Australian Government

Department of Health

National Industrial Chemicals
Notification and Assessment Scheme

INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)

HUMAN HEALTH TIER II ASSESSMENT FOR

Chromium trioxide and related compounds

Chemical name in AICS	CAS Number
Chromium oxide (CrO3)	1333-82-0
Chromic acid (H2CrO4)	7738-94-5
Chromic acid (H2Cr2O7)	13530-68-2
Chromium, dichlorodioxo-	14977-61-8

PREFACE

As part of the reform regarding assessment of Existing Chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is implementing a new framework to address the human health and environmental impacts of industrial chemicals, not yet assessed, on the Australian Inventory of Chemical Substances (AICS).

The framework provides a more rapid, flexible and transparent approach for the assessment of existing chemicals.

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was developed, with significant input from stakeholders, and will be applied in stages.

Stage One of this program, which will take four years, started 1 July 2012 and is examining 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This includes chemicals for which NICNAS already holds exposure information, chemicals identified as a concern or for which regulatory action has been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

This chemical/group of chemicals is/are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.
For more detail on the new program please visit: www.nicnas.gov.au

ACRONYMS & ABBREVIATIONS

ACToR	Aggregated Computational Toxicology Resource (US)
AICS	Australian Inventory of Chemical Substances
ATSDR	Agency for Toxic Substances and Disease Registry (US)
bw	bodyweight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations (US)
CHO	Chinese hamster ovary
CosIng	Cosmetic Substances and Ingredients database (EU)
d	day
DNA	Deoxyribonucleic acid
EC	European Commission
EC3	Estimated concentration to produce a three-fold increase in lymphocyte proliferation
ECHA	European Chemicals Agency
ESIS	European Chemical Substances Information System
EU	European Union
EU RAR	European Union Risk Assessment Report
FDA	Food and Drug Administration (US)
FSANZ	Food Standards Australia and New Zealand
g	gram
g/mol	grams per mole
GHS	Globally Harmonized System of Classification and Labelling of Chemicals*
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPMT	Guinea pig maximisation test
h	hour
HGPRT	hypoxanthine guanine phosphoribosyltransferase
HPV	high production volume
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
HVICL	High Volume Industrial Chemicals List
IARC	International Agency for Research on Cancer
INCHEM	International Programme on Chemical Safety (also known as IPCS)
INCI	International Nomenclature of Cosmetic Ingredients
ip	intraperitoneal
IRIS	Integrated Risk Information System (US)
IUCLID	International Uniform Chemical Information Database
iv	intravenous
kg	kilogram
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LCLo	lowest published lethal concentration
LDLo	lowest published lethal dose
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
m^3	cubic metre
mg	milligram
mg/cm^3	milligrams per cubic centimetre
mg/kg bw/d	milligrams per kilogram bodyweight per day
min	minute
mL	millilitre
µg	microgram
µL	microlitre
(m)SDS	(material) Safety Data Sheet

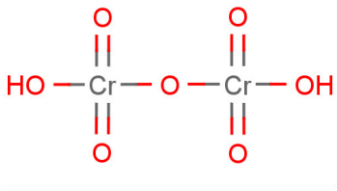
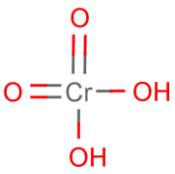
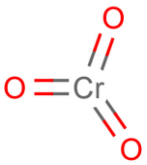
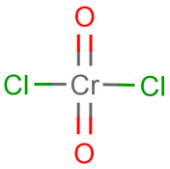
NIOSH	National Institute for Occupational Safety and Health (US)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (US)
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
PCBU	person conducting a business or undertaking
PEL	permissible exposure limit
PND	postnatal day
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
QSAR	Quantitative Structure-Activity Relationship
REACH	Registration Evaluation Authorisation of Chemicals (ECHA)
SD	Sprague Dawley
SIAP	SIDS Initial Assessment Profile (OECD)
SIAR	SIDS Initial Assessment Report (OECD)
SIDS	Screening Information Data Set (OECD)
SMILES	simplified molecular-input line-entry system
SPIN	Substances in Preparations in the Nordic Countries
STEL	short-term exposure limits
STV	short-term value
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard**)
TCLo	lowest published toxic concentration
TDLo	lowest published toxic dose
TEEL	temporary emergency exposure limits
TSCA	Toxic Substances Control Act (US EPA)
TG	test guideline
TGA	Therapeutic Goods Administration
TLV	threshold limit values
TWA	time weighted average
UN	United Nations
US	United States of America
US EPA	United States Environmental Protection Agency
WHS	Work, Health and Safety
wt	weight
w/w	weight per weight

