

Chromium

Toxicological Overview

Key Points

Kinetics and metabolism

- Uptake of chromium depends on the valency (III or VI) and solubility of the chromium-containing compound
- About 0.5-1% of chromium (III) present in the normal diet is adsorbed by the gastrointestinal tract, while chromium (VI) is more readily absorbed by both inhalation and oral routes
- Insoluble inhaled chromium particles can remain in the lung for a long time
- Absorbed chromium is distributed to all tissues of the body.
- Chromium (VI) is unstable in the body, and is rapidly reduced to chromium (V), chromium (IV) and ultimately to stable chromium (III) by endogenous reducing agents
- Absorbed chromium is excreted primarily in the urine and to a lesser extent in faeces

Health effects of acute exposure

- The respiratory tract is the primary target organ for inhaled chromium
- Ingestion of large amounts of chromium (VI) can lead to severe respiratory, cardiovascular, gastrointestinal, hepatic and renal damage and potentially death
- Chromium (VI) may cause occupational asthma in sensitised individuals

Health effects of chronic exposure

- Chronic inhalation of chromium (III) salts causes a range of inflammatory changes in the respiratory tract
- Chronic inhalation of high levels of chromium (VI) (in poorly-controlled occupational settings) may cause nasal septum ulceration and perforation, respiratory irritation, lung cancer and possible renal effects
- Dermal contact in chromium-sensitised individuals can lead to allergic dermatitis and chronic dermal exposure can result in deeply penetrating skin ulcers if left untreated
- Chromium (VI) compounds have mutagenic potential
- Chromium (VI) compounds are carcinogenic to humans but chromium (III) compounds are not classifiable as to their carcinogenicity to humans
- Potassium dichromate may be toxic to the reproductive system and the developing foetus. There is not sufficient evidence to suggest that chromium (III) compounds are reproductive or developmental toxicants

Toxicological Overview

Summary of Health Effects

The toxicity of chromium depends on the oxidation state, chromium (VI) being more toxic than the trivalent form chromium (III). In addition, chromium (VI) is the more readily absorbed by both inhalation and oral routes.

The respiratory tract is the primary target for inhaled chromium following acute exposure, although effects on the kidney, gastrointestinal tract and liver have also been reported.

Acute ingestion of high doses of chromium (VI) compounds, the exact quantity of which is not usually known, results in acute, potentially fatal, effects in the respiratory, cardiovascular, gastrointestinal, hepatic, renal, and neurological systems.

Due to the corrosive nature of some chromium (VI) compounds, dermal exposure can lead to dermal ulcers and at high doses, systemic toxicity leading to effects on the renal, haematological and cardiovascular system and death.

Studies of the effects of chronic occupational exposure to chromium compounds have proven difficult due to co-exposures to other toxic substances in the relevant working environments. Occupational exposure to some inhaled chromium (VI) mists may cause nasal septal ulceration and perforation, respiratory irritation and inflammation, dyspnoea, cyanosis and gastrointestinal, hepatic, renal, haematological effects and lung cancer. Chronic exposure to chromium (VI) compounds can also cause allergic responses (e.g. asthma and allergic dermatitis) in sensitized individuals.

Chronic exposure to chromium (III) resulted in weight loss, anaemia, liver dysfunction and renal failure

Chromium (VI) compounds are positive in the majority of *in-vitro* mutagenicity tests reported and may cause chromosomal aberrations and sister chromatid exchanges in humans. The mechanism of genotoxicity has been proposed to be a result of sequential reduction of chromium (VI) within the cells to chromium (III) and the binding of chromium (III) to macromolecules, including DNA.

Chromium (III) is not considered to be mutagenic in most cellular systems and there is no firm evidence that *in vivo* it is mutagenic to humans or experimental animals. Studies have not shown chromium (III) to be carcinogenic.

Chromium (VI) has been classified as a Group 1 known human carcinogen by the inhalation route of exposure and chromium metal and chromium (III) compounds are not classifiable as to their carcinogenicity to humans (Group 3) due to inadequate evidence in humans.

