Regulatory Toxicology and Pharmacology 136 (2022) 105276

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Occupational exposure to Cr(VI) in Finland in 1980–2016 and related lung cancer risk assessment

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ARTICLE INFO

Keywords:
Hexavalent chromium
Human biomonitoring
Occupational exposure
Risk assessment
Lung cancer
HBM4EU

ABSTRACT

Occupational exposure to hexavalent chromium [Cr(VI)], a known lung carcinogen, remains a relevant concern. When performing exposure assessment for risk assessment, biomonitoring is an important tool, reflecting actual internal exposure of workers. Here, we present total urinary chromium (U–Cr) biomonitoring data from several occupational sectors, spanning 1980–2016 ($n > 42,000$). Based on these data, we estimated lifelong (40-year) occupational lung cancer risks in the Cr-plating and welding sectors. We used published regression formulas to relate internal (U–Cr) and external Cr(VI) inhalation exposures, allowing risk assessment based on a published lung cancer dose-response. Generally, measured U–Cr levels decreased considerably over the study period. The overall highest U–Cr P95 levels (representing realistic worst-case) were measured in the interval 1980–1989 in casters, maintenance workers and welders (40–45 μg/L). By the interval 2010–2016, the U–Cr P95 had decreased to ≤9.5 μg/L in all studied sectors. Lifelong external Cr(VI) exposure estimation for 1980–2019 was 0.16–0.32 mg/m^3 x year for platers and 1.03 mg/m^3 x year for welders. Worst-case lifelong lung cancer relative risk (RR) estimates were 1.28–1.56 for platers and 2.80 for welders; attributable risks (AR) were 22–36% for platers and 64% for welders. Uncertainties that may have impacted the risk assessment are discussed.

1. Introduction

Hexavalent chromium [Cr(VI)] compounds (chromates) are known occupational lung carcinogens. In addition, there is evidence for an increased risk for nose and nasal sinus cancer in chromate exposed workers (IARC 2012; Palmen et al., 2018). Also an association with stomach cancer has been suspected and in animal studies, Cr(VI) compounds caused an increased incidence of intestinal cancers (ECHA 2013). Non-cancer effects of Cr(VI) include nasal septum ulcerations and perforation, chronic lung diseases, respiratory allergy (asthma and rhinitis) and allergic contact dermatitis in humans, and reproductive and developmental toxicity in experimental animals (Kapp 2005).

Despite the use of chromates being subject to authorisation under the European regulation concerning Registration, Evaluation, Authorization and Restriction of Chemicals (REACH; EC, 1907/2006), occupational exposure to Cr(VI) remains a relevant concern also in Europe. Cr(VI) compounds are still widely used in authorised industrial applications, mostly due to their technical advantages in producing hard and corrosion tolerant coatings. More than 100 authorisations, some covering hundreds of workers, have already been requested and granted, meaning continuing exposure of thousands of European workers to Cr(VI) in these activities (ECHA 2019a). Cr(VI) is also present in process-generated fumes that are not covered by REACH, e.g. in manufacturing and welding of stainless steel (Scheepers et al., 2008).

Health risk assessment consists of exposure and hazard assessment. In occupational settings, occupational hygiene measurements, such as air monitoring, are a gold standard for external exposure assessment. In addition, internal exposure assessment, meaning biomonitoring, typically from workers' urine or blood, has a long-standing tradition in occupational health interventions. It is an important addition to external exposure assessment information, because when performed correctly, biomonitoring reflects the actual exposure, and encompasses all

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https://doi.org/10.1016/j.yrtph.2022.105276
Received 30 December 2021; Received in revised form 27 September 2022; Accepted 7 October 2022

occupationally relevant routes of exposure (inhalation, dermal, ingestion due to hand to mouth contact) (Viegas et al., 2020).

Management of occupational exposure to Cr(VI) is achieved by compliance with occupational exposure limit values (OELs). The recent binding occupational limit value (BOELV) for the air concentrations of Cr(VI), set under the EU Directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (2004/37/EC), is 0.01 mg Cr(VI)/m^3 for a period of 5 years after the transposition date of 2017; after that period a limit of 0.005 mg Cr(VI)/m^3 will apply. For welding or plasma-cutting processes or similar work processes that generate fumes, there is a derogation, with an OEL value of 0.025 mg Cr(VI)/m^3 until 5 years after the transposition date; after that period, the limit will be 0.005 mg Cr(VI)/m^3. No EU-wide biological limit value (BLV) has been set for Cr(VI), but some EU member states have defined national BLVs for the internal occupational exposure to Cr(VI), measured as total urinary chromium (U–Cr). For example, in Finland and France, BLVs of 10 μg/L and 2.5 μg/L, respectively, have been set, corresponding to the respective OELs of 5 μg/m^3 and 1 μg/m^3 for Cr(VI) (ANSES 2017; STM 2020).

While compliance with the current OELs and BLVs helps to ensure relatively safe working environments, particularly historically this has not always been achieved. When making health risk assessment based on past exposure, either for epidemiological studies examining dose-responses or for individual workers, e.g. for a diagnosis of a possible occupational disease, assessment of exposure as reliably as possible is essential. In such cases, measured data on exposure, i.e. Cr(VI) air concentrations and/or Cr biomonitoring data, are needed. Biomonitoring gives information on the actual internal exposure of individual workers, and may in some companies be more readily available from several timepoints than information on air concentrations. On the other hand, exposure by inhalation is the most crucial for lung cancer, and the current dose-response estimations for adverse health effects caused by Cr(VI) are based on Cr(VI) air concentrations.

