IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Concise International Chemical Assessment Document 78

INORGANIC CHROMIUM(VI) COMPOUNDS

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

World Health Organization

The **International Programme on Chemical Safety (IPCS)** was established in 1980. The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase international coordination in the field of chemical safety. The Participating Organizations are: FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS)—a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.[1]

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world—expertise that is required to produce the high-quality evaluations of toxicological, exposure and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

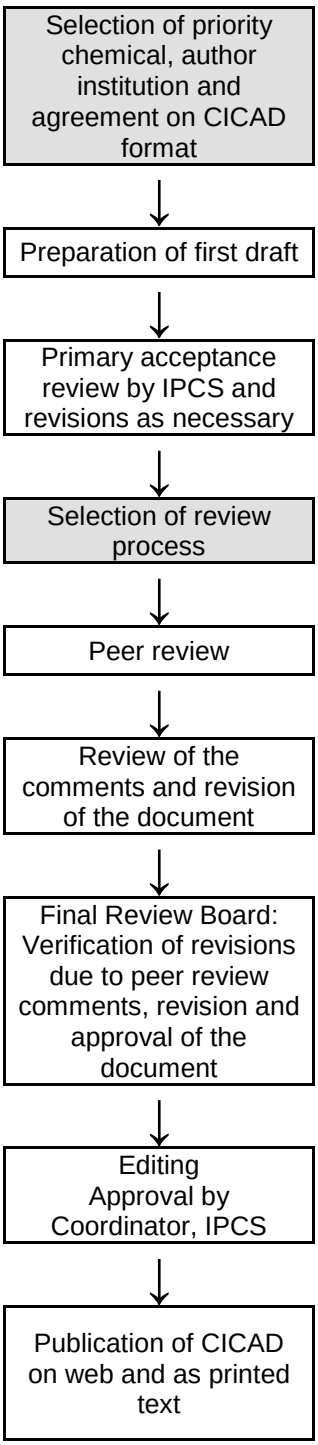
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a de novo CICAD) and which institution bears the responsibility for the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional or international review. When no appropriate source document is available, a CICAD may be produced de novo. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced de novo, provided it is not controversial. If no source document is available, IPCS may produce a de novo risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared de novo, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This Concise International Chemical Assessment Document (CICAD)[1] on inorganic chromium(VI) compounds was based principally on the *Toxicological profile for chromium* prepared by the United States Agency for Toxic Substances and Disease Registry (ATSDR, 2000) and updated to include information that appeared in a draft updated profile released by ATSDR for public comment[2] (ATSDR, 2008). Information on the nature of the peer review and the availability of the source documents is presented in Appendix 2. A literature search to identify any human health references published subsequent to those incorporated in the source documents was carried out by the Secretariat, with an end date of December 2008. The *Toxicological review of hexavalent chromium (CAS No. 18540-29-9) in support of summary information on the Integrated Risk Information System (IRIS)*, prepared by the United States Environmental Protection Agency (USEPA, 1998), was also consulted. Sections 10 (Effects on other organisms in the laboratory and field) and 11.2 (Evaluation of environmental effects) are based on the European Union (EU) risk assessment report on chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate (EU, 2005). Details on the nature and availability of the USEPA (1998) and EU (2005) documents are also provided in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was first discussed as an international assessment at a meeting of the Final Review Board held in Helsinki, Finland, on 26–29 March 2007. Participants at this Final Review Board meeting are listed in Appendix 4. Following a decision to update the carcinogenicity section, the draft CICAD was referred to a World Health Organization (WHO) Consultative Group, which met at the University of Bradford, Bradford, England, on 1–2 November 2010. Participants in the Consultative Group meeting are listed in Appendix 5. The amended draft document following the Consultative Group meeting was made available for public and peer review via the International Programme on Chemical Safety (IPCS) web site. The draft document was revised by the Secretariat following the peer review. The Secretariat took the decision to maintain the end date for the data in this CICAD as the end of 2008. The CICAD was approved as an international assessment by members of the Final Review Board (by correspondence) during June–October 2012. Details on the Final Review Board members who participated in this process are presented in Appendix 6. The International Chemical Safety Cards for lead chromate (ICSC 0003), zinc chromate (ICSC 0811), strontium chromate (ICSC 0957), chromium(VI) oxide (ICSC 1194), ammonium dichromate (ICSC 1368), sodium dichromate (anhydrous) (ICSC 1369), sodium chromate (ICSC 1370), potassium dichromate (ICSC 1371) and barium chromate (ICSC 1607), produced by WHO in collaboration with the International Labour Organization, have also been reproduced in this document.

Chromium is a naturally occurring element found in rocks, soil, animals, plants and volcanic dust and gases. The most stable forms are chromium(0), trivalent chromium (chromium(III)) and hexavalent chromium (chromium(VI)).

This CICAD focuses on chromium(VI), but mentions other valence states when dealing with speciation within the environment and within the organism that is essential to understanding the mode of action. A separate CICAD (CICAD 76; IPCS, 2009) has been published on inorganic chromium(III) compounds.

Chromium(VI) compounds produced by the chemical industry are used in a wide range of applications, including chrome plating, the manufacture of dyes and pigments, wood preservatives, surface coatings and corrosion inhibitors.

Chromium is emitted into the air by anthropogenic sources (including combustion of fuels and from metal industries) and also by natural sources, including forest fires. Chromium is present in the atmosphere primarily in particulate form.

Domestic and industrial effluents containing chromium(VI) are emitted into surface waters. Chromium(VI) may be reduced to chromium(III) and then adsorbed to particulate matter if large amounts of organic matter are present. Reduction of chromium(VI) to chromium(III) occurs rapidly under the anaerobic and reducing conditions that generally exist in deeper groundwaters. Most of the chromium released into water will ultimately deposit in the sediment.

Chromium in soil is present mainly as insoluble oxide and is not very mobile. Chromium(VI) appears to be much less strongly adsorbed to soils than chromium(III). The mobility of soluble chromium in soil will depend on the sorption characteristics of the soil. Living plants and animals absorb the hexavalent form in preference to the trivalent form, but once absorbed, the hexavalent chromium is reduced to the more stable trivalent state.

[1] For a complete list of acronyms and abbreviations used in this report, the reader should refer to Appendix 1.

[2] During the preparation of this CICAD for publication, the updated *Toxicological profile for chromium* was finalized and published by ATSDR in 2012. All information taken from ATSDR (2000, 2008) was verified against the final 2012 version of the toxicological profile.

Bioconcentration factors for chromium(VI) in freshwater fish are low, at around 1, because chromium(VI) is reduced to chromium(III) in the organism, resulting in the accumulation of total chromium to a factor approximately 100 times the water concentration.

The atmospheric concentrations of total chromium in remote areas range from 0.005 to 2.6 ng/m^3, with typical concentrations of <10 ng/m^3 in rural areas and 10–30 ng/m^3 in urban areas. Higher concentrations (>500 ng/m^3) have been reported near anthropogenic sources. Total chromium concentrations in river water in the USA usually range from <1 to 30 µg/l, with a median value of 10 µg/l. In Europe, a median total chromium concentration of 0.38 µg/L (<0.01–43.3 µg/l) has been reported for surface waters. Total chromium concentrations in lake water generally do not exceed 5 µg/L. Mean chromium(VI) concentrations of up to 3 µg/l have been reported for surface waters. Higher levels of chromium can be related to sources of anthropogenic pollution, with levels of up to 648 µg chromium(VI) per litre reported for industrial wastewater.

In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The mean total chromium concentration in ocean water is 0.3 µg/l, with a range of 0.2–50 µg/l. In the suspended materials and sediment of water bodies, total chromium levels ranged from 1 to 500 mg/kg. Total chromium levels in soil vary greatly and depend on the composition of the parent rock from which the soils were formed. The concentration range of total chromium in soils and other surficial materials surveyed in North America was 1–2000 mg/kg, with a geometric mean concentration of around 40 mg/kg. In Europe, median chromium concentrations for topsoil were 60 mg/kg (<3–6230 mg/kg) after hydrofluoric acid extraction and 22 mg/kg (<1–2340 mg/kg) after nitric acid extraction. Higher levels have been reported at contaminated sites.

Exposure of the general population occurs through inhaling ambient air and ingesting food and drinking-water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products.

Levels of chromium in ambient air (<0.01–0.03 µg/m^3) and tap water (<2 µg/l) have been used to estimate the daily intake of chromium via inhalation (<0.2–0.6 µg) and via tap water (<4 µg). The chromium content of foods varies greatly. Estimated dermal exposures of workers engaged in packing chromate products and of those weighing and charging dry ingredients to mixers in the manufacture of chromium(VI) pigments are 0–0.1 and 0.1–1 mg/cm^2 per day, respectively.

Workers in chromium-related industries in the past were exposed to much higher levels of chromium than present-day workers; in many industries, exposure levels were several hundreds of micrograms per cubic metre. In modern installations, exposures are typically below 20 µg/m^3.

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 (e.g. 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.

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.

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.

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.

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.

Occupational exposure to chromium(VI) by inhalation is causally associated with an increased incidence of lung cancer. Several studies have also shown an association of chromium(VI) exposure with cancer of the nose and nasal sinuses. Very limited data are available on the association between exposure to chromium(VI) in drinking-water and cancer in humans. Chromium(VI) has caused cancer in experimental animals after exposure by inhalation, intratracheal and oral administration.

Occupational exposure by dermal contact 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.

Chromosomal aberrations and DNA damage have been observed in some humans occupationally exposed to chromium(VI) compounds. Chromium(VI) has also been shown to be genotoxic in in vivo and in vitro tests.

A tolerable concentration of 0.005 µg chromium(VI) per cubic metre for chromium trioxide/chromic acid was derived based on a lowest-observed-adverse-effect concentration (LOAEC) of 2 µg chromium(VI) per cubic metre for non-cancer upper respiratory effects in humans.

A tolerable concentration of 0.03 µg chromium(VI) per cubic metre for inhalation exposure to chromium(VI) in the form of chromium(VI) salts was derived for non-cancer effects on the respiratory tract based on a benchmark analysis of increased lactate dehydrogenase activity in bronchoalveolar lavage (BAL) fluid from chromium(VI)-exposed rats, used as an indicator of pulmonary damage. This tolerable concentration is supported by findings of nasal irritation effects in workers engaged in chromate production.

An oral tolerable daily intake for non-cancer effects of 0.9 µg chromium(VI) per kilogram body weight (bw) per day was derived from findings of diffuse epithelial hyperplasia in the duodenum observed in female mice after exposure to sodium dichromate dihydrate in drinking-water. This was based on a lower limit on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.094 mg/kg bw per day and application of an uncertainty factor of 100.

The cumulative lifetime excess risk of lung cancer from occupational exposure to 1 µg chromium(VI) per cubic metre based on the epidemiological study with the best exposure information (in chromate production workers) is 6×10^{-3}. This estimate assumes beginning work at age 20 and working 8 hours/day, 5 days/week, for 45 years. An estimate of the lifetime risk of lung cancer from environmental exposure to 0.001 µg chromium(VI) per cubic metre (24 hours/day, 365 days/year, for 70 years) is 4×10^{-5}.

After exposure to sodium dichromate via drinking-water, there was an increased incidence of benign and malignant tumours in the oral cavity in rats and small intestine in mice. There is significant uncertainty associated with the carcinogenic risk to humans of chromium(VI) compounds via oral exposure.

Short-term and long-term ecotoxicological data on the effects of chromium(VI) compounds are available for a wide variety of organisms, life stages, end-points and test conditions. In general, chromium(VI) toxicity increases with decreasing pH (i.e. from 8.0 to 6.0), increasing temperature (i.e. from 15 °C to 25 °C) and decreasing water hardness or salinity. Where saltwater organisms have been tested in water of low salinity (<2‰), their sensitivity appears to become comparable with that of freshwater organisms.

The predicted no-effect concentration (PNEC) for freshwater organisms based on the lower 95% confidence limit on the hazardous concentration for the protection of 95% of species (the 5th percentile of the species sensitivity distribution), the HC_5-95%, is 4 µg/l. In salt water, chromium(VI) would be expected to be less toxic, except perhaps at very low salinities.

Most natural waters contain total chromium concentrations lower than the freshwater PNEC; even in cases where the PNEC is exceeded, the values are given as total chromium, and it is likely that the bioavailability of natural chromium would be very low. However, higher chromium and, more specifically, chromium(III) and chromium(VI) concentrations have been reported near sources of anthropogenic emissions. For example, within 80 m of a disused tannery, a free chromium(VI) concentration of 63 µg/l was measured in river water. Therefore, the risk to aquatic organisms in general is low, but there is a risk to aquatic organisms in the vicinity of some anthropogenic releases of chromium(VI). The toxicity test data tend to indicate that marine organisms are not more sensitive than freshwater organisms. This suggests that the value of 4 µg/l derived for freshwater species should be protective of marine species. The same conclusion that was drawn for freshwater organisms (i.e.

that chromium(VI) would not represent a significant risk to organisms unless there is a local pollution source) then holds for the marine environment.

In the absence of more data on the bioavailability of chromium in soils, it is difficult to assess the risk of chromium(VI) to soil organisms.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Information regarding the identity of selected key chromium(VI) compounds is located in Table 1, and information on their physical and chemical properties is included in Table 2. Data on organic chromium compounds are not considered.

Chromium is a metallic element with oxidation states ranging from −2 to +6. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite ($FeCr_2O_4$). Chromium(VI) is the second most stable state. However, it rarely occurs naturally, but is produced from anthropogenic sources (USEPA, 1984a). Chromium(VI) occurs naturally in the rare mineral crocoite ($PbCrO_4$) (Hurlburt, 1971).

Some chromium(VI) compounds, such as chromium(VI) oxide (or chromic acid) and the ammonium and alkali metal salts (e.g. sodium and potassium) of chromic acid, are readily soluble in water. The earth-alkaline metal salts (e.g. calcium, strontium) of chromic acid are less soluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water (Table 2). Chromic acid is also soluble in, or forms compounds with, organic compounds, such as anhydrous acetic acid and pyridine (note: these reactions may be hazardous).

Chromate and dichromate anions are strong oxidizing reagents under strongly acidic conditions (i.e. at low pH). They are, however, only moderately oxidizing under neutral and alkaline conditions (i.e. at high pH). Chromium(VI) compounds can be reduced to the trivalent form in the presence of oxidizable organic matter. In natural waters where there is a low concentration of reducing materials, chromium(VI) compounds are more stable (USEPA, 1984a).

3. ANALYTICAL METHODS

Several methods are available for the analysis of chromium in different biological media. Several other reviews on the subject provide a more detailed description of the available analytical methods (Torgrimsen, 1982; Fishbein, 1984; USEPA, 1984a; IARC, 1986, 1990; IPCS, 1988; ATSDR, 2008). A difficulty with the analytical methods used to detect chromium is the ability of the applied analytical method to distinguish between chromium(VI) and chromium(III) (IPCS, 2006).

The determination of trace quantities of chromium requires special precautionary measures, from the initial sample collection process to the final analytical manipulations of the samples. Contamination in the analysis of total chromium and loss of the analyte, mainly through reduction to chromium(III) in the analysis of chromium(VI), are the main analytical problems.

The four most frequently used methods for determining low concentrations of total chromium in biological samples are mass spectrometry, graphite furnace atomic absorption spectrometry (GFAAS), neutron activation analysis and graphite spark atomic emission spectrometry. Of these four methods, only GFAAS is readily available in conventional laboratories, and this method is capable of determining chromium concentrations in biological samples when an appropriate background correction method is used (Greenberg & Zeisler, 1988; Plantz et al., 1989; Urasa & Nam, 1989; Veillon, 1989). GFAAS has been used to detect chromium in blood with a detection limit of 0.09 µg/l (Dube, 1988), in serum with a detection limit of 0.005 µg/l (Randall & Gibson, 1987), in erythrocytes (no detection limit reported) (Lewalter et al., 1985) and in urine with detection limits ranging from 0.005 to 0.09 µg/l (Veillon et al., 1982; Harnly et al., 1983; Kiilunen et al., 1987; Randall & Gibson, 1987; Dube, 1988).

United States National Institute for Occupational Safety and Health (NIOSH) Method No. 8005 for blood or tissue and NIOSH Method No. 8310 for urine use inductively coupled plasma atomic emission spectrometry (ICP-AES) (NIOSH, 1994a, 1994b). The preparation for blood and tissue involves ashing with nitric acid/perchloric acid/sulfuric acid. The detection limits are 10 µg/kg blood and 0.2 µg/g tissue, and the recovery is 114% at 10 µg/sample. The preparation for urine involves sorption onto polydithiocarbonate resin, ashing in low-temperature oxygen plasma and dissolving in nitric acid/perchloric acid. The sample detection limit is 0.1 µg/sample, with 100% recovery at 20 µg/l urine. These methods do not distinguish between chromium species.

Table 1: Chemical identity of key chromium(VI) compounds (from ATSDR, 2008).

Compound	Synonym(s)	Registered trade name(s)	Chemical formula	Chemical Abstracts Service registry number
Ammonium dichromate	Chromic acid, diammonium salt	No data	$(NH_4)_2Cr_2O_7$	7789-09-5
Calcium chromate	Chromic acid, calcium salt	Calcium Chrome Yellow	$CaCrO_4$	13765-19-0
Chromium trioxide	Chromic acid, chromium anhydride	No data	CrO_3	1333-82-0
Lead chromate	Chromic acid, lead salt	Chrome Yellow G	$PbCrO_4$	7758-97-6
Potassium chromate	Chromic acid, dipotassium salt	No data	K_2CrO_4	7789-00-6
Potassium dichromate	Dichromic acid, dipotassium salt	No data	$K_2Cr_2O_7$	7778-50-9
Sodium chromate	Chromic acid, disodium salt	Caswell No. 757	Na_2CrO_4	7775-11-3
Sodium dichromate, dihydrate	Chromic acid, disodium salt; dihydrate	No data	$Na_2Cr_2O_7 \cdot 2H_2O$	7789-12-0
Strontium chromate	Chromic acid, strontium salt	No data	$SrCrO_4$	7789-06-2
Zinc chromate	Chromic acid, zinc salt	CI Pigment Yellow	$ZnCrO_4$	13530-65-9

Table 2: Physical and chemical properties of key chromium(VI) compounds (from ATSDR, 2008).

Compound	Relative molecular mass	Colour	Melting point	Solubility in water
Ammonium dichromate	252.06	Orange	Decomposes at 170 °C	308 g/l at 15 °C
Calcium chromate	156.01	Yellow	No data	223 g/l
Chromium trioxide	99.99	Red	196 °C	617 g/l at 0 °C
Lead chromate	323.18	Yellow	844 °C	58 µg/l
Potassium chromate	194.20	Yellow	968 °C	629 g/l at 20 °C
Potassium dichromate	294.18	Red	398 °C	49 g/l at 0 °C
Sodium chromate	161.97	Yellow	792 °C	873 g/l at 30 °C
Sodium dichromate, dihydrate	298.00	Red	356.7 °C	2300 g/l at 0 °C
Strontium chromate	203.61	Yellow	No data	1.2 g/l at 15 °C
Zinc chromate	181.97	Lemon-yellow	No data	Insoluble

For most ambient environmental and occupational samples, chromium may be present as both chromium(III) and chromium(VI), and sometimes distinction between soluble and insoluble forms of chromium(VI) is required (Ashley et al., 2003). The quantification of soluble and insoluble chromium is done by determining chromium concentrations in aqueous filtered and unfiltered samples. However, soluble chromium(VI) may be reduced to chromium(III) on filtering media, particularly at low concentrations and under acidic conditions. Teflon filters and alkaline solutions are most suitable to prevent this reduction (Sawatari, 1986). Routine analytical methods are not available that can quantify the concentration of chromium(VI) in air samples if present at concentrations below 1 µg/m^3 (USEPA, 1990a), although there are ion chromatography/colorimetric methods that can determine chromium(VI) concentrations alone in air at a minimum detection limit of 0.1 ng/m^3 for a 20 m^3 sample (CARB, 1990; Sheehan et al., 1992). NIOSH methods for detecting total chromium and chromium(VI) in occupational settings include Method 7024 for total chromium using flame atomic absorption at a detection limit of 0.06 µg/sample for a sample size of 10–1000 litres (NIOSH, 1994c), Method 7300 for total chromium using ICP-AES with a detection limit of 1 µg/sample for a sample size of 200–2000 litres (NIOSH, 1994d) and Method 7600 for welding fumes (total chromium and chromium(VI)) using spectrophotometry at 540 nm with a detection limit of 0.05 µg/sample for a sample size of 8–400 litres (NIOSH, 1994e). Sequential extraction procedures for soluble and insoluble chromium(VI) compounds have been developed (ISO, 2005; ASTM, 2008).

Measurements of low concentrations of chromium in water have been made by specialized methods, such as GFAAS—for example, USEPA Method 218.2 for total chromium, with a detection limit of 1 µg/l (USEPA, 1983). For chromium(VI) in drinking-water, ground-water and water effluents, USEPA Method 7199 involves ion chromatography followed by derivatization with diphenylcarbazide and spectrophotometry at 530 nm, with a detection limit of 0.3 µg/l (USEPA, 1996). More recently, Thomas et al. (2002) described an ion chromatography method for chromium(VI) in drinking-water with a detection limit as low as 0.06 µg/l.

High-performance liquid chromatography interfaced with a direct current plasma emission spectrometer has been used for the determination of chromium(VI) in water samples (Krull et al., 1983). USEPA Methods 3060A and 7196A describe an alkaline digestion procedure followed by ultraviolet/visible spectroscopy that can quantify chromium(VI) in soil, sediment and sludge (USEPA, 1997a, 1997b).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

When presenting information on sources of human and environmental exposure to chromium, it is often necessary to describe exposures in terms of total chromium, because information on speciation is frequently not available.

4.1 Natural sources

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

4.2 Production

Sodium chromate and sodium dichromate are produced by roasting chromite ore with soda ash. Most other chromium compounds are produced from sodium chromate and sodium dichromate. For example, basic chromic sulfate ($Cr(OH)SO_4$), which is a chromium(III) compound commonly used in tanning, is commercially produced by the reduction of sodium dichromate with organic compounds (e.g. molasses) in the presence of sulfuric acid or by the reduction of dichromate with sulfur dioxide. Lead chromate, commonly used as a pigment, is produced by the reaction of sodium chromate with lead nitrate or by the reaction of lead monoxide with chromic acid solution (EU, 2005; ATSDR, 2008).

The world production capacity of chromium chemicals in 2008 was 272 000 tonnes as chromium (USGS, 2008). EU annual production figures in 1997 were 103 000 tonnes for sodium chromate, 110 000 tonnes for sodium dichromate, 32 000 tonnes for chromium trioxide, 1500 tonnes for potassium dichromate and 850 tonnes for ammonium dichromate (EU, 2005).

4.3 Use

Chromium compounds are widely used. Table 3 lists the approximate distribution of use for chromium chemicals in the major applications in the USA and other developed countries in 1996, including wood preservation, leather tanning, metals finishing and pigments, with a comparison with use in the USA in 1951 (Barnhart, 1997). Smaller amounts are used in drilling muds, chemical manufacturing and dye setting on textiles and as catalysts (USEPA, 1984a; CMR, 1988a, 1988b; USDI, 1988; IARC, 1990). Many uses are predominantly in the form of chromium(III) compounds (e.g. leather tanning). The primary uses of chromium(VI) compounds are in electroplating (chrome plating), the manufacture of dyes and pigments, wood preservatives, surface coatings and corrosion inhibitors. Chromium(VI) has also been used in cooling towers as a rust and corrosion inhibitor.

Table 3: Historical use of chromium chemicals in the USA and other developed countries (Barnhart, 1997).

	Historical use (%)		
Use	Developed countries, 1996	USA, 1996	USA, 1951
Wood preservation	15	52	2
Leather tanning	40	13	20
Metals finishing	17	13	25
Pigments	15	12	35
Refractory	3	3	1
Other	10	7	17

4.4 Releases to air

Chromium occurs naturally in Earth's crust. Continental dust flux is the main natural source of chromium in the atmosphere; volcanic dust and gas flux are minor natural sources of chromium in the atmosphere (Fishbein, 1981). Combustion processes, such as forest fires, also release chromium into air.

According to the United States Toxics Release Inventory, the estimated releases of chromium of 76 836 kg to the air from 2026 large processing facilities accounted for about 1.6% of total environmental releases in the USA in 2004 (Toxics Release Inventory, 2006). The estimated releases of chromium compounds in the USA in 2004 of 292 242 kg from 1605 reporting facilities accounted for 1.1% of total environmental releases.

EU (2005) reported emission data for chromium(VI) compounds for all three European production sites from the 1990s: 3677 kg/year in 1996 and 5611 kg/year in 1997 from site 1, 565 kg/year in 1996 from site 2 and 65 kg/year from site 3. The releases cover the processing of chromite ore and the production of five chromium(VI) compounds in the EU. They also include some of the subsequent processing of these compounds into other products that takes place at the sites.

Chromium is released into the atmosphere mainly by anthropogenic stationary point sources, including industrial, commercial and residential fuel combustion via the combustion of natural gas, oil and coal. Another important anthropogenic stationary point source of chromium emissions to the atmosphere is the metal industry. It has been estimated that approximately 16 000 tonnes of chromium were emitted into the atmosphere from anthropogenic sources in the USA in 1970 (USEPA, 1984b). These older estimates indicated that emissions from the metal industry ranged from 35% to 86% of the total, and emissions from fuel combustion ranged from 11% to 65% of the total (USEPA, 1978). A report by Cass & McRae (1986) indicated that emissions from stationary fuel combustion were approximately 46–47% of the total, and emissions from the metal industry ranged from 26% to 45% of the total. The primary stationary non-point source of chromium emissions into the atmosphere is fugitive emissions from road dusts. Other potentially small sources of atmospheric chromium emissions are cement-producing plants (cement contains chromium), incineration of municipal refuse and sewage sludge, and emissions from chromium-based automotive catalytic converters. Emissions from cooling towers that previously used chromate chemicals as rust inhibitors were also sources of chromium in the atmosphere (Fishbein, 1981; USEPA, 1984b).

4.5 Releases to water

On a worldwide basis, the predominant source of chromium in aquatic ecosystems is domestic wastewater effluents (32.2% of the total). Other major sources are metal manufacturing (25.6%), ocean dumping of sewage (13.2%), chemical manufacturing (9.3%), smelting and refining of non-ferrous metals (8.1%) and atmospheric fallout (6.4%) (Nriagu & Pacyna, 1988). The annual anthropogenic input of chromium into water has been estimated to exceed the anthropogenic input of chromium into the atmosphere (Nriagu & Pacyna, 1988). However, land erosion, a natural source of chromium in water, was not included in the Nriagu & Pacyna (1988) estimation of chromium contributions to the aquatic environment.

According to the United States Toxics Release Inventory, the estimated releases of chromium to water of 48 843 kg from 2026 large processing facilities accounted for approximately 1% of total environmental releases in the USA in 2004 (Toxics Release Inventory, 2006). The estimated release of chromium compounds to water from 1605 reporting facilities was 313 724 kg, accounting for 1.2% of total environmental releases. The most significant anthropogenic point sources of chromium in surface waters and groundwaters are the wastewaters from electroplating operations, leather tanning industries and textile manufacturing. In addition, deposition of airborne chromium is also a significant non-point source of chromium in surface water (Fishbein, 1981). In a 1972 survey, the contribution of different sources to chromium load in the influent wastewater of a treatment plant in New York City, USA, was estimated to be as follows: electroplating industry, 43%; residential wastewater, 28%; other industries, 9%; runoff, 9%; and unknown, 11% (Klein et al., 1974).

