Environmental Research 228 (2023) 115797

Contents lists available at ScienceDirect

Environmental Research

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

Burden of lung cancer and predicted costs of occupational exposure to hexavalent chromium in the EU – The impact of different occupational exposure limits

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ARTICLE INFO

Handling Editor: Jose L Domingo

Keywords:
Hexavalent chromium
Occupational exposure
Public health
Lung cancer
Burden of disease
Health costs

ABSTRACT

Background: Exposure to hexavalent chromium [Cr(VI)] occurs widely in occupational settings across the EU and is associated with lung cancer. In 2025, the occupational exposure limit is set to change to 5 μg/m^3. Current exposure limits are higher, with 10 μg/m^3 as a general limit and 25 μg/m^3 for the welding industry. We aimed to assess the current burden of lung cancer caused by occupational exposure to Cr(VI) and to evaluate the impact of the recently established EU regulation by analysing different occupational exposure limits.

Methods: Data were extracted from the literature, the Global Burden of Disease 2019) study, and Eurostat. We estimated the cases of cancer attributable to workplace exposure to Cr(VI) by combining exposure-effect relationships with exposure data, and calculated related DALYs and health costs in scenarios with different occupational exposure limits.

Results: With current EU regulations, 253 cases (95%UI 250.96–255.71) of lung cancer were estimated to be caused by Cr(VI) in 2019, resulting in 4684 DALYs (95%UI 4683.57–4704.08). In case the welding industry adopted 10 μg/m^3, a decrease of 43 cases and 797 DALYs from current values is expected. The predicted application of a 5 μg/m^3 limit would cause a decrease of 148 cases and 2746 DALYs. Current costs are estimated to amount to 12.47 million euros/year (95%UI 10.19–453.82), corresponding to 39.97 million euros (95%UI 22.75–70.10) when considering costs per DALY. The limits implemented in 2025 would lead to a decrease of 23.35 million euros when considering DALYs, with benefits of introducing a limit value occurring after many decades. Adopting a 1 μg/m^3 limit would lower costs to 1.04 million euros (95%UI 0.85–37.67) and to 3.33 million euros for DALYs (95%UI 1.89–5.84).

Discussion: Assessing different scenarios with different Cr(VI) occupational exposure limits allowed to understand the impact of EU regulatory actions. These findings make a strong case for adapting even stricter exposure limits to protect workers' health and avoid associated costs.

1. Introduction

Chromium is a metal that is essential in biochemical processes in the human and non-human species, including insulin, sugar and lipid metabolism. In its natural form it is present in the trivalent state, Cr(III), while other oxidation forms tend to be converted back to Cr[III]. Hexavalent chromium, Cr(VI), is the second most stable form of chromium and is an environmental contaminant in industrial settings (Hiller and Leggett, 2020).

Exposure to Cr(VI) may occur in several activities and uses, e.g., welding, Cr(VI) electroplating and other surface treatment processes. Soluble hexavalent compounds, like chromium trioxide, sodium or potassium dichromate are used in chrome plating in baths (electroplating) but can also be used in surface treatment by spraying, brush or pen applications or in passivation processes. Sparingly soluble strontium chromate and zinc chromate hydroxide are used in chromate paints for the aviation sector (European Chemicals Agency, 2021). Welding and flame cutting of stainless-steel leads to ultra-fine and nano-sized chromium oxide particles in both trivalent and hexavalent form (IARC, 2012;

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https://doi.org/10.1016/j.envres.2023.115797
Received 24 January 2023; Received in revised form 28 March 2023; Accepted 28 March 2023
Available online 29 March 2023

List of abbreviations

COI	Cost of Illness
Cr(III)	Trivalent Chromium
Cr(VI)	Hexavalent Chromium
DALYs	Disability-adjusted Life Years
D-Cost	Cost quantified by DALY
ECHA	European Chemicals Agency
EU	European Union
GBD	Global Burden of Disease
IARC	WHO International Agency for Research on Cancer
LFS	Labour Force Survey
NACE	Statistical Classification of Economic Activities in the European Community
OEL	Occupational Exposure Limit
PAF	Population Attributable Fraction
TLV	Threshold Limit Value
TWA	Time-weighted Average
UI	Uncertainty Interval
YLD	Years lived with disability
YLL	Years of life lost
WTP	Willingness to Pay

Scheepers et al., 2008). Considering all these uses, exposure to Cr(VI) occurs widely at EU level (Cherrie et al., 2017).

Levels of exposure via inhalation differ according to the occupational setting. High exposure settings include: the manufacturing of chemicals and chemical products, basic metals, fabricated metal products, machinery, and transport equipment. Other settings have a slightly lower exposure to Cr(VI), such as workplaces that use chromate pigments and paint, the manufacturing of electrical equipment, crushing concrete, and metal cutting (Cherrie et al., 2011; European Commission, 2016). The limit set for higher exposure varies according to literature sources, however a 2 μg/m^3 is found to be moderately consensual as the threshold between low and high exposure (Cherrie et al., 2011; European Commission, 2019).

The binding OEL for Cr(VI) set under EU Directive 2004/37/EC is currently of 10 μg/m^3 (8-h time-weighted average (8-h TWA)) until January 17, 2025; after that period, the OEL for an 8-h TWA will be limited at 5 μg/m^3. For welding, plasma-cutting processes and similar work processes that generate fumes, there is a derogation with an even higher value of 25 μg/m^3 until 2025 (Santonen et al., 2022b).

Some European countries, such as France, Germany, and the Netherlands, have stricter limits for Cr(VI) exposure in all contexts, with an OEL of 1 μg/m^3 8-h TWA for Cr(VI) (Denmark and Beskæftigelsesministeriet, 2020; République Française, 2012; The Netherlands and MinSZW, 2016), with plans in Denmark to reduce the limit to 0.25 μg/m^3, if technically and economically feasible. In the United States, ACGIH has an updated threshold limit value (TLV) of 0.2 μg/m^3 for an 8-h TWA for Cr(VI) based on the respiratory tract effects of Cr(VI) (American Conference of Governmental Industrial Hygienists, 2021).

The International Agency for Research on Cancer (IARC) assessed the carcinogenicity of metals, and classified Cr(VI) as "carcinogenic to humans" (Group 1) causing lung cancer (IARC, 2012). Several studies evaluated the risk of lung cancer due to exposure to Cr(VI), estimating relative risks (RR) ranging between 1.85 and 4.52 comparing the exposed group to non-exposed groups (Beveridge et al., 2010; Pesch et al., 2019; Seidler et al., 2013). In the welding industry, a RR of 2.80 has been estimated (Mahiout et al., 2022). A more recent study of pooled case-controls in different occupational contexts from Europe and Canada revealed an Odds Ratio (OR) of 1.32 (Behrens et al., 2023). A risk assessment conducted in 2004 showed that the exposure to Cr(VI) for 45 years, with a threshold of 0.10 mg/m^3, would cause a 25% excess risk of death (Park et al., 2004).

