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Original Article

HBM4EU chromates study: the Portuguese integrated and harmonized study on exposure to hexavalent chromium and related early effects

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Abstract

In the scope of the European Union (EU) human biomonitoring initiative, a multicentric study on different occupational settings from several European countries was performed, to provide information on occupational exposure to hexavalent chromium [Cr(VI)], a known lung carcinogen. Biomonitoring approaches were used to obtain exposure data to support the implementation of new risk management measures and policy actions at the national and European levels. This work describes the Portuguese contribution to the study, which aimed to assess workers' exposure to Cr, by using exposure biomarkers (urinary chromium [U-Cr]), and industrial hygiene samples (air and hand wipes) and to link exposure to potential long-term health effects by using effect biomarkers. Exposure determinants influencing exposure were explored from the contextual information and human biomonitoring data. The ultimate goal of the study was to appraise the risk management measures contributing to minimize exposure and protect workers' health. Several occupational settings and activities were considered, including plating, welding, and painting. A control group from the Portuguese general population was also included. Data on age, sex, and smoking habits from both groups were considered in the statistical analysis. Information on the risk management measures available for workers was collected and used to identify the ones that mainly contributed to reduce exposure. Environmental monitoring and human biomonitoring revealed that painters were the highest exposed group. The use of respiratory protection equipment showed an influence on total U-Cr levels for workers involved in painting activities. Concerning early health effects, the painters presented also a significantly higher level of DNA and chromosomal damage in peripheral blood cells, as compared to the control group, suggesting a plausible association between exposure to Cr(VI) and early genotoxic effects. The results showed that workers are exposed to Cr(VI) in those occupational settings. These findings point to the need to improve the prevention and risk management measures and the implementation and enforcement of new regulatory actions at the national level.

Key words: biomonitoring; effect biomarkers; hexavalent chromium; occupational exposure.

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What's Important About This Paper?

This study provides human biomonitoring information regarding occupational exposure to hexavalent chromium in Portugal that can be used to support the implementation of new and effective risk management measures and policy actions at both national and international levels. The results also highlight the need to update the hexavalent chromium occupational limit value as it is being discussed at the European level.

Introduction

Preventing workers from being exposed to carcinogens is a main goal for reducing the number of occupational cancer cases. This is of utmost importance because cancer has been recognized as the leading cause of work-related deaths in the EU (Roadmap on carcinogens | Safety and health at work EU-OSHA [europa.eu]). Among the goals recently agreed upon by several EU organizations to prevent exposure to carcinogens at the workplace (2020–2024), those focused on creating awareness among employers and workers on the risks from exposure to carcinogens and the need for preventive actions should be highlighted. In addition, bridging research and innovation findings and employers' needs and engaging relevant stakeholders will be crucial to successfully achieving the abovementioned goal.

Hexavalent chromium [Cr(VI)] has been used in several industrial activities, such as welding, Cr(VI) electroplating, and other surface treatment processes, and although it is a carcinogenic substance (IARC 2012), no appropriate replacement has been found for some of its industrial applications. 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 (IARC 2012; ECHA 2013; den Braver-Sewradj et al. 2021). In addition, it is a common cause of occupational asthma and allergic dermatitis, and there is a concern about adverse effects on reproductive health (Sun and Costa 2022). In workplaces, exposure to Cr(VI) occurs mainly by inhalation of dust, mists, or fumes from Cr-containing products in several occupational activities, some already mentioned and others, such as paint application and removal of old paint containing Cr(VI) should also be targeted for exposure assessment and risk assessment and management intervention (European Commission 2017). Dermal contact and ingestion associated with hand-to-mouth contact may also assume some relevance in these workplaces.

In the EU several regulations are in place to limit workers' exposure, being the most relevant the Registration, Evaluation, Authorization and Restriction of Chemicals 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) (European Commission 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, TWA) until 17 January 2025. After that period, the OEL (8-h TWA) will decrease 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, an OEL (8-h TWA) of 5 μg/m^3 will be applicable. No EU-wide biological limit values (BLVs) for Cr(VI) are available. Nevertheless, France and Finland have derived BLVs of 2.5 μg/l (1.8 μg/g creatinine) and 10 μg/l, corresponding to OELs of 1 and 5 μg/m^3, respectively, for Cr(VI) (ANSES 2017; STM 2020). Since these current national BLVs are mainly defined and supported by studies on plating workers, they have uncertainties, mainly concerning their applicability to workplaces other than the electroplating industry such as welding or painting (Santonen et al. 2023).

The EU human biomonitoring initiative (HBM4EU, www.hbm4eu.eu) was a European Joint Programme, developed between 2017 and 2022 aiming to harmonize the collection and use of biomonitoring data to better understand human exposure to chemicals in occupational settings to improve chemical risk assessment and management efforts and to support policy making in the workplaces (Gerofke et al. 2023).