Dose-response estimates of Cr(VI) induced lung cancer risk in humans have been studied in several epidemiological cohorts. The most well-known are the 'Baltimore' cohort (Braver et al., 1985; Gibb et al., 2000; Hayes et al., 1979) and the 'Painesville' cohort (Luippold et al., 2003; Mancuso 1997a, 1997b), both from the American chromate industry. After a systematic search, five studies based on these cohorts, reporting on exposure to occupational Cr(VI) and respiratory tract cancers, were included in a meta-analysis of (Seidler et al., 2013). They established a dose-response for Cr(VI) caused lung cancer: $RR = 1.75 \times C + 1$, in which RR is the relative risk and C the lifelong occupational exposure in mg/m^3 x year.

The analysis by (Seidler et al., 2013) has been used by several expert groups as a basis to estimate lung cancer risks caused by different lifelong Cr(VI) exposure levels: European Chemicals Agency's (ECHA) Risk Assessment Committee (RAC) (ECHA 2013), the Dutch DECOS committee (DECOS, 2016) and the EU Scientific Committee on Occupational Exposure Limits (SCOEL) (European Commission et al., 2017). Resulting excess life-time cancer risks for 40 years of occupational exposure have been 4 x 10-5 at 0.01 μg Cr(VI)/m^3, 4 x 10-3 at 1 μg Cr(VI)/m^3, 20 x 10-3 at 5 μg/m^3 and 94 x 10-3 at 25 μg/m^3. It was not possible to derive dose-effect relationship for stomach cancer and nose and nasal sinus cancer based on human data. As Cr(VI) is considered a non-threshold carcinogen, no safe limit can be set for it and occupational exposure to it should be minimised to as low as reasonably achievable (ALARA). For fertility effects, RAC has established for workers inhalation and dermal DNELs of 43 μg Cr(VI)/m^3 and 43 μg Cr(VI)/kg/bw/d, respectively (ECHA 2015). For developmental toxicity, the inhalation and dermal DNELs established by RAC were 85 μg Cr(VI)/m^3 and 93 μg Cr(VI)/kg/bw/d, respectively. No thresholds could be established for allergic contact dermatitis, allergic asthma and rhinitis.

The Finnish Institute of Occupational Health (FIOH) has collected information on occupational exposure to chemicals in its registries, which include the Register of Biomonitoring Exposure Assessments. This register includes the results of the biomonitoring analyses performed at FIOH as part of the expert services provided to the Finnish workplaces and occupational health care units since the early 1960s. Biomonitoring of chromium exposure at workplaces is recommended by FIOH as part of occupational health surveillance for workers exposed to Cr(VI), and U–Cr analysis is still one of the most frequently performed biomonitoring analyses at Finnish workplaces. The FIOH register of biomonitoring exposure assessments includes results of U–Cr analyses from the beginning of the 1980s.

In this study, we collected the existing U–Cr biomonitoring data from the FIOH register of biomonitoring exposure assessments, covering Cr exposure in several occupational sectors. This resulted in a rather unique dataset, which can help in the assessment of past exposures, e.g. for epidemiological studies or for the diagnosis of occupational lung cancer related to Cr(VI) exposure, which typically has a long latency period.

Based on the dataset, we also assessed occupational lung cancer risks related to Cr(VI) exposure in platers and welders. As lifelong exposure is essential in the Cr(VI) related cancer incidence increase, all U–Cr biomonitoring data covering a ~40-year period (1980–2016) were compiled. We then converted the measured biomonitoring data (U–Cr, P95), representing internal exposure, into estimates of corresponding Cr(VI) air levels (μg/m^3). This was done using published regression formulas, based on simultaneous measurements for the internal and external exposure (U–Cr and Cr(VI) air concentrations, respectively) from platers and welders (Chen et al., 2002; Lindberg and Vesterberg 1983; Viegas et al., 2022). The conversion to achieve the estimates was needed to assess the lung cancer risks. We then used these estimates to assess lifelong occupational lung cancer risks related to the Cr(VI) exposures in the plating and welding sectors, using the dose-response formula by (Seidler et al., 2013).

Earlier within the HBM4EU project, the resulting cancer risk estimates were compared to the estimates of a recent Dutch risk assessment for military Cr(VI) uses during the years 1980–1999, covering similar tasks related to surface treatment but lacking exposure data that would have allowed a quantitative exposure assessment. The aim of the comparison was to study whether inclusion of biomonitoring data could improve the reliability of the earlier risk assessment, which was found to be the case. The comparison also demonstrated the merits of using biomonitoring data above semi-quantitative approaches based on external exposure estimates to improve the quality and reliability of risk assessment. Here, we cover a longer study period (1980–2016 vs. earlier 1980–1999), and extend the cancer risk estimate calculations with new data from the HBM4EU occupational chromate study (Santonen et al., 2022; Viegas et al., 2022).

The risk assessment presented here is not intended to have direct regulatory implications. The main purpose is to give risk estimates based on the presented biomonitoring data, and to more generally illustrate how biomonitoring data can improve the Cr(VI) health risk assessment.

