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Per- and polyfluoroalkyl substances exposure in hexavalent chromium exposed workers and the effects of exposure mixtures on oxidative stress and genomic instability☆

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ABSTRACT

Hexavalent chromium (Cr(VI)) can induce oxidative stress, genomic instability, and epigenetic modifications. In occupational settings, Cr(VI)-exposed workers may also be exposed to other toxicants, such as elements besides Cr, and per- and polyfluoroalkyl substances (PFAS). However, research on the extent of these co-exposures and their combined effects remains limited. The objective of this study was to characterize the exposure levels of ten elements and eight PFAS in Cr(VI)-exposed workers and to assess the combined effects of these exposure mixtures on biomarkers of oxidative stress and genomic instability. This study included 138 Cr(VI)-exposed workers and 96 controls from Swedish SafeChrom and Danish SAM-Krom studies. Concentrations of elements were measured by inductively coupled plasma mass spectrometry (ICP-MS), and PFAS were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Effect biomarkers, including 8-hydroxy-2′-deoxyguanosine (8-OHdG), mitochondrial DNA copy number (mtDNA-cn), telomere length (TL) and O6-methylguanine-DNA methyltransferase promoter (*MGMT*) methylation, were analyzed in blood. Bayesian Kernel Machine Regression and quantile-based g-computation models were used to evaluate the mixture effects. Exposed workers had higher concentrations of Cr, manganese, copper, zinc, lead, and perfluoroheptanoic acid (PFHpA), lower mtDNA-cn and longer TL compared to controls. In the SAM-Krom study, perfluorooctane sulfonic acid (PFOS) levels were significantly elevated among exposed workers, with the P95 reaching 2044 ng/mL. The exposure mixtures were associated with increased 8-OHdG and *MGMT* hypermethylation. Together, these findings highlight the complexity of multiple occupational exposures in Cr(VI)-related work environments and suggest that combined exposure may contribute to early biological alterations related to oxidative stress and DNA methylation.

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Abbreviations

8-OHdG	8-hydroxy-2′-deoxyguanosine
BKMR	Bayesian Kernel Machine Regression
Cd	Cadmium
CMS	Chrome mist suppressant
Cr	Chromium
Cr(III)	Trivalent chromium
Cr(VI)	Hexavalent chromium
Cu	Copper
CV	Coefficient of variation
EU	European Union
HBB	Hemoglobin subunit beta
HBM4EU	Human biomonitoring for Europe
Hg	Mercury
ICP-MS	Inductively coupled plasma mass spectrometry
IQR	Interquartile range
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
Ln	Natural logarithmic
LOD	Limit of detection
Mn	Manganese
MGMT	O6-methylguanine-DNA methyltransferase promoter
MN	Micronuclei
MNRET	Micronuclei in peripheral blood reticulocytes
mtDNA-cn	Relative mitochondrial DNA copy number
Ni	Nickel
P5	5th percentile
P95	95th percentile
PAHs	Polycyclic aromatic hydrocarbons
Pb	Lead
PFAS	Per- and polyfluoroalkyl substances
PFDA	Perfluorodecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHpS	Perfluoroheptane sulfonic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFUnDA	Perfluoroundecanoic acid
PIP	Posterior inclusion probability
QC	Quality control
qgcomp	Quantile-based g-computation
RBC	Red blood cells
r_S	Spearman's rank correlation coefficients
Sb	Antimony
Se	Selenium
TL	relative telomere length
WQS	Weighted quantile regression
Zn	Zinc
β	Beta coefficient

1. Introduction

Recently, three studies in Europe have investigated occupational exposure to Cr(VI), including the Human Biomonitoring for Europe (HBM4EU) Chromates project (Santonen et al., 2022), the Swedish SafeChrom study (Jiang et al., 2024), and the Danish SAM-Krom study (Saber et al., 2025). All three studies found that workers exposed to Cr (VI) had higher concentrations of Cr in their urine and blood compared to controls. Cr(VI) is classified as a Group 1 carcinogen and increases the risk of lung cancer (IARC, 2012). Occupational exposure to Cr(VI) can occur in electroplating, chromate production, steel manufacturing and welding (Viegas et al., 2022). In the HBM4EU Chromates project, Cr(VI) exposure was linked to elevated genotoxicity (higher micronuclei (MN) in lymphocytes and reticulocytes and higher comet tail intensity) and oxidative damage (higher urinary malondialdehyde and 8-hydroxy-2′-deoxyguanosine (8-OHdG)) (A. Tavares et al., 2022). The SafeChrom study showed elevated oxidative stress, telomere elongation, reduced relative mitochondrial DNA copy number (mtDNA-cn), and epigenetic changes among exposed individuals (Jiang et al., 2025). The SAM-Krom study identified increased levels of MN among exposed individuals (Saber et al., 2025).

Chrome plating is an electroplating process used to deposit a thin layer of Cr onto a metal surface (Bao et al., 2019). It serves various purposes, including enhancing aesthetics, increasing surface hardness, and improving corrosion resistance (Pelar et al., 2018). Workers occupationally exposed to Cr(VI) may also encounter other hazardous environmental substances at their workplace. In the SafeChrom study, we found that Cr(VI)-exposed workers had significantly higher concentrations of copper (Cu) and zinc (Zn) in red blood cells (RBC), compared with controls. The HBM4EU chromates study reported high perfluorooctane sulfonic acid (PFOS) exposure in platers and welders (Göen et al., 2024).

Per- and polyfluoroalkyl substances (PFAS) consist of a fluorinated alkyl chain and a polar head group, which give them surfactant-like properties, enabling them to withstand extreme temperatures and resist water and grease (Dickman & Aga, 2022). Epidemiological studies have assessed the health impacts of PFAS exposure, with findings linking it to various cancers, elevated cholesterol levels, reduced immune and liver function, and birth defects (Fenton et al., 2021). Perfluorooctanesulfonic acid (PFOS) was employed as a chrome mist suppressant (CMS) in plating operations across Europe (Uhl et al., 2023). According to the Swedish Chemicals Agency, approximately 10 kg of PFOS was imported for use in the metal processing industry in both 2018 and 2019, and most of it was used in hard chrome plating (Kemikalieinspektionen, 2020). A survey of PFOS usage in the Danish chrome plating industry revealed that the annual consumption of PFOS ranged from 10 to 28 kg during 2008 and 2009 (Poulsen et al., 2011). In 2017, the Danish Environmental Protection Agency stated that an annual consumption of approximately 20 kg PFOS was reported, whereas data from the Danish Product Register suggest a consumption of more than 100 kg PFOS and PFOS salts (Miljøstyrelsen, 2017). Due to prolonged use and the high bioaccumulation of PFOS, Cr(VI)-exposed workers may have accumulated significant amounts of PFOS in their bodies. In November 2023, the International Agency for Research on Cancer (IARC) classified PFOS as "possibly carcinogenic to humans" (Group 2B) (Zahm et al., 2024). However, we do not know the specific levels of PFAS accumulation in Cr(VI)-exposed workers, nor the potential long-term health effects associated with co-exposure of PFAS and Cr (VI).

To comprehensively analyze the exposure of Cr(VI)-exposed workers to environmental contaminants, we measured ten elements (Cr, manganese (Mn), nickel (Ni), Cu, Zn, selenium (Se), cadmium (Cd), antimony (Sb), mercury (Hg), and Pb) and eight types of PFAS, including perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonic acid (PFHxS), perfluoroheptane sulfonic acid (PFHpS), and PFOS in the SafeChrom and SAM-Krom studies, alongside urinary concentrations of PAH metabolites in SafeChrom study. To assess the levels of oxidative stress and genomic instability, we analyzed several effect biomarkers, including 8-OHdG, mtDNA-cn, relative telomere length (TL), and MN frequency. The methylation of the O6-methylguanine-DNA methyltransferase promoter (*MGMT*) was measured in SafeChrom study. Finally, we assessed the combined effects of multiple elements and PFAS on the measured biomarkers using mixture modeling approaches, including Bayesian Kernel Machine Regression (BKMR) and quantile-based g-computation (qgcomp).

