Workplace Exposure Standard (WES) review

CHROMIUM (VI) COMPOUNDS
(CAS NO: 7440-47-3)

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New Zealand Government

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for chromium (VI) compounds, including calcium, lead and strontium chromates should be changed.

The WES review considers the potential for exposures to chromium (VI) compounds in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

It includes a recommendation to change the WorkSafe WES for chromium (VI) compounds, including calcium, lead and strontium chromate, which are currently set at a **WES-TWA** for chromium (VI) compounds (all chromium (VI) compounds except barium, lead and poorly soluble zinc chromates) of 0.01**mg/m³**, as Cr for **inhalable fraction**; for calcium chromate of 0.001mg/m³, as Cr for inhalable fraction; for lead chromate of 0.05mg/m³, as Cr for inhalable fraction; and, for strontium chromate of 0.001mg/m³, as Cr for inhalable fraction, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: Hexavalent chromium; Lead(II) chromate; Chromic acid, lead salt; Chrome Yellow; **C.I.** Pigment Yellow; Strontium chromate VI; Chromic acid, strontium salt; Strontium Yellow; C.I. Pigment Yellow 32.

2.0 Chemical and physical properties

Chromium (VI) compounds form a large group of chemicals with varying chemical properties, including corrosion-resistance, durability and hardness.

SUBSTANCE/SYNONYMS	CAS NUMBER	FORMULA	ATOMIC/ MOLECULAR WEIGHT
Ammonium dichromate (Chromic acid, diammonium salt)	7789-09-5	$(NH_4)_2Cr_2O_7$	252.06
Barium chromate	10294-40-3	$BaCrO_4$	253.33
Calcium chromate (Chromic acid, calcium salt; Calcium chrome Yellow)	13765-19-0	$CaCrO_4$	156.09
Chromium trioxide (Chromic acid; chromium anhydride)	1333-82-0	CrO_4	99.99
Lead chromate (Chromic acid, lead salt; Chrome Yellow G)	7758-97-6	$PbCrO_4$	328.18
Lead chromate oxide	18454-12-1	Pb_2OCrO_4	546.37
Potassium chromate (Chromic acid, dipotassium salt)	7789-00-6	K_2CrO_4	194.20
Potassium dichromate (Dichromic acid, dipotassium salt)	7789-50-9	$K_2Cr_2O_7$	294.18
Silver chromate	7784-01-2	Ag_2CrO_4	331.73
Sodium chromate (Chromic acid, disodium salt; Caswell No. 757)	7775-11-3	Na_2CrO_4	161.97
Sodium dichromate	10588-01-9	$Na_2Cr_2O_7$	261.97
Strontium chromate (Chromic acid, strontium salt)	7789-06-2	$SrCrO_4$	203.61
Zinc chromate (Chromic acid, zinc salt; CI Pigment Yellow)	13530-65-9	$ZnCrO_4$	181.36
Zinc chromate hydroxide (Basic zinc chromate)	15930-94-6	$Zn_2CrO_4(OH)_2$	280.74
Zinc potassium chromate hydroxide	11103-86-9	$KZn_2(CrO_4)_2(OH)$	418.85
Basic zinc potassium chromate	37300-23-5	$\approx 4\ ZnO \times K_2O \times 4\ CrO_3 \times 3H_2O$	825

DFG, 2012; **NIOSH**, 2013; **IPCS**, 2013

TABLE 1: Names, CAS numbers, synonyms, formulae and mass of some commonly used chromium (VI) compounds

Chemical and physical properties include:

SUBSTANCE	DESCRIPTION	MELTING POINT °C	BOILING POINT °C	SOLUBILITY
Ammonium dichromate	Orange	Decomposes at 180	–	Water: 308**g/L** (15°C); Insoluble in alcohol; slightly soluble in NH_3, acetone
Barium chromate		–	–	Water: 2.6g/L (15°C); Soluble in mineral acid
Calcium chromate	Yellow			Water: 22.3g/L (20°C)
Chromium trioxide	Red	196	Decomposes	Water: 625g/L (20°C); Soluble in alcohol, ether, sulphuric acid, nitric acid
Lead chromate	Yellow	844	Decomposes	Water: 0.058**mg/L** (20°C); Soluble in strong acids and alkalis; insoluble in acetic acid and ammonia
Lead chromate oxide		–	–	Water: Insoluble; Soluble in acid, alkali
Potassium chromate	Yellow	968.3; 975		Water: 629g/L (20°C); Insoluble in alcohol
Potassium dichromate	Red	398	Decomposes at 500	Water: 49g/L (0°C); 1,020g/L (100°C); Insoluble in alcohol
Silver chromate		Decomposes	–	Soluble in NH_4OH, KCN
Sodium chromate	Yellow	19.92	–	Water: 873g/L (30°C); Slightly soluble in alcohol; soluble in methanol
Sodium dichromate	Red	356.7	Decomposes at 400	Water: 2,300g/L (0°C); Insoluble in alcohol
Strontium chromate	Yellow	–	Decomposes ca. 500	Water: 1.2g/L (15°C); Soluble in HCl, HNO_3, acetic acid, NH_4 salts
Zinc chromate	Lemon-yellow	–	–	Water: 78–115mg/L; Soluble in acid, liquid NH_3; insoluble in acetone
Zinc chromate hydroxide				Water: 40mg/L
Zinc potassium chromate hydroxide				Water: 600–1,500mg/L
Basic zinc potassium chromate				Water: 2,500–5,000mg/L

DFG, 2012; NIOSH, 2013; IPCS, 2013

TABLE 2: Physicochemical properties of some commonly used chromium (VI) compounds

Health-related hazard classifications for chromium (VI) compounds include:

SUBSTANCE	HSNO CLASSIFICATION
Ammonium dichromate	6.1B (All); 6.1B (I); 6.1C (O); 6.1D (D); 6.5A; 6.5B; 6.6A; 6.7A; 6.8A; 6.9A (All); 6.9A (O); 8.2C; 8.3A
Chromium trioxide	6.1C (All); 6.1C (I); 6.1C (D); 6.1C (O); 6.5A; 6.5B; 6.6A; 6.7A; 6.8A; ; 6.9A (All); 6.9A (O); 8.2B; 8.3A
Lead chromate	6.6A; 6.7B; 6.8A; 6.9B (All); 6.9B (O)
Potassium chromate	6.3A; 6.4A; 6.5B; 6.6A; 6.7A
Sodium chromate	6.1B (All); 6.1B (I); 6.3A; 6.5B; 6.6A; 6.7A; 8.3A
Sodium dichromate	6.1A (All); 6.1A (I); 6.5A; 6.5B; 6.6A; 6.7A; 6.8A; 8.2C; 8.3A
Strontium chromate	6.1D (All); 6.1D (O); 6.7A
Zinc potassium chromate	6.1D (All); 6.1D (O); 6.5B; 6.7A

TABLE 3:
HSNO health-related hazard classifications of some chromium (VI) compounds (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.
[O] Oral exposure route.
[D] Dermal exposure route.
[I] Inhalation exposure route.

3.0
Uses

Chromium (VI) compound exposure can occur in various industries, including electroplating, welding and painting, and due to its presence in cement.

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)) (IPCS, 2013). Chromium is chiefly found as the trivalent form in nature, with chromium (VI) generally produced by industrial processes (IPCS, 2013; **SCOEL**, 2004).

The NIOSH review of hexavalent chromium (2013) noted that:

> "Chromium (VI) compounds include a large group of chemicals with varying chemical properties, uses, and workplace exposures. Their properties include corrosion-resistance, durability, and hardness. Workers may be exposed to airborne chromium (VI) when these compounds are manufactured from other forms of chromium (for example, the production of chromates from chromite ore); when products containing chromium (VI) are used to manufacture other products (for example, chromate-containing paints, electroplating); or when products containing other forms of chromium are used in processes that result in the formation of chromium (VI) as a by-product (for example, welding). In the marketplace, the most prevalent materials that contain chromium are chromite ore, chromium chemicals, ferroalloys, and metal. Sodium dichromate is the most common chromium chemical from which other chromium (VI) compounds may be produced. Chromium (VI) compounds commonly manufactured include sodium dichromate, sodium chromate, potassium dichromate, potassium chromate, ammonium dichromate, and chromium (VI) oxide. Other manufactured materials containing chromium (VI) include various paint and primer pigments, graphic arts supplies, fungicides, and corrosion inhibitors." (NIOSH, 2013)

In the US, the industries in which the largest numbers of workers are exposed to high concentrations of airborne chromium (VI) compounds include electroplating, welding and painting. Dermal exposure to chromium (VI) can also occur, most notably in the construction industry where chromium (VI) is present in cement (NIOSH, 2013).

Lead chromate is used in industrial surface coatings for metals, automotive, aerospace, and road markings; in inks; and, as pigments for plastics and ceramics **(NLM HSDB**, 2019a; **NICNAS**, 2015).

Strontium chromate is used as a corrosion inhibitor in pigments; in electrochemical processes to control the sulphur concentration of solutions; as a colourant in polyvinyl chloride resins; in aluminium flake coatings; in chrome plating; and, in pyrotechnics (NLM HSDB, 2019b; **NTP RoC**, 2016a).

Occupational exposure to chromium (VI) compounds can occur during production, storage, transportation and end-use.

Workers can be exposed in the workplace to chromium (VI) compounds via inhalation and eye or dermal contact.

The number of workers exposed or potentially exposed to chromium (VI) compounds in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 116,930 New Zealand workers were working in the areas of:

- basic organic chemical manufacturing
- basic inorganic chemical manufacturing
- synthetic resin and synthetic rubber manufacturing
- polymer film and sheet packaging material manufacturing
- rigid and semi-rigid polymer product manufacturing
- paint and coatings manufacturing
- cement, lime, plaster and concrete product manufacturing
- metal coating and finishing
- building construction
- heavy and civil engineering construction
- automotive body, paint and interior repair (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

The toxicological profiles of chromium (VI) compounds are considered to be largely driven by the bioavailability of chromium (VI) (NICNAS, 2015). As a generalisation, the less soluble the chromium (VI) compound, the less toxic for non-genotoxic endpoints. However, in contrast to this generalisation lead chromate and other poorly soluble chromium (VI) compounds have been shown to be more potent in genotoxicity and clastogenicity assays, while strontium chromate has been shown to be a potent tumour inducer in specific animal models (SCOEL, 2017; IPCS, 2013; DFG, 2012).

The toxicological database for lead chromate is relatively limited, and cross-reference is made to studies with other chromium (VI) compounds. One such reference compound is lead sulphochromate yellow, CAS No.: 1344-37-2; Pb(Cr,S)O_4; C.I. Pigment Yellow 34 [max. 15% Cr] (**ECHA REACH**, 2019a).

The toxicological database for strontium chromate is relatively limited, and cross-reference is made to studies with other chromium (VI) compounds.

4.1 Non-cancer

Humans

The NICNAS review of chromates and dichromates (insoluble) noted that:

> "Human exposure to high levels of airborne chromium(VI) in occupational and environmental settings produced symptoms of dizziness, headache, and weakness when the workers were over the chromate tanks. Additional studies are needed to provide conclusive information regarding the effect of chromium(VI) compounds on human neurological and behavioural changes (**ATSDR**, 2012)." (Reference cited in NICNAS, 2018).

Effects in humans exposed occupationally to airborne chromium (VI) compounds may include respiratory tract and eye irritation, which may lead to nasal septum ulceration and perforation, and increased incidence of respiratory tract cancer. Exposure to chromium (VI) compounds may also induce asthma (IPCS, 2013).

Occupational exposure by dermal contact to chromium (VI) compounds can result in deeply penetrating ulcers on the skin. Chromium (VI) is a frequent cause of allergic contact dermatitis, which can be a serious and long-term disability (IPCS, 2013).

Accidental or intentional ingestion of high doses of chromium (VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, haematological, hepatic, renal and neurological effects (IPCS, 2013).

The NLM HSDB for strontium chromate noted that:

> "If ingested, violent gastroenteritis, severe circulatory collapse and toxic nephritis may ensue." (NLM HSDB, 2019b).

The IPCS **CICAD** for inorganic chromium(VI) compounds noted:

> "In a retrospective cohort study of 2357 workers at a chromate production plant in Baltimore, Maryland, USA, first employed between 1 August 1950 and 31 December 1974, the clinical findings that had been identified by the plant physician (nasal irritation and ulceration, irritated skin, perforated eardrum and conjunctivitis) were analysed using percentages of the cohort with the various clinical findings, the time from hire to occurrence of the first findings, and the mean and median annual chromium(VI) concentrations for the job

title where the clinical findings first occurred. The most common findings were nasal irritation (68.1% of the cohort) and ulcerated nasal septum (62.9%), and the mean and median times on the job were shorter (<3 months) for these findings than for the other clinical findings (>7 months), which included irritated and ulcerated skin, dermatitis, perforated eardrum and conjunctivitis. The mean **TWA** annual exposures at time of diagnosis were approximately 25–36**µg** chromium(VI) per cubic metre [0.025–0.036mg/m^3] for all findings, with median exposure concentrations of 10–15µg chromium(VI) per cubic metre [0.010–0.015mg/m^3]. Chromium(VI) exposure was correlated with the occurrence of nasal septum ulceration (*P* = 0.0001), ulcerated skin (*P* = 0.004) and perforated eardrum (*P* = 0.03). The **relative risks** associated with an increase of 52µg chromium(VI) per cubic metre [0.052mg/m^3] were 1.20, 1.11 and 1.35 for ulcerated nasal septum, ulcerated skin and perforated eardrums, respectively. The authors noted that annual average exposure may not be a good predictor of irritative effects (Gibb *et al*., 2000a).