EU (2005) reported emission data for chromium(VI) compounds for all three European production sites from the 1990s. Emissions to water were reported as 474 kg/year in 1996 and 400 kg/year in 1997 at one site; at the second site, no measurable chromium(VI) emissions were reported; and at the third site, emissions of less than 216 kg/year (estimated from the detection limit and flow rate for the site) were reported.

4.6 Releases to soil

On a worldwide basis, the disposal of commercial products that contain chromium may be the largest contributor to chromium in soil, accounting for approximately 51% of the total chromium released to soil (Nriagu & Pacyna, 1988). Other significant sources of chromium release to soil include the disposal of coal fly ash and bottom fly ash from electric utilities and other industries (33.1%), agricultural and food wastes (5.3%), animal wastes (3.9%) and atmospheric fallout (2.4%)

(Nriagu & Pacyna, 1988). Solid wastes from metal manufacturing contributed less than 0.2% to the overall chromium release to soil.

According to the United States Toxics Release Inventory, the estimated releases of chromium of approximately 4 million kilograms to soil from 2026 large processing facilities accounted for about 85.7% of total environmental releases in the USA in 2004 (Toxics Release Inventory, 2006). The estimated release of chromium compounds was approximately 21.8 million kilograms from 1605 reporting facilities, accounting for 85.2% of environmental releases.

Information on possible releases to land in the 1990s for all three European production sites for chromium(VI) has been reported (EU, 2005). At the first site, landfill waste was estimated to contain approximately 15 mg chromium(VI) per kilogram, equivalent to an annual load of 1.7 tonnes of chromium. At site 2, residual solid sodium hydrogen sulfate, which contains approximately 1% chromium(VI) oxide from the production of chromium trioxide, was disposed of via landfill (the content of chromium(VI) oxide in the waste is regulated). Site 3 had a solid waste treatment plant that received solid waste from the kiln and the sludge from the wastewater treatment plant. Chromium(VI) impurities in the solid waste from this facility were present at a concentration of 8 mg/kg. The solid waste was eventually transported to a waste disposal site.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

There is a complete chromium cycle from rocks or soil to plants, animals and humans and back to soil. Only part of the chromium is diverted to a second pathway leading to the repository, the ocean floor. This part consists of chromium from rocks and soil carried by water (concentrations of a few micrograms per litre) and animal and human excreta, a small part of which may find their way into water (e.g. runoff from sewage sludge). Another cycle consists of airborne chromium from natural sources, such as fires, and from the chromate industry. This cycle also contains some chromium(VI), with by-products going into the water and air. Part of the chromium in air completes the cycle by settling on the land, but a very significant portion goes into the repository, the ocean, where it ends up as sediment on the ocean floor (IPCS, 1988)

5.1 Environmental transport and distribution

5.1.1 Air

Chromium is emitted into the air, not only by anthropogenic sources, but also by natural sources, including forest fires. The oxidation state of chromium emissions is not well defined quantitatively, but it can be assumed that the heat of combustion may oxidize an unknown proportion of the element to chromium(VI). While suspended in the air, this chromium state is probably stable, until it settles down and comes into contact with organic matter, which will eventually reduce it to the trivalent form (IPCS, 1988).

Chromium is present in the atmosphere primarily in particulate form. Naturally occurring gaseous forms of chromium are rare (Cary, 1982). The transport and partitioning of particulate matter in the atmosphere depend largely on particle size and density. Atmospheric particulate matter is deposited on land and water via wet and dry deposition. In the case of chromium, the mass median diameter of the ambient atmospheric particle is approximately 1 μm (Milford & Davidson, 1985; Ondov et al., 1989), and the deposition velocity is 0.5 cm/s (Schroeder et al., 1987). This combination of size and deposition velocity favours dry deposition by inertial impaction (Schroeder et al., 1987). Wet removal of particulate chromium also occurs by rainout within a cloud and washout below a cloud, and acid rain may facilitate the removal of acid-soluble chromium compounds from the atmosphere. The wet scavenging ratio (i.e. the ratio of the concentration of contaminant in precipitation to its concentration in unscavenged air) ranges from 150 to 290 for chromium (Schroeder et al., 1987; Dasch & Wolff, 1989). The wet deposition ratio increases with particle size and decreases with precipitation intensity (Schroeder et al., 1987). Chromium particles of aerodynamic diameter less than 20 μm may remain airborne for longer periods of time and be transported for greater distances compared with larger particles. The monthly dry deposition flux rate of chromium measured in Bologna, Italy, over the course of 1 year ranged from about 40 to 270 $\mu g/m^2$, with the highest values occurring during the winter months (Morselli et al., 1999). Golomb et al. (1997) reported an annual chromium deposition rate (wet plus dry) of 2700 $\mu g/m^2$ for Massachusetts Bay, USA, during 1992 and 1993.

A maximum of 47% of the total chromium in ferrochrome smelter dust may be bioavailable, as indicated by acid/base extraction. About 40% of the bioavailable chromium may exist as chromium(VI), mostly in the form of $Cr_2O_7^{2-}$ or CrO_4^{2-} (Cox et al., 1985). There are no data in the reviewed literature indicating that chromium particles are transported from the troposphere to

the stratosphere (Pacyna & Ottar, 1985). By analogy with the residence time of general particles with mass median diameters similar to that of chromium particles, the residence time of atmospheric chromium is expected to be less than 10 days (Nriagu, 1979). Based on a troposphere to stratosphere turnover time of 30 years (USEPA, 1979), atmospheric particles with a residence time of less than 10 days are not expected to be transported from the troposphere to the stratosphere.

5.1.2 Water

Domestic and industrial effluents containing chromium, some of which is in the chromium(VI) form, are emitted into surface waters. If large amounts of organic matter are present in the water, the chromium(VI) may be reduced to chromium (III), which may then be adsorbed on the particulate matter. If it is not adsorbed, the chromium(III) will form large, polynucleate complexes that are no longer soluble. These may remain in colloidal suspension and be transported to the ocean as such, or they may precipitate and become part of the stream sediment (IPCS, 1988). Whalley et al. (1999) found that a proportion of the chromium(III) may subsequently be remobilized in the form of soluble chromium(III)–organic complexes. Similar processes occur in the oceans, where chromium(VI) is reduced and settles on the ocean bed (IPCS, 1988). In seawater, the proportion of chromium(III) increases with increasing depth (Fukai, 1967).

As chromium compounds cannot volatilize from water, transport of chromium from water to the atmosphere is not likely, except in windblown sea sprays. Most of the chromium released into water will ultimately be deposited in the sediment. A very low percentage of chromium can be present in water in both soluble and insoluble forms. Soluble chromium generally accounts for a very small percentage of the total chromium. Most of the soluble chromium is present as chromium(VI) and soluble chromium(III) complexes. Less than 0.002% of total chromium in water and sediment in the Amazon and Yukon rivers was present in a soluble form (Cary, 1982). The ratio of suspended to dissolved solids in an organic-rich river in Brazil was 2.1 (Malm et al., 1988). Soluble forms and suspended chromium can undergo intramedia transport. It has been estimated that the residence time of chromium (total) in Lake Michigan ranges from 4.6 to 18 years (Fishbein, 1981; Schmidt & Andren, 1984).

5.1.3 Soil

Chromium in soil is present mainly as insoluble oxide ($Cr_2O_3 \cdot nH_2O$) (USEPA, 1984a) and is not very mobile. A leachability study was conducted to investigate the mobility of chromium in soil (Sahuquillo et al., 2003). Because of different pH values, a complicated adsorption process was observed, and chromium moved only slightly in soil. Chromium was not found in the leachate from soil, possibly because it formed complexes with organic matter. These results support previous data finding that chromium is not very mobile in soil (Lin et al., 1996). These results are also supported by a leachability investigation in which chromium mobility was studied for a period of 4 years in a sandy loam (Sheppard & Thibault, 1991). The vertical migration pattern of chromium in this soil indicated that after an initial period of mobility, chromium forms insoluble complexes, and little leaching is observed. Flooding of soils and the subsequent anaerobic decomposition of plant detritus may increase the mobilization of chromium(III) in soils owing to the formation of soluble complexes (Stackhouse & Benson, 1989a). This complexation may be facilitated by a lower soil pH. A lower percentage of total chromium in soil exists as soluble chromium(VI) and chromium(III), which are more mobile in soil. The mobility of soluble chromium in soil will depend on the sorption characteristics of the soil. The relative retention of metals by soil is in the order of lead > antimony > copper > chromium > zinc > nickel > cobalt > cadmium (King, 1988). The sorption of chromium to soil depends primarily on the clay content of the soil and, to a lesser extent, on the iron(III) oxide content and the organic content of the soil. Chromium that is irreversibly sorbed onto soil in the interstitial lattice of geothite (FeOOH), for example, will not be bioavailable to plants and animals under any conditions (Calder, 1988; Hassan & Garrison, 1996). Chromium(III) appears to be much more strongly adsorbed to soils than chromium(VI) (Hassan & Garrison, 1996). Organic matter in soil is expected to convert soluble chromate (chromium(VI)) to insoluble chromium(III) oxide (Cr_2O_3) (Calder, 1988). Chromium in soil may be transported to the atmosphere as an aerosol. Surface runoff from soil can transport both soluble and bulk precipitate of chromium to surface water. Soluble and unadsorbed chromium(VI) and chromium(III) complexes in soil may leach into groundwater. The leachability of chromium(VI) in the soil increases as the pH of the soil increases. In contrast, lower pH present in acid rain may facilitate the leaching of acid-soluble chromium(III) and chromium(VI) compounds in soil.

5.1.4 Biota

Living plants and animals absorb chromium(VI) in preference to chromium(III); once absorbed, however, chromium(VI) is reduced to the more stable chromium(III) (IPCS, 1988). Chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary, 1982).

5.2 Transformation and degradation

5.2.1 Air

In the atmosphere, chromium(VI) may be reduced to chromium(III) at a substantial rate by vanadium (V^{2+}, V^{3+} and VO^{2+}), Fe^{2+}, HSO_3^- and As^{3+} (USEPA, 1987). Conversely, chromium(III), if present as a salt other than Cr_2O_3, may be oxidized to chromium(VI) in the atmosphere in the presence of at least 1% manganese oxide (USEPA, 1990b). However, this reaction is unlikely under most environmental conditions. The estimated atmospheric half-time for chromium(VI) reduction to chromium(III) was reported to be in the range of 16 hours to about 5 days (Kimbrough et al., 1999).

5.2.2 Water

The reduction of chromium(VI) to chromium(III) by S^{2-} or Fe^{2+} ions under anaerobic conditions was found to be fast, and the reduction half-life ranged from instantaneous to a few days (Saleh et al., 1989). However, the reduction of chromium(VI) by organic sediments and soils was much slower and depended on the type and amount of organic material and on the redox condition of the water. The reaction was generally faster under anaerobic conditions compared with aerobic conditions. The reduction half-life of chromium(VI) in water with soil and sediment ranged from 4 to 140 days. Dissolved oxygen by itself in natural waters did not cause any measurable oxidation of chromium(III) to chromium(VI) in 128 days. When chromium(III) was added to lake water, a slow oxidation of chromium(III) to chromium(VI) occurred, corresponding to an oxidation half-life of 9 years. Addition of manganese oxide (50 mg/l) accelerated the process, decreasing the oxidation half-life to approximately 2 years. Therefore, this oxidation process would not be important in most natural waters. The oxidation of chromium(III) to chromium(VI) during chlorination of water was highest in the pH range of 5.5–6.0. However, the process would rarely occur during chlorination of drinking-water because of the low concentrations of chromium(III) in these waters and the presence of naturally occurring organics that may protect chromium(III) from oxidation, either by forming strong complexes with chromium(III) or by acting as a reducing agent for free available chlorine (USEPA, 1988). In chromium(III)-contaminated wastewaters having a pH in the range of 5–7, chlorination may convert chromium(III) to chromium(VI) in the absence of chromium(III) complexing and free chlorine reducing agents.

Chromium speciation in groundwater depends on the redox potential and pH conditions in the aquifer. Chromium(VI) predominates under highly oxidizing conditions, whereas chromium(III) predominates under reducing conditions. Oxidizing conditions are generally found in shallow aquifers, and reducing conditions generally exist in deeper groundwaters. In natural groundwater, the pH is typically 6–8, and CrO_4^{2-} is the predominant species of chromium in the hexavalent oxidation state, whereas $Cr(OH)_2^+$ will be the dominant chromium(III) species. This and other chromium(III) species will predominate in more acidic pH; $Cr(OH)_3$ and $Cr(OH)_4^-$ predominate in more alkaline waters (Calder, 1988). In seawater, chromium(VI) is generally stable (Fukai, 1967).

5.2.3 Sediment and soil

The fate of chromium in soil is largely dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) state (Barnhart, 1997). Under oxidizing conditions, chromium(VI) may be present in soil as CrO_4^{2-} and $HCrO_4^-$ (James et al., 1997). In this form, chromium is relatively soluble, mobile and toxic to living organisms. In deeper soil where anaerobic conditions exist, chromium(VI) will be reduced to chromium(III) by S^{2-} and Fe^{2+} present in the soil. The reduction of chromium(VI) to chromium(III) is possible in aerobic soils that contain appropriate organic energy sources to carry out the redox reaction. The reduction of chromium(VI) to chromium(III) is facilitated by low pH (Cary, 1982; Saleh et al., 1989; USEPA, 1990b). From thermodynamic considerations, chromium(VI) may exist in the aerobic zone of some natural soil. The oxidation of chromium(III) to chromium(VI) in soil is facilitated by the presence of low oxidizable organic substances, oxygen, manganese dioxide and moisture. Oxidation is also enhanced at elevated temperatures in surface soil that result from brush fires (Cary, 1982; Calder, 1988). Organic forms of chromium(III) (e.g. humic acid complexes) are more easily oxidized than insoluble oxides. However, oxidation of chromium(III) to chromium(VI) was not observed in soil under conditions of maximum aeration and a maximum pH of 7.3 (Bartlett & Kimble, 1976). It was later reported that soluble chromium(III) in soil can be partly oxidized to chromium(VI) by manganese dioxide in the soil, and the process is enhanced by pH higher than 6 (Bartlett, 1991). Because most chromium(III) in soil is immobilized due to adsorption and complexation with soil materials, the barrier to this oxidation process is the lack of availability of mobile chromium(III) to immobile manganese dioxide in soil surfaces. Because of this lack of availability of mobile chromium(III) to manganese dioxide surfaces, a large portion of chromium in soil will not be oxidized to chromium(VI), even in the presence of manganese dioxide and under favourable pH conditions (Bartlett, 1991; James et al., 1997).

The microbial reduction of chromium(VI) to chromium(III) has been discussed as a possible

remediation technique in heavily contaminated environmental media or wastes (Chen & Hao, 1998). Factors affecting the microbial reduction of chromium(VI) to chromium(III) include biomass concentration, initial chromium(VI) concentration, temperature, pH, carbon source, oxidation–reduction potential and the presence of both oxyanions and metal cations. Although high levels of chromium(VI) are toxic to most microbes, several resistant bacterial species have been identified that could ultimately be employed in remediation strategies (Chen & Hao, 1998). Elemental iron, sodium sulfite, sodium hydrosulfite, sodium bisulfite, sodium metabisulfite, sulfur dioxide and certain organic compounds such as hydroquinone have also been shown to reduce chromium(VI) to chromium(III) and have been discussed for possible use in remediation techniques in heavily contaminated soils (Higgins et al., 1997; James et al., 1997). The limitations and efficacy of these and all remediation techniques are dependent upon the ease with which the reducing agents are incorporated into the contaminated soils.

5.3 Bioaccumulation

Bioconcentration factors (BCFs) for chromium(VI) in freshwater fish are low (at around 1), because chromium(VI) is reduced to chromium(III) in the organism, resulting in the accumulation of total chromium in the organisms to a factor approximately 100 times the water concentration.

In bottom feeder bivalves, such as the oyster (*Crassostrea virginica*), blue mussel (*Mytilus edulis*) and soft shell clam (*Mya arenaria*), the BCF values for chromium(III) and chromium(VI) range from 86 to 192 (USEPA, 1980, 1984a; Fishbein, 1981; Schmidt & Andren, 1984).

Chromium is not expected to biomagnify in the aquatic food-chain (Ramelow et al., 1989). The bioavailability of chromium(III) to freshwater invertebrates (*Daphnia pulex*) decreased with the addition of humic acid. This decrease in bioavailability was attributed to lower availability of the free form of the metal due to its complexation with humic acid.

Although higher concentrations of chromium have been reported in plants growing in high chromium-containing soils (e.g. soil near ore deposits or chromium-emitting industries and soil fertilized by sewage sludge) compared with plants growing in normal soils, most of the increased uptake in plants is retained in roots, and only a small fraction is translocated to the aboveground part of edible plants (Cary, 1982; IPCS, 1988). Therefore, bioaccumulation of chromium from soil to the aboveground parts of plants is unlikely (Petruzzelli et al., 1987).

There is no indication of biomagnification of chromium along the terrestrial food-chain (Cary, 1982).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Many of the data in section 6 are reported as total chromium because no speciation has been carried out, although chromium(III) is likely to be the dominant species in most environmental samples. Further, the analysis of chromium(VI) is difficult and expensive (see section 3).

6.1 Environmental levels

6.1.1 Air

The atmospheric total chromium concentration in the USA is typically below 10 ng/m^3 in rural areas and 10–30 ng/m^3 in urban areas (Fishbein, 1984). Levels of total chromium in the ambient air in urban and non-urban areas in the USA during 1977–1984 are reported in the USEPA's National Aerometric Data Bank (ATSDR, 2008). The arithmetic mean total chromium concentrations from a total of 2106 monitoring stations ranged from 5 to 525 ng/m^3. The two locations that showed the highest arithmetic mean total chromium concentrations were in Steubenville, Ohio, in 1977 (525 ng/m^3) and in Baltimore, Maryland, in 1980 (226 ng/m^3). Arithmetic mean total chromium concentrations in only 8 of 173 sites monitored in 1984 were higher than 100 ng/m^3 (ATSDR, 2008). Airborne concentrations of chromium over the North Sea and adjacent areas varied from 1 to 14 ng/m^3, with concentrations in precipitation ranging from 1.8 to 77 µg/l (Injuk & Van Grieken, 1995).

The concentrations of atmospheric chromium in remote areas range from 0.005 to 2.6 ng/m^3 (ATSDR, 2008). Saltzman et al. (1985) compared the levels of atmospheric chromium at 59 sites in cities in the USA during 1968–1971 with data from the USEPA's National Aerometric Data Bank file for 1975–1983. They concluded that atmospheric chromium levels may have declined in the early 1980s from the levels detected in the 1960s and 1970s.

Chromium concentrations in air vary with location. Background levels determined at the South Pole ranged from 2.5 to 10 pg/m^3 and are believed to be due to the weathering of crustal material (IPCS, 1988). Data collected by the United States National Air Sampling Network in 1964 gave the national average concentration for chromium in the ambient air as 15 ng/m^3, ranging from non-measurable levels to a maximum

concentration of 350 ng/m^3. Chromium concentrations in most non-urban areas and even in many urban areas were below detection levels. Yearly average concentrations for cities in the USA varied from 9 to 102 ng/m^3. Concentrations ranging from 17 to 87 ng/m^3 have been reported for Osaka, Japan (IPCS, 1988). The chromium content of the air in the vicinity of industrial plants may be higher. In 1973, the reported chromium concentrations ranged from 1 to 100 mg/m^3 for coal-fired power plants, from 100 to 1000 mg/m^3 for cement plants, from 10 to 100 mg/m^3 for iron and steel industries and from 100 to 1000 mg/m^3 for municipal incinerators (IPCS, 1988). Ferrochromium plants have the highest emission rates (IPCS, 1988). However, modern chromium chemical plants contribute very little to pollution today because of the installation of collecting equipment that returns the material for reuse. Drift from cooling towers contributes to atmospheric pollution when chromium is used as a corrosion inhibitor.

6.1.2 Water

Total chromium concentrations in river water in the USA usually range from <1 to 30 µg/L (ATSDR, 2008), with a median value of 10 µg/L (Smith et al., 1987; Eckel & Jacob, 1988). In Europe, a median total chromium concentration of 0.38 µg/l (range <0.01–43.3 µg/l) has been reported for surface waters (Salminen et al., 2005). Total chromium concentrations in lake water generally do not exceed 5 µg/l (Cary, 1982; Borg, 1987). The higher levels of chromium can be related to sources of anthropogenic pollution. Except for regions with substantial chromium deposits, the natural content of chromium in surface waters is very low, most of the samples containing between 1 and 10 µg/l (IPCS, 1988). Chromium concentrations ranging from 1.2 to 94.4 µg/l for unfiltered surface water and from 0.1 to 0.5 µg/l for filtered (<0.45 µm) water were reported for the source area of the Yangtze River, China (Zhang & Zhou, 1992). Mean dissolved chromium concentrations ranging from 0.3 to 6.8 µg/l were found for 14 rivers in the United Kingdom with particulate chromium concentrations of 0.1–4 µg/l (Neal et al., 2000). Cranston & Murray (1980) reported that less than 2% of the total dissolved chromium in the Columbia River, USA, was present as trivalent chromium. Dissolved chromium concentrations of 0.6–1.3 µg/l were reported in the Delaware River near Marcus Hook and Fieldsboro, Pennsylvania, USA, in January 1992, with chromium(III) constituting 67% of the total; in March 1992, these concentrations decreased to 0.03–0.2 µg/l (Riedel & Sanders, 1998). Sumida et al. (2005) reported a mean total chromium concentration of 0.22 µg/l for the Kokubu and Kagami rivers in Japan and a mean chromium concentration of 1.57 µg/l for post-treatment wastewater from a metal recycling plant. The river water samples contained around 60% chromium(III), and the wastewater contained around 70% chromium(III). Motomizu et al. (2003) found mean total dissolved chromium concentrations ranging from 0.41 to 0.48 µg/l for the Asahi and Zasu rivers in Japan, with chromium(III) comprising 75% of the total chromium concentration. Tang et al. (2004) reported mean concentrations of 2 µg chromium(III) per litre and 3 µg chromium(VI) per litre for river water in China. The mean total chromium concentration 80 m from a disused tannery in Sweden was found to be 225 µg/l, with 1.1 µg/l as free chromium(III) species and 63 µg/l as free chromium(VI) species; chromium concentrations were below the detection limit (<0.05 µg/l) at a distance of 300 m (Djane et al., 1999). Chromium(III) and chromium(VI) concentrations ranging up to 85.2 and 3.5 µg/l, respectively, were reported downstream of a tannery in the upper Dunajec River in Poland; mean concentrations of 0.52 µg chromium(III) per litre and 0.1 µg chromium(VI) per litre were found in the unpolluted Bialka River (Bobrowski et al., 2004). Giusti & Barakat (2005) found that chromium(III) concentrations ranged from 0.5 to 97.5 µg/l in the Fratta River, Italy, with the highest concentrations close to tannery effluent discharges. Similarly, Dominguez Renedo et al. (2004) reported a mean chromium(III) concentration of 104 µg/l for an industrial area in Spain. Water samples from Lake Ontario revealed that 75–85% of dissolved chromium was chromium(VI), whereas chromium(III) levels were consistently below detection limits (<21 ng/l) (Beaubien et al., 1994). Liang et al. (2003) reported mean chromium(III) concentrations of 0.57 µg/l for East Lake, Wuhan, China, about 50% of chromium(VI) concentrations.

Mean wastewater chromium(III) and chromium(VI) concentrations ranging from 60 to 126 µg/l and from 185 to 648 µg/l, respectively, were reported by Tang et al. (2004), and mean wastewater concentrations of 410 µg chromium(III) per litre and 296 µg chromium(VI) per litre were found at a dye plant (Hashemi et al., 2004). Chromium(III) and chromium(VI) concentrations in plating industry effluents ranged from 5 to 50 µg/l and from 25 to 100 µg/l, respectively (Prasada Rao et al., 1998).

In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The mean chromium concentration in ocean water is 0.3 µg/l, with a range of 0.2–50 µg/l (Cary, 1982). Florence & Batley (1980) reported that in seawater, typical chromium(III) concentrations lie in the range 0.002–0.05 µg/l, and typical chromium(VI) concentrations range from 0.1 to 1.3 µg/l. In nearshore and river waters, there is a general lowering of the chromium(VI) to chromium(III) ratio; for example, Batley & Matousek (1980) found labile chromium(III) and chromium(VI) concentrations ranging from 0.03 to 0.22 µg/l and from 0.13 to 0.68 µg/l, respectively, in nearshore and saline river water samples in Australia. Seawater samples from the south-western coast of India contained chromium(III) at

concentrations ranging from 0.08 to 0.26 µg/l (Prasada Rao et al., 1998). Prasada Rao et al. (1998) noted that chromium(VI) is not detected in seawater samples that have been preserved for more than 4 hours. In samples analysed immediately after collection, chromium(III) and chromium(VI) concentrations were found to be 0.04 and 0.05 µg/l, respectively.

The concentration of chromium in the particulate portion of melted snow collected from two urban areas (Toronto and Montreal) of Canada ranged from 100 to 3500 mg/kg (Landsberger et al., 1983).

6.1.3 Sediment

In the suspended materials and sediment of water bodies, chromium levels ranged from 1 to 500 mg/kg (Byrne & DeLeon, 1986; Ramelow et al., 1987; Mudroch et al., 1988; Heiny & Tate, 1997). In Europe, median stream sediment chromium concentrations were 64 mg/kg (<3–3324 mg/kg) after hydrofluoric acid extraction and 22 mg/kg (2–1750 mg/kg) after nitric acid extraction, and for floodplain sediment, 59 (5–2731 mg/kg) and 23 mg/kg (3–1596 mg/kg), respectively (Salminen et al., 2005). Chromium was detected in sediment obtained from the coastal waters of the eastern USA at concentrations of 3.8–130.9 mg/kg in 1994 and 0.8–98.1 mg/kg in 1995 (Hyland et al., 1998). A total mean chromium concentration of 93 mg/kg was reported for sediment from the Po River delta in Italy (Fabbri et al., 2001). A mean chromium concentration of 20.3 mg/kg (<2 mm fraction) was reported for Terra Nova Bay sediment, Antarctica, in 1993–1994 (Giordano et al., 1999). In Africa, measured concentrations of chromium in aquatic sediments ranged from 2.7 µg/g at the River Msimbaze, United Republic of Tanzania, to 1500 µg/g in the Nile River downstream from Cairo, Egypt (Nriagu, 1992).

6.1.4 Soil

Chromium levels in soils vary greatly and depend on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks and phosphorites may contain chromium at concentrations as high as a few thousand milligrams per kilogram (Merian, 1984), whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine & Mitchell, 1960). The concentration range of chromium in 1319 samples of soils and other surficial materials collected in the conterminous USA was 1–2000 mg/kg, with a geometric mean concentration of 37 mg/kg (Shacklette & Boerngen, 1984). Chromium concentrations in Canadian soils ranged from 5 to 1500 mg/kg, with a mean of 43 mg/kg (Cary, 1982). In Europe, median chromium concentrations for topsoil were 60 mg/kg (<3–6230 mg/kg) after hydrofluoric acid extraction and 22 mg/kg (<1–2340 mg/kg) after nitric acid extraction (Salminen et al., 2005). In a study with soils from 20 diverse sites, including old chromite mining sites in Maryland, Pennsylvania and Virginia, USA, the chromium concentrations ranged from 4.9 to 71 mg/kg (Beyer & Cromartie, 1987). Soil beneath decks treated with copper chrome arsenate wood preservative contained chromium at a mean concentration of 43 mg/kg (Stilwell & Gorny, 1997). Chromium has been detected at a high concentration (43 000 mg/kg) in soil at the Butterworth landfill site in Grand Rapid City, Michigan, USA, which was a site listed on the National Priorities List (ATSDR, 2008). Hu & Deming (2005) found the mean "bioavailable" (ethylenediaminetetraacetic acid extractable) total chromium concentration in soil samples to be 0.053 mg/kg (dry weight), with 57% as chromium(III) (0.03 mg/kg).