2. Materials and methods

2.1. Human biomonitoring data

The biomonitoring data used in this work originated from a register of biomonitoring measurements upheld by the Finnish Institute of Occupational Health (FIOH), according to the law on the activities and funding of FIOH (STM 159/1978). This law defines the information gathered in the FIOH databases and gives FIOH permission to use the gathered data for research purposes. The database, which is not publicly available, conforms to the European General Data Protection Regulation (GDPR, EU, 2016/679). It consists of the original analytical results and is not a biobank, as no samples are stored. Informed consent, including a consent to store the measurement results to the FIOH database, is obtained from all workers providing samples for analysis. Contextual information stored to the database includes sample timing, sex, smoking information, job title and company information.

The data used here consisted of >42,000 urinary total chromium (U–Cr) measurement results from 1980 to 2016, sent to the Institute for exposure monitoring by occupational health care units. Earlier analyses of the samples (during 1980–1999) were performed using electrothermal atomic absorption spectrometry (EAAS), as described in (Kiilunen et al., 1987). Later, U–Cr was analysed using inductively coupled plasma mass spectrometry (ICP-MS), application as described in (McShane et al., 2007). During the whole study period, the FIOH laboratory has taken part in external and internal quality programmes, and has been accredited by the Finnish Accreditation Service (Finas T013) since the 1990s. All the U–Cr measurements were normalised to specific gravity, thus, the results covering the whole study period are comparable.

All samples have been classified according to the national Standard Industrial Classification (SIC) TOL 2008, which complies with NACE Rev. 2. The results of U–Cr analysis were divided to the groups based on work task, SIC and exposure to different chromium compounds.

The group of “platers” consists of electroplating process workers and of those, whose workplace was classified as "treatment and coating of metals", excluding workers who were classified into another group according to their job title (e.g. welders and grinders). A large part of “sprayers” worked in car repair workshops, but also painters in different industrial areas were included. The “sandblasting and other mechanical surface treatments” group was collected according to job titles. “Mechanics” includes all workers that had “mechanic” or “installer” in their job title. “Maintenance workers” were divided into two groups: maintenance workers” and “mechanical maintenance workers”, as the exposure to Cr(VI) compounds could be different. The group “maintenance workers” includes for example electricians and telecommunications installers and repairers. The group “mechanical maintenance workers” includes machining workers and others that work metal. The group “welders” includes all workers using different welding techniques and metal sheet workers who cut, form, or weld sheets of metal. Moulders, founders and other casting process workers that are exposed to casting fumes were collected to the group “casting”.

2.2. Data processing and conversion into corresponding air levels

Aggregated biomonitoring data were used in this work. The original data unit μmol/L was converted into nmol/L, μg/L and μg/g of creatinine (crea) as required by the subsequent calculations. The approximation into μg/g of crea assumed that 1 L of urine contains 1.36 g of crea (Cocker et al., 2011).

Published regression formulas were used to convert the measured biomonitoring data (U–Cr, P95), representing internal exposure, into corresponding Cr(VI) air levels (μg/m^3). These formulas, presented below, are based on simultaneous biomonitoring (U–Cr) and occupational hygiene (airborne Cr(VI) concentration) measurements on workers doing either chromium plating (formulas 1-3) or welding (formula 4). The conversions were made only for the FIOH data from platers and welders. The following assumptions were made, and it was presumed that their contribution to the overall U–Cr levels did not produce such a significant variation that would have hampered the analysis: 1) background (non-occupational) Cr exposures remained comparable, 2) occupational exposure to the non-carcinogenic trivalent chromium [Cr (III)] was comparable within each of the two occupational sectors and 3) contribution of skin-to-mouth exposure was comparable within each of the two occupational sectors. These are general assumptions that must be made when such regression formulas are used, e.g. for the setting of BLVs, and must be recognised as sources of uncertainty.

For plating, three different regression formulas were included for comparison and to provide more confidence in the estimates. The older formulas 1 and 2 have been used previously in e.g. setting of BLVs for Cr (VI). Formulas 3 and 4 are based on very recent data.

Formula 1) for plating by (Lindberg and Vesterberg 1983): $[\mathrm{Cr_{air}}](\mu g/m^3) = 0.43 + 0.013 \times [\mathrm{Cr_{urine}}](\mathrm{nmol/L})$. This formula is based on Cr (VI) exposure data from chromium plating, n = 57, r (correlation coefficient) = 0.71. Atmospheric samples were taken from the exposed workers’ breathing zone with personal air samplers over one work-shift. In the same week, urine samples were collected immediately before and after the work-shifts on Monday and Thursday.

Formula 2) for plating by (Chen et al., 2002): $[\mathrm{Cr(VI)_{air}}](\mu g/m^3) = [[\mathrm{Cr_{urine}}](\mu g/g\ \mathrm{crea}) + 0.21]/1.86$. This formula is based on data from decorative and hard-surface chromium plating, n = 57, r^2 (goodness of fit) = 0.87. Atmospheric samples of inhalable Cr(VI) aerosols were taken with personal samplers over one whole working day (last day of the work week). Urine samples (one sample from each exposed worker) was collected at end of the work week, at the end of shift.