"In a steel mill, where exposure to chromium(VI) was generally below 0.5**µg**/m^3 [0.0005mg/m^3], no increase in respiratory symptoms, no sign of pneumoconiosis and no adverse effects on lung function were observed among workers who had worked for an average of 23 years. Similarly, in a 5-year follow-up, no decrease in lung function was observed (Huvinen *et al*., 1996, 2002b). In the same facility, no association was observed between exposure to chromium(VI) and nasal symptoms, nasal mucociliary clearance, frequency of cellular atypia or frequency of inflammatory cells. However, the chromium(VI)-exposed workers more often had livid or oedemic epithelium (Huvinen *et al*., 2002a).

"Respiratory symptoms, lung function and changes in nasal mucosa were studied in 43 chrome plating workers in Sweden exposed almost exclusively to chromic acid (chromium(VI) trioxide), with 22 persons exposed to chromic acid at an 8-hour mean concentration below 2µg chromium(VI) per cubic metre [0.002mg/m^3] and 21 persons exposed to 2µg chromium(VI) per cubic metre [0.002mg/m^3] and above. The highest 8-hour TWA exposure to chromium(VI) was 20µg/m^3 [0.020mg/m^3]; the highest peak exposure was 46µg/m^3 [0.046mg/m^3]. Exposure durations ranged from 0.2 to 23.6 years (median = 2.5 years). The reference group for lung function tests was a group of 119 automobile mechanics, and 19 office employees were used as controls for changes in the nasal mucosa. Exposure measurements were made with stationary samplers placed close to the chromic acid baths and with personal samplers. No subject with exposure to less than 1µg chromium(VI) per cubic metre [0.001mg/m^3] complained of subjective symptoms; the frequency of subjective symptoms was 4 out of 19 among workers with exposure less than 2µg/m^3 [0.002mg/m^3]. The clinical findings noted at or below 2µg chromium(VI) per cubic metre [0.002mg/m^3] were a smeary and crusty septal mucosa in 11 out of 19 workers and atrophied mucosa in 4 out of 19 workers. Severity of effect correlated better with highest (peak) exposure levels than with mean exposure levels. Nasal mucosal ulceration and septal perforation occurred in individuals exposed at 8-hour TWA concentrations of ≥2µg chromium(VI) per cubic metre [0.002mg/m^3] and at peak levels of ≥20µg chromium(VI) per cubic metre [0.02mg/m^3], nasal mucosal atrophy and irritation occurred at 8-hour TWA concentrations of ≥2µg chromium(VI) per cubic metre [0.002mg/m^3] and at peak exposure concentrations of 2.5–11µg chromium(VI) per cubic metre [0.0025–0.011mg/m^3], and no significant nasal effects were seen at peak exposure concentrations of 0.1–1.2µg chromium(VI) per cubic metre [0.0001–0.0012mg/m^3]. Non-smoking workers exposed to 8-hour TWA concentrations of ≥2µg chromium(VI) per cubic metre [0.002mg/m^3]

had slight, transient decreases in forced vital capacity, forced expiratory volume in 1 second (**FEV1**) and forced mid-expiratory flow during the workday. Workers exposed to less than 2µg chromium(VI) per cubic metre [0.002mg/m^3] showed no effects on lung function (Lindberg & Hedenstierna, 1983)." (References cited in IPCS, 2013).

The NICNAS assessment of lead chromates noted that based on information from chromates and dichromates (insoluble) compounds and selected lead-based pigments, lead chromate did not warrant a skin, eye or respiratory tract irritant hazard classification (NICNAS, 2015).

The ECHA REACH dossier on strontium chromate noted the irritation/corrosion potential in humans:

"At a strontium chromate plant, with poor hygienic conditions, cases of rhinitis and nasal ulceration were observed. In addition, this report (also referred to under skin irritation) showed increased chromium levels in biomonitoring samples. Also in studies examining signs of respiratory symptoms of chrome platers, the numbers of nasal perforation or ulceration have traditionally been increased, and these have generally been recognized as typical effects of soluble chromates. As there are no standard test methods available for respiratory irritation, and only limited data available, classification for respiratory irritation is suggested based on weight of evidence from occupational reports on various chromates." (ECHA REACH, 2019b).

The IPCS CICAD for inorganic chromium(VI) compounds noted:

"Cases of asthma with positive bronchial provocation tests to chromium salts have been described among workers exposed to chromium(VI) salts and among chromium electroplaters. The total number of verified cases is between 10 and 20. Case reports of asthma have also been described in stainless steel welders; whether the causative agent was chromium(VI) or nickel is not certain (Keskinen *et al*., 1980; Olaguibel & Basomba, 1989; Park *et al*., 1994; Shirakawa & Morimoto, 1996; Bright *et al*., 1997; Cruz *et al*., 2006; Fernandez-Nieto *et al*., 2006).

"In a sensitized individual, exposure via inhalation by a nebulizer to 0.029mg chromium(VI) per millilitre as sodium chromate caused an anaphylactoid reaction, characterized by dermatitis, facial angio-oedema, bronchospasms accompanied by a tripling of plasma histamine levels, and urticaria (Moller *et al*., 1986). Similar anaphylactoid reactions were observed in five individuals who had a history of contact dermatitis to chromium, after exposure, via nebulizer, to an aerosol containing 0.035mg chromium(VI) per millilitre as potassium dichromate (Olaguibel & Basomba, 1989)." (References cited in IPCS, 2013).

The NICNAS review of chromates and dichromates (insoluble) summarised the sensitisation potential in humans:

"Patch testing has identified chromium(VI)-sensitised workers in the printing and lithography industry, in automobile factories (where assemblers handled nuts, bolts, and screws), and in wet sandpapering of primer paint (where workers were exposed to zinc chromate). Other sources that resulted in chromium sensitivity included manufacturing match heads (which may contain barium chromate) (ATSDR, 2012).

> "Direct skin contact with chromium compounds results in an allergic response that is characterised by eczema or dermatitis. Chromium-induced allergic contact dermatitis is usually isolated to areas at the site of contact. The acute response phase lasts between a few days and a few weeks; it is characterised by erythema, oedema, and small and large blisters. The chronic phase is similar and may also include thickened, scaly, and fissured skin. Oral exposure to chromium(VI) has been shown to exacerbate dermatitis in sensitive individuals (ATSDR, 2012).
>
> "Several studies have attempted to estimate the exposure level required to elicit a dermal response in chromium-sensitised individuals, with exposure levels of 4–25**ppm** producing sensitisation and leading to chromium-induced allergic dermatitis. However, it is anticipated that the exposure level required to elicit a dermal response in sensitised individuals could be highly variable (ATSDR, 2012)." (Reference cited in NICNAS, 2018).

The NICNAS assessment of lead chromates noted that based on information from chromates and dichromates (insoluble) compounds, lead chromate should be classified as a contact sensitiser (NICNAS, 2015). The ECHA REACH dossier on lead sulfochromate yellow noted that based on the skin and respiratory sensitising properties of hexavalent chromium compounds, C. I. Pigment Yellow 34 should be classified as a skin and respiratory sensitiser, but this was not confirmed by tests for the pigment itself (ECHA REACH, 2019a).

The ECHA REACH dossier on strontium chromate noted the sensitisation potential in humans:

> "There are no reports on sensitisation caused by strontium chromate, but zinc chromate-containing primers have been reported to cause allergic contact dermatitis in humans. Moreover, soluble chromates show positive results in several animal skin sensitisation tests. Some case reports, supported by bronchial challenge tests, indicate that hexavalent chromium compounds may induce respiratory sensitisation, including occupational asthma. Strontium chromate has previously not been classified for sensitisation. Zinc chromate is currently classified for skin sensitisation (**Skin Sens. 1**), and soluble chromates are classified both for skin and respiratory sensitisation (Skin Sens. 1, **Resp. Sens. 1**). Based on read-across from zinc chromate, strontium chromate should also be classified as [sic] skin sensitiser." (ECHA REACH, 2019b).
>
> "Strontium chromate has not been reported to cause respiratory sensitisation. Data on respiratory sensitisation caused by zinc chromate is limited to a few old case reports, and compared to the amount of workers potentially exposed to various sparingly soluble chromates, the number of reported cases can be considered as very low. Other cases of occupational asthma have been reported among metalplating workers exposed to highly soluble chromium compounds. Some of these cases were evaluated and confirmed by bronchial challenge tests.
>
> "At the moment, there are no validated test methods for respiratory sensitisation.
>
> "No sparingly soluble chromates have previously been classified as respiratory sensitizers, but highly soluble chromates are classified for respiratory sensitisation under **EU**." (ECHA REACH, 2019b).

The ECHA REACH dossier on strontium chromate noted the repeated dose toxicity potential in humans:

> "A large number of studies are available relating to repeated exposure of workers to highly water-soluble Cr(VI) (**EU RAR** 2005). The main effects reported are irritant and corrosive responses in relation to inhalation and dermal exposure. These include inflammation in the lower respiratory tract, and nasal septum perforation in the upper respiratory tract. However, it is not possible to relate these effects to reliable measures of Cr(VI) exposure.
>
> "Nasal ulceration and perforation caused by exposure to chromates were recognized already in the 19th century. However, based on the available reports on nasal ulceration and perforation it is not possible to locate threshold doses for these effects (see reports described under title 'human information').
>
> "According to Cross *et al.* (1997) and EU RAR (2005), two reviews also covering the repeated inhalation experiments, it is not possible to identify with confidence a no observed adverse effect level (**NOAEL**) for Cr(VI) compounds." (References cited in ECHA REACH, 2019b).

The NICNAS review of chromates and dichromates (insoluble) summarised the reproductive/developmental toxicity in humans:

> "The chemicals in this group are not expected to be systemically available due to poor bioavailability, which may explain the lack of reliable data on reproductive and developmental toxicity. Toxicologically significant amounts of insoluble chromium(VI) are unlikely to be transported to reproductive organs or developing foetuses as the compounds are poorly absorbed and tend to act at the site of exposure." (NICNAS, 2018).

The IPCS CICAD for inorganic chromium(VI) compounds noted:

> "Studies involving workers exposed to chromium(VI) in stainless steel welding, dichromate production or electroplating did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers (Husgafvel-Pursiainen *et al.*, 1982; Littorin *et al.*, 1983; Nagaya, 1986; Nagaya *et al.*, 1991; Gao *et al.*, 1994; Benova *et al.*, 2002; Medeiros *et al.*, 2003). Similarly, no increase in the micronuclei in nasal mucosa was observed among workers in a ferrochrome smelter or stainless steel mill, where exposure to chromium(VI) was generally below 0.5μg/m^3 (Huvinen *et al.*, 2002a). No increases in micronuclei, sister chromatid exchanges or chromosomal aberrations were observed in the buccal mucosa of chromium platers (Benova *et al.*, 2002). No elevations in **DNA** strand breaks or hydroxylation of deoxyguanosine were detected in lymphocytes of workers exposed to chromium(VI) during the production of dichromate (Gao *et al.*, 1994). In contrast, other studies involving electroplaters, welders or ferrochromium alloy foundry workers reported higher levels of DNA strand breaks, DNA–protein crosslinks, micronuclei, chromosomal aberrations or sister chromatid exchanges in workers exposed to chromium(VI) compared with controls (Sarto *et al.*, 1982; Stella *et al.*, 1982; Koshi *et al.*, 1984; Deng *et al.*, 1988; Lai *et al.*, 1998; Werfel *et al.*, 1998; Vaglenov *et al.*, 1999; Wu *et al.*, 2000, 2001; Halašová *et al.*, 2001; Benova *et al.*, 2002; Gambelunghe *et al.*, 2003; Medeiros *et al.*, 2003).

> "The studies in humans were limited in several aspects. Generally, the levels of exposure to chromium(VI) were not known, and co-exposure to other potentially active compounds (that is, ultraviolet rays and other potentially genotoxic metals) occurred in several studies. Some of the studies used groups that were too small to have the statistical power to reliably assess the cytogenetic changes in workers.
>
> "Urine samples from six workers working in chromium plating factories were tested for the induction of unscheduled DNA synthesis in pleural mesothelial cells. The mean total chromium concentration in the urine samples was 11.7 ± 8.8**µg**/l. The urine from five of the workers showed a significant elevation in unscheduled DNA synthesis over control subjects who were nonsmokers (Pilliere *et al*., 1992)." (References cited in IPCS, 2013).

Animals

Oral exposure of animals to very high doses of chromium (VI) compounds has resulted in gastrointestinal, hepatic, renal, immunological, haematological, neurological, developmental and reproductive effects. Dermal exposure of animals to chromium (VI) compounds has resulted in skin ulcers and allergic response (IPCS, 2013).

Among the effects of oral exposure of rats and mice to drinking-water containing chromium (VI) for 13 weeks or 2 years were transient anaemia, lesions in the oral cavity and intestines, inflammation in the liver, lymph nodes and pancreas and tumours in the oral cavity in rats and in the small intestine in mice (IPCS, 2013).