Glossary

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary, which includes:
Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and
Part 2: IPCS Glossary of Key Exposure Assessment Terminology.
The IPCS Risk Assessment Terminology can be accessed at:
http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

*****Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

******The Poisons Standard (the SUSMP) can be accessed at: http://www.tga.gov.au/publication/poisons-standard-susmp

Chemical Name in AICS (Including Synonyms)	CAS Number	Structural Formula	Molecular Formula	Molecular Weight (g/mol)
Chromic acid (H2Cr2O7) Bichromic acid Dichromic acid (H2Cr2O7) Dichromic(VI) acid	**13530-68-2**		Cr2H2O7	218.00
Chromic acid (H2CrO4) Acide chromique Chromic(VI) acid Chromium hydroxide oxide	**7738-94-5**		CrH2O4	118.01
Chromium oxide (CrO3) Chromium (VI) trioxide Chromic trioxide Chromium (6+) oxide Monochromium trioxide Chromium anhydride	**1333-82-0**		CrO3	99.99
Chromium, dichlorodioxo- Chromyl chloride Chlorochromic anhydride Chromic oxychloride Chromium chloride oxide Chromoxychlorid	**14977-61-8**		Cl2CrO2	154.90

Grouping Rationale

This group consists of chromium trioxide and its related compounds. All the chemicals are hexavalent (VI) chromium compounds that contain chromium in the hexavalent or +6 oxidation state. Compounds covered by this document are likely to behave in a similar manner in respect of toxicokinetics. The toxicity of the chromium compounds depends principally on valency, as well as physical/chemical properties of the specific compounds, with hexavalent chromium being generally more toxic than trivalent (III) chromium. For this group, the toxicity is considered to be as a result of the chromium (VI) component. The chemicals in this group will all readily dissolve in aqueous environments in the body releasing chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) ions. These two ions will co-exist, in equilibrium, regardless of the particular chromium compound (Cr (VI)) involved. The chromate/dichromate ions produced from all the compounds will behave similarly in biological tissues, hence, the potential toxicity will be similar. This group is distinguished from other chromium (VI) compounds (in the form of chromate salts) due to volatility and corrosive properties. Once the chromium (VI) has been converted to a chromium (III) substance then this is not considered further in the assessment.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical chromium oxide (CrO_3) (CAS No. 1333-82-0) has been reported to have the following uses (commercial) including as:

- corrosion inhibitors;
- oxidising agents; and
- as a rust converter.

Three chemicals of this group have been identified as having no specific Australian use, importation, or manufacturing information:
- chromium, dichlorodioxo- (CAS No. 14977-61-8);
- chromic acid (H_2CrO_4) (CAS No. 7738-94-5); and
- chromic acid ($H_2Cr_2O_7$) (CAS No. 13530-68-2).

International
The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR), Galleria Chemica, and Substances in Preparations in Nordic Countries (SPIN) database.

One chemical of this group (chromium oxide—CrO_3) (CAS No. 1333-82-0) has reported domestic uses including:
- as cleaning/washing agents;
- as corrosion inhibitors;
- in paints, lacquers and varnishes; and
- as a surface treatment.

One chemical of this group (chromium oxide—CrO_3) (CAS No. 1333-82-0) has reported commercial use including as:
- absorbents and adsorbents;
- anti-set-off and anti-adhesive agents;
- flux agents for casting or joining materials;
- impregnation materials;
- oxidising agents; and
- process regulators.

One chemical of this group (chromium oxide—CrO_3) (CAS No. 1333-82-0) has reported site-limited uses including as:
- electroplating agents; and
- intermediates.

Two chemicals of this group (chromium oxide—CrO_3 CAS No. 1333-82-0 and chromic acid—$H_2Cr_2O_7$ CAS No. 13530-68-2) have reported site-limited use including as laboratory chemicals.

One chemical of this group (chromium oxide—CrO_3) (CAS No. 1333-82-0) has reported non-industrial uses including in:
- food/feedstuff flavourings and nutrients; and
- non-agricultural pesticides and preservatives.

