
# SCOEL/REC/386
# Chromium VI compounds

Recommendation from the
Scientific Committee on Occupational Exposure Limits


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**EUROPEAN COMMISSION**

Directorate-General for Employment, Social Affairs and Inclusion
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2017

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Luxembourg: Publications Office of the European Union, 2017

ISBN: XXX
doi:XXX



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Scientific Committee on Occupational Exposure Limits

2017

## Contents

# RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR CHROMIUM VI COMPOUNDS

| | |
|---|---|
| 8-hour TWA: | See Table on page 9 in Recommendations and Summary |
| STEL: | None recommended |
| BLV: | None |
| Additional categorisation: | Carcinogen group A (genotoxic carcinogen without a threshold) |
| Notation: | Sensitisation (respiratory and dermal)<br>No skin notation |

**The present Recommendation was adopted by SCOEL on 2017-xx-yy.**

# RECOMMENDATION EXECUTIVE SUMMARY

## Outcome Considerations

The critical effect of inhalation of hexavalent chromium containing compounds is lung cancer. In addition, occupational exposure can lead to nephrotoxicity, hypersensitivity (sensitization), corrosion of the skin, irritation of the respiratory tract and gastrointestinal tract.

Hexavalent chromium compounds have been classified as a carcinogen, in Category 1 based on both humans and animal data by IARC. Most hexavalent chromium compounds are classified by the European Union in Category 1B (*substance presumed to be carcinogenic to humans*). The exceptions are chromium trioxide, zinc chromate and zinc potassium chromate which are classified in Category 1A (*substance known to be carcinogenic to humans*).

Reevaluation of the information on the mode of action underlying carcinogenicity has resulted in the conclusion that in case of Cr(VI) the formation of ternary DNA adducts are relevant. These DNA lesions are not easily repaired and eventually may lead to the outgrowth of repair-deficient cell clones exerting genomic instability. Thus, Cr(VI) acts as a directly genotoxic carcinogen for which no threshold can be assumed and linear extrapolation is commonly applied by SCOEL in this situation if the available data permits.

## Derived Limit Values

Several epidemiological studies, from a number of countries including Germany, the UK and the USA have shown that an excess lung cancer risk exists after occupational hexavalent chromium exposure (Birk et al., 2006; Frentzel-Beyme, 1983; Gibb, et al., 2000; Luippold et al., 2003; Luippold et al., 2005; Mancuso, 1997; Park et al., 2004; Sorahan et al., 1998; Sorahan et al., 1987). Excess lung cancer risk is observed in populations with occupational exposure to both soluble and poorly soluble hexavalent chromium compounds (Steenland et al., 1996). The available human evidence on risk differences between soluble and poorly soluble chromium compounds does not allow a distinction in risk which can be used in risk assessments. Since the late 1990-ies, no new animal experiments have been conducted and published and several reviews of these studies have been published (IARC, 1990, 2012; Levy et al., 1986; NTP, 2008). Animal experiments show that a number of hexavalent chromium compounds are carcinogenic because they induce tumours in the lung after repeated inhalation (Adachi, 1987; Adachi et al., 1986; Glaser et al., 1985; Glaser et al., 1986; Nettesheim et al., 1971), and intracheal and intrabronchial administration (Steinhoff et al., 1986). Animal experiments confirm that differences exist in the carcinogenic potential of the different hexavalent chromium compounds, which are probably related to solubility and the resulting bio-availability. However, variation in experimental designs of the animal studies and lack of complete and reliable data on poorly soluble hexavalent chromium compounds do not allow a differentiation on the role of solubility in relation to carcinogenic potency on the basis of animal experiments (DECOS, 2016; IARC, 1990, 2012; SCOEL, 2004). Also, with regard to mechanistic studies, no distinction can be made between the genotoxicity of poorly soluble and soluble chromium VI compounds.

Therefore, no distinction can reliably be made in the risk assessment between soluble and poorly soluble hexavalent chromium compounds.

A limited number of the epidemiological studies have described quantitative exposure response relations that can be utilised for risk assessment purposes. Recently, these studies have been evaluated by Seidler and others (Seidler et al., 2013). They performed a systematic review for studies with quantitative exposure response relations for chromium VI. Studies which had more than one chromium exposure category and were adjusted for smoking habits were selected. Studies were reviewed for quality using the SIGN (Scottish Intercollegiate Guidelines Network) approach. Only high quality studies (Sign scores ++) were considered to assess a meta-exposure response relation. Exposure response relations were obtained by fitting linear models to the data using least square statistics weighted by persons' years in each exposure category. Five studies, originating from two USA cohorts were selected. One study, which estimated chromium VI exposure on the basis of biomonitoring data, was not selected because of the uncertainties resulting from the exposure estimation process (Birk et al., 2006). Urinary chromium measurements cannot distinguish between chromium III and VI exposure because chromium VI is reduced in the human body.

Excess risk was calculated using the exposure response relationships from the last updates of the two cohort studies. Excess risk was calculated for a 40 year exposure period from age 20-60 and a latency period of 10 years. Calculation were made using a lifetable analysis using European lung cancer and total mortality data obtained from all EU countries for males and females. For the calculations, a hypothetical cohort was follow till all members were deceased. Risk assessments using lifetable analysis take into account other causes of mortality in human populations. The following risk estimates were produced for the combined studies (with confidence interval based on the the s.e.'s of the exposure response slope), together with the points estimates for the individual studies used:

| | **Number of excess lung cancer cases / 1000** | | | |
|---|---|---|---|---|
| **Exposure 8 hour time weighted average** | **Point estimate combined exposure response slopes** | **Confidence interval** | **(Crump et al., 2003)** | **(Park et al., 2004)** |
| 0.1 µg/m$^3$ | **0.4** | **0.3-0.5** | **0.2** | **0.6** |
| 1 µg/m$^3$ | **4** | **3.2-4.8** | **2** | **6** |
| 5 µg/m$^3$ | **20** | **16-24** | **8** | **32** |
| 10 µg/m$^3$ | **39** | **31-47** | **15** | **62** |
| 25 µg/m$^3$ | **94** | **76-112** | **38** | **146** |

Exposure at which risk benchmarks of 4/1000 and 4/100 000 are realized, are similar to the exposure estimates which have recently been published by other organisations and researchers. These benchmarks are in some countries considered as 'acceptable' and 'negligible' risk levels. Although the exposure which corresponds with these risks are similar, differences exist in the approaches taken to calculate these exposure estimates (AGS, 2014; DECOS, 2016; Seidler et al., 2013) The differences relate to a) methodology to estimate risk, b) age at which the risk is estimated, c) use of average male and female rates instead of male rates only. The different combinations of assumptions lead in the end to similar estimates as produced by the different sources. SCOEL believes it is essential that the exposure response relationship should be based on the most reliable exposure response studies and that the lifetime risk should be calculated on the basis of a lifetable analysis, which gives the most accurate and precise estimate of the risk.

## Notations

### Skin notation

Substantial dermal uptake of hexavalent chromium is not anticipated and therefore a skin notation is not recommended.

### Sensitisation notation, dermal and respiratory

Chromium(VI) compounds show a strong potential for sensitisation following exposure both dermal and respiratory.

A notation should be added: **'sensitisation dermal and respiratory'**

Skin sensitisation resulting from exposure to hexavalent compounds has been demonstrated in patch-testing studies of contact dermatitis patients and in various chromate-exposed occupational groups (Sun, 1984; Samoen et al, 1984; Fregert et al, 1970; Engel & Calnan, 1963). Hexavalent chromium-sensitised subjects may react to trivalent chromium compounds although the latter are less able to penetrate the skin and thus have a lower skin sensitising potential (Fregert & Rorsman, 1964; Samitz & Shrager, 1966). Available case reports, together with supporting evidence from bronchial challenge tests, show that inhaling hexavalent chromium compounds can induce occupational asthma (Park et al, 1994). As with skin sensitisation, hexavalent chromium-sensitised subjects may react following exposure by inhalation to trivalent chromium compounds.

## Biological Monitoring

Methods are available for the biomonitoring of hexavalent chromium. However, hexavalent chromium will be reduced in the human body, to trivalent chromium in urine; thus when there is co-exposure to chromium III compounds it will be difficult to know what proportion came from the hexavalent and trivalent compounds. In such cases, speciation of the inhaled exposure is important in order to interpret biomonitoring data.

# RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR CHROMIUM VI COMPOUNDS

# RECOMMENDATION REPORT

## 1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Hexavalent chromium compounds are one of a number of oxidation states in which chromium occurs. Chromates and dichromates exist as a wide variety of compounds with 20 to 30 being of major industrial importance. These include, ammonium chromate and dichromate, barium chromate, calcium chromate and dihydrate, chromic chromate, chromium (IV) chloride, chromium trioxide (chromic acid), chromyl chloride, lead chromates, molybdenum orange ($PbCrO_4PbMoO4Pb.SO_4Al_2O_3$), potassium chromate and dichromate, sodium chromate and dichromate and zinc chromates. The solubility of chromates varies widely and ranges from virtually insoluble to highly soluble. The various uses of the term solubility have caused much confusion and to harmonise discussions and classification it has been proposed that the water solubility of hexavalent chromium compounds can be defined as: poorly soluble (<1g/l), sparingly soluble (1-10g/l); highly soluble (>100g/l).(Cross et al., 1997) Thus, poorly soluble includes lead and barium chromate, sparingly soluble includes strontium, calcium and zinc chromate and highly soluble would include sodium and potassium chromates and dichromate.

**Table 1:** Basic descriptive information on some widely used hexavalent chromium compounds (based on (AGS, 2014; DECOS, 2016; IARC, 1990))

| Substance | CAS No. | EC No. | Molecular Formula | | Solubility in water (mg/l) |
|---|---|---|---|---|---|
| Lead sulfochromate yellow (C.I. Pigment Yellow 34) | 1344-37-2 | 215-693-7 | | | |
| Lead chromate | 7758-97-6 | 231-846-0 | $PbCrO_4$ | | 0.58mg/L (25°C) |
| Lead chromate molybdate sulphate red (C.I. Pigment Red 104) | 12656-85-8 | 235-759-9 | | | |
| Acids generated from chromium trioxide and their oligomers. Names of the acids and their oligomers: Chromic acid, Dichromic acid, Oligomers of chromic acid and dichromic acid | 7738-94-5<br>13530-68-2 | 231-801-5<br>236-881-5 | | | |
| Ammonium chromate | 7788-98-9 | | $(NH4)_2CrO_4$ | | 405g/L (30°C) |
| Ammonium dichromate | 7789-09-5 | 231-143-1 | $(NH_4)_2CrO_4$ | | 308 g/L (15°C) |
| Barium chromate | 10294-40-3 | | $BaCrO_4$ | | 4.4mg/L (28°C) |
| Chromium trioxide | 1333-82-0 | 215-607-8 | $CrO_3$ | | 625g/L (20°C) |
| Potassium chromate | 7789-00-6 | 232-140-5 | $K_2CrO_4$ | | 49g/L (0°C) |

| Substance | CAS No. | EC No. | Molecular Formula | | Solubility in water (mg/l) |
|---|---|---|---|---|---|
| | | | | | 793g/L (100°C) |
| Potassium dichromate | 7778-50-9 | 234-190-3 | $K_2Cr_2O_7$ | | 49g/L (0°C) 1020g/L (100°C) |
| Sodium chromate | 7775-11-3 | 231-889-5 | $Na_2CrO4$ | | 873g/L (30°C) |
| Sodium dichromate dihydrate | 7789-12-0 10588-01-9 | 234-190-3 | $Na_2Cr_2O_7.2H_2O$ | | 2300-2380g/L (0°C) |
| Pentazinc chromate octahydroxide | 49663-84-5 | 256-418-0 | | | °C |
| Dichromium tris(chromate) | 24613-89-6 | 246-356-2 | | | °C |
| Potassium hydroxyocataoxodizincatedichromate | 11103-86-9 | 234-329-8 | | | °C |
| Strontium chromate | 7789-06-2 | 232-142-6 | $SrCrO_4$ | | 1.2g/L(0) 30g/L(100) |

## 2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for chromium VI compounds is provided by ECHA (2017) in their Classification and Labelling Inventory database. Whether compounds contain chromium VI is not always obvious purely from their name. Three strings indicating three 'groups' of chemicals containing chromium VI were found: "chromate", "chromium", "chromyl".

Using the search string "chromate", "chromium" and "chromyl", the number of entries found in the C&L Inventory was respectively 33, 5 and 1.

The two hazards that are considered most relevant to this SCOEL recommendation are carcinogenicity (1A or 1B; both H300) and skin sensitisation (Skin Sens.; H317).

The three hazards that are considered most relevant to this SCOEL recommendation are mutagenicity (1B; H340), carcinogenicity (1A or 1B; both H350) and skin sensitisation (Skin Sens.; H317). Many chromium VI compounds found at the ECHA website as being in commerce in the EU have entries for skin sensitisation and mutagenicity. Moreover, for most chromium VI compounds at least an entry for carcinogenicity was found (1A or 1B).

A tabulated overview of classification and skin sensitisation is provided in the table below.

**Table 2:** Classification of many chromium VI compounds according to CLP Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances" with respect to carcinogenicity and skin sensitisation (ECHA, 2017)

| Index no. | CAS no. | EC / List no. | EC / List name | IUPAC Name |
|---|---|---|---|---|
| various | various | various | various | Various |
| **Classification** | | | | |
| **Hazard Class & Category Codes** | | | **Hazard Statement Codes** | |
| Skin sens. 1 | | | H317 | |
| Muta. 1B | | | H340 | |
| Carc. 1A or Carc. 1B | | | H350 | |

## 3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Chromium (VI) compounds are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Chromium (VI) compounds are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and fall within the scope of this legislation.

## 4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Several chromium (VI) compounds have been classified as carcinogen by many regulatory authorities. In the EU CLP Regulation (EC) No 1272/2008 they are classified as genotoxic (Muta. 1B) and as carcinogen (Carc. 1B or 1A); see chapter 2. Also, the German DFG categorized chromium (VI) compounds (respirable fraction) as carcinogenic substance in Category 1 (meaning a genotoxic mechanism of action is likely or cannot be excluded). Because of this, DFG does not recommend specific exposure limits. In contrast, in various EU Member States as well as outside the EU OEL's are established. These OEL's are presented in Table 4 as examples and the list should not be considered as exhaustive.