The NICNAS assessment of lead chromates noted that lead chromate was of low acute oral toxicity in animal tests with a **LD_{50}** in mice >12,000**mg/kg b.w**.; and, expected to be of low acute dermal toxicity due to the low dermal absorption of insoluble chromium VI compounds (NICNAS, 2015). NICNAS also noted that based on information on chromate and dichromate (insoluble compounds), lead chromate should be seen as an acute inhalation hazard (NICNAS, 2015).

The ECHA REACH dossier on strontium chromate noted for the acute toxicity in experimental animals:

> - Acute inhalation toxicity of strontium chromate in rats, **LC_{50}** = 0.27 to 0.51mg/L air [**OECD TG** 403; Reliability, 1]:
>
> "Male and female albino rats were exposed four [sic] 4-hours nose-only to target concentrations 0.25, 0.5 and 1mg/L air of strontium chromate (analytical concentrations were 0.27, 0.51 and 0.81mg/L air, respectively), and observed for 14 days after the exposure. At the concentrations of 0.51 and 0.81mg/L, all animals died within eight days. The 0.27mg/L concentration resulted in the death of two animals. Tachypnea and ruffled fur as well as body weight loss were seen at all aerosol concentrations. Treatment related changes were discoloration and incompletely collapsed lungs, as well as hardened and pale lungs."
> - Acute oral toxicity of strontium chromate in male rats, LD_{50} = 3,118mg/kg b.w. [no guideline; Reliability, 3].
> - Acute toxicity of strontium chromate in male rats via intratracheal instillation, LD_{50} = 16.6mg/kg b.w. [no guideline; Reliability, 3].
>
> (ECHA REACH, 2019b).

No acute dermal toxicity studies for strontium chromate were reported in ECHA REACH (2019b) or noted in the DFG review (DFG, 2012).

The ECHA REACH dossier on lead sulfochromate yellow noted the irritation/corrosion potential in experimental animals:

> "One study with [sic] conducted according to the OECD guideline 404 (Acute Dermal Irritation/Corrosion; Ciba-Geigy LTD, 1983 is available, where the test substance is reported to be not irritating to the rabbit skin."
>
> "The eye irritation capacity of the test substance can be evaluated based on structure analogy to CI Pigment Red 104 (CAS No: 12656-85 -8) which was shown in at least two studies (one according to the OECD Guideline 405: Acute Eye Irritation / Corrosion) to be not irritating to the rabbit eye."
>
> "Respiratory irritation: No data available." (ECHA REACH, 2019a).

The ECHA REACH dossier on strontium chromate noted the irritation/corrosion potential in experimental animals:

> "No signs of skin irritation were observed in a standard rabbit OECD test. Cases of skin ulceration were, however, reported at a strontium chromate plant with poor hygienic conditions. This report also indicated high chromium concentrations in biomonitoring samples. As only one report from a single factory was available, and it did not clearly describe, for example, what other exposures the workers had, it was concluded that the data obtained in the guideline animal skin irritation test was more reliable. Therefore the standard animal test was selected as key study, and according to the results of the test no classification is suggested for skin irritation.
>
> "Strontium chromate was slightly irritating in a standard OECD rabbit eye irritation test. Based on the classification criteria, no classification is required for this substance.
>
> "There are no animal data on respiratory irritation caused by chromates." (ECHA REACH).

The NICNAS assessment of lead chromates noted that there was no data available on the sensitisation potential in experimental animals (NICNAS, 2015).

The ECHA REACH dossier on strontium chromate noted the sensitisation potential in experimental animals:

> "There are no reports on sensitisation caused by strontium chromate, but zinc chromate-containing primers have been reported to cause allergic contact dermatitis in humans. Moreover, soluble chromates show positive results in several animal skin sensitisation tests. Some case reports, supported by bronchial challenge tests, indicate that hexavalent chromium compounds may induce respiratory sensitisation, including occupational asthma. Strontium chromate has previously not been classified for sensitisation." (ECHA REACH, 2019b).

The NICNAS review of lead chromates summarised the repeated dose toxicity in experimental animals:

> "In a repeated dose toxicity study similar to OECD TG 409, the lowest observed adverse effect level (LOAEL) of 75.4mg/kg bw/day determined from a 90-day study in beagle dogs (C.I. Pigment Yellow 34—CAS No. 1344-37-2) was based on haematological changes and lesions involving the kidney, bone marrow, intestines and liver (REACH).

> "In another 90-day oral gavage study in male and female Sprague Dawley rats, a LOAEL of 1600mg/kg bw/day was reported after exposure to C.I. Pigment Yellow 34 (CAS No. 1344-37-2). Effects observed at this concentration included a statistically elevated kidney to body weight ratio, and liver to body weight ratio, in males. (REACH)." (References cited in NICNAS, 2015).

The NICNAS review of chromates and dichromates (insoluble) summarised the repeated dose toxicity in experimental animals:

> "In a non-guideline study (summary only) C57BL/6 mice were exposed to 0.043mg/L of chromium(VI) as calcium chromate dust for 18 months (five days/week for 5.5 hours/day). The LOAEL was determined to be 0.043mg chromium(VI)/L (0.129mg/L calcium chromate) based on epithelial necrosis and marked hyperplasia of the large and medium bronchi, with numerous openings in the bronchiolar walls (ATSDR, 2012; REACH). A no observed adverse effect level (NOAEL) could not be determined as only one concentration level of the chemical was studied.
>
> "Effects that may be indicative of altered immune function (altered white blood cell counts and cytokine levels in bronchoalveolar lavage—**BAL** fluid) were observed in rats exposed to 0.0036mg chromium(VI)/L as barium chromate for 2–4 weeks. However, results of this study are difficult to interpret, since effects were not clearly adverse, only one exposure level of the chemical was studied, and histopathological assessment of respiratory tissues (or other tissues) was not conducted (ATSDR, 2012).
>
> "Many chronic exposure studies relating to exposure through inhalation of insoluble particulate chromium(VI) compounds do not clearly identify adverse effects or are older studies that do not report sufficient experimental details to make a definite classification (ATSDR, 2012).
>
> "Given the effects reported and their similarity to effects seen following acute toxicity by inhalation, a hazard classification is warranted. Sparingly soluble and insoluble chromium(VI) compounds that are inhaled take longer to clear the lungs than soluble chromium(VI) compounds (ATSDR, 2012); the risk of adverse effects from repeated exposure increase when a chemical accumulates in the organ." (References cited in NICNAS, 2018).

The IPCS CICAD for inorganic chromium(VI) compounds concluded that:

> "the fertility of rats was not affected by inhalation of chromium(VI) in limited studies. Oral exposure to sodium or potassium dichromate and chromium trioxide may affect the fertility of rats and mice at high doses, but extensive NTP (1996a, 1996b, 1997) studies found no effects on fertility or reproduction of male or female rats or mice given a range of doses of potassium dichromate in the diet." (References cited in IPCS, 2013).

The ECHA REACH dossier on lead sulfochromate yellow noted the reproductive/developmental toxicity in experimental animals:

> "In the voluntary Risk Assessment Report for lead and inorganic lead compounds, all available studies in humans and experimental animals have been evaluated for the observed effect of lead upon sexual maturation and semen quality, pregnancy outcome, and neurobehavioural effects of prenatal and postnatal lead exposure. Lead compounds were found to have effects on male fertility, female reproductive parameters, and on neurobehavioural development, which was the most critical effect.

"Effects on neurobehavioural performance after [sic] pre-natal and post-natal have been reported in several animal studies. However, the available data are inadequate to establish dose-effect relationships. Observed effects are upon early measures of mental and physical development, but could not be associated with impacts upon measures such as IQ. Furthermore, effects of prenatal lead exposure can be difficult to dissociate from those of postnatal exposure. Effects of pre-natal lead exposure are secondary in magnitude to those produced by exposures after birth. The **vRAR** suggest a blood lead level above 10**µg/dL** (in females) to take into account for the risk assessment with regard to developmental effects.

"In the opinion of the Scientific Committee on Health and Environmental Risks (**SCHER**) on the voluntary Risk Assessment Report (vRAR), it is concluded that the health part of the vRAR is of good quality, comprehensive, and that the exposure and effects assessment follow the Technical Guidance Document.

"In the risk assessment on lead from food which was performed by the European Food Safety Authority (**EFSA**, 2010), the Bench Mark Dose approach (**BMD**) is used to estimate the **BMDL01**, which is the blood-lead concentration corresponding to the lower limit 95-percentile of the Confidence Interval of the chosen Bench Mark Response of an IQ deficit of 1 IQ point. The **BMR** is chosen and set at 1 IQ point by the **CONTAM** panel of EFSA. Using this approach, the BMDL01 for lead was estimated to be 1.2µg/dL (mentioned as 12µg/L by EFSA).

"A supporting study is included in the dossier in which adverse changes were observed when female Swiss albino mice were treated with potassium dichromate at 0, 53.2, 101.1, and 152.4mg of eq. chromium(VI)/kg/day in drinking at days 6–14 of gestation (Junaid *et al*., 1996).

"The number of dead fetuses (higher in the high-dose group), fetal weight (lower in both intermediate- and high-dose groups; high dose = 1.06g, intermediate dose = 1.14g) were changed as compared to the control value of 1.3g. A dose-response relationship was also observed in the number of resorption sites (0.31 for controls, 1.00 for the low dose, 1.70 for the intermediate dose, and 2.30 for the high dose), as well as a significantly greater incidence of post-implantation loss (in the two highest-dose groups of 21 and 34.60% as compared to control value of 4.32%).

"The gross structural abnormalities observed were drooping of the wrist (carpal flexure) and subdermal hemorrhagic patches on the thoracic and abdominal regions (in 16% in the offspring of the high-dose group). Significant reduced ossification in nasal frontal, parietal, interparietal, caudal, and tarsal bones were observed only in the 152.4mg chromium(VI)/kg/day-treated animals." (References cited in ECHA REACH, 2019a).

The ECHA REACH dossier on strontium chromate noted the reproductive/developmental toxicity in experimental animals:

"No studies on reproductive toxicity of strontium chromate have been found. Data on highly soluble chromates show a varying range of effects on fertility or development. Soluble chromates (potassium dichromate, sodium chromate, sodium dichromate and ammonium dichromate) are classified for reproductive toxicity (**Repr. 1B**) in EU.

> "A well-conducted 2 -generation continuous breeding study (NTP 1997) with mice did not show any significant fertility effects even at the highest concentration of potassium dichromate (up to 30mg Cr(VI)/kg/day). The other relevant study described in the assessment (Junaid *et al*. 1996b) showed a NOAEL of 63mg Cr(VI)/kg/day for fertility effects. The other studies focused mainly on effects on testes and ovaries and did not reveal direct fertility effects.
>
> "Although there is no specific information on the toxicokinetics of strontium chromate, the available data on other sparingly soluble chromates suggest that chromates can enter the body via inhalation or at lesser extent via gastrointestinal tract (see Toxicokinetics). Therefore, the reprotoxic risk of these chromates cannot be excluded." (References cited in ECHA REACH, 2019b).

Chromium (VI) has also been shown to be genotoxic in *in vivo* and *in vitro* tests (IPCS, 2013).

The SCOEL recommendation on hexavalent chromium noted:

> "Medium or sparingly soluble chromates such as those of calcium, strontium and zinc have also yielded positive results in bacterial and mammalian cell assays. In most tests, the genotoxic activity was enhanced by prior solubilisation with sodium hydroxide." (SCOEL, 2004).

The NLM HSDB dossier on lead chromate summarised the genotoxic potential in *in vitro* test systems:

> "The potential mutagenicity of lead chromate was tested by following [a] battery of microbial tests: the Escherichia coli pola+/pola- survival test; the Salmonella/microsome his+ reversion assay; the E coli trp+ reversion test plate assay; the E coli gal+ forward mutation test; & the Saccharomyces cerevisiae assay for mitotic recombination. Lead chromate was mutagenic in Salmonella & in Saccharomyces. Metabolic activation by rat liver homogenate (S9) was not required. Apparently, chromate ion is responsible for mutagenicity of lead chromate. An insoluble chromic compound, lead chromate ($PbCrO_4$), was not cytotoxic nor mutagenic on V79 cells, probably because it is taken up by the cells very slowly." (NLM HSDB, 2019a).

The SCOEL recommendation on chromium VI compounds noted for lead chromate:

> "The formation of DNA adducts appears to play an important role in Cr VI-induced genotoxicity (Hartwig, 2013; Wise & Wise, 2012). Soluble Cr 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 5µg/m^2 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 0.58µm and barium chromate particles from 0.4 to 32µm 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/m^2 (Wise, Holmes,

> & Wise, 2006). Lead chromate in concentrations of 0.5 and 1µg/m² 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/m² caused an increase in deletions in the **gpt** gene in a cell line derived from V79 cells (Klein *et al*., 2002)." (SCOEL, 2017).

The DFG **MAK** Value Documentation on chromium (VI) compounds summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "Strontium chromate was found to have genotoxic effects in bacteria and mammalian cells (De Flora *et al*. 1990)." (Reference cited in DFG, 2012).

4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of chromium (VI) compounds concluded that:

> There is *sufficient evidence* in humans for the carcinogenicity of chromium (VI) compounds.
>
> There is *sufficient evidence* in experimental animals for the carcinogenicity of chromium (VI) compounds.

