentrations were measured and Cr results were normalized to creatinine.

According to the WHO (WHO, 1996) the acceptable creatinine concentration range of the urine specimen is 0.3–3.0 g/l, although data to justify these limits is hard to find. We tested the Spearman correlations of original, un-adjusted urinary Cr data both with all creatinine corrected Cr data and with creatinine corrected Cr data including only those within the aforementioned 'acceptable creatinine range' for both workers and controls. There were only marginal differences in correlation between these two test groups - in all cases the Spearman correlation coefficient was either high (0.7–0.8) or very high (0.9). Accordingly, no data were discarded according to low/high creatinine concentration.

All the laboratories analyzing the blood and urine samples had successfully passed ICI (Interlaboratory Comparison Investigations) rounds within the HBM4EU Quality Assurance (QA) program (Esteban Lopez et al., 2021; Nübler et al., 2021).

2.5. Exhaled breath condensate (EBC) sample collection and Cr analysis

EBC was collected using the TurboDECCS system (Medivac, Parma Italy). Two EBC samples were collected from exposed workers; the first before the start of shift on the first day of the working week and a second sample at the end of the shift in the end of the working week (typically on Thursday or Friday). For the control group only one EBC sample was collected during the working week.

To inhibit the degradation or interconversion of Cr(III) and Cr(VI), the EBC samples were complexed with an EDTA solution and stored refrigerated (not frozen). Immediately after the collection of each EBC sample, an aliquot of EBC was diluted 10-fold with 0.5 mM EDTA (pH adjusted to pH 8 using 10% v/v ammonia solution). The volume of EBC collected can vary from one individual to another, and consequently the concentration of Cr(VI) may also vary. As there is currently no proposed volume correction marker, the results were reported in μg/L per volume of EBC collected. In order to do this, the amount of EBC sample aliquoted to be complexed with the EDTA solution was recorded, and the remainder of the uncomplexed EBC sample was weighed upon return to the analysing laboratory.

Supplementary Table S1 gives an overview of the methods used to measure Cr in the different matrices, by country.

2.6. Data management and analyses

A harmonized codebook, accompanied by a Microsoft Excel (Microsoft, Redmond, Washington, US) data template, was provided to the research teams to insert study data to allow for pooling of the data for analysis. This data template included information from both the questionnaires and the analytical results (blood, urine, EBC, air and wipes). After minor spreadsheet calculations and data cleaning, the final data template was imported into IBM© SPSS© Statistics software (version 25/27, IBM Corporation, NY, US) for statistical analysis. Descriptive statistics including geometric mean (95% CI), arithmetic mean, median, and percentile levels (P5, P25, P75, P95) were calculated. Shapiro-Wilk test, Mann-Whitney *U* test, Wilcoxon signed-rank test, and Spearman Rank Correlation were applied for the statistical analysis of the data. *p*-Values of <0.05 were considered statistically significant. All data with $n > 10$ followed a log-normal distribution. For data with $n < 10$, the sample distribution could not be reliably determined. Shapiro-Wilk test was used to test for normality of the data, Mann-Whitney *U* test was used to compare two independent sample sets (like urinary concentrations of workers and controls), and Wilcoxon signed-rank test was used to compare two dependent sample sets (like pre-shift and post-shift urinary concentrations of the same workers). Values below the limit of quantification (LOQ) were substituted by LOQ/2 during the statistical processing (Hornung and Reed, 1990). Where >50% of results were below LOQ, statistics were not presented. Box plots were prepared using Stata Statistics/Data analysis software (version 15.1, StataCorp LLC, TX, US).

3. Results

3.1. Description of the study population and the samples collected

A total of 602 workers, including 399 exposed workers and 203 controls gave their informed consent to participate in the study. Exposed workers were mainly men (98%), whereas in controls, the ratio men/women was approximately 3:1 (73% vs. 27%). Exposed workers were on average 42 ± 11 years old (mean ± SD) and controls 44 ± 10 years. A total of 164 (29%) participants were smokers (smoking data were missing from 8 persons); this proportion being higher in the exposed workers (35.4%, n = 139) as compared to the controls (12.4%, n = 25). Characteristics of the study population is described more in detail in Table 1.

Original categorization of workers was made according to the sectors that were primarily targeted in the recruitment, i.e. chrome plating in baths, surface treatment by e.g. using chromate containing paints, and stainless-steel welders. However, there were some participants who were performing other specific jobs which could not be grouped under these three categories. These workers were categorized as workers mainly engaged in machining work in chrome plating or surface treatment companies; thermal spraying workers (coating process in which heated metallic Cr is sprayed onto a surface with possible formation of Cr(VI) fumes); steel production workers (involved in operating cold strip mill, in pickling and annealing process); and finally, maintenance and laboratory workers in chrome plating or surface treatment companies. Distribution of the participants in groups according to these work activities are presented in Table 1. Table 2 presents the number of samples collected for each work activity. The task distribution covered by the monitoring campaigns varied among the countries, with some countries involving mainly welders and others primarily bath platers or workers performing paint applications. This was dependent on the types of companies and workers willing to participate in the study in each country. Work distribution by country is presented in Supplementary Table S2.

Control workers were either office workers recruited from the same companies as the exposed workers (n = 147, referred to “within company controls”), or from other companies with activities known not to be associated with Cr(VI) exposure (n = 56, referred to “outwith company controls”).

Supplementary Table S3 gives an overview of the total number of samples that were collected from each participating country of the HBM4EU Chromates study. The main focus of the study was to collect exposure data based on biomonitoring from different occupational sectors. The U–Cr was the main parameter, which was collected from all the exposed workers in all countries. For the study of the usefulness of other exposure biomarkers, RBC-Cr and EBC-Cr(VI), samples were not collected in all countries. This explains the lower numbers of RBC-Cr and EBC-Cr(VI) samples when compared to the numbers of U–Cr samples.

Industrial hygiene samples were collected to identify the main exposure routes to chromium in the different exposure scenarios considered. The final numbers of different types of air measurements were dependent on the workplace and country specific aspects, including technical resources. Although all countries collected air samples, three countries measured only total Cr. From other countries, a total of 194 personal inhalable Cr(VI) samples were collected. In France, Finland and the Netherlands personal respirable Cr(VI) measurements were also performed (n = 91 samples). Only few samples were collected inside the RPE, mainly from welders (Table S3, data on these measurements not presented). The number of wipe samples collected per worker was dependent on the length of work task involving exposure to Cr and number of breaks/hand washings during the shift. A minimum of two and a maximum of 6 wipe samples were collected per worker. Not all workers provided wipe samples. Total number of workers providing wipe samples was 267 (from 8 countries, Table 2 and Supplementary Table S3). The number of industrial hygiene samples collected from different work activities are presented in Table 2.

Table 1
Characteristics of the study population.