For monitoring Cr VI using urine samples it is important to understand that al Cr VI ends up in urine as Cr III due to reduction whether you inhale III, VI or a mixture of both. In other biological matrices such as blood or exhaled breath condensate, both Cr VI and Cr III occur. They can be separated using ion chromatography and subsequently quantified using ICP-MS (see references in chapter 7.1.2).

BLVs (Biological Limit Value) have not been adopted for chromium (VI) compounds at EU level nor in the US (EU SCOEL, Germany DFG, USA OSHA and NIOSH). In the EU, only the Spanish authorities set a BLV for chromium (VI)(INSHT, 2016). The values were 'total chromium concentration increase in urine during one shift' 10 µg/L and 'total chromium at the end of the workweek' 25 µg/L. In addition, in the UK, a biological monitoring guidance value (BMGV) of 10µmol/mol creatinine in post shift urine was established (HSE, 2011). In Germany, in line with the absence of an OEL (MAK), no BLV (German BGW) was established. Instead, in order to help interpretation of occupational biomonitoring results, DFG did set a BAR (Biologischer Arbeitsstoff-Referenzwert) for the general not occupationally exposed population of working age of 0.6 µg/L urine for chromium VI compounds (inhalable fraction) (DFG, 2012). DFG further established the DFG-EKA values (biological exposure equivalents for carcinogenic substances) for chromium VI (DFG, 2015). For an overview of these biological values see table 3a and 3b.

**Table 3a:** Biological exposure equivalents for Chromium VI (DFG, 2015)

| Air ($CrO_3$ ($mg/m^3$) | Sampling time : long-term exposure : after several shifts Erythrocye fraction of whole blood * Chromium (µg/l whole blood) | Sampling time : end of exposure or end of shift urine ** Chromium (µg/l) |
|---|---|---|
| 0.03 | 9 | 12 |
| 0.05 | 17 | 20 |
| 0.08 | 25 | 30 |
| 0.10 | 35 | 40 |

*not applicable for exposure to welding fumes
**also applicable for exposure to welding fumes

**Table 3b:** Biomonitoring values for chromium VI*

| Term | Concentration | Reference |
|---|---|---|
| BLV | total chromium increase in urine<br>• during one shift 10 µg/L<br>• at the end of the workweek 25 µg/L | (INSHT, 2016) |
| BAR | 0.6 µg/L urine** | (DFG, 2012) |
| BMGV | 10 µmol/mol creatinine in urine (post shift) | (HSE, 2011) |
| BEI | 0.6 mol/litre (30 µg/litre) | |
| BAT | 11 µg/l (212 nmol/l) | (SUVA, 2016) |

* BAR = (Biologischer-Arbeitsstoff Referenzwert) Biological Reference Value; i.e. the background level of a substance in biological material in a reference population of persons of working age not occupationally exposed to this substance; BARs are based on the 95th percentile without regarding effects on health; BAT = (Biologische Arbeitsstofftoleranzwerte) biological occupational chemical tolerance level; BMGV = biological monitoring guidance value; BEI = biological exposure index.
** Total chromium

**Table 4:** Overview of existing OELs for chromium (VI) compounds as Cr in EU Member States and elsewhere[1]

| | TWA (8 hrs) | STEL (15 min) | Remarks | Refs |
|---|---|---|---|---|
| | mg/m³ | mg/m³ | | |
| **European Countries** | | | | |
| Austria | 0.1 (arc welding with coated rod electrodes, production of soluble Cr (VI) compounds)<br>0.05 (otherwise) | 0.4 (arc welding with coated rod electrodes, production of soluble Cr (VI) compounds)<br>0.2 (otherwise) | TMW and KZW (both TRK); inhalable aerosol | (GKV, 2011) |
| Belgium | 0.05<br><br>0.01 | - | All soluble chromium VI compounds<br>All insoluble chromium VI compounds | (KB, 2002) |
| Denmark | 0.005 (7738-94-5 Chromsyre og chromater. beregnet som Cr<br>0.0005<br>(7789-06-2 Strontiumchromat. beregnet som Cr | | | (DWEA, 2011) |
| Finland | 0.005 | - | | (MSAH, 2012) |
| France | 0.001 | 0.005 | VME; VLE | (INRS, |

| | TWA (8 hrs) | STEL (15 min) | Remarks | Refs |
|---|---|---|---|---|
| | mg/m³ | mg/m³ | | |
| | | | | 2012) |
| Germany | 0.001 | - | Tolerance value | (BAuA, 2014) |
| Hungary | - | 0.05 | Chromium (VI) inorganic compounds | (MHSFA, 2000) |
| Ireland | 0.05 (Water soluble);<br>0.01 (Insoluble);<br>0.001 (calcium chromate CAS nr 237-366-8) | - | Chromium (VI) compounds (as Cr) | (HSA, 2016) |
| The Netherlands | 0.01<br>0.05 | 0.05 | Applies for soluble compounds<br>Poorly soluble chromium compounds | (STSCR, 2014) |
| Spain | 0.05 (Chromium VI insoluble compounds)<br>0.01 (Chromium VI soluble compounds)<br>0.001 (Calcium chromate)<br>0.0005 (Strontium chromate)<br>0.012 (Lead chromate) | - | VLB® | (INSHT, 2016) |
| Sweden | 0.005 | 0.015 | LLV; STV<br>Total aerosol | (SWEA, 2015) |
| United Kingdom | 0.05 | - | Chromium (VI) compounds (as Cr) | (HSE, 2011) |
| **Non-European Countries** | | | | |
| Australia | 0.05 | - | Certain water insoluble. water soluble | (SWA, 2013) |
| Canada (Ontario) | 0.05 (Water soluble)<br>0.01 (Insoluble) | - | Cr VI compounds | (OML, 2015) |
| Canada (Québec) | 0.05 (soluble)<br>0.01 (insoluble) | - | TWAEV<br>Inorganic compounds | (IRSST, 2010) |
| Japan | 0.05 | - | | (JSOH, 2015) |
| New Zealand | 0.05 (soluble)<br>0.05 (insoluble) | - | as Cr (bio) | (WSNZ, 2016) |
| Norway | - | - | | (NLIA, 2011) |

| | TWA (8 hrs) | STEL (15 min) | Remarks | Refs |
|---|---|---|---|---|
| | mg/m³ | mg/m³ | | |
| Singapore | 0.05 (water soluble)<br>0.01 (insoluble) | - | | (IFA, 2016) |
| South Korea | 0.05 (water soluble)<br>0.01 (insoluble) | - | | (IFA, 2016) |
| Switzerland | 0.05 | - | MAK; inhalable aerosol | (SUVA, 2016) |
| USA (NIOSH) | 0.0002 | - | REL (8 hr TWA); | (OSHA, 2017) |
| USA (Cal OSHA) | 0.005 | 0.1 | PEL (TWA respective ceiling value | (OSHA, 2017) |

[1] Abbreviations are explained below

- LLV= Level limit value =TWA
- MAK [Maximale Arbeitsplatz Konzentration] = maximum workplace concentration.
- PEL = Permissible Exposure Level (OSHA).
- REL = Recommended Exposure Limit (NIOSH).
- STEL = Short Term Exposure Limit (usually 15 minutes average).
- TMW [Tagesmittelwert] = TWA; KZW [Kurzzeitwert] = STEL.
- TRK [Technische Richtkonzentration] = Technical Guidance Concentration. Used when no 'safe' exposure level can be derived. Value based on technical feasibility.
- TWA = Time-Weighted Average (usually 8 hours average).
- TWAEV = Time-Weighted Average Exposure Value = TWA.
- STV = Short-term value =STEL
- VME [Valeur Moyenne d'Exposition] = TWA.

# 5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

Information on sources of human and environmental exposure to chromium is often described in terms of total chromium, because information on speciation is frequently not available. So unless specified, chromium reflect total chromium.

## *5.1. Occurrence*

Chromium is a relatively common element, occurring naturally in rocks, soil, plants, animals and volcanic dust and gases. The most stable valence states are chromium(0), trivalent chromium (chromium(III)) and hexavalent chromium (chromium(VI)). Chromium is chiefly found as the trivalent form in nature, with chromium(VI) generally produced by industrial processes.(WHO-IPCS-CICAD, 2013)

Hexavalent compounds, with the exception of some small amounts in minerals, do not occur naturally in the environment but are formed from trivalent chromium during chromate-production processes. The starting point for all hexavalent compounds is chromite ore, which contains trivalent chromic oxide and this is oxidised to sodium chromate during kiln roasting in the chromate-producing industry. This is the usual starting material for all other hexavalent compounds. Apart from in the chromate-producing industry, occupational exposure may occur in the production of ferrochromium alloys and chromium metal, production and welding of stainless steels, metal finishing processes (chromium plating) and the manufacture and use of chromium chemicals. These latter include corrosion inhibitors (strontium, calcium, zinc and barium chromates); pigments in paints and in metal primers (lead and zinc chromates and molybdenum orange); wood preservatives (sodium and potassium chromates and chromium trioxide); dye mordants, catalyst and leather tanning (ammonium, sodium and potassium chromate). It should be noted that within the European Community, leather tanneries invariably use basic trivalent chromium sulphate, which contains no measurable hexavalent chromium. Some hexavalent chromium is present in cement as a contaminant arising from its manufacture and possibly from the clinker or gypsum constituents, or from the kiln dust during the firing stage which comes from chromium-containing refractories. The hexavalent form is, however, reduced to the trivalent form by the addition of ferrous sulphate to the cement.

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Chromium is released into the atmosphere mainly by anthropogenic stationary point sources, including industrial, commercial and residential fuel combustion via the combustion of natural gas, oil and coal. Another important anthropogenic stationary point source of chromium emissions to the atmosphere is the metal industry.

EU reported in 2005 air emission data for chromium(VI) compounds for all three European production sites from the 1990s 65 - 5611 kg/year/site. The releases cover the processing of chromite ore and the production of five chromium(VI) compounds. They also include some of the subsequent processing of these compounds into other products that takes place at the sites.

Regarding aquatic ecosystems, on a worldwide basis, the predominant source of chromium is domestic wastewater effluents (32.2% of the total) next to metal manufacturing (25.6%), ocean dumping of sewage (13.2%), chemical manufacturing (9.3%), smelting and refining of non-ferrous metals (8.1%) and atmospheric fallout (6.4%). EU reported in 2005 water emission data for chromium(VI) compounds for all three European production sites from the 1990s. Emissions to water were reported from 474 kg/year to 216 kg/year to negligible (WHO-IPCS-CICAD, 2013).

On a worldwide basis, disposal of chromium containing commercial products may be the largest contributor to chromium in soil, accounting for approximately 51% of the total chromium released to soil, followed by the disposal of coal fly ash and bottom fly ash from electric utilities and other industries (33.1%), agricultural and food wastes (5.3%), animal wastes (3.9%) and atmospheric fallout (2.4%). Solid wastes from metal manufacturing contributed less than 0.2% to the overall chromium release to soil. Soil emission of chromium (VI) was reported in 2005 for all three European production sites. At the first site, landfill waste of chromium (VI) was equivalent to an annual load of 1.7 tonnes of chromium. At site 2, residual solid sodium hydrogen sulfate, which contains approximately 1% chromium(VI) oxide from the production of chromium trioxide, was disposed of via landfill (the content of chromium(VI) oxide in the waste is regulated). Site 3 had a solid waste treatment plant that received solid waste from the kiln and the sludge from the wastewater treatment plant. Chromium(VI) impurities in the solid waste from this facility were present at a concentration of 8 mg/kg. The solid waste was eventually transported to a waste disposal site.

The general population is exposed to chromium by inhaling ambient air and ingesting food and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products that contain chromium, such as certain wood preservatives, cement, cleaning materials, dyed textiles and leather tanned with chromium (WHO IPCS CICAD, 2013). In 1984, levels of chromium in ambient air of <0.01–0.03 μg/$m^3$ were reported (Fishbein, 1984) in (WHO-IPCS-CICAD, 2013).

## *5.2. Production and use information*

Sodium chromate and sodium dichromate (both chromium VI compounds) are produced by roasting chromite ore with soda ash. Most other chromium compounds are produced from sodium chromate and sodium dichromate. For example, basic chromic sulfate ($Cr(OH)SO_4$), which is a chromium III compound commonly used in tanning, is commercially produced by the reduction of sodium dichromate with organic compounds (e.g. molasses) in the presence of sulfuric acid or by the reduction of dichromate with sulfur dioxide. Lead chromate, commonly used as a pigment, is produced by the reaction of sodium chromate with lead nitrate or by the reaction of lead monoxide with chromic acid solution.

The world production capacity of chromium chemicals in 2008 was 272 000 tonnes as chromium. EU annual production figures in 1997 were 103 000 tonnes for sodium chromate, 110 000 tonnes for sodium dichromate, 32 000 tonnes for chromium trioxide, 1500 tonnes for potassium dichromate and 850 tonnes for ammonium dichromate (WHO IPCS CICAD 2013). Since 2007, all the hexavalent chromates used in the EU are imported and the imports are being reduced.

Chromium compounds are widely used. Major applications reported in 1996 included wood preservation, leather tanning, metals finishing and pigments. Smaller uses are in drilling muds, chemical manufacturing and dye setting on textiles and as catalysts. Many uses are predominantly in the form of chromium(III) compounds (e.g. leather tanning). The primary uses of chromium( VI) compounds are in electroplating (chrome plating), the manufacture of dyes and pigments, wood preservatives, surface coatings and corrosion inhibitors. Chromium(VI) has also been used in cooling towers as a rust and corrosion inhibitor(WHO-IPCS-CICAD, 2013).

Recently, the following uses of the main chromium (VI) compounds were published by the Health Council of the Netherlands (DECOS, 2016).