2. Material and methods

2.1. Study population and sample collection

This study included 113 Cr(VI)-exposed workers and 72 controls from the Swedish SafeChrom study, along with 25 exposed workers and 24 within company controls from the Danish SAM-Krom study. The details of participant recruitment and sample collection for SafeChrom (Jiang et al., 2024) and SAM-Krom (Saber et al., 2025) have been

published previously. The participated companies were categorised into four groups: manufacture/processing of metal products, steel production, bath plating and non-categorised. Work tasks of the workers were classified into four categories: welding, process operation, machining, and others. The within company controls in SAM-Krom were recruited from the participating companies and from a vocational school.

Venous blood samples from all participants were collected in two vacutainer sodium-heparin tubes (BD, Plymouth, UK) to measure elements concentration in RBC and assess MN in peripheral blood reticulocytes (MNRET) levels. Samples for MNRET were transported to the Finnish Institute of Occupational Health and stored refrigerated until processing and analysis. Another venous blood sample was collected in a VACUETTE Serum Separator Clot Activator tube (Greiner Bio-One GmbH, Kremsmünster, Austria) containing an inert gel to obtain serum and measure PFAS and 8-OHdG. Additionally, in SafeChrom, one venous blood sample was collected in an EDTA tube (BD) to measure mtDNA-cn, TL and *MGMT* methylation. One post-work urine sample (after at least 4 h of work) was collected to measure PAHs concentrations. All participants filled in a questionnaire including questions about birth year, sex, current tobacco smoking, and consumption of alcoholic beverages. Each participant gave informed written consent to participate in the study. SafeChrom was approved by the Swedish Ethical Review Authority (Dnr, 2024-07499-02) and SAM-Krom was approved by The Scientific Ethics Committee for the Copenhagen Capital Region (H-20077777).

Volunteer recruitment, sample collection and storage, laboratory analyses, and the categorization of companies and work tasks among exposed workers were conducted according to the same standardized operating procedures in both studies and aligned as much as possible with HBM4EU protocols.

2.2. Measurements of elements in blood cells

Biomonitoring for Cr(VI) exposure was carried out by measuring Cr concentration with inductively coupled plasma mass spectrometry (ICP-MS) in RBC for all participants. RBC were isolated before the measurement as previously described (Jiang et al., 2024). In addition to Cr, Mn, Ni, Cu, Zn, Se, Cd, Sb, Hg, and Pb were also measured in blood cells. Detailed protocols for the analysis of elements in RBC within the SafeChrom study have been published previously (Jiang et al., 2024). Briefly, all determinations were performed using an ICP-MS equipped with a collision cell operating with kinetic energy discrimination and helium as the collision gas. A 100 μL aliquot of RBC was diluted 20-fold with an alkaline solution and analyzed in peak-jumping mode, with scandium, rhodium, terbium, and iridium serving as internal standards. Each sample was prepared and measured in duplicate, and the mean value was used for subsequent statistical analyses. The methodology for elemental analysis in RBCs from the SAM-Krom study was also described earlier (Saber et al., 2025). Instrumental configuration and parameters for SAM-Krom study are listed in Table S1. The analytical accuracy and LOD for SAM-Krom study are verified and detailed in Table S2.

2.3. Measurements of PFAS and 8-OHdG

PFAS and 8-OHdG were measured in serum samples from the SafeChrom study and in plasma samples from the SAM-Krom study. The samples were prepared using a method previously described by Norén E *et al.* (Norén et al., 2021). Briefly, an aliquot of 0.1 mL of sample was prepared in a 96-well plate and de-conjugated using β-glucuronidase. Isotope-labelled internal standards of PFAS (Wellington Laboratories, Guelph, Ontario, Canada) and $^{15}N_5$-8-OHdG (Cambridge Isotope Laboratories, USA), and proteins were precipitated with acetonitrile. The supernatant was analyzed using 2D liquid chromatography-triple quadrupole linear ion trap mass spectrometer (LC-MS/MS; QTRAP 7500, AB Sciex, Framingham, MA, USA). PFAS was analyzed with a modified method (Norén et al., 2021) with online extraction using a Strata C8 (20*2.1 mm; Phenomenex, Torrance, USA) and Biozen Oligo (50*2.1 mm; Phenomenex) column. 8-OHdG was analyzed with a modified method (Jiang et al., 2025) using a Kinetex XB-C18 (100 * 3 mm; Phenomenex) and an Ultra AQ C18 (100*4.6 mm; Restek, Bellefonte, USA) column. Each analysis batch included calibration standards, quality control (QC) samples as well as chemically blank samples. The limit of detection (LOD) for the PFAS calculated from blank samples was between 0.04 and 0.15 ng/mL and the coefficient of variation (CV) of the QC samples were between 5 and 37 %. The LOD for 8-OHdG calculated from blank samples was 0.016 ng/mL. Not any sample of PFAS and 8-OHdG were below the LOD of the respective method. The between-run precision determined by analyses of QC samples was 16 and 22 %. The laboratory participates in German External Quality Assessment Scheme (G-EQUAS) for the analyses of PFAS and is a qualified laboratory in Partnership for the Assessment of Risks from Chemicals (PARC) for PFHxS, PFOA, PFNA, PFOS, and PFDA.

2.4. PAHs concentration in urine

The PAH metabolites in urine were measured using a modified method described by Krais AM *et al.* (Krais et al., 2021). Briefly, 0.2 mL urine was transferred to 96-well plates, added with buffer (pH 6.5), deuterated internal standards and de-conjugated using β-glucuronidase for 30 min at 37 °C. The samples were analyzed using 2D LC-MS/MS (QTRAP 7500, AB Sciex). Separation was achieved using online extraction Luna C8 (20*2.1 mm; Phenomenex) and Infinitylab poroshell 120 EC-C18 (100*4.6 mm, Agilent, Santa Clara, CA, USA) columns. We measured the following monohydroxylated PAH metabolites: a mixture of 2- and 3-hydroxyfluorene (2,3-OH Flu); 1-hydroxyphenanthrene (1-OH Phe), a mixture of 2- and 3-hydroxyphenanthrene (2,3-OH Phe), and 1-hydroxypyrene (1-OH Pyr). Each analysis batch included calibration standards, QC samples as well as chemically blank samples. The LOD calculated from the blank samples was 0.07 ng/mL for all metabolites. The CV of the QC samples was between 5 and 9 %. The laboratory participates in G-EQUAS inter-laboratory comparison of 1-OH Pyr with good results. The density of urine samples was measured with a hand-held refractometer (30PX; Mettler Toledo, Columbus, USA) as previously described (Jiang et al., 2024), and used for dilution adjustment. Density-adjusted PAHs concentrations were present in this study (Verheyen et al., 2021).

2.5. DNA extraction, mtDNA-cn and TL

Genomic DNA was isolated from 200 μL whole blood sample (SafeChrom), or 200 μL blood sample after plasma isolation (SAM-Krom), using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA samples were diluted to a concentration of 25 ng/μL for DNA methylation and 5 ng/μL for mtDNA-cn and TL. The methods of mtDNA-cn and TL measurement were described previously (Jiang et al., 2025). Briefly, the mtDNA and telomere were measured by SYBR Green-based quantitative PCR in a 7900HT Fast Real-Time PCR System (Applied Biosystems, Waltham, USA). A single-copy gene (hemoglobin subunit beta (*HBB*)) was used as a reference to determine the copies per cell of the mtDNA and telomere sequences. One reference DNA sample was diluted serially twofold per dilution to produce six concentrations of 0.5–16 ng/μL for the standard curve. A control sample was included in each run to monitor the variance between runs. The standard curve, samples (with 2.5 μL DNA diluted to 5 ng/μL), control sample and one blank were run in triplicate. SDS 2.4.1 software (Thermo Fisher Scientific) calculated the relative quantity of mtDNA, telomere and *HBB* for each reaction based on the standard curve. Then, the relative quantity of mtDNA was divided by the quantity of *HBB* to calculate the mtDNA/*HBB* ratio (mtDNA-cn). Likewise, the TL was the quotient of the quantity of telomere and *HBB*. Both mtDNA-cn and TL are therefore arbitrary values.