Formula 3) for plating by Viegas et al. (2022): $[\mathrm{Cr(VI)_{air}}](\mu g/m^3) = [[\mathrm{Cr_{urine}}](\mu g/g\ \mathrm{crea}) - 0.742]/1.235$. This formula is based on data from chromium bath plating, n = 42, r_s (Spearman correlation coefficient = 0.858, $r^2 = 0.679$. Atmospheric samples of the inhalable and respirable fractions of Cr(VI) were taken with personal samplers over a representative period of a work shift. Urine samples were collected at the beginning and end of the same work week (pre- and post-shift samples, respectively).

Formula 4) for welding by Viegas et al. (2022): $[\mathrm{Cr(VI)_{air}}](\mu g/m^3) = [[\mathrm{Cr_{urine}}](\mu g/g\ \mathrm{crea}) - 0.647]/0.541$. This formula is based on data from welding, n = 46, $r_s = 0.515$, $r^2 = 0.324$. Atmospheric samples of Cr(VI) were taken with personal samplers over a representative period of a work shift. Urine samples were collected at the beginning and end of the same work week (pre- and post-shift samples, respectively).

The estimates of external exposure concentrations resulting from these conversions allowed the subsequent risk estimate calculations.

2.3. Risk estimate calculations

The estimates of external Cr(VI) exposure concentrations were used to calculate 40-year (lifelong) occupational lung cancer risks (1980–2019). First, for calculation of the external exposure over 40 years, average annual exposures for each time interval (1980–1989, 1990–1999, 2000–2009 and 2010–2016) were calculated from the external exposure data estimates (μg/m^3, P95). These were then converted to lifelong occupational exposure over 40 years (expressed as mg/m^3 x year) using an average exposure each year multiplied by the number of years with that exposure (total 40 years). The results from 2010 to 2016 were extrapolated to also cover exposure during 2017–2019.

This sum was then used for the lung cancer risk calculations. RR was calculated using the formula from Seidler et al. (2013), which is based on five high-quality epidemiological studies, investigating the dose-response for lung cancer caused by exposure to air Cr(VI) in the American chromate industry. The inclusion criteria for this meta-analysis contained providing data for more than one level of Cr(VI) exposure, adequate consideration of smoking status as confounder, and sufficient methodological quality. Applying linear exposure-response models, the calculated dose-effect relationship for lung cancer derived by Seidler et al. (2013) was $RR = 1.75 \times C + 1$, where RR = relative risk and C = lifelong occupational exposure in mg/m^3 x year. RR is a ratio of the probability of an adverse health event occurring in an exposed group vs. the probability of the same event occurring in an occupationally non-exposed group.

Attributable risk (AR) was then calculated using the formula $AR = (RR-1)/RR$ (Miettinen 1974). AR is the proportion of a disease (or an excess risk of a disease) that is caused by the exposure.

3. Results

3.1. Measured total U–Cr levels in Finnish workers in 1980–2016

Overall, the measured U–Cr levels have decreased over the study period. This applies to almost all occupational sectors over the period

1980–2016 (Table 1), and also when all sectors were combined (period 2000–2016, Fig. 1). For sandblasters and other mechanical surface treaters, the data are inconclusive, as the number of samples was very low (n = 30 in 1980–2016).

The highest levels for most occupational sectors were measured in the 10-year interval 1980–1989 (Table 1). The overall highest U–Cr P95 levels were measured in casters (44.7 µg/L in 1980–1989, n = 15), maintenance workers (42.1 µg/L in 1980–1989, n = 36) and welders (40.0 µg/L in 1980–1989, n = 3232). By the interval 2010–2016, the measured U–Cr P95 levels in all sectors had decreased to ≤9.5 µg/L. The highest measured P95 level of 9.5 µg/L was in sprayers (n = 54 in 2010–2016). In sprayers, the measured P95 U–Cr levels do not appear to have decreased over the whole study period of 1980–2016. However, the n in the intervals 2000–2009 and 2010–2016 were low, probably contributing to variability. Also for sprayers, the median levels over the whole study period decreased considerably.

3.2. Risk assessment

The key endpoint considered in the risk assessment was lung cancer. RR and AR were calculated based on the biomonitoring data, representing internal exposure. The biomonitoring data of platers and welders were converted into estimated external exposure (µg/m^3) using four available regression formulas (Table 2). Three of these formulas were based on measurements from plating activities, and one from welding. Only these two occupational sectors were included in this examination, as the exposure scenarios for the rest of the sectors were considered to differ too much from those represented by the regression formulas, or the n was considered too low.

The 40-year (lifelong) occupational external exposure estimates were 160–320 µg/m^3 x year for platers and 1030 µg/m^3 x year for welders (Table 3), when calculated based on P95, reflecting the realistic worst-case exposure.

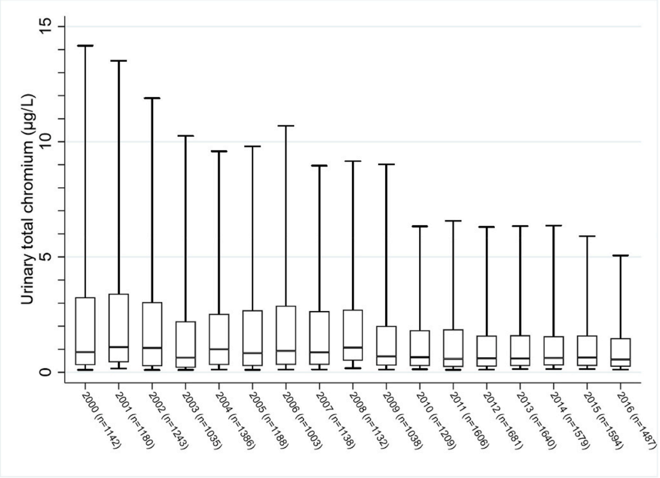

Fig. 1. Overall urinary total chromium concentrations in Finnish workers in years 2000–2016 (x-axis), all occupational sectors combined. Box plots: The bottom and top of the box are, respectively, the 25th and 75th percentiles. The horizontal line inside the box is the median (50th percentile). The lower and upper ends of the whiskers are the 5th and 95th percentiles, respectively.