The European Chemicals Agency (ECHA) also estimated an excess lifetime lung cancer mortality risk of 4×10^{-3} per μg Cr(VI)/m^3 (European Chemicals Agency, 2013). A recent study analysed the trends of air concentration of Cr(VI) in different occupational contexts, reporting progressively lower average exposures from 8 to 2 μg/m^3 between 2010 and 2016, a 40-year life-long Cr(VI) exposure of 160–1030 μg/m^3, estimating 22%–64% of lung cancer cases to be attributed to Cr(VI), depending on the industry sector (Mahiout et al., 2022).

A study evaluated the exposure of Cr(VI) and the time of diagnosis of lung cancer, showing that it decreased the onset of the disease by 3.5 years. It also showed that around one quarter of the exposed workers developed small cell lung carcinoma (Halasova et al., 2010).

Previous studies have estimated the burden of lung cancer due to Cr (VI), predicting the number of cases, deaths, and health costs, considering 2010 as a reference and analysing higher Occupational Exposure Limits (OELs) (Cherrie et al., 2017; European Commission, 2016). With the evolution of OELs and legislation related to Cr(VI), the overall context has changed, with more stringent OELs than in 2010. Hence, the analysis of the burden of lung cancer due to Cr(VI) is of particular relevance for the time period between the date when the ongoing binding OEL (10 μg/m^3 for general OEL and 25 μg/m^3 for welding) was put in force until 2025, when a stricter binding value will be applied (5 μg/m^3) (European Commission, 2022).

The aim of this study was to estimate the burden of disease (BoD) of lung cancer caused by occupational exposure to Cr(VI) in the European Union (EU) and respective countries, excluding the United Kingdom, in terms of disability adjusted life years (DALY) and cost of illness (COI).

The evaluation of BoD with different OEL will allow to support or not the sooner application of the stricter OEL and provide scientific evidence for future policy actions aiming to protect workers' health.

2. Methods

2.1. Burden of disease model and scenarios of exposure

BoD studies aim to quantify the health impact of diseases and risk factors in composite metrics, such as the DALY. DALY is a widely used health metric, which was developed for and is used in the Global Burden of Disease study (GBD) (Murray and Lopez, 1996). DALY is composed of two parameters: the assessment of morbidity through years lived with disability (YLD), and of premature mortality, through the years of life lost (YLL). The calculation of DALYs is carried out by adding these two parameters. (Devleesschauwer et al., 2014; European Burden of Disease Network, 2020; Wyper et al., 2021). A counterfactual analysis approach is used to estimate the burden attributed to risk factors and applies the population attributable fraction (PAF), which represents the fraction of the burden that would be prevented, if exposure to the risk factor in question was removed or reduced to a minimum risk level. Therefore, the burden attributable to a risk factor is estimated by multiplying the PAF with the total burden irrespective of risk factors of a specific health outcome in a specific population (also referred to as the "disease envelope") (Jakobsen et al., 2022; Plass et al., 2022).

In this study, we estimated the burden of lung cancer attributed to occupational exposure to Cr(VI) by building a model consisting of the following four components: assessment of exposed population; number of estimated attributed cases; attributable fraction (AF); and DALY (Fig. 1).

We theorised that the changes would be implemented in 2019, as we worked with available data. We calculated the burden of disease under current OELs and for six different scenarios of OELs, to estimate the change in burden expected when compared to the current limits. Specifically, the following current and six alternative scenarios were investigated:

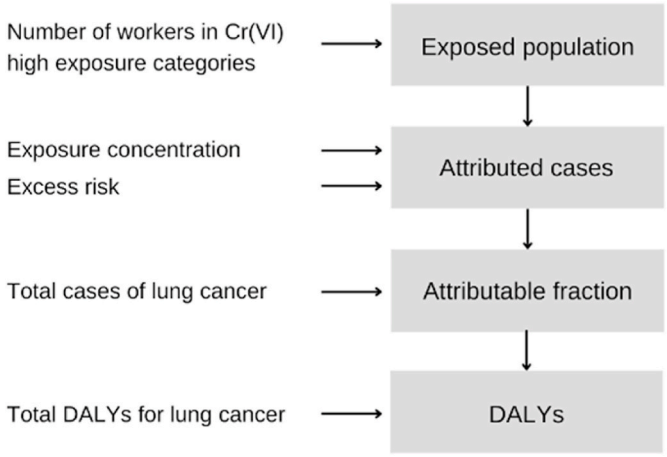

Fig. 1. Model adopted for DALYs estimation of lung cancer associated with occupational exposure to Cr(VI).

- Current scenario, with a general OEL of 10 μg/m^3 and a 25 μg/m^3 limit for welding and plasma-cutting processes;
- Scenario 1: with a general limit of 10 μg/m^3 for all industries;
- Scenario 2: to be adopted from 2025 onwards according to EU Directive 2004/37/EC, with an OEL of 5 μg/m^3;
- Scenario 3: general limit of 2 μg/m^3;
- Scenario 4: general limit of 1 μg/m^3, as adopted by Germany and France;
- Scenario 5: general limit of 0.5 μg/m^3;
- Scenario 6: general limit of 0.2 μg/m^3, as adopted in the United States.

2.2. Assessment of exposed population

The baseline population was defined as those working in the EU in Cr (VI) exposure contexts within the categories of the Statistical Classification of Economic Activities in the European Community (NACE) in 2019. The average number of workers per NACE category in 2019 were retrieved from the Labour Force Survey (LFS) and EU wide structural business statistics data, available at the Eurostat website (https://ec.europa.eu/eurostat/).

Low exposure in workers was considered to have residual exposure to Cr(VI), according to an analysis of risk factors associated with the GBD 2019 study. As such, it is comparable to that of the low-exposed population (Murray et al., 2020), which translated to a RR of the high-exposed population to be equivalent to the excess risk. Thus, low exposure workers were not considered in the model (Ebrahimi et al., 2021; Murray et al., 2020).