With an overall evaluation that:

> Chromium (VI) compounds are *carcinogenic to humans* (Group 1) (IARC, 2012).
>
> "Chromium (VI) compounds cause cancer of the lung. Also positive associations have been observed between exposure to Chromium (VI) compounds and cancer of the nose and nasal sinuses." (IARC, 2012)

The International Agency for Research on Cancer [IARC] evaluation of inorganic and organic lead compounds concluded that:

> There is *sufficient evidence* in experimental animals for the carcinogenicity of lead acetate, lead subacetate, lead chromate, and lead phosphate. (IARC, 2006).

The US National Toxicology Program [NTP] Report on Carcinogens [RoC], Fourteenth Edition concluded that:

> "Chromium hexavalent (VI) compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans." (NTP RoC, 2016a).

And,

> "Lead and lead compounds are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals." (NTP RoC, 2016b).

Humans

The IARC Monograph on chromium (VI) compounds concluded that:

> "The large majority of informative cohort studies indicate that there is an excess risk of lung cancer among workers exposed to chromium (VI), particularly in chromate production, chromate pigment production, and chromium electroplating. It is unlikely that any biases or chance can explain these findings.
>
> "There are some case reports, cohort studies and case-control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to chromium (VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports." (IARC, 2012).

The meta-analyses carried out by Cole and Rodu (2005) and Steenland *et al*. (1996) clearly show a significantly increased risk of lung cancer in workers exposed to chromium (VI) in chromate (pigment) production and in chrome-plating plants. It is not clear whether exposure to chromium (VI) contributes to an increase in lung cancer risk also where welding is involved. (References cited in DFG, 2012).

In addition, there is evidence of a possibly increased risk of cancer in the region of the nasal epithelium and the nasal sinuses after exposure to chromium (VI) compounds (DFG, 2012).

The NIOSH 2013 review on chromium (VI) compounds based its quantitative risk assessment on several studies and meta-analyses, including that on [sic] the Baltimore cohort (Gibb *et al*., 2000b) because it had the greater number of lung cancer deaths, better smoking histories, and a more comprehensive retrospective exposure archive (NIOSH, 2013):

> "Gibb *et al*. [2000b] conducted a retrospective analysis of lung cancer mortality in a cohort of Maryland chromate production workers first studied by Hayes *et al*. [1979]. The cohort studied by Hayes *et al*. [1979] consisted of 2,101 male salaried and hourly workers (restricted to 1,803 hourly workers) employed for at least 90 days between January 1, 1945, and December 31, 1974, who had worked in new and/or old production sites. Gibb *et al*. [2000b] identified a study cohort of 2,357 male workers first employed between 1950 and 1974. Workers who started employment before August 1, 1950, were excluded because a new plant was completed on that date and extensive exposure information began to be collected. Workers starting after that date, but with short-term employment (that is, < 90 days) were included in the study group to increase the size of the low exposure group. The Hayes *et al*. [1979] study identified deaths through July 1977. Gibb *et al*. [2000b] extended the follow-up period until the end of 1992, and included a detailed retrospective assessment of Cr(VI) exposure and information about most workers' smoking habits. The mean length of employment was 3.3 years for white workers (n = 1,205), 3.7 years for nonwhite workers (n = 848), 0.6 years for workers of unknown race (n = 304), and 3.1 years for the total cohort (n = 2,357). The mean follow-up time ranged from 26 years to 32 years; there were 70,736 person-years of observation. The mean cumulative exposures to Cr(VI) were 0.18mg/m^3-years for nonwhite employees (n = 848) and 0.13mg/m^3-years for white employees (n = 1,205). The mean exposure concentration was 43µg/m^3 [0.043mg/m^3] [Park and Stayner 2006; NIOSH 2005b].

> "Lung cancer mortality ratios increased with increasing cumulative exposure (that is, mg CrO_3/m^3-years) – from 0.96 in the lowest quartile to 1.57 (**95% CI** 1.07–2.20; 5-year exposure lag) and 2.24 (95% CI 1.60–3.03; 5-year exposure lag) in the two highest quartiles. The number of expected lung cancer deaths was based on age-, race-, and calendar year-specific rates for Maryland. Proportional hazards models that controlled for the effects of smoking predicted increasing lung cancer risk with increasing Cr(VI) cumulative exposure (relative risks: 1.83 for second exposure quartile, 2.48 for third exposure quartile, and 3.32 for fourth exposure quartile, compared with first quartile of cumulative exposure; confidence intervals not reported; 5-year exposure lag) [Gibb *et al*. 2000b]." (References cited in NIOSH, 2013).

The IPCS CICAD for inorganic chromium(VI) compounds noted that:

> "Luippold and co-workers (2003) reported findings of a retrospective cohort mortality study of former employees of the chromate production plant in Painesville, Ohio, USA, a facility earlier studied by Mancuso (1975, 1997a, 1997b). The cohort consisted of 493 workers employed for at least 1 year beginning in 1940 or later. The cohort did not overlap with the previous studies by Mancuso (1975, 1997a, 1997b), which included only workers employed between 1931 and 1937. The exposure assessment was based on over 800 air sampling measurements from 21 industrial hygiene surveys describing airborne concentrations of chromium(VI), encompassing the years 1943–1971. A job–exposure matrix was constructed for 22 exposure areas for each month of plant operation from January 1940 to April 1972, when the plant closed. Gaps in the matrix—months between exposure surveys—were filled by computing from area sampling data the arithmetic mean concentration, averaged by exposure area, over three time periods (1940–1949, 1950–1964, 1965–1971). Exposure to chromium(III) was not estimated. The mean cumulative chromium(VI) exposure was 1.58(mg/m^3)·years (standard deviation [**SD**] = 2.5(mg/m^3)·years; range = 0.003–23(mg/m^3)·years) for the total cohort and 3.28(mg/m^3)·years (SD = 4.59(mg/m^3)·years; range = 0.06–23(mg/m^3)·years) for the workers who died from lung cancer. Cumulative exposure total cohort and 3.28(mg/m^3)·years categories were formed, and person-years and observed deaths were assigned to these categories in a time-dependent manner. **SMRs** were calculated based on the population of the USA as a whole and the population of the state of Ohio. The observed/expected ratio for lung cancer was 51/21.2 for Ohio (SMR = 241, 95% CI = 180–317). Increased lung cancer SMRs were associated with workers hired during the first two decades, with the highest excess for workers hired between 1940 and 1949 (SMR = 326, 95% CI = 220–465). SMRs increased with the duration of employment and for employees working 20 or more years (SMR = 497, 95% CI = 328–723). SMRs were also increased with time since first exposure for 0–9 years and 10–19 years and were dramatically increased for more than 20 years since first exposure. In a related study (Crump *et al*., 2003), the data were analysed using relative risk and additive risk dose–response models. The estimated lifetime additional risk of lung cancer mortality associated with 45 years of occupational exposure (8 hours/day exposure on 240/365 days/year from the age of 20 years to 65 years) to 1µg chromium(VI) per cubic metre was 0.002 05 for the relative risk model and 0.002 16 for the additive risk model, assuming a linear dose–response relationship for cumulative exposure with a 5-year lag. For environmental exposure (1µg/m^3 for 24 hours/day over a lifetime), the corresponding excess risks were 0.009 78 (90% CI = 0.006 40–0.0138) and 0.0125 (90% CI = 0.008 33–0.0175) for the relative and additive risk models, respectively (Crump *et al*., 2003).

> "In addition to lung cancer, increased risks of cancer of the nasal cavity (see Appendix 7) have consistently been reported in workers involved in chrome plating and chromate production.
>
> "Some occupational cohort studies (Langård *et al*., 1980, 1990; Silverstein *et al*., 1981; Korallus *et al*., 1993; Rosenman & Stanbury, 1996; Sorahan & Harrington, 2000), but not all (Axelsson *et al*., 1980; Satoh *et al*., 1981; Korallus *et al*., 1982, 1993; Davies *et al*., 1991; Itoh & Shimada, 1996; Rafnsson *et al*., 1997; Boice *et al*., 1999), also report elevated mortality from cancer of the stomach, but the relative risks were low, and only in two studies was statistical significance for the cohort or a subcohort reached. Thus, the contribution of chance, bias and confounding in this association cannot be excluded. Similarly, for cancer of the whole gastrointestinal tract, some studies report a positive association with exposure to chromium(VI) (Enterline, 1974; Franchini *et al*., 1983; Horiguchi *et al*., 1990; Deschamps *et al*., 1995), but others do not (Hayes *et al*., 1979, 1989; Dalager *et al*., 1980; Bertazzi *et al*., 1981; Luippold *et al*., 2005; Birk *et al*., 2006)." (References cited in IPCS, 2013).

The **ACGIH**® review of lead chromate noted:

> "Davies (1978, 1979) studied three small British factories engage [sic] in the manufacture of chrome pigments. In the two factories where both $PbCrO_4$ and zinc chromate ($ZnCrO_4$) pigments were produced, a statistically significant excess of lung cancer deaths was found in workers with "high" and "medium "levels of exposure (observed/Expected ratios: Factory A, 18/8.17 = 2.20; Factory B, 7/1.43 = 4.90). In the factory where only $PbCrO_4$ pigment was produced, there was a very small cohort size that limited the finding of a statistically significant excess. No information was provided on smoking habits.
>
> "Frentzel-Beyme (1983) studied male chromate pigment workers from three German and two Dutch factories who were employed between 1945 and 1976. Although the primary exposure was to $PbCrO_4$, $ZnCrO_4$ was also produced at all factories. Inclusion in the study required a minimum employment of at least 12 months. Excess deaths from lung cancer were found in production and maintenance workers. Although a positive cancer study, it suffered from mixed exposures, incomplete follow-up of the cohort, and inconsistent sources of information for causes of death." (References cited in ACGIH®, 2018a).

The NLM HSDB dossier on lead chromate noted:

> "In 1975, five manufacturers of chromate pigment in Japan were examined in a study of the carcinogenicity of chromates. These companies were producing lead chromate, zinc chromate, molybdate orange and/or strontium chromate. The current study covers a cohort of 666 workers involved in the manufacture of chromate pigment for at least 1 year between 1950 and 1975. The workers were followed up for 15–40 years, until 1989. Many previous reports have found an excess lung cancer risk among workers involved in the manufacture of chromate pigments and chromate chemicals. In the current study, subjects were classified on the basis of years worked, years of observation, characteristics of company, type of work engaged in for the longest period of time, and involvement in the manufacture of zinc chromate. Mortality was compared with that of all Japanese males by means of the person-year method. The route of exposure was primarily inhalation through the respiratory system. None of the results showed statistically significant differences that would suggest an excess risk for malignant neoplasms, particularly lung cancer, among workers engaged in the manufacture of chromate pigment in Japan." (Kano *et al*., 1993 cited in NLM HSDB, 2019a).

The IARC evaluation of inorganic and organic lead compounds noted:

> "Sheffet *et al*. (1982) studied mortality among 1296 white and 650 non-white men in a pigment plant producing lead and zinc chromates in the USA who were employed for at least 1 month between 1940 and 1969, and followed through 31 March 1979. Moderate exposure was defined as work in jobs with an average exposure of 0.5–2mg/m^3 airborne chromium, while high exposure was defined as >2mg/m^3 airborne chromium; 76% of the cohort had high or moderate exposure. A statistically significant relative risk of 1.6 (95% CI, 1.1–2.2; 31 deaths) for lung cancer was found among male employees, increasing to a significant 1.9 for those exposed for at least 2 years to moderate or high exposure. Stomach cancer had a SMR of 2.0 (95% CI, 0.9–3.6; 8 deaths). SMRs varied depending on whether or not those decedents with cause of death unknown (15%) were excluded from the observed count of lung cancers or added in proportion corresponding to the distribution of observed deaths with known causes. [SMRs for other cancers were calculated, but numbers were small and there were no significant findings.]" (Reference cited in IARC, 2006).

While the role of strontium chromate in the excess risk of cancers noted in these studies was not elucidated, strontium chromate is associated with chromate production, chromate pigment production and chromium electroplating, and could have contributed to the total exposure.

The ECHA REACH dossier on strontium chromate noted that:

> "The epidemiological evidence on the inhalation carcinogenicity of poorly soluble hexavalent chromium is obvious. Tumors have been produced in nearly every study utilizing the slightly soluble or insoluble particulates such as zinc, lead, strontium and sintered calcium chromate. A large number of published reports show that particulate chromates embody the highest risk because of adhesion to the cell surface followed by slow but chronic dissolution in the immediate microenvironment of the cell surface allowing released chromate oxyanions to escape extracellular reduction and be absorbed into the cell. Specific epidemiological studies where strontium chromate had been the sole or principal exposing agents do not exist. However, in some cohorts Sr-chromate exposures have been likely. Because the carcinogenic potential originates from the Cr(VI)-anions, this report reviews epidemiological studies where the exposing agents have been hexavalent chromium compounds. Exposures in various industries to hexavalent chromium have had association with elevated risks of respiratory system cancers." (ECHA REACH, 2019b).