2.6. MNRET

The measurement of MNRET was described previously (Andersen et al., 2021; A. Tavares et al., 2022). Briefly, the whole blood samples were stored at 4 °C and processed within seven days after collection. Transferrin-positive (+CD71) reticulocytes were isolated by immunomagnetic separation according to the instructions of the CELLection Pan Mouse IgG Kit (Thermo Fisher Scientific) using a FITC Mouse Anti-human CD71 antibody (BD Biosciences, San Jose, USA). Thereafter, samples were fixed in 2 % paraformaldehyde in PBS with 10 μg/mL of sodium dodecyl sulfate (Sigma-Aldrich, Darmstadt, Germany) and kept at 4 °C until analysis. Before the analysis, DNA was stained with Hoechst 33342 (Thermo Fisher Scientific). The samples were analyzed using blue (488 nm) laser for the identification of +CD71 reticulocytes and near UV (375 nm) laser for the detection of DNA-containing MN. A CytoFlex S flow cytometer and CytExpert software version 2.3 (Beckman Coulter, Brea, USA) were used for data acquisition and analysis of a minimum of 20000 +CD71 reticulocytes per sample. The MN frequency was quantified as permille of micronucleated + CD71 reticulocytes from all analyzed + CD71 reticulocytes.

Due to six missing blood samples and four samples contained an insufficient number of cells for analysis, resulting in a final dataset of 105 exposed workers and 70 controls for MNRET in SafeChrom.

2.7. DNA methylation

DNA methylation of the promoter region of *MGMT* was analyzed in SafeChrom and detailed elsewhere (Jiang et al., 2025). Briefly, bisulfite conversion of 20 μL DNA (25 ng/μL) was performed with EZ DNA Methylation-Gold kit (Zymo Research, Irvine, USA) according to the manufacturer's protocol. The PCR amplifications were performed on a T100 Thermal Cycler (Bio-Rad, Hercules, USA) with PyroMark PCR Kit (Qiagen). Pyrosequencing was analyzed on the PyroMark Q48 Autoprep Instrument (Qiagen) with PyroMark Q48 Advanced CpG reagents (Qiagen) according to the manufacturer's protocol. The results of pyrosequencing were stored in PyroMark Q48 Autoprep software for further analysis.

2.8. Statistical analysis

Age was calculated based on recruitment date and birth. Descriptive statistics, including median, 5th and 95th percentiles (P5, P95), were reported. The Mann-Whitney *U* test was used to compare continuous variables between exposed workers and controls, and the Pearson Chi-square test was used to assess differences in the distribution of categorical variables. Spearman's rank correlation was applied to examine correlations between exposure biomarkers and effect biomarkers. Due to the right-skewed distributions of all effect biomarkers, natural logarithmic (ln) transformations were computed to approximate normality. Multivariate linear regression models were constructed to examine associations between exposure biomarkers and effect biomarkers. The models were adjusted for potential confounders, including age, sex (male/female), smoking status (non-smoker/smoker), alcohol consumption (non-alcohol drinker/alcohol drinker) and different studies (SafeChrom/Sam-Krom).

BKMR, a semi-parametric approach, was employed to estimate both the individual and overall effects of the multi-exposure mixture on each effect biomarker (Bobb et al., 2015). To incorporate potential dependencies among exposure components, we applied a hierarchical BKMR model, in which correlated exposures (Spearman's rank correlation coefficients (r_S) > 0.6) were grouped to inform the prior covariance structure in the regression model. Additionally, we standardized all exposure biomarkers and confounders to ensure all covariates are on the same scale. The posterior inclusion probability (PIP) was calculated to identify the most contributing exposure to the overall associations among the mixture exposures. For each effect biomarker, the overall effect of the entire exposure mixture and the univariate effect of each single exposure were estimated. Furthermore, the qgcomp method was applied to assess joint effects based on parameter inference. This approach benefits from the inferential simplicity of weighted quantile sum (WQS) regression and the flexibility of g-computation. Specifically, it transforms all exposure variables into quartiles and fits a linear model to estimate the joint effect of the mixture by simultaneously increasing all individual exposures (Keil et al., 2020). In summary, the combined use of BKMR and gqcomp provides a more robust and less biased estimation than traditional mixture models: BKMR captures nonlinearity and nonadditivity within the mixture, while gqcomp provides interpretable estimates of the overall effect and allows components to contribute in both positive and negative directions.

All statistical analyses above were conducted with SPSS 28.0 (IBM Corp., Armonk, NY, USA) and R (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria), with the "bkmr" (version 0.2.2) and "qgcomp" (version 2.15.2) packages implemented for BKMR and qgcomp analyses, respectively. A two-tailed p-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study participants and results of effect biomarkers

Table 1 summarizes the demographic and lifestyle characteristics of the study participants, along with the results of effect biomarkers. For all participants, exposed workers had a larger proportion of males and were more likely to drink alcohol than the controls. Exposed workers were younger than the controls in SafeChrom study. No significant differences in characteristics were observed between exposed workers and controls in SAM-Krom study.

Four effect biomarkers were measured in all participants (Table 1). No significant differences were observed in 8-OHdG levels between exposed workers and controls in the combined dataset or in either individual study. Consistent patterns were observed, with exposed workers exhibiting significantly lower levels of mtDNA-cn and longer TL in both the overall population and the SafeChrom study, but not in the SAM-Krom study. There were contrasting findings for MNRET in the two studies: levels were significantly lower among exposed workers in SafeChrom study, whereas they were significantly higher in SAM-Krom exposed workers. Exposed workers had higher degree of *MGMT* methylation compared with controls.

3.2. Distributions of exposure biomarkers

Significantly higher concentrations of Cr, Mn, Cu, Zn, and Pb were observed in the exposed group (Table 2) and were included in the subsequent analyses. Other elements did not show significance and were therefore left out of further analysis and therefore not mentioned in tables. Eight PFAS were measured in all participants and exposed workers had higher concentrations of PFHpA compared with controls. This difference was also observed in SafeChrom study but not in SAM-Krom study. Additionally, PFOS levels were significantly higher in the exposed workers of the SAM-Krom study, with the P95 reaching 2044 ng/mL. Both total PAHs and 2,3-dihydroxyfluorene were significantly higher in exposed workers compared with controls.

Concentrations of elements, PFAS, and PAH metabolites were categorised by company and work task (Table S3). Steel production companies showed the highest levels of Mn, Pb, and PAHs. The highest concentrations of Cr, PFHpA, PFHxS, PFHpS, and PFOS were observed in bath plating companies. Subgroup analyses in SAM-Krom study were presented in Table S4. In the SAM-Krom study, exposed workers in bath plating company had higher concentrations of Cr and PFHpA but lower concentrations of PFOA, PFNA, PFDA and PFUnDA compared with the controls recruited in the same company. Controls at the bath plating

Table 1
Characteristics of study participants and results of effect biomarkers.