	Total number	Age (years), mean ± SD	Males	Females	Smokers	Non-smokers (smoking status not available)
Control workers	203	44 ± 10	148	55	25	176 (2)
All Exposed Workers	399	42 ± 11	390	9	139	254 (6)
Bath plating workers	90	43 ± 11	88	2	40	49 (1)
Chromate Paint applications	52	42 ± 9	49	3	16	32 (4)
Welders	195	41 ± 11	194	1	63	131 (1)
Machining workers	38	42 ± 10	38	0	13	25
Steel production	11	45 ± 7	11	0	3	8
Thermal sprayers	5	41 ± 6	5	0	2	3
Maintenance and laboratory workers	5	50 ± 11	5	3	2	6

Table 2
Work distribution of the participants of the HBM4EU Chromates study and number of samples collected for each work activity.

	Total number of workers	U– Cr pre-shift (n)	U–Cr post-shift (n)	RBC-Cr (n)	EBC-Cr(VI) post-shift (n)	Inhalable Cr(VI) outside RPE	Respirable Cr(VI) outside RPE	Wipe samples [a] (n)
Bath plating workers	90	90	90	70	65	57	54	77
Chromate paint applications	52	52	45	48	0	7	0	32
Machining workers	38	38	36	35	21	15	10	25
Welders	195	193	189	171	81	107	20	115
Thermal spraying	5	5	5	5	5	5	5	5
Steel production	11	11	10	9	0	0	0	5
Maintenance and laboratory workers	8	8	8	7	3	3	2	8
All exposed workers	**399**	**397**	**383**	**345**	**175**	**194**	**91**	**267**
Within company controls	147	94	–	134	67	–	–	–
Outwith company controls	56	41	–	41	31	–	–	–
All controls	**203**	**135**	**-**	**175**	**98**	**-**	**-**	**-**
All participants	**602**	**532**	**383**	**520**	**273**	**194**	**91**	**267**

[a] Number of workers sampled (2–6 wipe samples per worker).

3.2. Determination of Cr in the biological samples (blood, urine and EBC)

3.2.1. Background levels in control subjects

U–Cr, RBC-Cr and EBC-Cr(VI) levels in the control population are presented in Table 3. The high levels observed in some control subjects raised the question of whether the controls recruited from the companies with processes involving exposure to Cr(VI) were really unexposed. When analysing separately the data from the "within company controls" (i.e. from the companies involving the use of Cr(VI)) and "outwith company controls" (from companies not using Cr(VI)) we observed that the "within company controls" showed statistically significantly higher U–Cr and RBC-Cr levels as compared to the "outwith company controls" (Table 3). Although the median RBC-Cr level was higher in "outwith company controls" when compared to the within company levels ($p = 0.003$, Mann-Whitney test), P95 level was clearly higher in "within company controls" (Table 3). Similarly, also AM and e.g. P75 levels were clearly higher in "within company controls" when compared to "outwith company controls" (AM 1.53 and 1.32 and P75 3.62 μg/l and 1.50 μg/l, respectively). This suggests that the "within company control" group included some individuals with high exposure to Cr. Table 3 includes also previous occupationally non-exposed population U–Cr data from Italy and UK that did not collect urine Cr samples for this study due to their already existing data on U–Cr levels in the occupationally non-exposed population. EBC-Cr levels in "outwith company controls" were all below the LOQ but nine of the 67 "within company controls" (13%) showed levels above the LOQ. Control groups included samples up to 21 current smokers, whose chromium levels did not differ significantly from non-smokers (data not shown). U–Cr and RBC-Cr levels in control workers showed small but inconsistent gender-related differences: median and P95 RBC-Cr levels in control females ($n = 48$) were 0.45 and 5.32 μg/l and in males ($n = 127$) 0.64 and 4.69 μg/l whereas creatinine corrected pre-shift U–Cr median and P95 levels in females ($n = 38$) were 0.28 and 1.97 μg/g creatinine and in males ($n = 97$) 0.19 and 0.96 μg/g creatinine. This difference in U–Cr was statistically significant ($p < 0.05$, Mann-Whitney test).

3.2.2. Urinary chromium in exposed workers

Fig. 1 presents the concentrations of U-Cr in the exposed workers and controls for the main worker groups (with >10 post-shift U–Cr results). For the exposed workers, both pre- and post-shift U–Cr are presented. Pre-shift levels of all worker groups, except for small groups of thermal sprayers and maintenance and laboratory workers, were significantly higher when compared to the levels observed in the controls (Mann-Whitney test, $p \leq 0.001$, all controls). As compared to the control groups, all worker groups showed significantly increased post-shift U–Cr levels (Fig. 1). The highest exposure levels were observed in chrome plating in baths. This was the case both for U–Cr pre-shift (median 0.77 μg/g creatinine, P95 4.99 μg/g creatinine) as well as for U–Cr post-shift (median of 1.12 μg/g creatinine and P95 of 7.70 μg/g creatinine). Among the 189 welders studied, 24 (13%) reported welding of other materials than stainless steel on the day of urine sampling. Exclusion of these 24 workers had, however, only minimal impact on the results: median and P95 post-shift U–Cr levels for all welders were 0.68 and 3.36 μg/g creatinine, and when these 24 welders were excluded the respective levels were 0.70 and 3.14 μg/g creatinine, respectively.

Within the total group of the exposed workers, post-shift U–Cr was significantly higher than pre-shift U–Cr for all worker groups except thermal sprayers, maintenance and laboratory workers (Wilcoxon test, $p \leq 0.01$). Median and P95 ΔCr levels (post-shift minus pre-shift within the same person) for all the workers combined was 0.20 and 2.58, respectively, for chrome plating in baths 0.31 and 4.06, for paint applications 0.12 and 2.58, and for machining workers 0.36 and 4.20, respectively. P10 was either negative or almost zero in all worker groups (−0.46–0.003) which reflects the negligible exposure of a proportion of the workers during the time of sampling. In occupational health, reference values (usually set to correspond the 95th percentile of the non-

Table 3
Exposure biomarker levels in controls and in the earlier studies from Italy and UK.

	U–Cr median, P95	RBC-Cr median, P95	EBC Cr(VI) median, P95
	μg/g creatinine	μg/l	μg/l
All controls	0.22, 1.35 ($n = 135$)	0.63, 5.00 ($n = 175$)	<LOQ, 0.05 ($n = 98$)
Within company controls	0.31, 1.39 ($n = 94$ *)	0.38, 5.06 ($n = 134$) **	<LOQ, 0.07 ($n = 67$)
Outwith company controls	0.11, 0.44 ($n = 41$)	1.02, 3.12 ($n = 41$)	<LOQ ($n = 31$)
Morton et al. (2014) (UK)	0.42, 1.31 ($n = 132$)	–	–
Aprea et al. (2018) (Italy)	0.218 (GM)#, 0.963 ($n = 260$)	–	–

Significant difference between within company controls vs outwith company controls *$p < 0.001$, **$p = 0.003$, #median level not available.