The chromium concentration in incinerated sewage sludge ash may be as high as 5280 mg/kg (USEPA, 1984a).

6.1.5 Biota

Mean chromium levels in periphyton and zooplankton sampled from the Calcasieu River/Lake Complex, Louisiana, USA, were 79 and 34 mg/kg dry weight, respectively (Ramelow et al., 1987).

Chromium levels in shellfish range from <0.1 to 6.8 mg/kg dry weight (Byrne & DeLeon, 1986; Ramelow et al., 1989). The chromium concentration in fish sampled from 167 lakes in the north-eastern USA ranged from 0.03 to 1.46 mg/kg, with a mean concentration of 0.19 mg/kg (Yeardley et al., 1998). Ramelow et al. (1989) reported mean chromium concentrations in freshwater fish species ranging from 0.15 to 5.5 mg/kg dry weight. Mean chromium concentrations ranging from 5 to 7.6 mg/kg were reported for fish liver samples from the South Platte River basin, USA (Heiny & Tate, 1997). Fish and shellfish collected from ocean dump sites off New York City, Delaware Bay and New Haven, Connecticut, USA, contained chromium at <0.3–2.7 mg/kg wet weight (Greig & Jones, 1976).

Pine snakes (*Pituophis melanoleucus*) contained whole body mean chromium concentrations ranging from 1.6 to 6.7 mg/kg dry weight (Burger & Gochfeld, 1992).

Mean chromium concentrations in birds' eggs from a variety of geographical areas ranged from <0.2 to 1 mg/kg dry weight (Hothem et al., 1995; Hui et al., 1998; Burger et al., 1999), and mean liver concentrations ranged from 0.1 to 4.4 mg/kg dry weight (Hui et al., 1998; Burger & Gochfeld, 1999, 2000). Mean concentrations of chromium in bird feathers from the USA, China and the Pacific basin collected between 1988 and

1997 ranged from 0.5 to 49.1 mg/kg dry weight. The lowest mean concentrations were reported for sooty terns (*Sterna fuscata*) on Midway Island, Pacific Ocean, and the highest for Chinese pond herons (*Ardeola bacchus*) in Szechuan, China (Burger & Gochfeld, 1992, 1993, 1995, 2000; Burger et al., 1994).

Mean chromium concentrations in European otter (*Lutra lutra*) livers ranged from 0.02 to 0.3 mg/kg dry weight (Mason & Stephenson, 2001).

6.2 Human exposure

The general population is exposed to chromium by inhaling ambient air and ingesting food and drinking-water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products that contain chromium, such as certain wood preservatives, cement, cleaning materials, dyed textiles and leather tanned with chromium (IPCS, 1988).

Levels of chromium in ambient air (<0.01–0.03 μg/m^3) (Fishbein, 1984) and tap water (<2 μg/l) (Great-house & Craun, 1978) have been used to estimate the daily intake of chromium via inhalation (<0.2–0.6 μg) and via tap water (<4 μg) for the general population. These estimates are based on an air inhalation rate of 20 m^3/day and a drinking-water consumption rate of 2 litres/day. Significant uncertainties are associated with the estimate of intake via inhalation.

The daily chromium intake for the population in the USA from consumption of selected diets (diets with 25% and 43% fat) has been estimated to range from 25 to 224 μg, with an average intake of 76 μg (Kumpulainen et al., 1979). The average value is close to the value of 60 μg reported by Bennett (1986).

The levels of chromium found in foods are very variable. The bioavailability of chromium from different foods may also vary. The chromium levels of various foods are reported in Table 4. No correlation was found between the insulin potentiation and the total chromium extractable from foods by acid hydrolysis. However, a significant correlation was found between the ethanol-extractable chromium and biological activity. The highest amounts of ethanol-extractable chromium were found in brewer's yeast, black pepper, calf liver, cheese and wheat germ (IPCS, 1988).

Occupational exposure to chromium(VI) occurs mainly in chromate production, production of chromium pigments and other chromium chemicals, spray painting using chromate pigments, ferrochrome and stainless steel production, stainless steel welding and chromium plating (Table 5).

Table 4: Total chromium content in various foods in the USA.

Sample	Mean concentration (μg/kg)	Reference
Fresh vegetables	30–140	USEPA (1984a)
Frozen vegetables	230	USEPA (1984a)
Canned vegetables	230	USEPA (1984a)
Fresh fruits	90–190	USEPA (1984a)
Fruits	20	USEPA (1984a)
Canned fruits	510	USEPA (1984a)
Dairy products	100	USEPA (1984a)
Chicken eggs	60	Kirkpatrick & Coffin (1975)
Whole fish	50–80	USEPA (1984a)
Edible portion of fresh finfish	<100–160	Eisenberg & Topping (1986)
Meat and fish	100–230	USEPA (1984a)
Seafoods	120–470	USEPA (1984a)
Grains and cereals	40–220	USEPA (1984a)
Sugar, refined[a]	<20	IPCS (1988)

[a] Value in Finnish sugar.

Historically, exposures to chromium(VI) have been high in many industries. The typical concentration ranges of airborne chromium(VI) to which workers were exposed during an average of 5–20 years of employment were as follows: chromate production, 100–500 μg/m^3; stainless steel welding, 50–400 μg/m^3; chromium plating, 5–25 μg/m^3; ferrochrome alloys, 10–140 μg/m^3; and chrome pigment, 60–600 μg/m^3 (Stern, 1982). Chromium oxide levels in the working environment of stainless steel welders in Germany had a maximum value of 80 μg/m^3, with a median value ranging from 4 to 10 μg/m^3 (Angerer et al., 1987).

More recently, at least in industrialized countries, exposure levels have been lower. In Europe, geometric mean exposures are generally below 20 μg/m^3 in most chromium chemical industries (Table 5; EU, 2005).

In 1999–2001, NIOSH conducted 21 field surveys on chromium(VI) exposure in different industries; 8-hour time-weighted average (TWA) exposures in the workers' breathing zone were reported. The authors noted that these field surveys are not a representative sampling of all industries in the USA, but rather a series of case-studies (Blade et al., 2007). Operations with highest exposures are listed in Table 6. In 11 operations, exposures did not exceed 0.1 μg/m^3: bright electro-plating, chromium-coating (non-electrolytic), welding (tungsten inert gas, fusion, dual-shield) and submerged-arc plasma cutting of stainless steel, casting operations in stainless steel foundry, welding (manual metal arc, metal inert gas), ductile iron manufacturing foundry,

Table 5: Exposure to chromium(VI) in different industries in Europe (from EU, 2005).

Industry	Number of samples	Concentration range (µg/m^3)	Geometric mean concentration (µg/m^3)
Manufacture of the five chromates[a]	1889	nd–780	4–20
Manufacture of other chromium-containing chemicals			
- dyestuffs	39	nd–400	20
- chrome tan[b]	115	0.01–25	2
- CCA	66	0.2–60	4
- chromium metal	73	nd–20	2
- formulation metal treatment products	25	nd–150	10
CCA use	35	nd–9	1
Metal treatment			
- electrolytic	315	42	1–50
- passivation	42	<1–50	<1
Manufacture of magnetic tapes	40	0–8.4	2
Use as a mordant in wool dyeing	3	1–42	15
Catalyst manufacture	22	0.1–9	5

CCA, copper chrome arsenate; nd, not detected

[a] The five chromates are chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate.

[b] Chrome tan is the general name given to various chromium(III) salts used in leather tanning that are manufactured by the reduction of sodium dichromate.

crushing and recycling of concrete from demolition, manufacturing of coloured glass products using chromate pigments, screen printing with inks containing chromate pigments and chromate conversion treatment process for electronic component boards. In seven operations, the exposures were below 2 µg/m^3: alodine/anodizing coating processes, tungsten inert gas–stainless steel welding of sheet metal, manufacturing of refractory brick using chromic oxide, manufacturing of chromium sulfate from sodium dichromate, abrasive blasting of chromate-containing paint, stainless steel welding (shielded metal arc welding, flux-cored arc welding, dual-shield, tungsten inert gas, metal inert gas) and manufacturing of products from wood treated with chromium–copper–arsenic. In four operations, the exposure was less than 5.5 µg/m^3: manufacturing screen-printing inks containing chromate pigments, metal inert gas welding of stainless steel, welding (metal inert gas, tungsten inert gas) and plasma cutting in sheet metal manufacture.

Table 6: Breathing zone chromium(VI) concentrations in different industrial sites in the USA in 1999–2001 (from Blade et al., 2007).

Operation (NIOSH site no.)	Job title	Chromium(VI) concentration (µg/m^3)	
		Range (*n*)	Geometric mean (SD)
Spray application and resanding of chromate-containing pigment (2)	Painter	3.8–5 (5)	16 (3.4)
Spray application and resanding of chromate-containing pigment (7)	Painter	<0.02–4.3 (13)	0.23 (6.3)
Hard electroplating (1)	Plater	3.0–16 (4)	7.9 (2.0)
Hard and bright electroplating (18)	Plater	0.22–8.3 (12)	2.5 (2.6)
Atomized chromium alloy spray coating (21)	Production worker	≤820, ≤1900 (2)	—
Metal cutting in ship demolition (13)	Burner	<0.07–27 (14)	0.35 (5.4)
Repair welding and cutting on alloy and stainless steel	Welder	0.37–22 (4)	6.6 (7.0)

SD, standard deviation

Worker exposures to chromium in electroplating factories in Taiwan, China, were 0.5–6.0 µg/m^3 near the electroplating tanks and 0.3 µg/m^3 in the manufacturing area (Kuo et al., 1997). In a modern ferrochromium and stainless steel mill in Finland, the median concentration of chromium(VI) in 1987 was ≤0.1 µg/m^3 in all production areas except one, where it was 0.5 µg/m^3.The highest measured airborne concentration of chromium(VI) was 6.6 µg/m^3 (Huvinen et al. 1993). In 1999, the median and maximum breathing zone chromium(VI) concentrations were 0.3 and 0.7 µg/m^3, respectively (Huvinen et al., 2002b).

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

A further database of occupational exposures to chromium(VI) in the USA is available from the Occupational Safety and Health Administration (OSHA, 2006).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

A physiologically based toxicokinetic model has been developed and demonstrated to fit reasonably well with existing experimental data. This model takes into account different absorption and reduction rates from the gastrointestinal and respiratory tracts, different efficiencies in the uptake of chromium(III) and chromium(VI) to the erythrocytes and other tissues, reduction of chromium(VI) to chromium(III) and retention thereof in the erythrocytes, storage in the bone, reabsorption from the gastrointestinal tract and concentration-dependent urinary clearance (O'Flaherty, 1993, 1996; O'Flaherty et al., 2001).

7.1 Absorption

The toxicokinetics of a given chromium compound depends on the valence state of the chromium atom and the nature of its ligands (ATSDR, 2008). Absorption of chromium(VI) compounds is higher than that of chromium(III) compounds via all exposure routes. This is because the chromate anion (CrO_4^{2-}) can enter cells through chloride–phosphate anion channels facilitated by the chloride intracellular channel carrier proteins, a protein group related to glutathione-*S*-transferases (Harrop et al., 2001). Absorption of chromium(III) compounds is via passive diffusion and phagocytosis (IPCS, 2009).

Experimental data on the absorption of chromium after inhalation exposure of humans are not available, but the identification of chromium in urine, serum and tissues of humans occupationally exposed to soluble chromium(VI) compounds in air indicates that chromium can be absorbed from the lungs (Gylseth et al., 1977; Tossavainen et al., 1980; Kiilunen et al., 1983; Cavalleri & Minoia, 1985; Randall & Gibson, 1987; Minoia & Cavalleri, 1988; Mancuso, 1997b). In most cases, chromium(VI) compounds are more readily absorbed from the lungs than chromium(III) compounds, in part due to differences in the capacity to penetrate biological membranes.

Animal studies indicate that the absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages.

Rats exposed via inhalation to 2.1 mg chromium(VI) per cubic metre as zinc chromate for 6 hours/day achieved steady-state concentrations in the blood after approximately 4 days of exposure (Langård et al., 1978). Rats that were exposed for a single inhalation of chromium(VI) trioxide mist from electroplating at a concentration of 3.18 mg chromium(VI) per cubic metre for 30 minutes rapidly absorbed chromium from the lungs. The content of chromium in the lungs declined from 13.0 mg immediately after exposure to 1.1 mg at 4 weeks in a triphasic pattern with an overall half-life of 5 days (Adachi et al., 1981). In a study of rats exposed to chromium(VI) and chromium(III) compounds, the amount of chromium(VI) transferred to the blood from the lungs was always at least 3 times greater than the amount of chromium(III) transferred (Suzuki et al., 1984). Other studies reporting absorption from the lungs are intratracheal instillation studies (Visek et al., 1953; Baetjer et al., 1959b; Bragt & van Dura, 1983; Wiegand et al., 1984, 1987; Vanoirbeek et al., 2003). These studies indicate that 53–85% of chromium(VI) compounds (particle size <5 μm) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance in the pharynx (to be eventually partially absorbed from the gastrointestinal tract); the rest of the chromium(VI) compounds remain in the lungs.

Chromium(VI), given as potassium chromate or dichromate (range approximately 2–8%), was better absorbed than chromium(III) after oral exposure in humans (Finley et al., 1996, 1997; Kerger et al., 1996, 1997; Kuykendall et al., 1996). In groups of six volunteers given chromium(VI) as sodium chromate labelled with ^{51}Cr, at least 2.1% was absorbed, as measured by urinary excretion (see section 7.4; Donaldson & Barreras, 1966).

Studies in animals support the poor absorption of chromium compounds from the gastrointestinal tract after oral exposure (Donaldson & Barreras, 1966; Henderson et al., 1979; Sayato et al., 1980; Sullivan et al., 1984; Witmer et al., 1989, 1991; NTP, 2007, 2008). However, even after drinking-water exposure of rats to low concentrations (3 or 10 mg/l) of potassium chromate, elevated concentrations of chromium were observed in the bone, liver, kidney and testis (Sutherland et al., 2000).

The absorbed fraction of chromium(VI) (as sodium chromate) was substantially higher when it was administered directly into the duodenum (approximately 10%) compared with when it was ingested (approximately 1.2%). A similar difference in the absorption of chromium(VI) after oral dosing and from isolated rat intestine has also been reported (Febel et al., 2001). The absorbed fractions for chromium(III) chloride were similar when administered directly into the small intestine and when administered by ingestion (0.5%; Donaldson & Barreras, 1966). These results are consistent with studies that have shown that gastric juice can reduce chromium(VI) to chromium(III) (De Flora et al., 1987, 1997).

Chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged (Mali et al., 1963; Liden & Lundberg, 1979; Corbett et al., 1997).

The dermal absorption of sodium chromate (chromium(VI)) by guinea-pigs was somewhat higher than that of chromium(III) chloride. The peak rates of absorption were 690–725 and 315–330 nmol/hour per square centimetre for sodium chromate at 0.261–0.398 mol/l and chromium(III) chloride at 0.239–0.261 mol/l, respectively. Percutaneous absorption of sodium chromate was higher at pH ≥6.5 compared with pH ≤5.6 (Wahlberg & Skog, 1965).

7.2 Distribution

The chromium concentrations in tissues and body fluids of the general population are given in Table 7.

Table 7: Total chromium content in tissues and body fluids of the general population.

Sample	Median/mean concentration	Concentration range	Reference
Serum	0.06 µg/l	0.01–0.17 µg/l	Sunderman et al. (1989)
Urine	0.4 µg/l	0.24–1.8 µg/l	Iyengar & Woittiez (1988)
Lung	201 µg/kg wet weight	28–898 µg/kg wet weight	Raithel et al. (1987)
Lung	~300 µg/kg wet weight	—	Garcia et al. (2001)
Bone	330 µg/kg wet weight	200–5800 µg/kg wet weight	Garcia et al. (2001)
Brain, kidney, liver	—	<125 µg/kg wet weight	Garcia et al. (2001)
Breast milk	0.30 µg/l	0.06–1.56 µg/l	Casey & Hambidge (1984)

At autopsy, tissues from Japanese chrome platers and chromate refining workers had higher chromium levels in the hilar lymph node, lung, spleen, liver, kidney and heart, compared with normal healthy males (Teraoka, 1981). Chromium accumulation in the lung was observed in pulmonary biopsy specimens and resected lung specimens from chromate workers (Kondo et al., 2003). Measurable levels of chromium were also found in the brain, pharyngeal wall, lung, liver, aorta, kidney, abdominal rectal muscle, suprarenal gland, sternal bone marrow and abdominal skin at autopsy of a man who died of lung cancer 10 years after his retirement from working in a chromate producing plant for 30 years (Hyodo et al., 1980).

Tissues from three individuals with lung cancer who were industrially exposed to chromium for 15, 10.2 or 31.8 years had estimated cumulative chromium exposures of 3.45, 4.59 and 11.38 $(mg/m^3)\cdot$years, respectively (Mancuso, 1997b). All tissues from the three workers had elevated levels of chromium, with the possible exception of neural tissues. Chromium concentrations in lung tissues from autopsy samples were 5 times higher in subjects who originated from the Ruhr and Dortmund regions of Germany, where emissions of chromium are higher, than in subjects from Munster and vicinity. The concentrations of chromium in the lung increased with increasing age. Concentrations of chromium in the lungs were twice as high in men as in women, which may reflect the greater potential for occupational exposure by men, the higher vital capacity of men and possibly a greater history of smoking (Kollmeier et al., 1990).

Experiments in animals confirm the wide distribution of chromium after absorption from the lungs. Three days after the intratracheal administration of 0.01 mg chromium(VI) per cubic metre as radioactive sodium dichromate in rats, the tissue distribution based on the relative concentrations in the tissues was lung > kidney > gastrointestinal tract > erythrocytes > liver > serum > testis > skin. Twenty-five days after dosing, the tissue distribution was lung > kidney > erythrocytes > testis > liver > serum > skin > gastrointestinal tract (Weber, 1983). At 24 hours after intratracheal instillation of potassium dichromate (chromium (VI)) in guinea-pigs, 11% of the original dose of chromium from potassium dichromate remained in the lungs, 8% in the erythrocytes, 1% in plasma, 3% in the kidney and 4% in the liver, and concentrations declined to low or non-detectable levels in 140 days, with the exception of the lungs and spleen. After 30 and 60 days, only 2.6% and 1.6%, respectively, of the chromium(VI) dose was retained in the lung (Baetjer et al., 1959a).

The distribution of chromium in human body tissue after acute oral exposure was determined in the case of a 14-year-old boy who died after ingesting 7.5 mg chromium(VI) per kilogram body weight as potassium dichromate. Upon autopsy, the chromium concentrations were as follows: liver, 29.4 mg/l (normal, 0.16 mg/l); kidneys, 6.4 and 8.2 mg/l (normal, 0.6 mg/l); and brain, 0.6 mg/l (normal, 0.02 mg/l) (Kaufman et al., 1970). Although these data were obtained after the boy was extensively treated to rid the body of excess chromium, the levels of chromium remaining after the treatment clearly demonstrate that these tissues absorbed at least these concentrations after an acute, lethal ingestion of a chromium(VI) compound.

Numerous studies in animals regarding the distribution of chromium after oral exposure are available and confirm its wide distribution after absorption

(MacKenzie et al., 1958; Mertz et al., 1969; Maruyama, 1982; Sullivan et al., 1984; Witmer et al., 1989, 1991; Saxena et al., 1990; Coogan et al., 1991a, 1991b; Kargacin et al., 1993; Aguilar et al., 1997; NTP, 2007, 2008). These studies indicate that the relative organ distribution of chromium depends on the dose and source of chromium, with dosing of rats with soil contaminated with chromium(VI) and/or chromium(III) resulting in higher levels of chromium in tissues than dosing with chromate salts alone (Witmer et al., 1989, 1991); greater distribution after treatment with chromium(VI) than with chromium(III), reflecting the greater tendency of chromium(VI) to traverse plasma membranes (MacKenzie et al., 1958; Maruyama, 1982; Witmer et al., 1989, 1991; Vanoirbeek et al., 2003; NTP, 2008); species differences between rats and mice, with higher tissue levels in mice, perhaps due to higher sequestering of chromium in red blood cells of rats than of mice (Kargacin et al. 1993); and transplacental transfer of chromium to fetuses after treatment of dams with chromium(VI) (Saxena et al., 1990).

A transient increase in the levels of total chromium in erythrocytes and plasma was observed in subjects immersed in a tank of chlorinated water containing potassium dichromate (chromium (VI) (Corbett et al., 1997).

Measurement of ^{51}Cr in the organs and body fluids after dermal administration of chromium(III) and chromium(VI) compounds revealed distribution to the blood, spleen, bone marrow, lymph glands, urine and kidneys in guinea-pigs (Wahlberg & Skog, 1965).

7.3 Metabolism

Chromium(VI) is unstable in the body and is ultimately reduced to chromium(III) in vivo by a variety of reducing agents. Chromium(V) and chromium(IV) are transient intermediates in this process.

In vivo and in vitro experiments in rats indicated that in the lungs, chromium(VI) can be reduced to chromium(III) by ascorbate. When ascorbate is depleted from the lungs, chromium(VI) can also be reduced by glutathione; reduction by glutathione is slower than that by ascorbate (Suzuki & Fukuda, 1990). Other studies reported the reduction of chromium(VI) to chromium(III) by bronchial epithelial lining fluid (Petrilli et al., 1986), post-mitochondrial (S12) preparations of human lung cells and pulmonary alveolar macrophages (De Flora et al., 1984). However, after occupational inhalation exposure to chromium(VI), the total chromium concentration in erythrocytes was elevated, indicating that the reduction was not complete before the passage of chromium from lungs to the blood (Minoia & Cavalleri, 1988).

After oral exposure, chromium(VI) is reduced to chromium(III) in the gastric environment, where gastric juice (De Flora et al., 1987) and ascorbate (Samitz, 1970) play important roles. Chromium(VI) is reduced to chromium(V) in vivo (Liu et al., 1994, 1995, 1997a, 1997b; Ueno et al., 1995). In vitro, low concentrations of ascorbate favour the formation of chromium(V), whereas higher concentrations of ascorbate favour the formation of the reduced oxidation state, chromium(III) (Liu et al., 1995). Chromium(VI) was rapidly reduced to chromium(V) on the skin of rats, with a 3-fold greater response when the stratum corneum was removed (Liu et al., 1997a). Thus, dermal effects from direct skin contact with chromium(VI) compounds may be mediated by rapid reduction to chromium(V). In whole blood and plasma, increasing ascorbate levels led to an increased reduction of chromium(VI) to chromium(III) (Capellmann & Bolt, 1992).

For humans, the overall chromium(VI) reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with faeces, 3300 mg/hour for liver, 234 mg/hour for males and 187 mg/hour for females for whole blood, 128 mg/hour for males and 93 mg/hour for females for red blood cells, 0.1–1.8 mg/hour for epithelial lining fluid, 136 mg/hour for pulmonary alveolar macrophages and 260 mg/hour for peripheral lung parenchyma (De Flora et al., 1997). However, in some subjects exposed to chromium(VI) in drinking-water, the chromium concentration in the erythrocytes was elevated (Finley et al., 1997; Kerger et al., 1997).

Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. The red blood cell membrane is permeable to chromium(VI) but not chromium(III); thus, the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the red blood cell. Eventually, the diffusion of chromium(VI), the reduction to chromium(III) and complexing to macromolecules within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane (Aaseth et al., 1982).

The capacity of plasma to reduce chromium(VI) is very limited (Korallus et al., 1984; Minoia & Cavalleri, 1988; Corbett et al., 1998).

In vitro studies have demonstrated the reduction of chromium(VI) by microsomal cytochrome P450 in the liver and lungs (Gruber & Jennette, 1978; Garcia & Jennette, 1981; Petrilli et al., 1985; Mikalsen et al., 1989).

Species differences in the ability of microsomes to reduce chromium(VI) have been demonstrated for

humans and rats (Pratt & Myers, 1993; Myers & Myers, 1998). In humans, the Michaelis-Menten constant (K_m) for chromium(VI) was 1–3 orders of magnitude lower than the K_m values in rats, although the maximum rate of reaction was similar. Contrary to the rodent data, oxygen and cytochrome P450 inhibitors (carbon monoxide, piperonyl butoxide, metyrapone and aminopyrine) did not inhibit chromium(VI) reduction. Thus, in humans, cytochrome P450 does not play a significant role in the reduction process, but other microsomal flavoproteins are responsible for reducing chromium(VI). Inhibition of flavoproteins by thallium chloride ($TlCl_3$) decreased chromium(VI) reduction by 96–100%, whereas inhibition of cytochrome *c* reductase (P450 reductase) by bromo-4′-nitroacetophenone resulted in an 80–85% inhibition of chromium(VI) reduction. Combined, these observations implicate P450 reductase, working independently of cytochrome P450, as a major contributor to the reduction of chromium(VI) in human microsomes. These findings suggest that metabolism of chromium(VI) in rodent systems may not be readily extrapolated to humans.

Microsomal reduction of chromium(VI) can also result in the formation of chromium(V), which involves a one-electron transfer from the microsomal electron transport cytochrome P450 system in rats. The chromium(V) complexes are characterized as labile and reactive. These chromium(V) intermediates persist for 1 hour in vitro, making them likely to interact with DNA, which may eventually lead to cancer (Jennette, 1982). Liu et al. (1994) demonstrated that chromium(V) is formed in vivo by using low-frequency electron paramagnetic resonance spectroscopy on whole mice. Reactions of chromium(VI) with glutathione produced two chromium(V) complexes and a glutathione thiyl radical. Reactions of chromium(VI) with DNA in the presence of glutathione produced chromium–DNA adducts. The level of chromium–DNA adduct formation was correlated with chromium(V) formation. The reaction of chromium(VI) with hydrogen peroxide produced hydroxyl radicals. Reactions of chromium(VI) with DNA in the presence of high concentrations of hydrogen peroxide produced significant DNA strand breakage and the 8-hydroxyguanosine adduct, which was correlated with hydroxyl radical production (Aiyar et al., 1989, 1991). Very little chromium(V) was generated by this pathway. The reaction of chromium(VI) with hydrogen peroxide may produce tetraperoxochromium(V) species that act as a catalyst in a Fenton-type reaction producing hydroxyl radicals in which chromium(V) is continuously being recycled back to chromium(VI). The regeneration of chromium(VI) through interactions with chromium(V) and hydrogen peroxide is consistent with the findings of Molyneux & Davies (1995). Chromium(VI) is ultimately reduced to chromium(III) within the cell. Chromium(III) can form stable complexes with DNA and protein (De Flora & Wetterhahn, 1989).

7.4 Elimination and excretion

Average concentrations of total chromium in people without occupational exposure to chromium compounds in different studies have usually been 0.1–0.5 µg/l in serum and 0.1–0.5 µg/g creatinine in urine (Brune et al., 1993).

In people exposed to chromium(VI) at work, chromium(III) but not chromium(VI) was detected in the urine, indicating that chromium(VI) was reduced before excretion (Cavalleri & Minoia, 1985; Minoia & Cavalleri, 1988).

Several studies are available on the relationship between inhalation exposure to chromium(VI) in manual metal arc welding and the concentration of chromium in urine, and thus there is a basis for biological monitoring (Aitio et al., 1988). For other chromium(VI) compounds and exposure scenarios, such information is not available.