Potassium dichromate may be toxic to the reproductive system and the developing foetus. There is not sufficient evidence to suggest that chromium (III) compounds are reproductive or developmental toxicants.

Kinetics and Metabolism

In mammals, chromium (III) is an essential trace element involved in lipid and glucose metabolism [1]. It is usually considered that almost all the chromium in food is present as chromium (III) [1]. About 0.5-1% of chromium (III) present in the normal diet is absorbed [2], although this appears to vary depending on the amount of chromium in the diet, more being absorbed at low levels of chromium intake [1]. Absorption of ingested chromium (VI) compounds is greater than for chromium (III) compounds, ranging from approximately 2-8% [1, 3], although most of ingested chromium (VI) is considered to be reduced to chromium (III) in the stomach prior to absorption [3].

The behaviour and toxicity of chromium is strongly dependent on the valency, physical-chemical properties of the substance, the particle characteristics and the route of exposure/administration [2, 3]. For example, chromium (III) is generally poorly absorbed and mainly taken up by cells when organically complexed [2]. Chromium (VI) chromate ions are transported into cells, whereas chromium (III) compounds enter into cells by passive diffusion and phagocytosis [3]. Furthermore, water soluble chromium (III) aerosols of respirable size are more efficiently absorbed from the respiratory system than from the gastrointestinal tract, with approximately 5% being absorbed within hours of exposure, followed by further slow systemic absorption over weeks or months [2]. Uptake of deposited and retained insoluble chromium (III) oxide particles is a very slow process and particles containing chromium may be retained in the lung for years following occupational exposure [2]. In contrast, once deposited in the lungs, chromium (VI) compounds are generally transferred to the systemic circulation more readily than chromium (III) compounds [1].

Chromium (VI) is more efficiently absorbed through the skin than chromium (III) compounds [3]. Transfer rates of chromium (VI) across forearm skin in volunteers exposed to sodium chromate (0.01, 0.1 and 0.2 M) were 1, 6 and 10 $\mu\text{g chromium (VI) cm}^{-2} \text{ h}^{-1}$ [1]. Water soluble chromium (III) salts are able to penetrate the skin but have not been shown to reach the systemic circulation [2].

In the blood, 95% of chromium (III) is bound to large molecular mass proteins (e.g. transferrin), while a small proportion associates with low molecular mass oligopeptides [2]. Chromium compounds are widely distributed in the body, with a greater distribution reported following exposure to chromium (VI) compounds compared to chromium (III), reflecting the greater tendency of chromium (VI) to cross plasma membranes [3].

Chromium (VI) is unstable in the body and is reduced to chromium (V), chromium (IV), and ultimately to chromium (III) by endogenous substances such as ascorbate and glutathione and it is believed that the toxicity of chromium may result from damage to cellular components during this process (e.g. through the generation of free radicals) [1, 3].

In humans, absorbed chromium is excreted primarily via urine. The half-life for elimination of chromium when given as potassium chromate (0.05 mg chromium (VI) kg^{-1} in drinking water) is estimated to be approximately 35-40 hours [3].

Sources and Route of Exposure

Chromium occurs naturally in the Earth's crust, predominately in the trivalent, chromium (III), form, and it is ubiquitous in air, water, soil and biological materials [4]. Chromium (VI) compounds are essentially anthropogenically-produced and do not occur naturally in the environment. Large amounts are produced through a range of activities, including the production of chromates and bichromates, stainless steel, welding, chromium plating, ferrochrome alloys and chrome pigment production, material tanning, the combustion of coal and oil, cement works, and waste incineration with the global production with the global production of the major chromium (VI) compounds estimated at about 1942 kT year⁻¹, and a proportion of this, estimated to be about 17.5 T year⁻¹, will be released into various environmental media [4, 5]. The releases of chromium (VI) from any source are expected to be reduced via abiotic and biotic processes to chromium (III) in most situations in the environment, and the impact of the chromium (VI) form is therefore likely to be limited to the area around an exposure source [4]. In biological systems, the oxidation of chromium (III) to chromium (VI) never occurs [1]. In foodstuffs, chromium is generally considered to be present as chromium (III) [1].