We selected NACE categories of workers exposed to high concentrations of Cr(VI), as considered in other studies (Cherrie et al., 2011). In our study, high exposure to Cr(VI) was defined as having an occupational exposure of at least 2 μg/m^3. These were grouped considering the NACE Revision 1.1 and Revision 2 classifications, obtaining six main categories of high exposure to Cr(VI): a) Manufacture of chemicals and chemical products; b) Manufacture of basic metals; c) Manufacture of fabricated metal products, except machinery and equipment; d) Manufacture, repair and installation of machinery and equipment; e) Manufacture of other transport equipment; and f) Other manufacture industries, including furniture.

We extracted from Eurostat the total number of workers in each of the NACE categories with high risk of exposure to Cr(VI) for 2019. For the purpose of this study, the UK was not included. The number of workers exposed to Cr(VI) were estimated from the Institute of Occupational Medicine SHEcan Report P937/5, which calculated the number of workers exposed by NACE code for 2006 based on the CAREX studies occurring across EU countries (Cherrie et al., 2011). Assuming a similar proportion of workers exposed to high concentrations of Cr(VI), an extrapolation was made to the 2019 data, allowing to account for 2019 employment trends in these sectors. The final number of high exposed workers per country for 2019 was the obtained (Supplementary Table A1).

2.3. Exposure concentration and number of cases attributed to Cr(VI)

A 40-year excess risk of 4×10^{-3} per μg Cr(VI)/m^3 was used, which accounted for a working schedule of 8 h per day, 5 days a week (European Chemicals Agency, 2013). A slope factor of 1.75, representing the upper bound of the lung cancer risk, and a background lifetime lung cancer risk of 48/1000 were considered based on empirical data (Seidler et al., 2013), allowing to adjust the excess risk. Temporal changes in exposure were determined using information from the literature, with an assumption of a 7% decrease per annum in concentration exposures for all industries considered, which were also considered in intermediate calculations for determining excess risk (Supplementary Table A2) (Cherrie et al., 2017; European Commission, 2016).

To calculate the number of lung cancer cases attributed to occupational exposure to Cr(VI), an annual individual excess risk was calculated (Table 2). For each scenario, different excess risks were applied.

$$Excess\ Risk = Risk_{Exposed} - Risk_{Non-exposed} \quad (1)$$

$$N_{Cr(VI)} = Exposed\ population \times Risk_{Exposed} \quad (2)$$

Where Excess Risk is the excess lifetime lung cancer risk estimates for workers exposed to an average of 8-h to Cr(VI) obtained from ECHA (European Chemicals Agency, 2013), $Risk_{Non\text{-}exposed}$ is the relative risk of the workers in occupational settings classified as low exposed, obtained from the GBD 2019 study (Ebrahimi et al., 2021), and $N_{Cr(VI)}$ is the number of cases of lung cancer attributed to Cr(VI).

2.4. Population attributable fraction (PAF) and DALYs

The incidence and DALY envelopes for lung cancer per country were obtained from the GBD 2019 Study, which presents the annual number of total cases and DALYs irrespective of its causes (Institute for Health Metrics and Evaluation, 2020). The total lung cancer incidence and DALY per country was derived for the EU population of age above 15 years old, as defined in Eurostat's Labour Force Suvey. To derive the fraction (AF) of lung cancer cases per country caused by Cr(VI) exposure out of total number of lung cancer cases, the number of cases attributed to Cr(VI) ($N_{Cr(VI)}$) was divided by the total number of cases of lung

Table 1
Exposure contexts according to NACE Category and total number of EU workers exposed to Cr(VI) in 2019.

Category	Total workers	Percentage of exposed from total workers	No. of exposed workers
Manufacture of chemicals and chemical products	1,234,280	1.88%	23,209
Manufacture of basic metals	1,054,720	2.13%	22,489
Manufacture of fabricated metal products, except machinery and equipment	3,453,240	6.72%	232,106
Manufacture, repair and installation of machinery and equipment	4,399,710	3.55%	156,210
Manufacture of other transport equipment	893,630	3.58%	31,987
Other manufacture industries, including furniture	2,405,138	0.67%	14,852
Total	13,244,258	3.63%	480,854

Table 2
Excess Risk estimations of lung cancer considering different Cr(VI) concentrations in a conditional method.

Cr(VI) Concentrations (μg/m^3)	40-year Cumulative Excess Risk/1000 in 2010	40-year Cumulative Excess Risk/1000 in 2019	Individual Yearly Excess Risk in 2019
0.2	0.68	0.62	0.000016
0.5	1.68	1.53	0.000038
1	3.36	3.07	0.000077
2	6.72	6.14	0.000153
5	16.8	15.35	0.000384
10	33.6	30.69	0.000767
25	84	76.74	0.001918

cancer ($N_{lung\ cancer}$):

$$AF = N_{Cr(VI)} \ / \ N_{lung\ cancer} \quad (3)$$

Then, the number of DALY associated with occupational exposure to Cr(VI) was derived by:

$$DALYs_{Cr(VI)} = AF \times DALY_{lung\ cancer} \quad (4)$$

where $DALY_{lung\ cancer}$ is the total DALY caused by lung cancer in the EU irrespective of risks and reported by the GBD 2019 Study. The DALYs attributed to Cr(VI) were also calculated for each country by applying the same methodology described above to disaggregated data to reflect individual countries, and aggregated to consider the EU level (Table 3), with 95% Uncertainty Intervals (UI). Uncertainty intervals calculations considered excess risks, exposure estimates, attributable fractions, and DALY envelopes.

2.5. Monetisation and costs

Costs were estimated by calculating cost of illness (COI) and willingness to pay (WTP), as applied by Cherrie et al. in previous studies and based on values estimated for France (Cherrie et al., 2011; 2017). The COI considers the direct costs, including in- and outpatient care, and indirect costs, such as loss of income due to absenteeism, and intangible costs, as disfigurement and functional limitations. For COI, two alternatives were estimated, one with no variation of prices since 2009, and another with a 4% discount rate and a 2% valuation increase. WTP was considered as the price that patients were willing to pay in order to avoid the suffering and inconvenience of lung cancer, which was evaluated at 1,793,776 euros (Cherrie et al., 2011; 2017).

As a third costs-indicator, we additionally estimated the cost-per-DALY (D-cost) by retrieving data for cancers from existing literature. In a meta-analysis by Garlasco et al. (2022) the mean D-cost for cancers for the countries Portugal, the Netherlands, Korea and Mexico was estimated. By using the data available in the literature we consider the estimated DALYs in calculations of costs, and translates in a reported D-cost of 8534.33 euros with a 95% UI of 4856.18 to 14,966.85 euros.

All estimations were performed in Microsoft Office Excel.