- *Chromium trioxide*: Metal finishing; for manufacturing of wood preservation products, catalysts, chromium dioxide and pigments
- *Sodium chromate*: Manufacturing of other chromium compounds
- *Sodium dichromate*: Manufacturing of other chromium compounds, wood preservative products, vitamin K and wax; mordant in dyeing; in metal finishing
- *Potassium dichromate*: Manufacturing of pigments, wood preservation products, dyes, catalysts and chromium metal; colouring agent in ceramics
- *Chromic acid*: Production of various chemicals (chromates, oxidizing agents, catalysts); as intermediate in chromium-plating, in ceramic glazes and colored glass.
- *Ammonium chromate*: Sensitiser for gelatin coatings used in photography; in textile printing pastes and fixing chromate dyes on wool; analytical reagent, catalyst, and corrosion inhibitor
- *Ammonium dichromate*: Intermediate and laboratory reagent
- *Calcium chromate*: Pigment, a corrosion inhibitor; in electroplating, photochemical processing, and industrial waste treatment
- *Potassium chromate*: Mordant in dyeing fabrics; tanning agent in the leather industry, in bleach oils and waxes; oxidizing agent in organic synthesis
- *Dichromium tris(chromate)*: Corrosion inhibitor; catalyst in the mordanting of yarns.

Main use of hexavalent chromium is found in wood preservatives, metal coatings, chromium production and catalyst manufacture followed by Montan wax manufacture, vitamin K manufacture and use as a fixative in wool dying (IOM, 2011).

## *5.3. Occupational exposure*

Occupational exposure can be to a simultaneous number of different hexavalent compounds, depending on the industry, and in some industries can be further complicated by exposure to both trivalent and hexavalent compounds. The chromate producing industry is an example of this. Such mixed exposures can make interpretation problematical for both hazard and risk assessment in human studies in relation to individual compounds, especially when exposures are expressed only as total chromium.

In 2006 about 917,000 workers in the EU were exposed to chromium across a wide range of industries. There were estimated to be 552,000 workers with relatively high levels of exposure who were employed in chemicals manufacture, basic metals production, manufacture of machinery and equipment, manufacture of other transport equipment and the manufacture of furniture. Since 2006, the manufacture of hexavalent chromium compounds and the use of copper chrome arsenate wood preservatives have ceased in the EU, hexavalent chromium has been banned in new vehicles or electronic/electrical equipment and plating processes are increasingly replacing hexavalent chromium with trivalent chromium or chrome-free substances. The number of workers in sectors relatively with relatively high levels of exposure is likely to have declined substantially since 2006(IOM, 2011).

There are no current hexavalent chromium exposure level data available. Exposure levels were estimated by extrapolation from data assumed to be representative of 1995 to 2010 assuming an annual decrease in air concentration of 7% and are presented below.

**Table 5:** Some estimated exposure levels in 1995 and 2010 from (IOM, 2011)

**Table 2.4** Estimated 1995 and 2010 hexavalent chromium exposure levels for high exposure NACE codes

| NACE Code | Industry | Estimated Geometric Mean 1995[1] mg/m$^3$ | Estimated Geometric Mean 2010[2] mg/m$^3$ | Estimated Geometric Standard Deviation |
|---|---|---|---|---|
| 24 | Manufacture of chemical and chemical products | 0.0050 | 0.002 | NK[3] |
| 27 | Manufacture of basic metals | 0.0060 | 0.002 | 3.8 |
| 28 | Manufacture of fabricated metal products, except machinery and equipment | 0.0047 | 0.002 | 9.3 |
| 29[4] | Manufacture of machinery, except electrical | 0.0047 | 0.002 | 9.3 |
| 35 | Manufacture of other transport equipment | 0.0160 | 0.005 | 14.0 |
| 36[4] | Other Manufacturing Industries | 0.0047 | 0.002 | 9.3 |

[1] The majority of the data were from 1990 – 2000 therefore the data was assumed to be representative of 1995
[2] 1995 levels were extrapolated to 2010 assuming an annual decrease in concentration of 7%.
[3] NK = Not Known
[4] No data were available for NACE 29 and 35 however because the exposure scenarios in these groups resemble those in NACE 28 we have used the exposure levels for NACE 28 to represent estimated exposures levels in NACE 29 and 35.

Although many exposures have been ceased or keep decreasing, a subset of chromium (VI) compounds (out of over 100) are listed in Annex XIV of the REACH Regulation (authorisation list) and so are, or will be, subject to 'authorisation' for continued use in the EU for a certain period, most of them being chromates and dichromates (ECHA, 2016).

### *5.4. Routes of exposure and uptake*

The routes of potential worker exposure to chromium VI encompass mainly inhalation. In the working environment of stainless steel welders in Germany, chromium oxide levels with a median value ranging from 4 to 10 µg/m$^3$ and a maximum value of 80 µg/m$^3$, were reported in 1987. In Europe in 2005, geometric mean exposures in most chromium chemical industries were reported to be generally <20 µg/m$^3$. In a modern ferrochromium and stainless steel mill in Finland, the median concentration of chromium (VI) in 1987 was ≤0.1 µg/m$^3$ in all production areas except one, where it was 0.5 µg/m$^3$. The highest measured airborne concentration of chromium (VI) was 6.6 µg/m$^3$. In 1999, the median and maximum breathing zone chromium VI concentrations were 0.3 and 0.7 µg/m$^3$, respectively (see several references in (WHO-IPCS-CICAD, 2013)).

It was estimated in the EU in 2005 that dermal exposure of workers engaged in packing chromium(VI) products was 0–0.1 mg/cm$^2$ per day, and dermal exposure of workers weighing and charging dry ingredients to mixers in the manufacture of chromium (VI) pigments was estimated to be 0.1–1 mg/cm$^2$ per day(WHO-IPCS-CICAD, 2013).

The average urinary excretion half-life of chromium VI following oral uptake of 0.05 mg/kg bw by volunteers was rather long, i.e. 39 h, indicating a risk for human biopersistency at those intake levels (WHO-IPCS-CICAD, 2013).

## 6. MONITORING EXPOSURE

### *6.1. External exposure*

There are several methods developed by various organizations to quantify Cr(VI) levels in workplace air. Recommended methods characterize time-weighted average (TWA), breathing zone exposure across full work shifts. Sampling considerations for determination of Cr(VI) levels in workplace air are well established in the literature (Ashley, Howe, Demange, & Nygren, 2003). An important consideration is reduction of Cr(VI) to Cr(III) during sampling and sample preparation. Another concern is the possibility of oxidation of Cr(III) to Cr(VI) during sample preparation. Factors that affect the reduction of Cr(VI) or oxidation of Cr(III) include the presence of other compounds in the sampled workplace air, which may affect reduction or oxidation (notably iron, especially Fe[II]), the ratio of Cr(VI) to Cr(III) concentrations in the sample, and solution pH (Ashley et al., 2003). The pH of a solution is an important factor, because in acidic conditions the reduction of Cr(VI) is favorable, while in basic conditions Cr(VI) is stabilized. The use of NIOSH Method 7703 in the field minimizes reduction of Cr(VI) during transport and storage (NIOSH, 2013). The use of polyvinyl chloride (PVC) filters are recommended (NIOSH Method 7605; OSHA Method ID-215). Other suitable filter materials that are generally acceptable for airborne Cr(VI) sampling include polyvinyl fluoride (PVF), polytetrafluoroethylene (PTFE), PVC- and PVF-acrylic copolymers, and quartz fiber filters (Ashley et al., 2003). Other filter types to be used for sampling should be tested before use. Sampling should be based on inhalable dust sampling. Inhalable dust samplers capture dust particulates that can penetrate all parts of the respiratory organ.

Chromium (VI) compounds can be monitored in workplace air using various analytical methods. Some methods are more or less specific for the occupational setting. Important aspects that determine which method is to be used preferably are the process that is monitored and which is linked to the matrix in which chromium (VI) occurs (e.g. chromium plating mists) and whether the actual chromium (VI) compound to be monitored is soluble or not. In all methods sampling is by trapping onto a filter. The relevant and easily accessible regulatory methods are listed below with their main characteristics that discern them from the other methods. They are summarised more extensively in Table 7.

- NIOSH Method 7600 - DPC derivatization, UV-VIS. (NIOSH, 2015a)
- NIOSH Method 7604 - Ion chromatography with conductivity detection. (NIOSH, 1994)
- NIOSH Method 7605 - Ion chromatography and post-column DPC derivatization, UV-VIS. (NIOSH, 2003)
- NIOSH. Method 7703 – SPE enrichment, DPC derivatization, UV-VIS. (NIOSH, 2015b)
- DFG Method Chromium-2-PHOT - DPC derivatization, UV-VIS and Method Chromium-3-IC - Ion chromatography and post-column DPC derivatization, UV-VIS. (DFG, 1993a, 1993b)
- HSE MDHS Chromium plating mist. DPC-derivatisation in combination with stationary measurements. (HSE, 2014)
- ISO 16740: ion chromatography and post-column derivatization. (ISO, 2005)
- OSHA Method ID-215 (version 2): ion chromatography and post-column derivatization. (OSHA, 2006)

This is followed by extraction with an inorganic buffer. Some are extracting with a buffer for the direct determination of soluble CrVI (only) and some other with the more strong digestion (wet ashing) for the determination of the soluble and insoluble chromium simultaneously. Once solubilised, further steps can be enrichment (decrease the volume to increase the concentration) and/or separation from chromium III. Subsequently, in several methods ion-chromatography and post-column derivatization by diphenylhydrazine (DPH) are used. Other methods use direct derivatization by DPH. The analytical determination of the coloured Cr(VI)-DPH complex occurs using UV-VIS photometry or by colorimetric comparison. There is one analytical method based on conductivity measurement (NIOSH, 1994b) but the sensitivity is limited as the LOQ is 10 µg/m$^3$.

Athough DFG IC-3 method is laborious, it has the advantage that it can simultaneously measure Cr (III) as well as Cr (VI). NIOSH Method 7703 (according to the method description) could be used in the field although elaborate laboratory treatment in separate instruments is needed for this method as well, i.e. the extraction process, the SPE clean-up and the derivatization.

In addition, there are several methods (Refs) focussing on settled dust samples or swipe samples. These are not being discussed here as inhalation exposure is regarded as the most relevant route of exposure to Cr (VI) compounds.

**Table 6:** Overview of sampling and analytical methods for monitoring of Cr (VI) in workplace air

| Method | Use purpose including | Sampling | Filters | Desorption solution | Analysis | LOD/LOQ | Concentration range | Evaluated # | Refs |
|---|---|---|---|---|---|---|---|---|---|
| NIOSH Method 7600 | Soluble chromates and chromic acid.<br>Insoluble chromates and chromates in the presence of iron or other reducing agents | Personal | PVC membrane | Soluble $Cr^{VI}$: $H_2SO_4$<br>Insoluble $Cr^{VI}$: NaOH / $Na_2CO_3$ | DPC-derivatization<br>UV-VIS detection | LOD: 0.05 µg | 0.2 - 7 µg<br>0.001 - 5 mg/m³ (200 L) | Yes | (NIOSH, 2015a) |
| NIOSH Method 7604 | Soluble and insoluble $Cr^{VI}$ | Personal | PVC membrane | Extraction and elution: NaOH / $Na_2CO_3$ | IC<br>Conductivity detection | LOD: 3.5 µg | 10 - 250 µg<br>0.01 – 4 mg/m³ (500 L) | Yes | (NIOSH, 1994) |
| NIOSH Method 7605 | Soluble chromates<br>Insoluble chromates | Personal | PVC membrane | Extraction - Solubles: $(NH_4)_2SO_4$ / $NH_4OH$<br>Insolubles: NaOH / $Na_2CO_3$<br>Elution: $(NH_4)_2SO_4$ / $NH_4OH$ | IC with post-column DPC-derivatization<br>UV-VIS detection | LOD: 0.02 µg<br>LOQ: 0.07 µg | 0.05 - 20 µg<br>0.00025 – 0.1 mg/m³ (200 L) | Yes | (NIOSH, 2003) |
| NIOSH Method 7703 | Soluble and insoluble $Cr^{VI}$<br>For insoluble ultrasonic extraction carbonate buffer required | Personal | PVC membrane or MCE or PTFE | Extraction and elution: $(NH_4)_2SO_4$ / $NH_4OH$<br>Elution: Use SPE cartridges | DPC-derivatization<br>UV-VIS detection | LOD: 0.08 µg | 0.00005 - 1 mg/m³ (200-500 L) | Yes | (NIOSH, 2015b) |

| Method | Use purpose including | Sampling | Filters | Desorption solution | Analysis | LOD/LOQ | Concentration range | Evaluated # | Refs |
|---|---|---|---|---|---|---|---|---|---|
| DFG Chromium-2-PHOT | Inhalable dust | Personal<br>Stationary | Glass fibre filter, wet ashing | NaOH / $Na_2CO_3$ | DPC-derivatization<br><br>UV-VIS detection | LOQ (calculated as $CrO_3$)<br>Personal sampling (0.42 $m^3$):<br>4.8 µg/$m^3$<br>Stationary sampling 45 $m^3$): 0.04 µg/$m^3$ | | | (DFG, 1993a) |
| DFG Chromium-3-IC | Inhalable dust | Personal<br>Stationary | Glass fibre filter, wet ashing | Aqueous solution of pyridine-2,2-dicarboxylic acid, disodium hydrogen phosphate dodecahydrate, NaI, ammonium acetate, lithium hydroxide monohydrate | IC with post-column derivatization (DPC)<br><br>UV-VIS detection | LOQ $CrO_3$:<br>Personal sampling:<br>0.2 ng and 0.24 µg/$m^3$ for 0.42 $m^3$ air.<br>Stationary sampling:<br>0.2 ng and 0.01 µg/$m^3$ for 45 $m^3$ air. | | | (DFG, 1993b) |
| HSE MDHS 52-4 | Chromium plating mists | Stationary | Membrane | Sulphuric acid | DPC derivatization.<br><br>Photometric detection or<br>colorimetric comparison | Theoretical:<br>LOD:<br>0.04 µg,<br>1.5 µg/$m^{-3}$<br>LOQ:<br>0.14 µg,<br>5 µg/$m^3$<br>Practice:<br>LOD 25 µg/$m^3$ | | | (HSE, 2014) |
| ISO 16740 | Personal air sampling | | | | IC with post-column derivatization (DPC)<br>UV-VIS detection | Working range 0.01 – 10 µg/$m^3$ | | | (ISO, 2005) |

| Method | Use purpose including | Sampling | Filters | Desorption solution | Analysis | LOD/LOQ | Concentration range | Evalua-ted [#] | Refs |
|---|---|---|---|---|---|---|---|---|---|
| ID-215 (version 2)<br>OSHA | Chromium plating operations<br><br>Soluble and insoluble chromium-containing chemicals | Personal | Plating operations:<br>37-mm PS cassettes containing NaOH coated binderless quartz fibre filters<br>Other operations:<br>PS cassettes containing PVC filters with cellulose back-up pads | $Na_2CO_3$ / $NaHCO_3$<br><br>$KH_2PO_4$ / $K_2HPO_4$ | IC with post-column derivatization (DPC)<br>UV-VIS detection | LOD and LOQ dependent on exact procedure:<br>LOD:<br>0.80-1.0 ng,<br>0.83-1.0 ng/$m^3$<br>LOQ:<br>2.67 – 3.12 ng,<br>2.9 – 3.5 ng/$m^3$ | | Validated method | (OSHA, 1998) |