The general population may be exposed to chromium by inhaling ambient air, or ingesting food and drinking water that contain chromium. Exposure may also occur through skin contact with certain consumer products containing chromium, e.g. some wood preservatives, cement, cleaning materials, textiles and leather tanned using chromium [6], and via cigarette smoke (the chromium content of cigarette tobacco from the USA has been reported to be 0.24-6.3 mg kg⁻¹) [7].

Chromium (III) is regarded as an essential element and has an important role in the maintenance of normal carbohydrate, lipid and protein metabolism [4]. Daily exposure from food sources, excluding supplements, is estimated at about 0.1 mg [4]. Absorption from the intestines is low (0.5-2%) and is thought to involve a mechanism other than passive diffusion [4]. The Expert Group on Vitamins and Minerals (EVM) noted that the Committee on the Medical Aspects of Food and Nutrition Policy (COMA) has not set a Reference Nutrient Intake (RNI) but did suggest that an adequate intake for chromium (III) was above 0.025 mg day⁻¹ for adults and between 0.00001 and 0.001 mg kg⁻¹ day⁻¹ for children and adolescents, while the US National Research Council (NRC) had published an Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 0.05-0.2 mg kg bw⁻¹ day⁻¹ for adults and 0.01-0.04 mg day⁻¹ for infants of up to 6 months of age. However, the EVM considered that there were insufficient data to derive a Safe Upper Level for chromium but noted that a total daily intake of approximately 0.15 mg kg⁻¹ day⁻¹ (or 10 mg person⁻¹) would be expected to be without adverse effects [4]. Signs of chromium deficiency, which is rare, are impaired glucose tolerance and glucose utilisation, weight loss, neuropathy, altered plasma fatty acid profile and nitrogen metabolism, and depressed respiratory quotient [4].

The average daily intake of chromium from foodstuffs for a UK adult has been estimated as approximately 117 µg day⁻¹, and the intake from drinking water at no more than 10 µg (based on consumption of 2 L day⁻¹, and an assumed concentration in drinking water of no more than 5 µg L⁻¹) [1]. Based on a UK atmospheric level of chromium 3 ng m⁻³ and assuming an inhalation rate of 20 m³ day⁻¹, the daily intake of chromium via inhalation for an adult has been estimated as 0.06 µg [1].

Workers in industries that use chromium can be exposed to higher levels of chromium than the general population. For example, Table 1 summarises data for the period 1986 to 1990 from the Health and Safety Executive (HSE) on personal occupational exposure levels to chromium (VI) during the manufacture of chromate compounds [5]. Based on these and other data, the European Chemicals Bureau (ECB) estimated reasonable worst-case

occupational exposures for a range of manufacturing activities; these included was 0.02 mg m⁻³ during manufacturer of the major chromates; 0.5 mg m⁻³ during chrome pigment weighing and mixing, 0.007 mg m⁻³ during chrome tanning; and 0.01 mg m⁻³ during manufacture of chromium metal [5].

Table 1. Personal exposure during the manufacturer of chromate compounds, nd = not detected

Activity	Range (mg m ⁻³ chromium (VI))	Geometric mean (mg m ⁻³ chromium (VI))
Packing/unpacking	nd - 0.07	0.0093
Impregnating	0.011 - 0.14	0.028
Kilning	0.001 - 0.12	0.0046
Leaching plant	0.01 - 0.05	0.0031
Crystal plant	0.001 - 0.54	0.0098
Evaporation	0.001 - 0.05	0.0043
Chromic acid plant	0.001 - 0.13	0.0038
Potassium dichromate plant	0.002 - 0.08	0.011
Chromium trioxide plant	0.001 - 0.01	0.0026
Chrome tan plant	0.001 - 0.005	0.0017
General plant	0.001 - 0.05	0.006

The Health and Safety Commission (HSC) has established a workplace exposure limit (WEL) of 0.5 mg m⁻³ (8-h TWA) for chromium (III) compounds (as chromium metal), and 0.05 mg m⁻³ (8-hour TWA) for chromium (VI) compounds (as chromium metal), based upon dermal ulceration, sensitisation potential and carcinogenicity as constituting the critical toxic properties of chromium (VI) compounds [8].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

The respiratory tract is the primary target for inhaled chromium [9] although effects on the kidney, gastrointestinal tract and liver have also been reported. No reports of fatalities resulting from inhalation of chromium compounds were found.