Peak urinary chromium concentrations were observed at 6 hours (the first time point examined) in rats exposed intratracheally to 0.44 mg chromium(VI) per kilogram body weight as sodium dichromate (Gao et al., 1993). Urinary chromium concentrations decreased rapidly, falling from 2947 µg chromium per gram creatinine at 6 hours to 339 µg chromium per gram creatinine at 72 hours.

Elimination of chromium was very slow in rats exposed by inhalation to 2.1 mg chromium(VI) per cubic metre as zinc chromate, 6 hours/day for 4 days. Urinary levels of chromium remained almost constant for 4 days after exposure and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langård et al., 1978). The urinary half-time of chromium was 8–21 hours in rats administered potassium dichromate or a chromium(VI) catalyst as a single intratracheal instillation (Vanoirbeek et al., 2003).

In humans dosed orally with 20 ng of radiolabelled sodium chromate or chromium(III) chloride, the amount of chromium in the 6-day faecal collection was 89.4% and 99.6% of the dose for chromium(VI) and chromium(III) compounds, respectively. The amount of chromium in the 24-hour urine collection was 2.1% and 0.5% of the dose for chromium(VI) and chromium(III) compounds, respectively (Donaldson & Barreras, 1966). In subjects drinking 0.001–0.1 mg chromium(VI) per kilogram body weight per day as potassium chromate in water for 3 days, <2–8% of the dose was excreted in the urine (Finley et al., 1997). The percentage of the dose excreted appeared to increase with increasing dose.

Urinary excretion rates have been measured in humans after oral exposure to several chromium compounds (Finley et al., 1996). Lower urinary excretion of chromium(III) occurred after exposure to chromic oxide than after exposure to potassium chromate, reflecting the poorer absorption of inorganic chromium(III) compounds compared with inorganic chromium(VI) compounds.

Ingestion by humans of 0.05 mg chromium(VI) per kilogram body weight in drinking-water resulted in an extended time course of excretion (Kerger et al., 1997). Approximately 76–82% of the 14-day total amount of chromium in the urine was excreted within the first 4 days (mean peak concentration 209 µg chromium per gram creatinine; range 29–585 µg chromium per gram creatinine). The average urinary excretion half-life for four of the volunteers was 39 hours at this dose. All subjects had returned to background concentrations (0.5–2.0 µg chromium per gram creatinine) by 14 days post-dosing. Kerger et al. (1996) examined urinary excretion half-lives following a bolus dose (approximately 0.06 mg chromium per kilogram body weight) as chromium(III) chloride, potassium dichromate reduced to chromium(III) complexes and ions with orange juice, or potassium dichromate. The calculated average urinary excretion half-lives for the three chromium solutions were 10.3, 15 and 39 hours (range, 36–43 hours), respectively. The potassium dichromate half-life is consistent with the results from the Kerger et al. (1997) study.

Measurement of the total chromium content in 255 milk samples from 45 lactating American women revealed that most samples contained less than 0.4 µg/l, with a mean value of 0.3 µg/l (Casey & Hambidge, 1984). Anderson et al. (1993) measured chromium levels in the breast milk of 17 women 60 days postpartum and reported mean concentrations of approximately 0.2 µg/l. Lactation therefore represents a route of excretion of chromium and a potential route of exposure of the nursing infant. Although there are apparently no analytical data on the oxidation state of chromium in breast milk, it is most likely chromium(III), not chromium(VI).

Chromium can be excreted in hair and fingernails. Mean levels of total chromium detected in the hair of individuals from the general populations of several countries were as follows: USA, 0.23 mg/kg; Canada, 0.35 mg/kg; Poland, 0.27 mg/kg; Japan, 0.23 mg/kg; and India, 1.02 mg/kg (Takagi et al., 1986). Mean levels of chromium in the fingernails of these populations were as follows: USA, 0.52 mg/kg; Canada, 0.82 mg/kg; Poland, 0.52 mg/kg; Japan, 1.4 mg/kg; and India, 1.3 mg/kg (Takagi et al., 1988).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

Acute inhalation median lethal concentrations (LC_{50} values) in rats (from 4-hour lethality studies) for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate and ammonium dichromate) ranged from 29 to 45 mg chromium(VI) per cubic metre for females and from 33 to 82 mg chromium(VI) per cubic metre for males (Gad et al., 1986), corresponding to acute toxicity category 1 in the Globally Harmonized System of Classification and Labelling of Chemicals. Acute 4-hour inhalation LC_{50} values for chromium trioxide were 87 and 137 mg chromium(VI) per cubic metre for female and male rats, respectively (American Chrome and Chemicals, 1989). Signs of toxicity included respiratory distress, irritation of the upper respiratory tract and body weight depression (Gad et al., 1986).

Acute oral median lethal doses (LD_{50} values) in rats exposed to chromium(VI) compounds varied with the compound and the sex of the rat. LD_{50} values for chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate and ammonium dichromate) ranged from 13 to 19 mg chromium(VI) per kilogram body weight in female rats and from 21 to 28 mg chromium(VI) per kilogram body weight in male rats (Gad et al., 1986). The LD_{50} values for chromium trioxide were 25 and 29 mg chromium(VI) per kilogram body weight for female and male rats, respectively (American Chrome and Chemicals, 1989). An LD_{50} of 811 mg chromium(VI) per kilogram body weight as strontium chromate was reported for male rats (Shubochkin & Pokhodzie, 1980).

Single-dose (24-hour) dermal LD_{50} values in New Zealand rabbits exposed to chromium(VI) as sodium chromate, sodium dichromate, potassium dichromate or ammonium dichromate ranged from 361 to 553 mg chromium(VI) per kilogram body weight for females and from 336 to 763 mg chromium(VI) per kilogram body weight for males (Gad et al., 1986). Signs of toxicity included dermal necrosis, eschar formation, dermal oedema and erythema, diarrhoea and hypoactivity. Application of potassium dichromate solutions (0.35–1.9 mg chromium(VI) per kilogram body weight) to the abraded skin of guinea-pigs resulted in skin ulcers (Samitz & Epstein, 1962; Samitz, 1970). Skin sensitization to chromium(VI) was also demonstrated in guinea-pigs following intradermal injections of 0.009 mg chromium(VI) per kilogram body weight as potassium dichromate (Gross et al., 1968). The dermal LD_{50} value for chromium trioxide was 30 mg chromium(VI) per kilogram body weight for both sexes of New Zealand

rabbits combined (American Chrome and Chemicals, 1989).

8.2 Short-term exposure

In a study designed to examine the influence of the solubility of chromium(VI) compounds on their immunotoxicity to pulmonary macrophages, rats were exposed by inhalation to 0.36 mg chromium(VI) per cubic metre as potassium chromate (soluble) or as barium chromate (insoluble) for 5 days/week, 5 hours/day, for 2–4 weeks. With the exception of basal nitric oxide production and interferon-γ-primed/zymosan-stimulated reactive oxygen intermediate production in pulmonary macrophages, potassium chromate induced more marked changes in parameters reflecting inflammation than did barium chromate (Cohen et al., 1998). Both the insoluble lead chromate and the soluble sodium chromate were toxic to cultured human bronchial epithelial cells (Wise et al., 2006).

Brain homogenates from mice that received 8.8 mg chromium(VI) per kilogram body weight per day as potassium dichromate (25 mg/kg bw per day) in drinking-water for 3 days indicated increased formation of reactive oxygen species and brain lipid peroxidation (Travacio et al., 2001).

Rats exposed by gavage to 13.5 mg chromium(VI) per kilogram body weight per day as potassium chromate for 20 days developed lipid accumulation in liver and kidneys and changes in liver and renal enzyme (acid phosphatase, alkaline phosphatase, lipase) activities (Kumar & Rana, 1984; Kumar et al., 1985). Rats that received 100 mg chromium(VI) per kilogram body weight per day as sodium chromate in drinking-water for 28 days developed proteinuria and oliguria and exhibited decreased motor activity (Diaz-Mayans et al., 1986).

8.3 Medium-term exposure

8.3.1 Inhalation

In an inhalation study by Glaser et al. (1990), 8-week-old male Wistar rats (30 animals in each group) were exposed for 22 hours/day, 7 days/week, to 0, 0.05, 0.1, 0.2 or 0.4 mg chromium(VI) per cubic metre as sodium dichromate aerosol. Groups of 10 animals were sacrificed after 30 or 90 days of exposure or after 90 days of exposure and a 30-day recovery period. For the 0.05 and 0.1 mg chromium(VI) per cubic metre concentrations, the mass median aerodynamic diameter (MMAD) was 0.28 μm, and the geometric standard deviation (GSD) was 1.63 μm. For the 0.2 and 0.4 mg chromium(VI) per cubic metre concentrations, the MMAD was 0.39 μm, and the GSD was 1.72 μm. Haematological, clinical chemistry and urine analysis tests were performed. Gross and histological examinations were limited to the upper airway epithelia, left lung lobes and kidneys. In addition, lung lavage fluid was analysed for total protein, albumin, lactate dehydrogenase and β-glucuronidase activities.

Body weight was significantly decreased at 0.2 and 0.4 mg chromium(VI) per cubic metre for 30 days, at 0.4 mg chromium(VI) per cubic metre for 90 days and at 0.2 and 0.4 mg chromium(VI) per cubic metre in the recovery group. White blood cell counts increased significantly after 90 days' exposure to ≥0.05 mg chromium(VI) per cubic metre and after 30 days' exposure to ≥ 0.1 mg/m^3. White blood cell counts were no longer significantly increased in the recovery group.

Obstructive respiratory dyspnoea occurred at 0.2 and 0.4 mg chromium(VI) per cubic metre after 30 and 90 days. Mean lung weight was significantly increased in all exposure groups after 30 days and was statistically increased at 0.1, 0.2 and 0.4 mg chromium(VI) per cubic metre for 90 days and in the 90-day plus recovery period groups at 0.1, 0.2 and 0.4 mg chromium(VI) per cubic metre. Histological examination revealed slight bronchoalveolar hyperplasia at high incidence at all concentrations at 30 days (1/10 in controls, 7/10 at 0.05 mg/m^3, 10/10 at 0.1 mg/m^3 and 9/10 at both 0.2 and 0.4 mg/m^3). With longer exposure, the incidence declined, indicating repair. Lung fibrosis occurred at 0.1 mg chromium(VI) per cubic metre (4/10) for 30 days (1/10 at 0.2 mg/m^3 and 3/10 at 0.4 mg/m^3), but was seen in only 1/10 rats exposed at 0.05 mg chromium(VI) per cubic metre for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. This histiocytosis probably accounts for the increased lung weight. Histology of upper airways revealed focal inflammation. Results of BAL analysis provided further information on the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups and durations, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group and showed statistical significance at all concentrations, but recovery started during the 90-day exposure and continued during the 30-day recovery period. The activities of lactate dehydrogenase and β-glucuronidase, which are measures of cytotoxicity, were significantly elevated at 0.2 and 0.4 mg chromium(VI) per cubic metre for both 30- and 90-day exposure durations, but returned to control values during the recovery period. The activities of lactate dehydrogenase were also increased at 0.1 mg chromium(VI) per cubic metre after 30 days of exposure and at 0.05 mg chromium(VI) per cubic metre after 90 days of exposure. The number of macrophages in the BAL fluid had significantly increased at 0.2 and 0.4 mg chromium(VI) per cubic metre after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This

activation of macrophages was not observed in the recovered rats.

In a supporting study by Glaser et al. (1985), groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1 or 0.2 mg chromium(VI) per cubic metre as sodium dichromate for 22 hours/day, 7 days/week, for 28 or 90 days. Lung and spleen weights were increased significantly at concentrations above 0.025 mg chromium(VI) per cubic metre after 28 and 90 days. Serum levels of triglycerides and phospholipids were significantly increased only in rats exposed to 0.2 mg chromium(VI) per cubic metre for 90 days. Serum contents of total immunoglobulins were significantly increased in the 0.05 and 0.1 mg chromium(VI) per cubic metre groups. At 0.025 and 0.2 mg chromium(VI) per cubic metre, serum immunoglobulin contents were not different from control values. The sheep red blood cell antibody response was increased in all dosed groups over control values. Chromium(VI) treatment at 0.2 mg/m^3 also significantly enhanced the mitogenic (concanavalin A) stimulation of splenic T lymphocytes. At 0.025 mg chromium(VI) per cubic metre, there were significant increases in polynuclear macrophages, the number of macrophages in telophase and lymphocytes in BAL samples. At 0.05 and 0.2 mg chromium(VI) per cubic metre, there were significant decreases in total numbers of macrophages. The percentages of polynuclear macrophages, lymphocytes and granulocytes were increased at exposures of 0.05 mg chromium(VI) per cubic metre, but at 0.2 mg chromium(VI) per cubic metre, the percentage of granulocyte cells was lower than control values. At 0.025 and 0.05 mg chromium(VI) per cubic metre, phagocytosis of latex particles by alveolar macrophages was increased over controls. However, at 0.2 mg chromium(VI) per cubic metre, the phagocytic activity was less than in controls, and there was a decrease in lung clearance of iron oxide particulates. Thus, as immunological effects occurred in all exposed rats in the Glaser et al. (1985, 1990) studies, 0.025 mg chromium(VI) per cubic metre is the LOAEC.

8.3.2 Ingestion

The main effects seen in animals after medium-term oral exposure to chromium compounds were effects on body weight gain, haematological indices and the immune system. Decreased body weight gain was observed in rats exposed via drinking-water to 42 mg chromium(VI) per kilogram body weight per day as potassium dichromate for 12 weeks (Bataineh et al., 1997) and in mice exposed to 6 mg chromium(VI) per kilogram body weight per day as potassium dichromate for 12 weeks (Elbetieha & Al-Hamood, 1997). Haematological effects in rats and mice exposed to potassium dichromate in the diet consisted of decreased mean corpuscular volume in rats (both sexes) at 8.4–9.8 mg chromium(VI) per kilogram body weight per day and mice (both sexes) at 32.2–48 mg chromium(VI) per kilogram body weight per day for 9 weeks (NTP, 1996a, 1996b) and in F_1 generation mice in a two-generation study of mice at 7.8 mg chromium(VI) per kilogram body weight per day (NTP, 1997). Snyder & Valle (1991) reported increased proliferation of T and B lymphocytes in response to mitogens and antigens in rats given 16 mg chromium(VI) per kilogram body weight per day as potassium chromate in drinking-water for 3–10 weeks.

In a medium-term drinking-water study, groups of 10 male and 10 female F344/N rats were given sodium dichromate dihydrate in drinking-water at a concentration of 0, 62.5, 125, 250, 500 or 1000 mg/l for 3 months (NTP, 2007). Based on drinking-water consumption, these concentrations were equivalent to doses of 0, 1.7, 3.5, 5.9, 11.2 and 20.9 mg chromium(VI) per kilogram body weight per day. Additional groups of 10 male and 10 female F344/N rats were similarly exposed for 4 weeks for clinical pathological examination. Decreased body weight gain was seen in both male and female rats at 20.9 mg chromium(VI) per kilogram body weight per day and in male rats at 11.2 mg chromium(VI) per kilogram body weight per day. Exposed rats displayed an exposure-related microcytic, hypochromic anaemia at all exposure levels (Table 8). Histopathological effects consisted of ulceration, hyperplasia and metaplasia of the forestomach in male and female rats at 20.9 mg chromium(VI) per kilogram body weight per day. In addition, increased histiocytic infiltration occurred in the liver of female rats at and above 3.5 mg chromium(VI) per kilogram body weight per day, in the duodenum of the small intestine at and above 3.5 mg chromium(VI) per kilogram body weight per day in both sexes and in the pancreatic lymph nodes in females at 20.9 mg chromium(VI) per kilogram body weight per day and in males at doses as low as 1.7 mg chromium(VI) per kilogram body weight per day.

In the NTP (2007) study, groups of 10 male and 10 female B6C3F1 mice were given sodium dichromate dihydrate in drinking-water at concentrations equivalent to doses of 0, 3.1, 5.2, 9.1, 15.7 and 27.9 mg chromium(VI) per kilogram body weight per day for 3 months. Decreased body weight gain occurred in all exposed male and female mice that received at least 5.2 mg chromium(VI) per kilogram body weight per day. Decreases in mean cell volume of erythrocytes occurred in male mice at and above 3.1 mg chromium(VI) per kilogram body weight per day and in females at and above 5.2 mg chromium(VI) per kilogram body weight per day. Haematocrit and haemoglobin concentrations were not changed in male mice, but female mice had increased erythrocyte counts and decreased haemoglobin concentrations at and above 5.2 mg chromium(VI) per kilogram body weight per day. Histopathological lesions in mice were limited to epithelial hyperplasia and

Table 8: Haematological effects in rats exposed to chromium(VI) in drinking-water for 3 months (from NTP, 2007).

	Haematocrit (%)[a]					
	0 mg Cr(VI)/kg bw per day	1.7 mg Cr(VI)/kg bw per day	3.5 mg Cr(VI)/kg bw per day	5.9 mg Cr(VI)/kg bw per day	11.2 mg Cr(VI)/kg bw per day	20.9 mg Cr(VI)/kg bw per day
Males						
Day 5	45.8 ± 1.0	45.0 ± 0.8	45.2 ± 0.9	43.8 ± 0.8	44.6 ± 0.6	46.2 ± 0.7
Day 23	48.5 ± 0.7	45.0 ± 1.0*	34.3 ± 1.8**	28.0 ± 1.4**	24.3 ± 0.9**	21.1 ± 1.6**
Week 14	46.0 ± 0.3	45.5 ± 0.4	45.3 ± 0.3	44.9 ± 0.7	43.1 ± 0.5**	30.8 ± 1.9**
Females						
Day 5	48.2 ± 1.3	48.4 ± 0.8	47.4 ± 1.3	46.8 ± 1.2	48.7 ± 0.6	48.5 ± 1.0
Day 23	47.7 ± 0.4	45.9 ± 0.9	35.2 ± 1.1**	29.6 ± 2.0**	24.1 ± 1.2**	19.5 ± 0.7**
Week 14	44.2 ± 0.3	45.8 ± 0.2	44.0 ± 0.2	42.8 ± 0.3*	42.8 ± 0.4*	38.4 ± 0.6**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test; ** $P \leq 0.01$

[a] Mean ± standard error. Values presented are instrument-derived values. Manual haematocrit values showed less marked effects, possibly resulting from the formation of abnormally small erythrocytes.

histiocytic infiltration of the duodenum and histiocytic infiltration of the mesenteric lymph nodes of both sexes at doses as low as 3.1 mg chromium(VI) per kilogram body weight per day.

In addition, the NTP (2007) studies included a comparative study of groups of 10 male B6C3F1 mice, 10 male BALB/c mice and 5 male *am3*-C57BL/6 mice exposed to drinking-water containing sodium dichromate dihydrate at concentrations equivalent to doses of 0, 2.8, 5.2 and 8.7 mg chromium(VI) per kilogram body weight per day for 3 months. Decreased mean body weights occurred in B6C3F1 and BALB/c mice at 5.2 and 8.7 mg chromium(VI) per kilogram body weight per day and in *am3*-C57BL/6 mice at all doses. Mean erythrocyte volume and/or mean erythrocyte haemoglobin values were decreased in a dose-related manner at all doses in all strains. Erythrocyte counts were increased at the high dose in B6C3F1 and BALB/c mice. Histopathological findings consisted of histiocytic cellular infiltration and epithelial hyperplasia of the duodenum in all strains at all doses and histiocytic cellular infiltration in the mesenteric lymph nodes at and above 5.2 mg chromium(VI) per kilogram body weight per day in the B6C3F1 mice and at 8.7 mg chromium(VI) per kilogram body weight per day in the *am3*-C57BL/6 mice.

8.4 Long-term exposure and carcinogenicity

8.4.1 Non-cancer effects

In 18-month inhalation studies in Wistar rats exposed to sodium dichromate at concentrations less than or equal to 0.1 mg chromium(VI) per cubic metre or to a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide at a concentration of 0.1 mg chromium per cubic metre, only the mixture produced effects, consisting of interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs (Glaser et al., 1986, 1988). The mixture-exposed rats also exhibited increased haematocrit, haemoglobin levels, and red and white cell counts.

Other long-term exposure studies involving inhalation of chromium(VI) compounds reported granulomata, giant cells, bronchopneumonia and lung abscesses in rats exposed to 1.6 mg chromium(VI) per cubic metre as a finely ground chromium roast intermittently for 2 years (Steffee & Baetjer, 1965); epithelial necrosis and hyperplasia in the large and medium bronchi, with numerous openings in the bronchiolar walls, in mice exposed intermittently to 4.3 mg chromium(VI) per cubic metre as calcium chromate for 18 months (Nettesheim & Szakal, 1972); and increased incidences of alveolar and interstitial inflammation, alveolar hyperplasia and interstitial fibrosis in guinea-pigs exposed intermittently to 1.6 mg chromium(VI) per cubic metre as chromium roast material along with mists of potassium dichromate or sodium chromate solutions for 4.5 years (Steffee & Baetjer, 1965).

An inhalation study in mice found emphysema and nasal septum perforation in mice exposed intermittently to 1.81 mg chromium(VI) per cubic metre as chromium trioxide for 12 months (Adachi, 1987).

No effects on the hepatic or renal system and no effects on body weight or haematological parameters were found in rats exposed for 1 year to 3.6 mg chromium(VI) per kilogram body weight per day as potassium chromate in drinking-water (MacKenzie et al., 1958).

NTP (2008) conducted a 2-year study of groups of 50 male and 50 female F344/N rats exposed to drinking-water containing sodium dichromate dihydrate at a concentration of 0, 14.3, 57.3, 172 or 516 mg/l. Based on water consumption data, these concentrations are equivalent to doses of 0, 0.21, 0.77, 2.1 and 5.95 mg chromium(VI) per kilogram body weight per day for males and 0, 0.25, 0.95, 2.45 and 7.0 mg chromium(VI) per kilogram body weight per day for females. No effect on survival was noted. As in the medium-term 3-month drinking-water study by NTP (2007), the rats developed a transient microcytic hypochromic anaemia at sodium dichromate dihydrate concentrations of ≥57.3 mg/l (≥0.77 mg chromium(VI) per kilogram body weight per day for males, ≥0.95 mg chromium(VI) per kilogram body weight per day for females). Non-neoplastic effects consisted of histiocytic infiltration of the liver, small intestine (duodenum) and mesenteric lymph nodes in both sexes of rats at sodium dichromate dihydrate concentrations of ≥57.3 mg/l (≥0.77 mg chromium(VI) per kilogram body weight per day for males, ≥0.95 mg chromium(VI) per kilogram body weight per day for females). Histiocytic infiltration of the pancreatic lymph nodes was also recorded in female rats at and above 2.45 mg chromium(VI) per kilogram body weight per day (see Table 9).

NTP (2008) also exposed groups of 50 male B6C3F1 mice to sodium dichromate dihydrate in drinking-water at 0, 14.3, 28.6, 85.7 or 257.4 mg/l and groups of 50 female B6C3F1 mice to 0, 14.3, 57.3, 172 or 516 mg/l for 2 years. These concentrations are equivalent to doses of 0, 0.39, 0.91, 2.45 and 5.95 mg chromium(VI) per kilogram body weight per day for males and 0, 0.39, 1.37, 3.15 and 8.75 mg chromium(VI) per kilogram body weight per day for females. Non-neoplastic effects consisted of increased epithelial hyperplasia in the duodenum at all doses in both sexes of mice. Mice also displayed histiocytic infiltration of the duodenum at the two highest doses in both sexes, in the jejunum of females at the highest dose, in the liver at all doses in females, of the mesenteric lymph nodes in both sexes at all doses and of the pancreatic lymph nodes at the two highest doses in male and female mice (see Table 9). The benchmark dose for a 10% response (BMD_{10}) and the lower limit on the benchmark dose for a 10% response ($BMDL_{10}$) for the best-fitting models for these findings are given in Table 10 (ATSDR, 2008).

8.4.2 Carcinogenicity

In 136 male and 136 female C57BL/6 mice that were exposed by inhalation for 5 hours/day, 5 days/week, for up to 18 months to 4.3 mg chromium(VI) per cubic metre as calcium chromate, 6 males and 8 females developed lung tumours (alveologenic adenomas and adenocarcinomas) compared with 3 male and 2 female air-exposed controls (Nettesheim et al., 1971). Lung tumours were observed in 3 of 19 male Wistar rats exposed for 22 hours/day, 7 days/week, for 18 months to 0.1 mg chromium(VI) per cubic metre as sodium dichromate, followed by 12 months of observation. The tumours included two adenomas and one adenocarcinoma. No lung tumours were observed in controls (n = 37) or the rats exposed to 0.025 (n = 18) or 0.05 (n = 18) mg chromium(VI) per cubic metre (Glaser et al., 1986, 1988). The increased incidence of lung tumours in the treated rats was significant (P = 0.03) (ATSDR, 2008).

In the NTP (2008) 2-year study of F344/N rats exposed to sodium dichromate dihydrate in drinking-water (Table 11), elevated incidences of squamous cell carcinoma in the oral cavity (oral mucosa or tongue) (statistically significant) were observed at the high doses in both sexes.

In B6C3F1 mice similarly exposed for 2 years to sodium dichromate dihydrate in drinking-water, benign and malignant tumours were observed in the small intestine—primarily adenomas in the duodenum (Table 12) (NTP, 2008).

Increases in tumour incidence have also been found in a number of studies involving intratracheal, intrapleural, intramuscular, intraperitoneal, intravenous and subcutaneous injections (ATSDR, 2008).

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).

A low incidence of tumours of the lung was observed in rats treated with sodium dichromate or calcium chromate by intratracheal instillation at a dose level of 1.25 mg/kg bw per week for 30 weeks, but not at lower dose levels (Steinhoff et al., 1986). The incidence of the tumours was markedly higher if the chromium(VI) compound was given as a single weekly dose (1.25 mg/kg bw) than if it was given as five daily doses (0.25 mg/kg bw, 5 times/week).

Table 9: Non-neoplastic lesions in rats and mice exposed to chromium(VI) in drinking-water for 2 years in an NTP (2008) study.

