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Hexavalent chromium still a concern in Sweden – Evidence from a cross-sectional study within the SafeChrom project

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ABSTRACT

Objectives: Hexavalent chromium (Cr(VI)) is classified as a human carcinogen. Occupational Cr(VI) exposure can occur during different work processes, but the current exposure to Cr(VI) at Swedish workplaces is unknown.
Methods: This cross-sectional study (SafeChrom) recruited non-smoking men and women from 14 companies with potential Cr(VI) exposure ($n = 113$) and controls from 6 companies without Cr(VI) exposure ($n = 72$). Inhalable Cr(VI) was measured by personal air sampling (outside of respiratory protection) in exposed workers. Total Cr was measured in urine (pre- and post-shift, density-adjusted) and red blood cells (RBC) (reflecting Cr(VI)) in exposed workers and controls. The Bayesian tool Expostats was used to assess risk and evaluate occupational exposure limit (OEL) compliance.
Results: The exposed workers performed processing of metal products, steel production, welding, plating, and various chemical processes. The geometric mean concentration of inhalable Cr(VI) in exposed workers was 0.15 μg/m^3 (95% confidence interval: 0.11–0.21). Eight of the 113 exposed workers (7%) exceeded the Swedish OEL of 5 μg/m^3, and the Bayesian analysis estimated the share of OEL exceedances up to 19.6% for stainless steel welders. Median post-shift urinary (0.60 μg/L, 5th-95th percentile 0.10–3.20) and RBC concentrations (0.73 μg/L, 0.51–2.33) of Cr were significantly higher in the exposed group compared with the controls (urinary 0.10 μg/L, 0.06–0.56 and RBC 0.53 μg/L, 0.42–0.72). Inhalable Cr(VI) correlated with urinary Cr ($r_S = 0.64$) and RBC-Cr ($r_S = 0.53$). Workers within steel production showed the highest concentrations of inhalable, urinary and RBC Cr. Workers with inferred non-acceptable local exhaustion ventilation showed significantly higher inhalable Cr(VI), urinary and RBC Cr concentrations compared with those with inferred acceptable ventilation. Furthermore, workers with inferred correct use of respiratory protection were exposed to significantly higher concentrations of Cr(VI) in air and had higher levels of Cr in urine and RBC than those assessed with incorrect or no use. Based on the Swedish job-exposure-matrix, approximately 17 900 workers were estimated to be occupationally exposed to Cr(VI) today.

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Conclusions: Our study demonstrates that some workers in Sweden are exposed to high levels of the non-threshold carcinogen Cr(VI). Employers and workers seem aware of Cr(VI) exposure, but more efficient exposure control strategies are required. National strategies aligned with the European strategies are needed in order to eliminate this cause of occupational cancer.

Abbreviations

8-h TWA	8-h time-weighted average
BLV	Biological limit value
BMI	Body mass index
CI	Confidence interval
CIS	Conical inhalable sampler
Cr	Chromium
Cr(III)	Trivalent chromium
Cr(VI)	Hexavalent chromium
EU	The European Union
EC	European Commission
EPA	Environmental Protection Agency
G-EQUAS	German External Quality Assessment Scheme
GM	Geometric mean
GSP	Gesamtstaubprobenahme sampler
HBM4EU	The European Human Biomonitoring Initiative
IARC	International Agency for Research on Cancer
ICP-MS	Inductively coupled plasma mass spectrometry
ISCO-08	International Standard Classification of Occupation 2008
JEM	Job-Exposure-Matrix
LEV	Local exhaustion ventilation
LOD	Limit of detection
LOQ	Limit of quantification
MAG	Metal active gas
MIG	Metal inert gas
MMA	Manual metal arc
NIOSH	National Institute for Occupational Safety and Health
OEL	Occupational exposure limit
P5	5th percentile
P25	25th percentile
P75	75th percentile
P95	95th percentile
RBC	Red blood cells
RBC-Cr	Chromium concentration in red blood cells
REACH	The Registration, Evaluation, Authorisation and Restriction of Chemicals
RPE	Respiratory protective equipment
SNI	Swedish Standard Industrial Classification
SOP	Standard operating procedure
SSYK	Swedish Standard Classification of Occupations
TIG	Tungsten inert gas
WBC	White blood cells

1. Introduction

The element chromium (Cr) is primarily present as trivalent chromium (Cr(III)) and hexavalent chromium (Cr(VI)) in occupational settings (Pan et al., 2018). Cr(VI) and its compounds are used in industrial applications like electroplating and chromate production and Cr(VI) can also be formed during steel production and welding (IARC, 2012). Occupational exposure to Cr(VI) can occur through inhalation, dermal contact and hand-to-mouth exposure (Beattie et al., 2017).

Cr(VI) is considered to be thousand times more toxic than Cr(III) due to its oxidizing ability and high solubility, resulting in increased cell membrane permeability (Saha et al., 2011; ATSDR, 2011). Cr(VI) is classified as a human carcinogen (Group 1) by the International Agency for Research on Cancer (IARC) and causes lung cancer (IARC, 2012). Epidemiological evidence suggests that workers exposed to Cr(VI) also have an increased risk of nose and nasal sinus cancer, and non-cancer effects, especially in the respiratory and reproductive systems, skin, kidneys, stomach and liver (IARC, 2018). Cr(VI) is considered a non-threshold carcinogen and the guiding principle is that the exposure should be 'as low as reasonably achievable' (Mahiout et al., 2022). It is worth noting that Cr(VI) exposed workers can be occupationally exposed to other toxic metals, such as nickel and lead, and co-exposure could play a crucial role in development of adverse health effects (Muller et al., 2022).

Exposure to Cr(VI) is often assessed by measurements in air, urine or blood (Viegas et al., 2022). Urinary Cr is a common biomarker with a half-life of approximately 7 h and post-shift urine is often compared with pre-shift urine to identify possible work-related Cr exposure (Viegas et al., 2022). However, urinary Cr represents total Cr and is therefore not specific for occupational Cr(VI) exposure (Viegas et al., 2022; Welinder et al., 1983). Red blood cells (RBC) take up Cr(VI) but not Cr(III), and the Cr concentration in RBC (RBC-Cr) thus reflects the amount of Cr(VI) that has entered the bloodstream in its non-reduced form (Goldoni et al., 2010a). Since Cr is bound to haemoglobin within the RBC, it is assumed that the half-life of RBC-Cr in humans corresponds to the half-life of RBC (Franco, 2012; Ndaw et al., 2022). It is suggested that RBC-Cr values reflect the exposure to Cr(VI) over the past four months (Ndaw et al., 2022).

In the European Union (EU), the use of Cr(VI) compounds is authorized under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation (Viegas et al., 2022). The current 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, the OEL will be 5 μg/m^3 (8-h TWA) (Santonen et al., 2022). In France and the Netherlands, OELs of 1 μg/m^3 have already been set for Cr(VI) (Viegas et al., 2022). Denmark has also implemented an OEL of 1 μg/m^3 and will consider lowering it further to 0.25 μg/m (Beattie et al., 2017; Santonen et al., 2022; Beskæftigelsesministeriet, 2020). It has been estimated that exposure to air concentrations of 5 μg/m^3, the current OEL in Sweden, corresponds to 20 extra lung cancer cases per 1000 exposed workers after 40 years of occupational exposure (i.e. lifetime risk) (C. European, 2017). In Germany and the Netherlands, acceptable risk is considered to be an additional risk of <4 cases per 100,000 after 40 years, and tolerable risk (during a transitional period) is considered to be < 4/1000 (Ding et al., 2014). In the 1990s, it was estimated that around 21 000 workers in Sweden were occupationally exposed to Cr(VI) (Kauppinen et al., 2000). However, despite the strong carcinogenicity of Cr(VI), it is not known how many workers are exposed today and at what levels.

In order to characterize and minimize occupational Cr(VI) exposure and toxicity in Sweden, all seven Occupational and Environmental Medicine clinics in Sweden, in collaboration with the Danish National Research Centre for the Working Environment and the Finnish Institute of Occupational Health, initiated the SafeChrom project. Specifically, SafeChrom aims to: 1. characterize Cr(VI) exposure at different workplaces by air monitoring of inhalable Cr(VI) and biomonitoring of Cr in urine and RBC and to identify adequate monitoring methods for Cr (VI) exposure; 2. investigate toxicity of current exposure levels by measuring early markers of Cr(VI)-related chromosome damage and DNA modifications; 3. evaluate the perception of regulations and risk management strategies at workplaces using Cr(VI); 4. take advantage of the Nordic expertise and increase the study base for examining occupational Cr(VI) exposure; 5. develop guidelines for minimizing Cr(VI) exposure. Here we present the results of the first study aim of SafeChrom.

2. Material and methods

2.1. Study participants and recruitment

This cross-sectional study of Cr(VI) exposure in the Swedish work environment (SafeChrom) was carried out by all seven Occupational and Environmental Medicine clinics in Sweden (Lund, Gothenburg, Linköping, Örebro, Stockholm, Uppsala, and Umeå) in collaboration with their corresponding university divisions. The occupational exposure assessment, along with the sampling of air, blood, and urine were performed by standard operating procedures (SOPs) used by all partners.