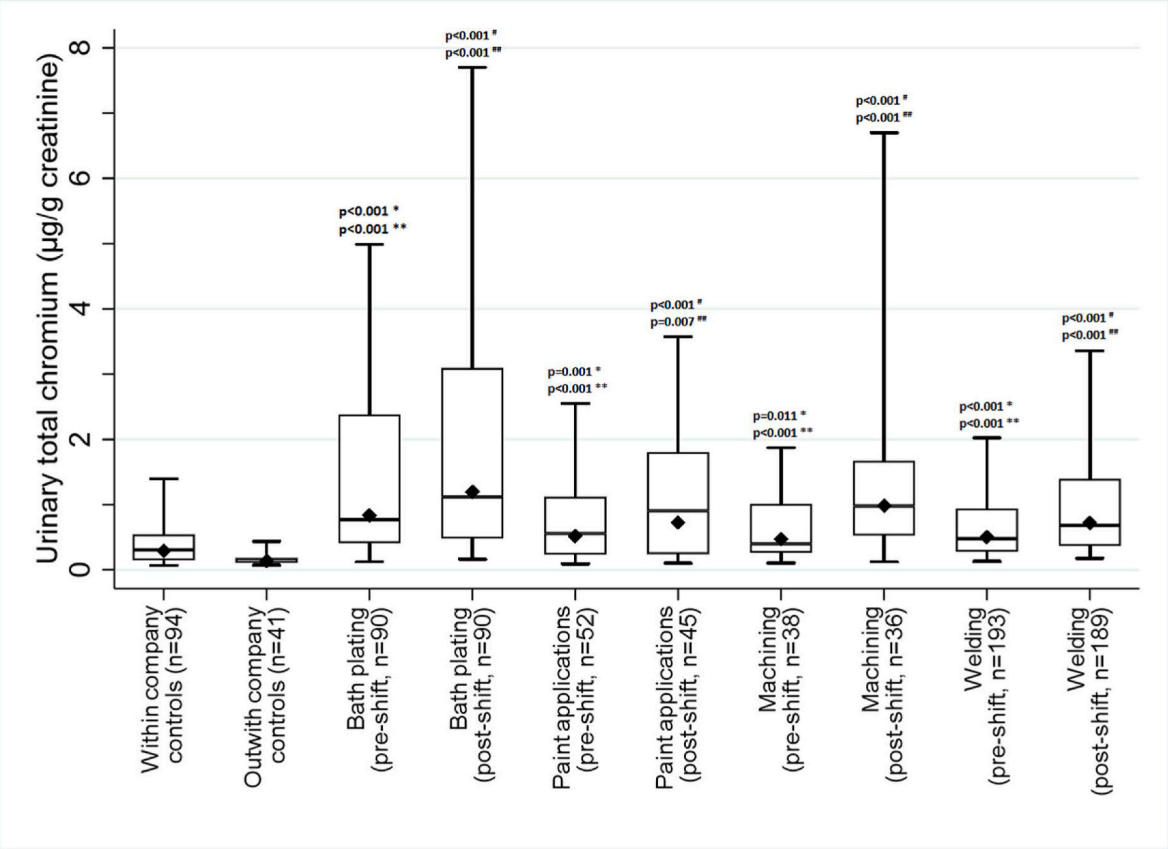

Fig. 1. Distribution of U-Cr in controls and in exposed workers (pre-shift, post-shift). * Pre-shift vs. within company controls, ** pre-shift vs. outwith company controls, # post-shift vs both within company controls and outwith company controls, ## post-shift vs. pre-shift. Box plots: The bottom and top of the box are, respectively, the 25th and 75th percentiles, and the horizontal line inside the box is the median (50th percentile). The lower and upper ends of the whiskers are the 5th and 95th percentiles, respectively. The solid diamond is the geometric mean.

occupationally population levels) are generally used to discriminate occupational exposure from the background exposure. Therefore, to better put the results into perspective, we have compared the post-shift U–Cr results of different worker groups to the 95 percentiles of controls (Table 4, first and second column). In addition, we have compared post-shift U–Cr in different worker groups with the BLVs for U–Cr available from France (2.5 μg/l or 1.8 μg/g creatinine, corresponding to an OEL for Cr of 1 μg/m^3) and from Finland (10 μg/l or 7.8 μg/g creatinine, corresponding to an OEL for Cr of 5 μg/m^3). These results are also given in Table 4, in columns three and four. As can be seen from Table 4, 78% of the workers in chrome bath plating had post-shift U–Cr levels greater than the P95 of the outwith company controls and 40% exceeded the P95 of all controls (within company and outwith company controls combined). Thirty four percent of the post-shift U–Cr levels in bath platers exceeded the French BLV of 1.8 μg/g creatinine, whereas these proportions were varying between 18% and 24% for other worker groups except for the workers performing maintenance and laboratory activities where no exceedances were observed. Five samples exceeded the Finnish BLV of 10 μg/l (corresponding 7.8 μg/g creatinine).

3.2.3. Cr in red blood cells (RBC-Cr)

Fig. 2 shows results on RBC-Cr measurements. Only groups of workers with >10 RBC-Cr results are presented. Chrome plating workers showed the highest levels of RBC-Cr with a median of 4.34 μg/l and P95 level of 8.88 μg/l. These levels were significantly higher when compared to the both control groups ($p < 0.001$, Mann-Whitney test). Similarly, machining workers (showing median and P95 levels of 3.3 and 5.36 μg/l) showed statistically significantly higher levels of RBC-Cr when compared to both control groups (Fig. 2). Maintenance and laboratory workers had also slightly higher levels of RBC-Cr compared to the both control groups but due to the small group size ($n = 7$) no clear conclusions can be drawn from this (data not shown). Welders (median and P95 RBC-Cr levels 0.40 and 5.18 μg/l) did not show increased exposure to Cr when compared to the control groups (median level was actually statistically significantly lower when compared to the outwith company controls). In chromate painting applications the levels showed borderline statistical significance when compared to within company controls but remained below the statistical significance when compared to outwith company controls or both control groups combined ($p = 0.103$, Mann-Whitney test).

3.2.4. Cr(VI) in exhaled breath condensate

EBC-Cr(VI) levels in controls remained generally below LOQ (see Table 3). Of all bath plating workers 67% showed EBC-Cr(VI) levels above LOQ, median EBC-Cr(VI) in post-shift samples being 0.05 and P95 1.95 μg/l for bath platers. In bath platers it was possible to detect measurable Cr(VI) levels also in pre-shift samples in 59% of cases, median and P95 pre-shift levels being 0.02, 0.62 μg/l, respectively. No EBC-Cr(VI) data was available from paint applications. Welders and machining workers had measurable EBC-Cr(VI) levels (above LOQ) only in 26% and 14% of cases and therefore, no statistics were applied. In thermal spraying, EBC-Cr(VI) levels remained below LOQ ($n = 5$).

3.2.5. Cr(VI) in the industrial hygiene samples (air, wipes)

In Table 5 the Cr(VI) air measurement results in different worker groups are presented. Subsequent manuscripts (in preparation) will discuss the additional air sampling results obtained during the measurement campaigns. It should be, however, noted that all of the tasks

Table 4

Comparison of post-shift U–Cr to P95 level observed in controls and to BLVs from France and Finland.