In the scope of this project, an occupational study on exposure to Cr(VI) and associated health outcomes was carried out, which was the first of a series of 3 different HBM4EU occupational studies (Santonen et al. 2019, 2022, 2023). A relevant aspect to consider in occupational exposure to carcinogens is whether biological effects can be identified early in cells or tissues of exposed workers, which may be associated with a greater risk of disease development in the long term. These biological effects include early biochemical, cellular, or molecular effects that are assessable in target or surrogate tissues (e.g. blood cells) and that may be linked to adverse health effects, e.g. cancer (Corradi et al. 2015). Concerning Cr(VI) exposure, biomarkers of oxidative stress, DNA damage, or chromosomal aberrations in blood cells (e.g. comet and micronucleus assays) have been the most frequently applied (Ventura et al. 2021). If workers are indeed exposed and early

effects are identified in workers compared with non-exposed individuals (controls), then the results are expected to support the implementation of mitigation measures to protect workers' health.

The main aim of this study was to provide relevant data on Cr(VI) internal exposure and early biological effects in different occupational settings in Portugal. In addition, it was also explored the determinants of exposure and the risk management measures contributing to minimize exposure using exposure biomarkers (UCr) and industrial hygiene samples. The data generated are expected to guide the implementation of risk management measures and be used as evidence for regulatory risk assessment and decision-making at the national and European levels, ultimately promoting work environments without Cr(VI) contamination/exposure, contributing to protect workers' health.

Materials and methods

This study was anchored in the HBM4EU chromates study, which has been designed cross-sectional survey, multicentric, carried out in 9 countries: Belgium, Finland, France, Italy, Poland, Portugal, the Netherlands, United Kingdom, and Luxembourg. The present paper addresses the results obtained for Portugal. The protocol for sampling has been described in detail in (Santonen et al. 2019), according to Standard Operating Procedures (Santonen et al. 2019). This allowed the teams involved from the different countries to perform harmonized data collection. The fieldwork took place from October 2018 to December 2020, and data analysis was performed between 2020 and 2021.

Setting up the Portuguese occupational study

The target population included Portuguese workers developing activities leading to occupational exposure to Cr(VI) mainly painting, bath plating, machining, laboratory work, and stainless-steel welding. Stainless steel welders were selected since they are expected to be exposed to higher Cr(VI) levels than mild steel welders. The inclusion and exclusion criteria for the recruitment of volunteers for the study were as follows: workers with ages ranging from 18 to 70 years, all genders, reporting good health and actively working during the samples collection period, undertaking activities likely exposing them to Cr(VI), namely, surface treatment with chromium-based products (spraying or painting), chrome-plating in baths, machining, or stainless-steel welding activities. For genotoxicity biomarkers, more strict inclusion criteria were fulfilled, the most important ones being age under 50 years, without reporting medical exams such as an X-ray or Computerised Axial Tomography scan in the last 3- months and not suffering or having suffered from cancer (more details are described in Santonen et al. 2019). In addition, the same criteria (except Cr exposure) were followed to select a non-exposed (control) group from companies not involved in those activities, in the same geographical area.

The recruitment of the companies and workers was aligned with the dedicated SOP developed under Project HBM4EU (Santonen et al. 2019). Briefly, interested companies received an information leaflet, and when a company accepted to participate, an authorized representative completed an employer certificate of informed consent. An information leaflet for the workers was distributed and discussed during the first contact. Each worker provided informed consent to participate in the study (Santonen et al. 2019). The same methodology was followed for control' recruitment.

Concerning ethical requisites, the study protocols have been submitted for approval by the Ethics Committees of Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa and Instituto Nacional de Saúde Doutor Ricardo Jorge/National Institute of Health Doutor Ricardo Jorge (INSA) and the data management was approved by the respective data protection officers, with the necessary approvals being granted before contact with companies and workers.

Collection of contextual information

Two questionnaires were developed to gather pertinent contextual information on companies' practices (e.g. training, safety practices, previous monitoring campaigns) and the workers' questionnaire was dedicated to 3 groups of workers (Cr plating in baths, welders, and surface treatment workers) and it was asked about the presence of local exhaust ventilation (LEV), the availability and use of personal protective equipment (PPE), previous information and training on safety issues, the possibility of washing one's hands during work, and the existence of a dedicated place for the storage of working clothes and respiratory protection equipment (RPE) (Santonen et al. 2019, 2022). The questionnaire for the company aimed to collect general information regarding the industry: previous training on safety issues related to working tasks, previous exposure monitoring campaigns, occupational health and safety practices, and general operating conditions related to chrome plating, surface treatment and welding operations (as applicable) (Santonen et al. 2019). Other eventual background exposures from non-workplace sources such as hobbies, diet, and air pollution based on home locations, were also interrogated in this questionnaire (Santonen et al. 2019). However, the collected information did not provide enough data in all cases (e.g. on the risk management measures in place in the companies),

hampering detailed statistical analysis. Missing answers were due to different reasons (e.g. workers who were not available to answer the questionnaire). As such, only possible some variables could be used to investigate the influence on workers' exposure results. The determinants of exposure included in the analysis were described in detail in Viegas et al. (2022) and were, for instance, the developing of previous monitoring campaigns (environment and biomonitoring), the availability of risk management measures such as the presence of LEV, gloves, RPE and the fit testing procedures, the existence of a dedicated place for storing working clothes and RPE, workers' experience in their jobs and non-workplace exposure sources (e.g. smoking status, home location [urban or rural] and home traffic density).