The study and the questionnaire were designed to be as similar as possible to The European Human Biomonitoring Initiative (HBM4EU) chromates study protocol (Santonen et al., 2019). The recruitment of study participants in the exposed group was performed between June 2021 and May 2022. Identification of suitable companies was done either by a) request of interest sent out to customers of Cr analyses (mainly occupational health care services or occupational safety and health consultants distributed all over Sweden) informing about the study or b) occupational hygienists at each clinic that identified companies with potential Cr(VI) exposure in the respective region. Recruitment was performed by each clinic in a harmonized way: 1. occupational hygienists contacted the companies via e-mail or phone, and invited the companies to join the project; 2. managers received an information leaflet about the background and aim of the project and the sampling plan; 3. managers informed employees about the study and identified workers willing to participate in the project; 4. a work site visit was conducted before the measurements to plan the sampling and to provide further information about the study; and 5. finally, a visit was scheduled to the company for air measurement, along with collecting blood and urine samples from workers who agreed to participate. Biological sampling was performed when the study participants had worked for at least three previous consecutive days (for those who worked Monday to Friday, sampling was carried out on Wednesday at the earliest).

Controls were recruited between March 2022 to October 2022 from occupational groups that were considered to have the same gender, a similar socioeconomic status, education, and exposure to physical workload but no genotoxic exposures (e.g. from metals, particles or organic chemicals) as exposed workers. The recruitment procedure of controls was the same as for the exposed workers. The sampling for controls was the same as for the exposed workers except that no air measurement was performed, and biological sampling was possible each working day. The recruitment of controls took place in southern and middle Sweden.

The inclusion criteria for the exposed workers were potential exposure to Cr(VI), being 20–68 years of age, and non-smoker >6 months (as tobacco smoke may contain Cr(VI) (Rowbotham et al., 2000)). The inclusion criteria of the control group were the same as the exposed group except that they should not have a potential exposure to Cr(VI) or other genotoxic agents via work. All study participants answered the same questionnaire, except for questions relating to work tasks that differed between exposed workers and controls. All study participants gave informed written consent to participate in the study. The study was approved by the Swedish Ethical Review Authority (Dnr 2021-00641).

2.2. Categorisation of companies and work tasks for exposed workers

Based on the expertise of the occupational hygienists, a categorisation of the companies was carried out according to the Swedish Standard Industrial Classification (SNI 2007). In addition, companies were categorised into four groups: manufacture/processing of metal products, steel production, bath plating and non-categorised (two companies that could not be classified into any of the previous categories) (Supplementary Table 1). One of the included companies had two different divisions and was thus categorised into both steel production and manufacture/processing of metal products. Based on the expertise of the occupational hygienists and the work tasks performed on the sampling day, a descriptive categorisation of the work tasks was carried out according to the Swedish Standard Classification of Occupations 2012 (SSYK 2012, 4-digit), which is based on the International Standard Classification of Occupation 2008 (ISCO-08). In addition, work tasks were categorised into four groups: welding, process operation, machining, and others (Supplementary Table 2).

2.3. Air monitoring

2.3.1. Sampling

The inhalable Cr(VI) fraction was collected using a conical inhalable sampler (CIS) (Casella, Rutland, United States) mounted with a 37 mm polyvinyl chloride filter, pore size 5 μm (Merck Millipore, Cork, Ireland). Battery-powered sampling pumps were used to provide a flow rate of 3.5 L/min, which was regularly checked with a digital flow meter before, during, and after sampling. Due to a temporary shortage of CIS from Casella, another type of CIS was used: ten individuals were sampled with a Gesamtstaubprobenahme sampler (GSP) mounted with the same filter and run at the same flow rate. Measurements were generally performed during full-shift work, with an average measurement time of 6.7 h. The sampler was placed within the breathing zone. For workers who were wearing respiratory protection equipment (RPE) (e.g powered air-purifying respirators, full- or half mask, or filtering half mask) during sampling, the air outside the RPE was sampled. At least one field blank was collected per sampling day. If the number of sampled individuals per day exceeded 10, two field blanks were collected. Field blanks were sampled by connecting the sampler to the pump without drawing any air through it whilst mounting and dismounting the equipment used for the participants at the beginning and the end of the day. Field blanks were analysed in parallel with the samples.

2.3.2. Chemical analysis

Filter samples of inhalable Cr(VI) were sent for analysis to the Occupational and Environmental Medicine Laboratory, University Hospital, Örebro. The samples were analysed by a method modified from the National Institute for Occupational Safety and Health (NIOSH) (NIOSH, 2003). The samples were placed in glass tubes and a 5 ml solution containing sodium hydroxide (1 g/L) and sodium carbonate (1.5 g/L) was added to each tube. The filters were then extracted in an ultrasonic bath for 35 min at 40 °C. Solid residues were separated from the samples by centrifugation at 2000 rpm for 10 min. Cationic metals were removed from the samples by solid phase extraction using Dionex OnGuardTM II M columns (Thermo Fisher Scientific, GmbH, Bremen, Germany) and vacuum filtration. The liquid samples were transferred to autosampler vials. Calibration solutions in six different concentrations (30–2000 ng/ml) were diluted from a 1000 μg/ml certified stock solution (Spectrascan, Ski, Norway). The calibration solutions were diluted with the same extraction solution used for the samples. The samples were analysed by ion chromatography with conductivity detection (Thermo Fisher Scientific, GmbH, Bremen, Germany, Dionex ICS-2100). The guard and separation columns used were model Dionex IonPacTM AG15-5 μm and AS15-5 μm, respectively. Ten filter blanks (i.e. non-exposed PVC filters) were extracted and analysed for the calculation of limit of detection (LOD). Mean value and standard deviation were calculated. The LOD was calculated using the following formula: LOD = mean value + 3 × standard deviation. The LOD was 0.08 µg/sample. The laboratory regularly participates in LGC AXIO proficiency testing scheme for air and stack emissions (LGC AXIO PT AIR). During the measurement campaign, proficiency tests showed good agreement between measured Cr(VI) concentrations in quality control samples and assigned concentrations.

Due to delayed delivery of solid phase extraction columns, four samples were analysed by ALS Scandinavia AB in Luleå by a method based upon SS-EN ISO 17294-2:2016 (CEN) and EPA Method 200.8:1994 (EPA US, 1994) using inductively coupled plasma mass spectrometry (ICP-MS) after alkaline leaching of Cr(VI) according to ISO 15192:2006 (CEN, 2006). The ALS laboratory used the limit of quantification (LOQ) as limit of the applied method and six filter blank samples were extracted and analysed for the calculation of LOQ. Mean value and standard deviation were calculated. The LOD was calculated using the following formula: LOQ = mean value + 10 × standard deviation. The LOQ was 0.3 µg/sample.

2.4. Biological monitoring

2.4.1. Sampling

An informed consent form and a urine sampling kit (including instruction, two acid-washed tubes, and one acid-washed cup) for the pre-shift urine was sent out to every participant before the sampling day. On the day of the visit, trained nurses collected the signed informed consent, the pre-shift urine sample and sampled blood and post-shift urine (after the workers had worked at least 4 h). The biological sampling was performed on the same day as the measurements of inhalable Cr(VI) fraction. Blood samples were collected in four vacutainer tubes (Becton, Dickinson and Company, Plymouth, UK): one sodium-heparin tube for analysis of metals, one lithium-heparin tube for micronuclei, one vacutainer EDTA tube for other biomarkers of genotoxicity, and one PAXgene blood RNA tube for RNA (the last three tubes were not included in this study). Urine and blood samples were kept at 4 °C and transported to the laboratory at the Div. of Occupational and Environmental Medicine, Lund University. After separating blood cells and plasma from whole blood in the sodium-heparin tubes (details described below), all blood and urine samples were stored at −20 °C until analysis.

In the exposed group, three participants abstained from providing blood samples, and one abstained from providing pre-shift urine sample.

2.4.2. Chemical analysis

Tubes and tips used in the chemical analysis were washed with acid (5% HNO_3 and 5% HCl) to remove potential metal contamination. To avoid haemolysis, plasma and RBC separation was conducted following the method described by Devoy et al. (2016). Blood samples were separated for 10 min at 1300 g, and the plasma supernatant was removed. After the separation, a wash step was conducted by adding 0.9% isotonic saline (with a volume corresponding to the initial blood volume) to the RBC, gently rocked for 5–10 min, separated for 10 min at 1300 g, whereafter the supernatant was removed. The wash was performed two more times before the RBC were processed for metal analysis.