Animals

The NIOSH 2013 review on chromium (VI) compounds summarised that the body of animal studies supported the classification of chromium (VI) compounds as occupational carcinogens (NIOSH, 2013):

> "The few chronic inhalation studies available demonstrate the carcinogenic effects of Cr(VI) compounds in mice and rats [Adachi *et al*. 1986, 1987; Glaser *et al*. 1986]. Animal studies conducted using other respiratory routes of administration have also produced positive results with some Cr(VI) compounds. Zinc chromate and calcium chromate produced a statistically significant ($P<0.05$) number of bronchial carcinomas when administered via an intrabronchial pellet implantation system [Levy *et al*. 1986]. Cr(VI) compounds with a range of solubilities were tested using this system.

Although soluble Cr(VI) compounds did produce tumors, these results were not statistically significant. Some lead chromate compounds produced squamous carcinomas, which although not statistically significant may be biologically significant because of the historical absence of this cancer in control rats.

"Steinhoff *et al*. [1986] administered the same total dose of sodium dichromate either once per week or five times per week to rats via intratracheal instillation. No increased incidence of lung tumors was observed in animals dosed five times weekly. However, in animals dosed once per week, a statistically significant ($P<0.01$) tumor incidence was reported in the 1.25mg/kg exposure group. This study demonstrates a dose-rate effect within the constraints of the experimental design. It suggests that limiting exposure to high Cr(VI) levels may be important in reducing carcinogenicity. However, quantitative extrapolation of these animal data to the human exposure scenario is difficult.

"Animal studies conducted using nonrespiratory routes of administration have also produced positive results with some Cr(VI) compounds [Hueper 1961; Furst 1976]. These studies provide another data set for hazard identification.

"IARC [2012] concluded "there is sufficient evidence in experimental animals for the carcinogenicity of chromium (VI) compounds".

"Molecular toxicology studies provide support for classifying Cr(VI) compounds as occupational carcinogens. They demonstrate the cytotoxic and genotoxic effects associated with carcinogenesis of Cr(VI) compounds." (References cited in NIOSH, 2013).

The IPCS assessment of inorganic chromium (VI) compounds summarised the carcinogenicity data in experimental animals:

"Comparative studies on the carcinogenic potency of different chromium(VI) compounds have been reported by Levy & Venitt (1986) and Levy *et al*. (1986). In these studies, highest frequencies of lung tumours were observed in rats dosed with strontium, zinc and calcium chromates, with lower frequencies observed after exposure to lead and sodium chromates, as well as chromic acid. However, as chromic acid and alkali chromates are readily soluble in water, the pulmonary dosing with these chemicals in this experimental setting is a single-dose approach, whereas dosing with the less soluble compounds yields a long-term local exposure. Thus, it is not clear that the relative carcinogenic potencies observed are relevant to the human exposure situation (continuous long-term exposure)." (References cited in IPCS, 2013).

The IARC evaluation of chromium (VI) compounds noted that:

"Lead chromate (and its derived pigments), administered by subcutaneous injection (Maltoni, 1974, 1976; Maltoni *et al*., 1982) or intramuscular injection cause malignant tumours at the site of injection and renal tumours (Furst *et al*., 1976) in rats. Subcutaneous administration of basic lead chromate caused local sarcomas in rats (Maltoni, 1974, 1976; Maltoni *et al*., 1982)." (References cited in IARC, 2012).

The ACGIH® review of lead chromate noted:

> "Levy *et al*. (1986) conducted a 2-year study on groups of 100 rats involving intratracheal implantation of 21 chromium-containing materials, including 7 lead chromate compounds. Each compound was mixed with an equal amount of cholesterol (sheep fat) to form a pellet that was implanted into the left bronchus of an anesthetized rat. The precise dosage information was not specified. Of the 700 animals exposed to a lead chromate compound, four developed carcinoma of the lung (one each for exposure to pure $PbCrO_4$, "Primrose Chrome Yellow," "LD Chrome Yellow Supra 70 FS," and "Medium Chrome Yellow"). None of the 100 control animals developed carcinoma of the lung. The small number of lung cancers found in the exposed animals makes interpretation of the results difficult, and the mode of administration may not be relevant to inhaled materials." (Reference cited in ACGIH®, 2018a).

The ECHA REACH dossier on strontium chromate summarised the Levy *et al*. (1986) study:

> "Two commericial [sic] strontium chromate preparations were strongly carcinogenic (incidences 43/100 and 62/100) when brochial [sic] carcinomas were detected two years after intrabrochial [sic] pellet inplantation [sic] in rats. The effect was stronger than with calcium chromate (25/100). Ba-, Pb-, and Zn-chromate did not show increased tumour incidence when exposed similarly." (ECHA REACH, 2019b).

The IARC Monograph on chromium (VI) compounds noted that strontium chromate had been reported to induce local sarcomas in rats after intrapleural and intramuscular administration (IARC, 2012).

The ECHA REACH dossier on strontium chromate summarised the Hueper (1961) study:

> "Pellets of strontium chromate were implanted in the pleural cavity or intramuscularly in the right thigh of rats and left there for their whole life span (maximum 24 months). The occurrence of tumours were followed in all animals.
>
> "Local tumours were observed in 17/28 treated rats vs. 0/34 for the untreated rats after intrapleural instillation.
>
> "Intramuscular implantation caused tumour formation in 15/33 rats in the strontium chromate group (0/32 for untreated).
>
> "The study lacks detailed information about the experimental procedure, which is an obvious weakness of the study. However, this study is the first report of the carcinogenicity of strontium chromate and often cited later in the literature of strontium chromate carcinogenesis." (ECHA REACH, 2019b).

4.3 Absorption, distribution, metabolism and excretion

The IPCS review of inorganic chromium (VI) compounds summarised the **ADME**:

> "The toxicokinetics of a given chromium compound depends on the valence state of the chromium atom and the nature of its ligands. Absorption of chromium(VI) compounds is higher than that of chromium(III) compounds via all exposure routes. This is because the chromate anion can enter cells

through cell membrane anion channels, whereas absorption of chromium(III) compounds is via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung via transfer across cell membranes and in the gastrointestinal tract from particles cleared from the lungs. Absorption after oral exposure in humans is approximately 2–8% for chromium(VI) as potassium chromate or dichromate. Absorption after oral exposure to chromium(VI) is lowered by reduction to chromium(III) in the acidic conditions of the stomach.

"Once in the blood, chromium compounds are distributed to all organs of the body. Particles containing chromium can be retained in the lung for years after occupational exposure. Chromium(VI) is unstable in the body and is reduced to chromium(V), chromium(IV) and ultimately to chromium(III) by many substances, including ascorbate and glutathione. It is believed that the toxicity of chromium(VI) compounds results from damage to cellular components during this process (for example, generation of free radicals). There is also the potential for interaction with deoxyribonucleic acid (DNA), causing structural DNA damage.

"Absorbed chromium is excreted primarily in urine, with the half-time for excretion of chromium orally administered as potassium dichromate estimated to be approximately 40 hours in humans. Hair and nails are minor pathways of excretion." (IPCS, 2013).

The ECHA REACH dossier on lead sulfochromate yellow summarised the ADME:

"No toxicokinetics studies are available for C.I. Pigment Yellow 34 and C.I. Pigment Red 104, but information on distribution is available from repeated dose toxicity studies. Furthermore, bioelution studies with C.I. Pigment Yellow 34 and C.I. Pigment Red 104 were performed in simulated gastric, interstitial, intracellular and perspiration fluid to determine bioavailability for absorption via the oral, inhalation and dermal route.

Information from repeated dose toxicity studies

"In the first rat study the animals received one treatment (10000mg/kg bw; Chromgelb 62 F, Chromgelb 72 GS and the equivalent amount of lead in the form of lead(II)acetate as positive control) test substance by gavage (BASF AG, 1974). In the remaining studies the animals received 0, 2000, 5000 and 20000ppm test substance (CI Pigment Yellow 34) in diet (corresponding to appr. 0, 152.9, 287.5 and 1602.1mg/kg bw per day in rats and to appr. 0, 75.4, 179.6 and 287.1mg/kg bw per day in dogs). In the first study, lead content levels were determined (atomic absorption spectroscopy; detection limit 1µg) in kidneys and bone (femur) 14 days after treatment. In the second and third studies, tissues and body fluids sampled – blood (lead); liver, kidney, brain, and bone (lead and chromium) – were analyzed using atomic absorption spectrophotometry (limits of detection and quantification: Pb 0.001**µg/g**; Cr 0.010µg/g in brain tissue; Cr 0.050µg/g in bone, liver, and kidney). Additional groups fed lead carbonate as positive control were also evaluated.

Blood lead determination

"In both oral subchronic studies, noticeable and dose-related increases were observed in the blood lead concentrations of all test animals after 30, 60, and 84 days of testing with test and positive control substances.

Tissue distribution

Lead

"14 days after single oral administration of the test substance and the equivalent amount of lead in the form of lead(II)acetate, the metal was detectable in kidneys and femurs of exposed animals.

"The lead content of the bone and kidney samples was markedly increased at all levels in the subchronic studies. The brain lead content (males only) and liver lead content (males and females) were slightly increased when compared with control values in the rat subchronic study and in all sexes in the dog subchronic study. Increases were generally directly proportional to length of time on test and/or dietary concentration.

Chromium

"Increases in chromium content were noted in the kidney and liver tissues among most test animals.

"In the rat subchronic study, the brain chromium content was slightly increased among a few females fed 2000ppm or more and among the males fed 20000ppm. Brain chromium content among male test animals fed 2000 or 5000ppm was either less than or comparable to that of the controls. Increases in chromium content in bone samples from animals fed either 5000 or 20000ppm were due to detectable amounts in 1 of 5 males fed 5000ppm and in 1 of 5 females fed 20000ppm. No detectable amount of chromium was found in the bone samples from any of the 2000ppm animals.

"Following observations were made in the dog subchronic study:

- At 2000ppm test substance, chromium content was elevated in all 4 tissues examined, the liver showing the highest concentration, kidneys the next highest, then bone; brain tissue showed the lowest concentration.
- At 5000ppm, a similar pattern of elevations was seen, with the concentrations in kidney, bone and brain tissues essentially comparable to those found in 2000ppm animals. However, in liver tissue, the chromium content in 2000ppm animals was considerably higher than that found in 5000ppm animals, though both levels were tested for 90 days.
- At 20000ppm, chromium content of liver and kidney tissues was much lower than that found in either 2000 or 5000ppm dogs and in bone, chromium was below detectable limits. These findings correlate with the short time (3 weeks) the animals were on test. In brain tissue, however, chromium content was comparable to concentrations found at the 2 lower levels.

Bio-elution studies

"The bio-elution potential of C.I. Pigment Yellow 34 and C.I. Pigment 104 was determined in four kinds of simulated body fluids: gastric, interstitial, intracellular and perspiration fluid, to determine bioavailability of chrome and lead for absorption. Incubation times were 2h for gastric fluid, and 24h and 7 days for interstitial, intracellular and perspiration fluid. Chrome and lead concentrations were measured by **ICP-MS** analysis.

"Results show highest bio-elution in gastric fluid, in which 22–24% of chromium and 23–26% of lead dissolved. For chromium, the percentages dissolved were 8.34 and 1.33% in interstitial, 3.44 and 3.77% in intracellular and 0.07 and 0.08% in perspiration fluid, for C.I. Pigment Yellow 34 and C.I. Pigment Red 104 respectively. For lead, the percentages dissolved were 0 and 0.02% in interstitial, 4.17 and 9.37% in intracellular and 1.64 and 1.8% in perspiration fluid, for C.I. Pigment Yellow 34 and C.I. Pigment Red 104 respectively.

> "The values may be used to determine bioavailability of lead and chrome for absorption via the different exposure routes. The relatively high percentage of dissolved chrome and lead in simulated gastric fluid indicates that the highest bioavailability will result from oral exposure. Interstitial fluid may be a measure for dissolution in lung fluid and bioavailability after inhalation. The low dissolution of lead in this fluid indicates that lead will not be very bioavailable via this route, whereas for chromium bioavailability is relevant via inhalation. Bioavailability via dermal absorption may be indicated by dissolution in perspiration fluid. This is very low for chromium (<0.1%) and therefore dermal absorption will not be relevant for chromium. Lead dissolution from C.I. Pigment Yellow 34 and C.I. Pigment Red 104 in perspiration fluid is less than 1.8%. Therefore, bioavailability of lead for dermal absorption will also be very low." (ECHA REACH, 2019a).