Sampling and analytical measurements

Air samples.

Individual inhalable dust was collected for workers and samples were analyzed by gravimetry and thereafter for the determination of Cr(VI) by NIOSH Method 7600 (NIOSH, 2003). Results were presented as 8-h TWA.

Dermal wipe samples (hand wipes).

Samples were collected from both hands using SKC Ghost sampling wipes or similar (OSHA 2002; NIOSH 2003) during the working shift (pre-shift, first break period, lunch, and post-shift) by a standardized procedure (Santonen et al. 2019). Wipe sampling (number of samples) differed according to the duration of tasks with potential exposure to Cr and the number of breaks/hand washing during the workday. Field blanks were collected to mitigate the potential for unrecognized contamination due to media or sample handling during fieldwork (NIOSH 2003).

Urine samples.

Urine sampling was conducted in 2 time points: pre-shift, i.e. beginning of the work week and post-shift, i.e. end of the work week. Sample containers were decontaminated with a 10% HNO_3 solution to avoid background contamination. Thereafter, samples were homogenized, aliquoted, and stored at −20 °C. Analytical determination was performed by atomic absorption spectrophotometry with a graphite chamber. The laboratory was certified by Interlaboratory Comparison Investigations for its performance in participating in the HBM4EU Quality Assurance Program, resulting in its qualification as an HBM4EU laboratory for the analysis of chromium in biological samples (urine, plasma, and blood). Urinary creatinine concentrations were determined, and urinary chromium (U-Cr) levels were adjusted to creatinine level (µg Cr/g creatinine) (Aitio 1996; Cocker et al. 2011). Results obtained were compared with BLV established by ANSES, 1.8 µg/g creatinine (ANSES 2017).

Blood.

Approximately 3 ml of peripheral blood was collected by venipuncture through standard procedures, for a tube containing sodium-heparin anticoagulant. Samples were kept refrigerated and protected from light during storage and transportation. The micronucleus (MN) assay and the comet assay in human peripheral blood lymphocytes were performed as previously described (Tavares et al. 2022). Briefly, for the MN assay 2 whole blood cultures were prepared per participant using RPMI-1640 medium supplemented with fetal bovine serum (15%; Thermo Fisher Scientific, UK) and phytohemagglutinin A (2.5%), and incubated at 37 °C. After 44 h, cytochalasin B (5 µg/ml; Sigma-Aldrich, USA) was introduced to block cytokinesis and cultures were further incubated till completing 68 h. Lymphocytes were harvested by standardized methods that include a mild hypotonic shock (KCl 0.1 M; Merck, Germany), and 2 fixation steps with methanol: acetic acid (Merck, Germany and VWR, France). Microscope preparations were prepared by dropping cells in fixative onto microscope slides and, air-drying, and staining with Giemsa (Merck, Germany). MN were blindly scored in 2,000 cytokinesis-blocked (binucleated) cells per individual, under a bright field microscope, and identified according to published criteria. The frequencies of micronucleated binucleated cells (MNBCs) and MN in BC were expressed per 1,000 BCs. The proportion of mono- (MC), BC, or multi-nucleate cells (MTC) was determined for a total of 1,000 cells per participant and the cytokinesis-block proliferation index (CBPI) was calculated as follows: CBPI = (MC + 2BC + 3MTC)/total cells. Regarding the alkaline comet assay, low melting point agarose gels (0.7%; Sigma-Aldrich, USA) incorporating 20 µl of blood were prepared on pre-coated microscope slides. A positive control (blood cells treated with ethyl methanesulfonate) was also included. The microscope slides underwent a step of lysis, followed by treatment with the alkaline electrophoresis buffer (pH > 13) and electrophoresis for 20 min (300 mA and 25 V), at 4 °C. After washing for neutralization, slides were stained with ethidium bromide (125 µg/ml; Sigma-Aldrich, USA), and observed under a fluorescence microscope, using Comet Assay IV software (Perceptive Instruments, UK). For each individual 100 nucleoids were randomly analyzed and the DNA damage was expressed as the percentage of the DNA in the tail (or tail intensity) (Tavares et al. 2022).

Statistical analysis

The analysis of the results was performed using IBM© SPSS© Statistics software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. IBM Corp version 26, IBM Corporation, New York, NY, USA). Left-censored data was considered by substitution by a fixed value, considering a middle-bound approach (<LOQ = ½ LOQ) (Hornung and Reed 1990). Considering the normal or non-normal distribution of variables, parametric, and nonparametric tests were used, with a level of significance of 5%. Spearman correlation coefficient (r_s) was used for correlations among continuous variables ($r_s \leq 0.2$ = poor; $0.2 < r_s \leq 0.5$ = fair; $0.5 < r_s \leq 0.7$ = moderate; $0.7 < r_s \leq 1.0$ = very strong) (Chan 2003).