3. Results

3.1. Exposure assessment and excess lung cancer risk

In 2019, more than 828 thousand people in the European Union (excluding the United Kingdom) were estimated to work in contexts where occupational exposure to Cr(VI) occurs (Supplementary Table A1). From these, almost 481 thousand workers (64.8%) were exposed to high concentrations of Cr(VI). The contexts of high exposure to Cr(VI) are described in Table 1.

The high-exposure contexts (Cherrie et al., 2011; 2017) with the highest number of exposed workers were in manufacturing metallic products (except machinery and equipment), which accounted for around 232 thousand workers (48.3% of the total exposed). The industries with the lowest contribution were the manufacture of furniture and mattresses, along with other manufacturing industries, which had 14,852 exposed workers (3.1% of the total exposed).

In terms of the proportion of exposed by industry, the manufacture of metallic products had a greater exposure of its workers, with 6.7% of these exposed to Cr(VI), whereas the other industries and the manufacture of furniture have a lower percentage (0.7%). On average, these industries had 3.6% of their workforce exposed to Cr(VI).

The estimated excess risk of incidence of lung cancer due to exposure to Cr(VI) varied according to the level of exposure (Supplementary Table A2), with a 40-year cumulative risk of 3.07×10^{-3} per μg Cr(VI)/m^3 in 2019, whereas the individual excess risk was of 7.70×10^{-5} per μg Cr(VI)/m^3 (Table 2).

3.2. Estimated incidence and DALYs

The calculation of lung cancer DALYs associated with occupational exposure to Cr(VI) was based on PAF and total lung cancer DALYs. The determination of DALYs by country made it possible to analyse the differences between the various member states of the European Union (Table 3). There were differences in the number of cases and DALYs, with Germany showing the highest values, with 27 cases of lung cancer and 470.34 DALYs with an occupational exposure limit of 5 μg/m^3, followed by Italy (19 cases, 312.35 DALYs) and Poland (10 cases, 244.53 DALYs). The countries with the lowest values were Malta, Luxembourg, and Cyprus, probably due to their demographic dimension. However, these countries accounted for less than one case of lung cancer attributed to occupational exposure to Cr(VI), for the same OEL. These data reflect the number of workers working in industries with potential exposure to CrVI in each country.

DALYs were also compared in terms of DALY rates (Table 4). Current DALY rates for occupational exposure to Cr(VI) showed different results. Czechia presented the highest values, with 2.182 DALY/100,000 population, followed by Slovenia with 1.927 DALY/100,000 population, and Poland with 1.552 DALY/100,000 population. The lowest rates were found in Malta (0.002 DALY/100,000 population), Austria (0.060 DALY/100,000 population) and Greece (0.259 DALY/100,000 population).

The number of DALY in the EU estimated for each scenario of future implementation of OELs are presented in Table 5. Regarding incident cases in the current scenario, estimates showed a number of 253 cases of lung cancer, corresponding to 4683 DALYs. Adopting the general OEL for Cr(VI) (10 μg/m^3) in the welding industry would decrease the number of cases by 15%, with 210 cases of lung cancer and 3896 DALYs. If the EU Directive 2004/37/EC was put in place in 2019 (scenario 2), it would decrease the number of cases by 58%. If EU countries adopted the Germany and France OEL of 2 μg/m^3 (scenario 4), this would lower the number of cases by 91.6%, resulting in 21 cases of lung cancer and 390 DALYs. Other scenarios would further decrease the incidence of lung cancer, with the adoption of the United States' threshold of 0.2 μg/m^3 (scenario 6) dramatically lowering the number of cases to 4 (difference of 98%). It is to note that, in any of the scenarios, there would be an incremental effect when estimating these values for a 40-year span.

When comparing DALY rates (Fig. 2), the current average rate corresponded to 0.903 DALY/100,000 population. The change in the welding industry to 10 μg/m^3 (scenario 1) would lead to its reduction to 0.750 DALY/100,000 population, while adopting the scenario 2 would double this value down to 0.375 DALY/100,000 population. The adoption of Cr(VI) OELs in Germany and France (scenario 4) would decrease in a twelve-fold proportion, with a rate of 0.075 DALY/100,000 population. Additional scenarios with lower OELs would further reduce DALYs in the population, with scenario 6 presenting a rate of 0.015 DALY/100,000 population.

Table 3
Number of new cases of lung cancer and DALYs for different OELs of Cr(VI).

Country	OEL = 25 μg/m^3			OEL = 10 μg/m^3			OEL = 5 μg/m^3		
	Number of cases	PAF	DALYs	Number of cases	PAF	DALYs	Number of cases	PAF	DALYs
Austria	11.11	0.00012	11.11	4.44	0.00005	4.44	2.22	0.000025	2.22
Belgium	8.26	0.00095	154.14	3.30	0.00038	61.66	1.65	0.000190	30.83
Bulgaria	8.12	0.00168	195.49	3.25	0.00067	78.20	1.62	0.000336	39.10
Cyprus	0.48	0.00093	9.00	0.19	0.00037	3.60	0.10	0.000186	1.80
Czechia	25.19	0.00363	484.33	10.07	0.00145	193.73	5.04	0.000726	96.87
Denmark	5.52	0.00112	95.99	2.21	0.00045	38.40	1.10	0.000224	19.20
Estonia	0.92	0.00127	19.20	0.37	0.00051	7.68	0.18	0.000254	3.84
Finland	5.03	0.00162	79.80	2.01	0.00065	31.92	1.01	0.000323	15.96
France	52.03	0.00116	1016.49	20.81	0.00046	406.60	10.41	0.000231	203.30
Germany	134.00	0.00211	2351.68	53.60	0.00084	940.67	26.80	0.000422	470.34
Greece	3.09	0.00034	57.63	1.24	0.00013	23.05	0.62	0.000067	11.53
Hungary	13.12	0.00138	293.15	5.25	0.00055	117.26	2.62	0.000276	58.63
Ireland	1.44	0.00058	25.04	0.57	0.00023	10.02	0.29	0.000115	5.01
Italy	93.25	0.00223	1561.74	37.30	0.00089	624.70	18.65	0.000447	312.35
Latvia	1.35	0.00133	28.14	0.54	0.00053	11.25	0.27	0.000265	5.63
Lithuania	3.06	0.00219	64.76	1.22	0.00088	25.91	0.61	0.000438	12.95
Luxembourg	0.23	0.00072	4.50	0.09	0.00029	1.80	0.05	0.000145	0.90
Malta	0.00	0.00001	0.03	0.00	0.000003	0.01	0.00	0.000001	0.01
Netherlands	15.75	0.00104	275.92	6.30	0.00042	110.37	3.15	0.000208	55.18
Poland	51.76	0.00172	1222.67	20.70	0.00069	489.07	10.35	0.000345	244.53
Portugal	10.65	0.00228	231.17	4.26	0.00091	92.47	2.13	0.000455	46.23
Romania	14.57	0.00126	344.80	5.83	0.00051	137.92	2.91	0.000252	68.96
Slovakia	6.42	0.00205	121.83	2.57	0.00082	48.73	1.28	0.000410	24.37
Slovenia	4.23	0.00303	83.80	1.69	0.00121	33.52	0.85	0.000606	16.76
Spain	44.34	0.00150	787.35	17.74	0.00060	314.94	8.87	0.000300	157.47
Sweden	11.84	0.00273	221.15	4.73	0.00109	88.46	2.37	0.000545	44.23
Total (95% UI)	**525.74 (523.07–528.40)**		**9740.92 (9729.77–9752.07)**	**210.29 (208.61–211.98)**		**3896.37 (3889.32–3, 903.42)**	**105.15 (103.96–106.34)**		**1948.18 (1943.20–1953.17)**