*DPC – diphenylcarbazide; IC – ion chromatography; ICP-OES - inductively coupled plasma optical emission spectrometry; LOD - limit of detection; LOQ - limit of quantification; MCE – mixed cellulose ester; SPE –solid phase extraction; VIS – visible absorption spectroscopy;*

[#] *Any evaluation statement is as given in the original method description. Wording may have different meanings in different methods*
** Information taken from summary on the internet*
[&] *For the ISO method, only an internet summary was available*

## *6.2. Internal exposure/Biomonitoring of exposure*

Biomonitoring of chromium (VI) exposure in the workplace can readily be done. by measuring total chromium in urine and blood. The first method (urine) does not allow any distinction as to the oxidation state of the inhalation/absorbed chromium so can only be used as a proxy and first indication of occupational exposure to specifically chromium (VI) as all the urinary chromium in the urine will be measured as the trivalent form. The second method (blood) can be used to estimate the exposure to chromium (VI) because erythrocytes can be measured separately from plasma. Based on references 5-7 in DFG (1990) that only chromium (VI) and not chromium (III) can pass the erythrocyte membrane, the 'total chromium' as measured in erythrocytes is thus assumed to be chromium (VI).

In Table 8, two regulatory methods are briefly summarised; the first for total chromium in urine, the second for total chromium in whole blood as well as in plasma and in erythrocytes. The analytical determination is done using a standard graphite or a pyrolytically coated graphite tube in combination with electrothermal atomic absorption spectroscopy (EAAS).

It should be noted that the blood method reports a correlation between concentrations found in blood and urine and air concentrations (DFG, 1990).

It is noted that several methods aiming at direct or indirect measurement of Cr VI are being published in the scientific literature. The biological sample used is urine or exhaled breath. They are usually based on some kind of separation of Cr III and Cr VI followed by ICP-MS quantification. As far as know, none of these methods have obtained the status of 'governmental method' yet nor have they undergone an inter-laboratory validation.

**Table 7:** Overview of the available methods for bio-monitoring of occupational exposures to total chromium*

| Method | Matrix | Analysis | | LOD | Linear range | References |
|---|---|---|---|---|---|---|
| DFG | Urine | Graphite tube / Pyrolytically coated graphite tube<br><br>EAAS | Standard tube<br>Pyrolytically coated tube | 0.5 µg /L<br>0.1 µg /L | 0.5 – 70 µg /L<br>0.1 – 30 µg /L | (DFG, 1985) |
| DFG | Blood | Pyrolytically coated graphite tube<br><br>EAAS | Whole blood<br>Plasma<br>Erythrocytes | 0.5 µg / L WB<br>0.5 µg / L WB<br>0.5 µg / L WB | 1.94 – 50 µg / L WB<br>12.5 – 50 µg / L WB<br>12.5 – 50 µg / L WB | (DFG, 1990) |

* EAAS – electro-thermal atomic absorption spectroscopy; LOD – limit of detection; WB – whole blood

# 7. HEALTH EFFECTS

## *7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)*

### 7.1.1. Human and animal data

The limited number of volunteer and worker studies would suggest much of the animal toxicokinetic data is relevant to humans. Biological monitoring of occupational exposure is routinely carried out using blood or urine, but the analytical techniques employed tend to express the amounts as total chromium.

### 7.1.2. Animal data

Absorption of inhaled hexavalent chromium from the respiratory tract varies according to the solubility of the compound with high or sparingly soluble compounds absorbed more rapidly than poorly soluble or insoluble compounds (Adachi et al., 1981). Repeated inhalation results in the accumulation of chromium in lung tissue. This is more marked for poorly soluble compounds. Absorption of orally-administered hexavalent chromium, which has only been studied with soluble compounds, is poor presumably due to its rapid reduction to the trivalent species in the acidic conditions of the stomach (Mackenzie *et al*, 1959; Donaldson & Barreras, 1966; Ogawa *et al*, 1976). Reduction from hexavalent to trivalent chromium will also take place in the lung (De Flora, 2000). Dermal absorption occurs following direct skin contact with soluble hexavalent compounds in aqueous solutions and this can amount to up to 4% of the applied dose (Wahlberg & Skog, 1963). Hexavalent chromium absorbed into the blood stream is taken up by blood cells, predominantly red blood cells (RBC), reduced to trivalent chromium in the plasma or distributed to the tissues. RBCs uptake is rapid and involves a specific anion transport carrier in the cell membrane. Following uptake, the hexavalent chromium is reduced and irreversibly bound to haemoglobin. Chromium can only be transported into cells when in the hexavalent oxidation state and extracellular reduction serves to prevent its uptake. Non-enzymatic reducing agents include glutathione, ascorbic acid and cysteine; enzymatic agents include microsomal P450 enzymes. Inhaled intratracheally-instilled hexavalent chromium has been shown to be distributed to the lungs, liver, kidneys, testes, spleen and GI tract. Parenteral administration studies in pregnant animals have shown that hexavalent chromium compounds can cross the placenta and be distributed within the embryo. These findings however, are of questionable relevance to occupational exposure. Inhaled or i.t. instilled hexavalent chromium is excreted in the urine or faeces with the relative contribution varying with compound solubility. Orally administered compounds are mainly excreted in the faeces.

### 7.1.3. In vitro data

### 7.1.4. Toxicokinetic modelling

### 7.1.5. Biological monitoring

Urinary chromium levels and blood or whole blood chromium levels are a measure of total chromium exposure as Cr(VI) is reduced within the body to Cr(III). Several studies have explored associations between environmental chromium exposure and urinary levels (Angerer et al., 1987).

## *7.2. Acute toxicity*

### 7.2.1. Human data

Data on the effects of single exposures in human is mainly from case-reports involving accidental exposures and only relates to highly soluble compounds. An incompletely and poorly reported volunteer study of 10 subjects exposed to chromic (IV) oxide reported that "brief exposures" to 10-24µg/m3 (apparently CrO3, thus 5-12µg Cr/m3) caused nasal irritation (Kuperman, 1964). The threshold for irritation was reported to be 2.5µg/m3 (apparently as CrO3; thus 1.3µg Cr/m3). Severe skin damage and renal toxicity have been reported in two fatal cases involving accidental exposure involving direct skin contact with hot (>90ºC) acidified solutions of highly soluble chromates (Fritz et al, 1960). Corrosive damage to the GI tract mucosa and renal toxicity have been reported in cases of accidental or intentional ingestion of soluble hexavalent compounds. In many of the case reports, avoidable death (Cross et al) was often the outcome with ingestion of approximately 350mg Cr and above.

Information relating to the irritant effects of hexavalent chromium compounds in human is only available for soluble compounds. Evidence, mainly from case reports, clearly shows that highly soluble compounds cause irritant and corrosive effects to the eyes. There are numerous reports of skin ulcers in workers exposed to soluble chromium compounds; in particular chrome plating workers or chromate-production workers (Cross et al., 1997). These "chrome ulcers" are mostly located on the hands and forearms.

### 7.2.2. Animal data

Single exposures to hexavalent compounds by inhalation cause inflammation and necrotic changes to the upper respiratory tract with effects in rats reported at 7.4mg Cr/m3 and above (Suzuki et al, 1984; Last et al, 1979). LC50 values of between 33 and 83mg Cr/m3 have been reported for rats (Gad et al, 1986). An oral LD50 With male rats using sodium chromate, sodium dichromate potassium dichromate and ammonium chromate has given values of 87, 59, 74, and 55mg Cr/kg respectively. Equivalent values for female rats were 13, 16, 17 and 20mg Cr/kg (Gad, 1986). Not surprisingly, higher LD50 are seen with sparing or poorly soluble chromate.

## *7.3. Specific Target Organ Toxicity/Repeated Exposure*

### 7.3.1. Human data

Kidney function has been investigated in chrome platers, chromate production workers, ferrochromium workers and stainless steel welders. Some but not all studies have reported renal dysfunction indicated by altered urinary levels of specific enzymes or proteins (Lindberg & Vesterberg, 1983; Nagaya et al, 1994; Verschoor et al, 1988; Wang et al, 1994; Mutti et al, 1985; Littorin et al, 1984). Irritant and corrosive effects on the GI tract and hepatotoxicity have been reported but these effects cannot be related to exposure data.

### 7.3.2. Animal data

*7.3.2.1. Inhalation*

The effect of repeat exposure in animals to hexavalent compounds has been studied in animals using inhalation exposure, intratracheal instillation, oral dosing and parenteral administration, In inhalation studies, near continuous exposure to aerosols of sodium dichromate at concentrations up to 0.1mg Cr/m3 for 18 months, or 0.2mg Cr/m3 for 90

days, had no effects on body weight gain, haematology or histopathology (Glaser et al, 1985). However, with exposure to 0.5mg Cr/m3 and above for 28 days or more, there was increased organ weights (lung, liver, spleen and kidney). Similar results were seen in another study (Miyai, 1980) in which sodium chromate or barium chromate dusts at concentrates between 0.01 and 0.13mg Cr/m3 for up to 8 months. Repeat exposure to chromic acid (1.81mg Cr/m3 and above) caused irritant and corrosive effects in the respiratory tract of mice (Adachi et al, 1986). Exposure to sodium chromate aerosol (0.9mg Cr/m3 for up to 6 weeks) caused no damage to the respiratory tract epithelium in rabbits, but had a stimulating effect on pulmonary macrophages (Johansson et al, 1986 a & b). From these repeat inhalation studies, it is not possible to identify with any confidence a NOAEL for hexavalent chromium compounds.

*7.3.2.2. Oral exposure*

In a number of oral-dosing studies, administration of highly soluble hexavalent compounds at concentrations up to 100ppm caused no sign of toxicity. One study at 70ppm in drinking water caused reduced body weight gain in rats. In a dietary study, high doses of lead chromate caused reduced weight gain, haematological effects and renal toxicity in rats and dogs although it is possible that both chromium and lead might have contributed to these effects. (Kennedy et al, 1976; Christofano et al, 1976)

## *7.4. Irritancy and corrosivity*

### 7.4.1. Human data

In humans occupationally exposed by inhalation to hexavalent chromium compounds, the main health effects are irritant and corrosive effects on the skin and respiratory tract. Effects on the respiratory tract include inflammation of the nasal septum. Lower respiratory effects include inflammation and obstructive disorders; transient impairment on lung function has been reported. It is uncertain to what extent shortterm exposure to high hexavalent chromium levels or direct contamination of the nasal mucosa with chromium may be involved in the development of the nasal lesions and this complicates a clear interpretation of the significance of the reported average exposure levels in relation to these health outcomes. Renal dysfunction has been reported in some studies, indicated by altered urinary protein or enzyme levels. In contrast, some studies have reported no effects on kidney function. Irritant and corrosive effects on the GI tract and effects in the liver have been reported following repeated exposure, but these cannot be related to exposure data. Hexavalent chromium compounds are potent skin sensitisers in humans and can cause respiratory sensitisation. Sensitised individuals may also react to trivalent chromium compounds. In general, the animal investigations from both single and repeated exposures are supportive of the effects seen in humans although the data do not cover the wide range of hexavalent chromium compounds in common use, most focussed on the highly soluble compounds, and do not allow clear NOAELs to be established for the health endpoints investigated.

A large number of studies are available, which have investigated the health of workers with repeated long-term exposure to hexavalent chromium compounds. The two most studied groups are chrome plate and chromate-production workers (Cross et al., 1997). Many of these studies have reported effects on the upper respiratory tract but few have presented exposure details for chromium exposure. Effects on the upper respiratory tract include inflammation, atrophy of the nasal mucosa and ulceration or perforation of the nasal septum (Colvin *et al*, 1993; Royle, 1975; Lin *et al*, 1994). In the lower respiratory tract, the reported effects include inflammation and various obstructive disorders (Ameille *et al*, 1983; Wieser *et al*, 1982). Transient impairment of lung function has also been reported (Lindberg & Hedenstierna, 1983). In this latter study on chrome platers, effects on the nasal passages were reported with exposures to average concentrations of

0.002mg Cr/m3 and above although some effects were even reported at lower average concentrations. However, it should be noted that short-term exposure to higher concentrations or, direct contamination of the nasal mucosa with chromic acid might have been involved in the development of these lesions.

### 7.4.2. Animal data

The carcinogenicity of a number of hexavalent chromium compounds has been investigated in animal studies using various route of exposure; the most informative for the purpose of estimating cancer risks to humans in occupational settings are inhalation, intratracheal instillation and intrabronchial studies. In an inhalation study, in which rats were exposed to sodium chromate (0.025, 0.05 or 0.1mg Cr/m3), increased lung tumours occurred only at the highest dose. In a mouse inhalation study, increased lung tumours were associated with exposure the calcium chromate at the concentration used of (4.3mg Cr/m3). Two mouse inhalation studies showed a nonsignificant increase in lung tumours following exposure to chromium (IV) oxide. These inhalation studies all suffered from some deficiencies in design. Other inhalation studies, some of which investigated less soluble hexavalent chromium compounds, had major deficiencies that prevented any conclusions being drawn. In one intratracheal instillation study, increased lung tumour incidence was reported in rats following exposure to calcium chromate. In the same study, sodium dichromate was associated with increased lung tumour incidence in rats with 1.25mg/kg/week (0.5mg Cr/kg/week) administered as one weekly dose, but not when the same weekly dose was administered in five instillations. Other intratracheal instillation studies had major limitations, which prevented any conclusions being drawn. An intrabronchial implantation study in rats demonstrated elevated lung cancer incidence with calcium chromate, strontium chromate and zinc chromate, but failed to demonstrate evidence for carcinogenicity of poorly soluble compounds (lead chromate or barium chromate) or sodium dichromate, although the method may be inappropriate for highly soluble compounds. On the basis of the animal carcinogenicity data, it is concluded that there is evidence to suggest a potency difference between hexavalent chromium compounds, probably related to solubility and consequently bioavailability. Howe ver, the variation in design of the animal studies and, crucially, the scarcity of reliable data for poorly soluble hexavalent chromium compounds precludes definite distinctions being made, either qualitative or quantitative, between hexavalent chromium compounds on the basis of the available animal studies done alone.