The risk management measures variables were dichotomized (yes/no) for inclusion in the statistical analysis.

Results

The main characteristics of the studied population are summarized in Table 1. The exposed workers were mainly male (90.0%), with mean ages of 46 ± 10 years old. Participants were recruited from 5 activity sectors: painting, bath plating, machining, laboratory work, and welding. As to the location of their homes, workers lived mainly in urban areas (88.0%). The workers reported their years of work in welding, metal plating, painting or spraying, and other metal works (Table 1). The mean length of experience in their jobs was 12 years for painting or spraying and welding (with a maximum of 42 years and 33 years, respectively) (Table 1). Seven participants (3 workers and 4 controls) were excluded from the analysis of effect biomarkers, after the application of the specific criteria for worker selection for effect biomarker analysis as previously defined in Santonen et al. 2019.

Total Cr and Cr(VI) in industrial hygiene samples (air and wipes)

Table 2 presents the results of Cr(VI) in air samples and total Cr in hand wipes from workers involved in painting activities.

Strong correlations were obtained between the levels of urinary total Cr and Cr(VI) in the inhalable and respirable air fractions outside the RPE ($r_s = 0.821$ and $r_s = 0.786$, respectively). A fair correlation was observed for the levels of total Cr in post-shift urine and in hand wipes ($r_s = 0.484$) (Table 2).

Exposure biomarkers

For the total Portuguese group of the workers exposed, the pre-shift levels of U-Cr were significantly higher as compared to the controls ($P = 0.011$). A similar pattern was described by Santonen et al. (2022) for the results of the whole occupational cohort. For workers involved in painting activities, post-shift levels of U-Cr were significantly higher than those of the controls ($P = 0.001$). Table 3 presents the urinary total chromium concentrations (total U-Cr) measured in urine samples of workers from the different activities, collected before and after the shift.

Regarding the comparison of exposure biomarkers with BLV available (1.8 µg/g creatinine), we observed that 21% of the painting workers exceeded these limit values. Despite the importance of this evaluation, it should be noted that this BLV was established by ANSES for bath platers, therefore some uncertainties may arise from this comparison.

Determinants of exposure

The risk management measures available in the companies engaged in the study, as well as other contextual information collected, and their impact on the levels of total Cr in urine and Cr(VI) in industrial hygiene samples (air and wipe), were assessed. Considering the number of workers in each activity, statistical analysis is presented only for painting workers.

It was possible to observe that the use of the RPE had an influence on total U-Cr levels for workers involved in painting activities. Indeed, workers who use RPE had significantly lower levels of total U-Cr ($P = 0.008$). The availability of LEV had no influence on the levels of total Cr in the urine or in the inhalable and respirable air fractions of Cr(VI) outside the RPE in the painting. However, when a dedicated place for storing work clothes was available, significantly higher levels of total U-Cr were observed. The use of gloves did not have an impact on the total U-Cr levels and hand wipe Cr levels.

Effect biomarkers

The genotoxicity biomarkers analysis in white blood cells from both exposed and control individuals is presented in Table 4. Data analysis showed that the workers' group presented significantly increased frequencies of micronucleated cells per 1,000 BC, micronuclei in binucleated cells, and increased levels of DNA strand breaks in leukocytes (measured as tail intensity by the comet assay) compared to those in the control group ($P < 0.0001$, 0.0001, and 0.0004, respectively), revealing increased chromosomal and DNA damage.

Considering the categorization of the workers according to the activities performed, the painters' group presented significantly increased frequencies of MN

Table 1. Characterization of workers and controls enrolled in the study.

	Workers (n = 50)		Controls (n = 27)	
	N	%	n	%
Sex				
Male	45	90.0	24	88.9
Female	5	10.0	3	11.1
Age				
20–29 years	2	4.0	-	-
30–39 years	14	28.0	12	44.4
40–49 years	10	20.0	8	29.6
50–59 years	14	28.0	6	22.2
60–68 years	4	8.0	-	-
Unknown/undetermined	6	12.0	1	3.7
Smoking status				
Smoker	19	38.0	4	14.8
Non smoker	20	40.0	18	66.7
Former smoker	7	14.0	4	14.8
Unknown/undetermined	4	8.0	1	3.7
Home location				
Urban	44	88.0	21	77.8
Rural	2	4.0	5	18.5
Unknown/undetermined	4	8.0	1	3.7
Home—traffic density				
Low density	12	24.0	9	33.3
Medium density	23	46.0	13	48.1
Heavy density	11	22.0	4	14.8
Unknown/undetermined	4	8.0	1	3.7
Sector of activity				
Painting	32	41.6	-	-
Bath plating	5	6.5	-	-
Machining	5	6.5	-	-
Laboratory work	5	6.5	-	-
Welding	3	3.9	-	-
	Mean ± SD	**Max**	**Mean ± SD**	**Max**
Years of experience				
Metal plating	27.1 ± 12.6	41.0	–	–
Painting or spraying	12.1 ± 12.1	42.0	–	–
Welding	31.3 ± 1.5	33.0	–	–
Other metal works	16.8 ± 17.1	33.0	–	–

SD, standard deviation.

and increased levels of DNA damage (comet assay) compared with the control group. Despite the small size of the other subgroups, some significant differences were also detected. Machining workers displayed significantly higher frequencies of MN than controls; however, the difference in DNA breaks between these workers and controls did not reach statistical significance. On the other hand, the bath platers and laboratory workers displayed a significantly raised level of DNA breaks compared to the controls.