Job title	Post-shift samples, n (%), exceeding the specific level			
	P95 of outwith company controls, 0.44 μg/g creatinine)	P95 of all controls, 1.35 μg/g creatinine)	French BLV of 2.5 μg/l (1.8 μg/g creatinine)	>Finnish BLV of 10 μg/l (7.8 μg/g creatinine[a])
Bath plating workers (n = 90)	70 (78)	36 (40)	31 (34)	4 (4)
Chromate paint applications (n = 45)	30 (67)	15 (33)	11 (24)	1 (2)
Machining workers (n = 38)	31 (86)	16 (44)	7 (18)	0 (0)
Welders (n = 189)	127 (67)	49 (26)	34 (18)	0 (0)
Thermal spraying (n = 5)	2 (40)	1 (20)	1 (20)	0 (0)
Steel production (n = 10)	9 (90)	5 (50)	2 (20)	0 (0)
Maintenance and laboratory workers in plating companies (n = 8)	3 (38)	1 (13)	0 (0)	0 (0)

[a] Creatinine corrected value calculated using the observed mean creatinine content of 1.29 g/l in post-shift worker samples.

involved exposure also to Cr(III). For example, in plating median and 95th percentile levels were 9.85 and 358.75 μg/m^3 for total inhalable Cr, respectively (outside RPE). In welding, median and 95th percentile levels were 16.10 and 481 μg/m^3 for total inhalable Cr outside RPE, respectively.

Fig. 3 shows the results from hand wipe samplings. In all the occupational groups, significant dermal Cr accumulation over the workday could be determined. The highest cumulative Cr levels were demonstrated in welders and chrome bath platers. Thermal sprayers had significantly higher dermal contamination (median 13.8 μg/cm^2, data not shown in Fig. 3) than other worker groups but taking into account the process and their low Cr biomarker levels these may mainly reflect Cr(III) exposure.

3.3. Correlations between the different exposure metrics

Fig. 4 shows heatmaps on the Spearman correlations between different markers of exposure. When all the worker groups were combined the correlations between different exposure markers remained low ($\rho < 0.5$). When chrome platers were analysed separately, high positive correlations were observed between U–Cr levels and respirable air Cr(VI) levels or between U–Cr levels and wipe sample Cr levels ($\rho = 0.805$, $\rho = 0.746$, respectively). Air levels (inhalable and respirable Cr (VI) outside RPE showed high correlation also with hand contamination ($\rho \geq 0.8$) in platers. In welders, high positive correlations were observed between U–Cr and respirable Cr(VI) outside RPE ($\rho = 0.745$). Correlations between different biomarkers (U–Cr, RBC-Cr and EBC-Cr) were generally low ($\rho < 0.5$).

3.4. Country differences

Since there were differences in the type of companies sampled in each country, only limited comparisons of the results among the countries were possible. Since France and the Netherlands have implemented

Table 5

Summary of the air Cr(VI) measurements in μg/m^3 (personal measurements, outside RPE). Data from worker groups with number of measurements <5 not presented.

Job title	Inhalable Cr(VI) levels, median; 95th percentile (n)	Respirable Cr(VI) levels, median; 95th percentile (n)
Bath plating workers	0.43; 5.13 (57)	0.09; 2.28 (54)
Chromate paint applications	5.61; 154 (7)	n.d.
Machining workers	0.10; 0.41 (15)	0.03; 0.05 (10)
Welders	0.50; 4.06 (107)	0.11; 22.31 (20)
Thermal spraying	9.63; 21.04 (5)	0.06; 0.10 (5)

n.d. - not determined.

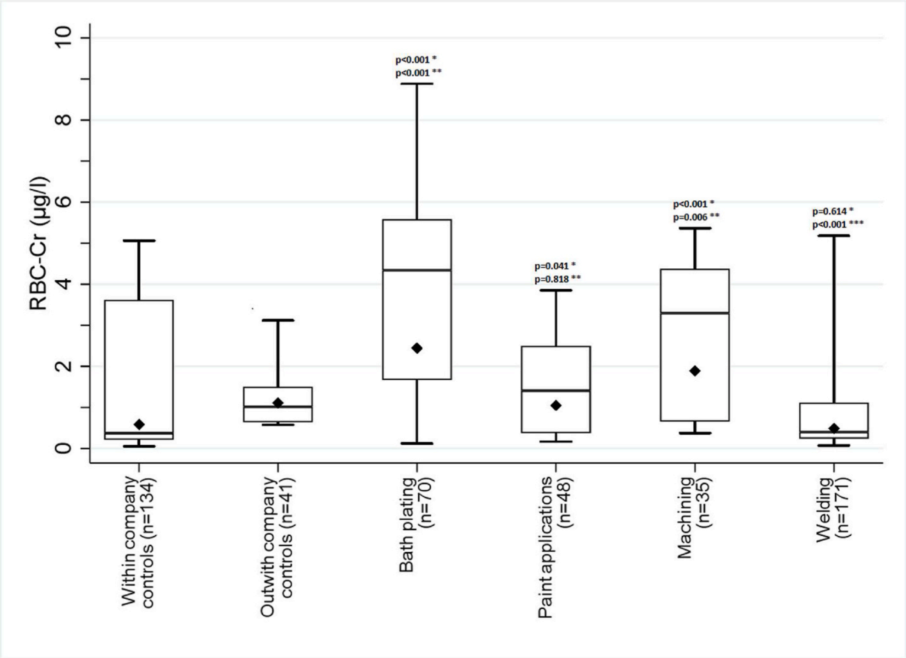

Fig. 2. RBC-Cr results of controls and different worker groups. Worker groups with n ≤ 10 are not presented. RBC-Cr data are adjusted for hematocrit value 2 (measured after the washing steps). * Workers vs. within company controls, ** workers vs. outwith company controls, *** welders vs. outwith company controls (note that RBC-Cr levels in welders were statistically significantly lower when compared to the outwith company controls). Box plots: The bottom and top of the box are, respectively, the 25th and 75th percentiles, and the horizontal line inside the box is the median (50th percentile). The lower and upper ends of the whiskers are the 5th and 95th percentiles, respectively. The solid diamond is the geometric mean.