## *7.5. Sensitisation*

### 7.5.1. Human data

Skin sensitisation resulting from exposure to hexavalent compounds has been demonstrated in patch-testing studies of contact dermatitis patients and in various chromate-exposed occupational groups (Sun, 1984; Samoen *et al*, 1984; Fregert *et al*, 1970; Engel & Calnan, 1963). Hexavalent chromium-sensitised subjects may react to trivalent chromium compounds although the latter are less able to penetrate the skin and thus have a lower skin sensitising potential (Fregert & Rorsman, 1964; Samitz & Shrager, 1966). Available case reports, together with supporting evidence from bronchial challenge tests, show that inhaling hexavalent chromium compounds can induce occupational asthma (Park *et al*, 1994). As with skin sensitisation, hexavalent chromium-sensitised subjects may react following exposure by inhalation to trivalent chromium compounds.

## *7.6. Genotoxicity*

### 7.6.1. Human data

In several studies increased frequencies of DNA strand breaks, sister chromatid exchanges and micronuclei were shown in lymphocytes of workers exposed to chromium(VI) compounds.(IARC, 2012) Chrome-plating workers (n=19), exposed at the workplace to chromium(VI) concentrations of 0.4 to 5.6 µg/m³, showed a higher level of chromium concentrations in urine, erythrocytes and lymphocytes as well as an increase of DNA strand breaks in the lymphocytes in comparison with two control groups (18 hospital workers and 20 university personnel). DNA strand breaks in lymphocytes were determined by comet assay (Gambelunghe et al., 2003).

The increase of the frequency of sister chromatid exchange in blood cells of workers employed in electroplating plants correlated with the duration of exposure to chromium (VI) and also with smoking habits. The duration of exposure was between 2 and 14 years. The results of biomonitoring showed a significant increase in the chromium concentration in urine (3.67 ± 3.89 µg/g creatinine compared with 1.21 ± 1.16 µg/g creatinine in control persons) and a significant decrease in superoxide dismutase activity in blood, 86.86 ± 0.80 U/mg hemoglobin compared with 7.16 ± 0.53 U/mg hemoglobin in control persons (Wu et al., 2001).

A significant increase in micronuclei in the peripheral lymphocytes and in buccal mucosa cells was found in chromium platers exposed to chromium concentrations at the workplace of 0.0249 to 0.0075 mg/m³. It was shown that half of the micronuclei contained fragments and the other half whole chromosomes, indicating clastogenic as well as aneugenic effects. However the incidence of sister chromatid exchanges and chromosomal aberrations was not increased in the exposed workers (Benova et al., 2002).

In another study with 40 workers from chrome plants, the number of micronuclei in the peripheral lymphocytes increased significantly in a dose-dependent manner. The mean chromium exposure was 0.083 ± 0.01 mg/m³ in the high exposure group (n=24) and 0.0043 ± 0.01 mg/m³ in the low exposure group (n=16) (Vaglenov et al., 1999).

At a steel production plant with very low exposure concentrations of 0.0004 to 0.0005 mg chromium/m³, no changes in the frequency of micronuclei in the cells of the nasal epithelium were found in 29 workers compared with in 39 controls (Huvinen et al., 2002).

### 7.6.2. Animal data

Animal studies have revealed that soluble chromium (VI) compounds induce genotoxic effects such as increased DNA repair, sister chromatid exchanges, micronuclei in somatic cells of rats and mice. In a few studies in which moderately to poorly soluble chromium(VI) compounds were administered, an increased incidence of sister chromatid exchanges, micronuclei and chromosomal aberrations were found in somatic cells of rats and mice. Also poorly soluble chromium(VI) compounds such as zinc potassium chromate and lead potassium chromate were shown to induce micronuclei in erythrocytes of mice after intraperitoneal injection. Dominant lethal mutations were induced in germ cells of mice after intraperitoneal injection of potassium dichromate but not, however, in rats after administration of the substance with the drinking water for 12 weeks. There are several studies in which chromium(VI) compounds were administered with the drinking water; their results are equivocal. In some studies a significant and concentration-dependent increase in micronuclei of bone marrow cells was found, but not in others (De Flora, Bagnasco, Serra, & Zanacchi, 1990; DFG, 2016; IARC, 2012; Proctor et al., 2014).

### *7.6.3. In vitro*

Soluble chromium(VI) compounds are genotoxic in bacteria, yeasts and mammalian cells. Also, strontium chromate and zinc chromate, poorly soluble compounds, induce genotoxic effects in bacteria and mammalian cells. The same accounts for lead chromate and barium chromate (IARC, 2012). Barium chromate in concentrations of 0.1 to 5 µg/cm² was clastogenic and induced chromatid and chromosome-type lesions in the human lung cell culture model WTHBF-6 (Wise, Schuler, Katsifis, & Wise, 2003) (Wise et al., 2003). Lead chromate particles from 0.45 to 0.58 µm and barium chromate particles from 0.4 to 32 µm were clastogenic in the near-normal human lung cell line WTHBF-6. In this assay barium chromate appears to be a stronger genotoxin than lead chromate (Wise et al., 2004). In bronchial epithelial cells (BEP2D), a significant concentration-dependent increase in chromosomal aberrations was observed for lead chromate concentrations of 0.5µg/cm² (Wise, Holmes, & Wise, 2006). Lead chromate in concentrations of 0.5 and 1µg/cm² induces centromere abnormalities, aneuploidy and DNA double-strand breaks in human lung cells WTHBF-6 (Holmes et al., 2006; Xie et al., 2005). Barium chromate at a concentration of 0.1µg/cm² caused an increase in deletions in the gpt gene in a cell line derived from V79 cells (Klein et al., 2002).

## *7.7. Carcinogenicity*

The basis for the carcinogenic classification of hexavalent chromium compounds has been established by the International Agency for research on Cancer (IARC) in 1990 (IARC, 1990). IARC concluded then that there was 'sufficient evidence' to consider hexavalent chromium to be carcinogenic in both humans and experimental animals and that classification in category 1 was justified (*'carcinogenic to humans'*). This IARC classification was again confirmed in 2009 and 2012 (IARC, 2012; Straif et al., 2009).

Most hexavalent chromium compounds are classified by the European Union for carcinogenicity in category 1B (*'substance presumed to be carcinogenic to humans'*). Exceptions are chromium trioxide, zinc chromate and zincpotassium chromate classified in category 1A (*'substance known to be carcinogenic to humans'*)(European Parliament and Council, 2008).

### 7.7.1. Human data

The first case of cancer associated with chromium compounds was reported by Newman (Newman, 1890) and described an adenocarcinoma in the nasal passages of a chromate pigment production worker. Since then, there have been several case reports of lung cancer among chromate pigment production workers, chromate-production workers and chrome platers and some case reports of cancer of the GI tract in chromate production workers (IARC, 1990, 2012). A large number of epidemiological studies are available for the evaluation of carcinogenicity and there have been a number of reviews published in recent years (AGS, 2014; ATSDR, 2000; BAuA, 2016; DECOS, 2016; ECHA, 2013; Goldbohm et al., 2006; IARC, 2012). IARC reviewed individual cohort studies available upto approximately 1990 and those that became available before approximately 2012 in detail (IARC, 1990, 2012).

**Chromate production workers:**
The most extensive studies are those in the chromate production industry and can be grouped into those from the US, the UK, Germany, Italy and Japan (H. J. Cross et al., 1997; IARC, 2012). These studies provide clear evidence of consistently increased mortality among chromate workers with various proxies of exposure. Values of standardised mortality ratios (SMRs) from 200 to over 2000 have been reported. In many cases, the study populations involved workers employed in the first half of the 20th

century. Steenland and others estimated a mean standardized SMR for lung cancer of 278 (Steenland et al., 1996).

Epidemiological studies have been performed in different groups of workers:

**Pigments-production workers:**
A number of studies have reported excess risk of cancer for workers employed in the chromate pigment production industry. Most of the plants studied produced both lead and zinc chromate and in some, exposure to other chromates including strontium, may have occurred. Therefore, the independent effects of lead chromate and zinc chromate with respect to lung cancer are difficult to identify. However, a series based in three UK factories provided strong suggestive evidence that zinc chromate, and not lead chromate is associated with lung cancer risks in this industry (Davies, 1984a, 1984b). No detailed exposure data are available to enable the relationship between chromium exposure and increased lung cancer mortality in the chromate pigment production industry to be investigated.

**Chrome plating workers:**
Several studies of chrome plating workers are available for evaluation. One study provides clear evidence of increased lung cancer mortality (Sorahan et al., 1987). Exposure data provided in this study suggests that exposure to CrO3 was generally below 0.05mg/m3 (0.026Cr/m3) but this figure should be treated with caution. Other, less well-conducted studies also report an elevated risk of mortality from lung cancer in chrome platers.

**Ferrochromium workers:**
Two studies are informative in the possible carcinogenicity of hexavalent chromium to ferrochromium workers. One study reported a non-significant excess of lung cancer (Langard, 1988; Langard & Vigander, 1983) and one study reported a non-significant deficit in lung cancer (Axelsson & Rylander, 1980). Both studies noted possible co-exposure to other known carcinogens.

**Stainless steel production workers:**
Studies in separate groups of French stainless steel production workers have been performed (Deschamps et al., 1995; Moulin et al., 1990; Moulin et al., 1993). A suggestive increase in lung cancer was considered to be more related to PAH exposure rather than chromium, but this form of potential confounding could not be dealt with quantitatively.

**Stainless steel welders:**
There are several studies that have investigated cancer mortality in stainless steel welders, but few have specifically investigated chromium (Cross et al., 1997). Of the available studies, some have reported increased risk of lung cancer mortality in stainless steel welders whilst others have not. By far the most comprehensive is a large study (Simonato et al., 1991) which reported increased lung cancer mortality in stainless steel welders, although a greater excess was reported for mild steel welders. In most of the studies reported, exposure to asbestos and other confounders were noted. Thus, any association between hexavalent chromium exposure and increased risk of lung cancer in stainless steel welders remains to be elucidated.

Quantitative exposure data are available for two cohorts – which have regularly been updated. The available exposure data enable the relationship between airborne chromium, in particular hexavalent chromium and increased lung cancer mortality in the chromate production industry to be investigated. Most importantly, no exposure data are provided regarding types of chromium compounds including specific hexavalent compounds.

The available epidemiological evidence has been used by several organizations in risk assessments:

**SCOEL 2004**

SCOEL earlier reviewed the toxicological and epidemiological evidence available for Chromium VI in 2004 (SCOEL, 2004). SCOEL made use of a number of reviews (ATSDR, 2000; Cross et al., 1997; Cross et al., 1997; EPA, 1984; IARC, 2012) and additional literature up to 2004. The SCOEL reported that exposure to hexavalent chromium compounds may lead to lung cancer. The SCOEL concluded that carcinogenicity was the critical effect of hexavalent chromium compounds in agreement with the classification of hexavalent chromium compounds by the EU. SCOEL based a quantitative risk assessment on the combined epidemiological data from ten cohort studies concerning employees occupationally exposed to chromate. These epidemiological studies were previously selected (mainly because of their size) by Steenland et al. in 1996 for a meta-analysis ((Alderson et al, 1981; Davies, 1984a, 1984b; Enterline, 1974; Frentzel-Beyme, 1983; Hayes et al., 1979; Korallus et al., 1993; Sorahan et al., 1987; Takahashi & Okubo, 1990). In addition to the analysis by Steenland et al. the SCOEL calculated cancer risk values for three different scenarios of exposure (500, 1,000 and 2,000 µg/$m^3$ for 15 years; cumulative 7,500, 15,000 en 30,000 µg x $m^{-3}$ x year) by assuming average exposure levels and an average duration of exposure for some of the cohorts for which quantitative exposure information was lacking. In its final recommendation the SCOEL decided to follow the first scenario and estimated that approximately 5-28 extra cases of cancer mortality would occur in a cohort of 1,000 employees, followed from age 20 to 85 and exposed to retirement at age 65, by using lifetable analyses which made use of mortality data for England and Wales. Lifetable analysis take into account competing causes of death, and are therefore referred to as an unconditional analysis of risk, and are most accurate:

- at an exposure level of 25 µg/$m^3$ this was estimated to be 2-14 extra mortality cases,
- at an exposure level of 10 µg/$m^3$ this estimate was 1-6 extra mortality cases,
- at 5 µg/$m^3$ this estimate was 0.5-3 extra mortality cases,
- at 1 µg/$m^3$ this estimate was 0.1-0.6.

**ECHA-RAC 2013**

The Committee for Risk Assessment (RAC) agreed on a proposal prepared by the ECHA secretariat for a risk assessment (ECHA, 2013). A review was performed for 14 hexavalent Chromium VI compounds. The committee acknowledged that extrapolating outside the range of observations inevitably introduces uncertainties in the risk assessment. As the mechanistic evidence is suggestive of non-linearity it is acknowledged that the excess risk in the low exposure range might be an overestimate of the true risk. RAC used the analysis published by Seidler in 2012 as a starting point for their risk calculations.(Seidler et al., 2013) Seidler evaluated the epidemiological literature, selected studies which had incorporated quantitative exposure estimates and conducted a quality review of the available papers. Only two studies were considered to be of sufficient quality, also because of the adjustment for the potential confounding effects of smoking. These were the Baltimore cohort and the Painesville cohort studies. Calculations were made assuming:

- a lifetime background cancer risk of 48 per 1000 for the EU male population;
- an 89 year life-expectancy;
- and according to the RAC-ECHA document (Annex 1), an excess risk linear function was derived from a RR (relative risk) of about 2, which seems obtained by rounding off the average exposure response slope as calculated by Seidler (beta = 1.75) on the basis of the two cohort studies, at the cumulative exposure of 0.5 mg Cr(VI)/$m^3$/year, which is equivalent to a RR of 2 for exposure to 12.5 µg Cr(VI)/$m^3$ for 40 years.