Cr(VI) exposed workers can be exposed to other toxic metals during work, thus manganese, cobalt, nickel, copper, zinc, selenium, cadmium, antimony, mercury, and lead were measured along with Cr. All determinations were performed with ICP-MS (iCAP Q, Thermo Fisher Scientific, Bremen, accuracy GmbH) equipped with collision cell with kinetic energy discrimination and helium as collision gas. A sample volume of 100 µL (RBC) and 250 µL (urine) was diluted 20 times with an alkaline solution according to Barany et al. (1997) and analysed in peak-jumping mode, with scandium, rhodium, terbium, and iridium used as internal standards. The detection limits were calculated as three times the standard deviation (SD) of the blank and were 0.20 µg/L both for Cr in blood and urine. All analysed samples were prepared and measured in duplicate, and the mean value was used in subsequent statistical analyses. During the measurement campaign, the laboratory participated in the German External Quality Assessment Scheme (G-EQUAS), with good agreement between obtained element concentrations in quality control samples used and expected values. The analytical accuracy was verified towards certified reference materials from G-EQUAS and SERO AS, Billingstad, Norway (Seronorm). The results (µg/L, mean ± SD) obtained for Seronorm (Lot. 2011920) were for Cr in blood 0.63 ± 0.06 vs. recommended 0.48–0.75 and for G-EQUAS Cr in blood (Lot. R64 1A) 1.80 ± 0.21 (n = 49) vs. recommended 1.1–2.3. For G-EQUAS Cr in urine (Lot. R64 8A and R64 2A) the results obtained were 0.22 ± 0.03 vs. recommended 0.16–0.34 and 3.67 ± 0.28 vs. recommended 2.8–4.0, respectively. Quality data for the other metals analysed are shown in Supplementary Table 3.

2.5. Measurement of creatinine and density in urine

Density and creatinine were measured in all urine samples for correction of dilution. The density was measured with a hand-held refractometer (30PX; Mettler Toledo, USA). The density adjustment was calculated using the following formula: $C_{(density\text{-}adjusted)} = C \times (1-\rho_{mean})/(1-\rho_{sample\ density})$, where C = the determined Cr concentration in the sample, ρ_{mean} = the mean of the urinary density of all participants, and $\rho_{sample\ density}$ = the density of the urine sample. Creatinine was measured with Atellica (Siemens Healthcare Diagnostics, Munich, Germany; accredited analysis) at the Clinical Chemistry University Hospital, Lund. Since creatinine excretion often is higher in men (due to gender differences in muscle mass (Thomas et al., 2012)), density adjustment was more appropriate for the correction of urinary dilution. Nevertheless, we also present the creatinine-adjusted urinary Cr for comparison with other studies.

2.6. Questionnaire and occupational hygienist protocol

A questionnaire was sent to each participant in advance. On the day of the visit, trained nurses checked that the questionnaires were completed. The questionnaire contained questions about birth year, height, weight, residential area, smoking (current smoker, former smoker, party smoker, and non-smoker), use of electronic cigarettes and snuff, consumption of alcoholic beverages, coffee, tea, energy drinks, and supplements, diet, implants, and any leisure activities that may result in exposure to Cr (e.g. welding, spray painting and metal work). Moreover, the questionnaire inquired about the respondent's working situation, including working years, working tasks, working place (outdoor or indoor), working shift, and hygiene options (changing rooms and opportunity to shower and wash hands). In addition, the questionnaire given to the exposed group enquired about the details of their working tasks (i.e. "plating", "painting", "grinding", "welding", "thermal spraying", "metal production", and "working in close connection with the tasks above"), working hour (5 categories, from never to about 3/4 of the working time), performing tasks manually or automatically, and use of personal protective equipment (nothing, compressed air or fresh air supplied breathing apparatus, fan-assisted respiratory protection, reusable respirators (half mask or full mask), disposable protection (filtering half mask), full protective overalls, gloves, apron), and use of stationary fume extraction.

During air sampling, the occupational hygienist filled in an observation protocol for the workplace, as well as an individual observation protocol for each sampled individual. The occupational hygienist asked about details of the company (number of employees, production, number of Cr exposed workers, working shift and working hours), production conditions during measurement (3 categories; low, normal, high), description of the design of the premises, general ventilation (mechanical, windows, doors, and no ventilation), and process ventilation (containment of emission source and point extraction at emission source) were recorded. Further, the occupational hygienist made an ocular assessment of the use and standard of local exhaustion ventilation (LEV) and RPE on sampling day. Based on these ocular observations LEV was categorised as either "inferred acceptable" or "inferred non-acceptable" while use of RPE was categorised as "yes and correctly", "yes but not correctly" or "no". Acceptable LEV was defined as working conditions inferred as providing air quality in which additional RPE was not needed. The workplaces where LEV was considered as not adding additional value beyond the general ventilation were also categorised as "inferred acceptable" LEV for the analyses herein. Inferred correct use of RPE was defined as: 1. using RPE when needed; 2. using the correct type of filter; 3. regular filter changes, and 4. correct storage of RPE when not used.

2.7. Risk assessment

In order to assess risk and evaluate OEL compliance, the Bayesian tool Expostats (Tool 1) was employed to assess the expected extent of OEL exceedances in the sampled population (Lavoué et al., 2019). The occupational and workplace categories were used in the present work to identify similar exposure groups. The category 'other work tasks' was not included as it does not represent the same work tasks across companies. We evaluated compliance with the current Swedish OEL (5 μg/m^3) and also estimated the share that would be expected to exceed 1 μg/m^3 and 0.25 μg/m^3, respectively. We defined overexposure as 5% of the population exceeding the exposure limit, and evaluated the probability of overexposure using the thresholds 30% (as proposed by e.g. CEN 2019 (CEN).

The estimations of workers exposed to Cr(VI) in Sweden was performed using a job-exposure-matrix (JEM) linked to register data on occupation from Statistics Sweden. The JEM was originally based on the Finnish JEM (Kauppinen et al., 1998) and later updates (Kauppinen et al., 2014). The estimated prevalence is for workers ever exposed during a year, meaning that some of them can have very low prevalence, maybe one time per year. Adaptions to Swedish working conditions have been made by Wiebert and Tinnerberg et al. (Gustavsson et al., 2022).

2.8. Statistical analysis

For inhalable Cr(VI), 51 samples analysed in Örebro (concentrations below the LOD (0.08 μg/sample)) and 2 samples analysed in Luleå (below the LOQ (0.3 μg/sample)) were substituted by values equal to half of the LOD (0.04 μg/sample) or LOQ (0.15 μg/sample) (Hornung and Reed, 1990). Age was calculated based on birth and recruitment dates. Body mass index (BMI) was obtained using the formula BMI = weight in kilograms/(height in meters) (IARC, 2012). Descriptive statistics including geometric mean (GM), 95% confidence interval (CI), median, 5th and 95th percentiles (P5, P95) were calculated. Mann-Whitney U test, Kruskal-Wallis test and Wilcoxon signed ranks test were used to compare differences between continuous variables. The Chi-square test and Fisher's exact test were used to compare differences in distribution of categorical variables between groups. Spearman's correlation was used to examine correlations between variables.

Multiple regression models were built to evaluate differences in Cr concentration between the exposure group and controls, adjusting for potential covariates and confounders. Possible confounders of exposure to Cr(VI) or Cr(III) were: smoking (Pääkkö et al., 1989), coffee (Olechno et al., 2021) and tea (Barman et al., 2020) drinking, diet (Smart and Sherlock, 1985), supplement (Saper et al., 2004), implant (Campbell and Estey, 2013) and leisure activity with Cr. Three models were built: model 1 without adjustment; model 2 adjusted for variables that had a significant difference in the bivariate analysis between exposed workers and controls; model 3 adjusted for all potential confounders. To deal with skewed data, log transformation was used for the urinary and RBC Cr.

The statistical analyses above were conducted with SPSS 28.0 (IBM SPSS Statistics, NY) and statistical significance (two-tailed) was denoted at P value < 0.05.

3. Results

3.1. Characteristics of the study participants

A total number of 44 companies with potential occupational exposure to Cr(VI) were contacted by the occupational hygienists, and 14 companies, geographically distributed from north to south of Sweden, agreed to participate (company participation rate 31.8%). Companies that did not participate did either: 1. not reply to the occupational hygienists; 2. not want to participate; or 3. not fulfill the inclusion criteria because of ceased or sporadic exposure to Cr(VI). The tasks performed by workers at the participating companies included production of stainless steel, welding, grinding, plating, surface treatment, and various chemical processes. The volunteers in the control group were recruited from one agricultural operator, one care home, two construction companies, one storage company, and one restaurant (company participation rate 66.7%).

One hundred and sixteen air samples were collected, but one pump did not work, thus 115 valid inhalable Cr(VI) results were obtained. Three exposed workers only provided air samples, and the remaining 113 workers completed the questionnaire and donated biological samples. Categorisation, number of individuals for each company, and their work tasks are shown in Table 1.

The demographic characteristics, lifestyle, and work-related factors of the exposed workers and controls are summarised in Table 2. The exposed workers and controls were similar in BMI, smoking history, coffee drinking, use of supplements, presence of implants, and leisure activities with Cr. However, significant differences ($P < 0.05$) were found with respect to age, sex, and tea drinking between the two groups. Participants in the exposed group were younger, more likely to be male and less likely to drink tea than those in the control group. There were 35.4% exposed workers with inferred non-acceptable LEV, and 54% did not use RPE on the sampling day. Fifteen exposed workers (13.2%) had non-acceptable LEV and did not use RPE.