The lifelong lung cancer risk calculations for platers showed an RR of 1.28–1.56 and an AR of 22–36%. This applied to the lifelong occupational exposure assessment obtained with the internal to external exposure conversion formulas based on measurement data from Cr plating activities (formulas 1–3). Of these, formula 2 and 3 have slightly

Table 1
Measured urinary total Cr (U–Cr) levels in Finnish workers in 1980–2016, stratified by occupational sectors and presented in three different units.

Occupational sector	Interval	n	µmol/L		µg/L		µg/g crea[a]	
			Md	P95	Md	P95	Md	P95
Plating	1980–1989	771	0.04	0.5	1.9	23.7	1.4	17.4
	1990–1999	857	0.02	0.3	1.0	17.2	0.8	12.6
	2000–2009	4657	0.01	0.2	0.7	10.6	0.5	7.8
	2010–2016	3631	0.01	0.1	0.5	6.3	0.4	4.6
Spraying	1980–1989	213	0.02	0.2	1.1	8.7	0.8	6.4
	1990–1999	254	0.01	0.2	0.5	9.9	0.4	7.3
	2000–2009	26	0.01	0.02	0.3	1.2	0.2	0.9
	2010–2016	54	0.004	0.2	0.2	9.5	0.1	7.0
Welding	1980–1989	3232	0.07	0.8	3.6	40.0	2.7	29.4
	1990–1999	6806	0.05	0.4	2.6	20.8	1.9	15.3
	2000–2009	5651	0.02	0.2	1.2	11.9	0.9	8.7
	2010–2016	5348	0.02	0.1	0.8	6.7	0.6	4.9
Mechanics	1980–1989	94	0.03	0.4	1.6	18.7	1.1	13.7
	1990–1999	757	0.02	0.2	1.0	10.4	0.8	7.6
	2000–2009	4568	0.01	0.2	0.7	10.6	0.5	7.7
	2010–2016	3740	0.01	0.1	0.5	5.8	0.4	4.3
Maintenance	1980–1989	36	0.02	0.8	1.2	42.1	0.9	30.9
	1990–1999	91	0.01	0.1	0.5	5.7	0.4	4.2
	2000–2009	2	0.08	0.1	4.2	7.0	3.1	5.1
	2010–2016	53	0.01	0.05	0.3	2.6	0.2	1.9
Mechanical maintenance	1980–1989	39	0.02	0.1	1.0	6.4	0.8	4.7
	1990–1999	495	0.01	0.2	0.5	8.8	0.4	6.5
	2000–2009	429	0.01	0.09	0.5	4.9	0.4	3.6
	2010–2016	507	0.005	0.05	0.2	2.7	0.2	2.0
Casting	1980–1989	15	0.12	0.9	6.1	44.7	4.5	32.8
	1990–1999	107	0.06	0.5	3.1	26.5	2.3	19.5
	2000–2009	22	0.09	0.3	4.9	16.2	3.6	11.9
	2010–2016	33	0.01	0.04	0.6	2.2	0.5	1.7
Sandblasting and other mechanical surface treatment, e.g. soda and glass bead blasting	1980–1989	3	0.01	0.02	0.5	1.0	0.4	0.8
	1990–1999	18	0.01	0.6	0.5	31.7	0.4	23.3
	2000–2009	2	0.01	0.01	0.3	0.3	0.2	0.2
	2010–2016	7	0.005	0.01	0.3	0.3	0.2	0.2

Md = Median, P95 = 95th percentile.

[a] µg/g crea approximations assumed that 1 l urine contains 1.36 g crea.

Table 2
Estimated occupational Cr(VI) air levels in Finland in 1980–2016 for plating and welding occupational sectors, based on biomonitoring data (P95, reflecting realistic worst-case). The measured U–Cr levels were converted into air concentrations using four published regression formulas, based on biomonitoring and occupational hygiene measurements related to either chromium plating (1–3) or welding (4) activities.

Occupational sector	Interval	n	U–Cr, P95 (μg/L)	Estimated air concentrations (μg/m^3), according to the four regression formulas:			
				1)	2)	3)	4)
Plating	1980–1989	771	23.7	6	10	13	–
	1990–1999	857	17.2	5	7	10	–
	2000–2009	4657	10.6	3	4	6	–
	2010–2016	3631	6.3	2	3	3	–
Welding	1980–1989	3232	40.0	10	16	23	53
	1990–1999	6806	20.8	6	8	12	27
	2000–2009	5651	11.9	3	5	6	15
	2010–2016	5348	6.7	2	3	3	8

Table 3
Lifelong (40-year, 1980–2019) occupational external exposure and risk assessments for platers and welders, based on biomonitoring data (P95, reflecting realistic worst-case). External exposure calculations were based on regression formulas related to either chromium plating (1–3) or welding (4) activities.

