National Research Centre
for the Working Environment

Chromium(VI) compounds:

Assessment of SCOEL/REC/386

Assessment

January 2019

National Research Centre for the Working Environment

Chromium(VI) compounds: Assessment of SCOEL/REC/386

The Danish Working Environment Authority has asked NFA to reassess the documentation for the Danish occupational exposure limit (OEL) for hexavalent chromium (Cr(VI)). The current Danish OELs for Cr(VI) compounds are 0.005 mg/m^3 for chromic acid and chromates, and 0.0005 mg/m^3 for strontium chromate (both calculated as Cr mass concentration).

The Scientific Committee on Occupational Exposure Limits, SCOEL, evaluated Cr(VI) in 2017 (Hartwig et al. 2017) and established dose-response relationship for Cr(VI)-induced excess lung cancer risk for occupational exposure limits. The present report is an assessment of whether the SCOEL report can be used for re-evaluation of the current Danish OEL for Cr(VI).

The present assessment of the SCOEL report (Hartwig et al. 2017) is primarily based on critical evaluation of the SCOEL report, the dose-response assessment by the EU Risk Assessment Committee published by ECHA in 2013 (ECHA 2013), and the meta-analysis performed (Seidler et al. 2013), which forms the basis of the risk assessments by both SCOEL (Hartwig et al. 2017) and ECHA (ECHA 2013) as well as relevant literature published after publication of the SCOEL report.

The present working group wishes to thank Chief Toxicologist Poul Bo Larsen, DHI, Denmark, for reviewing this assessment.

Evaluation of SCOEL/REC/386

SCOEL has identified lung cancer as the critical effect of occupational inhalation of Cr(VI)-containing compounds (Hartwig et al. 2017). SCOEL further concludes that “Cr(VI) compounds are carcinogens with no threshold, carcinogen group A” (Hartwig et al. 2017).

In the SCOEL report (Hartwig et al. 2017), the following dose-response estimates of excess lung cancer cases caused by 40 years of occupational exposure to Cr(VI) are given (table 1). These are based on two epidemiological studies (Crump et al. 2003 and Park et al. 2004). Both studies are identified by SCOEL as high quality studies using quantitative exposure estimates:

Table 1. Estimates of excess lung cancer cases per 1000 workers exposed at the listed levels (reproduced from Hartwig et al. 2017).

Exposure 8 hour time weight average	Point estimate combined response slopes	Confidence interval	Crump et al. 2003	Park et al. 2004
25 µg/m^3	94	76 - 112	38	146
10 µg/m^3	39	31 - 47	15	62
5 µg/m^3	20	16 - 24	8	32
1 µg/m^3	4	3.2 - 4.8	2	6
0.1 µg/m^3	0.4	0.3 - 0.5	0.2	0.6

Overall, the present working group regards the SCOEL report (Hartwig et al. 2017) as a thorough evaluation of the available scientific evidence for the toxicity of Cr(VI) and the scientific evidence for risk assessment.
The present working group has the following comments to the report:

Exposure and monitoring

Estimations of Cr(VI) exposure levels in Europe

SCOEL (Hartwig et al. 2017) cites a report from Institute of Occupational Medicine (IOM) (Cherrie et al. 2011) on page 23 regarding European occupational exposure levels of Cr(VI). The current working group notes that exposure data were collected from 1990-2000. These exposure levels were assigned to year 1995. Then exposure levels in 2010 were extrapolated by assuming an annual decrease in the air concentration of 7%. The reason for this assumption is that a trend analysis of 38 aerosol exposure studies from 2007 found that on average, exposure levels decreased by 7% per year. IOM found no evidence to suggest that the temporal trend in Cr(VI) exposure levels should differ from the typical trend (Cherrie et al. 2011).