3.2. Cr(VI) in air

The inhalable Cr(VI) concentrations are presented in Table 3. There were 74 samples below 0.25 μg/m^3, 20 samples between 0.25 and 1 μg/m^3, 13 samples between 1 and 5 μg/m^3 and eight samples higher than 5 μg/m^3 (Fig. 1A). The GM and 95% CI of inhalable Cr(VI) in the exposed group were 0.15 and 0.11–0.21 μg/m^3, but the P95 was 8.03 μg/m^3 (Table 3). At company level, steel production had the highest GM and non-categorised companies had the lowest ($P < 0.05$). In relation to work tasks, process operators had the highest GM, and machining workers the lowest GM, but no significant difference was found between work tasks (Table 3 and Fig. 1B). Workers with inferred non-acceptable LEV were exposed to around two times higher levels of inhalable Cr(VI) compared with those with inferred acceptable LEV ($P < 0.05$), and workers with inferred correct use of RPE on the sampling day were exposed to significantly higher inhalable Cr(VI) compared with those who did not use RPE or had inferred incorrect use ($P < 0.001$) (Fig. 2A). Stratified analysis showed that among workers with acceptable LEV, a significant difference in inhalable Cr(VI) was found between different usage of RPE. A significant difference was also found between different usage of RPE among the workers with non-acceptable LEV (Supplementary Fig. 1A).

3.3. Risk assessment

Table 4 shows the estimated likelihood of overexposure when using the Bayesian analysis performed by Expostats. The estimated fractions of exceedances over the Swedish OEL ranged from 0.02 % for machining in

Table 1
Categorisation in SafeChrom of 14 companies (15 work sites) and work task for individuals (n = 116, exposed group) for whom air sampling was performed.

SafeChrom Categorisation	Companies[a] n	Work task on sampling day				Total individuals n
		Welding	Process operation	Machining	Others	
Manufacture/processing of metal products	7	32	14	6	6	58
Steel production	3		28		4	32
Bath plating	3		9	5	4	18
Non-categorised[b]	2		7		1	8
Total	15	32	58	11	15	116

[a] One company with two different work sites was categorised into both steel production and manufacture/processing of metal products.
[b] Two companies that could not be classified in manufacture/processing of metal products, steel production or bath plating were classified as non-categorised (details in Supplementary Table 1).

Table 2
Characteristics of the study groups in SafeChrom.

	Exposed group n = 113	Controls group n = 72	*P*
Age, median (P5, P95)	39 (21.7, 60.3)	43.5 (27.7,60.4)	0.016[a]
Female, n (%)	15 (13.3)	22 (30.6)	<0.001[b]
BMI[d], median (P5, P95)	27.9 (20, 37.6)	27.2 (20.6, 35.1)	0.368[a]
Smoking, n (%)			0.854[c]
Never smoker	68 (60.2)	45 (62.5)	
Previous smoker	35 (31)	23 (31.9)	
Party smoker	6 (5.3)	2 (2.8)	
Current smoker	4 (3.5)	2 (2.8)	
Coffee drinking (yes/no), n (%)	96/17 (85/15)	56/16 (77.8/22.2)	0.24[b]
Tea drinking (yes/no), n (%)	35/77 (31.9/68.1)	34/38 (47.2/52.8)	0.042[b]
Diet (mix, vegetarian, vegan), n (%)	113/0/0 (100/0/0)	70/1/1 (97.2/1.4/1.4)	0.205[c]
Supplement (yes/no), n (%)	32/81 (27.4/72.6)	21/51 (29.2/70.8)	1[b]
Implant (yes/no), n (%)	11/102 (11.5/88.5)	12/60 (16.7/83.3)	0.177[b]
Leisure activity with Cr (yes/no), n (%)	10/103 (8.8/91.2)	4/68 (5.6/94.4)	0.571[b]
LEV[e] (inferred acceptable/non-acceptable), n (%)	73/40 (64.6/35.4)		
RPE[f] (yes and correctly/yes but not correctly/no), n (%)	30/22/61 (26.5/19.5/54)		

[a] Mann-Whitney *U* test.
[b] Chi-square test.
[c] Fisher's exact test.
[d] BMI, body mass index.
[e] LEV, Local exhaustion ventilation.
[f] Using respiratory protective equipment (RPE) on sampling day.

Table 3
Concentrations of inhalable hexavalent chromium (Cr(VI); μg/m^3) measured in the exposed group and stratified by company and work task.

	<LOD/LOQ n (%)	GM (CI)[b,c]	Median	P5, P95	*P*
Exposed group, N = 115	54 (47)	0.15 (0.11–0.21)	0.1	0.02, 8.03	
Company					0.001[a]
Manufacture/processing of metal products, n = 57	33 (57.9)	0.12 (0.07–0.21)	0.03	0.02, 13.58	
Steel production, n = 32	8 (25)	0.30 (0.17–0.55)	0.25	0.03, 9.78	
Bath plating, n = 18	7 (38.9)	0.15 (0.07–0.29)	0.10	0.03, 1.92	
Non-categorised, n = 8	6 (75)	0.04 (0.02–0.08)	0.02	0.02, 0.28	
Work task					0.151[a]
Welding, n = 31	15 (48.4)	0.17 (0.08–0.37)	0.10	0.02, 14.73	
Process operation, n = 58	22 (37.9)	0.19 (0.12–0.31)	0.16	0.02, 6.93	
Machining, n = 11	8 (72.7)	0.05 (0.03–0.11)	0.04	0.02, 0.44	
Others, n = 15	9 (60)	0.09 (0.04–0.21)	0.04	0.02, 2.55	

[a] Kruskal-Wallis test.
[b] GM, Geometric mean, CI: 95% confidence interval of the geometric mean.
[c] Concentrations below the limit of detection (LOD) and limit of quantification (LOQ) were substituted by a value equal to half of the LOD/LOQ.

manufacture/processing to 8.8 % for welding in manufacture/processing with the 95% credible interval ranging up to 19.6% for the welders. Only three groups had less than 30% probability of overexposure of the Swedish OEL (shown by the shading in Table 4), defined as 5% or more exceeding the OEL. All groups had more than 30% probability of overexposure for the upcoming Danish OEL (0.25 μg/m3).

In order to identify how many workers are at risk for exceeding the Swedish OEL, the total number of workers exposed to Cr(VI) in Sweden was estimated. Initially, different branch organizations were contacted but no information on numbers of exposed workers could be retrieved. Thus, estimations were done using the Swedish JEM: in 2021, approximately 16 000 men and 1900 women distributed within 14 different occupations were estimated to be exposed to Cr(VI). Among those, 2570 were welders.

3.4. Cr in urine and red blood cells

The Cr concentrations in urine and RBC are presented in Table 5. Both pre-shift and post-shift urinary Cr in the exposed group were significantly higher compared with controls ($P < 0.001$). In the exposed group, but not among the controls, Cr concentrations in after-work urine were statistically significantly higher than in the pre-shift urine. In addition, the difference between post-shift and pre-shift urinary Cr concentrations in the exposed group were significantly higher than the controls (Supplementary Table 4). The median RBC-Cr in the exposed group was significantly higher than in the controls.

The workers in non-categorised companies had the lowest post-shift urinary Cr/density and RBC-Cr, while those working in steel production had the highest urinary and RBC Cr ($P < 0.01$). Among different work tasks, machining workers had the lowest post-shift urinary Cr/density. It was significantly lower than the welders, but non-significantly higher than the controls ($P = 0.068$). For RBC-Cr, machining workers had significantly higher concentrations than the controls, but not significantly different from exposed workers doing other work tasks (Fig. 1C–D).

Regarding using LEV and RPE, urinary and RBC Cr concentrations showed a similar trend as the inhalable Cr(VI). Workers with inferred non-acceptable LEV had higher urinary and RBC concentrations than those with inferred acceptable LEV. Contrarily, workers who were assessed to use RPE correctly on the sampling day had higher concentrations of Cr in urinary and RBC than workers who did not (Fig. 2B–C). Stratified analysis for acceptable and non-acceptable LEV, showed that