Occup. sector	Parameter	Regression formula used			
		1)	2)	3)	4)
Plating	Lifelong external Cr exposure (mg/m^3 x year) over 1980–2019	0.16	0.23	0.32	–
	Relative lung cancer risk	1.28	1.41	1.56	–
	Attributable lung cancer risk (%)	22	29	36	–
Welding	Lifelong external Cr exposure (mg/m^3 x year) over 1980–2019	–	–	–	1.03
	Relative lung cancer risk	–	–	–	2.80
	Attributable lung cancer risk (%)	–	–	–	64

better fits or correlation coefficients than formula 1 (formula 2 $r^2 = 0.87$, formula 3 $r^2 = 0.679$ and $r_s = 0.858$, formula 1 $r = 0.71$).

For welders, the 40-year (lifelong) occupational exposure assessment based on regression formulas 1–3 produced RR estimations of 1.38–1.78 and AR estimations of 27–44% (data not shown). However, formula 4, which is based on measurements from welding ($r_s = 0.515$), produced much higher risk estimates, an RR of 2.80 and an AR of 64% (Table 3).

When the same calculations were performed using the median values, all RRs were close to 1 and ARs ≤10% for both platers and welders (data not shown).

4. Discussion

Cr(VI) compounds are hazardous for health, their key endpoint being lung carcinogenicity. Despite regulatory measures aiming to protect workers in Europe, occupational exposure to chromates remains a relevant concern. Therefore, risk assessment and, when prompted by it, appropriate risk management measures are essential. For a reliable exposure assessment, biomonitoring is an important tool in addition to occupational hygiene measurements of air concentrations, as it provides information on the actual internal exposure of workers. Here, we presented urinary total chromium data collected from Finnish workers during 1980–2016, encompassing >42,000 samples. Based on these data and published correlations between air Cr(VI) and urinary total Cr levels (Chen et al., 2002; Lindberg and Vesterberg 1983; Viegas et al., 2022), we calculated 40-year (lifelong) exposure levels to Cr(VI) compounds in the occupational sectors of plating and welding. This allowed us to calculate the RR and AR of occupational lung cancer for these two occupational sectors for the 40-year exposure period of 1980–2019. The risk assessment presented here is not intended to have direct regulatory implications, but to rather give risk estimates based on the presented biomonitoring data, and to more generally exemplify how biomonitoring data can be useful in the Cr(VI) risk assessment.

Over the whole study period, the measured U–Cr levels decreased overall (Table 1); even during the past two decades, the median and P95 levels have decreased 40% and 64%, respectively (Fig. 1). A similar decreasing trend was observed also in Belgium, when Verdonck et al. (2021) analysed almost 3800 samples between 1998 and 2018, and observed a decreasing time trend of 30% in U–Cr levels. In our dataset, the only occupational sector that stood out in this regard was spraying, where the measured P95 U–Cr levels did not appear to have decreased, although median levels did. The workers in this sector performed varying tasks, but a large part were car painters in repairing shops. However, the number of samples in this sector, especially in the last two intervals of 2000–2009 and 2010–2016, were lower than in many other sectors, which may have affected the results.

Of all the occupational sectors, the overall highest U–Cr levels were measured in casting, maintenance and welding in the interval of 1980–1989. When the most recent task-specific data from years 2010–2016 are compared to the literature data, the Finnish data are in line with the data from other countries. In a recent European biomonitoring study, covering workers from nine different countries, Santonen et al. (2022) reported median post-shift U–Cr levels of 1.12 μg/g crea in chrome platers (P95 was 7.70 μg/g crea). Similarly, Beattie et al. (2017) reported mean U–Cr of 1.2 μg/g crea and P90 level of 4.9 μg/g crea among 354 UK electroplating workers. Comparable U–Cr levels were reported also in an Italian study (Goldoni et al., 2010), whereas studies from Asia and Brazil showed clearly higher exposure levels in platers than those observed in European studies (summarised in a systematic review by (Verdonck et al., 2021)). In European welders (Santonen et al., 2022), reported median post-shift U–Cr levels of 0.68 μg/g crea, which are close to the levels observed here in Finnish welders during the interval 2010–2016. Similarly, in studies performed in Germany and in Italy, median U–Cr levels were between 0.74 and 0.9 μg/g crea (Pesch et al., 2018; Riccelli et al., 2018), whereas a recent Polish study showed somewhat higher urinary levels (median 3.81 μg/g crea) (Stanislawska et al., 2020). Also the above mentioned Belgian dataset showed U–Cr levels of 3.75 μg/L (geometric mean) for a job category “sheet and structural metal workers, moulders and welders, and related workers” during years 1998–2018 (Verdonck et al., 2021).To allow lung cancer risk assessment, published regression formulas were used to relate the measured internal exposures of workers to estimations of their external exposure levels. Such conversion methodology is commonly used by expert groups in setting of occupational exposure limits (ECHA 2019b; European Commission 2018). As chromates are soluble, bioavailable and readily excreted in urine, U–Cr concentration is a relevant biomarker of Cr exposure. All of the regression formulas used here are based on measured data from workplaces on both total U–Cr and Cr(VI) air concentrations (Chen et al., 2002; Lindberg and Vesterberg 1983; Viegas et al., 2022). Recently, the new data from the HBM4EU project (Viegas et al., 2022) supported the earlier studies on the correlation of air Cr(VI) and U–Cr concentrations, providing further confidence to the use of U–Cr data in risk assessment.