There is no unequivocal evidence that exposure to chromium (III) compounds induces asthma and chromium (III) compounds are not regarded as respiratory sensitizers [2].

Ingestion

Accidental or intentional ingestion of high doses of chromium (VI) compounds, the exact quantity of which is not usually known, results in acute, potentially fatal, effects in the respiratory, cardiovascular, gastrointestinal, hepatic, renal, and neurological systems [3, 5, 9]. Some of these effects can be attributed to the corrosive nature of the compound [8]. For example, in one case a 17-year-old male died 14 hours from respiratory distress with severe haemorrhages after ingesting potassium dichromate (29 mg chromium (VI) kg^{-1}) in an attempted suicide. Caustic burns in the stomach and duodenum and gastrointestinal haemorrhage were noted [9]. Several other cases have reported fatalities following ingestion of lower doses of chromium (VI). In one case, a 14-year-old boy suffered gastrointestinal ulceration and severe liver and kidney damage and died 8 days after hospitalisation after ingesting potassium dichromate (7.5 mg chromium (VI) kg^{-1}), while in another case, a 44-year-old man died of severe gastrointestinal hemorrhage one month after ingesting chromic acid (4.1 mg chromium (VI) kg^{-1}) [9]. Reports of poisoning cases have not reported respiratory or cardiovascular effects at non lethal doses [9], although clinical manifestations of liver and renal damage have been reported among individuals surviving beyond 24 hours [8]. A number of case reports have indicated that the lethal oral dose of dichromates and chromium trioxide is within the range 2.5-195 mg chromium (VI) kg^{-1} [5].

There are fewer documented cases of chromium (III) poisoning. In one fatal case, a woman who ingested 400 ml of a leather tanning solution containing 48 g basic chromium sulphate died of cardiogenic shock 36 hours after hospital admission despite haemodialysis treatment [2]. Post-mortem revealed haemorrhagic erosive gastroenteritis of the entire gut, severe haemorrhagic pancreatitis, pulmonary congestion and oedema, peritonitis, ascites and widespread petechial haemorrhages.

Dermal/ocular exposure

Several case studies have reported effects on the renal, haematological and cardiovascular system, gastric mucosa hyperaemia and death following dermal exposure to chromium (VI) compounds, although indications of the exposure amount were not given and in most instances subjects had pre-existing medical conditions (carcinoma of the face, scabies infection), which may have contributed to the reported effects [9]. Broken skin or skin damaged during chromium (VI) exposure by the corrosivity of the compound, or high temperature, probably facilitated absorption in these cases [5].

Animal and In-Vitro Data

Inhalation

Symptoms of chromium (IV) toxicity following inhalation exposure include irritation of the respiratory tract and respiratory distress and decreased body weight gain [3, 5]; female rats appear slightly more sensitive to most chromium (VI) compounds than males with the exception of sodium chromate for which toxicity is similar in both sexes and chromium trioxide, where males appear to be more sensitive (Table 2) [3]. These differences are of doubtful biological significance

Table 2. Acute inhalation LC₅₀ values in rats exposed to chromium (VI) aerosols for 4 h [3, 5]

Chromium (VI) compound	Sex	Inhalation LC₅₀ (mg chromium (VI) m⁻³)
Sodium chromate, sodium dichromate, potassium dichromate, ammonium dichromate	M	33 - 82
	F	29 - 45
Chromium trioxide	M	87
	F	137

Death occurred in rats following a 6 h exposure to potassium dichromate aerosols >13 mg m⁻³ chromium (VI), while no deaths were reported at 11 mg m⁻³ chromium (VI) [5]. Lung oedema, inflammation and tracheal epithelium necrosis were reported in rats exposed to sodium chromate (9 mg m⁻³ chromium (VI)) for 24 h, while only minimal effects (reduction in glycoprotein secretion in the trachea) were noted at 3 mg m⁻³ chromium (VI) [5].