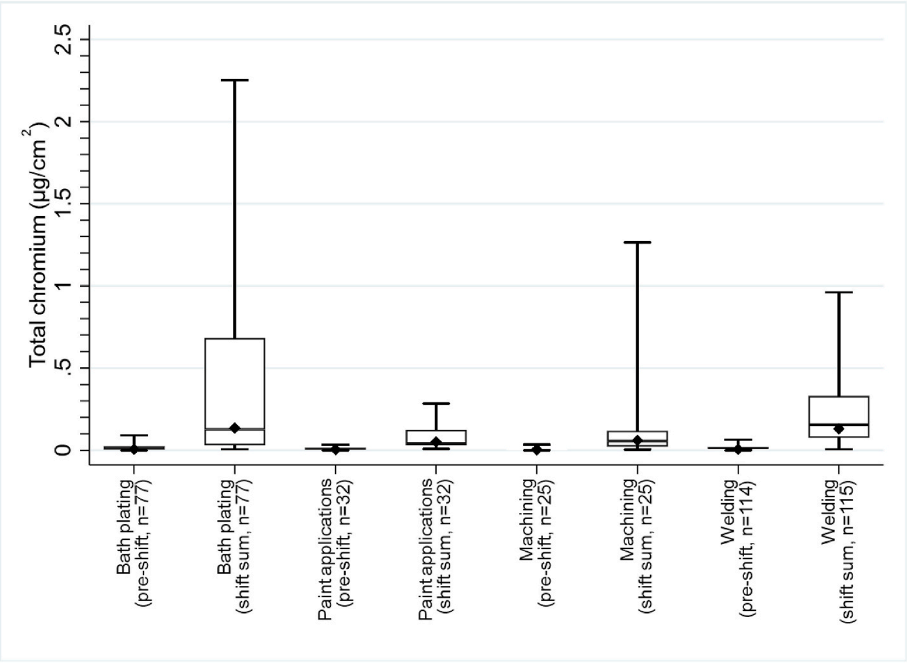

Fig. 3. Hand contamination of workers measured as wipe samplings before the beginning of the shift and during the shift before any break (e.g. before hands were washed in the lunch break) and post-shift. Sum of the samples taken during the shift and post-shift was calculated and presented as a "shift sum". Only worker groups with n > 10 are included in the figure. Box plots: The bottom and top of the box are, respectively, the 25th and 75th percentiles, and the horizontal line inside the box is the median (50th percentile). The lower and upper ends of the whiskers are the 5th and 95th percentiles, respectively. The solid diamond is the geometric mean.

lower OELs for Cr(VI) than other countries it was interesting to see whether these countries showed lower exposure levels. For bath platers, exposure levels as measured by U–Cr (post-shift) and air inhalable Cr(VI) were lower in France when compared to the data from other countries ($p < 0.001$, Mann-Whitney test, data not shown). When data from France and Netherlands were combined and compared to the data from other countries, U–Cr levels showed borderline significantly lower levels in these two countries ($p = 0.049$) whereas the difference in air inhalable Cr(VI) levels was not statistically significant. RBC-Cr and EBC-Cr(VI) levels showed significantly lower levels ($p < 0.001$) in chrome platers when the combined results of France and the Netherlands were compared to the data from other countries. It must be, however, noted that the sample size in France and Netherlands was only 20 and 19 for platers, respectively. For welders it was possible to compare French data to the data from other countries (Dutch data were not available from welders). Similar trend as in chrome platers was not seen in welders: on the contrary, French welders showed higher U–Cr and RBC-Cr levels when compared to the respective data in other countries ($p = 0.008$ and $p < 0.001$, respectively, data not shown).

4. Discussion

4.1. Exposure of control population

An important finding of this study is that in addition to those workers directly exposed to Cr(VI) in plating, welding or other surface treatment activities, some of the office workers recruited as controls from these companies might have been indirectly exposed to Cr(VI). This can be seen by the significantly higher U–Cr levels in the within company controls when compared to the outwith company controls (see Table 2). This might reflect bystander exposure of some of the industrial controls working in these companies. However, it should be noted that the group of "outwith company controls" consisted of only Portuguese and Finnish workers for U–Cr and for EBC-Cr(VI) Finnish and UK workers, whereas "within company controls" were from Belgium, Poland, France, Luxembourg and the Netherlands, and for EBC-Cr(VI) and RBC-Cr also from Italy. Thus, contribution of country differences in background Cr(VI) (or Cr(III)) exposure cannot to be excluded. The general population is exposed to Cr species (both trivalent and hexavalent chromium) via the diet, ambient air and drinking water (IPCS, 2009, 2013). Therefore, environmental pollution in the area of residence may have some impact on the levels observed in controls. According to the study by Morton et al. (Morton et al., 2014) from UK, P95 of occupationally non-exposed population was 1.31 µg/g creatinine, which is only slightly lower than the P95 observed in "within company controls" in our study. Median U–Cr level in the Morton et al. study was 0.42 µg/g creatinine. On the other hand, in an Italian study (Aprea et al., 2018) GM and P95 levels were 0.218 and 0.963 µg/g creatinine whereas Hoet et al. (Hoet et al., 2013) reported median and P97.5 levels of 0.109 and 0.341 µg/g creatinine, respectively, among Belgian occupationally non-exposed population. Overall, although there might be some differences related to the environmental exposure, these might not fully explain the high levels observed in some of our "within company controls". Thus, office persons working in the companies but not involved in the production process may also be exposed to Cr at their workplace. This finding might imply that not all the exposures are being identified and this can have an impact on the exposure and risk assessment results, which may have consequences in defining the proper RMMs. Smoking and gender seemed to have either no or only a minor effect on the internal chromium exposure. This is in accordance with earlier studies (Aprea et al., 2018; Hoet et al., 2013; Morton et al., 2014). Slightly higher creatinine corrected U–Cr levels in females might be at least partly explained by the creatinine correction as male controls had higher creatinine levels than female controls (data not shown). The higher proportion of females in our control group when compared to the exposed workers is, however, unlikely to have a significant impact on the comparison between exposed workers and controls, which show clearly elevated U–Cr levels in occupationally exposed workers compared to the controls.

4.2. Exposure of chrome bath platers

Our overall results suggest that workers performing electrolytic plating in baths are the group with highest internal exposure to Cr(VI). In the plating process Cr(VI) exposure occurs as ultrafine condensation droplets containing Cr(VI) are emitted from warm baths. These workers showed significantly elevated U–Cr, RBC-Cr and EBC-Cr(VI) levels when compared to the controls. In addition to elevated post-shift U–Cr levels, pre-shift urinary levels were significantly elevated when compared to