Restrictions

Australian

Chromium trioxide is listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2012) in Schedule 6 under the listing chromium trioxide (excluding its salts and derivatives).

International

The compounds appear on the following:

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient Hotlist);
- the EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the

composition of cosmetic products; and
• the New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

Existing Work Health and Safety Controls

Two chemicals of this group are currently classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia). These chemicals are:

• Cas No. 1333-82-0:
Carc. Cat. 1; R45 Muta. Cat. 2; R46 Repr. Cat. 3; R62 T+; R26 T; R24/25-48/23 C; R35 R42/43 N

• Cas No. 14977-61-8:
Carc. Cat. 2; R49 Muta. Cat. 2; R46 C; R35 R43 N

No specific classifications are available for the remaining chemicals in the group (CAS Nos 7738-94-5, 13530-68-2).

Exposure Standards

Australian

The chromium (VI) compounds have the following exposure standard in the Hazardous Substances Information System (HSIS) (Safe Work Australia). These exposure standards apply to all the compounds in this assessment:

• time weighted average (TWA): 0.05 mg/m³ for chromium (VI) compounds (as Cr), water soluble compounds; and
• short-term exposure limits (STEL): No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

• Cas No. 1333-82-0:
TWA = 0.001−2.0 mg/m³ [USA, Estonia].
STEL = 0.015−0.15 mg/m³ [Sweden, Canada]; and
Ceiling limit = 0.1 mg/m³ [Canada, USA].

• Cas Nos. 7738-94-5, 13530-68-2:
TWA = 0.005−2.0 mg/m³ [Denmark, Norway, Sweden, USA, Estonia].
STEL = 0.015−0.3 mg/m³ [Sweden, Poland]; and
Ceiling limit = 0.1 mg/m³ [Canada, Thailand, USA].

• Cas No. 14977-61-8:
TWA = 0.005−2.0 mg/m³ [Sweden, Canada, Indonesia, Ireland, Malaysia, Singapore, Spain, USA, Estonia];
STEL = 0.015 mg/m³ [Sweden] and 0.07 ppm [Canada]; and
Ceiling limit = 0.1 mg/m³ [USA].

Health Hazard Information

In this group of chemicals, the main concern regarding effects on human health is expected to be driven by the systemic toxicity chromium (VI) component of the compound. These compounds are also highly acidic and oxidising, leading to serious local corrosive effects. The chemicals in this group are either volatile (CrO3, Cl2CrO2) or exist in equilibrium with volatile CrO3 (H2CrO4, H2Cr2O7).

Toxicokinetics

The hexavalent chromium compounds have similar absorption, distribution, and excretion patterns (EC, 2005).

The extent of absorption of ingested hexavalent chromium [Cr (VI)] compounds from the gastrointestinal (GI)

tract is determined by its solubility and how rapidly it is reduced to trivalent chromium [Cr (III)]. While the Cr (III) does not readily diffuse across cell membranes, Cr (VI) does, due to its ability to use existing sulphate and phosphate anion transport mechanisms. Once formed, Cr (III) is stable, as the conversion back to the hexavalent state is not a favourable reaction due to the high energy required (EC, 2005).

Following inhalation exposure, animal studies have shown that 20–30 % of the administered Cr (VI) is absorbed via the respiratory tract. Highly water-soluble Cr (VI) is poorly absorbed via the gastrointestinal tract (only 2–9 % of the dose was absorbed in human studies) due to reduction to the relatively poorly absorbed Cr (III). Limited dermal absorption takes place through intact skin, with 1–4 % Cr (VI) from an aqueous solution crossing the skin in guinea pig studies. According to the results of animal testing, chromium derived from these compounds can remain in the lungs for several weeks after inhalation exposure (EC, 2005).

Generally, absorbed Cr (VI) is distributed throughout the body, but the blood, liver, kidney, and spleen are the primary sites of distribution, in addition to local deposition in either the respiratory or the GI tract. Bone is also a site of distribution and this may contribute to the long-term retention kinetics of chromium. Absorbed chromium can be transferred to foetuses through the placenta and to infants via breast milk. Hexavalent chromium penetrates red blood cells, where it is reduced by glutathione to trivalent chromium, which binds to haemoglobin and tends to stay for the lifespan of the cells. Chromium interacts with iron by affecting its binding to transferrin, and has been shown to impair iron metabolism and storage (EC, 2005).