No acute inhalation toxicity information is available for chromium (III) compounds.

Ingestion

For chromium (VI), acute oral lethal doses in rats are compound specific and, as for inhalation toxicity, show a slight sex difference in susceptibility although this is of doubtful biological significance (Table 3).

Chromium (III) oxide has low oral toxicity because it is insoluble in water and poorly absorbed. In rats dosed with 5 g kg⁻¹ of chromium (III) oxide no deaths or pathological changes were noted after 14 days (LD₅₀ > 5 g kg⁻¹) [2]. In male Wister II rats given a single oral dose of 10 or 15 g/kg chromium oxide the only sign reported was ruffled hair (LD₅₀ >15 g kg⁻¹) [2]. Other LD₅₀ values reported for rats include: 3.5 g kg⁻¹ (CI 3.19-3.79 g kg⁻¹) for chromium sulphate; 11.3 g kg⁻¹ for chromium (III) acetate; 3.3 g kg⁻¹ for chromium nitrate; and 1.5 g kg⁻¹ chromium nitrate nonahydrate [2].

Table 3. Acute oral LD₅₀ values in rats [3, 5, 9].

Chromium (VI) compound	Sex	Oral LC ₅₀ (mg chromium (VI) kg ⁻¹)
Sodium chromate, sodium dichromate, potassium dichromate, ammonium dichromate	M	21-28*
	F	13-19*
Chromium trioxide	M	29**
	F	25
Calcium chromate	M	249
	F	108
Strontium chromate	M	811 N/A
	F	21-28*

N/A Not available

*Pulmonary congestion and corrosion of gastrointestinal tract mucosa noted at necropsy

**Bleeding and stomach ulcerations noted

Dermal / ocular exposure

Dermal exposure to aqueous chromium (VI) compounds results in acute toxicity. In New Zealand rabbits, given single dermal exposures to chromium (VI) as sodium chromate, sodium dichromate, potassium dichromate or ammonium dichromate, LD₅₀ values ranged from 36-553 mg chromium (VI) kg⁻¹ in females and 336-763 mg chromium (VI) kg⁻¹ in males [3, 9]. Reported signs of toxicity included: dermal necrosis, eschar formation, oedema and erythema, diarrhoea and hypoactivity. A dermal LD₅₀ of 30 mg chromium (VI) kg⁻¹ has been reported for chromium trioxide [5]. Neutralised sodium chromate solution was not irritating to the rabbit eye [5].

No indication of skin irritation or corrosion was found in rabbits exposed to chromium (III) oxide (500 mg moistened with water) under an adhesive patch for 4 h and chromium (III) oxide is not irritating to the eye [2]. It has also been reported that chromium sulphate is not irritating to eye and skin in rabbits [2].

Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

The metallurgical, refractory and chemical industries are the prime users of chromium and many occupational studies on workers chronically exposed (for several months or years) to chromium (VI) dust or vapour have reported effects of the respiratory system such as nasal irritation, itching and soreness, sneezing, rhinorrhea, nose bleeds, nasal mucosa lesions e.g. septum atrophy, ulcerations and perforations, bronchitis, reduced lung function, and damage to the skin, such as ulcerations and dermatitis [3, 5, 9]. In some chromium-sensitive individuals occupational exposure to airborne chromium (VI) may result in asthma [3].

Exposure to multiple chemical agents in the workplace and the presence of chromium (VI) in chromium (III) compounds makes assessment of the toxicity of chromium (III) difficult [2, 9].

Inhalation

Case reports have shown that occupational inhalation of aqueous chromium (VI) mists (levels in air not reported) can result in irritation and inflammation of the respiratory tract, dyspnoea and cyanosis [5]. Two subjects inhaling “massive amounts” of chromium (VI) trioxide developed dyspnoea, cough and wheeze, with marked hyperaemia of the nasal mucosa but not nasal septum perforation [3].