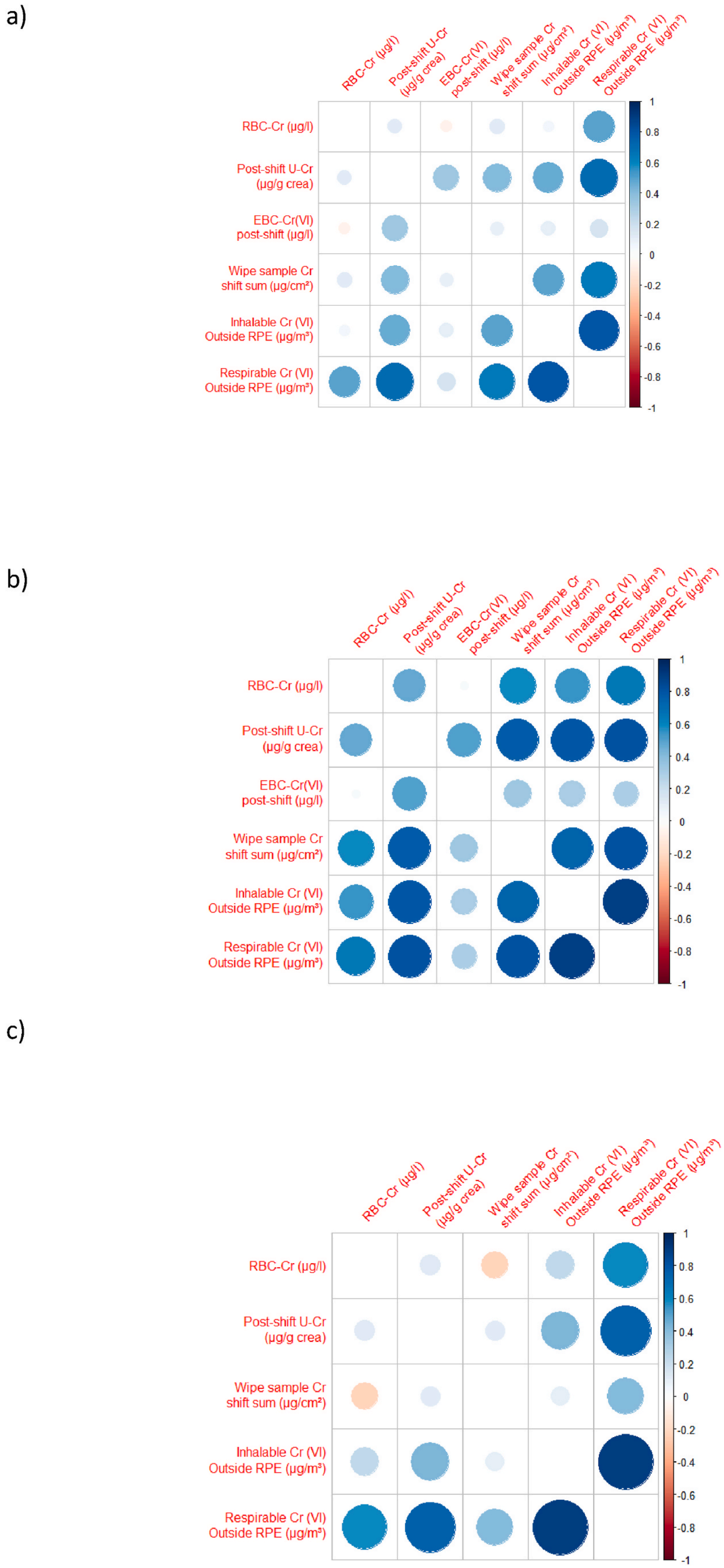

Fig. 4. Heatmap on Spearman correlation coefficients. a) All worker groups combined b) Chrome platers and c) welders. Note that EBC-Cr(VI) is not included in correlations in welders because of the low number of samples exceeding LOQ.

the controls. This may reflect the specific kinetics of chromic acid derived from the previous working week. Elevated pre-shift U–Cr of up to one week were previously reported to occur in chrome platers with skin burns resulting from occupational accidents (Matey et al., 2000). A recent study suggested fast kinetics to explain an increase from pre-to post-shift U–Cr within one work period in a group of electroplating workers and, additionally, an increase of the average pre-shift U–Cr level from Monday to Friday by 45%, indicating slower kinetics (Remy et al., 2021).

In addition to inhalation exposure, also the observed Cr contamination (measured as total Cr) in the hand wipes may be a contributing factor to explain the systemic exposure of bath platers to Cr. In our study, we observed high correlations between urinary Cr levels and wipe sample results. There are three potential explanations that may each by itself or combined explain what we observed: First, chromates may be skin absorbed but so far, such effects have only been reported in workers suffering from serious accidents where tissue burns may have caused breaches in the skin barrier. Second, the skin contamination could have resulted in hand-mouth contact as a potential secondary uptake route. Third, it is also possible that the observed association is not causal but just reflecting the common source of airborne particles that can be inhaled as long as they are airborne but may later settle down on surfaces on the workplace to be picked up skin exposure in our hand wipes.

The urinary levels observed in this study in bath platers are very similar to those reported in the study by Beattie et al. (2017), which contained 354 UK electroplating workers showing mean U–Cr of 1.2 μg/g creatinine and P90 level of 4.9 μg/g creatinine. Similar U–Cr levels were reported also in an Italian study (Goldoni et al., 2010) whereas studies from Asia and Brazil showed clearly higher exposure levels than those observed in European studies (summarized in a systematic review by (Verdonck et al., 2021).

Our results from RBC-Cr and EBC-Cr(VI) measurements also support the higher internal exposure of bath platers when compared to the other worker groups. There are only few earlier studies on the RBC-Cr or EBC-Cr(VI) levels in electroplaters. Goldoni et al. (Goldoni et al., 2010) report median RBC-Cr levels of 3.4 μg/l (range 1.2–5.8) in 14 Italian electroplaters, which are slightly lower than observed in our study showing median levels of 4.34 and P95 of 8.88 μg/l. A study by Zhang et al. (2011) from China shows RBC-Cr levels of 4.41 μg/l (median, range 0.93–14.98) among 157 electroplater workers. EBC-Cr(VI) levels have been measured earlier by Goldoni et al. (Goldoni et al., 2010) reporting median levels of 0.5 μg/l (range nd-10.1). In addition, Leese et al. (Leese et al., 2017) also reported EBC-Cr(VI) levels among a group of Cr(VI) exposed workers including chrome platers and measured median levels of 0.91 μg/l. Both these studies are one order of magnitude higher than the levels measured in our study. However, Goldoni et al. (Goldoni et al., 2010) reported air measurements one order of magnitude higher than measured in our study, with a geometric mean of 2.6 $\mu g/m^3$ and 3.6 $\mu g/m^3$ for Cr(VI) and total chromium, respectively. In our study, geometric mean of inhalable Cr(VI) level in bath plating was 0.34 $\mu g/m^3$. Air measurements were not collected by Leese et al. (Leese et al., 2017).

4.3. *Exposure of stainless steel welders*

Welders showed very similar external exposure to Cr(VI) to chrome platers (see Table 5 on air levels). However, internal exposure to Cr, measured as U–Cr, RBC-Cr and EBC-Cr(VI) remained lower when compared to the platers. According to the questionnaire, more than 50% of welders used RPE when performing welding, which may partly explain lower internal exposure of welders when compared to the chrome platers. Another explanation may be lower bioavailability of Cr(VI) particles formed during welding (Walter et al., 2015). In welders significant hand contamination was observed but the more frequent use of PPE when compared to bath platers might contribute to avoid exposure by ingestion due hand-to-mouth contact. Since dermal wipe samples were measured only for total Cr it is not possible to estimate the proportion of Cr(VI) of total Cr levels in different work tasks. Our results in welders are in accordance with the biomonitoring results reported recently in literature in Europe. According to the review by (Verdonck et al., 2021) median U–Cr levels in welders were between 0.74 and 0.9 μg/g creatinine in recent studies performed in Germany and in Italy (Pesch et al., 2018; Riccelli et al., 2018) whereas recent Polish study showed somewhat higher urinary levels (median 3.81 μg/g creatinine) (Stanislawska et al., 2020). In our study median post-shift U–Cr level was 0.68 μg/g creatinine. An earlier study by Weiss et al. (2013) reported on RBC-Cr levels among 16 highest exposed welders with median RBC-Cr level of 1.95 μg/l (P75 2.37 μg/l) and U–Cr level 9.95 μg/g creatinine (P75 38.99 μg/g creatinine). These were clearly higher exposures than observed in our study (median RBC-Cr 0.4 μg/l and P75 1.12 μg/l).