	All participants		SafeChrom		SAM-Krom	
	Exposed workers (N=138)	Controls (N=96)	Exposed workers (n=113)	Controls (n=72)	Exposed workers (n=25)	Controls (n=24)
Age, median (P5, P95)	41.0 (22.0, 60.1)	45.5 (21.0, 64.1)	39.0 (21.7, 60.3)[a]	43.5 (27.7, 60.4)	50.0 (26.3, 66.8)	53.0 (18.5, 69.8)
Male, n (%)	123 (89.1)[b]	70 (72.9)	98 (86.7)[b]	50 (69.4)	25 (100)	20 (83.3)
Current smokers, n (%)	20 (14.5)	11(11.5)	10 (8.8)	4 (5.6)	10 (40.0)	7 (29.2)
Alcohol drinkers, n (%)	125 (90.6)[b]	77 (80.2)	103 (91.2)[b]	56 (77.8)	22 (88.0)	21 (87.5)
Effect biomarkers, median (P5, P95)						
8-OHdG[c]	60.7 (29.5, 104.5)	60.2 (28.7, 96.2)	58.2 (29.0, 92.9)	52.4 (27.2, 91.4)	71.8 (47.9, 136.9)	80.7 (46.2, 114.9)
mtDNA-cn[d]	1.5 (0.9, 2.4)[a]	1.6 (1.0, 2.4)	1.6 (1.0, 2.3)[a]	1.7 (1.0, 2.5)	1.4 (0.6, 4.7)	1.5 (1.0, 2.8)
TL[e]	0.8 (0.4, 1.3)[a]	0.7 (0.4, 1.1)	0.8 (0.5, 1.4)[a]	0.7 (0.4, 1.1)	0.5 (0.2, 0.9)	0.7 (0.3, 1.8)
MNRET[f]	1.9 (0.6, 6.1)	2.1 (0.7, 7.2)	2.0 (0.6, 6.0)[a]	2.5 (1.0, 8.3)	1.6 (0.8, 10.9)[a]	1.1 (0.7, 2.1)
MGMT[g]			1.9 (1.5, 3.6)[a]	1.8 (1.3, 2.7)		

a. Mann-Whitney U test, Exposed workers versus Controls, $P<0.05$.
b. Pearson Chi-Square test, Exposed workers versus Controls, $P<0.05$.
c. 8-hydroxy-2'-deoxyguanosine concentration (8-OHdG), pg/mL
d. Relative mitochondrial DNA copy number (mtDNA-cn)
e. Relative telomere length (TL)
f. Micronuclei in peripheral blood reticulocytes (MNRET, ‰). Due to 6 missing samples and 4 samples having too few cells, the result was for 105 exposed workers and 70 controls in SafeChrom study.
g. Methylation level of O-6-methylguanine-DNA methyltransferase promoter (*MGMT*, %), only measured in the SafeChrom study.

Table 2
Results of exposure biomarkers; data presented as median (P5, P95)

	All participants		SafeChrom		SAM-Krom	
	Exposed workers (N=138)	Controls (N=96)	Exposed workers (n=113)	Controls (n=72)	Exposed workers (n=25)	Controls (n=24)
Elements[a]						
Chromium	0.75 (0.52, 2.48)*	0.54 (0.44, 0.82)	0.73 (0.51, 2.33)*	0.53 (0.42, 0.72)	0.89 (0.54, 4.91)*	0.60 (0.50, 0.93)
Manganese	16.1 (10.0, 27.5)*	14.9 (9.8, 25.2)	16.9 (11.1, 28.6)	15.6 (10.7, 27.2)	13.8 (7.8, 25.6)	12.4 (7.7, 21.4)
Copper	557 (411, 658)*	507 (372, 603)	571 (468, 667)*	525 (433, 619)	465 (321, 584)	447 (331, 531)
Zinc	10670 (8641, 12821)*	10356 (7432, 12516)	10728 (8640, 12834)*	10496 (7981, 12772)	10488 (8712, 13007)*	9512 (6347, 11549)
Lead	23.7 (10.3, 139.5)*	20.1 (8.2, 48.0)	22.7 (10.32, 112.2)	20.5 (8.2, 49.6)	25.7 (10.0, 221.2)*	16.1 (4.8, 66.5)
PFAS[b]						
PFHpA	0.02 (0.01, 0.12)*	0.02 (0.00, 0.06)	0.02 (0.01, 0.07)*	0.01 (0.01, 0.05)	0.04 (0.01, 2.41)	0.03 (0.00, 0.13)
PFHxS	0.83 (0.29, 2.83)	0.83 (0.34, 1.87)	0.82 (0.31, 2.55)	0.83 (0.38, 1.88)	0.88 (0.18, 8.86)	0.77 (0.27, 2.76)
PFOA	1.11 (0.49, 2.04)	1.06 (0.32, 2.19)	1.12 (0.53, 2.07)	1.02 (0.33, 1.93)	0.94 (0.26, 2.70)	1.10 (0.18, 4.56)
PFHpS	0.10 (0.02, 1.88)	0.11 (0.03, 0.41)	0.09 (0.02, 0.27)	0.09 (0.03, 0.26)	0.18 (0.04, 16.04)	0.13 (0.03, 4.04)
PFNA	0.39 (0.14, 0.89)	0.43 (0.13, 1.13)	0.37 (0.13, 0.94)	0.40 (0.13, 1.12)	0.43 (0.15, 0.77)	0.48 (0.12, 1.18)
PFOS	4.17 (1.60, 243.54)	4.42 (1.54, 16.34)	3.85 (1.60, 16.78)	4.27 (1.35, 11.23)	6.44 (1.74, 2044)*	4.80 (1.89, 579)
PFDA	0.15 (0.05, 0.43)	0.14 (0.04, 0.41)	0.15 (0.05, 0.50)	0.14 (0.04, 0.38)	0.16 (0.05, 0.28)	0.15 (0.06, 0.46)
PFUnDA	0.11 (0.03, 0.43)	0.12 (0.03, 0.33)	0.12 (0.03, 0.36)	0.13 (0.03, 0.35)	0.09 (0.04, 0.19)	0.11 (0.02, 0.25)
PAHs[c]			0.61 (0.21, 2.03)*	0.45 (0.15, 2.38)		
1-hydroxypyrene			0.08 (0.02, 0.37)	0.07 (0.01, 0.29)		
2-hydroxyphenanthrene			0.13 (0.04, 0.66)	0.11 (0.03, 0.65)		
2,3-dihydroxyfluorene			0.22 (0.07, 1.08)*	0.16 (0.04, 0.73)		
1-hydroxyphenanthrene			0.11 (0.04, 0.37)	0.10 (0.02, 0.64)		

a. Elements concentration in red blood cells, μg/L
b. Per- and polyfluoroalkyl substances (PFAS) concentration, ng/mL
c. Total polycyclic aromatic hydrocarbons (PAHs) concentration in post-work urine, only measured in SafeChrom study, density-adjusted ng/mL
*. Mann-Whitney U test, Exposed workers versus Controls, $P<0.05$

company showed higher concentrations of six out of eight PFAS compared with controls from other companies.

Correlations between elements and PFAS in all participants are presented in Fig. S1A. The strongest correlation within elements was between Cu and Zn ($r_S = 0.45$), while other metal–metal correlations were generally weak ($-0.30 < r_S < 0.30$). Most correlations between elements and PFAS were not statistically significant. The only positive significant correlation was between Cr and PFHpS ($r_S = 0.18$). Other significant correlations involving Mn and Cu with PFAS were negative and relatively weak ($r_S > -0.30$). All correlations between PFAS were significant and relatively strong. When considering only the exposed workers (Fig. S1B), the correlations between Cr and PFAS strengthened, showing positive associations with PFHpA, PFHxS, PFOA, PFHpS, PFNA, and PFOS ($0.19 < r_S < 0.40$), and negative associations with PFDA and PFUnDA ($r_S = -0.34$ and -0.14, respectively). In addition, the r_S of the correlation between Cr and Pb increased from 0.25 to 0.33. The remaining correlations showed minimal or no notable changes.

3.3. Single association between effect biomarkers and exposure biomarkers

Table S5 presents the correlations between effect biomarkers and age, elements, and PFAS across all participants. All correlations were rather weak from 0 to 0.35. Age was significantly positively correlated with 8-OHdG and negatively correlated with TL. Cu was significantly positively correlated with TL, while Zn, PFHpA, PFHpS and PFOS were negatively correlated. Incorporating additional data on *MGMT* and PAHs, correlations were further examined in the SafeChrom study (Table S6), where we found that Cr, PFOS and PFDA were significantly positively correlated with *MGMT* ($r_S < 0.20$) and PAHs were significantly negatively correlated with 8-OHdG, with r_S ranging from -0.35 to -0.20.