	Incidence of lesions				
	Conc. 1	**Conc. 2**	**Conc. 3**	**Conc. 4**	**Conc. 5**
Male rats					
Concentration in drinking-water (mg/l)	*0*	*14.3*	*57.3*	*172*	*516*
Dose (mg Cr(VI)/kg bw per day)	*0*	*0.21*	*0.77*	*2.1*	*5.95*
Liver: Infiltration cellular, histiocyte	1/50	0/50	2/49	5/50	34/49
Small intestine, duodenum: Infiltration cellular, histiocyte	0/48	0/48	6/47	36/46	47/48
Lymph node, mesenteric: Infiltration cellular, histiocyte	13/49	11/50	30/49	39/50	41/49
Female rats					
Concentration in drinking-water (mg/l)	*0*	*14.3*	*57.3*	*172*	*516*
Dose (mg Cr(VI)/kg bw per day)	*0*	*0.25*	*0.95*	*2.45*	*7.0*
Liver: Infiltration cellular, histiocyte	1/50	5/50	21/50	42/50	47/50
Small intestine, duodenum: Infiltration cellular, histiocyte	0/46	0/49	1/48	30/46	47/50
Lymph node, mesenteric: Infiltration cellular, histiocyte	21/50	18/50	27/50	36/50	42/50
Lymph node, pancreatic: Infiltration cellular, histiocyte	17/31	20/37	23/31	32/34	27/36
Male mice					
Concentration in drinking-water (mg/l)	*0*	*14.3*	*28.6*	*85.7*	*257.4*
Dose (mg Cr(VI)/kg bw per day)	*0*	*0.39*	*0.91*	*2.45*	*5.95*
Small intestine, duodenum: Epithelium, hyperplasia	0/50	11/50	18/50	42/50	32/50
Small intestine, duodenum: Infiltration cellular, histiocyte	0/50	2/50	4/50	37/50	35/50
Lymph node, mesenteric: Infiltration cellular, histiocyte	14/47	38/47	31/49	32/49	42/46
Lymph node, pancreatic: Infiltration cellular, histiocyte	0/12	2/16	2/15	5/12	12/20
Female mice					
Concentration in drinking-water (mg/l)	*0*	*14.3*	*57.3*	*172*	*516*
Dose (mg Cr(VI)/kg bw per day)	*0*	*0.39*	*1.37*	*3.15*	*8.75*
Liver: Infiltration cellular, histiocyte	2/49	15/50	23/50	32/50	45/50
Small intestine, duodenum: Epithelium, hyperplasia	0/50	16/50	35/50	31/50	42/50
Small intestine, duodenum: Infiltration cellular, histiocyte	0/50	0/50	4/50	33/50	40/50
Small intestine, jejunum: Epithelium, hyperplasia	0/50	2/50	1/50	0/50	8/50
Small intestine, jejunum: Infiltration cellular, histiocyte	0/50	0/50	0/50	2/50	8/50
Lymph node, mesenteric: Infiltration cellular, histiocyte	3/46	29/48	26/46	40/50	42/50
Lymph node, pancreatic: Infiltration cellular, histiocyte	0/21	1/15	2/17	7/18	8/16

Conc., concentration

8.5 Genotoxicity and related end-points

8.5.1 In vitro studies

In vitro studies indicated that soluble chromium(VI) compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (ATSDR, 2008). In addition, lead chromate, a water-insoluble compound, was mutagenic in bacteria when dissolved in sodium hydroxide or sulfuric acid (Nestmann et al., 1979). Only one study reported negative results with chromium(VI) in all tested strains (Kanematsu et al., 1980). After preincubation with mammalian microsomes, the mutagenicity of chromium(VI) compounds was reduced or abolished due to concentrations of the reductant glutathione, cysteine or reduced nicotinamide adenine dinucleotide phosphate (NADPH) capable of converting chromium(VI) to chromium(III) compounds (De Flora, 1978, 1981; Nestmann et al., 1979; Bennicelli et al., 1983). Chromium(VI) compounds caused gene mutations in *Bacillus subtilis* and *Escherichia coli* (ATSDR, 2008).

Studies in eukaryotic organisms indicated that chromium(VI) was genotoxic in *Saccharomyces cerevisiae* and in *Schizosaccharomyces pombe* (Bonatti et al., 1976). Sodium chromate induced DNA damage (DNA interstrand crosslinks, DNA strand breaks, DNA–protein crosslinks) in cultured chick embryo hepatocytes. The vast majority of studies reported genotoxic effects of chromium(VI) in mammalian cells in vitro (ATSDR, 2008). Although no increase in DNA damage was observed in Chinese hamster ovary cells exposed to lead chromate, probably due to the limited solubility of

Table 10: Summary of BMD_{10} and $BMDL_{10}$ values from the best-fitting models for non-neoplastic lesions of the liver, duodenum, mesenteric lymph nodes and pancreas in female rats and male and female mice after exposure to sodium dichromate dihydrate in drinking-water for 2 years (from ATSDR, 2008).

End-point	Species/sex	Model	Number of doses	BMD[a] (mg/kg bw per day)	BMDL[a] (mg/kg bw per day)
Liver: Chronic inflammation	Rat/female	Log-logistic	5	0.22	0.14
Duodenum: Diffuse epithelial hyperplasia	Mouse/male	One-degree polynomial/ multistage/quantal linear	4	0.16	0.13
Mesenteric lymph node: Histiocytic cellular infiltration[b]	Mouse/male	—	—	—	—
Duodenum: Diffuse epithelial hyperplasia	Mouse/female	Gamma/multistage/ quantal linear/Weibull	3	0.12	0.094[c]
Mesenteric lymph node: Histiocytic cellular infiltration[b]	Mouse/female	—	—	—	—
Liver: Histiocytic cellular infiltration	Mouse/female	Log-logistic	5	0.17	0.12
Pancreas: Acinus, cytoplasmic alteration	Mouse/female	Log-logistic	5	0.68	0.52

[a] BMDs/BMDLs from dichotomous data are associated with a 10% extra risk; doses are in terms of mg chromium(VI)/kg bw per day.
[b] None of the models provided an adequate fit to the data.
[c] Used for the derivation of a tolerable daily intake (see section 11.1.2.1).

Table 11: Oral tumours in rats after drinking-water exposure to sodium dichromate dihydrate (from NTP, 2008).

	Incidence in male rats			Incidence in female rats		
Dose (mg/kg bw per day)	*N*[a]	Carcinoma	Papilloma or carcinoma	*N*[a]	Carcinoma	Papilloma or carcinoma
0	48	0	0	49	0	1
0.21	45	0	1	—	—	—
0.25	—	—	—	48	0	1
0.77	46	0	0	—	—	—
0.95	—	—	—	49	0	0
2.1	49	0	0	—	—	—
2.45	—	—	—	47	2	2
5.95	50	6	7	—	—	—
7.0	—	—	—	47	11	11

[a] *N* at the time of the first tumour incidence = day 506 (females).

Table 12: Small intestinal tumours (duodenum, jejunum or ileum) in mice after drinking-water exposure to sodium dichromate dihydrate (NTP, 2008).

Dose	Incidence in male mice				Incidence in female mice			
(mg/kg bw per day)	*N*[a]	Adenoma	Carcinoma	Adenoma or carcinoma	*N*[a]	Adenoma	Carcinoma	Adenoma or carcinoma
0	49	1	0	1	49	0	1	1
0.39	49	1	2	3	50	1	0	1
0.91	49	1	1	2	—	—	—	—
1.37	—	—	—	—	49	2	2	4
2.45	50	5	3	7	—	—	—	—
3.15	—	—	—	—	49	15	3	17
5.95	48	17	5	20	—	—	—	—
8.75	—	—	—	—	49	16	7	22

[a] *N* at the time of the first tumour incidence = day 451 (females). The number of animals alive at the time when the first tumour was observed was taken as the number of animals at risk, derived from the female groups and used in subsequent assessments for both sexes.

the tested compound (Douglas et al., 1980), an increase in chromosomal aberrations was found in Chinese hamster ovary cells treated with lead chromate in another study (Wise et al., 1993). Furthermore, both particulate chromium(VI) as lead chromate and soluble chromium(VI) as sodium chromate were clastogenic in cultured human lung cells (Wise et al., 2002).

8.5.2 In vivo studies

An increase in DNA–protein crosslinking was found in the livers of rats that had been exposed to potassium chromate in the drinking-water at and above 6 mg chromium(VI) per kilogram body weight per day for 3 or 6 weeks (Coogan et al., 1991a). No unscheduled DNA synthesis was found in rat hepatocytes after the rats were exposed to potassium chromate in drinking-water (Mirsalis et al., 1996). In the NTP (2007) 3-month drinking-water studies (see section 8.3), four micronucleus tests were conducted in three strains of mice. In the male and female B6C3F1 mice, there were no significant increases in micronucleated normochromic erythrocytes in peripheral blood samples; however, there were significant dose-related increases in micronuclei in the male *am3*-C57BL/6 mice. Results were equivocal in the male B6C3F1 mice in the comparison study, and negative results were found in male BALB/c mice. In another study, no increases in the micronuclei in bone marrow cells or circulating peripheral blood cells were observed in mice after administration of potassium or sodium dichromate in drinking-water or by gavage (De Flora et al., 2006).

Oral intubation of mice with potassium dichromate at 0.59–76 mg/kg bw resulted in DNA damage assessed by comet tail length in leukocytes at all doses, with maximum increase at 9.5 mg/kg bw, followed by repair at higher doses (Devi et al., 2001). Bone marrow cells from male mice fed chromium(VI) trioxide at 20 mg chromium(VI) per kilogram body weight by gavage had a 4.4-fold increase in chromosomal aberrations over controls (Sarkar et al., 1993).

DNA–protein crosslinks and DNA fragmentation were seen in the lung, but not the liver, of rats exposed to sodium dichromate by intratracheal instillation (Izzotti et al., 1998) and in mice similarly treated with potassium dichromate (Cheng et al., 2000).

Micronucleated polychromatic erythrocytes were found in mice following intraperitoneal exposure to chromium(VI) as potassium chromate (Itoh & Shimada, 1996; De Flora et al., 2006). Intraperitoneal exposure to chromium(VI) as potassium dichromate induced dominant lethality in mice (Paschin et al., 1982), chromosomal aberrations in bone marrow and spermatocytes (Fahmy et al., 2002) and a significant increase in mutant frequency within mouse hepatocytes (Itoh & Shimada, 1997, 1998) and bone marrow cells (Itoh & Shimada, 1998). Intraperitoneal injection in rats with chromium(VI) in the form of sodium dichromate resulted in DNA crosslinks in liver, kidney and lung nuclei (Tsapakos et al., 1983). Potassium dichromate, sodium dichromate, chromium trioxide and calcium chromate induced gene mutations in *Drosophila melanogaster* (ATSDR, 2008).

8.6 Reproductive and developmental toxicity

8.6.1 Effects on fertility

Histopathological examination of the testes of groups of 20 male Wistar rats exposed to up to 0.2 mg chromium(VI) per cubic metre as sodium dichromate for 28 or 90 days (Glaser et al., 1985), to 0.1 mg chromium(VI) per cubic metre as sodium dichromate for 18 months or to up to 0.1 mg chromium per cubic metre as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al., 1986, 1988) revealed no abnormalities. No effects on reproduction were found in groups of Wistar rats exposed to 0.2 mg chromium(VI) per cubic metre as sodium dichromate for three generations (Glaser et al., 1984).

A number of studies have reported reproductive effects in rats and mice orally exposed to chromium(VI). Sodium dichromate was administered by gastric intubation to groups of 10 mature male Charles Foster strain rats at a dose of 20, 40 or 60 mg chromium(VI) per kilogram body weight per day for 90 days (Chowdhury & Mitra, 1995). Testis weight, population of Leydig cells, seminiferous tubular diameter, testicular protein, DNA and ribonucleic acid (RNA) were all significantly reduced at 40 and 60 mg chromium(VI) per kilogram body weight per day. Resting spermatocytes (high dose), pachytene spermatocytes (high and intermediate doses) and stage-7 spermatid counts (high and intermediate doses) were significantly reduced, and the reductions were treatment related. Testicular activity of succinic dehydrogenase was significantly lowered in the two high-dose groups, testicular cholesterol concentrations were elevated in the highest-dose group and both serum testosterone and testicular levels of 3β-Δ5-hydroxysteroid dehydrogenase were significantly lowered. At the low dose (20 mg chromium(VI) per kilogram body weight per day), testicular protein, 3β-Δ5-hydroxysteroid dehydrogenase and serum testosterone levels were decreased. Thus, at low doses, partial loss of cellular activity of testicular tissue occurred, whereas at high doses, effects on spermatogenic and steroidogenic activity occurred.

Significant alterations in sexual behaviour and aggressive behaviour were observed in a group of 12 male Sprague-Dawley rats exposed to 42 mg

chromium(VI) per kilogram body weight per day as potassium dichromate in the drinking-water for 12 weeks compared with a control group (Bataineh et al., 1997). No other dose levels were tested. The alterations in sexual behaviour included decreased number of mounts, lower percentage of ejaculating males and increased ejaculatory latency and post-ejaculatory interval. The treated rats also showed decreased aggressive behaviour towards other males, lower final body weights and lower absolute weights of testes, seminal vesicles and preputial glands. No significant alterations in fertility were observed when the exposed males were mated with unexposed females, but the rates of ejaculations during encounters with unexposed females decreased.

In male and female Swiss mice exposed to potassium dichromate in drinking-water for 12 weeks, effects included an increase in testes weight, decreased number of implantations and viable fetuses, and increased number of mice with resorptions at and above 6 mg chromium(VI) per kilogram body weight per day. The males (groups of 9–20) received a dose of 0, 3, 6, 11 or 14 mg chromium(VI) per kilogram body weight per day and were then mated with non-treated females. No significant difference in the number of females that became pregnant was observed. At 6 and 11 mg chromium(VI) per kilogram body weight per day, the number of implantations and the number of viable fetuses decreased. At 14 mg chromium(VI) per kilogram body weight per day, decreases in seminal vesicle and preputial gland weights were observed. The treated female mice (groups of 11–18) received a dose of 0, 6 or 14 mg chromium(VI) per kilogram body weight per day and were then mated with non-treated males. Significant decreases in the number of implantations and the number of viable fetuses and an increase in the number of mice with resorptions were observed at both dose levels. An increase in relative ovarian weight was observed in female mice at 14 mg chromium(VI) per kilogram body weight per day (Elbetieha & Al-Hamood, 1997).

In male Wistar rats fed with 0, 10 or 20 mg chromium(VI) per kilogram body weight per day as chromium trioxide for 6 days, epididymal sperm counts were significantly reduced and the number of sperm abnormalities was significantly increased in a dose-related manner at both doses compared with controls (Li et al., 2001).

Groups of seven male BALB/c mice exposed for 7 weeks to potassium dichromate concentrations in the diet that resulted in doses of 0, 15.2, 28 and 61.7 mg chromium(VI) per kilogram body weight per day had reduced sperm counts and degeneration of the outer cellular layer of the seminiferous tubules at 15.2 mg chromium(VI) per kilogram body weight per day and morphologically altered sperm at 28 mg chromium(VI) per kilogram body weight per day. Weights of testes and epididymides were not significantly different at any dose (Zahid et al., 1990).

The reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP, 1996a, 1996b). Haematological effects (decreased mean corpuscular volume) were identified in rats and mice at the high dose levels (as described in section 8.3). There were no effects on reproductive organs and tissues or sperm in either species.

Several studies have reported increases in preimplantation losses and resorptions in rats and mice exposed to chromium(VI). In groups of 15 female Swiss albino mice exposed to potassium dichromate in drinking-water for 20 days prior to mating at concentrations that resulted in doses of 0, 52, 98 and 169 mg chromium(VI) per kilogram body weight per day and then mated, the number of corpora lutea was decreased at 169 mg chromium(VI) per kilogram body weight per day, preimplantation loss and resorptions were increased at and above 98 mg chromium(VI) per kilogram body weight per day and placental weights were decreased at and above 52 mg chromium(VI) per kilogram body weight per day. Three high-dose mice died, and high-dose mice showed no body weight gain during gestation (Junaid et al., 1996a).

Increases in the number of resorptions were also found in groups of 10 female Swiss albino rats exposed to 37, 70 or 87 mg chromium(VI) per kilogram body weight per day (as potassium dichromate in the drinking-water) for 20 days prior to mating (Kanojia et al., 1996). Post-treatment mating success with untreated males was inversely related to dose (100%, 80%, 70% and 40% success in the 0, 37, 70 and 87 mg chromium(VI) per kilogram body weight per day groups, respectively). Premating treatments resulted in dose-related decreased fertility (96%, 75%, 57% and 31% in the 0, 37, 70 and 87 mg chromium(VI) per kilogram body weight per day groups, respectively). Additional reproductive effects observed at 70 or 87 mg chromium(VI) per kilogram body weight per day included decreased number of corpora lutea, decreased number of implantations and increased number of preimplantation losses. A treatment-related increase in the length of the estrous cycle was significantly different from controls only in the 87 mg chromium(VI) per kilogram body weight per day group. There were no notable effects on behaviour or clinical signs in the treated dams. Gestational weight was reduced by 8%, 14% and 21% in the 37, 70 and 87 mg chromium(VI) per kilogram body weight per day dose groups, respectively.

Decreased mating, decreased fertility (67%, 58% and 50%, respectively) and increased preimplantation

and post-implantation losses were observed in groups of 10 female Druckrey rats receiving doses of 45, 89 or 124 mg chromium(VI) per kilogram body weight per day (as potassium dichromate in the drinking-water) for 3 months prior to mating; the 89 and 124 mg chromium(VI) per kilogram body weight per day groups exhibited increased resorptions as well. Hair loss and reduction of body weight gain were observed in the 89 and 124 mg chromium(VI) per kilogram body weight per day groups. Mortality within the first 2 weeks of treatment occurred in 15% and 10% of the 89 and 124 mg/kg bw per day groups, and the remaining rats in these groups became lethargic. The estrous cycles were absent at the end of the treatment period of all rats, but returned 15–20 days post-treatment. Maternal gestational weight gains were reduced by 11%, 17% and 22% in the 45, 89 and 124 mg chromium(VI) per kilogram body weight per day groups, respectively (Kanojia et al., 1998).

Murthy et al. (1996) reported a number of reproductive effects in groups of 30 female Swiss albino mice exposed to potassium dichromate in drinking-water for 20 days. The mice received a dose of 0, 60, 120 or 180 mg chromium(VI) per kilogram body weight per day. The observed effects included a significant reduction in the number of follicles at different stages of maturation at and above 60 mg chromium(VI) per kilogram body weight per day, a reduction in the number of ova per mouse at and above 120 mg chromium(VI) per kilogram body weight per day, a significant increase in estrous cycle duration at 180 mg chromium(VI) per kilogram body weight per day and histological alterations in the ovaries (e.g. proliferated, dilated and congested blood vessels, pyknotic nuclei in follicular cells and atretic follicles) at and above 120 mg chromium(VI) per kilogram body weight per day. In an ancillary study, it was observed that electron microscopy of selected ovarian tissues revealed ultrastructural changes (disintegrated cell membranes of two-layered follicular cells, altered villiform cristae of mitochondria and decreased lipid droplets in interstitial cells) in mice exposed to 1.2 mg chromium(VI) per kilogram body weight per day for 90 days (Murthy et al., 1996); the toxicological significance of these alterations is not known.

In a multigeneration reproductive assessment by continuous breeding study, BALB/c mice were fed a diet containing chromium(VI) as potassium dichromate. Males and females were exposed to chromium(VI) for a 7-day premating period, and then 20 pairs (F_0) in each dose group were allowed to continuously mate for 85 days (NTP, 1997). The mean doses of chromium(VI) in F_0 animals were 6.8, 13.5 and 30.0 mg/kg bw per day (exposure to test material continued throughout all phases). Litters produced during the 85-day mating period were examined on postnatal day 1. The mean doses of chromium(VI) in F_1 animals that were allowed to produce F_2 litters were 7.8, 16.0 and 36.7 mg/kg bw per day. There were no treatment-related changes in any reproductive parameters.

In conclusion, 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.

8.6.2 Developmental toxicity

No developmental effects were seen in a three-generation study involving inhalation exposure (130 days per generation) of rats to sodium dichromate at 0.2 mg chromium(VI) per cubic metre (Glaser et al., 1984).

A number of animal studies using oral administration have shown that chromium(VI) is a developmental toxicant following premating and/or in utero exposure.

Groups of 10 female Swiss albino rats received a dose of 37, 70 or 87 mg chromium(VI) per kilogram body weight per day for 20 days (Kanojia et al., 1996) and groups of 10 Druckrey rats received 45, 89 or 124 mg chromium(VI) per kilogram body weight per day for 90 days (Kanojia et al., 1998) as potassium dichromate in drinking-water. Treated dams were then mated to non-treated males. In the rats exposed for 20 days, maternal body weight gain was decreased by 8%, 14% and 21% at doses of 37, 70 and 87 mg chromium(VI) per kilogram body weight per day, respectively, compared with controls. In addition to significantly increased resorptions and preimplantation and post-implantation losses in all treatment groups, significantly reduced numbers of corpora lutea, implantations and fetuses per litter and significantly increased incidences of reduced ossification in fetal caudal bones were observed in rats at 70 and 87 mg chromium(VI) per kilogram body weight per day. The incidences of reduced ossification of parietal and interparietal bones, subdermal haemorrhagic patches on thoracic and abdominal areas and kinky short tails of fetuses were increased in the 87 mg chromium(VI) per kilogram body weight per day group. In the rats exposed for 90 days, hair loss, significant reduction in body weight gain, early mortalities and lethargy occurred in the mid- and high-dose groups. Maternal gestation weights were decreased, preimplantation and post-implantation losses were increased and fetal weights were reduced at all dose levels.

Groups of 15 female Swiss albino mice received 52, 98 or 169 mg chromium(VI) per kilogram body weight per day as potassium dichromate in drinking-water for

20 days, followed by mating to unexposed males (Junaid et al., 1996a). Three high-dose mice died, and no body weight gain during gestation occurred in the surviving high-dose mice (no implantations were recorded in this group). No notable changes in behaviour, external features or weight gain were observed in the dams in the two low-dose groups. Fetuses from the 98 mg chromium(VI) per kilogram body weight per day group had decreased crown–rump length, decreased fetal weights, increased incidence of post-implantation loss, subdermal haemorrhagic patches, kinky and short tails, and reduced ossification of parietal and interparietal bones. Fetuses from the 52 mg chromium(VI) per kilogram body weight per day group had decreased fetal weight, increased incidence of post-implantation loss and reduced caudal ossification. Exposure to test material was not continued during mating, so any effects were attributed to chromium(VI) in maternal tissues. In groups of 10 female Swiss albino mice receiving 53, 101.1 or 152.4 mg chromium(VI) per kilogram body weight per day as potassium dichromate in drinking-water during gestational days 6–14, increased resorptions were observed at all dose levels, and fetal mortality, subdermal haemorrhagic patches and reduced ossification were observed in the offspring at the two highest doses. No mortality or changes in external features were observed in the treated dams; the weight gain was decreased in the two highest dose groups (Junaid et al., 1996b).

Similar effects (increased resorptions, increased post-implantation losses, subdermal haemorrhages, decreased cranial ossification, tail kinking, decreased fetal body weight and decreased crown–rump length) were observed in the offspring of groups of 10 albino mice exposed to 98 or 234 mg chromium(VI) per kilogram body weight per day as potassium dichromate in drinking-water during gestational days 1–19. Dams receiving 234 mg chromium(VI) per kilogram body weight per day had significantly reduced body weight gain compared with lower treatment groups or the control group and displayed no implantations. Body weight gain was also reduced in the 98 mg chromium(VI) per kilogram body weight per day dams. At a dose level of 46 mg/kg bw per day in this study, no overt toxicity was observed in the dams, and the only abnormal findings in the offspring were decreased crown–rump length, decreased fetal weight, increased post-implantation loss and reduced cranial ossification (Trivedi et al., 1989).

8.7 Modes of action

Chromium(VI) exists as the tetrahedral chromate anion at physiological pH and resembles the forms of anions, such as sulfate and phosphate, that are permeable across non-selective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity of chromium(III) compared with chromium(VI) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells and therefore a decreased toxicity.

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 has formulated a framework for evaluating laboratory animal carcinogens (IPCS, 2007), the main considerations being 1) whether the information available allows the establishment of a mode of action for the observed cancer in animals and 2) whether this mode of action is relevant to humans. In other words, can the findings of cancer in animals be ignored as non-relevant in human health risk assessment? The key issues in deciding whether the mode of action is relevant to humans are 1) whether there are fundamental, qualitative

differences in the key events between animals and humans and 2) whether there are quantitative differences in either kinetic or dynamic factors between animals and humans.

The findings of lung cancer after exposure to chromium(VI) are mainly from epidemiological studies, and thus the assessment of the mode of action for this endpoint is moot, and the mode of action analysis can concentrate on the oral cancer observed in rats and the intestinal cancer observed in mice (NTP, 2008). With regard to these cancers in rats and mice, there is evidence that genotoxic mechanisms may be involved in the mode of action, in which case there are no grounds for excluding human relevance on the basis of fundamental, qualitative differences in key events in the mode of action between experimental animals and humans.

The processes that determine absorption and metabolism of chromium(VI) following ingestion are not fully understood at this time. The evaluation of quantitative differences in either kinetic or dynamic factors between animals and humans is uncertain.

9. EFFECTS ON HUMANS

9.1 Acute effects

As discussed more fully in ATSDR (2008), accidental or intentional ingestion of generally unknown but probably extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, haematological, hepatic, renal and neurological effects. After dermal application of potassium chromate for treatment of scabies, renal failure, fatty degeneration of the heart, hyperaemia and necrosis of kidney tubules, and hyperaemia of the gastric mucosa have been described (ATSDR, 2008) .

9.2 Cancer

Occupational exposure to chromium compounds in workers engaged in chromate production, chromate pigment production and chrome plating industries is associated with increased risk of respiratory cancer, as demonstrated in many studies from the 1950s onwards (IARC, 1990; ATSDR, 2008).

Quantitative estimates of the cancer risk associated with exposure to chromium(IV), based on actual measurements of exposure in the populations studied, are available for only two populations—namely, one working in chromate production in Baltimore, Maryland, USA, and the other in Painesville, Ohio, USA. Several studies have been published on different populations in these two locations, and the key findings from these populations are described below. Summaries of other studies are presented in Appendix 7. In addition to the lack of quantitative exposure data, in many published studies of stainless steel welders, exposure to nickel and other welding fume components, such as polycyclic aromatic hydrocarbons, and asbestos have confounded the results on lung cancer occurrence. Therefore, with the exception of the European multicentre study (Simonato et al., 1991; Gérin et al., 1993), which made a special effort to perform a quantitative assessment of exposure to chromium(VI) and the main confounders, studies on welders are not included in Appendix 7.

The mortality from lung cancer at the chromate production facility in Baltimore, Maryland, where chromate production was first started in the USA in 1824, has been previously studied by Hayes et al. (1979) and Braver et al. (1985). A retrospective study of 2357 workers at this facility, first employed between 1 August 1950 and 31 December 1974, was reported by Gibb et al. (2000b). Follow-up of this cohort was conducted from the first date of employment until 31 December 1992. Vital status ascertainment for the cohort through July 1977 was achieved in an earlier study by Hayes et al. (1979). The Gibb et al. (2000b) study extended the follow-up of this cohort by using the National Death Index to identify deaths between 1 January 1979 and 31 December 1992 and by using Social Security to identify deaths that occurred between July 1977 and 31 December 1978. Smoking status (yes/no) at the time of hire was identified for 2137 of the cohort from company medical records. Based on 70 000 contemporary measurements of airborne chromium(VI) (diphenylcarbazide reaction) concentrations spanning the study period, annual average exposure estimates were made for each job title in the plant from 1950 to 1985 and were used to calculate cumulative chromium(VI) exposure (mean = 0.134 (mg/m^3)·years, median = 0.009 (mg/m^3)·years; range = 0–5.3 (mg/m^3)·years). Settled dust samples (72 samples at 17 locations) were collected and analysed for chromium(VI) and chromium(III) and were used to estimate cumulative trivalent chromium exposure (mean = 1.98 (mg/m^3)·years, median = 0.11 (mg/m^3)·years, range = 0–64.7 (mg/m^3)·years) for each individual. Although a lime process was used, exposure to chromates with low solubility in water (calcium chromate) was “very low”, based on limited measurements (Braver et al., 1985). A proportional hazards model was used to analyse the lung cancer risk from chromium(VI) and chromium(III) exposure, duration of exposure and smoking. Standardized mortality ratios (SMRs) were calculated using age-, calendar- and race-specific mortality rates for the USA and Maryland. Lung cancer for the entire cohort had an SMR of 180 (95% confidence interval [CI] = 149–214). The SMR was found to increase with categories of chromium exposure, with the SMR in the highest exposure group (0.077–5.25

(mg/m^3)·years) being 224 (95% CI = 160–303). In a proportional hazards model that included the variables cumulative chromium(VI) exposure, cumulative chromium(III) exposure and cigarette smoking, only cumulative chromium(VI) exposure and cigarette smoking were found to be statistically significant predictors of lung cancer risk. In a model that examined duration of employment, chromium(VI) exposure and cigarette smoking as independent variables, again, only chromium(VI) exposure and cigarette smoking were found to be significantly associated with lung cancer risk. Cumulative exposure to chromium(VI) in the chromium production workers showed a strong dose–response relationship for lung cancer. There is thus no evidence from this study that chromium(III) is carcinogenic, but equally the data cannot preclude the possibility.