Cr(VI) exposure levels in France

The SCOEL report also describes several recent occupational exposure studies (Hartwig et al. 2017). Among these is a comprehensive study of occupational exposure levels of Cr(VI) in France 2010-2013 (Vincent et al. 2015). The study included 741 measurements in 99 companies of 166 inspected, in 19 different activity sectors. The sampling included 436 personal samples, 301 area samples and 4 measurements of emissions over a mean of 5.5 hours. 556 of the samples were considered to be representative of an 8-hour working day. The geometric mean for the 556 samples representative of a working day was 0.38 $\mu g/m^3$ with 35% of the measurements exceeding 1 $\mu g/m^3$ (the French OEL since 2014). The Cr(VI) levels varied extensively between activity sectors and tasks. The present working group notes that current occupational Cr(VI) exposure levels in Denmark are not known.

New data on Cr(VI) exposure levels in German welders

The present working group identified only one relevant study on Cr(VI) exposure published after the SCOEL report: In a German biomonitoring study (WELDOX II) of 50 welders from 14 companies, Cr and Cr(VI) exposure levels were compared with urinary excretion of Cr (Pesch et al. 2018). 62% of the measurements of respirable Cr(VI) were below the detection level of 0.37-0.43 $\mu g/m^3$, the 75th percentile was 0.5 $\mu g/m^3$ and for 8 out of 50 welders, the Cr(VI) level exceeded 1 $\mu g/m^3$. The majority of the welders exceeded the German biological reference value for urinary content of Cr 0.6 µg Cr/L in both pre- and post-shift samples.

Existing methods for Cr(VI) monitoring

The current working group notes that urine content of Cr reflects the content of the sum of Cr III and Cr(VI), whereas erythrocyte content of Cr is regarded as specific for Cr(VI), since Cr III is not taken up by erythrocytes. Furthermore, the current working group notes that the detection limits of air sampling methods for Cr(VI) range from 0.0008 to 25 $\mu g/m^3$. Thus, it is possible with current technology to detect very low levels of Cr(VI) in air.

Toxicity

SCOEL has identified lung cancer as the critical effect of occupational inhalation of Cr(VI)-containing compounds (Hartwig et al. 2017). In addition a number of other serious effects of occupational Cr(VI) exposure have been documented (nephrotoxicity, hypersensitivity, corrosion of the skin, irritation of the respiratory tract and gastrointestinal tract) (Hartwig et al. 2017).

Data on genotoxicity and carcinogenicity

Cr(VI) has been classified as carcinogenic to humans by IARC (IARC 2012) in several evaluations since 1990, and in EU, Cr(VI) compounds has a harmonized classification as either Carc. 1A or Carc. 1B and as mutagenic in Muta. 1B. Both SCOEL and ECHA (European Chemicals Agency) conclude that there is evidence of genotoxicity and that a non-threshold mechanism of action should be used for risk assessment. In Denmark, there are occupational exposure limits for Chromates (0.005 mg/m^3 Cr) and in addition, a specific occupational exposure limit for Strontium Chromate (0.0005 mg/m^3 Cr). The current working group notes that neither SCOEL nor ECHA presents evidence that strontium chromate should be more hazardous than other chromate compounds. The present working group furthermore agrees with ECHA (ECHA 2013) that it is likely that poorly soluble chromates are more carcinogenic after inhalation simply because they are cleared away from the lung more slowly than soluble chromate compounds. The present working group therefore proposes that the same (lowered) OEL should apply to strontium chromate and other chromates.

Risk assessment

Previous risk assessments by SCOEL (2004) and ECHA (2013)

SCOEL has previously made a risk assessment of Cr(VI) (SCOEL 2004). At that time, SCOEL based their risk assessment on a meta-analysis of 10 studies which found association between occupational exposure to Cr(VI) and lung cancer. However, the Cr(VI) exposure levels and duration were not assessed. Instead, SCOEL calculated a dose response relationship by assuming that the exposure levels were either 500 µg/m^3, 1000 µg/m^3 or 2000 µg/m^3 for 15 years. SCOEL (2004) included the following table containing risk estimates (table 2):

Table 2. Excess lung cancer risk by SCOEL 2004 (SCOEL 2004).