The associated excess lifetime risk (ELR) at this cumulative exposure for a RR of 2 was determined by multiplying the excess RR (RR – 1) by the background lung cancer risk in the EU population (Po) according to the equation for calculation of a conditional excess lifetime risk (ELR), which is an excess lifetime risk not taking into account other competing causes of dealth ELR = Po(RR-1), where Po was rounded off to a value of 0.05 (48/1000=0.048). This resulted in a ELR of 50 x$10^{-3}$ at 12.5 µg Cr(VI)/$m^3$ for 40 years

(equivalent to a ELR of 4 $x10^{-3}$ at 1 µg Cr(VI)/$m^3$ for 40 years). It should be made explicit that these calculations made did not allow for competing risks as is usually considered in a life-table analysis to derive risk estimates.

**AGS (2014)**

In 2014 the "Ausschuss für Gefahrstoffe (AGS)" published a report based on the evaluation of existing human and experimental toxicological literature. The AGS confirmed the EU classification of hexavalent chromium compounds. According to the AGS both 'direct genotoxic'mechanisms and mechanisms affecting 'tumor initiation and promotion underly the carcinogenicity of all hexavalent chromium compounds. For the quantitative risk assessment the AGS selected the study by Birk and others (Birk et al., 2006), which reported the German part of the multi-plant study by Mundt et al. (Mundt et al., 2002). This study involved 739 employees in the chromate production in Leverküsen en Uerdingen. Exposure data was established by biomonitoring chromium in urine and urine chromium levels were converted to concentrations in air. An increase in lung cancer mortality was observed in 22 cases. The AGS concluded that occupational exposure to 12.5 µg/$m^3$ would potentially lead to a doubling of the lung cancer risk (5/100). The AGS derived a cancer risk value of 4 per 1,000 (4 x $10^{-3}$) at 40 year occupational exposure to 1 µg/$m^3$ by using a conditional analysis of lifetime risk, and thus ignoring competing causes of death. The AGS did not extrapolate to lower exposure levels because of the uncertainty related to the shape of the dose-effect relationship and the uncertainty in the outcome of the risk calculation. See the AGS advice and the study by Birk et al. for details of the calculation (AGS, 2014; Birk et al., 2006). It should be made explicit that these calculations made did not allow for competing risks as is usually considered in a life-table analysis to derive risk estimates.

**NIOSH (2013)**

The US National Institute for Occupational Safety and Health (NIOSH) of the Centers of Disease Control (CDC) published a criteria document containing a quantitative risk assessment for hexavalent chromium compounds in 2013 (NIOSH, 2013). NIOSH summarized in its report existing human and experimental animal studies. NIOSH used human data for the quantitative risk assessment. Data were considered from two American cohorts of employees in the chromate industry (in Baltimore, Maryland and in Painesville, Ohio respectively). NIOSH used the data of Gibb et al. (Gibb et al., 2000)(Baltimore cohort) to conduct its risk assessment (Park et al., 2004). This involved a cohort of 2,357 employees in the chromate production industry with 122 mortality cases from lung cancer. NIOSH selected Gibb et al. (Gibb et al., 2000) because of the quality of the exposure data, the large number of mortality cases, detailed data on smoking and a better retrospective archive of exposure data. NIOSH used a linear extrapolation model and calculated an extra cancer mortality risk of

- 255 per 1,000 exposed to 52 µg Cr VI/$m^3$ during a working life,
- 6 per 1,000 at 1 µg/$m^3$
- and approximately 1 per 1,000 at 0.1 µg/$m^3$ (which is the Recommended Exposure Limit (REL)).

See the NIOSH criteria document for details of the calculations.

**DECOS 2016**

DECOS has drafted a guideline for the calculation of risks of (developing or dying from) lung cancer as a consequence of occupational exposure. DECOS is of the opinion that data from only a limited number of cohorts are suitable for a reliable risk assessment.(DECOS, 2016) In this regard DECOS shares the opinion of AGS and NIOSH. These are the American 'Baltimore cohort' (Braver, Infante, & Chu, 1985; Gibb et al., 2000; Hayes et al., 1979), the American 'Painesville cohort' (Luippold et al., 2003; Mancuso, 1997), and an American (Texas & North Carolina)(Luippold et al., 2005) and a European cohort (Leverküsen & Uerdingen)(Birk et al., 2006) involving employees participating in a 'multiplant study ' (Mundt et al., 2002). These four cohorts consist of employees in the chromate production industry, show an increased lungcancer risk (except the study by Luippold et al. (2005), exclude smoking as cause of lung cancer and have used a well-documented database of exposure measurements.

Seidler et al. selected five studies to establish an exposure-effect relationship (Gibb et al., 2000; Park et al., 2004; Park & Stayner, 2006) from the Baltimore cohort); (Crump et al., 2003) and (Luippold et al., 2003) from the Painesville cohort). In a subsequent meta-analysis an average dose-effect relationship was calculated, applying linear exposure-response models, for the Crump (2003) and the Park (2004) studies (characterized by a weighted average ß value of 1.75). Thereafter, Seidler et al. (2013) calculated an extra lung cancer risk for hexavalent chromium compounds of 4 per 10,000 ($4 \times 10^{-4}$) after 40 year occupational exposure to 0.1 µg/m$^3$ and 4 per 1,000 ($4 \times 10^{-3}$) after 40 year occupational exposure to 1 µg/m$^3$. See the study by (Seidler et al., 2013) for details of the calculation. DECOS considered it important that the calculations are based on multiple studies when possible (and thus not only by the study of Park (2004) as has been done in the risk assessment by NIOSH (2013)). Therefore DECOS prefers the study by Seidler et al. as starting point for its further risk assessment.

As a first step DECOS evaluated the calculations by Seidler et al. Based on the average slope of the dose-effect relationship of the two selected studies in the meta-analysis an extra risk is using mortality data from the Netherlands' population (from 2000 to 2010), separated by age and sex). Moreover, the cancer risk values are calculated taking into account a higher age (end of cohort at 100 years). This results into extra risks of respectively:

- 4 per 100,000 at exposure to 0.0104 µg/m$^3$
- and 4 per 1,000 at exposure to 1.04 µg/m$^3$.

These exposure levels are almost equal to those calculated by Seidler et al. [DECOS notes that the expected higher risks at higher age are probably compensated because male and female mortality data are combined in the DECOS calculation. When using only male mortality data, as was done by Seidler et al., the DECOS calculation would lead to an approximately 28% lower exposure level.

In addition, DECOS notes that the calculated exposure of 1 µg/m$^3$ at an extra risk of 4 per 1,000 (based on the Seidler et al. data) equals the exposure calculated by the RAC-ECHA (also based on the Seidler et al. data) and the AGS (based on the data by Birk et al.).

DECOS estimates that the additional lifetime cancer risk for hexavalent chromium compounds amounts to:

- $4 \times 10^{-5}$ for 40 years of occupational exposure to 0.01 µg/m$^3$
- and, $4 \times 10^{-3}$ for 40 years of occupational exposure to 1 µg/m$^3$.

**Present evaluation by SCOEL**

The SCOEL considers that a risk assessment should be made using the best available data and methodology, leading to unbiased risk estimates. Therefore, SCOEL considers that a risk assessment from Cr VI should be made using exposure response studies that made use of Cr VI quantitative exposure estimates. In addition, the exposure response studies should be high quality studies, meaning that these studies do not suffer from strong epidemiological biases and preferably have made adjustments for smoking habits. SCOEL is also convinced that the lifetime excess risk should be calculated on the basis of a lifetable analysis, which gives the most accurate and precise estimate of the risk.

In case of Cr VI a few of such studies are available and these have recently been reviewed (Seidler et al., 2013). They estimated from an average dose-effect relationship, applying linear models, for the Crump et al., (2003) and the Park et al., (2004) studies (characterized by a weighted average ß value of 1.75). This exposure-response slope was used for linear extrapolation and forms the basis for the SCOEL calculations. SCOEL used European lung cancer and total mortality data, to account for competing risks in a lifetable analysis, and assumed occupational exposure from age 20-60 (40 years) and calculated the excess risk for lung cancer. A latency period of 10 years was assumed. Calculations were made using a lifetable analysis which allows for competing risks (other causes of death) and as a result leads to precise risk estimates.
Risk calculations are shown below in chapter 8.

## *7.8. Reproductive toxicity*

### 7.8.1. Human data

Studies, which have reported complications in pregnancy and childbirth in women employed in the chromate manufacturing industry, provide unreliable data (Shmitova 1978; Shmitova, 1980). Several investigations of male fertility have focussed on welding as an occupation. Some of these studies report effects on semen quality (Mortensen, 1988) whilst others do not (Bonde & Ernst, 1992; Jelnes & Knudsen, 1988). The general absence of exposure data in these studies precludes any assessment of the relationship to hexavalent chromium.

### 7.8.2. Animal data

A number of studies have investigated the effect of chromates on reproduction in animals. Parenteral administration of maternally toxic doses of chromium trioxide (3.9mg Cr/kg and above) to pregnant hamsters during gestation resulted in resorption and embryotoxicity (increased foetal resorption; subcutaneous oedema, delayed skeletal ossification and cleft palate in surviving embryos) (Gale, 1974; Gale 1978). Doses, which caused no maternal toxicity, caused cleft palate, hydrocephalus and delayed skeletal ossification in hamsters (2.6mg Cr/kg), but failed to induce embryotoxicity in rats (2mg Cr/kg). (Gale & Bunch, 1979; Mason et al, 1989). Repeat injection studies of sodium chromate in male rats (1- 4mg Cr/kg for 5 days) caused a reduction in body weight, a reduction in testicular weight, atrophy of seminiferous tubules and reduced sperm count. Caution is needed in the interpretation as the relevance of these studies on reproduction as the route of introduction by parenteral administration would avoid the normal reducing route by oral or inhalation routes.

## *7.9. Mode of action and adverse outcome pathway considerations*

As opposed to many other metal compounds, in case of Cr(VI) the formation of DNA adducts appears to play an important role in generating genomic instability and thus tumor formation (Hartwig, 2013; Wise & Wise, 2012). Under physiological conditions, Cr(VI) enters the cell as the anionic tetrahedral species chromate, $CrO_4^{2-}$, via anion transport systems such as the sulfate carrier, and is intracellularly reduced to Cr(III), described by the so-called "uptake-reduction" model. Within the cell, reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols such as glutathione and cysteine; during this process, potentially toxic intermediates such as oxygen and sulfur radicals are generated, dependent on the intracellular reductant. In case of poorly water soluble chromium(VI) compounds such as barium chromate and lead chromate, uptake is mediated via endocytosis. DNA lesions generated after exposure towards Cr(VI) consist of two categories, namely oxidatively induced DNA damage and DNA lesions resulting from Cr(III)-DNA interactions. With respect to the formation of ROS during the intracellular reduction process, the induction of oxidatively damaged DNA by Cr(VI) appears to be restricted to high exposure concentrations, and its relevance on physiological conditions has been questioned. In contrast, especially ternary Cr-DNA adducts may be of special importance for chromate-induced carcinogenicity, where Cr bridges DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed Cr-ligand complexes during the reduction process. Under physiological conditions, ascorbate appears to be the major reductant, and especially ternary adducts formed from Cr-ascorbate are potent premutagenic DNA lesions. One other additional aspect of chromate-induced carcinogenicity is the induction of genomic instability, as evident by simultaneous occurrence of microsatellite instability and chromosome instability in Cr(VI)-induced tumors. This may be a consequence of disturbed DNA mismatch repair (MMR). Thus, Cr(VI)-induced DNA lesions lead to aberrant MMR, and upon chronic

exposure to toxic doses of Cr(VI) the selective outgrowth of MMR-deficient clones exerting a high degree of genomic instability has been postulated. In summary, Cr(VI) acts directly genotoxic by inducing specific DNA lesions, which are not easily repaired; genomic instability is increased via mismatch-repair deficient cell clones which survive on the expense of hypermutability.

### *7.10. Lack of specific scientific information*

On the basis of the animal carcinogenicity data, it is concluded that there is evidence to suggest a potency difference between hexavalent chromium compounds, probably related to solubility and consequently bioavailability. However, the variation in design of the animal studies and, crucially, the scarcity of reliable data for poorly soluble hexavalent chromium compounds precludes definite distinctions being made, either qualitative or quantitative, between hexavalent chromium compounds on the basis of the available animal studies done alone.

The genotoxicity of hexavalent chromium compounds has been widely investigated in assays for different genetic endpoints and has, with a few possible exceptions, been uniformly positive in in vitro assays for mutagenicity and clastogenicity, with evidence of in vivo expression of these effects in some compounds. The possible exceptions are lead and barium chromate and these two compounds have required solubilisation to elicit positive results in bacterial cell assays or to enhance their genotoxic activity in mammalian cells. Although there appears to be a difference in genotoxic potential between the various hexavalent chromium compounds tested based on solubility, positive results were obtained with the poorly soluble compounds in some assays. It is therefore not possible to exclude any compounds tested from possessing some mutagenic or clastogenic potential.

## 8. CANCER RISK ASSESSMENT

It was concluded that hexavalent chromium compounds are carcinogens with no threshold, carcinogen group A.

The SCOEL considers that a risk assessment should be made using the best available data and methodology, leading to unbiased risk estimates. Therefore, SCOEL considers that a risk assessment from Cr VI should be made using exposure response studies that made use of Cr VI quantitative exposure estimates. In addition, the exposure response studies should be high quality studies, meaning that these studies do not suffer from strong epidemiological biases and preferably have made adjustments for smoking habits. SCOEL is also convinced that the lifetime excess risk should be calculated on the basis of a lifetable analysis, which gives the most accurate and precise estimate of the risk.