The ECHA REACH dossier on strontium chromate summarised the ADME:

> "There is no information on the toxicokinetics of strontium chromate by any route of exposure. Some data is available on the toxicokinetics of other sparingly soluble chromates but most of the available information on the toxicokinetics of chromates comes from water soluble chromates. In one study, workers in strontium chromate plants showed significantly elevated urine chromium levels suggesting bioavailability of inhaled strontium chromate. After inhalation of highly water soluble chromates, considerable amount of chromium deposited in the lung is rapidly transferred into the blood and taken up by erythrocytes or visceral organs. According to some studies, the uptake of chromium from the lungs may be up to 50%. Inhalation of sparingly soluble zinc chromate has also shown to result in increases in blood and urine chromium levels, and in one study comparing the kinetics of sodium and zinc chromate after intratracheal instillation in rats zinc chromate resulted in higher maximum blood levels than sodium chromate, although the absorption was slower than the absorption of sodium chromate. Absorption of chromium from strontium chromate after inhalation is assumed to resemble that of zinc chromate.
>
> "Oral absorption of hexavalent chromium is limited by reducing conditions in stomach resulting in the reduction of the hexavalent chromium to trivalent chromium. Absorption of hexavalent chromium from gastrointestinal tract shows significant variation between individuals. Generally absorption of <10% has been identified in humans after oral administration of highly water soluble chromates. No data is available on the oral absorption of less soluble chromates in humans. Comparative repeated animal experiments using sodium chromate and sparingly soluble calcium chromate suggest that there may be no huge differences in oral bioavailability between these chromates.
>
> "Dermal absorption of <1% for water soluble sodium chromate has been identified in animals. No data is available on poorly soluble chromates.
>
> "Once in the blood, chromium is distributed to various organs in the body. Especially chromium levels in kidneys, liver, spleen and testes have been shown to increase in animals after inhalation or oral exposure to water soluble chromates. In blood, hexavalent chromium is rapidly taken up by the erythrocytes by specific transport mechanisms, reduced to trivalent chromium mainly by intracellular glutathione and bound irreversibly in hemoglobin. Also plasma can reduce hexavalent chromium to trivalent chromium and reduction has been shown to occur also in lungs. Chromium intake into cells is much greater when in the hexavalent oxidation state and extracellular reduction to trivalent chromium serves to prevent its uptake. In addition to glutathione, ascorbic acid is another important reducer of hexavalent chromium.

> "Transplacental transfer has been shown to occur after intravenous administration of soluble hexavalent chromium (sodium chromate). No data on the transplacental transfer of strontium chromate is available.
>
> "Excretion of chromium occurs in the urine and faeces. In urine no hexavalent chromium has been detected because of the reduction of hexavalent chromium to trivalent form in the body. After oral administration, most of the chromium is excreted in the faeces with only few percents entering the urine (usually <2%). Inter-individual variation in urinary excretion may be high. Inhaled chromium absorbed into the body is excreted mainly into the urine. Urine as the main route of excretion of absorbed chromium is supported also by intravenous studies showing that 60% of the administered dose of sodium chromate is excreted into the urine within 25 days." (ECHA REACH, 2019b).

The DFG MAK Value Documentation on chromium (VI) compounds noted:

> "There are no studies relevant to the evaluation available for the dermal absorption of barium chromate, lead chromate, strontium chromate or zinc chromate or of their toxicity after dermal application. Some toxicokinetic studies with animals do show, however, that even the poorly soluble lead chromate is bioavailable after transport into the organism. The same can be assumed for the more readily soluble barium chromate. For the zinc chromate compounds the data for water solubility and skin sensitization likewise indicate bioavailability." (DFG, 2012).

The IPCS assessment of inorganic chromium (VI) compounds summarised some of the mechanistic data for carcinogenesis:

> "Once it is taken into cells, chromium(VI) has been shown to undergo a reduction to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as **NADPH**, ascorbate, glutathione or amino acids. During the reduction of chromium(VI) to chromium(V), molecular oxygen is reduced to hydrogen peroxide, which reacts with the chromium(V)–NADPH complex to generate the hydroxyl radical via a Fenton-like reaction (Shi & Dalal, 1990a, 1990b; Leonard *et al*., 2000). Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (ATSDR, 2008).
>
> "The products of metabolic reduction of chromium(VI) (free radicals, chromium(IV) and chromium(V)) and the newly generated chromium(III) are thought to be primarily responsible for the carcinogenic effects seen in human and experimental animal studies. The interaction of free radicals, chromium(V), chromium(IV) and chromium(III) with DNA can result in structural DNA damage, functional damage and cellular effects. The types of structural damage include DNA strand breaks, DNA–protein crosslinks, DNA–DNA interstrand crosslinks, chromium–DNA adducts and chromosomal aberrations.
>
> "In vitro, low chromium(VI) concentrations cause persistent activation of the mitogen-activated protein kinases **ERK-1**, **ERK-2**, **JNK** and **p38** (Kim & Yurkow, 1996; Chuang & Yang, 2001) and the phosphorylation of the mitogenic transcription factors **NFκB**, **ATF-2** and **c-Jun** (Ye *et al*., 1995; Samet *et al*., 1998). As these protein kinases and transcription factors constitute important mediators in inflammatory processes and tumour growth, effects on cellular signal transduction that deregulate cell growth are also to be expected in the case of chromium(VI), in addition to the direct genotoxic mechanisms involved (Hartwig, 2007)." (IPCS, 2013).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 4 below shows chromate (VI) compound exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	CHROMIUM (VI) COMPOUNDS		CALCIUM CHROMATE		LEAD CHROMATE		STRONTIUM CHROMATE	
	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE
	mg/m³	mg/m³	mg/m³	mg/m³	mg/m³	mg/m³	mg/m³	mg/m³
Australia	0.05				0.05			
Austria	0.05[1,2]	0.2[1,2]	0.05[2]	0.2[2,3]	0.05[2]	0.2[2]	0.05[2]	0.2[2,3]
Belgium	0.05 0.01[11]		0.001[4]		0.012		0.0005[4]	
Canada – Ontario	0.05 0.01[11]		0.001		0.012		0.0005	
Canada – Québec					0.012		0.0005	
Denmark	0.005	0.01					0.0005	0.001
European Union	0.005[5] 0.01[5,6] 0.025[5,7]							
Finland	0.05		0.005				0.005	
France	0.05 0.001[8]	0.005[8]						
Germany – AGS	0.001[2,9]	0.008[2,3,9]						
Hungary		0.05		0.05				0.05
Ireland	0.05[10] 0.01[11]		0.001				0.0005	
Israel	0.01[11]		0.001		0.012		0.0005	
Japan – MHLW	0.05							

1 **TRK** value (based on technical feasibility).

2 Inhalable fraction.

3 15 minutes average value.

4 Additional indication "C" means that the agent falls within the scope of Title 2 concerning carcinogenic, mutagenic and reprotoxic agents of Book VI of the Codex on well-being at work.

5 Carcinogens defined as a substance which meets the criteria for classification as a category 1 or 2 carcinogen set out in Annex VI to Directive 67/548/EEC.

6 Limit value until 17.01.25.

7 Limit value for welding or plasma cutting work or similar smoke-producing work procedures until 17.01.25 Bold-type: Binding Occupational Exposure Limit Value (**BOELV**).

8 Restrictive statutory limit values will come into force on 1 July 2014.

9 Assessment scale, risk-based.

10 Water soluble.

11 Insoluble.

12 Soluble.

13 Total aerosol.

14 10-hour TWA.

JURISDICTION OR ADVISORY BODY	CHROMIUM (VI) COMPOUNDS		CALCIUM CHROMATE		LEAD CHROMATE		STRONTIUM CHROMATE	
	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE
Japan – **JSOH**	0.05							
New Zealand	0.01		0.001		0.05		0.001	
Romania	0.05							
Singapore	0.05[10] 0.01[11]		0.001		0.012		0.0005	
South Korea	0.05[10] 0.01[11]				0.012		0.0005	
Spain	0.05[11] 0.01[12]		0.001		0.012		0.0005	
Sweden	0.005[13]	0.015[13]			0.005[2]	0.015[2,3]	0.005[2]	0.015[2,3]
Switzerland	0.005[2]							
The Netherlands	0.025[12]	0.05[12]		0.01		0.025		0.01
USA – NIOSH	0.001[14]							
USA – OSHA	0.005							
UK	0.05				0.05			

TABLE 4: Exposure standards for chromate (VI) compounds, as Cr from around the world.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on chromium (VI) compounds were ACGIH®, SCOEL, **DECOS**, NIOSH, DFG and Safe Work Australia.

5.2 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review of chromium and inorganic compounds recommended a **TLV-TWA** of 0.0002mg/m^3, measured as Cr(VI), inhalable particulate matter, with a **TLV-STEL** of 0.0005mg/m^3, as Cr(VI), inhalable particulate matter; **RSEN** and **DSEN** notations; and, **Skin** notations for water-soluble compounds, for occupational exposure to hexavalent chromium compounds (ACGIH®, 2018b).

The rationale for their conclusions was:

> "Water-soluble Cr(VI) compounds are highly irritating to the dermis and mucous membranes, and may cause sensitization of the skin and respiratory tract. The severe corrosive effects of Cr(VI) compounds can lead to ulceration of the skin ("chrome holes") and mouth, rhinitis, and perforation of the nasal septum (DaCosta *et al*., 1916; Bloomfield and Blum, 1928: Lieberman, 1941; Hanslain *et al*., 1967 as cited in IPCS, 2013).
>
> "Animal data on long-term inhalation exposures to Cr(VI) are sparse, but the clearest information came from 30- and 90-day exposures to aerosols of sodium dichromate in rats (Glaser *et al*., 1985, 1990) that showed a lowest-observed-adverse effect level (LOAEL) of 0.096mg Cr(VI)/m^3 (converted to 8 h/day for 5 days/week) for persistent inflammatory changes in the lungs.

Using the rat LOAEL, the human-equivalent concentration (HEC) for the same daily deposited dose was derived using species-specific dosimetry modelling (MPPD v 2.1, ARA 2009). Assumptions were made that deposition occurred in all regions of the respiratory tract, work place exposures occurred under conditions of light physical exertion, and that the material-specific density value for sodium chromate (2.52g/cm^3) was appropriate. The human-equivalent LOAEL derived was 0.0022mg Cr(VI)/m^3, which was then further adjusted to obtain a NOAEL of 0.0002mg Cr(VI)/m^3.

"In a large retrospective cohort study, Gibb and colleagues (2000b) estimated the risks of ulcerated nasal septum, ulcerated skin, perforated nasal septum, and perforated eardrum from exposures to CrO_3. Symptoms of nasal irritation (68.1%) or signs of an ulcerated nasal septum (62.9%) were common at some time during employment. The nasal and ear effects usually occurred within 1 month after the onset of exposure to median exposures of 0.010–0.015mg Cr(VI)/m^3. A NOAEL was not defined.

"In a U.S. National Institute for Occupational Safety and Health (NIOSH) Health Hazard Evaluation of a U.S. electroplating facility (Lucas and Kramkowski, 1975), 7/111 workers reported a history of skin ulcers and 9/11 had scars characteristic of healed chrome ulcers; epistaxis, rhinitis, and nasal ulceration were also reported, with 4/11 showing nasal septal perforation. These workers had been employed for an average of 7.5 years and were exposed to a mean concentration of only 0.004mg Cr(VI)/m^3.

"Lindberg and Hedenstierna (1983) found significant excess rates (P<0.05) for nasal irritation, mucosal atrophy and ulceration, and decreased lung function (FEV_1, **FVC**, **MMEF**) in chrome platers who were mostly exposed to mean 8-hour TWA levels of 0.002–0.020mg Cr(VI)/m^3. Nasal irritation and signs of mucosal atrophy were also noted in 4/19 (21%) of workers exposed to mean 8-hour TWA levels less than 0.002mg/m^3.

"When "peak exposures" were examined, a NOAEL was observed in the range of 0.0002–0.0012mg Cr(VI)/m^3. Overall, these data suggest that a TLV-STEL of 0.0005mg Cr(VI)/m^3 (that is, 0.5µg/m^3) would be protective for transient peak exposures to Cr(VI) compounds, and a TLV-TWA of 0.0002mg Cr(VI)/m^3 (that is, 0.2µg/m^3) would likely protect nearly all workers from severe irritation of the upper and lower respiratory tract, and from decreases in lung function. Because adverse health effects from Cr(VI) compounds occur throughout the upper and lower respiratory tract, the appropriate sampling size fraction is inhalable particulate matter.

"Extensive research has identified Cr(VI) compounds as human carcinogens, causing lung and sinonasal cancers (U.S. ATSDR, 1989, 2012; UK **HSE**, 1989; IARC, 1990; IPCS, 1988, 2013; U.S. NIOSH, 2013). Park and colleagues (2004), using a data set of Gibbs *et al*. (2000a), found that exposure-response relationships in the cohort were best described by a linear relative rate model that used terms for cumulative smoking, race, a race-chromium interaction term, and cumulative chromium exposures. An excess risk of lung cancer death was estimated at 1 per 1000 workers exposed to 0.0002mg Cr(VI)/m^3. Data from another U.S. cohort (Luippold *et al*., 2003) were analysed by Crump and colleagues (2003) who found and excess of lung cancer deaths of 2 per 1000 workers exposed to 0.001mg/m^3 for a working lifetime, similar to the excess risk calculated by Park and colleagues (Park *et al*. 2004; Park and Stayner, 2006). A follow-up survey of the Baltimore cohort (Gibb *et al*., 2015) showed significant associations between lung cancer and various symptoms of nasal irritation, implying that reducing the irritant effects of Cr(VI) would likely decrease the risk of lung cancer from Cr(VI). Based on strong evidence in humans and animals, all Cr(VI) compounds are assigned an A1, Confirmed Human Carcinogen, cancer designation.