Exposure (Working lifetime to a range of Cr(VI) compounds)	Excess relative lung cancer risk per 1000 male workers
50 µg/m^3	5 - 28
25 µg/m^3	2 - 14
10 µg/m^3	1 - 6
5 µg/m^3	0.5 - 3
1 µg/m^3	0.1 – 0.6

The authors of the ECHA report (ECHA 2013) criticized the SCOEL (SCOEL 2004) report. ECHA (2013) thought that the SCOEL (2004) risk estimate underestimated the hazard potential of Cr(VI). SCOEL (2004) based their dose-response relationships on assumptions on the Cr(VI) exposure levels which were relatively high, leading to low dose-response relationships. ECHA (2013) wrote that: *"The unit risk estimates derived by SCOEL (2004) are more than one order of magnitude lower, ranging from 0.1 to 0.6x10^{-3}. These estimates derive from a meta-analysis of 10 studies (Steenland et al. 1996) which lacked information on exposure intensity and duration. Thus, SCOEL* *assumed that the overall SMR of 266 (RR = 2.66) derived from these 10 studies was associated with an average exposure duration of 15 years at three possible (but relatively high) Cr(VI) exposure concentrations of 500, 1000 or 2000 µg/m^3 (equivalent to cumulative Cr(VI) exposures of 7500, 15000 and 30000 µg/m^3–yr). These exposure assumptions are significantly higher than those measured in the US plants and might explain why lower risk estimates were calculated by SCOEL in comparison to the other risk evaluations of Cr(VI) considered in this document. It is the contractor's view that the SCOEL (2004) risk estimates are less reliable: are not consistent with the other available estimates; are less conservative; are based on exposure assumptions rather than actual exposure data; and did not include the more recent epidemiological studies providing exposure-response relationships between Cr(VI) and lung cancer mortality (Gibb et al. 2000; Park et al. 2004, Luippold et al. 2003; Crump et al. 2003). These limitations restrict the value of the SCOEL assessment."*

ECHA (ECHA 2013) provided the following risk estimate for excess lung cancer risk following inhalation exposure to Cr(VI), which is similar to the risk estimate by Seidler et al (Seidler et al. 2013)(further described in the paragraph below):

Table 3. Proposed excess lifetime (up to age 89) lung cancer risk estimates for workers exposed at different 8h-TWA concentrations of Cr(VI) (respirable fraction) for 40 years

TWA Cr(VI) exposure concentration -respirable fraction (µg/m^3)	**Excess lung cancer risk in EU workers (x10^{-3})**
25	100
12.5	50
19	40
5	20
2.5	10
1	4
0.5	2#
0.25	1#
0.1	0.4#
0.01	0.04#

#The authors of ECHA 2013 mention that this is the best dose-response relationship that can be derived by linear extrapolation from the available data, but they also acknowledge the considerable uncertainties surrounding these risk estimates.

The risk estimates for Cr(VI) exposure and lung cancer risk in (ECHA 2013) and (Hartwig et al. 2017) both rely on the systematic meta-analysis in the systematic review by (Seidler et al. 2013)

Systematic review by Seidler et al. 2013

In the systematic review by Seidler et al. (Seidler et al. 2013), a systematic literature search aiming at identifying studies of occupational exposure to chrome(VI) and cancer risk identified 386 hits, of which 6 fulfilled the inclusion criteria. These were: reporting of dose-risk relationship and consideration of smoking. Additional searchers by the present working group in Medline and ISI Web of Science did not identify new relevant studies.

The identified six studies were based on data from 3 retrospective cohorts (Gibb et al. 2000;Park et al. 2004;Park and Stayner 2006;Crump et al. 2003;Luippold et al. 2003;Gerin et al. 1993). Of these, one cohort (Gerin et al. 1993) was excluded because it did not sufficiently consider smoking and because it lacked detailed description of the exposure assessment.

The two included retrospective cohorts were the Baltimore cohort and the Painesville cohort, which are briefly summarized in table 4.