Absorbed chromium is mainly excreted via urine, with only small amounts being eliminated in perspiration and bile. Inhaled or intratracheally administered Cr (VI) is excreted in urine and faeces in similar amounts (20–70 % of the administered dose). When orally administered, most appears in faeces, due to poor GI tract absorption. Chromium in urine and faeces is in the form of Cr (III) complexes, e.g. glutathione. Chromium can also be eliminated from the body in hair, nails, and breast milk (EC, 2005).

Acute Toxicity

Oral

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). Based on the information available, this hazard classification is supported for all the chemicals in this group.

Available oral LD50 values in rats exposed to chromium (VI) compounds varied with the compound and the sex of the rat. The LD50 values for chromium trioxide were 25 and 29 mg Cr (VI)/kg for female and male rats, respectively (ATSDR, 2012). Toxic effects included hypoactivity, lacrimation, mydriasis, diarrhoea, change in body weight, pulmonary congestion and corrosion of mucosa in the gastrointestinal tract (EC, 2005).

Dermal

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia). Based on the information available, this hazard classification is supported for all the chemicals in this group.

A dermal LD50 value of 57 mg/kg bw/day has been reported for chromium trioxide. Signs of toxicity included dermal necrosis, eschar formation, dermal oedema and erythema, diarrhoea and hypoactivity (EC, 2005).

Inhalation

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T; R26) in HSIS (Safe Work Australia). Based on the information available, this hazard classification is supported for all the chemicals in this group.

An LC50 value of 217 mg/m³ (equivalent to 0.21 mg/L) for chromium trioxide has been reported for rats with a 4-hour exposure period. Signs of toxicity included severe damage to the respiratory tract, respiratory distress, irritation, and body weight depression (EC, 2005).

Observation in humans

compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, haematological, hepatic, renal, and neurological effects. After dermal application of potassium chromate to treat scabies, renal failure, fatty degeneration of the heart, hyperaemia and necrosis of kidney tubules, and hyperaemia of the gastric mucosa have been described (ATSDR, 2012).

Irritation / Corrosivity

Corrosivity

The following chemicals in this group are currently classified as hazardous with the risk phrase ‘Causes severe burns’ (R35) in HSIS (Safe Work Australia): chromium trioxide (CAS No. 1333-82-0) and chromyl chloride (CAS No. 14977-61-8). Based on the information available, this hazard classification is supported for all the chemicals in this group.

The chemicals in this group are considered highly corrosive because of their low pH. An aqueous solution of chromium (VI) trioxide produced bleeding and ulceration of the stomach (due to its corrosive properties) in acute toxicity studies (EC, 2005). Airborne chromium trioxide is rapidly absorbed in the broncho-pulmonary tract causing corrosive reactions (IPCS, 1988).

In workers regularly exposed to highly water-soluble Cr (VI) in solution, chrome ulcers developed after some initial damage to the skin. This has been described for dye workers handling sodium or potassium dichromate solutions, and frequently in exposed workers in the chromate production and chrome plating industries. The severity of the ulcer depends upon the frequency and duration of skin contamination, the condition of the skin and the pH of the solution (EC, 2005). Favoured sites for ulcer development are the nailroot areas, the creases over the knuckles, finger webs, the backs of the hands, and the forearms. Ordinarily, a chrome sore, if not deep, persists for about three weeks after exposure is discontinued (IPCS, 1988). Exposure of the skin to airborne fumes and mists of chromium (VI) compounds may also contribute to the development of chrome sores, apart from direct dermal contact (ATSDR, 2012).

Skin Irritation

The chemicals in this group are recommended for classification with the risk phrase 'Causes severe burns' (R35). When a substance is classified with R35, the risk of damage by irritation is implicit and they are considered as if R36/37/38 has been assigned.

Eye Irritation

The chemicals in this group are recommended for classification with the risk phrase 'Causes severe burns' (R35). When a substance is classified with R35, the risk of damage by irritation is implicit and they are considered as if R36/37/38 has been assigned.

Sensitisation

Respiratory sensitisation

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (R42) in HSIS (Safe Work Australia). Based on the information available, this hazard classification is supported for all the chemicals in this group.

Sensitisation of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies (EC, 2005). The exposure route for the initial sensitisation in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures (ATSDR, 2012).

Symptoms of asthma and signs of respiratory distress consistent with a type I allergic response (decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, blocked nasal passages, cough, and wheeze) are produced in individuals previously sensitised to chromium compounds (ATSDR, 2012).