Here, external exposure estimation and subsequent lung cancer risk assessment was made only for plating and welding, as specific regression formulas to extrapolate from internal to external exposure were available only for these two occupational sectors. In addition, these sectors had enough U–Cr measurements for a reliable assessment. Three different regression formulas were used for plating, only one was available for welding. Applying an appropriate regression formula is essential to gain representative results, as is illustrated by the differences in Table 2. All three plating regression formulas, and particularly the two more recent ones, yielded similar results for the plating sector, while the results for the welding sector obtained with the welding vs. plating regression formulas were quite different. It should be noted that in plating and welding, the exact chromium species are different. In plating, exposure is to highly soluble Cr(VI) compounds, like chromium trioxide (chromic acid), in an aerosol form. These highly soluble Cr(VI) particles are easily absorbed from the lungs, reduced to Cr(III) in the body and excreted rapidly to the urine (ATSDR 2012). However, welding of stainless steel leads to exposure to ultra-fine and nano-sized chromium oxides, encapsulated in welding particles with lower water-solubility when compared to the soluble chromates. This results in higher lung retention and slower release in the systemic circulation, and consequently slower urinary excretion (Antonini et al., 2010; Scheepers et al., 2008). This difference in the kinetics is reflected in the regression formulas for plating and welding activities.

Using the appropriate regression formulas, the resulting estimates of external exposure over the 40-year period (1980–2019) allowed us to assess lung cancer risks based on a published dose-response formula (Seidler et al., 2013). The realistic worst-case RR estimates for lung cancer risk, based on P95 values, were 1.28–1.56 for plating and 2.80 for welding. The RRs represent ratios of the probability of lung cancer occurring in the group occupationally exposed to Cr(VI) vs. the occupationally non-exposed group. The respective AR estimates for plating and welding were 22–36% and 64%, representing the excess risk of lung cancer caused by occupational Cr(VI) exposure. When calculated based on median values instead of the realistic worst-case P95 values, all RRs were close to 1 and ARs $\leq$10% for both platers and welders. However, extrapolation to the much lower median values may have introduced some added uncertainty.

Risks can be also expressed as an estimate of excess cancer cases. Earlier cancer risk assessments by RAC (2013), DECOS (2016) and SCOEL (European Commission et al., 2017) resulted in excess life-time cancer risk estimations (for 40 years of occupational exposure) of 4 x 10-3 at 1 μg Cr(VI)/m^3, 20 x 10-3 at 5 μg/m^3 and 94 x 10-3 at 25 μg/m^3. Here, the 40-year lifelong occupational external exposure estimates were 160–320 μg/m^3 x year for platers and 1030 μg/m^3 x year for welders, averaging for platers 4–8 μg/m^3 per year and for welders 26 μg/m^3 per year. According to the above-mentioned excess cancer risk estimations, these would correspond with rather high excess life-time cancer risks of 16–32 x 10-3 for platers and 98 x 10-3 for welders. These would mean 16–32 and 98 excess lung cancer cases per 1000 workers due to occupational Cr(VI) exposure in plating and welding, respectively. It should be noted that these risk estimates are based on P95 levels, which can be considered to represent the realistic worst-case estimates. In addition, high exposure levels observed in the past have greater impact on the overall risk than the current exposure levels.

In this paper, we have made a retrospective exposure and risk assessment, using a rather unique dataset of U–Cr biomonitoring data covering almost 40 years. Retrospective assessment may be needed for example for the diagnosis of occupational disease. In Finland, compensation for occupational cancer can be granted only if work can be established as the main cause of the cancer, meaning an AR of >50% or a 100% increased RR (Santonen and Oksa 2013). For Cr(VI), Finnish guidelines have regarded a lifelong external occupational exposure level of 1 mg/m^3 x year as the lower limit for high exposure that may be considered to support the diagnosis of occupational cancer. Based on this, most lung cancers in workers exposed to Cr(VI) compounds have not been registered as occupational diseases in Finland. Based on our biomonitoring data from welding, some cases with a long and pronounced occupational exposure history may reach those levels and fulfil this criterion for the compensation of occupational cancer.

However, the lung cancer risk estimates presented here include several uncertainties, which must be considered. Foremost, the calculations estimating external exposure levels (air concentrations) based on the biomonitoring data depend on the quality of the available regression formulas, as already briefly discussed above in relation to the data presented in Table 2. Particularly the correlation coefficient $r_s = 0.515$ of the welding regression formula by (Viegas et al., 2022) can be considered only moderate instead of very strong. Regarding the three regression formulas used for plating, the oldest one (formula 1 (Lindberg and Vesterberg 1983),) produced external exposure estimates that deviated quite a lot from those of the two newer formulas (2 and 3, (Chen et al., 2002; Viegas et al., 2022). As mentioned in the discussion by (Viegas et al., 2022), the r^2 value of formula 1 was not reported by (Lindberg and Vesterberg 1983), but the correlation coefficient was somewhat lower. The reasons for the differences between the two newer and the older formula cannot be stated for sure, but they could include several aspects that have changed over the years, e.g. in the analytics and in the working environments (Viegas et al., 2022). suggested that the regression formula by (Lindberg and Vesterberg 1983) should not be used anymore for Cr(VI) BLV setting. Here however, considering that we estimated cancer risks related to an exposure period of 40 years, we consider that using multiple regression formulas from the different time periods provides more confidence to our assessment than only using one of the available regression formulas. Moreover, related to the use of regression formulas to convert biomonitoring data into estimates of external exposure concentrations, the assumptions made in this context (see chapter 2.2) must be considered. While all uncertainties related to the conversions of U–Cr to Cr(VI) air concentrations cannot be excluded, overall we consider that these uncertainties do not produce such a significant variation that would have hampered the analysis.