A study on chrome plating workers occupationally exposed to chromic acid (mean 2-200 $\mu\text{g m}^{-3}$ chromium (VI) for 8 h day for 0.2-23.6 years) found that at low concentrations (mean <2 $\mu\text{g m}^{-3}$ chromium (VI)) workers developed smeary, crusty and atrophied septum mucosa and at higher concentrations (2-200 $\mu\text{g m}^{-3}$ chromium (VI)) nasal irritation, mucosa ulceration and atrophy and septum perforation was observed [3], although these effects may not have resulted from exposure levels actually measured, but may have occurred from earlier exposures [9]. Another study on electroplating workers exposed to chromic acid (>0.1 mg m^{-3} chromium (VI)) for less than 1 year reported frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea, nose-bleed, nasal septum ulceration and perforation.

Evidence suggests that exposure to chromium (VI) may induce occupational asthma and chromate sensitive workers acutely exposed to chromium (VI) compounds may develop asthma and other signs of respiratory distress [2, 3, 9]. For example, a study of 5 individuals with a history of contact dermatitis to chromium, found that exposure via nebuliser to a potassium dichromate aerosol containing 0.035 mg ml^{-1} chromium (VI) resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritis, blocked nose, coughing and wheezing [3, 9].

Some studies of workers exposed to airborne chromium (VI) have found increased levels of low-molecular-weight urinary proteins, such as retinol binding protein, β_2 -microglobulin and tubular antigens, indicative of early kidney changes, for example one such study identified a LOAEL of 4 $\mu\text{g m}^{-3}$ chromium (VI) [9]. Other studies have found no association.

Work-related cough or dyspnoea, production of phlegm, and shortness of breath was also noted in workers exposed to dust containing chromium oxide at an approximate concentration of 240-480 $\mu\text{g m}^{-3}$ chromium (III) [2].

Ingestion

There are few human data on the adverse effects of chronic chromium (VI) intake. One study of 155 villagers living in the vicinity of a chromium smelting plant in China, whose well-water was contaminated with approximately 20 mg L⁻¹ chromium (VI), reported an association between water consumption and various health effects, principally of the gastrointestinal tract (oral ulcer, diarrhoea, vomiting, abdominal pain and indigestion) and the blood (leucocytosis and immature neutrophils [9]). However, it was not possible to derive a dose-response relationship in this study.

Chromium (III) is an essential element involved in carbohydrate and lipid metabolism, although there is some evidence that repeated intake above the recommended dose may cause toxic effects. In one case an individual developed renal failure after taking 12-14 times the normal chromium (III) intake in the form of chromium picolinate supplement (600 µg day⁻¹ for six weeks), which was attributed to chromium (III) ingestion [4]. In another case, ingestion of 1200-2400 µg day⁻¹ of chromium (III) picolinate for 4-5 months was reported to result in weight loss, anaemia, haemolysis, liver dysfunction (elevated aminotransferases and total bilirubin) and renal failure [4]. The subject received hospital treatment (transfusions and haemodialysis and all measured parameters returned to normal within one year.

Dermal / ocular exposure

Dermal exposure to chromium (VI) and to a lesser extent chromium (III) compounds, can cause contact dermatitis and eczema in chromium sensitised individuals [2, 3, 9]. The allergen is considered to be the chromium (III)-protein complex, but chromium (VI) is more readily able to cross the dermal barrier [1]. While occupational exposure to chromium compounds appears to be the major cause of contact dermatitis [2], clinical evidence on the allergenic potential of soluble chromium (III and VI) relating to the wearing of leather articles tanned with chromium, has been noted [9].

Chronic occupational exposure to chromium (VI) compounds can cause chrome holes (sores or dermal ulcers), which if left untreated, may penetrate deeply into the skin and under prolonged exposure conditions can be very slow to heal. Skin contact with chromate salts may cause rashes [3].

Limited studies suggest that chromium sulphate is a moderate (Grade III) sensitizer and potassium dichromate is an extreme sensitizer (Grade V) [2].

Genotoxicity

Most *in-vivo* studies concerned with occupational exposure have involved exposure to other suspected genotoxic agents besides chromium (III and VI), which makes the assessment of the genotoxicity of chromium difficult. Furthermore the few studies reported here are limited in that the exposure concentrations were not always known and in many cases the group size was too small [9].