Chromium-sensitive patients, when challenged with chromium compounds from a nebuliser, displayed anaphylactoid reactions characterised by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory

volume (ATSDR, 2012).

It is not possible to determine a no-effect level or exposure-response relationship for induction or elicitation of respiratory sensitisation due to high individual variability.

Skin sensitisation

The following chemicals in this group are currently classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in HSIS (Safe Work Australia):

- chromium trioxide (CAS No. 1333-82-0); and
- chromyl chloride (CAS No. 14977-61-8).

Based on the information available, this hazard classification is supported for all the chemicals in this group.

In animals, Cr (VI) chemicals produced a positive skin sensitisation response in guinea pig maximisation studies and a mouse ear-swelling test (EC, 2005).

In humans working with the chemicals, skin sensitisation resulting from contact with Cr (VI) is relatively common (EC, 2005). Sensitisation may occur from inhalation, oral, and/or dermal exposure. The acute response phase lasts from a few days to a few weeks and is characterised by erythema, oedema, and small and large blisters. The chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin (ATSDR, 2012).

Several studies have estimated that exposure levels of 4–25 ppm are required to elicit a dermal response in chromium-sensitised individuals (ATSDR, 2012). It has also been reported that concentrations of potassium dichromate at 0.5 % and below elicited a response in patch testing studies. In one study, a minimum (10 % reacting) elicitation concentration of 0.09 μg Cr (VI)/cm² was calculated after Cr (VI)-sensitive volunteers were exposed to potassium dichromate (EC, 2005).

However, it is anticipated that the exposure level required to elicit a dermal response in sensitised individuals will be highly variable due to individual sensitivity and, therefore, it is not possible to reliably determine a threshold for either the induction or challenge phase in an exposed population using the available data.

Repeat dose toxicity

Oral

The chemicals in this group are not currently classified as hazardous in HSIS (Safe Work Australia). No particular studies were identified for the chemical.

Dermal

No repeated dermal studies are available, although these substances are recognised as being corrosive following repeated dermal exposure.

Inhalation

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (R48/23) in HSIS (Safe Work Australia). Based on the information available, this hazard classification is supported for all the chemicals in this group.

Repeated exposure to the chemical (as mist) produced irritant and corrosive effects in the respiratory tract at 3.5 mg/m³ and above in an 8-month study in rats (EC, 2005).

Another inhalation study found emphysema and nasal septum perforation in mice exposed intermittently to 1.81 mg/m³ as chromium trioxide for 12 months (ATSDR, 2012).

An 18-month inhalation study in Wistar rats exposed to the chemical (0.1 mg/m³) showed interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs;

along with decreases in body weight gain, haematocrit, haemoglobin levels, and red and white blood cell counts (ATSDR, 2012).

Observation in humans

Workers exposed to dissolved chromium (VI) aerosols and chromium trioxide mists (mean exposure duration of 2.5 years), reported effects on the respiratory, renal, and gastrointestinal systems.

Respiratory effects included bleeding in the nasal septum, nasal mucosal atrophy, nasal septal ulceration and perforation, epistaxis, rhinorrhoea, and decreased lung function (LOAEL is 0.002–0.414 mg chromium(VI)/m^3).

Effects indicating renal toxicity included increased retinol binding protein, tubular antigen and urinary β-2μ-globulin (LOAEL is 0.002-0.414 mg chromium(VI)/m^3).

Gastrointestinal effects reported in workers include stomach pains, cramps and ulcers, with a LOAEL value of 0.004 mg chromium(VI)/m^3.

Based on a comparison of LOAEL values for respiratory, renal and gastrointestinal effects in workers, the respiratory tract was identified as the most sensitive target of chronic-duration inhalation exposure to dissolved chromium (VI) aerosols and mists (ATSDR, 2012).

Genotoxicity

The following chemicals in this group are currently classified as hazardous as a Category 2 mutagen with the risk phrase ‘May cause heritable genetic damage' (R46) in HSIS (Safe Work Australia): chromium trioxide (CAS No. 1333-82-0) and chromyl chloride (CAS No. 14977-61-8). Based on the information available, this hazard classification is supported for all the chemicals in this group.