> "Chromium(VI) compounds, depending on water solubility, penetrate the skin and mucosae to a much greater degree than Cr(III) compounds, and this is important in the development of skin and respiratory sensitization. Chromium(VI) compounds are converted to Cr(III) intracellularly, and an immune response is likely directed at Cr(III)-protein complexes that serve as haptens (U.S. ATSDR, 2012). Hypersensitivity reactions to CR(VI) compounds are common and, once sensitized, an individual is likely to experience allergic dermatitis or asthma when exposed to either Cr(III) or Cr(VI) compounds. There may be no safe level of exposure for someone who has already become sensitized. Both water-soluble and sparingly soluble Cr(VI) compounds can induce dermal or respiratory sensitization, and for this reason Cr(VI) compounds as a group have been assigned DSEN and RSEN notations. A TLV-TWA of 0.0002mg/m^3 and a TLV-STEL of 0.0005mg/m^3 for Cr(VI) compounds should minimize respiratory sensitization and reduce the likelihood of asthmatic responses in already sensitized individuals, but severe reactions might still occur. Even at this low airborne exposure level, good housekeeping is essential to prevent skin contact and the resulting risk of sensitization.
>
> "A Skin notation is assigned for Cr(VI) compounds based on the systemic absorption of chromium following dermal exposures to water-soluble Cr(VI) compounds, which can be detected by increased chromium excretion in the urine." (References cited in ACGIH®, 2018b).

The ACGIH® review specific for lead chromate recommended a TLV-TWA of 0.0002mg/m^3, measured as Cr(VI), inhalable particulate matter with a TLV-STEL of 0.0005mg/m^3, as Cr(VI), inhalable particulate matter, for occupational exposure to lead chromate to minimise the potential for respiratory tract cancers, irritant effects, and sensitisation of the skin and respiratory tract (ACGIH®, 2018a).

The rationale for their conclusions was:

> "The **TLV** is based on values set for exposures to other Cr(VI) compounds (see the TLV® *Documentation* for Chromium and inorganic compounds). At the recommended TLV for Cr(VI) exposure, the corresponding exposure for lead is an 8-hour TWA of 0.0008mg/m^3, as Pb, which is substantially less than the current TLV and much lower than the level at which any lead-related health effects are expected to occur (see the TLV® *Documentation* for Lead and inorganic compounds). Because upper and lower respiratory tract irritation, sensitization and cancers are associated with exposure to Cr(VI) compounds, and absorption from the **GI** tract of swallowed particles is an important route for chromium and lead uptake, the relevant particle size fraction is inhalable particulate matter.
>
> "Studies in isolated human lung cells (Holmes *et al*., 2006; Wise *et al*., 1994, 2002; Wise *et al*., 2004a, b, 2006a, b, 2010; Xie *et al*., 2005, 2007) have shown that the solubility of lead chromate is increased in the presence of cells, and that the chromate component is responsible for marked genotoxic and clastogenic effects, with effects being greater for poorly soluble Cr(VI) compounds than water-soluble forms. An A1, Confirmed Human Carcinogen, carcinogenicity notation is assigned based on *in vitro*, animal, and epidemiological studies showing that all Cr(VI) compounds are likely human carcinogens.
>
> "Sensitization of the skin (DSEN) and respiratory tract (RSEN) is expected, in keeping with other Cr(VI) compounds. Based on the low solubility of lead chromate, a Skin notation is not assigned." (References cited in ACGIH®, 2018a).

The earlier specific ACGIH® review of strontium chromate recommended a TLV-TWA of 0.0005mg/m^3, measured as chromium (Cr), for occupational exposure to strontium chromate (ACGIH®, 2001).

The rationale for their conclusions was:

> "No published epidemiological or clinical studies of workers exposed to strontium chromate were identified in the open scientific or medical literature. However, long-term oncogenic studies with rodents resulted in statistically significant numbers of implantation-site tumors, including up to a 62% incidence of bronchial carcinomas compared with 0% in pellet-vehicle control animals. Furthermore, strontium chromate is of greater potency for tumorigenesis when compared to the reference carcinogens calcium chromate and methylcholanthrene. For these reasons, an A2, Suspected Human Carcinogen, notation is justified. In addition, for A2 carcinogens with a TLV, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV." (ACGIH®, 2001).

ACGIH® concluded that there was insufficient data to recommend Skin or **SEN** notations, or a TLV-STEL (ACGIH®, 2001).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] assessment of chromium VI compounds concluded that:

> "On the basis of all the available evidence, it was concluded by SCOEL that Cr VI 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). SCOEL is aware of discussion in the literature on exposure thresholds and non-linear exposure response relations, regarding carcinogenic effects of Cr VI (see for instance Haney *et al*., 2015). First, the totality of the evidence regarding the mode of action mitigate against the conclusion that there is an exposure threshold. Second, some of the discussion in the epidemiological literature considers that the excess risk is only statistically significant for some of the higher exposed exposure categories. This observation is interpreted as evidence for an exposure threshold. However, the SCOEL does not agree with this interpretation because it focusses only on part of the exposure response curve, is not based on all exposure response information and ignores the statistically significant overall exposure response association (test for trend for the relation). Therefore, reliable published exposure-response slopes were used for linear extrapolation and they form 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 lifetable analysis was conducted as described by Goldbohm *et al*., (2006). Lifetable calculated risk, represents the excess risk from 40 years of occupational exposure, starting at age 20 and onwards, till a certain age, in this case a near maximum age of 100. Lifetable calculated risks take into account that individuals die of other causes of disease as well, apart from the disease of interest, in this case lung cancer. 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:"

	NUMBER OF EXCESS LUNG CANCER CASES/1,000			
Exposure 8-hour TWA µg/m³	Point estimate combined exposure response slopes	Confidence Interval	(Crump *et al*., 2003)	(Park *et al*., 2004)
0.1	0.4	0.3–0.5	0.2	0.6
1	4	3.2–4.8	2	6
5	20	16–24	8	32
10	39	31–47	15	62
25	94	76–112	38	146

TABLE 5:
Estimates of excess lung cancer risk at different exposure levels during a work shift

"Exposure at which excess risk benchmark values of 4/1000 and 4/100 000 workers are realised, 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 [sic] some countries considered as 'acceptable' and 'negligible' risk levels respectively. 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)." (References cited in SCOEL, 2017).

5.4 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] concluded that all hexavalent chromium compounds should be considered as carcinogens, that underlying processes include a stochastic genotoxic mechanism, and that in the health-based cancer risk calculation no distinction should be made between soluble and poorly soluble hexavalent chromium compounds (DECOS, 2016).

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

- 4×10^{-5} for 40 years of occupational exposure to 0.01µg/m³, and
- 4×10^{-3} for 40 years of occupational exposure to 1µg/m³.

The rationale for their conclusions was:

> "The methodology as applied in the risk assessment made by Seidler *et al*. (2013) and subsequently processed by **RAC**-ECHA, is generally in line with the recent DECOS guideline and scientific views (DECOS, 2012; Seidler *et al*., 2013). First Seidler *et al*. evaluated all existing epidemiological studies regarding exposure to hexavalent chromium at work and the risk of lung cancer. These studies were evaluated based on compliance with previously defined quality criteria, the use of data regarding more than one exposure level and the correction for the effect of smoking on the development of cancer. Based on these inclusion criteria Seidler *et al*. selected five studies to establish an exposure-effect relationship (Gibb *et al*. (2000), Park *et al*. (2004) and Park & Stainer (2006) from the Baltimore cohort); Crump *et al*. (2003) and Luippold *et al*. (2003) from the Painesville cohort) (Gibb *et al*., 2000; Luippold *et al*., 2003; Crump *et al*., 2003; Park *et al*., 2004; Park and Stayner, 2006; Proctor *et al*., 2016). In a subsequent meta-analysis an average dose-effect relationship was calculated, applying linear models, for the Crump (2003) and the Park (2004) studies (characterized by a weighted average ß value of 1.75) (Crump *et al*., 2003; Park *et al*., 2004). Thereafter, Seidler *et al*. (2013) calculated an extra lung cancer risk for hexavalent chromium compounds of 4 per 10,000 (4×10^{-4}) after 40 year occupational exposure to 0.1µg/m³ and 4 per 1,000 (4×10^{-3}) after 40 year occupational exposure to 1µg/m³. [See the study by Seidler *et al*. (2013) for details of the calculation (Seidler *et al*., 2013).] 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)) (NIOSH, 2013; Park *et al*., 2004). Therefore DECOS prefers the study by Seidler *et al*. as starting point for its further risk assessment."
>
> "Based on the average slope of the dose-effect relationship of the two selected studies in the meta-analysis an extra risk was calculated for 40 years exposure, during the ages 20–60, and a latency period of 10 years. This resulted in extra risks of 4 per 10,000 and 4 per 1,000 for exposure to hexavalent chromium concentrations of 0.1µg/m³ an 1µg/m³, respectively, up to age 75 years and using European (male) mortality data for lung cancer.
>
> "Subsequently, DECOS performed calculations using mortality data from the Netherlands' population (from 2000 to 2010), separated by age and sex). Moreover, the cancer risk values were calculated taking into account a higher age (end of cohort at 100 years)." (References cited in DECOS, 2016).

5.5 NIOSH

The National Institute for Occupational Safety and Health [NIOSH] review of hexavalent chromium concluded that the available scientific evidence supported the inclusion of all chromium (VI) compounds into their recommendation. NIOSH recommended that airborne exposure to all chromium (VI) compounds be limited to a concentration of 0.2µg Cr(VI)/m^3 [0.0002mg Cr(VI)/m^3] for an 8-hour TWA exposure, during a 40-hour workweek, based on the quantitative risk assessment of the Baltimore cohort (Gibb *et al*., 2000b; Park *et al*., 2004 cited in NIOSH, 2013). The **REL** was intended to reduce workers' risk of lung cancer associated with occupational exposure to chromium (VI) compounds over a 45-year working lifetime. The NIOSH risk assessment estimated an excess lifetime risk of lung cancer death of approximately 1 per 1,000 workers at the REL of 0.2µg Cr(VI)/m^3 and a lifetime added risk for a 45-year working lifetime exposure of 1 in 10,000 at 0.02µg Cr(VI)/m^3 [0.00002mg/m^3]. The REL for chromium (VI) compounds is expected to also reduce the non-malignant respiratory effects, including irritated, ulcerated, or perforated nasal septa and other potential adverse health effects. NIOSH noted that because of the residual risk of lung cancer at the REL, continued efforts should be made to reduce exposures to Cr(VI) compounds below the REL (NIOSH, 2013).

5.6 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] MAK Value Documentation on chromium (VI) compounds concluded that no MAK Value could be recommended because the substances were classified **Carcinogen Category 1**, and noted that:

> "Chromium(VI) compounds are carcinogenic and genotoxic in humans and animals."
>
> "A number of epidemiological studies found there to be an increased relative risk of mortality from lung cancer for workers in chromate (pigment) production plants and chrome-plating plants. The carcinogenic effects of chromium(VI) compounds have been confirmed in animal studies with calcium chromate, chromium trioxide, sodium dichromate (dihydrate) and strontium or zinc chromates." (DFG, 2012).
>
> "Chromium(VI) compounds were found to be genotoxic in numerous studies with bacteria and mammalian cells. After intraperitoneal injection, micronuclei were induced *in vivo* in the bone marrow of mice. Although the genotoxic potential increases with the solubility, genotoxic effects occurred also with poorly soluble chromium(VI) compounds. In addition to the positive results in *in vitro* and *in vivo* investigations of genotoxicity in somatic cells, dominant lethal mutations were induced also in mouse germ cells after single and repeated intraperitoneal injections. Like other chromium(VI) compounds, also the poorly soluble lead chromates and barium chromate are genotoxic. Lead chromate can induce chromium–DNA adducts, DNA strand breaks, chromosomal abberations and aneuploidy in mammalian cells *in vitro*. Also barium chromate causes chromosomal aberrations. In mice, lead chromate causes an increase in the incidence of micronuclei in polychromatic erythrocytes in bone marrow. There are no dominant lethal mutation tests available for the lead chromates and barium chromate. As also lead chromate and barium chromate can be absorbed into the cells, and the results of *in vitro* and *in vivo* genotoxicity studies with somatic cells were similar for all chromium(VI) compounds, chromium(VI) compounds must be regard [sic] as genotoxisch [sic]." (DFG, 2012).

5.7 Safe Work Australia

Safe Work Australia proposed a TWA of 0.007µg/m³ (0.000007mg/m³) of chromium VI (as Cr) to reduce the risk of cancer in exposed workers (Safe Work Australia, 2019).

Their rationale was:

> "Water-soluble Cr(VI) compounds are highly irritating to the skin and mucous membranes and may cause sensitisation of the skin and respiratory tract. Based on evidence in animals and humans, Cr(VI) is characterised as a non-threshold based genotoxic carcinogen (ACGIH, 2018; DFG, 2016; US EPA, 1998). Its carcinogenicity is demonstrated to act *via* a mutagenic mode of action."
>
> "The recommended TWA of 0.007µg/m³ has been calculated at a minimal cancer risk level applying an inhalation unit risk value. This value is based on data from a study reporting an increased risk of lung cancer in exposed workers (US EPA, 1998)."
>
> "Classified as a skin sensitiser but not a respiratory sensitiser according to the **GHS**."
>
> "A skin notation is recommended based on evidence of dermal absorption in animals." (Safe Work Australia).

Safe Work Australia also proposed a TWA of 0.007µg/m³ (0.000007mg/m³) for Lead chromate (as Cr) to reduce the risk of cancer in exposed workers (Safe Work Australia, 2019).