Country	OEL = 2 μg/m3			OEL = 1 μg/m3			OEL = 0.5 μg/m3			OEL = 0.2 μg/m3		
	Number of cases	PAF	DALYs	Number of cases	PAF	DALYs	Number of cases	PAF	DALYs	Number of cases	PAF	DALYs
Austria	0.89	0.000010	0.89	0.44	0.000005	0.44	0.22	0.000002	0.22	0.09	0.000001	0.09
Belgium	0.66	0.000076	12.33	0.33	0.000038	6.17	0.17	0.000019	3.08	0.07	0.000008	1.23
Bulgaria	0.65	0.000134	15.64	0.32	0.000067	7.82	0.16	0.000034	3.91	0.06	0.000013	1.56
Cyprus	0.04	0.000074	0.72	0.02	0.000037	0.36	0.01	0.000019	0.18	0.00	0.000007	0.07
Czechia	2.01	0.000290	38.75	1.01	0.000145	19.37	0.50	0.000073	9.69	0.20	0.000029	3.87
Denmark	0.44	0.000090	7.68	0.22	0.000045	3.84	0.11	0.000022	1.92	0.04	0.000009	0.77
Estonia	0.07	0.000102	1.54	0.04	0.000051	0.77	0.02	0.000025	0.38	0.01	0.000010	0.15
Finland	0.40	0.000129	6.38	0.20	0.000065	3.19	0.10	0.000032	1.60	0.04	0.000013	0.64
France	4.16	0.000092	81.32	2.08	0.000046	40.66	1.04	0.000023	20.33	0.42	0.000009	8.13
Germany	10.72	0.000169	188.13	5.36	0.000084	94.07	2.68	0.000042	47.03	1.07	0.000017	18.81
Greece	0.25	0.000027	4.61	0.12	0.000013	2.31	0.06	0.000007	1.15	0.02	0.000003	0.46
Hungary	1.05	0.000110	23.45	0.52	0.000055	11.73	0.26	0.000028	5.86	0.10	0.000011	2.35
Ireland	0.11	0.000046	2.00	0.06	0.000023	1.00	0.03	0.000011	0.50	0.01	0.000005	0.20
Italy	7.46	0.000179	124.94	3.73	0.000089	62.47	1.87	0.000045	31.23	0.75	0.000018	12.49
Latvia	0.11	0.000106	2.25	0.05	0.000053	1.13	0.03	0.000027	0.56	0.01	0.000011	0.23
Lithuania	0.24	0.000175	5.18	0.12	0.000088	2.59	0.06	0.000044	1.30	0.02	0.000018	0.52
Luxembourg	0.02	0.000058	0.36	0.01	0.000029	0.18	0.00	0.000014	0.09	0.00	0.000006	0.04
Malta	0.00	0.000001	0.00	0.00	0.000000	0.00	0.00	0.000000	0.00	0.00	0.000000	0.00
Netherlands	1.26	0.000083	22.07	0.63	0.000042	11.04	0.32	0.000021	5.52	0.13	0.000008	2.21
Poland	4.14	0.000138	97.81	2.07	0.000069	48.91	1.04	0.000034	24.45	0.41	0.000014	9.78
Portugal	0.85	0.000182	18.49	0.43	0.000091	9.25	0.21	0.000046	4.62	0.09	0.000018	1.85
Romania	1.17	0.000101	27.58	0.58	0.000050	13.79	0.29	0.000025	6.90	0.12	0.000010	2.76
Slovakia	0.51	0.000164	9.75	0.26	0.000082	4.87	0.13	0.000041	2.44	0.05	0.000016	0.97
Slovenia	0.34	0.000242	6.70	0.17	0.000121	3.35	0.08	0.000061	1.68	0.03	0.000024	0.67
Spain	3.55	0.000120	62.99	1.77	0.000060	31.49	0.89	0.000030	15.75	0.35	0.000012	6.30
Sweden	0.95	0.000218	17.69	0.47	0.000109	8.85	0.24	0.000055	4.42	0.09	0.000022	1.77
Total (95% UI)	**42.06 (41.30–42.81)**		**779.26 (776.12–782.43)**	**21.03 (20.50–21.56)**		**389.64 (387.41–391.87)**	**10.51 (10.14–10.89)**		**194.82 (193.24–196.40)**	**4.20 (3.97–4.44)**		**77.93 (76.93–78.92)**

95% UI: 95% Uncertainty Interval; Cr(VI): hexavalent chromium; OEL: Occupational Exposure Limit.

Table 4
DALY rates for different OELs of Cr(VI) across the European Union.