Furthermore related to the uncertainties, U–Cr reflects total Cr exposure, while particularly welders are exposed to both non-carcinogenic Cr(III) and carcinogenic Cr(VI) compounds (Pesch et al., 2018; Scheepers et al., 2008). Moreover, biomonitoring data reflects exposure via also other than the inhalation route, particularly ingestion due to hand to mouth contact might have an important role in both sectors. Other routes than the inhalation route are, however, not relevant to lung cancer. On the other hand, when using occupational sector specific regression formulas for the conversion of urinary levels into air levels, the relative contribution of dermal contamination and air exposure can be assumed to be similar. Finally, related to the uncertainties, the RRs obtained from the systematic review and meta-analysis by Seidler et al. (2013) are based on epidemiological data from the chromates industry. Therefore, they are not necessarily very well representative for welding, as different chromium species are present in these two occupational sectors, as summarised above (Pesch et al., 2018; Scheepers et al., 2008). In addition, welders are exposed also to nickel oxides, which may increase the overall lung cancer risk in this group of workers (Pesch et al., 2019).

The occupational sectors involving Cr(VI) exposure covered in this study are in the scope of different regulatory frameworks in Europe. Welding and e.g. production of stainless-steel are covered only under the Carcinogenic and Mutagenic Directive (CMD; 2004/37/EC), whereas for example chrome plating is covered both under CMD and REACH. Concerning welding, the analysis performed in this study suggests that inhalation exposure levels in welding activities are nowadays well below 10 μg/m^3, and most workplaces can achieve even levels well below 5 μg/m^3, which is the upcoming EU binding limit value for Cr(VI) in the CMD. Thus, the derogation given in CMD for welding or plasma-cutting processes, with an OEL value of 25 μg/m^3 until 5 years after the transposition date, seems unnecessary.

According to the REACH regulation, all companies using Cr(VI) compounds must apply for authorisation of their uses. The REACH authorisation process is meant to promote the substitution of the most hazardous chemicals. However, due to technical reasons, substituting Cr (VI) compounds has not yet been possible in many applications, explaining the high number of authorisations being requested and granted at EU level (ECHA 2021a). In many authorisation applications published at ECHA's webpages (ECHA 2021a), exposures in surface treatment activities (covering e.g. plating and spraying) have been estimated to stay below 2 μg/m^3. These estimates are, in many cases, based on modelling. In cases that estimation was obtained through measured data, further adjustments were done for the use of respiratory protection devices and for the frequency of the task being considered. Less common were the authorisation processes that included biomonitoring data. Recently, ECHA's RAC Capacity Building Seminar was organised to discuss the assessment of biomonitoring data in the context of the authorisation process under REACH (ECHA 2021b). In this meeting, it was decided that where there is a serious exposure concern, and suitable sampling and analytical methods are available, RAC may recommend biomonitoring. This will allow the European Commission the option of adding this to the decision, and if there is a history of biomonitoring evident in an application, RAC can recommend to the applicant to continue biomonitoring and use the data in an anonymised form as part of their future exposure assessment. Therefore, hopefully in the future, biomonitoring data will be more frequently used to support exposure and risk assessment also in the REACH authorisation process.

In conclusion, the biomonitoring data presented here constitutes a rather unique dataset, which can help in the assessment of past occupational Cr exposures. In addition, our study exemplifies how U–Cr biomonitoring data can be converted to inhalation exposure estimates, and how it can be used to estimate lung cancer risks quantitatively. In addition, it summarises Finnish urinary chromium data from the past 40 years, demonstrating a decreasing trend in occupational exposure to Cr (VI). The most recent data from 2010 to 2016 supports the other recently published Cr(VI) exposure data from Europe. However, even these exposure levels still correspond to a relatively high estimated occupational cancer risk.

Funding body information

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032; co-funding was received from the authors' organizations: Finnish Institute of Occupational Health (FIOH), Dutch National Institute for Public Health and the Environment (RIVM) and National School of Public Health from NOVA University of Lisbon (ENSP-UNL).

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Selma Mahiout: Conceptualization, Formal analysis, Investigation, Project administration, Writing – original draft. **Mirja Kiilunen:** Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **Theo Vermeire:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Susana Viegas:** Conceptualization, Investigation, Writing – review & editing. **Marjolijn Woutersen:** Writing – review & editing. **Tiina Santonen:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

The authors do not have permission to share data.

Acknowledgments

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032 (www.HBM4EU.eu); co-funding was received from the authors' organizations: Finnish Institute of Occupational Health (FIOH), Dutch National Institute for Public Health and the Environment (RIVM) and National School of Public Health from NOVA University of Lisbon (ENSP-UNL). We would like to warmly thank Dr. Simo Porras for producing Fig. 1.

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