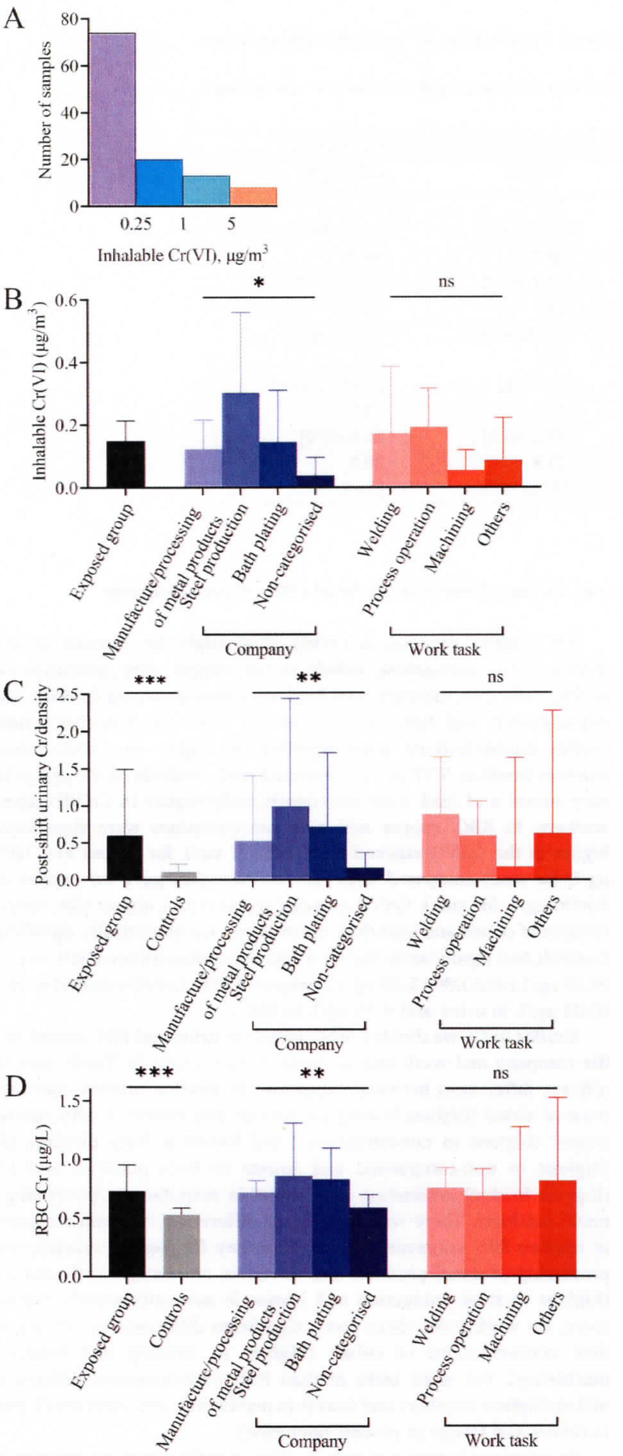

Fig. 1. Inhalable hexavalent chromium (Cr(VI)), urinary and red blood cells (RBC) Cr in controls and exposed workers across company and work task. A. Frequency distribution histogram for inhalable Cr(VI). B. Inhalable Cr (VI). Kruskal-Wallis Test, $^*P < 0.05$. C. Post-shift urinary Cr/density. Kruskal-Wallis Test and Mann-Whitney U test, $^{**}P < 0.01$, $^{***}P < 0.001$. D. RBC-Cr. Kruskal-Wallis Test and Mann-Whitney U test, $^{**}P < 0.01$, $^{***}P < 0.001$. The data are presented as geometric mean and 95% CI for inhalable Cr(VI), median and interquartile range for post-shift urinary Cr/density and RBC-Cr. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

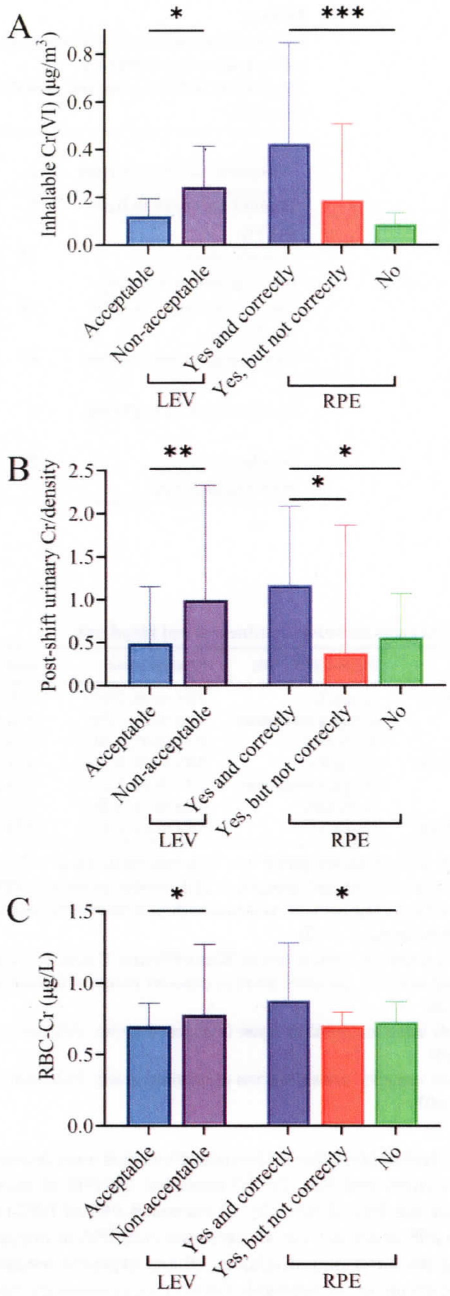

Fig. 2. Inhalable hexavalent chromium (Cr(VI)), urinary and red blood cells (RBC) Cr in exposed group according to the local exhaustion ventilation (LEV) and using respiratory protective equipment (RPE). A. Inhalable Cr(VI). B. Post-shift urinary Cr/density. C. RBC-Cr. Mann-Whitney U test, $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. The data are presented as geometric mean and 95% CI for inhalable Cr(VI), median and interquartile range for post-shift urinary Cr/density and RBC-Cr. LEV and RPE centered under inferred acceptable/non-acceptable and yes, and correctly/yes, but not correctly/no, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

among workers with acceptable LEV, there were less pronounced differences in urinary and RBC Cr between usage of RPE. However, with non-acceptable LEV, workers using RPE correctly still showed the highest urinary and RBC Cr (Supplementary Figs. 1B–C).

When urinary and RBC Cr concentrations were compared to the P95

Table 4
Estimated exceedance fractions of hexavalent chromium for 5, 1 and 0.25 μg/m^3 across the different exposure groups using Expostats.
The shading indicates that the probability of overexposure (defined as an exceedance fraction >5%) is more than 30%.

Work task across company	n	Estimated exceedance fraction % [95% credible interval] 5 ug/m^3	1 ug/m^3	0.25 ug/m^3
Process operators in bath plating	8	0.2 [7.4E-5, 6.7]	5.2 [0.3, 26.7]	32 [11.3, 60.1]
Process operators in manufacture/processing	14	8.5 [1.8, 24.6]	20.6 [7.9, 41.3]	36.2 [17.7, 58.2]
Process operators in steel production	28	7.0 [2.1, 17.1]	26 [14.8, 40.4]	53.2 [37.8, 68.3]
Machining in manufacture	6	0.02 [8.4E-9, 4.9]	0.4 [1.7E-4, 11.4]	3.0 [5.6E-2, 25.0]
Machining in bath plating	5	0.8 [1.4E-4, 22.4]	7.8 [0.2, 43.3]	30.7 [6.5, 69.0]
Welding in manufacture/proc.	29	8.8 [3.1, 19.6]	21.8 [11.6, 35.6]	38.8 [24.9, 54.2]

Table 5
Chromium (Cr) concentration in urine and red blood cells.

	Median (P5, P95)	Exposed group	Control group
Pre-shift urine[a]	Cr (μg/L)	0.54 (0.08, 2.91)[d]	0.10 (0.01, 0.45)
	Cr (μg/g creatinine)	0.33 (0.05, 1.75)[d]	0.08 (0.01, 0.54)
	Cr/density	0.51 (0.07, 2.44)[d]	0.10 (0.01, 0.84)
Post-shift urine[b]	Cr (μg/L)	0.55 (0.10, 3.83)[d, e]	0.11 (0.04, 0.30)
	Cr (μg/g creatinine)	0.41 (0.08, 2.12)[d, g]	0.10 (0.03, 0.58)
	Cr/density	0.60 (0.10, 3.20)[d, f]	0.10 (0.06, 0.56)
Red blood cells[c]	Cr (μg/L)	0.73 (0.51, 2.33)[d]	0.53 (0.42, 0.72)

[a] Pre-shift urine (exposed group n = 112, control group n = 72).
[b] Post-shift urine (exposed group n = 113, control group n = 72).
[c] Red blood cells sample was collected with post-shift urine (exposed group n = 110, control group n = 72).
[d] Exposed group vs. control group, Mann-Whitney *U* test, $P < 0.001$.
[e] Post-shift urine vs. pre-shift urine in exposed group, Wilcoxon signed ranks test, $P < 0.05$
[f] Post-shift urine vs. pre-shift urine in exposed group, Wilcoxon signed ranks test, $P < 0.01$
[g] Post-shift urine vs. pre-shift urine in exposed group, Wilcoxon signed ranks test, $P < 0.001$

of controls (reference value), 42 exposed workers were below the P95 of controls' urinary and RBC Cr; 10 exceeded the P95 of urinary Cr but were below the P95 of RBC-Cr; 13 exceeded P95 of RBC-Cr but were below the P95 of urinary Cr; 45 exceeded both P95 of urinary and RBC Cr. Among the latter 45 individuals, 15 had exposure measurements of less than 0.25 μg/m^3 of inhalable Cr(VI) (Supplementary Table 5).

3.5. *Inhalable Cr(VI), urinary and RBC Cr in welders*

Four types of welding processes (manual metal arc (MMA), metal active gas (MAG), metal inert gas (MIG) and tungsten inert gas (TIG)) were performed by 30 welders, including 14 welders that performed more than one type of welding (data not shown). The most common welding process reported was TIG (n = 24). Workers using TIG had the lowest level of inhalable Cr(VI) (GM 0.11 μg/m^3) and workers welding using MMA had the highest (GM 1.13 μg/m^3) ($P = 0.02$). The same pattern was found in urinary and RBC Cr: workers using TIG had the lowest (median 0.54 and 0.74 for urinary and RBC Cr, respectively) and workers using MMA had the highest (median 1.45 and 0.82 for urinary and RBC Cr, respectively), but without significant difference between types of welding ($P = 0.41$ for urinary Cr and $P = 0.33$ for RBC-Cr).