Hexavalent chromium (VI) compounds are mutagenic as shown in gene mutation assays (including reverse mutations, frame shift mutations and base pair substitutions) and DNA damage (including DNA interstrand crosslinks, DNA strand breaks and DNA-protein crosslinks) in bacterial cells (*Salmonella typhimurium*, *Escherichia coli* and *Bacillus subtilis*) (ATSDR, 2012).

Chromium (VI) compounds also showed positive results in forward mutations and mitotic gene conversion in yeast (*Saccharomyces cerevisiae*), and DNA damage (such as DNA strand breaks, fragmentation, DNA-protein crosslinks and DNA–DNA crosslinks), chromosomal damage (such as sister chromatid exchanges and chromosomal aberrations), and DNA synthesis inhibition in mammalian cell lines and primary cultures (including primary cultures of human gastric mucosal cells, respiratory tract cells and lymphocytes) (ATSDR, 2012).

Hexavalent chromium (VI) compounds also tested positive for mutations in *Drosophila melanogaster* and for DNA damage (such as DNA-protein crosslinks and DNA strand breaks), mutations (in mice exposed in utero, in mouse germ cells, and in transgenic mice), chromosomal damage (sister chromatid exchanges, chromosomal aberrations, and micronuclei), and DNA synthesis inhibition in rats and mice (IARC, 1990 and 2012).

Results of an occupational exposure study in humans showed that lymphocytes of workers exposed to dusts of chromium (VI) compounds had elevated frequencies of DNA strand breaks, sister chromatid exchange, and micronuclei (ATSDR, 2012). Findings from occupational exposure studies are supported by the above-mentioned in vivo studies in animals; in vitro studies in mammalian cells, yeast and bacteria; and studies in cell-free systems.

Carcinogenicity

Chromium trioxide (CAS No. 1333-82-0) is currently classified hazardous as a Category 1 carcinogen with the risk phrase ‘May cause cancer (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The chemical chromyl chloride (CAS No. 14977-61-8) in this group is currently classified hazardous as a Category 2 carcinogen with the risk phrase ‘May cause cancer by inhalation' (T; R49) in HSIS (Safe Work Australia). The available data support an amendment to the classification (refer to the Recommendation section below).

Based on the information available (epidemiological and animal data on carcinogenicity by inhalation, also some animal data on oral tumour induction), all the chemicals in this group should be classified as a Category 1 carcinogens (based on sufficient evidence in humans and animals) with the risk phrase ‘May cause cancer' (T; R45) in HSIS (Safe Work Australia).

Chronic exposure to the chemical in drinking water resulted in a dose-dependent increase in the incidence of neoplasms of the digestive tract in B6C3F1 mice (increased incidences of neoplasms of the duodenum, jejunum, or ileum in males at 7 mg/kg bw/day and females at 9 mg/kg bw/day), and F344/N rats (increased incidences of squamous cell neoplasms of the oral cavity increased in males at 17 mg/kg bw/day and females at 20 mg/kg bw/day) (NTP, 2008).

Chronic inhalation studies provide evidence that chromium (VI) compounds are carcinogenic in animals. The chemical produced lung tumours in rats when administered by continuous inhalation of aqueous aerosol or long-term repeated intratracheal administration in saline (EC, 2005). Also, there was a single incidence of a squamous cell carcinoma of the pharynx in rats after inhalation of the chemical as an aerosol (EC, 2005). Mice exposed to 4.3 mg chromium (VI)/m^3 had a 2.8-fold greater incidence of lung tumours, compared to controls (ATSDR, 2012).

Exposure to the chemical by inhalation as mist, caused nasal papillomas in mice (IARC, 2012).

In addition, numerous animal (rats and mice) studies with intratracheal, intrapleural, and intrabronchial exposure show that chromium (VI) produces respiratory tract tumours (EC, 2005). Local tumours in rats treated by intrapleural or intramuscular administration has also been documented (IARC, 1990).

Occupational exposure to chromium (VI) compounds (based on retrospective studies) in various industries (such as those involved in chromate production, chromate pigment production and use, chrome plating, stainless steel welding, and ferrochromium alloy production) have been associated with an increased risk of respiratory system cancers—primarily bronchogenic and nasal (ATSDR, 2012). One study also found significantly higher stomach cancer death rates in areas where well water chromium levels had been elevated (ATSDR, 2012).