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 1 µg 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 (1 $\mu g/m^3$ 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).

An association between gastrointestinal tract cancer and exposure to chromium(VI) in drinking-water has been reported at a contaminated location in China (Zhang & Li, 1997), but there are major uncertainties, especially in the estimation of the exposure (Brandt-Rauf, 2006; Beaumont et al., 2008 [and follow-up author correspondence]; Smith, 2008).

9.3 Non-cancer respiratory tract diseases

9.3.1 Studies on mortality

In an early report from three chromate factories in the USA, an elevated mortality of workers from non-malignant respiratory diseases was observed (SMR =

242, 95% CI = 146–378) (Taylor, 1966). Mortality from non-cancer respiratory disease was not elevated (proportionate mortality ratio [PMR] = 1.01, 95% CI = 0.81–1.24) among workers from former chromium smelters in New Jersey, USA (for cohort description, see Appendix 7; Rosenman & Stanbury, 1996).

In the Luippold et al. (2005) study (for cohort description, see Appendix 7) of two chromate-producing factories in the USA, 2 deaths from non-malignant respiratory diseases were observed, whereas 2.27 were expected (SMR = 0.89, 95% CI = 0.11–3.23).

Among British chromate workers (for cohort description, see Appendix 7; Davies et al., 1991), 41 deaths from chronic obstructive lung disease were recorded for the group of the earliest cohort entrants, whereas 28.66 were expected (SMR = 1.43, 95% CI = 1.03–1.94). For later entrants, no elevated mortality from non-malignant lung disease was observed. Among German chromate workers (for cohort description, see Appendix 7; Birk et al., 2006), 2 deaths from respiratory disease other than cancer were observed, whereas 9.14 were expected (SMR = 0.22, 95% CI = 0.03–0.79).

Mortality from non-malignant respiratory disease was not significantly elevated among workers in three chromate pigment–producing factories in England (for cohort description, see Appendix 7; Davies, 1984a). In two factories, where there was exposure to both zinc and lead chromates, the SMRs (95% CI) were 1.27 (0.92–1.71) and 0.79 (0.26–1.86); in the third, where there was exposure to lead chromate only, the SMR (95% CI) was 1.32 (0.72– 2.31). In a subpopulation of 57 chromate workers who had suffered clinical lead poisoning, 7 deaths from respiratory diseases were observed, whereas 3.59 were expected (SMR = 1.95, 95% CI = 0.78–4.0) (Davies, 1984b).

A slightly elevated mortality from non-cancer respiratory disease (SMR = 127, 95% CI = 1.03–1.55) was observed among nickel–chromium platers in Yorkshire, England (Sorahan et al., 1987).

9.3.2 Respiratory irritation and lung function

Occupational exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhoea, nasal itching and soreness, nasal mucosal atrophy, and ulceration and perforation of the nasal septum (ATSDR, 2008). The chromium-related industries associated with these effects include chrome plating, chromate and dichromate production, and possibly ferrochromium production. A study with exposure mainly to sodium chromate and sodium dichromate (and trivalent chromium compounds) (Gibb et al., 2000a) and another with exposure to chromic acid (Lindberg & Hedenstierna, 1983) are described below.

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 for all findings, with median exposure concentrations of 10–15 µg chromium(VI) per cubic metre. 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 52 µg chromium(VI) per cubic metre 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, 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 2 µg chromium(VI) per cubic metre and 21 persons exposed to 2 µg chromium(VI) per cubic metre and above. The highest 8-hour TWA exposure to chromium(VI) was 20 µg/m^3; the highest peak exposure was 46 µg/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 1 µg chromium(VI) per cubic metre complained of subjective symptoms; the frequency of subjective symptoms was 4 out of 19 among workers with exposure less than 2 µg/m^3. The clinical findings noted at or below 2 µg chromium(VI) per cubic metre 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 ≥2 µg chromium(VI) per cubic metre and at peak levels of ≥20 µg chromium(VI) per cubic metre, nasal mucosal atrophy and irritation occurred at 8-hour TWA concentrations of ≥2 µg chromium(VI) per cubic metre and at peak exposure concentrations of 2.5–11 µg chromium(VI) per cubic metre, and no significant nasal effects were seen at peak exposure concentrations of 0.1–1.2 µg chromium(VI) per cubic metre. Non-smoking workers exposed to 8-hour TWA concentrations of ≥2 µg chromium(VI) per cubic metre had slight, transient decreases in forced vital capacity, forced expiratory volume in 1 second (FEV_1) and forced mid-expiratory flow during the workday. Workers exposed to less than 2 µg chromium(VI) per cubic metre showed no effects on lung function (Lindberg & Hedenstierna, 1983).

Lowered forced expiratory volume (FEV_1) was reported in a cross-sectional study on chromium electroplaters; exposure levels were not reported (Bovet et al., 1977).

9.3.3 Respiratory sensitization and asthma

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 0.029 mg 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 0.035 mg chromium(VI) per millilitre as potassium dichromate (Olaguibel & Basomba, 1989).

9.4 Dermal effects

9.4.1 Irritation and corrosion

Skin contact with compounds containing chromium(VI) may cause rashes and ulcers or sores (also called chrome holes) on the skin, which can be a major problem, because they can deeply penetrate the skin with prolonged exposure (Da Costa et al., 1916). Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to their development. Industries that have been associated with the development of chrome sores in workers include chromate and dichromate production, chrome plating, leather tanning, planographic printing and chromite ore processing (ATSDR, 2008). Among the chromium(VI) compounds to which workers in these industries are exposed are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate and ammonium dichromate.

9.4.2 Sensitization

Chromium(VI) compounds can induce sensitization, resulting in contact dermatitis. The prevalence of chromium sensitivity in the general population has been estimated to be between 0.5% and 1.7% in studies in several European countries (Peltonen & Fräki, 1983; Hartwig, 2007). Based on several studies in the USA, mainly on dermatological clinical patients, and a correction factor to compensate for the difference between patient populations and the general population, Paustenbach et al. (1992) estimated that the prevalence of chromium sensitivity in the general population in the USA is 1.6%. Using another compensation factor, Proctor et al. (1998) arrived at an estimate of 0.08% for chromium(VI) sensitivity in the general population in the USA. Chromium(VI) compounds are more potent in eliciting reactions in sensitized individuals than chromium(III) compounds (Levin et al., 1959; Samitz & Shrager, 1966; Peltonen & Fräki, 1983; Hansen et al., 2003).

Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals (Kaaber & Veien, 1977; Goitre et al., 1982).

Patch testing has identified chromium-sensitized workers in the printing and lithography industry, in automobile factories where assemblers handled nuts, bolts and screws, in wet sandpapering of primer paint where exposure to zinc chromate occurred, in railroad systems and diesel locomotive repair shops where

antirust diesel engine coolants and radiator fluids contained sodium chromate, in the plating, wood and paper industries, and in the cement industry (ATSDR, 2008). Zachariae et al. (1996) provided evidence that lowering the amount of soluble chromate in cement from 50 to 2 mg chromium(VI) per kilogram by the addition of ferrous sulfate lowered the prevalence of eczema due to chromium sensitivity. Other sources that have resulted in chromium sensitivity include dichromate-containing detergents and bleach, glues, machine oils, foundry sand, match heads, boiler linings, magnetic tapes, chromium-tanned products and chromium(VI)-plated cellular phones (ATSDR, 2008).

In the standard occlusive patch test on 54 persons previously sensitized to chromium, the lowest concentration that induced a positive reaction, the so-called 10% minimum elicitation threshold (MET_{10}), was 0.089 µg/cm^2 (Nethercott et al., 1994). Hansen et al. (2003) tested potassium dichromate as a source of chromium(VI) in 22 patients with known chromium allergy and found an MET_{10} for chromium(VI) of 0.03 µg/cm^2. In a study on 66 chromium-sensitized people, using the repeated open application text (Hannuksela & Salo, 1986), the MET_{10} was estimated to be 0.12 µg/cm^2 (Proctor et al., 2006; Proctor, 2008).

9.5 Genotoxic effects

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 0.5 µg/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 (i.e. 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 non-smokers (Pilliere et al., 1992).

9.6 Reproductive effects

Studies of effects on pregnancy due to exposure to chromium(VI) in pregnant women and in spouses of male stainless steel welders are inconclusive (Bonde et al., 1992; Hjollund et al., 1995, 1998, 2000, 2005). Increased incidence of "toxicosis" and "complications during pregnancy and childbirth" were reported among female workers of a dichromate production facility (Shmitova, 1978, 1980). The nature of the complications and toxicosis was not specified. The poor quality and reporting of these studies preclude their use for drawing conclusions regarding potential reproductive effects of chromium(VI) in humans.

The effect of chromium(VI) exposure on sperm quality was studied in 21 electroplating workers in Henan, China. Significant ($P < 0.05$) decreases in sperm count, sperm motility and concentrations of lactate dehydrogenase and lactate dehydrogenase C4 isoenzyme and significantly increased follicle stimulating hormone concentrations were found in the exposed workers compared with the controls (Li et al., 2001). Semen quality was also assessed in 57 welders exposed to chromium and nickel in a plant in India. Significant correlations with chromium blood concentration included increased tail defects, decreased sperm count and decreased rapid linear progressive motility. Sperm vitality decreased as chromium concentrations increased (Danadevi et al., 2003). Similar correlations with blood nickel concentrations were found.

9.7 Susceptible populations

Reliable information on susceptible populations is not available.[1]

[1] In a study published after the Final Review Board meeting (Gibb et al., 2011), it was reported that in chromate producers,

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Unless otherwise specified, reference to "chromium" means total chromium.

10.1 Aquatic organisms

Chromium(VI) is generally more toxic than chromium(III) to aquatic biota (Pawlisz et al., 1997). Freshwater invertebrates (especially crustaceans) are more sensitive than fish to chromium(VI) in both acute and chronic studies, whereas freshwater organisms are generally more sensitive than marine organisms to chromium(VI). In general, chromium(VI) toxicity is increased with decreased pH (i.e. from 8.0 to 6.0), increased temperature (i.e. from 15 °C to 25 °C) and decreased water hardness or salinity.

Ross et al. (1981) reported that a chromium(VI) concentration of 10 mg/l reduced the efficiency of a model activated sludge plant by 5%, as measured by effluent chemical oxygen demand. Similar results were also found by Barth et al. (1967) using a pilot-scale activated sludge sewage treatment plant. There is evidence that some species of microorganism are much more tolerant to chromium(VI) than others. It has been reported that a strain of *Pseudomonas aeruginosa* was able to grow at a chromium(VI) concentration of 428 mg/l (as potassium chromate), and another *Pseudomonas* species at a chromium(VI) concentration of 5356 mg/l (as potassium chromate). Similarly, species of *Arthrobacter* and *Agrobacterium* could tolerate chromium(VI) concentrations of up to 400 mg/l and 100 mg/l (as potassium dichromate), respectively.

The toxicity data for aquatic organisms are summarized in Table 13. The available information indicates that, when expressed on a total chromium concentration basis, there are no significant differences between the toxicities of sodium chromate, sodium dichromate and potassium dichromate (allowing for differences in water properties). The available median effective concentrations (EC_{50} values) for algae and plants range from 0.13 to 4.6 mg chromium(VI) per litre; no-observed-effect concentration (NOEC) values are in the range 0.01–0.64 mg/l. For marine algae, the toxicity of chromium(VI) is generally highest at low salinities (<2‰) and low sulfate ion concentrations (Frey et al., 1983; Riedel, 1984, 1985). At higher salinities and consequently higher sulfate concentrations, marine algae tend to be of lower sensitivity to chromium(VI), as sulfate competes with chromate for uptake into algal cells. Potassium dichromate is recommended as a reference substance in the algal inhibition test (Method C.3; EEC, 1992) and the acute toxicity to *Daphnia* test (Method C.2; EEC, 1992). A ring test involving 16 laboratories determined the mean 72-hour EC_{50} value (based on growth rate) for *Scenedesmus subspicatus* and *Selenastrum capricornutum* to be 0.3 mg chromium(VI) per litre. A ring test involving 129 EC_{50} determinations from 46 laboratories determined the mean 24-hour EC_{50} value for *Daphnia magna* to be 0.53 mg chromium(VI) per litre (EEC, 1992).

The toxicity of chromium(VI) to freshwater invertebrates and fish in short-term tests appears to depend on water properties such as hardness, pH and temperature. Higher toxicity has generally been seen in soft water and at more acidic pH values, particularly those below 6.5. Persoone et al. (1989) noted decreasing EC_{50} values for *Daphnia magna* with decreasing hardness and with increasing temperature. Some studies have looked at the effects of chromium(VI) on fish of different ages. Van Der Putte et al. (1981) reported LC_{50} values of 7.6 mg/l for fish at 4 months, rising to 45 mg/l at 9 months.

As well as effects on survival and reproduction, sublethal effects of exposure to chromium(VI) have been reported. Approximately 41% of surviving grass shrimp (*Palaemonetes pugio*) possessed cuticular lesions, usually associated with articulations of the appendages and abdomen, after exposure to 0.5 mg chromium(VI) per litre for 28 days; nearly 50% of limbs were lost at the highest exposure concentration (4 mg/l) (Doughtie et al., 1983). In a series of experiments with *Channa punctatus*, fish were exposed to sublethal concentrations of chromium(VI) (as potassium dichromate) of 2.6 mg chromium(VI) per litre for 15 and 30 days at pH 7.4. Fish were found to be hyperglycaemic and hyperlactaemic. An elevation of the activity of enzymes involved in glycolysis and the Kreb's cycle was also seen in muscles and liver, indicating that the metabolic rate of the exposed fish was higher than that of controls (Sastry & Tyagi, 1982; Sastry & Sunita, 1983, 1984). Similar results were found with a 120-day exposure to the same concentration (Sastry & Sunita, 1983).

Gill & Pant (1978) found that acute (12 and 24 hours) and chronic exposures (30 and 60 days) of the freshwater fish *Barbus conchonius* to potassium dichromate (chromium(VI) concentration 41.2 mg/l for acute exposures, 0.687 and 1.03 mg/l for chronic exposures) in hard water (395 mg/l as calcium carbonate, pH 7.1) resulted in anomalies in peripheral blood and tissues of fish. Pathological changes were also observed in gills, kidneys and liver of chromium(VI)-exposed fish.

the lung cancer risk was highest among workers exposed at an early age.

Table 13: Toxicity of hexavalent chromium to aquatic organisms.

Species	End-point	Chromium salt	Concentration (mg Cr(VI)/l)	Reference[a]
Freshwater				
Protozoans				
Chilomonas paramecium	19–25 h NOEC (growth)	Potassium dichromate	1	Cairns et al. (1978)
Colpidium campylum	24 h IC_{50} (biomass)	Potassium dichromate	2.8–4.6	Dive et al. (1990)
Microregma heterostoma	28 h NOEC (feeding rate)	Potassium dichromate	0.21	Bringmann & Kühn (1959)
Blue-green algae				
Lyngbya sp.	18 d NOEC (growth)	Potassium dichromate	0.1	Cairns et al. (1978)
Microcystis aeruginosa	96 h NOEC (growth)	Potassium dichromate	0.35	Slooff & Canton (1983)*
Green algae				
Chlamydomonas sp.	10 d NOEC (growth)	Potassium dichromate	0.5	Cairns et al. (1978)
Chlorella pyrenoidosa	96 h NOEC (biomass)	Potassium dichromate	0.1	Meisch & Schmitt-Beckmann (1979)*
Chlorella sp. (wild)	96 h NOEC (biomass)	Potassium dichromate	0.1	Meisch & Schmitt-Beckmann (1979)*
Chlorella vulgaris	72 h EC_{50} (growth)	Potassium dichromate	0.47	Jouany et al. (1982)
Scenedesmus subspicatus	72 h EC_{10} (growth)	Potassium dichromate	0.64	Kűhn & Pattard (1990)
	72 h EC_{50} (growth)	Potassium dichromate	4.6	Kűhn & Pattard (1990)
Scenedesmus pannonicus	96 h NOEC (biomass)	Potassium dichromate	0.11	Slooff & Canton (1983)*
Selenastrum capricornutum	72 h EC_{10} (growth)	Potassium dichromate	0.11	Nyholm (1991)*
	72 h EC_{50} (growth)	Potassium dichromate	0.99	Nyholm (1991)
	72 h EC_{10} (growth)	Potassium dichromate	0.01	Christensen et al. (1983)*
	72 h EC_{50} (growth)	Potassium dichromate	0.23	Christensen et al. (1983)
Aquatic plants				
Lemna gibba	8 d NOEC (growth)	Sodium chromate	0.1	Staves & Knaus (1985)*
Lemna minor	7 d NOEC (growth)	Potassium dichromate	0.11	Slooff & Canton (1983)*
Spirodela polyrhiza	8 d NOEC (growth)	Sodium chromate	0.1	Staves & Knaus (1985)*
Spirodela punctata	8 d NOEC (growth)	Sodium chromate	0.5	Staves & Knaus (1985)*
Invertebrates				
Hydra (*Hydra littoralis*)	11 d NOEC (reproduction)	Potassium dichromate	0.035	Dannenberg (1984)*
Hydra (*Hydra oligactis*)	21 d NOEC (growth)	Potassium dichromate	1.1	Slooff & Canton (1983)*
Snail (*Biomphalaria glabrata*)	96 h LC_{50}	Potassium dichromate	37.3	Bellavere & Gorbi (1981)
Snail (*Goniobasis livescens*)	48 h LC_{50}	Potassium dichromate	2.4	Cairns et al. (1976)
Snail (*Lymnaea acuminata*)	96 h LC_{50}	Potassium dichromate	6	Khangarot et al. (1982)
Snail (*Lymnaea emarginata*)	48 h LC_{50}	Potassium dichromate	34.8	Cairns et al. (1976)
Snail (*Lymnaea stagnalis*)	40 d NOEC (reproduction)	Potassium dichromate	0.11	Slooff & Canton (1983)*
	7 d NOEC (hatchability)	Potassium dichromate	0.35	Slooff & Canton (1983)
Pouch snail (*Physa integra*)	48 h LC_{50}	Potassium dichromate	0.66	Cairns et al. (1976)
Segmented worm (*Aelosoma headleyi*)	48 h LC_{50}	Potassium dichromate	7.0–8.6[b]	Cairns et al. (1978)
White worm (*Enchytraeus albidus*)	96 h LC_{50}	Potassium dichromate	0.67	Römbke & Knacker (1989)
Rotifer (*Philodina acuticornis*)	48 h LC_{50}	Potassium dichromate	29	Cairns et al. (1976)
Rotifer (*Philodina roseola*)	96 h LC_{50}	Sodium chromate	5.5–8.9[c]	Schaefer & Pipes (1973)
Water flea (*Ceriodaphnia* sp.)	48 h LC_{50}	Potassium dichromate	0.03	Dorn et al. (1987)
Water flea (*Ceriodaphnia dubia*)	24 h EC_{50} (immobilization)	Potassium dichromate	0.05	Hickey (1989)
	7 d NOEC (reproduction)	Potassium dichromate	0.0047	De Graeve et al. (1992)*
Water flea (*Ceriodaphnia pulchella*)	24 h EC_{50} (immobilization)	Potassium dichromate	0.2	Hickey (1989)

Species	End-point	Chromium salt	Concentration (mg Cr(VI)/l)	Reference[a]
Water flea (*Ceriodaphnia reticulata*)	48 h EC_{50} (immobilization)	Sodium dichromate	0.2	Elnabarawy et al. (1986)
Amphipod (*Crangonyx pseudogracilis*)	96 h LC_{50}	Potassium dichromate	0.42	Martin & Holdich (1986)
	96 h LC_{50}	Potassium chromate	0.81	Martin & Holdich (1986)
Water flea (*Daphnia carinata*)	24 h EC_{50} (immobilization)	Potassium dichromate	0.42	Hickey (1989)
	14 d NOEC (reproduction)	Potassium dichromate	0.05	Hickey (1989)*
Water flea (*Daphnia magna*)	24 h EC_{50} (immobilization)	Potassium dichromate	0.22	Hickey (1989)
	24 h EC_{50} (immobilization)	Potassium dichromate	0.33	Kűhn et al. (1989)
	24 h EC_{50} (immobilization)	Potassium dichromate	0.44	Jouany et al. (1982)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.035–0.11[d]	Stephenson & Watts (1984)
	48 h EC_{50} (immobilization)	Sodium dichromate	0.11	Elnabarawy et al. (1986)
	48 h EC_{50} (immobilization)	Sodium chromate	0.05	Trabalka & Gehrs (1977)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.32	Berglind & Dave (1984)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.39	Hermens et al. (1984)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.9	Cairns et al. (1978)
	21 d NOEC (reproduction)	Potassium dichromate	0.018	Kűhn et al. (1989)*
	21 d NOEC (reproduction)	Potassium dichromate	0.035	Slooff & Canton (1983)*
	21 d NOEC (growth)	Potassium dichromate	0.06	Van Leeuwen et al. (1987)
	21 d NOEC (survival)	Potassium dichromate	0.35	Van Leeuwen et al. (1987)
	14 d NOEC (reproduction)	Potassium dichromate	0.025	Hickey (1989)*
	14 d NOEC (reproduction)	Sodium dichromate	0.0005	Elnabarawy et al. (1986)*
Water flea (*Daphnia obtusa*)	48 h EC_{50} (immobilization)	Potassium dichromate	0.06	Coniglio & Baudo (1989)
Water flea (*Daphnia pulex*)	48 h EC_{50} (immobilization)	Potassium dichromate	0.06	Dorn et al. (1987)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.36	Stackhouse & Benson (1989b)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.76	Cairns et al. (1978)
	48 h EC_{50} (immobilization)	Sodium dichromate	0.12	Elnabarawy et al. (1986)
	48 h EC_{50} (immobilization)	Potassium chromate	0.18	Jop et al. (1987)
	48 h EC_{50} (immobilization)	Potassium dichromate	0.18	Jop et al. (1987)
Prawn (*Macrobrachium lamarrei*)	96 h LC_{50}	Potassium dichromate	0.65	Murti et al. (1983)
Water flea (*Simocephalus vetulus*)	24 h EC_{50} (immobilization)	Potassium dichromate	0.15	Hickey (1989)
Midge (*Chironomus tentans*)	48 h LC_{50}	Potassium dichromate	11.8	Khangarot & Ray (1989)
	48 h LC_{50}	Potassium dichromate	61	Batac-Catalan & White (1983)
Mosquito (*Culex pipiens*)	25 d NOEC (development)	Potassium dichromate	1.1	Slooff & Canton (1983)*
Fish				
Zebrafish (*Brachydanio rerio*)	96 h LC_{50}	Potassium dichromate	58.5	Bellavere & Gorbi (1981)
Goldfish (*Carrasius auratus*)	96 h LC_{50}	Potassium dichromate	37.5[e]	Pickering & Henderson (1966)
Green snakehead (*Channa punctatus*)	96 h LC_{50}	Potassium dichromate	45.2	Saxena & Parashari (1983)
Banded gourami (*Colisa fasciatus*)	96 h LC_{50}	Chromium trioxide	20.8	Srivastava et al. (1979)
	96 h LC_{50}	Chromium trioxide	31.2	Nath & Kumar (1988)
Channel catfish (*Ictalurus punctatus*)	24 h LC_{50}	Potassium dichromate	58	Cairns et al. (1978)
	30 d NOEC (growth; egg-fry)	Sodium dichromate	0.15	Sauter et al. (1976)*
	30–60 d NOEC (growth; egg-fry)	Sodium dichromate	0.31	Sauter et al. (1976)

Table 13 (continued)

Species	End-point	Chromium salt	Concentration (mg Cr(VI)/l)	Reference[a]
Guppy (*Poecilia reticulata*)	96 h LC_{50}	Potassium dichromate	30[e]	Pickering & Henderson (1966)
	28 d NOEC (growth; 3–4 weeks)	Potassium dichromate	3.5	Slooff & Canton (1983)*
Bluegill (*Lepomis macrochirus*)	96 h LC_{50}	Potassium dichromate	110	Trama & Benoit (1960)
	96 h LC_{50}	Potassium dichromate	113	Cairns & Scheier (1958)
	96 h LC_{50}	Potassium chromate	120–168[f]	Cairns & Scheier (1959)
	96 h LC_{50}	Potassium dichromate	118[e]	Pickering & Henderson (1966)
	96 h LC_{50}	Potassium dichromate	133[g]	Pickering & Henderson (1966)
	96 h LC_{50}	Potassium chromate	182	Jop et al. (1987)
	96 h LC_{50}	Potassium dichromate	154	Jop et al. (1987)
	96 h LC_{50}	Potassium chromate	183	Dorn et al. (1987)
	96 h LC_{50}	Potassium chromate	170	Trama & Benoit (1960)
Striped bass (*Morone saxatilis*)	96 h LC_{50}	Sodium chromate	28–38[h]	Palawski et al. (1985)
Golden shiner (*Notemigonus crysoleucas*)	96 h LC_{50}	Potassium dichromate	55	Hartwell et al. (1989)
Rainbow trout (*Oncorhynchus mykiss*)	96 h LC_{50}	Potassium dichromate	63.6	Brown et al. (1985)
	96 h LC_{50}	Sodium dichromate	69	Benoit (1976)
	96 h LC_{50}	Sodium chromate	3.4–65.5[i]	Van Der Putte et al. (1981)
	60 d NOEC (growth; egg-fry)	Sodium dichromate	0.05	Sauter et al. (1976)*
	8 mo NOEC (growth; alevin-juvenile)	Sodium dichromate	0.1	Benoit (1976)*
Chinook salmon (*Oncorhynchus tshawytscha*)	96 h LC_{50}	Sodium chromate	111	Hamilton & Buhl (1990)
Fathead minnow (*Pimephales promelas*)	96 h LC_{50}	Potassium dichromate	17.6[e]	Pickering & Henderson (1966)
	96 h LC_{50}	Potassium dichromate	27.3[g]	Pickering & Henderson (1966)
	96 h LC_{50}	Potassium dichromate	36.9	Pickering (1980)
	96 h LC_{50}	Potassium dichromate	26.1	Dorn et al. (1987)
	96 h LC_{50}	Sodium dichromate	33.2	Broderius & Smith (1979)
	96 h LC_{50}	Potassium chromate	45.6[e]	Pickering & Henderson (1966)
	96 h LC_{50}	Potassium chromate	46	Jop et al. (1987)
	96 h LC_{50}	Potassium dichromate	34	Jop et al. (1987)
	7 d NOEC (growth; larvae)	Potassium dichromate	1.1[j]	De Graeve et al. (1991)*
	9 wk LOEC (growth)	Potassium dichromate	<0.018	Pickering (1980)
	412 d NOEC (growth)	Potassium dichromate	4	Pickering (1980)*
	60 d NOEC (growth; egg-larvae)	Potassium dichromate	1	Pickering (1980)*
	30 d NOEC (growth; larvae)	Sodium dichromate	0.05	Broderius & Smith (1979)*
Brook trout (*Salvelinus fontinalis*)	96 h LC_{50}	Sodium dichromate	59	Benoit (1976)
	8 mo NOEC (growth; embryo-juvenile)	Sodium dichromate	0.01	Benoit (1976)*
Lake trout (*Salvelinus namaycush*)	60 d NOEC (growth; egg-fry)	Sodium dichromate	0.105	Sauter et al. (1976)*
White sucker (*Catostomus commersoni*)	30 d NOEC (growth; egg-fry)	Sodium dichromate	0.96	Sauter et al. (1976)