3.6. *Further elements in red blood cells and post-shift urine*

For workers exposed to Cr(VI), they might be exposed to other metals. Hence manganese, cobalt, nickel, copper, zinc, selenium, cadmium, antimony, mercury, and lead were also measured in urine (density-adjusted) and RBC (Supplementary Table 6). Post-shift urinary copper concentrations were significantly higher in Cr(VI)-exposed workers (median 9.77 μg/L) compared with controls (8.41 μg/L). Urinary nickel and lead were non-significantly higher in Cr(VI)-exposed workers. In RBC, copper and zinc concentrations were significantly higher in the Cr(VI)-exposed workers (571 μg/L for copper and 10728 μg/L for zinc) compared with the controls (525 μg/L for copper and 10496 μg/L for zinc). Cr(VI)-exposed workers had higher RBC concentrations of cobalt and lead than controls, but not statistically significant. Controls had significantly higher antimony concentrations both in urine (0.57 μg/L) and RBC (5.30 μg/L) compared with Cr(VI)-exposed workers (0.08 μg/L in urine and 4.46 μg/L in RBC).

Similar to Cr, we divided other metals in urine and RBC according to the company and work task (Supplementary Table 7). There were significant differences between companies in median urinary concentrations of nickel (highest in steel production and lowest in bath plating), copper (highest in non-categorised and lowest in bath plating), zinc (highest in non-categorised and lowest in bath plating), and lead (highest in steel production and lowest in manufacture/processing of metal products. There were significant differences between companies in median RBC concentrations of antimony (highest in manufacture/processing of metal products and lowest in non-categorised) and lead (highest in steel production and lowest in non-categorised). Furthermore, for work tasks, there was a significant difference in urinary median concentrations of cobalt (highest in welding and lowest in machining). For work tasks median RBC concentrations differed for nickel (highest in others and lowest in machining) and mercury (highest in others and lowest in process operation).

Correlations between metals in RBC in Cr(VI)-exposed workers are presented in Supplementary Fig. 2. The strongest correlations were found between cobalt and nickel ($r_S = 0.53$). Positive correlations between zinc and copper as well as between zinc and selenium were also observed ($r_S = 0.46$ and $r_S = 0.44$, respectively). The strongest correlation with Cr was observed with nickel ($r_S = 0.37$) and other moderate correlations were found between Cr and cobalt, copper, zinc, selenium and lead ($0.2 < r_S < 0.4$).

3.7. Correlations between exposure biomarkers and multivariate analysis

There were strong correlations between pre-shift and post-shift urinary Cr concentrations in exposed workers (r_S = 0.89 both for creatinine-adjusted Cr and density-adjusted Cr, Supplementary Table 8). Inhalable Cr(VI) correlated with urinary Cr (density-adjusted) (r_S = 0.64) and RBC (r_S = 0.53). Urinary Cr (density-adjusted) correlated with RBC-Cr (r_S = 0.72) (Supplementary Table 8 and Supplementary Fig. 3).

In multivariate regression analysis, post-shift urinary and RBC Cr concentrations were significantly higher in the exposed group compared with the controls (Table 6 A, model 1). After adjustment for sex, age and tea drinking (model 2), and further adjustment for smoking, coffee drinking, supplements consumption, implants, and leisure activities exposed to Cr (model 3), the results remained statistically significant. Regression analysis showed that post-shift urinary Cr was higher after welding, process operation and other work tasks, than after machining ($P < 0.05$). Workers doing other work tasks also had higher RBC-Cr than machining workers (Table 6 B). At company level, urinary and RBC Cr for workers in steel production companies were higher than for workers in non-categorised companies ($P < 0.05$) (Table 6 B).

4. Discussion

We have, by short-term and long-term markers of Cr(VI) exposure, identified workplaces and various occupations throughout Sweden where employees are exposed to Cr(VI).

4.1. Comparison with previous studies and risk assessment

Our study was designed to be similar to the HBM4EU chromates study, hence the results of our study and HBM4EU chromates study are comparable. However, it should be noted that differences in methods of air-sampling and biomonitoring could potentially influence comparability with other studies.

Table 6
Linear regression models for logarithm-transformed red blood cells (RBC) and density adjusted post-shift urinary chromium (Cr).

A. Multiple linear regression models with beta coefficient (β) were to evaluate differences between exposed group and controls.

		Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Exposed group[a]	Urinary Cr	1.57 (1.26, 1.89)[b]	1.63 (1.30, 1.96)[b]	1.60 (1.26, 1.93)[b]
	RBCCr	0.40 (0.30, 0.50)[b]	0.41 (0.30, 0.51)[b]	0.40 (0.30, 0.51)[b]

B. Linear regression model with β were to evaluate differences between companies in exposed group. All analyses are unadjusted.

		Urinary Cr β (95% CI)	RBC-Cr β (95% CI)
Work task[c]	Welding	1.15 (0.31, 1.98)[b]	0.08 (−0.19, 0.36)
	Process operation	0.90 (0.12, 1.68)[b]	0.04 (−0.22, 0.30)
	Others	1.06 (0.12, 2.00)[b]	0.33 (0.02, 0.64)[b]
Company[d]	Manufacture/processing of metal products	0.83 (−0.06, 1.71)	0.24 (−0.05, 0.52)
	Steel production	1.42 (0.50, 2.34)[b]	0.53 (0.23, 0.82)[b]
	Bath plating	0.95 (−0.06, 1.94)	0.29 (−0.04, 0.61)

[a] Model 1 is unadjusted; model 2 is adjusted for sex, age and tea drinking; model 3 is adjusted for sex, age, tea drinking, smoking, coffee drinking, using of supplements, implants, and leisure activities exposed to Cr. The reference is controls.

[c] The reference is machining.

[d] The reference is non-categorised companies.

[b] $P < 0.05$

4.1.1. Inhalable Cr(VI)

Airborne Cr has been commonly measured as inhalable total Cr, inhalable Cr(VI), respirable total Cr or respirable Cr(VI). Several studies have measured airborne Cr(VI) without specifying which particle fraction has been measured. A study conducted in Iran reported a mean value of 2 μg/m^3 for welding and 5 μg/m^3 for back welding (welding inside pipes as confined space) (Golbabaei et al., 2012). Studies in India and Egypt measured airborne Cr(VI) in the leather tanning industry with a mean value of 21 μg/m^3 (Balachandar et al., 2010) and 10.4 μg/m^3 (Abdel Rasoul et al., 2017), respectively. HBM4EU carried out a study on occupational exposure to Cr(VI) and involving nine countries (Belgium, Finland, France, Italy, Luxembourg, the Netherlands, Poland, Portugal, and United Kingdom) (Santonen et al., 2022). The median concentration of inhalable Cr(VI) in HBM4EU chromates study (0.43 μg/m^3) was higher compared with our study (0.1 μg/m^3), but their P95 value was lower (5.13 μg/m^3 versus 8.03 μg/m^3). The same trend was also observed if only welders were considered. The median and P95 of inhalable Cr(VI) for welders in HBM4EU chromates study were 0.5 and 4.06 μg/m^3, while in our study they were 0.1 and 14.73 μg/m^3. The lower median value in our study suggests that, on average, the inhalable Cr(VI) concentrations among exposed workers were relatively low in Sweden. However, the higher P95 value indicates a higher upper range of exposure. These studies clearly show that the distribution and range of inhalable Cr(VI) concentrations among Cr(VI) exposed workers vary between different countries, and further, the necessity to perform national exposure assessment.

4.1.2. Risk assessment

In our study, 5 individuals (4.3%) exceeded 10 μg/m^3 of inhalable Cr (VI) (i.e. current EU OEL), 8 (7.0%) exceeded 5 μg/m^3 (the current Swedish OEL), 22 (19.1%) exceeded 1 μg/m^3 (the current Danish, French and Dutch OEL) and 42 (36.5%) exceeded 0.25 μg/m^3 (the expected future Danish OEL). Further, the Bayesian tool Expostats analysis indicates that there is a non-negligible, and often high, probability that the Swedish OEL is exceeded for at least 5% of the occupational groups we investigated, assuming similar conditions as during the performed measurements. However, the broad definitions of and the low number of samples in our similar exposure groups contribute to the variability and hence the high estimates of probability of overexposure.

In the present study, 7% of workers exceeded the current Swedish OEL of 5 μg/m^3 and we estimated that 17 900 workers were exposed to Cr(VI) in Sweden. Therefore, we can speculate that around 1250 workers in Sweden are at risk of exceeding the Swedish OEL (17 900 * 7% ≈ 1250). However, it should be noted that the Swedish JEM includes everyone exposed to Cr(VI) regardless of exposure level. Thus, occupations with low and/or very intermittent exposure are also included. On the other hand, a recent time trend study of exposure to respirable crystalline silica, welding fumes, wood dust, and chlorinated hydrocarbon solvents in Sweden showed that occupational exposures tended to shift from large companies to small companies (Gustavsson et al., 2022). Technological progress and automatization have eliminated many hazards in large companies, however, without supervision by an occupational physician and limited resources for preventive work in many small and middle-sized companies, high-risk workplaces may still prevail (Funke, 2007).