4.4. *Exposure in machining and painting applications*

Machining workers included in this study were operating either in companies performing bath plating operations or other surface treatment activities. Their personal air measurements and dermal total Cr contamination were lower than bath platers and welders but U–Cr and RBC-Cr levels were between those reported for the platers and welders. Other activities performed in the companies might have had an impact on the exposure of these workers who might have been performed also other tasks in the company in the days preceding the measurement, although in the day of measurements the main tasks were machining tasks.

Paint applications and thermal spraying showed highest air Cr(VI) levels when measured outside RPE. However, the use of RPE in these tasks reduced exposure effectively to clearly a lower level than observed in platers. Paint applications included spray painters, paint removal and application with different contents of Cr(VI) e.g. in manual brush painting. Biomonitoring of these workers in combination with air measurements is of special importance to ensure the effectiveness of personal protective equipment but also to identify the role of other exposure routes besides inhalation. Although dermal total Cr contamination over the working day was also observed in these workers, it was clearly lower than that observed in bath platers and in welders. This aspect might be explained by the fact that the tasks undertaken by this group of workers imply commonly the use of protective clothes and gloves due to the simultaneous handling of solvents and other chemicals.

4.5. *Use of RPE in the prevention of exposure to Cr(VI)*

Use of RPE seems to reduce internal Cr exposure in chromate paint applications to a clearly lower level than in bath plating operations. In our study, chrome plating workers generally did not wear RPE, or used RPE only in some short, specific tasks like sampling: only 16% reported to use RPE in bath operations, and only 23% reported to use RPE in any tasks during the day of sampling (data not shown). This is likely to reflect the current recommendations on the risk management at chrome bath plating: in the applications for authorization for the use of Cr(VI) for functional or decorative plating in baths, use of RPE has been usually recommended mainly for tasks involving handling of solid chromates (e.g. weighting and mixing and re-filling baths with solid chromates) or waste handling activities (ECHA, 2021). Less frequent use of RPE among bath platers may be one factor explaining the higher internal exposure of this sub-category when compared e.g. to welders, which showed very similar (or even slightly higher) inhalable air levels of Cr(VI). Impact of personal protection on the internal exposure in different exposure scenarios will be analysed further in detail in follow-up papers (in preparation).

4.6. *Compliance with guidance and limit values*

Since this study focused primarily on biomonitoring, there was some variability in the air samples collected in different countries (Galea et al., 2021). Some laboratories were only able to measure total Cr from the air samples which limited the number of air samples informing specifically on air levels of Cr(VI). These measurements are discussed in more detail in the follow-up paper on industrial hygiene measurements. However, a significant number of Cr(VI) measurements were performed in bath platers and in welders. The use of Cr(VI) in bath plating falls under EU REACH authorization and several authorizations have to date been granted under REACH for this use. Some of these authorizations are so-called "up-stream" authorizations covering possibly hundreds of "down-stream" users whereas some are covering only one or few sites. In some up-stream uses reasonable worst-case exposure of workers in bath plating processes have been estimated to be 2 μg/m^3 (inhalable Cr(VI) as 8 h TWA) (ECHA, 2021). In our study, the majority of exposures were below 1 μg/m^3 with geometric mean being 0.34 μg/m^3 and median 0.43 μg/m^3. However, P90 and P95 levels were 3.4 and 5.13 μg/m^3, respectively, suggesting that there is a need for more effective RMMs to achieve low levels in all instances.

The same conclusion can be made also on the basis of biomonitoring results. Correlation equations published by Lindberg and Vesterberg (Lindberg and Vesterberg, 1983) and Chen et al. (Chen et al., 2002) have been used to set biological limit values of 2.5 μg/l (1.8 μg/g creatinine) and 10 μg/l (7.8 μg/g creatinine) for Cr(VI) corresponding to OELs of 1 or 5 μg/m^3 in electroplating activities, respectively (see Table 4). In our study, 34% of platers samples exceeded the level of 1.8 μg/g creatinine, but the level of 7.8 μg/g creatinine was exceeded only in four workers.

It should be noted that a significant proportion of the total exposure to Cr in chrome plating activities may be related to dermal contamination which is suggested by high Spearman correlation coefficients between U–Cr and wipe sample results. Significant contribution of dermal contamination has been noted already in earlier studies in the electroplating sector (Lumens et al., 1993; Mäkinen and Linnainmaa, 2004). Systemic uptake of Cr has been only described with skin burns caused by chromic acid resulting in retention in RBC and elevated urinary excretion levels over several weeks (Boloorchi et al., 2007; Matey et al., 2000; Terrill and Gowar, 1990). However, significant uptake of Cr may also be caused by hand-to-mouth contact resulting inadvertent ingestion (Cherrie et al., 2006).

Cr(VI) absorbed into the skin may cause skin sensitization, and ingested Cr(VI) may increase the risk of gastrointestinal cancers (ECHA, 2013). Systemically absorbed Cr(VI) is also a reproductive toxicant but the exposure levels measured in the current study are well below the derived no effect level (DNEL) given by ECHA for the reproductive toxicity of Cr(VI) (ECHA, 2015). The most significant risk at these exposure levels is, however, the respiratory tract carcinogenicity which is mainly related to the amount of chromium inhaled. At air levels of 1–5 μg Cr(VI)/m^3, lung cancer risk is still in the range of 4–20 extra cancers/1000 workers (ECHA, 2013; SCOEL, 2017).

When looking at the welders' data, an important aspect to note is that based on our data, the derogation given in EU Carcinogens and Mutagens directive (EU, 2004) for welding or plasma-cutting processes, with an OEL value of 25 μg/m^3 until 5 years after the transposition date, seems unnecessary. The median inhalable Cr(VI) level in welders in this study was only 0.5 μg/m^3 and even P95 level of inhalable Cr(VI) was below the proposed BOELV of 5 μg/m^3. This suggests that it is already feasible to meet the requirements of EU Carcinogens and Mutagens Directive for welding and plasma-cutting processes, if the appropriate RMMs are in place.

4.7. Application of different biomarkers

In this study, we applied three different biomarkers of exposure: U–Cr, RBC-Cr and EBC-Cr(VI). U–Cr is a standard method used at workplaces to measure internal exposure to chromium. The weakness of this method is that it is unspecific and any significant exposure to Cr(III) may have an impact on U–Cr levels. In addition, there are significant background levels of U–Cr in the general population mainly due to the exposure to Cr(III) via e.g. food (Domingo et al., 2012; IPCS, 2009). Therefore, we explored also the applicability of more specific biomarkers, RBC-Cr and EBC-Cr(VI), to assess the exposure to Cr(VI) at the current exposure levels. RBC-Cr is considered to reflect exposure specifically to Cr(VI) during the whole lifespan of the red blood cell (i.e. 120 days). U–Cr reflects both past and recent exposure, which leads to daily accumulations through the working week. Studies in welders suggest a two or three stage process of elimination with half-lives of 7 h, 15–30 days and 3–5 yrs (ATSDR, 2012). Studies in chrome platers have shown half-lives of 2–3 days followed by 1 month (Lindberg and Vesterberg, 1989). The kinetics of EBC-Cr(VI), on the other hand, is currently unknown. However, Goldoni et al. (Goldoni et al., 2010) reported Cr(VI) levels in EBC samples at least 36 h after exposure. The low correlations observed between U–Cr/EBC-Cr(VI) and RBC-Cr are likely reflecting different kinetics. Therefore, biomarkers might provide complementary information and their choice should be based on the information needed to keep improving the RMMs in place. The role of these additional biomarkers will be further analysed in follow-up publications (in preparation) to define their role more precisely in the assessment of occupational exposure to Cr(VI). However, the strong correlations observed between U–Cr levels and air Cr(VI) in platers and welders support the use of U–Cr as a primary method for the biomonitoring of Cr(VI) exposure at workplaces. In this study we collected paired urine samples (both pre-shift and post-shift samples) for U–Cr measurement to calculate urinary ΔCr within persons. When aggregated on the group level, the increase in U–Cr levels was demonstrated in most worker groups suggesting recent occupational exposure to Cr between the samplings.