Species	End-point	Chromium salt	Concentration (mg Cr(VI)/l)	Reference[a]
	60 d NOEC (growth; egg-fry)	Sodium dichromate	0.29	Sauter et al. (1976)*
Pike (*Esox lucius*)	20 d NOEC (survival)	Sodium dichromate	0.538	Sauter et al. (1976)*
Medaka (*Oryzias latipes*)	40 d NOEC (behaviour; embryo-larval)	Potassium dichromate	3.5	Slooff & Canton (1983)*
Amphibians				
Black-spined toad (*Bufo melanostictus*)	96 h LC_{50}	Potassium dichromate	49.3	Khangarot & Ray (1987)
Indian green frog (*Euphlyctis hexadactylus*)	96 h LC_{50}	Potassium dichromate	100	Khangarot et al. (1985)
	96 h LC_{50}	Potassium chromate	42.6	Khangarot et al. (1985)
Indian skipper frog (*Euphlyctis cyanophlyctis*)	96 h LC_{50}	Potassium dichromate	81	Joshi & Patil (1991)
	96 h LC_{50}	Sodium dichromate	85	Joshi & Patil (1991)
	96 h LC_{50}	Chromium trioxide	43	Joshi & Patil (1991)
African clawed frog (*Xenopus laevis*)	100 d NOEC (mortality)	Potassium dichromate	0.35	Slooff & Canton (1983)*
	100 d NOEC (growth)	Potassium dichromate	1.1	Slooff & Canton (1983)
Marine				
Green algae				
Dunaliella tertiolecta	2 h EC_{50} (galactosidase inhibition)	Potassium dichromate	7	Peterson & Stauber (1996)
	72 h EC_{50} (growth)	Potassium dichromate	17.8	Stauber (1995)
Diatoms				
Nitzschia closterium	72 h EC_{50} (growth)	Potassium dichromate	2.4	Stauber (1995)
Skeletonema costatum	6 h EC_{50}	Potassium dichromate	26 µmol/l	Kusk & Nyholm (1991)
Invertebrates				
Pacific oyster (*Crassostrea gigas*)	48 h EC_{50}	Potassium dichromate	4.5	Martin et al. (1981)
Mollusc (*Macoma balthica*)	96 h LC_{50}	Potassium dichromate	29–320[k]	Bryant et al. (1984)
Clam (*Rangia cuneata*)	96 h LC_{50}	Potassium dichromate	0.21–35[l]	Olson & Harrel (1973)
Bristleworm (*Capitella capitata*)	96 h LC_{50}	Chromic acid	5	Reish et al. (1976)
	28 d LC_{50}	Chromic acid	0.28	Reish et al. (1976)
	5 mo NOEC (reproduction)	Potassium dichromate	0.05	Reish (1977)
Ragworm (*Neanthes arenaceodentata*)	96 h LC_{50}	Potassium dichromate	3.1	Mearns et al. (1976)
	7 d LC_{50}	Potassium dichromate	1.6	Mearns et al. (1976)
	96 h LC_{50}	Potassium dichromate	2.2–4.3	Oshida et al. (1981)
	7 d LC_{50}	Potassium dichromate	1.66	Oshida et al. (1981)
	28 d LC_{50}	Chromic acid	0.55	Reish et al. (1976)
Ragworm (*Nereis diversicolor*)	96 h LC_{50}	Potassium dichromate	7.5–65[m]	Bryant et al. (1984)
Polychaete worm (*Ophryotrocha diadema*)	21 d NOEC (mortality and reproduction)	Chromic acid	0.5	Reish & Carr (1978)
Rotifer (*Brachionus plicatilis*)	24 h LC_{50}	Potassium dichromate	51.6–126[n]	Persoone et al. (1989)
Amphipod (*Allorchestes compressa*)	96 h LC_{50}	Potassium dichromate	5.6 and 6.3[o]	Ahsanullah (1982)
Brine shrimp (*Artemia* sp.)	24 h LC_{50}	Potassium dichromate	13.7	Vanhaecke & Persoone (1981)
Brine shrimp (*Artemia salina*)	24 h LC_{50}	Potassium dichromate	7.8–45.2[n]	Persoone et al. (1989)
	48 h LC_{50}	Sodium chromate	7.9	Kissa et al. (1984)
	48 h LC_{50}	Sodium chromate	12.8	Verriopoulos et al. (1987)
Blue crab (*Callinectes sapidus*)	96 h LC_{50}	Potassium dichromate	34–98[p]	Frank & Robertson (1979)

Table 13 (continued)

Species	End-point	Chromium salt	Concentration (mg Cr(VI)/l)	Reference[a]
Dungeness crab (*Cancer magister*)	96 h LC_{50}	Potassium dichromate	3.4	Martin et al. (1981)
Scud (*Corophium volutator*)	96 h LC_{50}	Potassium dichromate	4.4–36[q]	Bryant et al. (1984)
Opossum shrimp (*Mysidopsis almyra*)	48 h EC_{50}	Potassium dichromate	5.1	Dorn et al. (1987)
Mysid shrimp (*Mysidopsis bahia*)	96 h LC_{50}	Potassium dichromate	2	Lussier et al. (1985)
	48 h EC_{50}	Potassium chromate	6	Jop et al. (1987)
	48 h EC_{50}	Potassium dichromate	6.3	Jop et al. (1987)
	48 h EC_{50}	Potassium dichromate	5.4 and 7[r]	Dorn et al. (1987)
	38 d NOEC (reproduction)	Potassium dichromate	0.088	Lussier et al. (1985)
Harpacticoid copepod (*Nitocra spinipes*)	96 h LC_{50}	Potassium dichromate	5.7	Lindén et al. (1979)
Grass shrimp (*Palaemonetes pugio*)	96 h LC_{50}	Sodium chromate	4.9	Conklin et al. (1983)
Mysid shrimp (*Praunus flexuosus*)	96 h LC_{50}	Potassium dichromate	10–13[s]	McLusky & Hagerman (1987)
Benthic copepod (*Tisbe holothuriae*)	48 h LC_{50}	Sodium chromate	8.1	Moraitou-Apostolopoulou & Verriopoulos (1982)
	48 h LC_{50}	Sodium chromate	14.1	Verriopoulos & Dimas (1988)
	48 h LC_{50}	Sodium chromate	15.8–17.4[t]	Verriopoulos (1980)
Fish				
Bleak (*Alburnus alburnus*)	96 h LC_{50}	Potassium dichromate	84.8	Lindén et al. (1979)
Chinook salmon (*Oncorhynchus tshawytscha*)	96 h LC_{50}	Sodium chromate	144	Hamilton & Buhl (1990)
Grey mullet (*Chelon labrosus*)	96 h LC_{50}	Potassium dichromate	47.2	Taylor et al. (1985)
Speckled sanddab (*Citharichthys stigmaeus*)	96 h LC_{50}	Potassium dichromate	30	Mearns et al. (1976)
	21 d LC_{50}	Potassium dichromate	5	Mearns et al. (1976)
Sheepshead minnow (*Cyprinodon variegatus*)	96 h LC_{50}	Potassium chromate	25	Jop et al. (1987)
	96 h LC_{50}	Potassium dichromate	25	Jop et al. (1987)
	96 h LC_{50}	Potassium dichromate	21.4	Dorn et al. (1987)
Three-spined stickleback (*Gasterosteus aculeatus*)	96 h LC_{50}	Potassium chromate	35	Jop et al. (1987)
	96 h LC_{50}	Potassium dichromate	33	Jop et al. (1987)
Dab (*Limanda limanda*)	96 h LC_{50}	Potassium dichromate	47	Taylor et al. (1985)

EC_{50}, median effective concentration; IC_{50}, median inhibitory concentration; LC_{50}, median lethal concentration; mo, months; NOEC, no-observed-effect concentration; wk, weeks

[a] Studies marked with an asterisk (*) have been used in the derivation of a freshwater PNEC in the evaluation of environmental effects (see section 11.2).
[b] Temperature ranging from 15 °C to 20 °C.
[c] Toxicity inversely related to temperature (15–25 °C).
[d] Range of three means.
[e] Hardness (calcium carbonate concentration) 20 mg/l.
[f] Body weights ranging from 0.96 to 54.3 g.
[g] Hardness (calcium carbonate concentration) 360 mg/l.
[h] Hardness (calcium carbonate concentration) ranging from 40 to 285 mg/l.
[i] Body weights ranging from 0.2 to 25 g, and pH ranging from 6.5 to 7.8.
[j] De Graeve et al. (1992) reported the results of a ring test, in which 18 determinations of the NOEC values were made. This value is the geometric mean of the NOEC values reported. Where the value reported was given as "<", half of the limit value has been used in calculating the mean (recognizing that the actual level of effect was not reported in this paper).
[k] Salinity ranging from 15‰ to 35‰, and temperature ranging from 10 °C to 15 °C.
[l] Salinity ranging from <1‰ to 22‰.
[m] Salinity ranging from 5‰ to 30‰, and temperature ranging from 10 °C to 15 °C.
[n] Salinity ranging from 5‰ to 35‰, and temperature ranging from 20 °C to 25 °C.
[o] Body weights 3.5 and 2.2 mg.
[p] Salinity ranging from 1‰ to 35‰.

Table 13 (continued)

[q] Salinity ranging from 10‰ to 35‰, and temperature ranging from 10 °C to 15 °C.
[r] Life stage 24 h and 24–96 h.
[s] Salinity ranging from 13.5‰ to 27‰.
[t] Temperature ranging from 14 °C to 18 °C.

Temmink et al. (1983) exposed fingerling trout (*Oncorhynchus mykiss*) to 3.2 mg chromium(VI) per litre at pH 6.5 for up to 11 days to induce hyperplasia of the gill epithelium. The toxic effect of chromium(VI) was thought to occur by a three-step process, with the first step being degeneration and eventual death of the epithelial cells; the plasma membrane was the primary target for oxidative action of chromium(VI).

An avoidance threshold of 0.028 mg chromium(VI) per litre was determined for fish (rainbow trout) not pre-exposed to chromium(VI), whereas avoidance thresholds for pre-exposed fish increased linearly with the level of pre-exposure (0.01–3.0 mg chromium(VI) per litre). A chromium(VI) concentration of 0.8 mg/l was proposed as a critical pre-exposure level for short-term recovery of normal chemoreceptive capacity (Anestis & Neufeld, 1986).

10.2 Terrestrial organisms

Once chromium(VI) is released into soil, it is likely that much of it will be reduced to chromium(III). Toxicity data are available for chromium(VI) in soil, but it is also likely that the majority of the chromium(VI) present in these experiments will be converted to chromium(III) during the test.

Ross et al. (1981) looked at the effect of chromium(VI) (as potassium dichromate) on the growth of a mixed bacterial population isolated from soil. A difference in sensitivity between Gram-negative and Gram-positive bacteria was found in the study. The growth of all Gram-negative bacteria was found to be almost completely inhibited by 10–11 mg chromium(VI) per litre. A chromium(VI) concentration of 1 mg/l had no effect on most Gram-positive bacteria, whereas significant growth inhibition was seen with some Gram-negative bacteria at the same concentration. Ueda et al. (1987) investigated the effects of chromium(VI) (as sodium chromate; 10–100 mg chromium(VI) per kilogram) and organic amendments on the composition and activity (as measured by carbon dioxide evolution) of microbial flora in soil for 20 days. The chromium(VI) added to the soil was found to be rapidly reduced to chromium(III). A marked decrease in carbon dioxide evolution occurred at and above 50 mg chromium(VI) per kilogram dry soil.

Chromium(VI) caused a slight, temporary reduction in soil nitrification at 10 mg/kg dry weight (3.2 mg chromium(VI) per kilogram soil), but completely inhibited nitrification at soil concentrations of ≥100 mg/kg dry weight (≥32.1 mg chromium(VI) per kilogram soil) in a 4-week experiment. Chromium(VI) was much less toxic to bacteria responsible for ammonification, with only partial inhibition of ammonification occurring over the first 3 days at 1000 mg/kg dry weight (321 mg chromium(VI) per kilogram soil). Overall, the lowest-observed-effect concentration (LOEC) from this study is around 3.2 mg chromium(VI) per kilogram soil (Ueda et al., 1988).

At a chromium(VI) concentration of 2710 mg/kg dry soil, the growth of green beans (*Phaseolus vulgaris*) and sweet corn (*Zea mays*) was severely reduced (10% of controls for beans and 4% of controls for sweet corn). At 452 mg chromium(VI) per kilogram dry soil, crop growth (yield) was slightly reduced from that of controls (80% of controls for beans and 85% of controls for sweet corn; reduction in growth statistically significant [$P = 0.01$] only for beans). Therefore, the exposure concentration of 452 mg chromium(VI) per kilogram dry soil can be considered as a LOEC for beans and a NOEC for sweet corn (Miller et al., 1980).

Pestemer et al. (1987) reported the results of the Organisation for Economic Co-operation and Development (OECD) Terrestrial Plant Growth Test for potassium dichromate for 15 plant species and compared them with results obtained from field studies. On a total chromium basis, EC_{50} values were 35.3 mg/kg soil for nine species and 3.53 mg/kg soil for six species. The NOEC for the laboratory studies was determined to be 0.35–3.53 mg chromium per kilogram soil. In field studies using the same plant species, stimulation of plant growth or no effects were generally observed. The exception to this was that a slight decrease in growth (<30% effect) was seen at 3.53 mg chromium per kilogram soil with *Sinapis alba*, *Brassica napus* and *Raphanus sativus*, but at higher concentrations of 35.3 mg chromium per kilogram soil, growth stimulation was seen with these species. Guenther & Pestemer (1990) found similar results for growth of seedlings exposed for 10–14 days to chromium(VI) (as potassium dichromate) in a sandy loam soil. The following results were reported for chromium(VI): *Avena sativa* 14-day EC_{50} (growth) = 30 mg chromium(VI) per kilogram dry soil; *Brassica rapa* 10-day EC_{50} (growth) = 8.25 mg chromium(VI) per kilogram dry soil; and *Lepidium sativum* 3-day EC_{50} (germination) = 30 mg chromium(VI) per kilogram soil.

Adema & Henzen (1989) carried out studies on the effects of chromium(VI) on seed germination and growth (OECD Test Guideline 208). The test was carried out from planting the seeds to 14 days after germination. NOECs for the two soils (a loam soil and a humic sand), respectively, were 3.5 and 11 mg chromium(VI) per kilogram dry weight for oats (*Avena sativa*), 0.35 and >11 mg chromium(VI) per kilogram for lettuce (*Lactuca sativa*) and 3.2 and 10 mg chromium(VI) per kilogram for tomato (*Lycopersicum esculentum*).

Turner & Rust (1971) studied the effects of chromium(VI) (as potassium dichromate) on growth of soya beans (*Glycine max* L. Merr.) in nutrient media (5 days) and soil (3 days). Nutrient media concentrations of ≥0.5 mg chromium(VI) per litre caused a significant reduction in yield of tops, and concentrations of ≥1.0 mg chromium(VI) per litre caused a significant reduction in yield of roots. In the soil experiments, plants receiving 10 mg chromium(VI) per kilogram soil showed severe wilting, and plants receiving ≥30 mg chromium(VI) per kilogram soil died. All soil treatments (5–60 mg chromium(VI) per kilogram) significantly reduced the yield of tops.

The growth of barley (*Hordeum vulgare*) and rape (*Brassica napus*) was found to be significantly reduced at chromium(VI) concentrations of ≥50 mg/l and ≥30 mg/l, respectively. Root length was found to be significantly reduced with all chromium(VI) treatments (10–100 mg chromium(VI) per litre) (Hauschild, 1993). A chromium(VI) concentration of 208 mg/l was found to cause an almost complete inhibition of root growth of *Allium cepa* over a 96-hour test period (Liu et al., 1992).

Soni & Abbasi (1981) studied the effects of chromium(VI) (as potassium dichromate) on the mortality of adult earthworms (*Pheretima posthuma*). The overall estimated times for 100% mortality ranged from 56–116 days at 10 mg chromium(VI) per kilogram soil to 5 days at 100 mg chromium(VI) per kilogram soil. Römbke (1989) reported the results of an earthworm acute toxicity test (OECD Test Guideline 207) carried out by Cabridenc et al. (1984) using *Eisenia foetida* and potassium dichromate. The 14-day EC_{50} was determined to be 792 mg chromium(VI) per kilogram dry soil. The 28-day LC_{50} for the terrestrial annelid *Enchytraeus albidus* was 146 mg chromium(VI) per kilogram dry soil (Römbke, 1989; Römbke & Knacker, 1989).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification

Occupational exposure to chromium(VI) compounds is causally associated with an increased incidence of lung cancer. An association between exposure to chromium(VI) and cancer of the nose and paranasal sinuses has also been observed.

Effects in humans exposed occupationally to airborne chromium(VI) include nasal septum ulceration and perforation and other effects reflecting respiratory irritation. Few studies have reported on long-term pulmonary effects other than cancer (e.g. chronic obstructive lung disease), and the results are not conclusive. Several case reports and case series have demonstrated that exposure to chromium(VI) may cause asthma.

Exposure to chromium(VI) compounds causes irritation of and corrosive damage to the skin and mucous membranes and may lead to chronic chrome ulcers. Chromium(VI) also causes dermal sensitization and may lead to debilitating allergic dermatitis.

Chromium(VI) compounds have consistently given positive results in studies for gene mutations in bacteria and other microorganisms and for clastogenicity in mammalian cells. Positive results for clastogenicity have also been obtained in in vivo studies in animals. Chromosomal aberrations and DNA damage have been observed in some humans occupationally exposed to chromium(VI).

Accidental or intentional ingestion of generally unknown but probably extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, haematological, hepatic, renal and neurological effects. Some cases have been fatal.

Consistent with limited evidence of respiratory sensitization in humans, inhalation exposure of other species to chromium(VI) compounds causes immunological reactions in the respiratory tract.

Chromium(VI) has caused cancer in experimental animals after exposure by inhalation, intratracheal and oral administration and by several parenteral administration routes.

Oral exposure of experimental animals to chromium(VI) compounds has resulted in gastrointestinal,

hepatic, renal, immunological, haematological, neurological, developmental and reproductive effects.

Dermal exposure of experimental animals to chromium(VI) compounds has resulted in skin ulcers and allergic response. Effects via dermal exposure are likely to be influenced by differences in solubility between chromium(VI) compounds.

11.1.2 Dose–response relationships and criteria for setting tolerable intakes and concentrations

11.1.2.1 Non-cancer effects

(1) Inhalation exposure to chromic acid/chromium trioxide

Chromium(VI) trioxide reacts with water and produces chromic acid. This is a strong mineral acid and a strong oxidant. The study by Lindberg & Hedenstierna (1983) found a LOAEC of 2 µg/m^3 for nasal irritation in workers exposed to chromic acid. Adjusting for occupational exposure by multiplying by 8 hours/24 hours and by 5 days/7 days yields an adjusted LOAEC of 0.5 µg chromium(VI) per cubic metre.

Association of chromic acid exposure with nasal irritation, mucosal atrophy and ulceration and decreases in spirometric parameters is well supported from the published literature, although quantitative data are limited (Sassi, 1956; Kleinfeld & Rosso, 1965; Hanslian et al., 1967; Gomes, 1972; Cohen et al., 1974; Lucas & Kramkowski, 1975; Royle, 1975; Bovet et al., 1977).

A tolerable concentration (TC) can be derived as follows:

$$TC = \frac{LOAEC}{UF}$$

where UF is the uncertainty factor.

$$TC = \frac{0.5\ \mu g\ Cr(VI)/m^3}{100}$$

$$= 0.005\ \mu g\ Cr(VI)/m^3 \text{ for chromium trioxide/chromic acid}[1]$$

The uncertainty factor of 100 consists of 10 for inter-individual variability and 10 for extrapolating from a LOAEC to a no-observed-adverse-effect concentration (NOAEC).

(2) Inhalation exposure to salts of chromium(VI) (chromates and dichromates)

The study by Glaser et al. (1990) on sodium dichromate is used as the primary study for the derivation of the tolerable concentration of chromium(VI) salts for non-cancer respiratory effects. In this study, rats were exposed 22 hours/day, 7 days/week, for 30 or 90 days to 0, 0.05, 0.1, 0.2 or 0.4 mg chromium(VI) per cubic metre as sodium dichromate aerosol particulates. The findings in this study are supported by another 90-day study conducted by the same group (Glaser et al., 1985), in which groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1 or 0.2 mg chromium(VI) per cubic metre as sodium dichromate for 22 hours/day, 7 days/week, for 90 days. A benchmark concentration (BMC) analysis of the Glaser et al. (1990) data was conducted by Malsch et al. (1994). Using the 90-day exposure data, Malsch et al. (1994) developed BMCs for lung weight, lactate dehydrogenase activity in BAL fluid, protein in BAL fluid and albumin in BAL fluid. The concentration–effect data were adjusted for intermittent exposure (22 hours/day), and the continuous data were fitted to a polynomial mean response regression model by the maximum likelihood method (Malsch et al., 1994; ATSDR, 2008). The $BMCL_{10}$s (lower 95% confidence limit on the concentration corresponding to a 10% relative change in the end-point) were 67 (lung weight), 16 (lactate dehydrogenase activity in BAL fluid), 35 (protein in BAL fluid) and 31 (albumin in BAL fluid) µg chromium(VI) per cubic metre, respectively. The lowest BMCL was 16 µg chromium(VI) per cubic metre for alterations in lactate dehydrogenase activity in BAL fluid. Alterations in lactate dehydrogenase activity in BAL fluid is considered a sensitive indicator of potential lung toxicity and may also reflect chronic lung inflammation, which may lead to pulmonary fibrosis through prevention of the normal repair of lung tissue (USEPA, 1998).

The adjusted BMCL ($BMCL_{ADJ}$) is derived as follows:

$$BMCL_{ADJ} = BMCL \times RDDR$$

$$= 16\ \mu g\ Cr(VI)/m^3 \times 0.630$$

$$= 10\ \mu g\ Cr(VI)/m^3$$

where RDDR (regional deposited dose ratio) is a factor used to adjust the inhalation particulate exposure concentration for an animal to the predicted inhalation particulate exposure concentration for a human; based

[1] During the preparation of this CICAD for publication, the updated *Toxicological profile for chromium* was finalized and published by ATSDR (2012). The Minimal Risk Levels (MRLs) derived in ATSDR (2012) for intermediate (up to 1 year) and chronic inhalation exposure to dissolved chromium(VI) aerosols and mists were the same as the tolerable concentration presented in this CICAD for exposure to chromic acid/ chromium trioxide and were derived on the same basis.

on an MMAD of 0.28–0.39 µm[1] and a GSD of 1.63 µm (Glaser et al., 1990), the RDDR for lung effects (thoracic region) is calculated to be 0.630 (USEPA, 1994).

The tolerable concentration (TC) is calculated as follows:

$$TC = \frac{BMCL_{ADJ}}{UF}$$

$$= \frac{10\ \mu g\ Cr(VI)/m^3}{300}$$

$$= 0.03\ \mu g\ Cr(VI)/m^3 \text{ for inhalation of chromium(VI) salts}^2$$

The uncertainty factor of 300 consists of 3 to account for interspecies pharmacodynamic differences not addressed by the dose conversion (ATSDR, 2008), 10 for inter-individual variability and 10 to extrapolate from 90-day exposure to long-term exposure (IPCS, 1994, 2005).

The tolerable concentration for non-cancer respiratory effects of chromium(VI) salts is supported by the Gibb et al. (2000a) study on workers in chromate production: nasal irritation was observed after a median exposure of 3 months to alkali chromates at a median chromium(VI) trioxide concentration of 20 µg/m^3, corresponding to 10 µg chromium(VI) per cubic metre. Applying an uncertainty factor of 10 for interindividual variation, 10 for LOAEC to NOAEC adjustment and 3 to compensate for the fact that the effects were observed shortly after the exposure started (as early as 3 months, justifying an additional uncertainty factor), a tolerable concentration of 0.03 µg chromium(VI) per cubic metre is obtained.

(3) Oral exposure to chromium(VI)

Drinking-water studies with sodium dichromate dihydrate (NTP, 2008) in rats and mice for 2 years have identified duodenal mucosa as the target organ, where effects were seen at lowest dose levels. The BMD_{10} and $BMDL_{10}$ for diffuse epithelial hyperplasia in female mice were 0.12 and 0.094 mg/kg bw per day, respectively.

The tolerable daily intake (TDI) is calculated as follows:

$$TDI = \frac{BMDL_{10}}{UF}$$

$$= \frac{0.094\ mg\ Cr(VI)/kg\ bw\ per\ day}{100}$$

$$= 0.9\ \mu g\ Cr(VI)/kg\ bw\ per\ day \text{ for oral exposure to Cr(VI) compounds}^3$$

The uncertainty factor of 100 consists of 10 for extrapolation from experimental animals to humans and 10 for human interindividual variability (IPCS, 1994, 2005).

(4) Dermal exposure to chromium(VI)

Recent human studies indicate that the concentration of chromium(VI) leading to a skin reaction in 10% of a previously sensitized population (10% minimum eliciting threshold, MET_{10}) varies from 0.03 to 0.12 µg chromium(VI) per square centimetre. No data are available on the quantitative relationship between chromium(VI) dermal exposure and induction of sensitization in previously non-sensitized people.

11.1.2.2 Cancer

Because of its more extensive data on exposure levels and on the large proportion of workers with low exposure, the study of Gibb et al. (2000b) was used as the basis of the quantitative dose–response assessment. The conclusions drawn are well in line with those of the other studies.

Using the Gibb et al. (2000b) data, Park et al. (2004) estimated from a linear relative rate Poisson regression model (with race, age, smoking and cumulative chromate exposure as variables) that the excess lifetime lung cancer risk associated with workroom atmospheric chromium(VI) trioxide concentrations of 1, 10 and 100 µg/m^3 would be 0.003 (95% CI = 0.001–0.006), 0.031 (95% CI = 0.012–0.059) and 0.255 (95% CI = 0.109–0.416), respectively. Examination of non-linear features in these data was considered to support using the traditional (lagged) cumulative exposure paradigm: no intensity (concentration) threshold, linearity in intensity and constant increment in risk following exposure (Park &

[1] Calculation based on minimum input parameter available: 0.5 µm.

[2] During the preparation of this CICAD for publication, the updated *Toxicological profile for chromium* was finalized and published by ATSDR (2012). The MRL derived in ATSDR (2012) for intermediate (up to 1 year) inhalation exposure to particulate chromium(VI) compounds was 0.3 µg Cr(VI)/m^3. The MRL was derived from the same data, but without the 10-fold uncertainty factor to extrapolate from 90-day exposure to long-term exposure. ATSDR (2012) did not set an MRL for chronic inhalation exposure to particulate chromium(VI) compounds.

[3] During the preparation of this CICAD for publication, the updated *Toxicological profile for chromium* was finalized and published by ATSDR (2012). The MRL derived in ATSDR (2012) for chronic oral exposure to chromium(VI) compounds was also 0.9 µg Cr(VI)/kg bw per day, derived on the same basis.

Table 14: Predicted lung cancer risk from exposure to chromium(VI).

Concentration of Cr(VI) (µg/m^3)	Cumulative lifetime lung cancer risk attributable to Cr(VI)	
	Occupational exposure	Environmental exposure
1	0.006	0.04
0.1	6×10^{-4}	0.004
0.01	6×10^{-5}	4×10^{-4}
0.001	6×10^{-6}	4×10^{-5}

Stayner, 2006). Linear extrapolation from these estimates of occupational exposure (8 hours/day, 5 days/week, 52 weeks/year for 45 years starting at age 20) to the environmental exposure scenario (exposure 24 hours/day, 365 days/year, starting at birth and continuing to age 70 years) at environmentally relevant concentrations are presented in Table 14.