Table 4. Description of the two retrospective cohorts of Cr(VI) exposed workers

	Baltimore cohort	**Painesville cohort**
Publications	(Gibb et al. 2000;Park et al. 2004;Park and Stayner 2006)	(Crump et al. 2003;Luippold et al. 2003)
Study design	Cohort study	Cohort study
Production type and study size	1 plant, chrome production N=2357 males including 122 lung cancer cases 70 736 person -years	1 plant, chrome production N=493 males including 51 lung cancer cases 14 048 person-years
Time span	Began working during 1950-1974 Work history available through 1980 (plant closure 1980)	Began working during 1940-April 1972 (plant closure 1972)
Follow-up	Until 1992	Until 1997
Chrome(VI) exposure assessment	Routine monitoring of ambient air Cr(VI) levels supplemented with personal samplers. Job-exposure matrix and job titles used to determine cumulative exposure	Exposure extrapolated from 21 measurements of Cr(VI) measurements from industrial hygiene surveys over the entire time period. Job-exposure matrix and job titles used to determine cumu-lative exposure
Smoking information	Information on smoking habits from employees records at beginning of employment	Information on smoking habits for 41% of the workers
Linear regression estimate of β of the regression: SMR= β* Cr(VI) (mg/m^3)-years + SMR_0	2.82	0.68

The Baltimore study included almost 5 times more persons and person-years than the Painesville study, better information on smoking habits (for all employees at onset of employment versus information for 41%) and better Cr(VI) exposure data (routine measurements of ambient air Cr(VI) levels versus a total of 21 Cr(VI) measurements). Of note, the Baltimore study also included 990 workers who had worked at the factory for less than 90 days to expand the size of the low exposure group. It is discussed in (Seidler et al. 2013) that there is no information available regarding the possible exposure of the short term workers to occupational carcinogens during later employment at other workplaces. The present working group notes this and furthermore notes that such exposures would lead to high SMRs for the lowest Cr(VI) exposure group, as both lung cancer caused by the short occupational exposure to Cr(VI) and the subsequent occupational exposure to other carcinogens would be attributed to the short term Cr(VI) exposure.

Exposure-risk relationships were estimated for the two cohorts based on reported Cr(VI) exposure levels and standardized mortality ratio (SMR) using a linear model:

$$SMR = \beta * Cr(VI)\ mg/m^3\text{-years} + SMR_0$$

The calculated β-values are given in table 4, and the two estimates are quite different (2.82 and 0.68 for the Baltimore and Painesville studies, respectively).

In the meta-analysis, an un-weighted mean β of 1.75 ([0.68+2.82]/2=1.75) was calculated.

Table 5. Risk estimates for occupational Cr(VI) air concentrations in relation to 40 years of occupational exposure estimated as excess lung cancer mortality per 1 000 males in a European population up to age 74 based on the average estimate of two cohorts and the two estimates based on the separate cohorts.

Cr(VI) exposure (µg/m^3)	Combined cohorts Risk x 10^{-3}	Baltimore cohort Risk x 10^{-3}	Painesville cohort Risk x 10^{-3}
0.0025	0.01	0.01	0.003
0.01	0.03	0.05	0.01
0.025	0.08	0.14	0.03
0.1	0.34	0.54	0.13
0.25	0.84	1.35	0.33
1	3.36	5.41	1.31
2.5	8.40	13.5	3.26
5 (Danish OEL)	**16.8**	**27.1**	**6.53**
25	84	135	32

Thus, depending on the risk estimate used, an OEL of 5 µg/m^3 (the current Danish OEL for chromates) leads to 17, 27 or 7 excess lung cancers per 1 000 male workers, corresponding to 1.7%, 2.7% or 0.7 %, respectively.

The present working group is of the opinion that the Baltimore study is of higher quality than the Painesville study because of the larger size, the complete information on smoking, and the high quality of the Cr(VI) exposure measurements. Thus, the approach to use an unweighted mean between the two studies may underestimate the true lung cancer risk associated with Cr(VI) exposure. However, as seen from table 5, the difference in risk estimates for the combined cohorts and for the Baltimore cohort is small. The current working group is of the opinion that the unweighted approach is an acceptable approach.

Summary

No further relevant new literature on Cr genotoxicity or risk assessment was identified by the present working group. A number of publications which were not cited in the SCOEL report discuss the selection of epidemiological studies that form the basis for risk assessment as well as the methods. In that respect the current working group is of the opinion that the ECHA report (ECHA 2013) provides an excellent, clear and thorough evaluation of this. It is noted that the evaluation of

SCOEL (2017) and the conclusion by the Risk Assessment Committee at ECHA (ECHA 2013) are similar and thus compliments each other with regard to the carcinogenic dose-response relationship of occupational exposure to Cr(VI).