4.8. The strengths and limitations of the study

This biomonitoring study on occupational exposure to Cr(VI) has a unique set-up including multiple countries producing biomonitoring and industrial hygiene information on exposure to Cr(VI) using harmonized protocols. The HBM4EU chromates study design allowed to achieve a number of participants which is typically more difficult to recruit in national occupational health studies. The study was focused on three major sectors with exposure to Cr(VI); electrolytic Cr(VI) plating in baths, other surface treatment activities and welding. However, variability of the tasks undertaken by the participants resulted in some smaller groups of workers being assigned. Overall, we achieved the target of including 400 exposed workers and 200 controls. There were no specific target numbers for the enrollment of participants representing specific job categories and it was dependent on those companies (and workers) who consented to participate in the campaign. Thus, the highest numbers of workers recruited were performing welding tasks and the second highest group was chrome bath platers. The "other surface treatment" group was more heterogenous and included workers engaged in painting procedures (removing old paint and application of new paint), machining tasks as well as a few thermal sprayers and some mainly involved in steel milling process. These workers were considered as separate groups.

The challenges and lessons learned from this kind of multi-center occupational health study have been discussed in detail in the paper by Galea et al. (2021). Several practical aspects were highlighted for improvement in future multi-center occupational studies, e.g., more thorough/earlier training on the implementation of SOPs for field researchers, training on the use of the data entry template, as well as improved company communication and interaction.

5. Conclusions and recommendations

This study gives information on the current occupational exposure to Cr(VI) in some industrial sectors in nine countries in Europe. It shows that among the studied industry sectors the highest internal exposures are still related to the use of Cr(VI) in electrolytic bath plating and, for example, in stainless steel welding the exposure is clearly lower when compared to plating activities.

Our results suggest significant association of dermal total Cr contamination to the internal exposure to chromium in all worker groups. This emphasizes the role of biomonitoring beside air measurements in the control of Cr(VI) exposure at workplaces since it allows better to understand which exposure routes are contributing to the total exposure.

Although being a non-specific biomarker, U–Cr showed its value as a first approach for the assessment of total, internal exposure. Differences in the kinetics and low correlations between U–Cr and other studied Cr (VI) exposure biomarkers indicate that these approaches may not be interchangeable but rather complementary. Thus, although U–Cr is practicable for routine monitoring of Cr(VI) exposure in occupational health, RBC-Cr and EBC-Cr(VI) may provide additional information when more specific information on exposure is needed.

Our results also found elevated U–Cr levels in pre-shift samples supporting low elimination/excretion of chromium from the body. In occupational health practice, paired samples (pre-shift in the beginning of the workweek – post-shift in the end of the workweek) are recommended to be used to give information on the recent exposure, which can be linked to exposure in specific tasks performed. Potential exposure of bystanders needs also to be further studied and considered in companies' health surveillance regimes.

This study showed that occupational biomonitoring studies can be conducted successfully by multi-national collaboration. Using a similar approach in future studies may lead to comparable data that can then be used to analyse trends in exposure over time. This solution can also serve as a model for national studies and for other chemicals of concern. Additionally, these kinds of studies can provide relevant and useful information to support policy actions aiming to reduce occupational exposure to chemicals.

Author contributions

Tiina Santonen: Conceptualization, Methodology, Investigation, Writing – original draft, Project administration, Supervision. Simo P. Porras: Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization. Beatrice Bocca: Conceptualization, Methodology, Investigation, Writing – review & editing. Radia Bousoumah: Conceptualization, Methodology, Investigation, Writing – review & editing. Radu Corneliu Duca: Conceptualization, Methodology, Investigation, Writing – review & editing. Karen S. Galea: Conceptualization, Methodology, Investigation, Writing – review & editing. Lode Godderis: Conceptualization, Methodology, Investigation, Writing – review & editing. Thomas Göen: Conceptualization, Methodology, Investigation, Writing – review & editing. Ivo Iavicoli: Conceptualization, Methodology, Investigation, Writing – review & editing. Veruscka Leso: Conceptualization, Methodology, Investigation, Writing – review & editing. Beata Janasik: Conceptualization, Methodology, Investigation, Writing – review & editing. Kate Jones: Conceptualization, Methodology, Investigation, Writing – review & editing. Elizabeth Leese: Conceptualization, Methodology, Investigation, Writing – review & editing. Henriqueta Louro: Conceptualization, Methodology, Investigation, Writing – review & editing. Sophie Ndaw: Conceptualization, Methodology, Investigation, Writing – review & editing. Flavia Ruggieri: Conceptualization, Methodology, Investigation, Writing – review & editing. Maria J. Silva: Conceptualization, Methodology, Investigation, Writing – review & editing. Susana Viegas: Conceptualization, Methodology, Investigation, Writing – review & editing. Wojciech Wasowicz: Conceptualization, Methodology, Investigation, Writing – review & editing. Hermínia Pinhal: Methodology, Investigation, Writing – review & editing, An van Nieuwenhuyse: Methodology, Investigation, Writing – review & editing, Nicole Majery: Methodology, Investigation, Writing – review & editing, Emilie Hardy: Methodology, Investigation, Writing – review & editing, Jelle Verdonck: Methodology, Investigation, Writing – review & editing, Ovnair Sepai: Project administration, Supervision. Paul T.J. Scheepers: Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision

Ethics

The study involves human subjects. Consent from subjects participating in the study was received prior to conducting the study. Study protocols have been approved by ethical review boards in each of the participating countries with the approvals granted before recruiting the study participants. The ethical boards reviewing and approving the study are as follows:

- Belgium: Ethische Commissie Onderzoek UZ/KU Leuven, Belgium
- Finland: Coordinating ethics committee, HUS Joint Authority, Helsinki, Finland
- France: Comité de Protection des Personnes (CPP) Sud-Ouest
- Italy: Ethical committee in Istituto Superiore di Sanità (ISS)
- The Netherlands: Medical ethical review board CMO Regio Arnhem-Nijmegen
- Poland: Bioethical Committee at the Nofer Institute of Occupational Medicine
- Portugal: Ethical Committees of Lisbon School of Health Technology and Doctor Ricardo Jorge National Health Institute
- UK: Ethical Committee the University of Sheffield Medical School
- Luxembourg: CNER Comité National d'Ethique de Recherche (National Ethics Committee for research)

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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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111984.

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