In case of Cr VI a few of such studies are available and these have recently been reviewed (Seidler et al., 2013). They estimated from an average dose-effect relationship, applying linear models, for the Crump et al., (2003) and the Park et al., (2004) studies (characterized by a weighted average ß value of 1.75). This exposure-response slope was used for linear extrapolation and forms the basis for the SCOEL calculations. SCOEL used European lung cancer and total mortality data, to account for competing risks in a lifetable analysis, and assumed occupational exposure from age 20-60 (40 years) and calculated the excess risk for lung cancer. A latency period of 10 years was assumed. Calculations were made using a lifetable analysis which allows for competing risks (other causes of death) and as a result leads to precise risk estimates.

For the calculations, a hypothetical cohort was followed till all members were deceased. The following risk estimates were produced for the combined exposure response slopes

and the individual studies used in the risk assessment. The confidence interval is based on a pooled standard error of the exposure response slopes:

**Table 8:** Estimates of excess lung cancer risk at different exposure levels during a work shift

| | Number of excess lung cancer cases / 1000 | | | |
|---|---|---|---|---|
| **Exposure 8 hour time weighted average** | **Point estimate combined exposure response slopes** | **Confidence interval** | **(Crump et al., 2003)** | **(Park et al., 2004)** |
| 0.1 µg/m$^3$ | **0.4** | **0.3-0.5** | **0.2** | **0.6** |
| 1 µg/m$^3$ | **4** | **3.2-4.8** | **2** | **6** |
| 5 µg/m$^3$ | **20** | **16-24** | **8** | **32** |
| 10 µg/m$^3$ | **39** | **31-47** | **15** | **62** |
| 25 µg/m$^3$ | **94** | **76-112** | **38** | **146** |

Exposure at which excess risk benchmark values of 4/1000 and 4/100 000 workers are realized, are similar to the exposure estimates which have recently been published by other organisations and researchers and are presented in an overview produced by the Dutch Expert Committee for Occupational Standards (DECOS, 2016) These benchmarks are is some countries considered as 'acceptable' and 'negligible' risk levels. Although the exposure which corresponds with these risks are similar, differences exist in the approaches taken to calculate these exposure estimates with some other risk assessments (AGS, 2014; DECOS, 2016; Seidler et al., 2013) The differences relate to a) methodology to estimate risk, b) age at which the risk is estimated, c) use of average male and female rates instead of male rates only. The different combinations of assumptions lead in the end to similar estimates as produced by the different sources.

Risk calculations require assumptions and practical choices. SCOEL used averaged male and female rates of lung cancer. Risk calculations based on male rates would have led to higher risk at the same exposure in comparison with a risk assessment based on average rates. Similarly, calculations till age 75 would lead to lower risks compared to the approach taken in this analysis (age 100). The effect of these assumptions has been quantified recently and can vary considerably depending on the combination of assumptions (DECOS, 2016; Seidler et al., 2013).

## 9. GROUPS AT EXTRA RISK

None identified

## 10. REFERENCES


Adachi, S., Yoshimura, H., Miyayama, R., Katayama, H., Takemoto, K., & Kawai, H. (1981). [Effects of chromium compounds to the respiratory system. Part 1. An experimental study of inhalation of chromic acid mist in electroplating (author's transl)]. *Sangyo Igaku, 23*(3), 294-299.

Adachi, S., Yoshimura, H., Katayama, H., & Takemoto, K. (1986). [Effects of chromium compounds on the respiratory system. Part 4. Long-term inhalation of chromic acid mist in electroplating to ICR female mice]. *Sangyo Igaku, 28*(4), 283-287.

Adachi, S. (1987). [Effects of chromium compounds on the respiratory system. 5. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation of our experimental studies]. *Sangyo Igaku, 29*(1), 17-33.

AGS. (2014). Committee on Hazardous Substances. Chrom(VI)-verbindungen.

Alderson, M. R., Rattan, N. S., & Bidstrup, L. (1981). Health of workmen in the chromate-producing industry in Britain. *Br J Ind Med, 38*(2), 117-124.

Angerer, J., Amin, W., Heinrich-Ramm, R., Szadkowski, D., & Lehnert, G. (1987). Occupational chronic exposure to metals. I. Chromium exposure of stainless steel welders--biological monitoring. *Int Arch Occup Environ Health, 59*(5), 503-512.

Ashley, K., Howe, A. M., Demange, M., & Nygren, O. (2003). Sampling and analysis considerations for the determination of hexavalent chromium in workplace air. [Review]. *J Environ Monit, 5*(5), 707-716.

ATSDR. (2000). Toxicological profile for Chromium: Agency for Toxic Substances and Disease Registry, .

Axelsson, G., & Rylander, R. (1980). Environmental chromium dust and lung cancer mortality. *Environ Res, 23*(2), 469-476.

BAuA. (2014). [Bundesanstalt für Arbeitsschutz und Arbeitsmedizin / Federal Institute for Occupational Safety and Health] (2014) Chrom(VI)-Verbindungen. Begründung zu Chrom (VI) in TRGS 910.

Benova, D., Hadjidekova, V., Hristova, R., Nikolova, T., Boulanova, M., Georgieva, I., . . . Nilsson, R. (2002). Cytogenetic effects of hexavalent chromium in Bulgarian chromium platers. [*Mutat Res, 514*(1-2), 29-38.

Birk, T., Mundt, K. A., Dell, L. D., Luippold, R. S., Miksche, L., Steinmann-Steiner-Haldenstaett, W., & Mundt, D. J. (2006). Lung cancer mortality in the German chromate industry, 1958 to 1998. *J Occup Environ Med, 48*(4), 426-433. doi: 10.1097/01.jom.0000194159.88688.f8

Braver, E. R., Infante, P., & Chu, K. (1985). An analysis of lung cancer risk from exposure to hexavalent chromium. *Teratog Carcinog Mutagen, 5*(5), 365-378.

Cross, H. J., Faux, S. P., & Levy, L. S. (1997). Establishing an occupational exposure limit for hexavalent chromium in the European Union. *Regul Toxicol Pharmacol, 26*(1 Pt 2), S72-76. doi: 10.1006/rtph.1997.1142

Cross, H. J., Faux, S. P., Sadhra, S., Sorahan, T., Levy, L. S., Aw, T. C., . . . Calvert, I. (1997). Criteria Document for Hexavalent Chromium. Paris, France: International Chrome Development Association (IDCA).

Crump, C., Crump, K., Hack, E., Luippold, R., Mundt, K., Liebig, E., . . . Proctor, D. (2003). Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. *Risk Anal, 23*(6), 1147-1163.

Davies, J. M. (1984a). Long term mortality study of chromate pigment workers who suffered lead poisoning. *Br J Ind Med, 41*(2), 170-178.

Davies, J. M. (1984b). Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. *Br J Ind Med, 41*(2), 158-169.

De Flora, S. (2000). Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. *Carcinogenesis, 21*(4), 533-541.

De Flora, S., Bagnasco, M., Serra, D., & Zanacchi, P. (1990). Genotoxicity of chromium compounds. A review. *Mutat Res, 238*(2), 99-172.

DECOS. (2016). Hexavalent Chromium compounds. Health-based calculated cancer risk values. The Hague: Health Council of the Netherlands.

Deschamps, F., Moulin, J. J., Wild, P., Labriffe, H., & Haguenoer, J. M. (1995). Mortality study among workers producing chromate pigments in France. *Int Arch Occup Environ Health, 67*(3), 147-152.

DFG. (1985). The MAK Collection for Occupational Health and Safety. Biomonitoring Methods: chromium, determination in urine. (Vol. 2, pp. 97-115).

DFG. (1990). The MAK Collection for Occupational Health and Safety. Biomonitoring Methods: Chromium, Determination in whole blood, plasma and erythrocytes. (Vol. 3, pp. 109-126).

DFG. (1993a). The MAK Collection for Occupational Health and Safety. Air Monitoring Methods. Methods for the determination of hexavalent chromium. Sampling with a pump and collection on a particle filter, photometry after wet-ashing. "Chromium-2-PHOT" (Vol. 4).

DFG. (1993b). The MAK Collection for Occupational Health and Safety. Air Monitoring Methods:"Methods for the determination of hexavalent chromium. Sampling with a pump and collection on a glass fibre filter, ion chromatography (IC) after wet-ashing. "Chromium-3-IC" (Vol. 4).

DFG. (2012). DFG [Deutsche Forschungsgemeinschaft] (2012a) Alkali chromates (Cr(VI)) [BAT Value Documentation, 1994]. H. M. Bolt, J. Lewalter. DOI: 10.1002/3527600418.bb0ek1e0001. The MAK Collection for Occupational Safety and Health. Published online 31 Jan 2012. Retrieved 27 September, 2016, from http://onlinelibrary.wiley.com/doi/10.1002/3527600418.bb0ek1e0001/full

DFG. (2015). [Deutsche Forschungsgemeinschaft] (2015) List of MAK and BAT Values 2015. Page 243. Retrieved 27 September, 2016, from http://onlinelibrary.wiley.com/doi/10.1002/9783527695539.ch2/pdf

DFG. (2016). Chromium(VI) compounds (inhalable fraction). In A. Hartwig (Ed.), *MAK Value Documentations*: Deutsche Forschungsgemeinschaft (DFG).

DWEA. (2011). Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer. BEK nr 1134 af 01/12/2011 (Gældende). Ministerium: Beskæftigelsesministeriet Journalnummer: Beskæftigelsesmin. Arbejdstilsynet. j.nr. 2011007144. Denmark. Retrieved 27 September, 2016, from https://www.retsinformation.dk/pdfPrint.aspx?id=139131.

ECHA. (2013). Services to support the assessment of remaining cancer risks related to the use of chromium- and arsenic-containing substances in Applications for Authorisation: Final Report for Hexavalent Chromium. Helsinki, Finland.

ECHA. (2016). Information on chemicals. Sodium chromate Retrieved 15 November, 2016, from https://echa.europa.eu/information-on-chemicals

ECHA. (2017). ECHA C&L inventory Retrieved 30-01-2017 https://echa.europa.eu/information-on-chemicals/cl-inventory-database

Enterline, P. E. (1974). Respiratory cancer among chromate workers. *J Occup Med, 16*(8), 523-526.

EPA. (1984). Health Assessment Document for Chromium. US Environmental Protection Agency.

European Parliament and Council. (2008). *REGULATION (EC) No 1272/2008 OF THE 27 EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and amending regulation (EC) No 197/2006*.

Frentzel-Beyme, R. (1983). Lung cancer mortality of workers employed in chromate pigment factories. A multicentric European epidemiological study. *J Cancer Res Clin Oncol, 105*(2), 183-188.

Gambelunghe, A., Piccinini, R., Ambrogi, M., Villarini, M., Moretti, M., Marchetti, C., . . . Muzi, G. (2003). Primary DNA damage in chrome-plating workers. *Toxicology, 188*(2-3), 187-195.

Gibb, H. J., Lees, P. S., Pinsky, P. F., & Rooney, B. C. (2000). Lung cancer among workers in chromium chemical production. *Am J Ind Med, 38*(2), 115-126.

GKV. (2011). Verordnung des Bundesministers für Arbeit. Soziales und Konsumentenschutz über Grenzwerte für Arbeitsstoffe sowie über krebserzeugende und über fortpflanzungsgefährdende (reproduktionstoxische) Arbeitsstoffe. (Grenzwerteverordnung 2011 – GKV 2011). Austria. Retrieved 27 september 2016, from http://www.auva.at/portal27/portal/auvaportal/content/contentWindow?&contentid=10008.542565&action=b&cacheability=PAGE

Glaser, U., Hochrainer, D., Kloppel, H., & Kuhnen, H. (1985). Low level chromium (VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. *Arch Toxicol, 57*(4), 250-256.

Glaser, U., Hochrainer, D., Kloppel, H., & Oldiges, H. (1986). Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. *Toxicology, 42*(2-3), 219-232.

Goldbohm, R. A., Tielemans, E. L., Heederik, D., Rubingh, C. M., Dekkers, S., Willems, M. I., & Dinant Kroese, E. (2006). Risk estimation for carcinogens based on epidemiological data: a structured approach, illustrated by an example on chromium. *Regul Toxicol Pharmacol, 44*(3), 294-310. doi: 10.1016/j.yrtph.2006.01.007

Hartwig, A. (2013). Metal interaction with redox regulation: an integrating concept in metal carcinogenesis? *Free Radic Biol Med, 55*, 63-72. doi: 10.1016/j.freeradbiomed.2012.11.009

Hayes, R. B., Lilienfeld, A. M., & Snell, L. M. (1979). Mortality in chromium chemical production workers: a prospective study. *Int J Epidemiol, 8*(4), 365-374.

Holmes, A. L., Wise, S. S., Sandwick, S. J., Lingle, W. L., Negron, V. C., Thompson, W. D., & Wise, J. P., Sr. (2006). Chronic exposure to lead chromate causes centrosome abnormalities and aneuploidy in human lung cells. *Cancer Res, 66*(8), 4041-4048. doi: 10.1158/0008-5472.CAN-05-3312

HSA. (2016). [Health and Safety Authority] (2016) 2016 Code of Practice for the Chemical Agents Regulations (S.I. No. 619 of 2001). Health and Safety Authority. Ireland. Retrieved 27 September, 2016, from http://www.hsa.ie/eng/Publications_and_Forms/Publications/Chemical_and_Hazardous_Substances/Chemical_Agents_COP_2016.pdf

HSE. (2011). [Health and Safety Executive] (2011) EH40/2005 Workplace Exposure Limits. EH40 (Second edition. published 2011). Health and Safety Executive (HSE). UK. Retrieved 27 September, 2016, from http://www.hse.gov.uk/pUbns/priced/eh40.pdf

HSE. (2014). Hexavalent chromium in chromium plating mists. Colorimetric field method using 1,5-diphenylcarbazide and spectrophotometry or colour comparator. .

Huvinen, M., Makitie, A., Jarventaus, H., Wolff, H., Stjernvall, T., Hovi, A., . . . Norppa, H. (2002). Nasal cell micronuclei, cytology and clinical symptoms in stainless steel production workers exposed to chromium. *Mutagenesis, 17*(5), 425-429.