Reproductive and developmental toxicity

Reproductive toxicity

Chromium trioxide (CAS No. 1333-82-0) is currently classified as hazardous as a Category 3 reproductive toxin with the risk phrase ‘Possible risk of impaired fertility’ (R62) in HSIS (Safe Work Australia). The data available support an amendment to the classification (refer to the Recommendation section below).

Based on the information available, all the chemicals in this group should be classified as a Category 2 reproductive toxins (based on sufficient evidence in animals) with the risk phrase ‘May impair fertility’ (R60) and ‘May cause harm to the unborn child’ (R61) in HSIS (Safe Work Australia).

Chromium trioxide exposure increased foetal death rate, caused growth retardation, and increased the frequency of skeletal deformities and cleft palates in rodents. Developmental effects have also been reported in mice exposed to chromyl chloride (IARC, 1990).

A number of studies have reported reproductive effects in rats and mice orally exposed to the chemical (63–333 mg/kg bw/day) in the drinking water. The chemical resulted in increased pre-implantation and post-implantation losses, resorptions and stillbirths; and decreased numbers of corpora lutea and numbers of foetuses, both live and dead (NTP, 2008).

Following a 6-day gavage administration of the chemical (0, 10 and 20 mg/kg bw/day) to Wistar rats, decreased

sperm count, increased percentage of abnormal sperm, and morphological changes to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed at six weeks after completion of treatment. A NOAEL was not determined in this study as effects were seen at all doses (Li et al., 2001).

Foetotoxicity was observed in mice following administration of the chemical in drinking water during gestation (days 0–19). Significant developmental effects in the absence of maternal toxicity (increased incidence of post-implantation losses and resorptions, reduced foetal weight, decreased crown-rump length and delayed cranial ossification) occurred at the lowest dose tested: 60 mg/kg bw/day. Therefore, no developmental NOAEL was determined (EC, 2005).

Other Health Effects

Neurotoxicity

Exposure of humans to high levels of airborne chromium (VI) in occupational and environmental settings produced symptoms of dizziness, headache, and weakness when they were working over the chromate tanks. Cerebral oedema was found in a case of fatal poisoning by ingestion. More recently, patients with 8–25-fold higher chromium blood levels resulting from parenteral feeding did not have increased signs of somatopsychic responses. However, the number of patients studied was small and they were suffering from serious clinical diseases. Additional studies are needed to provide further information on the effect of hexavalent chromium compounds on neuro-behavioural changes in humans (ATSDR, 2012).

Risk Characterisation

Critical Health Effects

The main critical effects to human health are carcinogenicity, reproductive/developmental toxicity, genotoxicity, acute toxicity (oral, dermal and inhalation), repeated dose toxicity from inhalation, irritation/corrosion (skin, eye and respiratory tract) and sensitisation (skin and respiratory).

Public Risk Characterisation

The use of chromium trioxide in products available to the public in Australia is restricted in Schedule 6 chemical in the Poisons Standard (SUSMP, 2012). Domestic use of the compounds that are relevant to Australia or internationally were not identified, therefore, it is unlikely that the public will be exposed to the chemical. Hence, the public risk from the chemical is considered low.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from these chemicals is considered high unless adequate control measures to minimise occupational exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business, or an employee at a workplace, has adequate information to determine appropriate controls.

NICNAS Recommendation

The chemicals are sufficiently assessed and risk managed provided the recommendation for classification and labelling is followed, and that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Considering the available information which indicates low public exposure to the chemicals, no regulatory controls are recommended.

Work Health and Safety

The health risk to workers from these chemicals is controlled when correct classification and labelling are considered, and adequate control measures to minimise occupational exposure and protective clothing are

implemented.

The chemical is recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This assessment does not consider classification of physical hazards and environmental hazards.

Note: * in the table below indicates existing hazard classification for one or more compounds in the group. It is proposed that the current classification is applied to all members of the group.

	Approved Criteria (HSIS)[a]	***GHS Classification***
Acute Toxicity	Toxic if swallowed (T; R25) Toxic in contact with skin (T; R24) Very toxic by inhalation (T+; R26)	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Causes severe burns (C; R35)	Causes severe skin burns and eye damage - Cat. 1 (H314)
Sensitisation	May cause sensitisation by inhalation (Xn, R42) May cause sensitisation by skin contact (Xi; R43)	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 1 - May cause cancer (T; R45)	May cause cancer - Cat. 1A (H350)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60) Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

* Existing Hazard Classification. No change recommended to this classification.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace

health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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