Their rationale was:

> "Based on evidence in animals and humans, Cr(VI) is considered a non-threshold based genotoxic carcinogen (ACGIH, 2018; DFG, 2016; US EPA, 1998). Its carcinogenicity is likely to act via a mutagenic mode of action."
>
> "As such, the recommended TWA of 0.007µg/m³ (in line with Cr[VI]) has been derived at a minimal cancer risk level applying an inhalation slope factor. This factor is based on data from a study reporting an increased risk of lung cancer in exposed workers (USEPA, 1998)." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne chromium (VI) compounds

One method available in New Zealand to measure airborne chromium VI compounds, as chromium VI (CrVI), is using a modification of NIOSH method 7600 (NIOSH, 1994).

Using this method, an air sample of 8 to 400 litres is collected onto a PVC membrane filter, using a flow rate of 1 to 4 litres per minute. Following extraction using alkaline solution, and after addition of a developing reagent, analysis is undertaken using visible spectrophotometry at 540nm. The detection limit of this modified method has been quoted as 0.01µg per sample for chromium VI.

Collection of 400 litres would allow reliable quantitation of the airborne concentration of chromium VI at airborne concentrations of approximately 0.00025mg/m^3. This corresponds to a concentration of approximately 0.0016mg of lead chromate per m^3 of air.

It is acknowledged that this method does not allow reliable quantitation of chromium VI levels around or below 0.00002mg/m^3 chromium VI, which is the proposed 8-hour WES-TWA. It is acknowledged that determination of the airborne concentration of chromium VI for comparison with the proposed **WES-STEL** cannot be achieved using this method.

7.0
Discussion

WorkSafe's WES for chromium (VI) compounds was last reviewed in 2017; since then ACGIH® has published its review, and a proposal has been made to combine all chromium (VI) compounds into one WES.

WorkSafe's WES for calcium, lead and strontium chromate have been unchanged since adoption in 1994.

The toxicological database reviewed above indicates that chromium (VI) compounds are locally and systemically toxic to humans, causing skin, eye and respiratory tract irritation, and occupations involving the use of chromium (VI) compounds are associated with increased risks of lung cancer; and locally and systemically toxic to laboratory species causing respiratory tract irritation and localised tumours [bronchial carcinoma; sarcoma].

Based on the aforementioned documentation, informed by the conclusions of the ACGIH®, SCOEL, DECOS, NIOSH and DFG reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA, for inhalable fractions of chromium (VI) compounds, as Cr, to be inadequate to manage health risks from possible workplace exposure:

- Chromium (VI) compounds are used in industries associated with increased risks of lung cancer (IARC, 2012).
- The ACGIH®, SCOEL, DECOS and NIOSH recommendations concluded that all hexavalent chromium compounds should be considered as carcinogens, that underlying processes include a stochastic genotoxic mechanism [that is, no threshold], and that in the health-based cancer risk calculation no distinction should be made between soluble and poorly soluble hexavalent chromium compounds (ACGIH®, 2018b; SCOEL, 2017; DECOS, 2016; NIOSH, 2013).
- The NIOSH review estimated, based on human data, that occupational exposure to 0.00002mg Cr(VI)/m^3 corresponded to 1 extra lung cancer case per 10,000 exposed workers (NIOSH, 2013).
- The ACGIH® review noted that their recommended TLV-TWA of 0.0002mg Cr(VI)/m^3 and TLV-STEL of 0.0005mg Cr(VI)/m^3 were based on NOAELs from exposed workers reporting nasal irritation, mucosal atrophy and ulceration, and decreased lung function, in addition to the excess cancer risk estimates. The TLV-STEL was set to minimise transient peak exposures that could trigger asthmatic responses (ACGIH®, 2018b).

- The DECOS review estimated, based on human data, that occupational exposure to 0.00001mg Cr(VI)/m^3 corresponded to the additional lifetime cancer risk for hexavalent chromium compounds of 4 extra cancer cases per 100,000 occupationally exposed people [40 years working life; the **acceptable risk** level]; and, concentrations of 0.001mg Cr(VI)/m^3 corresponded to the **tolerable risk** level of 4 extra cancer cases per 1,000 exposed workers (DECOS, 2016).
- The draft Safe Work Australia review of their WES for chromium VI compounds recommended a TWA of 0.000007mg/m^3 to reduce the risk of cancer in exposed workers, calculated at a minimal cancer risk level applying an inhalation unit risk value, and based on data from a study reporting an increased risk of lung cancer in exposed workers (US EPA, 1998 cited in Safe Work, 2019).
- The proposed WES-TWA of 0.00002mg Cr(VI)/m^3 is set to be protective against all non-carcinogenic and non-genotoxic endpoints, based on the premise that all hexavalent chromium compounds should be considered as carcinogens, and NOAELs from exposed workers reporting respiratory tract effects, with an expectation of an additional lifetime cancer risk of between 8 cases per 10,000 exposed workers and 1 case per 10,000 (ACGIH®, 2018b; DECOS, 2016; NIOSH, 2013).
- The proposed WES-STEL of 0.0005mg Cr(VI)/m^3 is set to be protective against peak concentrations triggering asthmatic responses or genotoxic events.
- The ACGIH® and DFG recommendations concluded that all soluble hexavalent chromium compounds should be designated with Skin or "**H**" notations based on the potential for systemic absorption following dermal exposures (ACGIH®, 2018b; DFG, 2012).
- A ***skin*** notation is not justified for lead or strontium chromate, based on the expected limited absorption after dermal exposure for "low solubility" chromates [<500g/L; US OSHA, 2006 cited in ACGIH®, 2018b] (ACGIH®, 2001, 2018a; DFG, 2012).
- Chromium (VI) compounds are associated with contact and rarely occupational asthma, and ACGIH® recommended both DSEN and RSEN notations (ACGIH®, 2018a). Available information does not clearly indicate whether or not lead chromate or strontium chromate are sensitisers. As individuals, once sensitised to either Cr(VI) or Cr(III) compounds, cross-reaction can occur with any such compound, so ***dsen*** *and* ***rsen*** notations are warranted for all chromium (VI) compounds (ACGIH®, 2018b).
- Allergic sensitisation is considered an irreversible change (OECD, 2012), and while threshold levels exist for allergic sensitisation by allergenic substances (OECD, 2012), the data for chromium (VI) compounds from human experience or animal studies was inadequate to quantitatively derive such a threshold, although the ACGIH® noted that a TLV-TWA of 0.0002mg/m^3 and a TLV-STEL of 0.0005mg/m^3 for Cr(VI) compounds should minimise potential for respiratory sensitisation (ACGIH®, 2018b).

8.0
Recommendations

WorkSafe considers its current WES-TWA for inhalable fraction of chromium (VI) compounds to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for all chromium(VI) compounds of 0.00002mg/m^3, as Cr(VI) [inhalable fraction]
2. adopt a WES-STEL for all chromium(VI) compounds of 0.0005mg/m^3, as Cr(VI) [inhalable fraction]
3. adopt *dsen* and *rsen* notations for all chromium(VI) compounds
4. adopt *skin* notations for all water-soluble [≥500g/L] chromium(VI) compounds
5. revoke individual WES for chromium(VI) compounds (calcium, lead and strontium chromates)
6. maintain individual **BEI**s for chromium(VI) compounds with biomarkers in addition to Cr(VI) (for example, for Pb with lead chromate).

It is acknowledged that currently there are no available analytical methods that would allow determination of airborne levels of chromium VI at the proposed WES values. WorkSafe recommends substituting alternative substances so far as is reasonably practicable.

Noting that the proposed WES-TWA of 0.00002mg Cr(VI)/m^3 and WES-STEL of 0.0005mg Cr(VI)/m^3 for chromium(VI) compounds may not eliminate all risk, due to the genotoxic potential of chromium (VI) compounds; the sensitisation and cross-reactivity potential of Cr(VI) and Cr(III) compounds; and for water-soluble chromium(VI) compounds, the potential contribution from dermal absorption; so all exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
95%CI/$CI_{95\%}$	95% Confidence Interval.
Acceptable [cancer] risk	EU criterion: 4 extra cases in a population of 10,000 until 2013; 4 extra cases in a population of 100,000 after 2013 [see Tolerable risk].
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
ATF-2	Activating transcription factor 2.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BAL	Bronchoalveolar lavage.
BEI	Biological Exposure Index.
BMD	Bench Mark Dose.
BMD(L)01/ BMDL 1%	Bench Mark Dose, lower limit of a 1% extra risk.
BMR	Basal metabolic rate.
BOELV	Binding Occupational Exposure Limit Value – an EU term.
Carcinogen category 1	DFG MAK designation: Substances that cause cancer in man and can be assumed to contribute to cancer risk. Epidemiological studies provide adequate evidence of a positive correlation between the exposure of humans and the occurrence of cancer. Limited epidemiological data can be substantiated by evidence that the substance causes cancer by a mode of action that is relevant to man.
C.I.; CI	Colour Index.
CICAD	Concise International Chemical Assessment Document.
c-Jun	c-Jun is a protein that in humans is encoded by the JUN gene.
CONTAM	Panel on Contaminants in the Food Chain, administered by EFSA.
DECOS	Dutch Expert Committee on Occupational Standards a Committee [DECOS] of the *Health Council of the Netherlands*. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
dL	Decilitre, or one-tenth of a litre.
DNA	Deoxyribonucleic acid.
dsen	A substance that can 'sensitise' the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
ECHA	The European Chemicals Agency (an agency of the European Union).

TERM	MEANING
EFSA	European Food Safety Authority (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
ERK-1	Extracellular signal–regulated kinase 1, also called mitogen-activated protein kinase 3 (MAPK3).
ERK-2	Extracellular signal–regulated kinase 2, also called mitogen-activated protein kinase 1 (MAPK1).
EU	European Union.
EU RAR	European Union Risk Assessment Report.
FEV1	Forced expiratory volume in 1 second.
FVC	Forced vital capacity: the volume of air that can be forcibly blown out after full inspiration (litres).
GHS	Globally Harmonised System of classification and labelling of chemicals.
GI	Gastrointestinal.
g/l or g/L	Grams of substance per litre.
gpt	Gene coding enzyme glutamic pyruvic transaminase, GPT [also known as alanine amino transferase, ALT].
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the *skin notation* in the WorkSafe WES special guide.
HEC	Human-equivalent concentration.
HSDB	Hazardous Substances Data Bank, administered by the US National Library of Medicine.
HSE	Health and Safety Executive, UK.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	International Agency for Research on Cancer – an agency of the World Health Organization.
ICP	Inductively-coupled plasma – a powerful method used in analytical chemistry to detect metals and some non-metal species.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
IPCS	International Programme on Chemical Safety – a World Health Organisation Programme.
JNK	c-Jun N-terminal kinase.
JSOH	Japan Society for Occupational Health.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
µg	Microgram or one millionth of a gram.
µg/dL	Microgram or one millionth of a gram per decilitre [1/10th of a litre].

TERM	MEANING
µg/g	Microgram or one millionth of a gram per gram of the matrix.
µg/L	Microgram or one millionth of a gram per litre.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w. or mg/kg bw	Milligram of a substance per kilogram body weight.
µg/m³	Micrograms of a substance per cubic metre of air.
mg/m³	Milligrams of a substance per cubic metre of air.
mg/L or mg/l	Milligrams of a substance per litre.
MHLW	Japanese Ministry of Health, Labour and Welfare.
MMEF	Maximum mid-expiratory flow, the peak expiratory flow taken from the flow-volume curve [L/s].
MS	Mass spectrometry/spectrometer.
NAD(P)H/ NADPH	Nicotinamide adenine dinucleotide phosphate, reduced.
NF-κB	NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NLM	National Library of Medicine, administered by the US National Institutes of Health.
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OSHA	Occupational Safety and Health Administration, US Department of Labor.
p38	P38 mitogen-activated protein kinase.
ppm	Parts of vapour or gas per million parts of air.
RAC	Committee for Risk Assessment, European Chemicals Agency.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
REL	Recommended Exposure Limit. A NIOSH term.
Relative Risk; RR	Risk Ratio or Relative Risk is a measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicated a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
Repr. 1B	EU notation: "May damage fertility. May damage the unborn child." Hazard Statement Code H360FD.
Resp. Sens. 1	EU notification: "May cause allergy or asthma symptoms or breathing difficulties if inhaled." Hazard Statement Code H334.
RoC/ROC	Report on Carcinogens.

TERM	MEANING
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
RSEN	A notation indicating the substance is a respiratory sensitiser. RSEN is used in place of SEN when specific evidence of sensitisation by the inhalation route is confirmed by human or animal data. An ACGIH® term.
SCHER	Scientific Committee on Health and Environmental Risks.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
SD	Standard deviation.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A term New Zealand also uses.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
Skin Sens. 1	EU notation: "May cause an allergic skin reaction." Hazard Statement Code H317.
SMR	Standardised Mortality Ratio (SMR) is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard). By convention, the figure is usually multiplied by 100 [an SMR of 200 corresponds to a RR of 2.0]. A *value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
STEL	See WES-STEL.
TG	Test Guidelines. An OECD term.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
Tolerable [cancer] risk	EU criterion: 4 extra cases in a population of 1,000 [see Acceptable risk].
TRK	Technische Richtkonzentration [technical guidance concentration level].
vRAR	Voluntary Risk Assessment Report.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40-hour week. A WorkSafe term.

TERM	MEANING
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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Notes

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