Furthermore, our study data showed that smoking habits also significantly influenced the MNBC (P =

Table 2. Levels of total Cr and Cr(VI) in industrial hygiene samples (air and hand wipe samples) collected from workers during painting activity.

Industrial samples		*n*	Mean	GM	Median	P75	P95	Range	r_s Total U-Cr	OEL Cr(VI)
Air samples										
Inhalable—Outside RPE	Cr(VI) (μg/m³)	7	–	–	5.6	–	–	0.6–154.4	0.821	25.0
Respirable—Outside RPE	Cr(VI) (μg/m³)	7	–	–	1.0	–	–	0.4–9.4	0.786	5.0*
Wipe samples **	Total Cr (μg/cm²)	28	0.08	0.05	0.05	0.12	0.29	<LOQ –0.3	0.484	NA

LOQ, limit of quantification; GM, geometric mean; RPE, respiratory protection equipment; P75, percentile 75; P95, percentile 95; OEL, occupational exposure limit for Cr(VI) (μg/m³); NA, not available; U-Cr, urinary chromium. *Stricter OEL to be applied in January 2025. **Sum of the samples taken during the shift and post-shift was calculated and presented as a "shift sum." (–) = results not presented due to the low number of observations.

Table 3. Total Cr urinary concentrations in workers and controls, adjusted for creatinine level.

			Total U-Cr (μg/g Creatinine)					
		n	Mean	GM	Median	P75	P95	Range
Pre-shift	Workers[a,b]	50	0.52	0.30	0.24	0.66	2.26	0.1–3.99
	Painting[a,b]	32	0.72	0.43	0.49	1.01	3.00	0.1–3.99
	Bath plating	5	0.16	0.16	0.15	0.22	–	0.1–0.23
	Machining	5	0.15	0.14	0.11	0.22	–	0.1–0.28
	Laboratory work	5	0.21	0.19	0.16	0.33	–	0.1–0.39
	Welding	3	0.14	0.13	0.14	–	–	0.1–0.17
	Controls	27	0.24	0.17	0.14	0.27	1.31	0.1–1.89
Post-shift	Workers[a,b]	50	1.01	0.45	0.33	1.03	3.66	0.1–12.34
	Painting[a,b]	32	1.29	0.57	0.65	1.71	6.68	0.1–12.34
	Bath plating	5	0.40	0.28	0.25	0.73	–	0.1–1.18
	Machining	5	1.03	0.44	0.52	2.19	–	0.1–3.70
	Laboratory work	5	0.20	0.10	0.16	0.28	–	0.1–0.39
	Welding	3	0.37	0.28	0.24	–	–	0.1–0.76

[a]Statistically significant differences ($P < 0.05$) between workers and controls. [b]Statistically significant differences ($P < 0.05$) between pre-shift and post-shift. U-Cr, urinary chromium; GM, geometric mean; P75, percentile 75; P95, percentile 95. (–) = results not calculated by SPSS due to low number of observations.

Table 4. Results of the biomarkers of genotoxicity analyzed in blood cells from participants in the exposed and control groups (mean ± SD).

		MN PBL		Comet assay	
	n	MNBC (‰)	MN in BC (‰)	*n*	Tail intensity (%)
Workers	46	6.55 ± 0.35*	7.44 ± 0.41*	47	5.43 ± 0.21*
Painting	31	6.32 ± 0.46*	7.15 ± 0.51*	32	5.41 ± 0.25*
Bath plating	5	5.80 ± 0.73	6.10 ± 0.91	5	6.38 ± 0.56*
Machining	5	7.90 ± 0.76*	9.80 ± 1.04*	5	5.12 ± 0.96
Laboratory work	5	7.40 ± 0.94	8.23 ± 1.15	5	4.95 ± 0.46*
Controls	23	4.21 ± 0.34	4.84 ± 0.44	**25**	**1.49 ± 0.22**

MN PBL, micronucleus in peripheral blood lymphocytes; MNBC, micronucleated binucleated cells (per 1000 binucleated cells); MN, micronuclei (per 1000 binucleated cells). *Significantly different from the control group ($P < 0.05$, one-way ANOVA and Dunnett T3 pos-hoc test). Welders were excluded because they did not meet the specific inclusion criteria.

Table 5. Comparison of values obtained for smokers and nonsmokers within each group of exposures.