Localisation	Population (N)	Current OELs	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Austria	8,901,064	0.060	0.050	0.025	0.010	0.005	0.002	0.001
Belgium	11,522,440	0.645	0.535	0.268	0.107	0.054	0.027	0.011
Bulgaria	6,951,482	1.355	1.125	0.562	0.225	0.112	0.056	0.022
Cyprus	888,005	0.488	0.405	0.203	0.081	0.041	0.020	0.008
Czechia	10,693,939	2.182	1.812	0.906	0.362	0.181	0.091	0.036
Denmark	5,822,763	0.794	0.659	0.330	0.132	0.066	0.033	0.013
Estonia	1,328,976	0.696	0.578	0.289	0.116	0.058	0.029	0.012
Finland	5,525,292	0.696	0.578	0.289	0.116	0.058	0.029	0.012
France	67,320,216	0.728	0.604	0.302	0.121	0.060	0.030	0.012
Germany	83,166,711	1.363	1.131	0.566	0.226	0.113	0.057	0.023
Greece	10,718,565	0.259	0.215	0.108	0.043	0.022	0.011	0.004
Hungary	9,769,526	1.446	1.200	0.600	0.240	0.120	0.060	0.024
Ireland	4,964,440	0.243	0.202	0.101	0.040	0.020	0.010	0.004
Italy	59,641,488	1.262	1.047	0.524	0.209	0.105	0.052	0.021
Latvia	1,907,675	0.711	0.590	0.295	0.118	0.059	0.029	0.012
Lithuania	2,794,090	1.117	0.927	0.464	0.185	0.093	0.046	0.019
Luxembourg	626,108	0.347	0.288	0.144	0.058	0.029	0.014	0.006
Malta	514,564	0.002	0.002	0.001	0.000	0.000	0.000	0.000
Netherlands	17,407,585	0.764	0.634	0.317	0.127	0.063	0.032	0.013
Poland	3,795,8138	1.552	1.288	0.644	0.258	0.129	0.064	0.026
Portugal	10,295,909	1.082	0.898	0.449	0.180	0.090	0.045	0.018
Romania	19,328,838	0.860	0.714	0.357	0.143	0.071	0.036	0.014
Slovakia	5,457,873	1.076	0.893	0.446	0.179	0.089	0.045	0.018
Slovenia	2,095,861	1.927	1.599	0.800	0.320	0.160	0.080	0.032
Spain	47,332,614	0.802	0.665	0.333	0.133	0.067	0.033	0.013
Sweden	10,327,589	1.032	0.857	0.428	0.171	0.086	0.043	0.017
European Union	443,261,751	0.903 (0.701–1.105)	0.750 (0.582–0.918)	0.375 (0.291–0.459)	0.150 (0.116–0.184)	0.075 (0.058–0.092)	0.037 (0.029–0.046)	0.015 (0.012–0.018)

3.3. Estimated health costs

The estimates of costs in each scenario are present in Table 5. The current scenario showed an annual cost associated with Cr(VI) exposure of 10.19 million euros (COI), going up to 453.82 million euros when considering WTP. These values are expected to decrease to less than half when the EU Directive is implemented in 2025 (scenario 2). However, this still reflected in a cost that varied from 4.23 million (COI) to 188.35 million euros per year (WTP). Adopting lower OELs would further decrease estimated costs - for example, an OEL of 1 μg/m^3 (scenario 4), the same limit set in Germany and France, would cut costs by 91.6% when comparing to the current scenario. An OEL of 0.2 μg/m^3 further decreases costs, which reflects in a 98.3% decrease in costs (scenario 6).

We estimated a D-cost of 39.97 (95%UI 22.75–70.10) million euros in the current scenario, and an estimated decrease to 16.62 (95%UI 9.46–29.16) million euros with the new EU legislation is in place (scenario 2). Scenarios with lower OELs would allow even higher savings, which can reach 39.3 million euros if the limit of 0.2 μg/m^3 (scenario 6) would be adopted.

4. Discussion

This study performed health and socioeconomic analysis to assess the current health and economic burden of occupational Cr(VI) exposure in the EU, and the potential impact of reducing the legally binding OELs for Cr(VI) to be enforced in 2025, as well as estimates for scenarios for lower OELs (Santonen et al., 2022a).

This analysis allowed to understand the magnitude of disease burden and associated cost of different OELs, relevant to inform and target interventions to reduce occupational exposure to Cr(VI).

Regarding the estimation of the exposed population, our study did not present a significant variation in the number of exposed workers to that reported in previous studies that applied the same methodology (Cherrie et al., 2017). Differences were observed regarding the overall number of exposed workers in several European countries and the data obtained in this study. Although Germany has an OEL of 1 μg/m^3, it is one of the countries with the highest new cases and years of life lost due to Cr(VI). On the other hand, Austria, for example, has a limit of 50 μg/m^3 and is not one of the countries with the most reported cases. When adjusting for the population, Czechia presented the highest DALY rate, followed by Slovenia. While these are not the countries with the highest number of cases, the workforce dimension in these industrial sectors and their proportion within the population might contribute to these results. It is also acknowledged that, while there are differences in the reporting rates of occupational lung cancer, which remains unrecognised and underreported in many countries (Del Bianco and Demers, 2013; Musu and Vogel, 2018), these might not significantly influence these results as these calculations were carried out considering the excess risk and size of workforce.

We estimated that 4,683 DALYs were attributed to lung cancer in 2019, caused by occupational exposure to Cr(VI) in 26 EU member states. Different scenarios led to health gains, with the expected stricter OEL of 5 μg/m^3 leading to a reduction to 1,948 DALYs. Comparing with previous studies that adopted the same methodology, in which 490 cases of lung cancer attributable to Cr(VI) were estimated in the work environment (Cherrie et al., 2017), there was a decrease in the number of cases and DALYs, while the population exposed to Cr(VI) in the workplace has remained stable over the last decade. The variation may be due to specific changes and the application of new risk management measures in industries to prevent exposure, which occurred in the first years of the last decade, resulting in an estimated decrease in exposure due to the yearly decrease in the progressive exposure concentration of 7% estimated for this substance (European Commission, 2016). Moreover, there might have been an underestimation in the calculations of exposed population and cases attributed to Cr(VI), due to the assumption made in this study that countries adopt and comply with the stricter OELs defined. Nonetheless, the context of exposure has changed across time, namely Cr(VI) exposure. As such, new definitions of high and low exposure limits are also needed to understand variations in these settings, and to better frame any legislation change.

In terms of health impacts, other studies in occupational contexts have found Cr(VI) to be one of the substances with high risk, along with respirable crystalline silica and diesel engine exhaust (Cherrie et al., 2017). In GBD, Cr(VI) is reported to be the ninth largest contributor to

Table 5
Differences attributed to the occupational exposure to Cr(VI) in 2019 and differences in the scenarios tested regarding number of cases, DALYs, Cost of Illness (COI), Willingness to Pay (WTP) and Cost quantified by DALYs (D-Cost).