Linear regression models showed that Mn, Cu and PFNA were inversely associated with 8-OHdG, while PFHxS and PFDA showed positive associations (Table 3). Cr, Pb, PFHpA, and PFHxS were all negatively associated with both mtDNA-cn and TL. PFOS was also negatively associated with mtDNA-cn. After adjusting for covariates, most associations remained statistically significant. However, the

associations of Mn, Cu and PFHxS with 8-OHdG, Cr with mtDNA-cn, and Pb and PFHxS with TL were no longer significant. Additionally, following covariate adjustment, PAHs were negatively associated with 8-OHdG, and Cr, PFNA and PFUnDA were positively associated with *MGMT* in SafeChrom study (Table S7).

3.4. Mixture analyses based on BKMR

Fig. 1 displays the overall associations between exposure mixtures and effect biomarkers in BKMR models. After adjusting for covariates, higher concentrations of the exposure mixture were associated with elevated 8-OHdG levels. Compared with the 25th percentile exposure of the mixtures, 8-OHdG concentration elevated as all exposure biomarkers simultaneously increased across percentiles. There were also suggestive inverse associations between the exposure mixtures and mtDNA-cn, but the findings did not reach statistical significance. The PIP results from the BKMR models (Table S8) indicated the relative contribution of each exposure to the overall mixture effect. PFDA had the highest PIP (0.95) in relation to 8-OHdG. PFDA also showed the strongest influence on mtDNA-cn (0.74), followed by Cr (0.60). For TL, Cr was the primary contributor with a PIP greater than 0.90. Fig. S2 illustrates the associations of individual exposure with effect biomarkers when holding the other exposure at the 25th, 50th, and 75th percentiles. Positive associations between PFDA and 8-OHdG were consistently observed in BKMR models. Consistent findings were observed in the SafeChrom study, incorporating additional data on *MGMT* and PAHs (Figs. S3 and S4, Table S9). A significant association was again observed between the exposure mixture and 8-OHdG, with PFDA identified as a major contributor. In addition, mtDNA-cn levels declined when all exposures were between the 30th and 55th percentiles compared to the 25th percentile; however, this association was no longer significant after adjusting for covariates.

3.5. Mixture analyses by qgcomp method

Fig. 2 and Table S10 show the joint associations between exposure mixtures and effect biomarkers, as assessed using qgcomp. The overall mixture was not significantly associated with any of the biomarkers. Among individual exposures, PFDA contributed most positively and PFNA most negatively to 8-OHdG levels. For TL, Cr and PFUnDA contributed positively, while PFOS contributed negatively. In relation to MNRET, Cr and PFHpA showed negative contributions, whereas PFOS had a positive contribution. Similar patterns were observed in the SafeChrom study, which included additional data on *MGMT* and PAHs (Table S11 and Fig. S5). Notably, the exposure mixture was significantly and positively associated with *MGMT*, primarily driven by Cr, the only component with a statistically significant contribution (positive weight = 0.24).

4. Discussion

In this study, we investigated occupational co-exposure to Cr(VI),

Table 3
Linear regression models for single association between logarithm-transformed effect biomarkers and exposure biomarkers for all participants; data are presented as beta coefficient (β) (95 % confidence interval (95 % CI)).

	Unadjusted				Adjusted[e]			
	8-OHdG[a]	mtDNA-cn[b]	TL[c]	MNRET[d]	8-OHdG	mtDNA-cn	TL	MNRET
Elements[f]								
Chromium	0.03 (−0.06, 0.11)	−0.08 (−0.14, −0.02)*	−0.16 (−0.24, −0.08)*	0.02 (−0.12, -0.17)	−0.03 (−0.11, 0.05)	−0.05 (−0.11, 0.02)	−0.11 (−0.19, −0.04)*	0.12 (−0.03, 0.27)
Manganese	−0.01 (−0.02, 0.00)*	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.01 (−0.01, 0.03)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.00 (−0.02, 0.02)
Copper	−0.08 (−0.15, −0.01)*	0.02 (−0.03, 0.07)	0.09 (0.03, 0.16)*	0.09 (−0.03, 0.21)	0.04 (−0.04, 0.11)	0.01 (−0.06, 0.07)	−0.01 (−0.09, 0.06)	−0.07 (−0.21, 0.08)
Zinc	0.00 (−0.04, 0.04)	−0.01 (−0.04, 0.02)	−0.03 (−0.07, 0.00)	0.05 (−0.01, 0.12)	0.01 (−0.02, 0.05)	−0.01 (−0.04, 0.01)	−0.04 (−0.08, −0.01)*	0.02 (−0.04, 0.09)
Lead	0.08 (−0.08, 0.24)	−0.17 (−0.29, −0.05)*	−0.18 (−0.32, −0.03)*	0.13 (−0.15, 0.41)	−0.02 (−0.18, 0.13)	−0.16 (−0.27, −0.04)*	−0.06 (−0.20, 0.08)	0.27 (−0.01, 0.54)
PFAS[g]								
PFHpA	0.22 (−0.01, 0.45)	−0.24 (−0.41, −0.07)*	−0.42 (−0.63, −0.21)*	−0.03 (−0.44, 0.39)	0.08 (−0.14, 0.30)	−0.19 (−0.36, −0.02)*	−0.28 (−0.48, −0.08)*	0.20 (−0.21, 0.61)
PFHxS	0.06 (0.00, 0.11)*	−0.05 (−0.09, −0.01)*	−0.07 (−0.12, −0.02)*	−0.01 (−0.10, 0.09)	0.02 (−0.04, 0.07)	−0.05 (−0.09, −0.00)*	−0.03 (−0.08, 0.02)	0.03 (−0.07, 0.13)
PFOA	0.07 (−0.02, 0.16)	−0.02 (−0.09, 0.04)	−0.02 (−0.10, 0.06)	0.02 (−0.13, 0.17)	0.03 (−0.06, 0.11)	−0.02 (−0.08, 0.05)	0.03 (−0.05, 0.11)	0.04 (−0.11, 0.19)
PFHpS	0.02 (−0.01, 0.05)	−0.02 (−0.05, 0.00)	−0.02 (−0.05, 0.01)	−0.01 (−0.07, 0.05)	−0.01 (−0.04, 0.03)	−0.02 (−0.05, 0.00)	0.00 (−0.03, 0.03)	0.02 (−0.04, 0.09)
PFNA	−0.28 (−0.45, −0.10)*	0.02 (−0.11, 0.16)	−0.02 (−0.19, 0.15)	−0.07 (−0.38, 0.24)	−0.34 (−0.50, −0.17)*	0.03 (−0.10, 0.16)	0.08 (−0.08, 0.24)	−0.09 (−0.39, 0.22)
PFOS	0.02 (−0.01, 0.04)	−0.02 (−0.04, −0.01)*	−0.02 (−0.05, 0.00)	−0.01 (−0.06, 0.04)	0.00 (−0.03, 0.02)	−0.02 (−0.04, −0.00)*	−0.01 (−0.03, 0.02)	0.02 (−0.03, 0.07)
PFDA	0.84 (0.44, 1.23)*	−0.27 (−0.57, 0.04)	−0.03 (−0.42, 0.36)	−0.84 (−1.58, −0.10)*	0.87 (0.50, 1.24)*	−0.29 (−0.59, 0.01)	0.03 (−0.33, 0.39)	−0.94 (−1.66, −0.23)*
PFUnDA	−0.44 (−0.98, 0.11)	0.18 (−0.23, 0.59)	0.24 (−0.28, 0.75)	0.07 (−0.92, 1.07)	−0.21 (−0.74, 0.33)	0.15 (−0.28, 0.57)	0.25 (−0.25, 0.75)	−0.36 (−1.37, 0.65)

*$P < 0.05$.
[a] 8-hydroxy-2′-deoxyguanosine (8-OHdG) concentration.
[b] Relative mitochondrial DNA copy number (mtDNA-cn).
[c] Relative telomere length (TL).
[d] Micronuclei in peripheral blood reticulocytes (MNRET).
[e] The adjusted model was adjusted for age, sex, smoking, alcohol drinking and study. The references were males, non-smokers, non-alcohol drinkers and participants in SafeChrom study.
[f] Elements concentration in red blood cells. To improve interpretability of the regression coefficients, the concentrations of copper, lead and PFOS were divided by 100, and zinc were divided 1000, prior to analysis.
[g] Per- and polyfluoroalkyl substances (PFAS) concentration.