Workers		*N*	Mean ± SD	*P* value
Total U-Cr, Post-shift (µg/g creatinine)	Nonsmokers	27	1.36± 0.47*	0.167
	Smokers	19	0.58 ± 0.19*	
MNBC (‰)	Nonsmokers	27	7.15 ± 0.52*	0.042
	Smokers	19	5.71 ± 0.35*	
MN in BC (‰)	Nonsmokers	27	8.09 ± 0.60*	0.057
	Smokers	19	6.51 ± 0.44*	
Tail Intensity (%)	Nonsmokers	27	5.51 ± 0.30*	0.589
	Smokers	19	5.29 ± 0.31*	
Controls		***N***	**Mean ± SD**	***P* value**
Total U-Cr, Post-shift (µg/g creatinine)	Nonsmokers	18	0.19 ± 0.03	0.758
	Smokers	4	0.16 ± 0.08	
MNBC (‰)	Nonsmokers	18	4.49 ± 0.39	0.0731
	Smokers	4	2.88 ± 0.43	
MN in BC (‰)	Nonsmokers	18	5.3 ± 0.50	0.0358
	Smokers	4	2.88 ± 0.43	
Tail Intensity (%)	Nonsmokers	18	1.31 ± 0.24	0.0616
	Smokers	4	2.44 ± 0.77	

The *P* value displayed refers to differences between smokers and nonsmokers for each parameter. *Significantly increased compared to controls ($P < 0.05$, Mann–Whitney test).

0.042), with nonsmoking workers presenting a significantly higher frequency of MN than smokers (Table 5). However, smoking did not affect Total U-Cr nor DNA damage ($P > 0.05$), as measured by the comet assay. Considering the nonsmokers ($n = 45$) subgroup only, there were significant differences between the workers' and the control groups for U-Cr µg/g creatinine, micronucleus frequencies, and DNA damage. The same pattern was observed when considering only smokers ($n = 23$), i.e. significant differences between workers and control groups for all biomarkers analyzed. Further statistical analysis comparing workers and controls stratified by smoking habit and activity status was not performed due to the small subgroup size and inherent low statistical power of the analyses.

Furthermore, correlation analysis between exposure and effect biomarkers revealed a significant but fair correlation between the micronucleus frequency or the level of DNA breaks and the post-shift total U-Cr (Table 6), suggesting an association between the level of exposure to Cr and genotoxic lesions in blood cells.

Table 6. Results of correlation analysis between exposure and effect biomarkers.

Biomarker	Total U-Cr, Post-shift (µg/g creatinine)	
MNBC (‰)	r_p	0.327**
	Sig. (2-tailed)	0.01
	N	69
MN in BC (‰)	r_p	0.265*
	Sig. (2-tailed)	0.028
	N	69
Tail intensity (%)	r_p	0.245*
	Sig. (2-tailed)	0.039
	N	71

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed); Strength of correlation according to the correlation coefficient (r_p) value: $r_p \leq 0.2$ = poor; $0.2 < r_p \leq 0.5$ = fair; $0.5 < r_p \leq 0.7$ = moderate; $0.7 < r_p \leq 1.0$ = very strong.

Discussion

The aim of this work was to characterize the exposure to Cr(VI) in different occupational settings, to identify the determinants of Cr exposure and the risk management measures contributing to minimize exposure using exposure biomarkers (U-Cr), industrial hygiene samples (air and hand wipe) and contextual information and link exposure to potential long-term health effects. It was possible to identify the risk management measures that impact more

workers' exposure to Cr(VI). Moreover, the use of a biomonitoring approach allowed to identify that the ingestion route due to hand-to-mouth contact was also an important exposure route, besides inhalation. In addition, the use of biomarkers of effect allowed the identification of the activities where workers were at a greater risk of developing disease. Therefore, as long as the substitution of Cr(VI) is not possible in several occupational settings, identifying which risk management measures are more effective in preventing workers' exposure allows to define priorities for investments and actions, as envisaged by the different regulatory frameworks in place. Moreover, the information obtained about exposure and risk management measures provides scientific support for the need for increasing awareness among workers and employers about the risks from exposure to a carcinogenic agent such as Cr(VI) and for evidence-informed policymaking.

Workers' exposure and related early biological effects

There was an increase in total U-Cr levels in workers, for the post-shift samples collected towards the end of the work week, indicating work-related uptake of chromate over the preceding work week. Such observation is most likely due to the tasks performed in the workplace, given that, otherwise, the environmental exposure to Cr(VI) is known to occur mainly through tobacco smoke, but the smokers do not show higher levels of post-shift urinary Cr than nonsmokers (IARC 2012).