IARC. (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum, 49*, 1-648.

IARC. (2012) Chromium (VI) compounds. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans-arsenic, metals, fibres and dusts. *Vol. 100C* (pp. 147-167). Lyon, France: International Agency for Research on Cancer.

IFA. (2016). Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (2016). GESTIS - International limit values for chemical agents. DGUV. IFA. Sankt Augustin. Germany. Retrieved 27 September, 2016, from http://limitvalue.ifa.dguv.de/

INRS. (2012). Valeurs limites d'exposition professionnelle aux agents chimiques en France. Institut National de Recherche et de Sécurité (INRS). France Retrieved 27 September, 2016, from http://www.inrs.fr/media.html?refINRS=ED%20984

INSHT. (2016). [Instituto Nacional de Seguridad e Higiene en el Trabajo] (2016). Límites de Exposición Profesional para Agentes Químicos en Espana. Spain. Retrieved 27 September, 2016, from http://www.insht.es/InshtWeb/Contenidos/Documentacion/LEP%20_VALORES%20LIMITE/Valores%20limite/Limites2016/LEP%202016.pdf

IOM. (2011). Health, social-economic abd environmental aspects of possible amendment of the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work. Hexavaleent Chromium. . Edinburgh, Scotland.Institute for Occupational Medicine.

IRSST. (2010). [Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail] (2010) Québec. Canada. Retrieved 27 September 2016, from http://www.irsst.qc.ca/en/laboratories/references-tools/workplace-air-contaminant/substance/i/439

ISO. (2005). Determination of hexavalent chromium in airborne particulate matter -- Method by ion chromatography and spectrophotometric measurement using diphenyl carbazide. (Vol. ISO 16740).

JSOH. (2015). Recommendation of Occupational Exposure Limits 2015-2016. . *J Occup Health, 57*, 394-417.

KB. (2002). [Koninklijk Besluit - Royal Decision] (2002) Revised version valid for after July 2014. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk. Belgium. Retrieved 27 September, 2016, from https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwj7hoam8f7LAhWBORoKHcMgAp4QFggcMAA&url=http%3A%2F%2Fwww.werk.belgie.be%2FDownloadAsset.aspx%3Fid%3D2162&usg=AFQjCNGhKN3FmC8o8vps9iLtBYFpdxEBXg&sig2=R62PTd6ymNQtN9MW1tgqZw&bvm=bv.119028448.d.d2s&cad=rja

Klein, C. B., Su, L., Bowser, D., & Leszczynska, J. (2002). Chromate-induced epimutations in mammalian cells. *Environ Health Perspect, 110 Suppl 5*, 739-743.

Korallus, U., Ulm, K., & Steinmann-Steiner-Haldenstaett, W. (1993). Bronchial carcinoma mortality in the German chromate-producing industry: the effects of process modification. *Int Arch Occup Environ Health, 65*(3), 171-178.

Langard, S., & Vigander, T. (1983). Occurrence of lung cancer in workers producing chromium pigments*Br J Ind Med, 40*(1), 71-74.

Langard, S. (1988). Chromium carcinogenicity; a review of experimental animal data. *Sci Total Environ, 71*(3), 341-350.

Levy, L. S., Martin, P. A., & Bidstrup, P. L. (1986). Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. [*Br J Ind Med, 43*(4), 243-256.

Luippold, R. S., Mundt, K. A., Austin, R. P., Liebig, E., Panko, J., Crump, C., . . . Proctor, D. (2003). Lung cancer mortality among chromate production workers. *Occup Environ Med, 60*(6), 451-457.

Luippold, R. S., Mundt, K. A., Dell, L. D., & Birk, T. (2005). Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. *J Occup Environ Med, 47*(4), 381-385.

Mancuso, T. F. (1997). Chromium as an industrial carcinogen: Part I. *Am J Ind Med, 31*(2), 129-139.

MHSFA. (2000). [Ministry of Health. Social and Ministry of Family Affairs] (2000). 25/2000. (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról. Hungary. Retrieved 27 September, 2016, from http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM

Moulin, J. J., Portefaix, P., Wild, P., Mur, J. M., Smagghe, G., & Mantout, B. (1990). Mortality study among workers producing ferroalloys and stainless steel in France. *Br J Ind Med, 47*(8), 537-543.

Moulin, J. J., Wild, P., Mantout, B., Fournier-Betz, M., Mur, J. M., & Smagghe, G. (1993). Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control, 4*(2), 75-81.

MSAH. (2012). [Ministry of Social Affairs and Health] (2012) HTP-värden 2012. Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6. Finland. Retrieved 27 September, 2016, from http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf

Mundt, K. A., Dell, L. D., Austin, R. P., Luippold, R. S., Skillings, A., & Gross, R. (2002). Collaborative cohort mortality study of four chromate production facilities, 1958-1998. Prepared for: Industrial Health Foundation, Inc. Amherst, Massachusetts: Prepared by: Applied Epidemiology Inc.

Nettesheim, P., Hanna, M. G., Jr., Doherty, D. G., Newell, R. F., & Hellman, A. (1971). Effect of calcium chromate dust, influenza virus, and 100 R whole-body x radiation on lung tumor incidence in mice. *J Natl Cancer Inst, 47*(5), 1129-1144.

Newman, D. (1890). A case of adenoma-carcinoma of the left inferior turbinated body, and perforation of the nasal septum, in the person of a welder in chrome pigments. *Glasgow Med J, 24*, 676-681.

NIOSH. (1994). NIOSH (1994) CHROMIUM, HEXAVALENT: METHOD 7604. NIOSH Manual of Analytical Methods (NMAM) (4th ed., pp. 1-3).
NIOSH. (2003). CHROMIUM, HEXAVALENT: METHOD 7605. NIOSH Manual of Analytical Methods (NMAM) (4th ed., pp. 1-5).
NIOSH. (2013). Occupational exposure to hexavalent chromium: criteria for a recommended standard. : National Institute for Occupational Safety and Health, Centers for Disease Control.
NIOSH. (2015a). CHROMIUM, HEXAVALENT: METHOD 7600. NIOSH Manual of Analytical Methods (NMAM) (5th ed., pp. 1-5).
NIOSH. (2015b). CHROMIUM, HEXAVALENT: METHOD 7703. NIOSH Manual of Analytical Methods (NMAM) (5th ed., pp. 1-6).
NLIA. (2011). [Norwegian Labour Inspection Authority] (2011) Administrative normer for forurensning i arbeidsatmosfære. Norway. Arbeidstilsynet. Veiledning. best.nr. 361 Retrieved 27 September, 2016, from http://www.arbeidstilsynet.no/binfil/download2.php?tid=77907
NTP. (2008). NTP Technical report on the toxicology and carcinogenesis of sodium dichromate dihydrate (CAS No. 7789-12-0). in F344/N rats and B6C3F1 mice (drinking water studies). (Vol. NTP TR 546; NIH Publication No. 08-5887): US Department of Health and Human Services, National Institutes of Health.
OML. (2015). [Ontario Ministry of Labour] (2015) Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833. June 29. 2015. Canada. Retrieved 27 September, 2016, from http://www.labour.gov.on.ca/english/hs/pubs/oel_table.php
OSHA. (1998). Hexavalent chromium. ID-215 (version2). T-ID215-FV-01-9806-M. OSHA Sampling and analytical methods. .
OSHA. (2006). Hexavalent chromium. ID-215 (version 2). OSHA Sampling and analytical methods. . USDL.
OSHA. (2017). Annotated PEL: Table Z1. USA. Retrieved 17 February 2017, from https://www.osha.gov/dsg/annotated-pels/index.html
Park, D., Yun, Y. S., & Park, J. M. (2004). Reduction of hexavalent chromium with the brown seaweed Ecklonia biomass. [Research Support, Non-U.S. Gov't]. *Environ Sci Technol, 38*(18), 4860-4864.
Park, R. M., Bena, J. F., Stayner, L. T., Smith, R. J., Gibb, H. J., & Lees, P. S. (2004). Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. *Risk Anal, 24*(5), 1099-1108. doi: 10.1111/j.0272-4332.2004.00512.x
Park, R. M., & Stayner, L. T. (2006). A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. *Risk Anal, 26*(1), 79-88. doi: 10.1111/j.1539-6924.2006.00709.x
Proctor, D. M., Suh, M., Campleman, S. L., & Thompson, C. M. (2014). Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. *Toxicology, 325*, 160-179. doi: 10.1016/j.tox.2014.08.009
SCOEL. (2004) SCOEL/SUM/86 December 2004Recommendation from the Scientific Committee on Occupational Exposure Limits: Risk assessment for Hexavalent Chromium
Seidler, A., Jahnichen, S., Hegewald, J., Fishta, A., Krug, O., Ruter, L., . . . Straube, S. (2013). Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. *Int Arch Occup Environ Health, 86*(8), 943-955. doi: 10.1007/s00420-012-0822-0
Simonato, L., Fletcher, A. C., Andersen, A., Anderson, K., Becker, N., Chang-Claude, J., . . . et al. (1991). A historical prospective study of European stainless steel, mild steel, and shipyard welders. *Br J Ind Med, 48*(3), 145-154.
Sorahan, T., Burges, D. C., & Waterhouse, J. A. (1987). A mortality study of nickel/chromium platers. *Br J Ind Med, 44*(4), 250-258.
Sorahan, T., Burges, D. C., Hamilton, L., & Harrington, J. M. (1998). Lung cancer mortality in nickel/chromium platers, 1946-95. *Occup Environ Med, 55*(4), 236-242.

Steenland, K., Loomis, D., Shy, C., & Simonsen, N. (1996). Review of occupational lung carcinogens. [Review]. *Am J Ind Med, 29*(5), 474-490. doi: 10.1002/(SICI)1097-0274(199605)29:5<474::AID-AJIM6>3.0.CO;2-M

Steinhoff, D., Gad, S. C., Hatfield, G. K., & Mohr, U. (1986). Carcinogenicity study with sodium dichromate in rats. *Exp Pathol, 30*(3), 129-141.

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens-Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009 May;10(5):453-4

STSCR. (2014). Staatscourant [Official journal] Nr. 36338, 18 December 2014. The Netherlands Retrieved 15 February 2017, from https://www.ser.nl/nl/taken/grenswaarden.aspx and https://www.ser.nl/en/sitecore/content/internet/nl/grenswaarden/chroom%20%20vi%20%20oplosbare%20verbindingen.aspx

SUVA. (2016). Grenzwerte am Arbeitsplatz 2016. Suva. Bereich Arbeitsmedizin. Luzern. Switzerland. Retrieved 15 February 2017, from https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiBpI_FhpXSAhWIVhoKHZVaChYQFggcMAA&url=https%3A%2F%2Fwww.suva.ch%2F-%2Fmedia%2Fprodukte%2Fdokumente%2F7%2F0%2F5%2F20209-1--1903_d_original_de_20209%2C-d-%2Cpdf.pdf%3Fsc_lang%3Dde-CH&usg=AFQjCNFUDTIHmHUdFSRX1YDnjvgVD3T8ag&sig2=luKWmwY4EKy3MCoYuj2URA&cad=rja

SWA. (2013). Workplace exposure standards for airborne contaminants date of effect: 18 April 2013. Australia. Retrieved 27 September, 2016, from http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/772/Workplace-exposure-standards-airborne-contaminants.pdf

SWEA. (2015). [The Swedish Work Environment Authority] (2015). Occupational Exposure Limit Values. Hygieniska gränsvärden. AFS 2015:7 Retrieved 15 February 2017, from https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf

Takahashi, K., & Okubo, T. (1990). A prospective cohort study of chromium plating workers in Japan. *Arch Environ Health, 45*(2), 107-111. doi: 10.1080/00039896.1990.9935934

Vaglenov, A., Nosko, M., Georgieva, R., Carbonell, E., Creus, A., & Marcos, R. (1999). Genotoxicity and radioresistance in electroplating workers exposed to chromium. *Mutat Res, 446*(1), 23-34.

Wahlberg, J. E., & Skog, E. (1963). The percutaneous absorption of sodium chromate (51Cr) in the guinea pig. *Acta Derm Venereol, 43*, 102-108.

WHO-IPCS-CICAD. (2013). WHO International Programme on Chemical Safety. Consise International Chemical Assessment Document 78. Inorganic Chromium (VI) Compounds. .

Wise, S. S., Schuler, J. H., Katsifis, S. P., & Wise, J. P., Sr. (2003). Barium chromate is cytotoxic and genotoxic to human lung cells. *Environ Mol Mutagen, 42*(4), 274-278. doi: 10.1002/em.10203

Wise, S. S., Schuler, J. H., Holmes, A. L., Katsifis, S. P., Ketterer, M. E., Hartsock, W. J., . . . Wise, J. P., Sr. (2004). Comparison of two particulate hexavalent chromium compounds: Barium chromate is more genotoxic than lead chromate in human lung cells. *Environ Mol Mutagen, 44*(2), 156-162. doi: 10.1002/em.20044

Wise, S. S., Holmes, A. L., & Wise, J. P., Sr. (2006). Particulate and soluble hexavalent chromium are cytotoxic and genotoxic to human lung epithelial cells. *Mutat Res, 610*(1-2), 2-7. doi: 10.1016/j.mrgentox.2006.06.005

Wise, S. S., & Wise, J. P., Sr. (2012). Chromium and genomic stability. *Mutat Res, 733*(1-2), 78-82. doi: 10.1016/j.mrfmmm.2011.12.002

WSNZ. (2016). Workplace Exposure Standards and Biological Exposure Indices. June 2016 8th Edition. Work Safe New Zealand. New Zealand Government. Retrieved 27 September, 2016, from http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices.

Wu, F. Y., Wu, W. Y., Kuo, H. W., Liu, C. S., Wang, R. Y., & Lai, J. S. (2001). Effect of genotoxic exposure to chromium among electroplating workers in Taiwan. *Sci Total Environ, 279*(1-3), 21-28.

Xie, H., Wise, S. S., Holmes, A. L., Xu, B., Wakeman, T. P., Pelsue, S. C., . . . Wise, J. P., Sr. (2005). Carcinogenic lead chromate induces DNA double-strand breaks in human lung cells. *Mutat Res, 586*(2), 160-172. doi: 10.1016/j.mrgentox.2005.06.002

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