Conclusion

Overall, the present working group regards the SCOEL report (Hartwig et al. 2017) as a thorough evaluation of the available scientific evidence for the toxicity of Cr(VI) and the scientific evidence for cancer as most critical effect of Cr(VI) inhalation exposure and the risk assessment based on lung cancer.

From the SCOEL risk estimates presented in table 1 (Hartwig et al. 2017), a Unit risk estimate of 4 x 10^{-3} is given (i.e. that excess risk level for lung cancer following at life-long (40 years) occupational exposure at 1 µg/m^3).

As **Risk level = Exposure level x Unit risk** and **Exposure level = Risk level /Unit risk** the following Cr(VI) occupational exposure levels can be associated to various pre-defined risk levels (table 6):

Table 6: Excess lung cancer incidence for Cr(VI) based on the unit risk

Excess lung cancer incidence	Cr(VI) air concentration (µg/m^3)
1: 1 000	0.25
1: 10 000	0.025
1: 100 000	0.0025

January 14, 2019
Anne Thoustrup Saber, Nicklas Raun Jacobsen, Niels Hadrup, Ulla Vogel

Reference list

Cherrie JW, Gorman Ng M, Shafrir A, van Tongeren M, Searl A, Sanchez-Jimenez A, Mistry R, Sobey M, Corden C, Rushton L, Hutchings S. Health, socio-economic and environmental aspects of the possible amendments to the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work. P937/99. IOM Research Project. IOM, 2011.

Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, Panko J, Paustenbach D, Proctor D. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 2003;23:1147-1163.

ECHA. Application for authorisation: Establishing a reference dose response relationship for carcinogenicity of hexavalent chromium. RAC/27/2013/06 Rev.1. European Chemicals Agency (ECHA), 2013.

Gerin M, Fletcher AC, Gray C, Winkelmann R, Boffetta P, Simonato L. Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. Int J Epidemiol 1993;22 Suppl 2:S22-S28.

Gibb HJ, Lees PS, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. Am J Ind Med 2000;38:115-126.

Hartwig A, Heederik D, Kromhout H, Levy L, Papameletiou D, Klein CL. Chromium(VI) compunds. SCOEL/REC/386. Recommendations from the Scientific Committee on Occupational Exposure Limits. Brussels: European Commision, 2017.

IARC. Chromium (VI) compunds. IARC Monogr Eval Carcinog Risks Hum 2012;100 C:147-167.

Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, Crump C, Crump K, Proctor D. Lung cancer mortality among chromate production workers. Occup Environ Med 2003;60:451-457.

Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. Risk Anal 2004;24:1099-1108.

Park RM, Stayner LT. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal 2006;26:79-88.

Pesch B, Lehnert M, Weiss T, Kendzia B, Menne E, Lotz A, Heinze E, Behrens T, Gabriel S, Schneider W, Bruning T. Exposure to hexavalent chromium in welders: Results of the WELDOX II field study. Ann Work Expo Health 2018;62:351-361.

SCOEL. Recommendation from Scientific Committee on Occupational Exposure Limits: Risk assessment for Hexavalent Chromium. SCOEL/SUM/86. SCOEL, 2004.

Seidler A, Jahnichen S, Hegewald J, Fishta A, Krug O, Ruter L, Strik C, Hallier E, Straube S. Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. Int Arch Occup Environ Health 2013;86:943-955.

Vincent R, Gillet M, Goutet P, Guichard C, Hedouin-Langlet C, Frocaut AM, Lambert P, Leray F, Mardelle P, Dorotte M, Rousset D. Occupational exposure to chrome(VI) compounds in French companies: Results of a national campaign to measure exposure (2010-2013). Ann Occup Hyg 2015:41-51.

Lersø Parkallé 105
DK-2100 Copenhagen
T +45 3916 5200
F +45 3916 5201
E nfa@nfa.dk
W www.nfa.dk