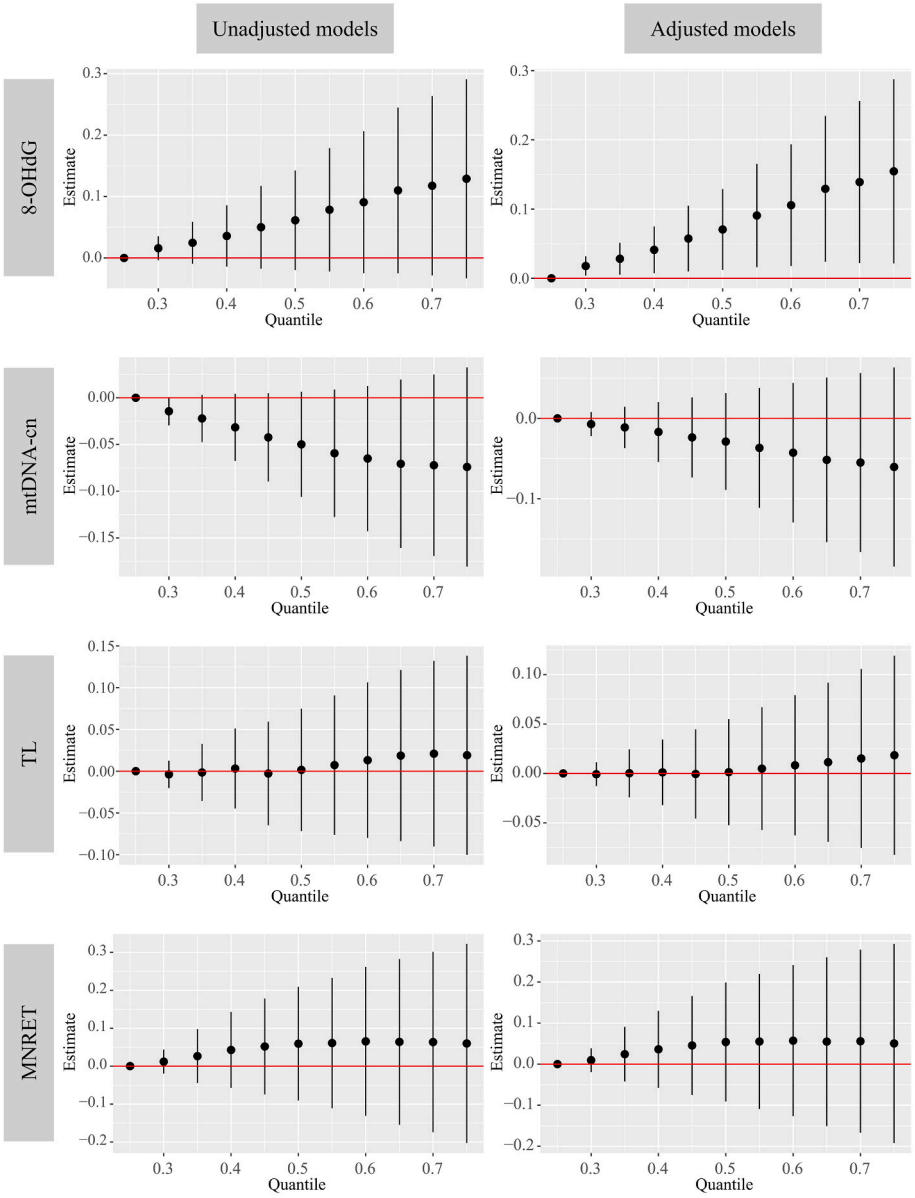

Fig. 1. Overall effect of the exposure mixture in relation to logarithm-transformed effect biomarkers for all participants: results from hierarchical Bayesian Kernel Machine Regression (BKMR) modeling. Overall effect of the mixture (95 % CI), defined as the difference in the response (y-axis) when all of exposures are fixed at a specific percentile (x-axis), as compared to when all exposures are fixed at the 25th percentile. Results are reported for unadjusted models and adjusted models (adjusted for age, sex, smoking and alcohol drinking) separately.

various elements, and PFAS, and their associations with several effect biomarkers. Our results revealed that Cr(VI)-exposed workers had significantly higher levels of multiple elements (Cr, Mn, Cu, Zn, and Pb) and selected PFAS (notably PFHpA and PFOS), compared with controls. These exposures were associated with changes in multiple biomarkers, including lower mtDNA-cn, longer TL, and higher levels of 8-OHdG and *MGMT* promoter methylation. While these substance-specific findings are important, they do not fully reflect the complex nature of occupational exposure. Therefore, we applied mixture analysis models to better capture the combined effects of co-occurring toxicants. These analyses revealed distinct exposure–effect patterns, particularly in relation to oxidative and epigenetic markers, that were not apparent when evaluating individual exposures alone. Given the central role of these findings in understanding cumulative risk, we begin the discussion by highlighting the significance of the mixed exposure analysis.

4.1. *Significance of mixed exposure analysis*

After adjusting for confounders, the BKMR approach revealed that higher concentrations of the exposure mixture were associated with increased levels of 8-OHdG. Notably, PFDA consistently emerged as the most influential contributor to elevated 8-OHdG levels, both among all participants and specifically within the SafeChrom study population. Among PFAS, PFDA is considered one of the most toxic compounds (Widhalm et al., 2025). Studies have shown that PFDA can induce genotoxicity by triggering oxidative stress at cellular and molecular levels (Xu et al., 2019). In our study, PFDA consistently emerged as the most influential contributor to elevated 8-OHdG levels and down-regulation of mtDNA-cn across both the BKMR and gqcomp models. These observations raise the possibility that PFDA may be involved in mitochondrial dysfunction via oxidative stress–related pathways. For TL, Cr(VI) demonstrated the strongest and most consistent positive association among all exposures, with a PIP greater than 0.90 in the BKMR