Most participated companies (86%) in our study are considered big companies (more than 100 employees), and this could be the reason that the inhalable Cr(VI) concentrations among exposed workers were relatively low. However, the working situation in small companies and the shifting of the exposure indicative of more serious negative health effects on the individual level even though the exposure level and prevalence overall diminished. Thereby, one can speculate that the exceedance of the OEL in the participating companies is an underestimation in comparison with companies without resources for preventive work. Our estimate of the number of workers currently exposed to Cr(VI) is lower than the numbers estimated in the 1990s, 17 900 today vs. 21 000 in the 1990s (Kauppinen et al., 2000). Comparison is somewhat difficult since it is not known if the former estimation also included low or intermittently exposed occupations. However, as pointed out above although the prevalence of exposure to Cr(VI) has decreased it does not mean the exposure level also has declined.

In our study, exposure was assessed according to four work tasks (welding, machining, process operation and others). Welder was the only homogenous occupation with known Cr(VI) exposure that could be easily assessed in the register from Statistics Sweden (Statistikdatabasen, 2021). In 2021, there were 12 703 registered welders (SSYK code 7212) in Sweden and based on the estimation in the Swedish JEM that 20% of welders are exposed to Cr(VI), we estimate that approximately 2570 welders are exposed to Cr(VI) today. However, many workers perform welding without having the job title welder. Sjögren and Gustavsson estimated that in 2013 there were 20 000–25 000 workers welding in their profession (Sjögren, 2013) but 70 306 workers exposed to welding fumes (Gustavsson et al., 2022). In the present study, 12.5% of welders exceeded the Swedish OEL of inhalable Cr(VI). Therefore, in the case of conservative estimation (exposure of non-welders to welding fumes was not considered), around 625 welders are at risk of exceeding the Swedish OEL nationally (25 000 welders * 20% * 12.5% = 625 welders) when welding. The Bayesian analysis' 95% credible interval for welders' overexposure of the Swedish OEL was 3.1%–19.6%. This translates to between 155 and 980 welders being at risk of exceeding the Swedish OEL nationally (25000 welders * 20% * 3.1% = 155 welders; 25000 * 20% * 19.6% = 980 welders).

The current OEL for Cr(VI) in Sweden corresponds to 20 extra lung cancer cases per 1000 exposed after 40 years of exposure (i.e. lifetime risk) (C. European, 2017). In Germany and the Netherlands, acceptable risk is considered to be an additional risk of <4 cases per 100,000 after 40 years and tolerable risk (during a transitional period) is considered to be < 4/1000 (Ding et al., 2014). It should be noted that the Swedish OEL corresponds to much higher levels of Cr(VI) and thus substantially higher risks. Further, the fact that 7.0% of workers in our study exceeded the Swedish OEL and 4.3% exceeded the EU OEL, suggests that a subpopulation of the Cr(VI)-exposed workers may be at even higher risk of lung cancer in Sweden. To lower the Cr(VI) exposure, there is a need for more effective risk management measures and increased incentives for workplaces to implement them. Important actions towards this aim are reduction of the current OEL and subsequent enforcement of it, including directed information campaigns supporting the adoption of proper risk management.

4.1.3. Urinary Cr

In a recent systematic review of biomonitoring data on occupational exposure to Cr(VI) (Verdonck et al., 2021), the median or mean urinary Cr levels were lower in European countries (ranging from 0.96 μg/L to 5.81 μg/L) compared with non-European countries (ranging from 1.66 μg/L to 48.4 μg/L). In HBM4EU chromates study, the median and P95 concentration of post-shift urinary Cr in exposed workers were 1.7 and 5.1 μg/g creatinine. In our study, the median urinary Cr was 0.55 μg/L, and after creatinine adjustment, the median and P95 were 0.41 and 2.12 μg/g creatinine, which are lower than all studies above. In HBM4EU chromates study, reference values were obtained by recruiting controls from the same companies as the exposed workers (within company controls) or from other companies without associated with Cr(VI) exposure (outwith (external) company controls). The values of the controls' urinary Cr in our study (median and P95, 0.08 and 0.54 μg/g creatinine) are similar with the outwith company controls in HBM4EU chromates study (0.1 and 0.4 μg/g creatinine) (Viegas et al., 2022).

France and the Netherlands have set a biological limit value (BLV) of 2.5 μg/L of Cr in urine based on their OEL of 1 μg/m^3 for Cr(VI) in air, and Finland has derived a BLV of 0.2 μmol/L (ca. 10 μg/L) in urine corresponding to its OEL of 5 μg/m^3 in air (Verdonck et al., 2021). In our study, two participants (1.8%) exceeded 10 μg/L of urinary Cr and 13 (11.5%) exceeded 2.5 μg/L.

4.1.4. RBC-Cr

RBC-Cr (median, 0.73 μg/L and mean, 0.89 μg/L) was lower in our study compared to welders in a German study (median, 1.95 μg/L) (Weiss et al., 2013), electroplaters in Italy (median, 3.4 μg/L) (Goldoni et al., 2010a) and China (median, 4.41 μg/L) (Zhang et al., 2011), and chromate production workers in China (mean, 12.45 μg/L). The median value of RBC-Cr in HBM4EU chromates study (0.73 μg/L) was the same as in our study but they had higher P95 (5.83 μg/L versus 2.33 μg/L) (Ndaw et al., 2022). With respect to controls, one study in China measured RBC-Cr in 93 controls (median, 1.54 μg/L) (Zhang et al., 2011) and HBM4EU chromates study measured 175 controls (median, 0.63 μg/L) (Ndaw et al., 2022). The median concentration of RBC-Cr in our controls was 0.53 μg/L, similar to in HBM4EU chromates study.

Despite that Cr in RBC is considered a specific biomarker of Cr(VI), there is no established BLV for RBC-Cr. It is worth mentioning that, in our study, plasma was removed from whole blood, and the blood cells were washed to eliminate interfering residual plasma-Cr. However, white blood cells (WBC) were retained along with RBC, which might increase the background level of RBC-Cr from Cr(III) accumulated in WBC.

4.2. Efficiency of using LEV and RPE

In earlier studies, LEV significantly influenced exposure to Cr(VI) during welding, resulting in a 68% reduction in median Cr(VI) concentrations (Meeker et al., 2010). In the HBM4EU chromates study, the use of LEV corresponded to about one third lower airborne Cr concentrations (Viegas et al., 2022). In our study, the reduction was around 50%. An inferred acceptable LEV also led to a reduction to half of the urinary Cr and corresponded to a statistically significantly lower concentration of RBC-Cr.

Compared to other preventive and protective measures (e.g., elimination of the high-risk substance, substitution by a less toxic alternative or separating the substance from the workers), RPE should be regarded as the last resort in the hierarchy of controls (Viegas et al., 2022). In HBM4EU chromates study, the use of RPE was associated with lower urinary Cr (except for machining workers). In addition, in chrome-platers, a stronger correlation between internal Cr and airborne Cr(VI) was observed in the group without RPE (Ndaw et al., 2022). In our study, workers who correctly used RPE were exposed to around four times higher inhalable Cr(VI) compared with those who did not, and higher concentrations of urinary and RBC Cr were found in workers who used RPE correctly. Stratified analysis showed that LEV had a greater protective effect compared with RPE, and among workers with non-acceptable LEV, the correct usage of RPE was still associated with the highest level of inhalable Cr(VI), and urinary and RBC Cr. There may be several explanations for the dysfunction of RPE: the exposed workers may have irregularly worn RPE over time; they may have been exposed to Cr(VI) via the skin; or workers may have been subject to secondary exposure. Furthermore, RPE only guarantees protection if no leaking occurs, and only works when it fits properly to the wearer's face (Viegas et al., 2022). Fit test is not formally required in Sweden as opposed to many other countries. Only around half of the workers who correctly used RPE used loose-fitting powered air-purifying respirators, which does not require the fit test. For the other workers, a reason for the low efficiency of RPE protection could be that no fit test was performed.

Our findings show that most employers and workers are aware of the risk of high levels of Cr(VI) in the air and thus use RPE, but that this is not enough to reduce the Cr(VI) exposure and more efficient exposure control strategies are needed.

4.3. Other metals

Apart from Cr, workers may be exposed to other toxic metals in their working environment. It was reported that urinary (Golbabaei et al., 2012; Stanislawska et al., 2020), serum (El Safty et al., 2018) and blood (Muller et al., 2022) nickel in Cr(VI)-exposed workers were significantly higher than controls. In our study, post-shift urinary nickel in the Cr (VI)-exposed group was non-significantly higher than controls ($P =$ 0.09), and nickel concentrations in RBC showed no significant difference between the two groups ($P = 0.36$). However, nickel concentrations in RBC was significantly higher in welders than in controls ($P = 0.02$). In addition, among all metals in RBC, we observed the strongest correlation with Cr for nickel ($r_S = 0.37$). The finding of co-exposure to nickel among some Cr(VI)-exposed workers indicate exposure to multiple carcinogens. We found some differences in urinary and RBC metal concentrations between companies and work tasks as well. This may lead to more serious health consequences than exposure only to one carcinogen, and thus, a more complex risk assessment is needed including monitoring of multiple carcinogens.