In the comparisons of the activity performed, the median results were similar between the different activities, although painting workers presented the highest values for the P95 of exposure. We suggest that this might be related to the absence of use of RPE, as this was confirmed by our analyses of contextual data and U-Cr, which revealed that 22% of workers reported not using RPE and that the use of RPE was associated with lower Cr exposure (Table 5). Furthermore, painters presented a consistent significantly greater level of DNA and chromosomal damage in blood lymphocytes than did the control group (Table 6), suggesting a plausible association between exposure to Cr(VI) and early biological effects. However, the higher total chromium in post-shift workers (Table 3) observed in the painters compared to the other groups of workers, is not reflected in the effect observed in the tail intensity in the comet assay (Table 4). Conversely, the 2 highest exposed group of workers, painting, and machining, revealed also the highest levels of chromosomal damage in the micronucleus assay (Table 5), suggesting that this biomarker is more sensitive to Cr(VI) exposure. It must be noted that these workers are exposed not only to Cr products but to complex mixtures of chemicals, including other carcinogenic metals, e.g. Ni and organic compounds. One of the major advantages of including effect biomarkers in occupational biomonitoring studies is that they reflect the effect from exposure to all chemicals and by all routes and, thereby, contribute to identify workers' groups or activities that pose higher risks, and that have not been identified by using exclusively exposure biomarkers. These results are in line with those previously reported in a study including European workers from different industrial sectors/activities (Tavares et al. 2022). These workers might be at increased risk of cancer development, considering the recognized association between increased frequencies of MN in blood lymphocytes and an increased risk of cancer development (Bonassi et al. 2007). The correlation between the levels of DNA or chromosomal damage and the urinary Cr concentration is also worth to note, suggesting a link between exposure and early biological effects.

Furthermore, pre-shift urinary chromium (U-Cr) levels were notably higher among the workers compared to the control group, indicating chromium retention within the body (Remy et al. 2021; Santonen et al. 2022). These findings suggest a slow elimination rate for certain inhaled chromium species, as reported by others (Pesch et al. 2018). Previous studies by Scheepers et al. and Pesch et al. also demonstrated a significant association between pre- and post-shift U-Cr levels in welders, implying a slow elimination process (Scheepers et al. 2008; Pesch et al. 2018). Therefore, besides considering the dynamics and availability of chromium species, it's crucial to note that post-shift samples predominantly contain more soluble chromium species excreted in urine compared to less soluble ones (Scheepers et al. 2008).

This research primarily focused on biomonitoring but also incorporated the collection of industrial hygiene samples such as air and hand wipes to complement the study findings (Galea et al. 2021; Santonen et al. 2022). Strong correlations were noted between inhalation and respirable fraction levels of total chromium and Cr(VI) beyond respiratory protective equipment (RPE), suggesting that task-related activities heightening total chromium exposure may also elevate exposure to Cr(VI). Thus, even in instances where measuring Cr(VI) directly might not be feasible, the commonly utilized measurement of total chromium in air offers insights into the presence and progression of Cr(VI) exposure.

When comparing the observed air concentrations of Cr(VI) with the BOEL established under EU Directive 2004/37/EC at 10 μg/m^3 (8h TWA), it's evident that for painting (n = 7) in the inhalable fraction, the median did not surpass this interim limit of 10 μg/m^3. However,

following the implementation of a more stringent OEL (8-h TWA) at 5 μg/m³ by 17 January 2025, the median exposure exceeded the prescribed threshold. It is important also to consider the high values measured in this workers group (up to 154.4 μg/m³). All these findings underscore the necessity for enhanced Risk Management Measures to curtail exposure levels, particularly in the case of painting. Although the BOEL for Cr(VI) targets the inhalable dust fraction, it's pertinent to consider the results obtained for the respirable fraction, as these particles deeply penetrate the airways and are eliminated at a slower pace. Moderate correlations were identified between post-shift urinary chromium (U-Cr) levels and chromium (VI) concentrations in both inhalable and respirable air, as well as total chromium in hand-wipe samples. These correlations bolster the recommendation provided by Santonen et al. (2022) to utilize U-Cr as a primary biomonitoring method for assessing Cr(VI) exposure in workplace settings.

Exposure determinants

Biomonitoring also allowed to assess the effectiveness of the risk management measures implemented. This is possible when planning biomonitoring campaigns with a defined purpose such as before and after putting in place risk management measures together with the collection of contextual information concerning the frequency of use of those measures or even difficulties with their use (Viegas et al. 2022; Santonen et al. 2023; Hopf et al. 2024). This is particularly relevant when exposure control depends mainly on PPE (e.g. RPE or gloves).

In painting, the nonuse of RPE (22%) influenced workers' exposure, as shown in Table 4, by a statistically significant effect of RPE use on U-Cr levels. These analyses further support our earlier theory that less frequent use of RPE explains the greater internal exposure of workers to Cr.

While the use of RPE should be the last resource in the hierarchy of controls, the use of PPE such as RPE can be an option to bear in mind as a temporary measure for emergency work or even during a temporary failure of controls where other means of control are not reasonably practicable or available at the moment. Fit testing is also to be considered and should be carried out by a competent person (HSE 2013).

Since most workers (n = 27) used gloves, it was not possible to assess the influence of gloves. Gloves can undeniably protect from chemical exposure by preventing hand contamination, if they are adequate for chemicals, but they can also promote exposure if they are not used adequately or are changed with the frequency (Picheansanthian and Chotibang 2015; Viegas et al. 2020) needed. In line with this, the lower levels observed in painter's hand wipe samples might be explained by the higher frequency of glove use.