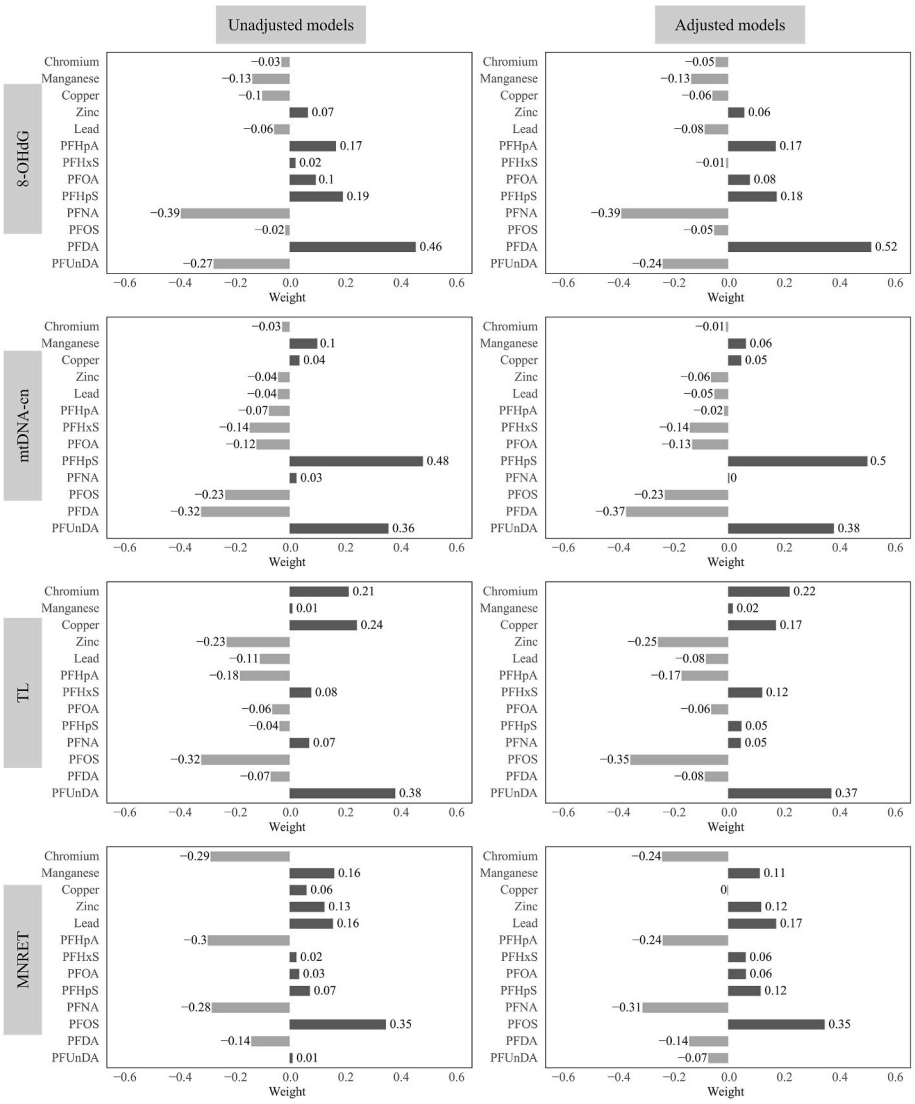

Fig. 2. The directions and magnitude of the assigned weights for each exposure biomarkers in the associations with logarithm-transformed effect biomarkers in all participants: results from quantile-based g-computation models. Each weight represents the proportion of the positive or negative partial impact per individual exposure biomarkers. The length of each bar indicates the effect size of each exposure in the same direction. Results are reported for unadjusted model and adjusted model (adjusted for age, sex, smoking and alcohol drinking) separately.

model and a dominant positive weight in qgcomp. These findings reinforce our earlier observations of TL elongation in workers exposed to Cr (VI). The results for *MGMT* promoter methylation in the SafeChrom study further highlight the role of exposure mixture to epigenetic changes, with Cr(VI) being the only statistically significant contributor in adjusted qgcomp models. This finding aligns with previous reports of Cr(VI)-induced epigenetic alterations and suggests that it may also impact DNA repair pathways (Hu et al., 2018). Despite relatively high concentrations of PFOS in some participants, no significant associations were found between PFOS levels and any of the analyzed effect biomarkers. This suggests that, within the exposure range observed, PFOS did not exert measurable biological effects on these endpoints.

4.2. Elevated elements, PFAS and PAHs levels

The elevated levels of Mn, Cu, Zn and Pb observed among Cr(VI)-exposed workers are consistent with occupational tasks such as machining, welding, grinding, and electroplating, where multiple metal exposures commonly co-occur. Welding fumes can contain various elements besides Cr(VI), and their composition varies depending on several factors, such as the type of metal being welded, surface coatings, welding technique, and the electrode material (Pourhassan et al., 2024). Mn is a critical component in steel welding, as it enhances the hardness and strength of the material, thereby reducing the risk of cracking during the manufacturing process (Ni et al., 2024). High exposure to Mn via welding fumes has been linked to neurological symptoms resembling Parkinson's disease (Sriram et al., 2015). Occupational co-exposure to Cu may occur during air carbon arc gouging, where Cu-coated carbon electrodes are commonly used (Berlinger et al., 2019). In addition, an animal study reported that Cr(VI) exposure altered the distribution of blood elements, including an increase in Cu levels (Li et al., 2024). The authors speculated that this elevation might be related to increased oxidative stress and inflammation. Steel production workers (Lan et al., 2024), galvanizing workers (Riccò et al., 2018), and galvanized welding workers (Laohaudomchok et al., 2010) may experience co-exposure to Zn. Chronic occupational exposure to zinc could impair lung function and asthma-like symptoms, while data remain limited on carcinogenicity, reproductive toxicity, and teratogenicity (Pakulska & Czerczak, 2017). Cr(VI)-exposed workers can also be exposed to Pbduring chrome plating (Muller et al., 2022), and may be present in welding fumes (Aksu et al., 2019), pipe repair workshops (Widyantoro et al., 2021), steel and alloy production (Bonberg et al., 2017), and during wall cleaning

processes such as sandblasting (Prokopciuk et al., 2023). Chronic occupational exposure to zinc could impair lung function and asthma-like symptoms, while data remain limited on carcinogenicity, reproductive toxicity, and teratogenicity (Kalahasthi et al., 2022). Cr (VI)-exposed workers can also be exposed to Pb, which is used as the anode during chrome plating, and may be present in welding fumes (Aksu et al., 2019), pipe repair workshops (Widyantoro et al., 2021), steel and alloy production (Bonberg et al., 2017), and during wall cleaning processes such as sandblasting (Prokopciuk et al., 2023). Substantial evidence indicates that chronic Pb exposure can adversely affect multiple organ systems, including cardiovascular, nervous, hepatic, and renal (Collin et al., 2022). Our findings support the notion that Cr(VI) exposure in occupational settings does not occur in isolation, but as part of a broader exposure profile, which may be underappreciated in regulatory risk assessments.

Commonly referred to as "forever chemicals" due to their exceptional chemical stability (Evich et al., 2022; Schlezinger & Gokce, 2024). Although contaminated drinking water has been widely studied, considerably less attention has been given to potential occupational exposure to PFAS (Gaines & Nylander-French, 2023). Occupational exposure to PFAS may occur through aerosolization or volatilization during the application or handling of PFAS-contaminated materials (Paris-Davila et al., 2023). Lucas K *et al.* conducted a comprehensive review to identify worker populations potentially experiencing occupational exposure to PFAS (Lucas et al., 2023). Their findings indicated that professional ski wax technicians, workers in fluoropolymer manufacturing facilities, PFOA production plants, fluorochemical plants, as well as firefighters, are among the occupational groups exposed to PFAS. Reported serum PFOS concentrations reached as high as approximately 1000 ng/mL in some exposed individuals. However, limited research has examined PFAS exposure among workers occupationally exposed to Cr(VI).

Co-exposure to Cr(VI) and PFOS occurs mainly in the electroplating industry, where PFOS-containing compounds have primarily been used as mist suppressants (Xie et al., 2013). The HBM4EU Chromates study reported that electroplaters and welders had higher concentrations of PFOS, PFHxS, and PFHpS compared with controls (median and P95 for electroplaters: PFOS (4.83 ng/mL, 192 ng/mL), PFHxS (1.29, 10.20), and PFHpS (0.26, 5.20); for welders: PFOS (4.97, 560), PFHxS (0.55, 22.3), and PFHpS (<0.2, 16.1)) (Göen et al., 2024). Similar patterns were observed among workers from bath plating companies in the present study (PFOS (16.2, 1803), PFHxS (1.2, 8.7), and PFHpS (0.2, 14.1)), especially in the Danish SAM-Krom study. In contrast, welders in the present study did not exhibit elevated levels of these compounds, with PFOS (4.4, 8.6), PFHxS (0.9, 2.5), and PFHpS (0.1, 0.2) remaining relatively low. The HBM4EU study attributed the elevated PFAS levels observed among welders to their recruitment from electroplating facilities, where they were likely exposed as bystanders in proximity to plating operations. However, the welders in our study were primarily recruited from companies involved in the manufacturing or processing of metal products, which involve minimal or no use of PFAS-containing substances. Notably, PFOS levels in the SAM-Krom study were exceptionally elevated, with the 95th percentile exceeding 2000 ng/mL. To our knowledge, these represent some of the highest concentrations reported worldwide, second only to the peak level of 12,830 ng/mL recorded in the 3M Company study in 1999 (Olsen et al., 1999). Given that PFHpS, PFHxS, and PFHpA are common impurities in the production of PFOS via electrochemical fluorination (Jiang et al., 2015), it is not surprising that we observed generally elevated levels of these PFAS among the bath platers.