We also found significantly higher concentrations of post-shift urinary and RBC copper in Cr(VI)-exposed workers compared with controls. On the contrary, Song et al. reported significantly lower levels of copper in whole blood in chromate production workers in China (Song et al., 2012). Besides that, our result for zinc concentrations in RBC was in line with Song et al., i.e. higher zinc among Cr(VI)-exposed workers. Unexpectedly, antimony was found to be significantly higher in urine and RBC in the control group. A potential explanation for the higher levels of antimony in controls could be exposure to antimony trisulfide; a lubricant in friction material and widely used in disc brake pads (Uexküll et al., 2005). In our study, 33 controls (45.8%) had the work task of car driving car, truck, forklift truck, or excavator. Other controls recruited from the same company as drivers may share the same work environment and be exposed to antimony-containing dust as well.

4.4. Correlations between exposure markers and monitoring strategy

The positive correlation between airborne Cr(VI) and urinary Cr concentrations ($r_S = 0.64$) in our study indicates that exposures to Cr(VI) occurred mainly via inhalation (Were, 2013). Moderate correlations were also found between inhalable Cr(VI) and urinary Cr in welders in Poland ($r_S = 0.58$) (Stanislawska et al., 2020), electroplaters in Great Britain ($r_S = 0.62$) (Beattie et al., 2017) and in the HBM4EU chromates study ($r_S = 0.46$) (Viegas et al., 2022). Regression analyses are commonly used to study the relationship between airborne Cr(VI) levels and urinary Cr levels. Published regression formulas could be used to convert the measured biomonitoring data, representing internal exposure, into corresponding Cr(VI) air levels (Mahiout et al., 2022), and conversely set BLVs corresponding to OELs. The regression analysis published by Lindberg and Vesterberg has been used as a basis for deriving a BLV for Cr(VI) in bath plating where a value of 13 μg/g creatinine (an average creatinine excretion of 1.36 g/L was used) corresponds to the OEL of 5 μg/m^3 (Lindberg and Vesterberg, 1983). Another widely used regression analysis for Cr(VI) in electroplating was published by Chen et al. in which the same OEL corresponds to urinary Cr of 8.8 μg/g creatinine (Chen et al., 2002). HBM4EU chromates study reported two regression analysis (Viegas et al., 2022), for platers the OEL of 5 μg/m^3 corresponds to a urinary Cr level of 6.9 μg/g creatinine and for welders it corresponds to 3.4 μg/g creatinine. In our study the Swedish OEL corresponds to 2.44 μg/g creatinine for all exposed workers and 1.26 μg/g creatinine for welders, respectively. It should be noted that we observed a low goodness-of-fit value (0.02) for all exposed workers. Furthermore, 21 workers exceeded the reference P95 of urinary Cr but had less than 0.25 μg/m^3 of inhalable Cr(VI) (Supplementary Table 5B). This indicates that the Cr(VI) exposure might not have occurred only via inhalation. Thus, aspects to asses for the relationships between exposure via air and biomarkers are sources and variations in Cr(VI) emissions, but also solubility of Cr(VI) compounds in water and particle size, which are expected to impact the toxicokinetic of Cr and subsequently influence the levels of chromium excreted in the urine (Wilbur et al., 2012). More studies are needed to establish the most suitable regression analysis to set up the BLV.

A few studies investigated the correlation between urinary and RBC Cr. A significant positive correlation between urinary and RBC Cr ($r_S =$ 0.74) was found in chrome-platers in Italy (Goldoni et al., 2010a) However, in chromate production workers in China, the correlation was weak ($r_S = 0.21$) (Wang et al., 2011). Also, poor correlation between urinary and RBC Cr was found in HBM4EU chromates study, but when only considering chrome-platers, the r_S coefficient became higher (only shown in figure, approximately $r_S = 0.1$ for all workers and $r_S = 0.5$ for chrome-platers) (Santonen et al., 2022). The correlation between urinary and RBC Cr in our study is relatively strong ($r_S = 0.72$). To date, only a few studies have investigated the correlation between inhalable Cr(VI) and RBC-Cr concentrations. No correlation ($r_S = -0.06$; $P = 0.73$) was reported for Polish welders (Stanislawska et al., 2020). In HBM4EU chromates study, no correlation was also reported for all worker groups combined, but among chrome-platers, the correlation between inhalable Cr(VI) and RBC-Cr was stronger ($r_S = 0.54$) (Ndaw et al., 2022). A similar correlation was found in our study for all exposed workers ($r_S =$ 0.53). RBC-Cr may primarily reflect exposure to water-soluble Cr and less to welding fumes, but there is also evidence that stainless steel welding fumes are retained in the lungs longer than mild steel welding fumes (Antonini et al., 2004). In our project, 97% of welders were welding stainless steel, and this could be a plausible explication of the high correlation observed between inhalable Cr(VI) and RBC-Cr. However, it should be noted that 27 workers exceeded the reference P95 of RBC-Cr but had less than 0.25 μg/m^3 of inhalable Cr(VI), among them, 12 workers even had normal levels of urinary Cr (Supplementary Table 5B). This indicates that RBC-Cr reflects elevated exposure in air prior to our exposure measurements. Since the air monitoring is transient and the short-term nature of total urinary Cr may mislead exposure to Cr(VI), a better strategy when assessing long-term Cr(VI) exposure would be repeated air measurement combined with biomonitoring of RBC-Cr.

4.5. Strengths and limitations

This is a comprehensive study of occupational exposure to Cr(VI), and, to the best of our knowledge, the very first in Sweden. The nationwide cover allowed us to obtain a more complete dataset of different types of companies across the country. Additionally, this study included environmental and biological monitoring information at the individual level. Overall, our results corroborate with previous published studies. The study design and the questionnaire were adapted from HBM4EU chromates study, and therefore our data should be directly comparable to the data from HBM4EU chromates study. In the present study, statistically significant relationships between RBC-Cr and different exposure biomarkers provided evidence that RBC-Cr is an appropriate biomarker for monitoring occupational Cr(VI) exposure. This study has the potential to enhance the significance of different biological indicators in monitoring Cr levels and contributes valuable data to bolster regulatory risk assessment and decision-making processes.

There were several limitations of the present study. The relatively low company participation rate indicates that the participating companies may not be representative for Cr(VI) exposure in Sweden. There may be bias due to unbalanced covariates in the exposed and control groups. Airborne Cr(VI) was measured only for one working day. There were higher Cr concentrations in pre-shift urine since pre-shift urine was sampled when workers had worked for at least three days. The wide range of work tasks and sectors has, because of different emission sources and exposure routes, influenced the analysis of correlations between inhalable Cr(VI) and biomarkers. Further, this study only measured inhalable Cr(VI), and dermal exposure was not assessed although dermal contamination is considered an important Cr(VI) exposure route. Finally, there may be uncertainties about usage of RPE over time.

5. Conclusions

Our study showed that although a majority of the individual air measurements were relatively low, some workers are exposed to high levels of Cr(VI), and 7.0% of participants' measured exposures exceeded the current Swedish OEL. Furthermore, the existing protective measures implemented at workplaces are inadequate and insufficient, and significant action to lower Cr(VI) exposure is warranted. Several workers showed higher concentrations of Cr in urine and RBC, but not in air, suggesting that a combination of workplace environmental and biological monitoring is necessary to assess Cr(VI) exposure. LEV showed promising protection efficiency, while further studies are needed to evaluate how RPE best should be used in preventing Cr(VI) exposure when other exposure control measures have been exhausted. Risk assessment and risk reduction need to be improved at the companies and supplemented with national policies to support risk awareness for non-threshold carcinogens as well as surveillance of exposure levels, in order to eliminate occupational cancer. Further studies are needed to clarify the health consequences of the current Cr(VI) exposure.

CRediT authorship contribution statement

Zheshun Jiang: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Linda Schenk:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Eva Assarsson:** Investigation, Writing – review & editing. **Maria Albin:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Helen Bertilsson:** Investigation, Writing – review & editing. **Eva Dock:** Investigation, Writing – review & editing. **Jessika Hagberg:** Investigation, Resources, Writing – review & editing. **Lovisa E. Karlsson:** Formal analysis, Methodology, Writing – review & editing. **Pete Kines:** Investigation, Writing – review & editing. **Annette M. Krais:** Investigation, Writing – review & editing. **Stefan Ljunggren:** Data curation, Investigation, Methodology, Writing – review & editing. **Thomas Lundh:** Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. **Lars Modig:** Funding acquisition, Investigation, Writing – review & editing. **Rickie Möller:** Investigation, Writing – review & editing. **Daniela Pineda:** Formal analysis, Methodology, Project administration, Writing – review & editing. **Niklas Ricklund:** Data curation, Investigation, Writing – review & editing. **Anne T. Saber:** Investigation, Writing – review & editing. **Tobias Storsjö:** Investigation, Writing – review & editing. **Evana Taher Amir:** Investigation, Writing – review & editing. **Håkan Tinnerberg:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Martin Tondel:** Investigation, Methodology, Writing – review & editing. **Ulla Vogel:** Conceptualization, Investigation, Writing – review & editing. **Pernilla Wiebert:** Data curation, Investigation, Writing – review & editing. **Karin Broberg:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Malin Engfeldt:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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