Concerning the existence of a dedicated place for storing work clothes, this was related to higher levels of Cr in urine and hand wipes in painting activities (urine sample results). In plating activities, a statistically significant difference was observed despite the low number of workers in the "no" group. This finding may be related to the fact that contaminated work clothes that are stored for use the next day may increase exposure by cross-contamination, e.g. by hand and mouth contact. Painting is recognized as an activity that implies high aerosolization resulting in contamination of the working clothes and PPE that, if not cleaned after use or disposed of, can promote secondary inhalation and dermal exposure. The same reasoning was discussed by Beattie et al., where the existence of PPE lockers and the wearing of workwear at break times were considered the 2 mechanisms that explained the spread of contamination into clean areas such as canteens (Beattie et al. 2017). Thus, explicit procedures on when/which activities imply washing/disposing of the working clothes/PPE combined with more stringent housekeeping measures (e.g. frequent cleaning of storage places for working clothes and workplace surfaces) emerge as fundamental measures for preventing exposure to Cr (Viegas et al. 2022).

Strengths and limitations

In this study, a major lesson learned is the value of collecting contextual data. Although the occupational hygiene dataset available in this study is considered a robust and valuable dataset, as mentioned in Galea et al. (2021), there were some deviations in the procedures for the collection and analysis of occupational hygiene data.

In addition, this study was dedicated to several aspects of the working conditions and provided an important dataset with quantified data (environmental and biological monitoring) at the individual level that were provided to the companies enrolled in the study in an aggregated manner and guaranteed confidentiality.

In this study, it is clearly demonstrated that biomonitoring is a valuable tool for exposure assessment and, even if the exposure levels to Cr(VI) drop as it is promoted and envisaged by the more stringent OELs, biomonitoring still has an important role to play due to the additional information that provides when compared with air monitoring approaches used alone. Indeed, Cr(VI) exposure characteristics follow in most of the reasons that justify the use of biomonitoring as preferred to other exposure assessment approaches, as explained in Hopf et al. (2024).

Moreover, incorporating effect biomarkers offers significant additional value by aiding in the identification of activities posing a heightened risk of long-term disease development among workers. This finding is

particularly relevant when discussing genotoxic carcinogens such as Cr(VI), where it is not possible to derive a health-based OEL and a BOEL is based on risk levels and not on no-effect levels. Our discovery of notably elevated genetic damage in individuals exposed to Cr(VI) occupationally suggests that despite exposure levels falling below the current binding OEL in the EU, Cr(VI) exposure may still pose a health risk.

Conclusions

This work provides biomonitoring data concerning occupational exposure to Cr(VI) that can be used to support the implementation of new and effective risk management measures and evidence-informed policy-making at both national and international levels.

Three main streams of conclusions should be highlighted:

i) Data showed that workers in the assessed occupational settings are still exposed to Cr(VI) even when 2 different regulatory frameworks are in place in the EU to prevent exposure to this carcinogen. Therefore, based on the results obtained, the implementation and enforcement of new regulatory actions should also be considered.
ii) Effect biomarkers results indicated the existence of early genetic damage in cells from workers exposed to Cr(VI), even at low exposure levels, which raises concern about a potential risk of disease development and further supports that the risk management measures in place need to be improved to protect workers' health. The results also highlight the need to update the Cr(VI) occupational limit value as it is being discussed at the European level.
iii) Differentiated data provided by human biomonitoring demonstrated that this exposure assessment tool should be used regularly to perform detailed exposure and risk assessments, and the concomitant use of effect biomarkers provides indications of health risks linked to internal exposure.

Overall, this work reflects the reality of Portuguese workers, in terms of occupational exposure to a recognized carcinogen, in agreement with the findings observed in other countries. The study findings also point to the need, when carcinogenic substances are used and cannot be avoided, e.g. nickel compounds, silica dust, formaldehyde, cytostatic drugs, or when the activities performed or processes used to result in exposure to carcinogens or carcinogenic mixtures, e.g. coke production, iron and steel founding, exposure to engine exhaust, diesel, rubber manufacturing industry, and welding fumes, and in line with the Carcinogens and Mutagens Directive (2004/37/EC), risk management measures should be implemented to reduce exposure to as low a level as is technically possible. This should be the commitment taken by employers, workers, and occupational health professionals.

Interdisciplinary teams developing projects such as HBM4EU contribute effectively to prevent occupational diseases and to support national policies and action plans aiming to promote and maintain workers' health, contributing to decreasing work-related cancer with expected gains in public health.

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Conflict of interest statement

The authors have no relevant financial or nonfinancial interests to disclose.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. Study protocols have been approved by ethical review boards in each of the participating institutions, with the approvals granted before recruiting the study participants. The ethical boards reviewing and approving the study were as follows: Ethical Committees of Lisbon School of Health Technology and National Institute of Health Dr. Ricardo Jorge (Ethics Committee for Health, INSA).

Informed consent

Informed consent was obtained from all subjects that were involved in the study.

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Data availability

The data underlying this article cannot be shared publicly due for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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