Context	OEL (μg/m^3)	Number of cases in 2019	95% UI Cases[b]	DALYs in 2019	95% UI DALYs	DALYs per 100,000 population	Number of cases avoided[a]	DALYs avoided[a]	Percentage of decrease in health risk[a]	Total COI [no change] (€ million)	Total COI [with change] (€ million)	WTP (€ million)	D-Cost (€ million) with 95% UI
Current Scenario	General limit: 10 Welding: 25	253.33	250.96–255.71	4683.82	4683.57–4704.08	0.903 (0.701–1.105)	0	0	0	12.47	10.19	453.82	39.97 (22.75–70.10)
Scenario 1	10	210.29	208.61–211.98	3896.37	3889.32–3903.42	0.750 (0.582–0.918)	43	797	17.0%	10.35	8.46	376.69	33.25 (18.92–58.31)
Scenario 2	5	105.15	103.96–106.34	1948.18	1943.20–1953.17	0.375 (0.291–0.459)	148	2746	58.4%	5.18	4.23	188.35	16.62 (9.46–29.16)
Scenario 3	2	42.06	41.30–42.81	779.27	776.12–782.43	0.150 (0.116–0.184)	211	3915	83.3%	2.07	1.69	75.34	6.65 (3.78–11.66)
Scenario 4	1	21.03	20.50–21.56	389.64	387.41–391.87	0.075 (0.058–0.092)	232	4304	91.6%	1.04	0.85	37.68	3.33 (1.89–5.84)
Scenario 5	0.5	10.51	10.14–10.89	194.82	193.24–196.40	0.037 (0.029–0.046)	243	4499	95.9%	0.54	0.44	19.73	1.66 (0.95–2.92)
Scenario 6	0.2	4.20	3.97–4.44	77.93	76.93–78.92	0.015 (0.012–0.018)	249	4616	98.3%	0.20	0.16	7.18	0.67 (0.38–1.17)

OEL: Occupational Exposure Limit; UI: Uncertainty Interval; DALY: Disability-adjusted Life Years; COI: Cost of Illness; WTP: Willingness to Pay; D-Cost: Costs quantified by DALYs.
[a] Against current scenario in 2019.
[b] Derived from the GBD 2019 study.

occupational cancer disease burden with the most DALYs (Li et al., 2021). A study on toxic waste in Asia reported a high exposure to lead and Cr(VI), which collectively accounted for 99.2% of the total DALYs for the identified chemicals (Chatham-Stephens et al., 2013).

When comparing to the GBD 2019 study (Global Burden of Disease Collaborative Network, 2020), which reported 0.38 DALY per 100,000 population (UI 0.34–0.43) in the European Union, our estimations presented a higher DALY rate (0.90; UI 0.701–1.105). The analysis of other occupational exposures in GBD places Cr(VI) in the same level, attributing the highest DALY rates to asbestos (248.90; UI 177.10–322.18), followed by silica (40.05; UI 10.25–68.27) and arsenic (7.24; UI -1.62 - 15.61). However, our DALY rate for Cr(VI) is closer to polycyclic aromatic hydrocarbons, which showed a DALY rate of 1.39 per 100,000 population (UI 1.18–1.60). Differences might be explained by the data used in the GBD, as it considers world population, and methodological choices in DALY calculation, by using of other approaches as the risk assessment analysis or the categorical attribution, which can be influenced by underreporting of occupational Cr(VI)-associated lung cancers (Del Bianco and Demers, 2013; Musu and Vogel, 2018).

We estimated that current COI amounts to 10.2 million euros per year in the EU, with an annual WTP of 453.8 million euros. These values are estimated to decrease by 58% with the EU Directive enforced from 2025. However, the COI will still be as high as 4.2 million euros, with an WTP of 188.4 million euros. Costs decrease with lower OELs, with a COI that can be as low as 0.16 million euros with an OEL of 0.2 μg/m^3, which translates in a 98.2% decrease in costs, which is the OEL adopted by the United States. Additionally, costs are expected to decrease yearly with a regular discount rate of 4% (Cherrie et al., 2017). Other studies conducted in different countries showed high costs, varying according to the respective healthcare system: annual direct costs for lung cancer are estimated to be around 8772 to 10,167 euros per patient in Turkey, with indirect costs accounting for 68.6% of total costs (Cicin et al., 2021). Another important fact to notice is that in Colombia, 43% of costs related to lung cancer are out-of-pocket, which reflects an overall mean cost of 11,560.75 dollars per patient, with the contributory regimen costing 14,303.58 dollars per patient and the subsidized system costing 4160.67 dollars per lung cancer patient (Torres et al., 2022). In Thailand, lower-income patients are willing to pay US Dollar 5,123 per QALY, while this increases significantly by wealth category (Thongprasert et al., 2015). Using a single estimate of costs for COI and WTP from France might under- or overestimate the costs related to lung cancer, depending on the country.

The annual cost per DALY analysis showed a higher but similar cost than that of COI, but lower than the WTP values. Other estimations of cost-per-DALY in cancers have been conducted before, with calculations comparing DALY costs to national gross domestic product (Garlasco et al., 2022; Neves et al., 2021; Noh et al., 2020; Oh et al., 2012; Vondeling et al., 2016). In this study, the considered cost-per-DALY estimates were derived from the aforementioned studies, which might underestimate costs due to the different pathologies presented (multiple myeloma, breast cancer and lung cancer) which present different prognosis than lung cancer, which is the main cause of death among cancer cases in Europe. Moreover, the cost-per-DALY estimates we apply are derived from several countries, however it is still not representative of all EU countries, which might also influence the results. Nevertheless, the estimations allowed to understand the impact of legislations in lung cancer-related costs, and the predicted impact of lowering an OEL.

The estimated values indicate the importance of the regulatory actions at EU level. In this context, it would be important to intervene in the Occupational Health sector, in order to identify contexts with increased risk and reinforce the importance of the proper notification of occupational cancers.

On the other hand, when implementing changes to exposure limits, different aspects that may influence the applicability of the measures must be considered. In addition to assessing the risk and potential health benefits of populations, it is necessary to consider the feasibility of the

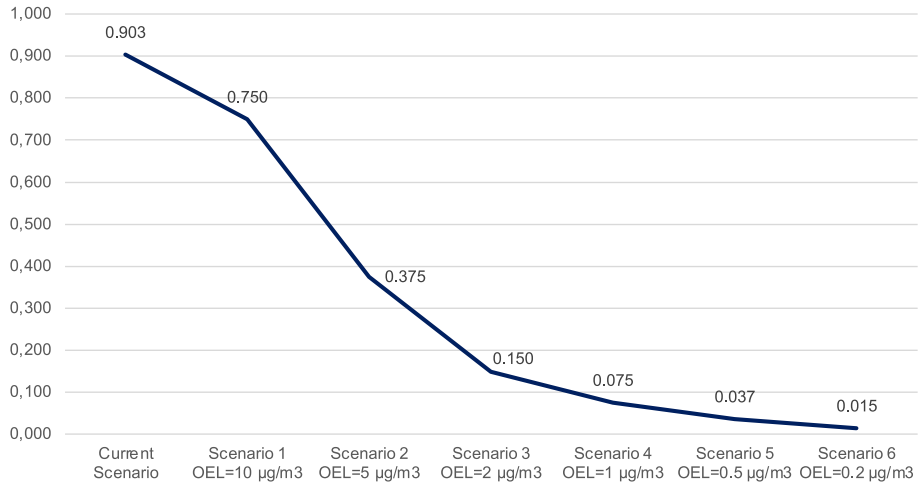

Fig. 2. DALY rates per 100,000 population in EU countries in 2019, for each of the scenarios adopted.