No difference in nasal cell micronuclei was reported in a study on Finnish workers exposed to chromite ore (median personal exposure level 22 µg m⁻³), in which no chromium (VI) could be detected and no increase in total chromosomal aberrations was found in cultured peripheral lymphocytes of tannery workers in comparison to controls [2]. Another study on residents living near a waste site for chromium slags and chromite ores found a significant

increase in the number of DNA-protein cross-links in mononuclear leukocytes in comparison to unexposed controls [2].

No increase in strand breaks or oxidative damage to DNA of lymphocytes was found in workers exposed to chromium (VI) during bichromate production [9]. In contrast other studies on electroplaters and stainless steel welders have reported increased incidences of chromosomal aberrations and sister chromatid exchanges compared with controls [4, 9].

Carcinogenicity

The International Agency for Research on Cancer (IARC) have classified chromium (VI) as carcinogenic to humans (Group 1) based on sufficient evidence in humans as encountered in the chromate production, chromate pigment production and chromium plating industries [7].

Epidemiology studies clearly indicate the link between exposure to chromium (VI) compounds and lung cancers [3, 4, 9, 10]. Studies of workers in the production of chromate and chromate pigments have consistently shown excess risks for lung cancer, while other studies have reported an excess of lung cancer in workers in the chromium plating industry, particularly among those with at least ten years of employment at chrome baths, although workers in this industry have been exposed to soluble chromium (VI) compounds and possibly also to nickel [7].

Several studies have identified an excess risk of rare sinonasal cancer associated with workers in primary chromate and chromate pigment production and chromium plating [7].

IARC have considered chromium metal and chromium (III) compounds as not classifiable as to their carcinogenicity to humans (Group 3) due to inadequate evidence in humans [7].

Reproductive and developmental toxicity

There is some limited evidence to suggest that chromium (VI) compounds may be toxic to the male reproductive system. One study of 21 electroplating workers in Henan, China, significant ($p < 0.05$) decreases in sperm count and motility, and significantly increased follicle stimulating hormone concentrations were found in workers exposed to chromium (VI) exposure compared with controls [3]. Furthermore, a limited study which assessed semen quality in 57 welders in India, where exposures to chromium and nickel were suggested, reported significant correlations with chromium blood concentrations and increased tail defects, decreased sperm count, rapid linear progressive motility and sperm vitality, although nothing was known about the exposure of control subjects [3]. There are no adequate data for assessing the effect of chromium on female reproduction.

Existing studies have not produced convincing evidence on the development toxicity of chromium (III) compounds.

Animal and In-Vitro Data

Inhalation

Repeated exposure of animals to chromium (VI) compounds causes similar effects to those observed in humans i.e. irritant and inflammatory effects on the respiratory system and

immunological changes such as increased serum immunoglobulin and white blood cell count, and alveolar macrophage and spleen lymphocyte activities [3, 5].

Longer-term exposure to chromium (VI) compounds (1-1.5 years in mice and 1.5-2 years in rats) can cause thickening of septa of the alveolar lumen, interstitial fibrosis bronchopneumonia, and lung abscesses (rats) and nasal septum perforation, emphysema, epithelial necrosis and hyperplasia in the large and medium bronchi, with numerous openings in the bronchiolar walls (mice) [3].

No treatment-related deaths or clinical signs were noted in rats exposed to chromium (III) oxide aerosols at approximately 4.4, 15, 44 mg m⁻³ (3, 10 and 30 mg m⁻³ chromium (III)) for 6 hours day⁻¹, 5 days week⁻¹, for 13 weeks [2]. Pathological changes were limited to pigment deposition and mild inflammation in the lungs. The Lowest Observed Adverse Effect Level (LOAEL) was 3 mg m⁻³ chromium (III). Studies with inorganic chromium (III) salts have established a systemic No Observed Adverse Effect Level (NOAEL) of 3 mg m⁻³ chromium (III) sulphate (based on decreased body weight and altered haematology), but a NOAEL was not established for respiratory inflammation effects since effects occurred at the lowest dose (3 mg m⁻³ chromium (III)) [2].