From an occupational hygiene perspective, it is especially worrying that within company controls at chrome plating companies also had a high PFOS level in the Danish SAM-Krom study. If PFOS is still present in the chrome plating baths even though PFOS use as CMS was discontinued 5–10 years ago, exposure may have occurred or still occur by inhalation of chrome bath mists or by hand-to-mouth contamination in direct contact with bath plating components, or mist residue settling on clothing, equipment and surroundings (e.g. door handles, staircase or walkway railings also used by company controls). This points to a need for continued focus on effective preventive measures, preferably in the higher levels of the hierarchy of controls through elimination, substitution and technical solutions, as well as ensuring proper hygiene (hand washing), cleaning and use of personal protective equipment.

Although PAH exposure is also associated with an increased risk of lung cancer, studies investigating co-exposure to PAHs and Cr(VI) remain relatively limited. Tavares, AM *et al.* found that workers in hazardous waste incinerators were simultaneously exposed to Cr(VI), nickel, and PAHs, and the combined exposure posed a health concern, as indicated by a Sum of Risk Quotients greater than 1 (A. M. Tavares et al., 2022). We also found that the Cr(VI)-exposed worker in the SafeChrom project had a higher concentration of urinary PAH metabolites, especially in steel production companies. This is consistent with the fact that steel enterprises are a significant source of PAHs, with processes such as coking, sintering, ironmaking, and steelmaking generating PAHs that are released into the surrounding environment (Sun et al., 2019). However, the overall exposure levels were generally low, even in SafeChrom exposed workers, suggesting limited additional PAH burden in this population.

4.3. Effect biomarker changes

Increased levels of oxidative stress are regarded as a key mechanism underlying Cr(VI)-induced cellular damage and carcinogenesis (DesMarais & Costa, 2019). Urinary 8-OHdG has been recognized as a biomarker not only related to oxidative damage but also to Cr (VI)-induced mutagenicity and cancer development (Ventura et al., 2021). We also found elevated urinary 8-OHdG concentrations in the SafeChrom project (Jiang et al., 2025). The present study found that 8-OHdG was negatively correlated with Mn, Cu and PAHs, and positively correlated with PFAS, suggesting that potential antagonistic or synergistic effects among different environmental contaminants may modulate the oxidative stress response in exposed individuals. These findings underscore the importance of considering combined exposures in the assessment of oxidative damage biomarkers.

Consistent with our previous findings in SafeChrom study (Jiang et al., 2025), the inclusion of the SAM-Krom study showed that exposed workers have lower mtDNA-cn and longer TL compared with controls. Cellular and animal studies have demonstrated that exposure to Cr(VI) reduces mtDNA-cn, mitochondrial mass and function, and suppresses mitochondrial biogenesis (Li et al., 2024; Zhong et al., 2017). This mitochondrial dysfunction is thought to result from increased oxidative stress, impaired DNA repair mechanisms, and direct mitochondrial DNA damage caused by Cr(VI) or its intracellular reduction intermediates (Alur et al., 2024). Telomere shortening is typically associated with oxidative stress and cellular aging (Gavia-García et al., 2021), however, longer telomeres have been linked to an increased risk of lung cancer (Rode et al., 2016). By extending cellular growth potential, they facilitate the accumulation of genetic alterations and the development of cancer-initiating somatic mutations (Tsatsakis et al., 2023). Although TL was slightly longer in exposed workers in our study, both the BKMR and qgcomp models showed no significant association between the exposure mixture and TL. In the SafeChrom study, the association was negative, though not statistically significant. One cross-sectional study found a negative association between blood Cr concentrations and TL in chromate production workers (Zhang et al., 2024). This discrepancy may be explained by the biphasic effects of Cr(VI) exposure on telomere dynamics: low exposure levels may induce mild oxidative stress that positively influences telomere length (Ahmed & Lingner, 2018), while higher levels generate more severe oxidative stress that can overwhelm cellular repair mechanisms, ultimately resulting in telomere shortening (Barnes et al., 2019).

The *MGMT* gene encodes a DNA repair enzyme that protects normal

cells from carcinogenic damage (Thon et al., 2013). Hypermethylation of the *MGMT* promoter leads to epigenetic silencing of its transcription (Butler et al., 2020). A previous study have shown that the *MGMT* gene promoter exhibits a higher methylation rate in the humoral tissue of lung cancer cases compared with controls (Chen et al., 2021). These findings indicate that MGMT promoter methylation status could serve as a potential biomarker for assessing cancer risk related to occupational Cr (VI) exposure.

4.4. Strengths and limitations

This study has several notable strengths. First, it combines data from two well-characterized and highly comparable occupational studies, the Swedish SafeChrom and Danish SAM-Krom studies. This allows a broader assessment of exposure profiles. Second, we evaluated co-exposure to Cr(VI), other elements, and PFAS, applying complementary mixture modeling approaches to examine their combined effects on multiple biologically relevant biomarkers. Third, all analyses were adjusted for key covariates (age, sex, smoking, alcohol consumption, and study), and study-stratified analyses were conducted to confirm the consistency of patterns across studies.

Study differences exist, including sex distribution and smoking prevalence, which were accounted for in the statistical analyses. The observed extremely high PFOS levels may influence pooled results, and caution should be exercised when interpreting individual high measurements. Additionally, the cross-sectional design does not allow causal inference. While the study provides important insights into mixture effects and early biological alterations, further longitudinal studies are needed to confirm these findings and assess potential long-term health impacts.

5. Conclusions

In conclusion, our findings indicate that workers exposed to Cr(VI) also encounter multiple occupational contaminants. Workers and bystanders in the chrome plating industry exhibit concerningly elevated PFOS levels. Combined exposure to Cr(VI), other elements, PFAS, and PAHs may contribute to early biological changes linked to oxidative stress and DNA methylation, underscoring the importance of accounting for co-exposures in occupational settings. Mixture models proved useful in identifying key contributors within complex exposure profiles, with PFDA primarily driving oxidative stress and Cr predominantly influencing *MGMT* DNA methylation changes. These results highlight the need for integrated exposure monitoring, targeted preventive measures, and further longitudinal research to clarify the health impacts of such multifaceted exposures.

CRediT authorship contribution statement

Zheshun Jiang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Yishan Liu:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Christian Lindh:** Writing – review & editing, Methodology, Formal analysis. **Daniela Pineda:** Writing – review & editing, Project administration, Methodology, Formal analysis. **Tanja K. Carøe:** Writing – review & editing. **Julia Catalán:** Writing – review & editing, Methodology. **Niels E. Ebbehøj:** Writing – review & editing, Methodology. **Lucas Givelet:** Writing – review & editing, Formal analysis. **Anja J. Huusom:** Writing – review & editing, Investigation. **Pete Kines:** Writing – review & editing, Methodology. **Annette M. Krais:** Writing – review & editing. **Kukka Aimonen:** Writing – review & editing, Methodology, Formal analysis. **Thomas Lundh:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Katrin Loeschner:** Writing – review & editing, Methodology. **Hamideh Rastkhani:** Methodology, Formal analysis. **Martin Tondel:** Writing – review & editing. **Anne T. Saber:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ulla Vogel:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Karin Broberg:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Karin Broberg reports financial support was provided by Forskningsrådet för hälsa arbetsliv och välfärd. Karin Broberg reports financial support was provided by Afa Försäkring. Ulla Vogel reports financial support was provided by Danish Working Environment Research Fund. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2025.127255.

Data availability

Data will be made available on request.

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