measures, including whether there will be resistance from industries in applying the new limits through investments in more effective risk management measures or even in the substitution of the substance. Compliance costs have not been considered in this study. The SHEcan Report P937/5 analysed potential costs for enterprises of implementing measures to reduce Cr(VI) concentrations in the air, reporting an annual cost of 1,000–2,000 euros for each enterprise (Cherrie et al., 2011). Specific studies on compliance costs are required given the technology advancements and the need to protect workers health besides industry innovation and competitiveness needs.

The long-term impact of the regulatory changes should also be emphasized. The adoption of restricted OELs only produces visible effects on the long run, as exposure to Cr(VI) can result in lung cancer after decades of repeated exposure (European Chemicals Agency, 2013). Thus, attempts to change the EU Directives are hindered, resulting in harming current and future generations of workers.

Several actions have been promoted by the European Agency for Safety and Health at Work, which has developed a roadmap on carcinogens that includes a strategy until 2024, with four main goals. These include not only raising awareness on the risks of carcinogens' exposure and the need for preventive actions among businesses and workers, but also assisting them in preventing exposure to these substances and minimising their effects at the workplace. This strategy also intends to mobilise important stakeholders and increasing the involvement of relevant parties to multiply efforts throughout Europe, as well as target innovation to bridge the gap between research findings and businesses' needs (European Agency for Safety and Health at Work, 2020).

4.1. Study limitations

Despite the great evolution and continuous improvement in DALY methodologies, some limitations are inherent to burden of disease studies and the DALY metric. Firstly, the origin and quality of the data is very important, and since the collection is heterogeneous and from different sources of information, as well as the norms that guide this process, this will inevitably lead to some fluctuations and uncertainty in the estimates. Moreover, occupational Cr(VI) lung cancers have an earlier onset than the general population, which is not reflected in the DALY envelopes.

We applied recent Eurostat data to allow for an updated assessment of the exposed population, however assumptions were made on the exposure levels of the industries, which were assumed to fulfil the legal requirements of OEL. Existing exposure data from 2006 to 2010 were also used to extrapolate the percentage of high-exposed population to 2019, which present slight differences according to the sources. We believe that these factors might underestimate our results.

Other data sources could have been utilized. HBM4EU provides urinary measures of Cr(VI), and it concluded that ingestion route of Cr (VI) had an important role in total exposure (Santonen et al., 2022b; Viegas et al., 2022). As lung cancer is not related with this exposure route, it would be interesting to understand whether urinary measures are associated with lung cancer. As such, HBM4EU has the potential to deliver a closer picture of the current exposure of Cr(VI) when such comparisons are possible.

As for methodology, using a DALY envelope approach could overestimate the estimations, as it uses incidence instead of the traditional prevalence in the direct approach via YLLs. Moreover, as we use incidence of lung cancer and DALYs of European countries retrieved from the GBD 2019 Study, this might influence the estimations. However, due to unavailability of data, this was the adequate approach to be applied.

When analysing dose-response, many different sources reported different relative and excess risks, which varied from RR = 1.18 to 4.52, with 1.75 being considered a "tolerable" excess risk associated with a Cr (VI) exposure of about 1 $\mu g/m^3$ (Cherrie et al., 2017; Ebrahimi et al., 2021; European Chemicals Agency, 2013; Seidler et al., 2013). As such, there is great variance in the literature and little consensus between the theoretical and empirical excess risks. A more recent study shows an OR = 1.32 for lung cancer associated with Cr(VI) exposure (Behrens et al., 2023). Having adopted a slope factor of 1.75 (Seidler et al., 2013), which represents the upper bound of the RR, might allow for some caution while not disregarding empirical data.

Economical costs related to health outcomes vary considerably both in methods and in cost estimates across studies in the literature. While the COI is the most wide-spread method for such economic evaluations, WTP allows accounting for the patient's perspective and their subjective value of life (Jo, 2014). On the other hand, cost-per-DALY reflects the negative impact of a disease, considering the loss of one year of healthy life and respective disabilities, which can be interpreted as a more holistic approach when comparing to COI. All in all, these methods differ from each other, with each presenting its own disadvantages, which contributed to the decision to calculate the three in this study. However, there is a lack of data in the literature for calculating each method, including baseline costs across European countries. In this study, we used data from France for COI and WTP, which may overestimate costs, whereas for costs based on DALYs, we considered a mean cost-per-DALY from several countries across the world, which may not reflect the European situation, posing a risk of not being representative for the EU.

5. Conclusion

Drawing scenarios with different exposure limits to Cr(VI) builds further on past studies regarding estimations on the impact of different OELs. The analysis of the scenarios made it possible to understand the impact of EU regulatory policies on occupational health, through the burden of disease, as well as associated costs, strengthening the rationale for acting in disease prevention, through structural measures, namely those of legal scope. By moving into a new OEL in 2025, the EU is taking a step closer to decreasing the burden of lung cancer, however this is still significant considering the advances made in the industry and in technology in the past decade. Adapting stricter occupational exposure limits will protect workers health and prevent cancer cases.

Author statement

JCX, SMP and LSJ designed the study. JCX collected and managed the data and performed the analysis. LSJ and SV contributed to the interpretation and discussion of results. JSX, SMP, LSJ and SV wrote and revised the manuscript.

Funding

This project received funding from the COST Action CA18218 European Burden of Disease Network, supporting the first author with a Short-Term Scientific Mission to the National Food Institute, Technical University of Denmark, with the aim of improving knowledge and applying the appropriate methodology on burden of disease on this project.

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

All data used in the study are publicly available and presented in the manuscript.

Acknowledgements

The authors would like to thank the researchers from the Research Group for Risk Benefit from the National Food Institute, Technical University of Denmark for raising questions to improve the robustness of the research project, as well as the COST Action CA18218 European Burden of Disease Network for funding and supporting the project, and to the researchers Carla Martins from NOVA National School of Public Health and Ricardo Assunção from Egas Moniz Cooperativa de Ensino Superior for contributing to the initial brainstorming on the disease pathology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115797.

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