Ingestion

Sub-chronic and chronic oral exposure of animals to chromium (VI) compounds does not appear to result in significant toxicological effects; some studies have reported minimal or transient changes in body weight gain, haematological indices and the immune system, while others have not [3, 5].

Low toxicity of chronic exposure to chromium (III) compounds can be expected due to poor bioavailability [1]. For example, no adverse effects were seen in rats fed chromium oxide at up to 1368 mg kg⁻¹ day⁻¹ chromium (III) for 90 days, or in rats fed up to approximately 7 mg kg⁻¹ chromium (III) as chromium chloride for 20 weeks, although the latter study was limited by the small number of animals used and endpoints assessed [2].

Genotoxicity

Soluble chromium (VI) compounds have been found to be mutagenic in virtually all *in-vitro* test systems [3, 5, 10], while negative results have been reported for chromium (III) in the majority of *in-vitro* tests in bacteria and mammalian cells, even though chromium (III) is generally more reactive with isolated DNA than chromium (VI) [2, 10].

Chromium (VI) compounds have been reported to cause DNA damage, DNA strand cross-links, DNA-protein cross-links, sister chromatid exchanges and chromosomal aberrations *in vivo* [3, 10], while there is no adequate evidence to suggest that chromium (III) compounds are genotoxic *in vivo* [2, 10].

Organic chromium (III) picolinate (up to 2500 mg kg bw⁻¹) administered to male rats once a day for 3 days by gavage was negative in the *in vivo* bone marrow micronucleus test [2]. Based on the available *in-vitro* data, the COM concluded in 2004, that chromium (III) picolinate should be regarded as not being mutagenic *in vitro*, and considered that since the available *in-vivo* tests in mammals are negative, no further *in-vivo* testing is currently required [10].

Carcinogenicity

The IARC has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of the following chromium (VI) compounds: calcium chromate, zinc chromates, strontium chromate and lead chromates and that the evidence is limited for chromic acid and sodium dichromate [7].

Lung tumours were observed in 3/19 male Wister rats exposed for 22 hours day⁻¹ 7 days week⁻¹ for 18 months to 0.1 mg m⁻³ chromium (VI) as sodium dichromate, followed by 12 months of observation. The tumours included two adenomas and one adenocarcinoma. No lung tumours were observed in controls or the rats exposed to ≤0.05 mg m⁻³ chromium (VI). The increased incidence of lung tumours in the treated rats was significant by the Fisher Exact Test (P=0.03) [9].

The IARC has also concluded that the evidence for carcinogenicity of barium chromate and chromium (III) compounds is inadequate [7].

Reproductive and developmental toxicity

A number of oral studies have reported developmental toxicity following pre-mating and/or *in utero* exposure. Potassium dichromate(VI) given in drinking water to female rats (37-87 mg kg⁻¹ day⁻¹ chromium (VI)) and mice at (52-169 mg kg⁻¹ day⁻¹ chromium (VI)) for 20 or 90 days followed by mating with unexposed males, resulted in foetal mortality (post-implantation loss, resorption and decreased number of live foetuses), developmental retardation (decreased fetal body weight and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails [3]. No developmental effects were noted in a multigeneration study in which rats were exposed by inhalation exposure to sodium dichromate at 0.2 mg m⁻³ chromium (VI) [3].

No reproductive or developmental effects were reported in rats given 1500 mg kg bw⁻¹ chromium (III) for 60 days prior to mating and throughout gestation [1, 2]. In contrast, chromium (III) chloride administered to mice via drinking water reduced both male and female fertility at an approximate dose of 150 mg kg bw⁻¹ chromium (III), and foetal toxicity in male offspring of pregnant females exposed to approximately 31-36 mg kg bw⁻¹ chromium (III) during gestation and lactation [1]. Although the validity of these results has been questioned due to insufficient reporting and inconsistent findings [2] and therefore there is no adequate evidence to indicate that chromium (III) compounds are reproductive or developmental toxicants.

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.