There is significant uncertainty associated with the carcinogenic risk to humans associated with oral exposure to chromium(VI) compounds. This extends to both the interpretation of an epidemiological study of a population exposed to chromium(VI)-contaminated drinking-water and the relevance to human exposures at low concentrations in drinking-water of the long-term animal studies that have been conducted. Owing to these uncertainties, a quantitative assessment of carcinogenic risk to humans from ingested chromium(VI) is not presented.

11.1.3 Sample risk characterization

The geometric mean TWA breathing zone concentration of chromic acid in a hard and bright chromium electroplating unit (Blade et al., 2007) was 2.5 (range 0.22–8.3) µg/m^3. This exceeds the tolerable concentration, based on nasal irritation effects of chromium trioxide/chromic acid, by 500-fold. If such an exposure starts at the age of 20 years and continues at the same level until the age of 65, it is expected to lead to an excess cancer incidence of 15 per 1000.

The geometric mean exposure to chromium(VI) in a facility producing sodium chromate and sodium dichromate (EU, 2005) was 5 µg/m^3 (concentration range 0.01–220 µg/m^3, arithmetic mean concentration 9 µg/m^3). This exceeds the tolerable concentration, based on irritation effects of chromates, by greater than 160-fold. If such an exposure starts at the age of 20 years and continues at the same level until the age of 65, it is expected to lead to an excess cancer incidence of 30 per 1000.

11.1.4 Uncertainties in the evaluation of health risks

Although the non-cancer hazards of chromium(VI) to human health are qualitatively well characterized, there are in practice only very few studies in humans available for the dose–response analysis of chromium trioxide/chromic acid and for the dose–response analysis of chromium(VI) salts. The nature of the exposure assessments is a source of uncertainty for these studies, because the most relevant exposure metrics for the respiratory tract effects may be peak exposures, but the studies available (which use, for example, cumulative exposure over a long term [annual averages] or 8-hour TWA exposures) do not capture peak exposures.

For chromium(VI) salts, a source of uncertainty is the practically non-existent comparative information on the irritation potency of the different salts.

The lung cancer risk assessment was based on workers exposed in chromate production, and the variety of chromium(VI) compounds to which these workers were exposed may not be representative of all chromium(VI) compounds. There are no comparative carcinogenicity data using inhalation exposure in other species. Studies using intrabronchial pellet implantation seem to indicate that strontium, zinc and calcium chromates may be more potent carcinogens than, for example, sodium chromate, but because a single dose schedule was used, these studies are difficult to interpret.

The relative potencies of different chromium(VI) compounds and the influence of different solubilities on health effects have not been studied in detail.

Experiments in rodents demonstrate that sodium dichromate may cause cancer after oral administration. However, the epidemiological study of a human population exposed to chromium(VI)-contaminated drinking-water is equivocal. There are uncertainties regarding the extrapolation of the results of the animal studies to low-level exposure of humans via drinking-water.

11.2 Evaluation of environmental effects

Short-term and long-term ecotoxicological data on the effects of hexavalent chromium compounds are available for a wide variety of organisms, life stages, end-points and test conditions. The toxicity of hexavalent chromium to aquatic organisms is summarized in Figure 1.

The results indicate that the acute toxicity of chromium(VI) is dependent on a number of factors, including pH, water hardness, salinity and temperature. In general, chromium(VI) toxicity is increased with

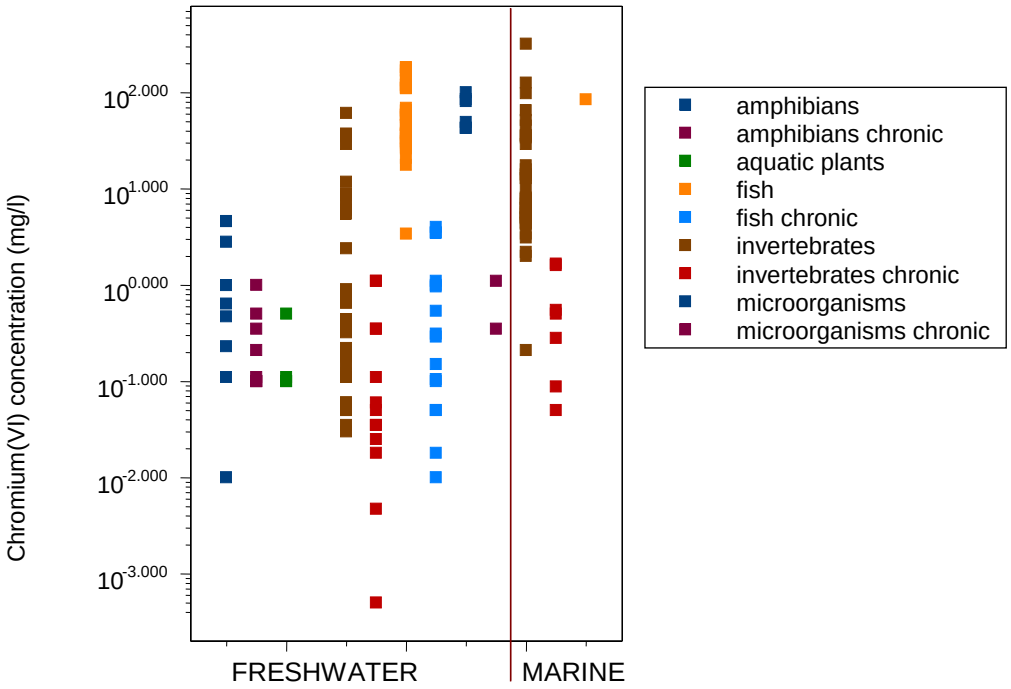


Figure 1: Toxicity of hexavalent chromium to aquatic organisms.

decreased pH (i.e. from 8.0 to 6.0), increased temperature (i.e. from 15 °C to 25 °C) and decreased water hardness or salinity. A comparison between freshwater and saltwater organisms shows that the former appear to be more sensitive. Decreasing salinity appears to lead to increased toxicity. Where saltwater organisms have been tested in water of low salinity (<2‰), their sensitivity appears to become comparable with that of freshwater organisms.

The long-term studies available do not appear to show any clear dependence of toxicity on the properties of the water. There are indications that toxicity may be higher in lower-hardness waters, but there are few, if any, studies that allow the comparison to be made for the same species at different levels of hardness or other properties. Although relationships between hardness and toxicity have been described for divalent metal cations, the fact that the chromium species here are oxoanions means that their toxicity may be less influenced by water properties. As no relationships can be established, the toxicity data will be treated together.

According to the standard assessment factor approach, the PNEC is derived from the lowest long-term NOEC available. The lowest freshwater long-term NOEC included in Table 13 is 4.7 µg/l, for reproduction of the cladoceran *Ceriodaphnia dubia* (note: 7 days is long enough to produce three generations in this species, compared with 21 days for *Daphnia magna*). As there are a large number of long-term effect data on a wide range of aquatic organisms, an assessment factor of 10 is used, giving a freshwater PNEC by this method of 0.5 µg/l.

However, according to the European Commission (EC) Technical Guidance Document (EC, 2003), the effects assessment can also be supported by a statistical extrapolation method if the database is sufficient for its application, and there is a considerable amount of ecotoxicological information available on exposure of freshwater organisms to hexavalent chromium compounds.

The data used for the derivation of the PNEC based on a species sensitivity distribution are summarized in Table 15, with the actual studies marked with an asterisk in Table 13. For species for which more than one value was available for an end-point, the geometric means of the values for survival/mortality, reproduction and growth/development were calculated to produce one value per end-point. Then for all species, the lowest value between these end-points was selected as the NOEC for the species.

There are 26 NOEC (or derived NOEC) values available for calculating a hazardous concentration for the protection of 95% of species (the 5th percentile of the species sensitivity distribution), HC_5, for chromium(VI) from a wide range of freshwater taxa, including fish, crustaceans, algae, aquatic plants, insects, molluscs, amphibians and coelenterates.

Table 15: Data used for freshwater PNEC derivation.

Species	NOEC (mg Cr(VI)/l)	End-point
Blue-green algae		
Microcystis aeruginosa	0.35	96 h NOEC (growth)
Algae		
Chlorella pyrenoidosa	0.1	96 h NOEC (biomass)
Chlorella sp. (wild)	0.1	96 h NOEC (biomass)
Scenedesmus pannonicus	0.11	96 h NOEC (biomass)
Selenastrum capricornutum	0.033	Geometric mean of EC_{10} (growth)
Macrophytes		
Lemna gibba	0.1	8 d NOEC (growth)
Lemna minor	0.11	7 d NOEC (growth)
Spirodela polyrhiza	0.1	8 d NOEC (growth)
Spirodela punctata	0.5	8 d NOEC (growth)
Crustaceans		
Ceriodaphnia dubia	0.0047	7 d NOEC (reproduction)
Daphnia carinata	0.05	14 d NOEC (reproduction)
Daphnia magna	0.009	Geometric mean of 14 d and 21 d NOECs (reproduction)
Coelenterates		
Hydra littoralis	0.035	11 d NOEC (reproduction)
Hydra oligactis	1.1	21 d NOEC (growth)
Insects		
Culex pipiens	1.1	25 d NOEC (development)
Molluscs		
Lymnaea stagnalis	0.11	40 d NOEC (reproduction)
Fish		
Catostomus commersoni	0.29	60 d NOEC (growth)
Esox lucius	0.538	20 d NOEC (survival)
Ictalurus punctatus	0.15	30 d NOEC (growth)
Oncorhynchus mykiss	0.07	Geometric mean of 60 d and 8 mo NOECs
Oryzias latipes	3.5	40 d NOEC (behaviour)
Pimephales promelas	0.68	Geometric mean of 7 d, 60 d and 412 d NOECs (growth)
Poecilia reticulata	3.5	28 d NOEC (growth)
Salvelinus fontinalis	0.01	8 mo NOEC (growth)
Salvelinus namaycush	0.105	60 d NOEC (growth)
Amphibians		
Xenopus laevis	0.35	100 d NOEC (mortality)

NOEC, no-observed-effect concentration; mo, month

A further consideration for the use of the method is whether the data fit to the expected distribution. The data set in Table 15 has been successfully tested against a log-normal distribution. Overall, the data set is considered suitable for use in the extrapolation method. The lower 5% value from the species sensitivity distribution (HC_5) has been calculated according to the equation for a log-normal distribution (Wagner & Lokke, 1991). Therefore, the statistical extrapolation approach has been used in this risk assessment.

The resulting value for the lower 50% confidence limit on the HC_5 (HC_5-50%) is 10 µg/l. The data set used in the extrapolation covers a wide range of aquatic species and a range of chronic end-points. It includes the types of organism indicated to be the most sensitive in acute tests, and there do not appear to be any groups of sensitive organisms that are missing from the data set. The organisms cover a range of trophic levels and feeding strategies, including primary producers, herbivores, fish that consume algae and invertebrates, fish that consume other fish and detritivores.

Against these points, there are a relatively large number of results for fish (although they cover different types) and only one each for insects and molluscs. There are also no results from mesocosm or field studies to compare with the derived values. Some values included in the data set lie below or at the HC_5-50% value, including one for the cladoceran *Ceriodaphnia dubia* and another for the fish *Salvelinus fontinalis*. In the case of *Ceriodaphnia dubia*, the NOEC for reproduction was 4.7 µg/l; from the same report, the NOEC for survival was 8.4 µg/l. These values come from a ring test and are derived from 18 individual results. In the same study, the 50% effect concentration for survival and reproduction over 7 days was 14 µg/l, indicating a steep dose–response curve. The NOEC for *Salvelinus fontinalis* is 10 µg/l, which is equal to the HC_5-50% value. The considerations above suggest that the lower 95% confidence limit (HC_5-95%) should be applied to give a more protective PNEC. Therefore, the freshwater PNEC based on the HC_5-95% is 4 µg/l.

In salt water, chromium(VI) would be expected to be less toxic than indicated by these values, except perhaps at very low salinities. There were insufficient toxicity data on marine organisms to calculate a guidance value using the probabilistic approach. However, there are long-term NOECs for freshwater species covering at least three trophic levels and long-term NOECs from an additional marine trophic group (annelids). Therefore, it is appropriate to apply an assessment factor of 50 to the lowest NOEC, which is a 14-day NOEC on reproduction in *Ceriodaphnia dubia* at 4.7 µg/l, giving a PNEC of 0.09 µg/l for the marine environment.

As chromium(VI) is converted to chromium(III) under some conditions in the environment, the possible effects of chromium(III) should also be considered. The toxicity of chromium(III) to aquatic organisms has been reviewed in a separate CICAD (IPCS, 2009). From the available data, chromium(III) appears to be less toxic than chromium(VI) in waters of medium hardness (calcium carbonate >50 mg/l). It should also be noted that the PNEC for chromium(III) refers to the dissolved water concentration. In laboratory tests, water-soluble forms of chromium(III) have generally been used. However, in the environment, chromium(VI) is likely to be reduced to forms of chromium(III) with limited water solubility, which will be associated mainly with the particulate (sediment and suspended matter) phases of the water compartment.

A comparison of the freshwater PNEC value for chromium(VI) (4 µg/l) with chromium concentrations in most natural waters reveals that total chromium concentrations will be lower than the PNEC in most cases. Even in cases where the PNEC is exceeded, the values are given as total chromium; under such circumstances, it is likely that the bioavailability of natural chromium would be very low. However, higher chromium and, more specifically, chromium(III) and chromium(VI) concentrations have been reported near sources of anthropogenic emissions. For example, within 80 m of a disused tannery, a free chromium(VI) concentration of 63 µg/l was measured in river water. Therefore, the risk to aquatic organisms in general is low, but there is a risk to aquatic organisms in the vicinity of some anthropogenic releases of chromium(VI). A comparison of the PNEC for marine organisms with chromium levels in the marine environment suggests that the value is at the lower end of typical naturally occurring chromium(VI) levels and is therefore overly precautionary. The main reason for the very low PNEC is that the critical study is based on a very sensitive freshwater end-point. However, as the toxicity test data tend to indicate that marine organisms are not more sensitive than freshwater organisms, this suggests that the value of 4 µg/l derived for freshwater species should be protective of marine species. The same conclusion that was drawn for freshwater organisms (i.e. that chromium(VI) would not represent a significant risk to organisms unless there is a local pollution source) then holds for the marine environment.

There are insufficient data available to derive a PNEC for sediment from studies on sediment-dwelling organisms. According to the EC Technical Guidance Document (EC, 2003), an equilibrium partitioning approach can be used in the absence of experimental data. However, such an approach for chromium(VI) would be very uncertain in nature, as chromium(VI) is likely to be reduced to chromium(III) under the conditions found in most sediments, and the chromium(III) formed is likely to be of much lower water solubility (and bioavailability).

There are a number of studies indicating that chromium(VI) is toxic to single species of bacteria. However, it is also clear that many bacteria are tolerant of high concentrations of chromium(VI). Both single-species and mixed population tests can be used to derive a PNEC for wastewater treatment plants. The lowest of the toxicity values relevant to the assessment of a wastewater treatment plant is 0.21 mg/l (a NOEC for *Microregma heterostoma*), and, according to the EC Technical Guidance Document (EC, 2003), the PNEC can be derived from the lowest reported NOEC using an assessment factor of 1. Therefore, a $PNEC_{microorganism}$ of 0.2 mg/l could be used in the risk characterization. However, there is evidence from studies on pilot-scale activated sludge plants that once acclimated to the presence of chromium(VI), plants can tolerate up to 10 mg chromium(VI) per litre in the influent, with only minor reductions in efficiency seen at substantially

higher concentrations. This observation indicates that the PNEC derived above may be overprotective of wastewater treatment plants that regularly receive, and are therefore acclimated to, chromium(VI) in the influent.

For the terrestrial compartment, long-term toxicity data are available for three trophic levels (plants, earthworms and soil processes/microorganisms), with plants generally being the most sensitive species (although a clear NOEC has not been determined for earthworms, the EC_{50} values are generally higher than those found in the plant experiments). The lowest NOEC from these studies is around 0.35 mg/kg dry weight of soil for plants. According to the EC Technical Guidance Document (EC, 2003), an assessment factor of 10 is appropriate, and so the $PNEC_{soil}$ can be estimated as 0.04 mg/kg dry weight. Using the water content of soil from the EC Technical Guidance Document (EC, 2003) of 11.8% by weight (20% by volume), this is equivalent to a $PNEC_{soil}$ of around 0.03 mg/kg on a wet weight of soil basis.

Chromium is a naturally occurring element, and, as such, there are natural background levels in the environment. The measured data show that these levels can vary widely. As a result, it is difficult to determine a representative background concentration to which the releases from industrial activity would add. Furthermore, it has been reported that the amount of chromium "available" to plants and other soil flora is usually low (e.g. 0.1–1% of the total) (Coleman, 1988), and, once released into soil, it is likely that much of the chromium(VI) present will be reduced to chromium(III). It should be noted that chromium(III) has generally been shown to be less toxic than chromium(VI) to soil organisms.

Therefore, assessing the risk to soil organisms is very difficult. Both the PNEC for soil and most of the monitoring data for soils are reported as total chromium and do not give any indication of the bioavailability of hexavalent chromium. It is clear from section 6.1.4 that there are many natural soils in which the levels of total chromium are well above the derived PNEC. It is important that the main form of the chromium be considered. In natural soils, the majority of chromium will be present as low-solubility chromium(III) complexes, for which bioavailability is limited. The PNEC derived is not appropriate for such situations. Therefore, in the absence of more data on the bioavailability of chromium in soils, it is difficult to assess the risk of chromium(VI) to soil organisms. To illustrate the importance of bioavailability, the EU Risk Assessment Report (EU, 2005) states that an ecological assessment based on surveys of species at locations close to a major production site found little evidence for any effects of chromium, even though measured levels of total chromium in the soil were up to 1000 mg/kg (all as chromium(III), as chromium(VI) was not detectable). Some of the species present were noted as being sensitive to environmental stress; the overall assemblage of plant and animal species was not considered to be atypical of the surrounding region.

12. EVALUATIONS BY INTERNATIONAL BODIES

The International Agency for Research on Cancer (IARC) has evaluated chromium(VI) compounds on a number of occasions since 1973. Chromium compounds (subsequently refined to chromium(VI) compounds) have been classified by IARC as *carcinogenic to humans* (Group 1) since the first evaluation. The classification was based on increased incidence of lung cancer following occupational exposure.

This IARC classification was reaffirmed at the most recent assessment (Straif et al., 2009; IARC, 2012), which was published during the preparation of this CICAD for publication. This assessment concluded that there is *sufficient evidence* in humans for cancer of the lungs and that positive associations have been observed between exposure to chromium(VI) compounds and cancer of the nose and nasal sinuses. The possible association between exposure to chromium(VI) compounds and cancer of the stomach was also assessed, including the studies based on a location with contaminated drinking-water in China. The IARC assessment concluded that the studies did not constitute rigorous evidence of an association between exposure to chromium(VI) and cancer of the stomach.

The WHO Air Quality Guideline (WHO, 2000) for chromium(VI) is based on lung cancer in humans. At an air concentration of chromium(VI) of 1 $\mu g/m^3$, the excess lifetime cancer risk is estimated to be 4×10^{-2}. It should be noted that chromium concentration in air is often expressed as total chromium and not chromium(VI).

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APPENDIX 1—ACRONYMS AND ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAL	bronchoalveolar lavage
BCF	bioconcentration factor
BMC	benchmark concentration
BMCL	lower 95% confidence limit on the benchmark concentration
$BMCL_{10}$	lower 95% confidence limit on the benchmark concentration corresponding to a 10% relative change in the end-point
BMD_{10}	benchmark dose for a 10% response
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
bw	body weight
CI	confidence interval
CICAD	Concise International Chemical Assessment Document
DNA	deoxyribonucleic acid
EC	European Commission
EC_{50}	median effective concentration
EU	European Union
FEV_1	forced expiratory volume in 1 second
GFAAS	graphite furnace atomic absorption spectrometry
GSD	geometric standard deviation
HC_5	hazardous concentration for the protection of 95% of species (the 5th percentile of the species sensitivity distribution)
HC_5-50%	lower 50% confidence limit on the hazardous concentration for the protection of 95% of species
HC_5-95%	lower 95% confidence limit on the hazardous concentration for the protection of 95% of species
IARC	International Agency for Research on Cancer
IC_{50}	median inhibitory concentration
ICD	International Statistical Classification of Diseases and Related Health Problems
ICP-AES	inductively coupled plasma atomic emission spectrometry
ICSC	International Chemical Safety Card
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (USEPA)
K_m	Michaelis-Menten constant
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
LOEC	lowest-observed-effect concentration
MET_{10}	10% minimum elicitation threshold
MIG	metal inert gas
MMA	manual metal arc
MMAD	mass median aerodynamic diameter
MRL	minimal risk level
NADPH	reduced nicotinamide adenine dinucleotide phosphate
nd	not detected
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEC	no-observed-adverse-effect concentration
NOEC	no-observed-effect concentration
OECD	Organisation for Economic Co-operation and Development
PAH	polycyclic aromatic hydrocarbon
PCMR	proportionate cancer mortality ratio
PMR	proportionate mortality ratio
PNEC	predicted no-effect concentration
RDDR	regional deposited dose ratio
RNA	ribonucleic acid
SD	standard deviation
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SMRA	adjusted standardized mortality ratio
TC	tolerable concentration
TDI	tolerable daily intake
TIG	tungsten inert gas
TWA	time-weighted average
UF	uncertainty factor
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

APPENDIX 2—SOURCE DOCUMENTS

ATSDR (2008): *Toxicological profile for chromium*

The *Toxicological profile for chromium* was prepared by ATSDR through a contract with the Syracuse Research Corporation. The profile was published in September 2000; an updated draft version was published in 2008[1]. Copies of the final (2012) profile can be obtained from:

Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry
United States Department of Health and Human Services
1600 Clifton Road NE, Mailstop F-62
Atlanta, Georgia 30333
USA

The document is also available on the web at: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=62&tid=17

The following individuals contributed to the development of the toxicological profile as chemical manager and authors:

Sharon Wilbur, Henry Abadin, Mike Fay, Dianyi Yu, Brian Tencza – ATSDR, Division of Toxicology and Human Health Sciences
Lisa Ingerman, Julie Klotzbach, Shelly James – Syracuse Research Corporation

The profile has undergone three ATSDR internal reviews, including a Health Effects Review, a Minimal Risk Level Review and a Data Needs Review. An external peer review panel was assembled for the updated profile for chromium. The panel consisted of the following members: Detmar Beyersmann, University of Bremen, Germany; John Pierce Wise, Sr, Maine Center for Toxicology and Environmental Health, University of Southern Maine, USA; and Richard Sedman, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, USA. These experts collectively have knowledge of chromium's physical and chemical properties, toxicokinetics, key health end-points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the United States *Comprehensive Environmental Response, Compensation, and Liability Act*, as amended. Additionally, the profile completed a public comment period.

Scientists from ATSDR reviewed the peer reviewers' and public comments and determined which comments were to be included in the profile. A listing of the responses to peer reviewers' and public comments both addressed and not incorporated in the profile, with a brief explanation of the rationale for any exclusion, exists as part of the administrative record for this substance. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

[1] During the preparation of this CICAD for publication, the updated *Toxicological profile for chromium* was finalized and published by ATSDR in 2012. All information taken from ATSDR (2000, 2008) was verified against the final 2012 version of the toxicological profile.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content.

USEPA (1998): *Toxicological review of hexavalent chromium in support of information on the Integrated Risk Information System (IRIS)*

The *Toxicological review of hexavalent chromium* was prepared by Peter C. Grevatt, USEPA. This document is available on the web at http://www.epa.gov/ncea/iris/toxreviews/0144tr.pdf.

This document received peer review both by USEPA scientists and by independent scientists external to USEPA. Subsequent to external review and incorporation of comments, this assessment underwent an Agency-wide review process whereby the IRIS Program Director achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Planning and Evaluation; and Regional Offices.

The internal USEPA reviewers were Robert Benson, Herman Gibb, Annie Jarabek, Charles Hiremath and Winona Victery. The external peer reviewers were Richard Anderson, United States Department of Agriculture; Robert Chapin, National Institute of Environmental Health Sciences; Robert Drew, Consultant; Günter Oberdörster, University of Rochester; and Elizabeth T. Snow, New York University Medical Center.

EU (2005): *European Union risk assessment report for chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate*

This document was prepared by the United Kingdom rapporteur on behalf of the EU. The scientific work on the environmental sections was carried out by the Building Research Establishment under contract to the environment rapporteur (United Kingdom Environment Agency).

Date of last literature search: 2000
Review of report by Member State Technical Experts finalized: 2002
Final report: 2005

This document is available on the web at http://echa.europa.eu/documents/10162/3be377f2-cb05-455f-b620-af3cbe2d570b.

The authors of the first draft of this CICAD from the above source documents were:-
Sharon B. Wilbur and L. Samuel Keith, Agency for Toxic Substances and Disease Registry, United States Department of Health and Human Services, Atlanta, Georgia, United States of America
Paul D. Howe, Centre for Ecology and Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, England.

APPENDIX 3—CICAD PEER REVIEW

The first draft of the CICAD on inorganic chromium(VI) compounds was sent for review in 2006 to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. An open invitation to participate in the peer review process was also published on the IPCS web site. Comments were received from:

M. Baril, Institut de recherche Robert Sauvé en santé et en securité du travail, Montreal, Quebec, Canada

R. Benson, United States Environmental Protection Agency, Denver, CO, USA

S. Bull, Chemical Hazards and Poisons Division, Health Protection Agency, London, England

A. Caitens, Health and Safety Executive, Bootle, England

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H. Gibb, Alexandria, VA, USA

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M. Nordberg, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

J. Stauber, CSIRO Centre for Environmental Contaminants Research, Sydney, New South Wales, Australia

F. Sullivan, Brighton, England

K. Ziegler-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Workplace Area (MAK Commission), Freising-Weihenstephan, Germany

The amended draft document following the 2010 Consultative Group meeting was also made available for public and peer review via the IPCS web site. Comments were received from:

C. Bowes, Pest Management Regulatory Agency, Ottawa, Ontario, Canada

C. Colosio, University of Milan, Milan, Italy

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M. Deveau, Health Canada, Ottawa, Ontario, Canada

S. Devotta, Chennai, India

J. Hopkins, Surrey, England

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APPENDIX 4—14TH CICAD FINAL REVIEW BOARD

Helsinki, Finland
26–29 March 2007

Members

Dr A. Aitio, Finnish Institute of Occupational Health, Helsinki, Finland

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Secretariat

Dr J. Bartram, Assessing and Managing Environmental Risks to Health, World Health Organization, Geneva, Switzerland

Mrs S. Marples, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Ms L. Onyon, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr M. Shibatsuji, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

[1] Invited but unable to participate.

APPENDIX 5 – CONSULTATIVE GROUP

University of Bradford, Bradford, England
1–2 November 2010

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APPENDIX 6—CICAD FINAL REVIEW BOARD 2012

(by correspondence)
June–October 2012

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Dr R. Brown, World Health Organization, Geneva, Switzerland

APPENDIX 7—CANCER STUDIES

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Hayes et al. (1979); Braver et al. (1985) Partial update of Machle & Gregorius (1948) and USPHS (1953) Chromate production plant in Baltimore, MD, USA	2101 workers newly employed 1945–1974 and with a working time ≥90 days. Follow-up through 1977, 438 deaths.	Lime process, but limited measurements indicated that the concentration of insoluble chromates in the air was "very low". Measurements of soluble chromium in 1945 (n = 88), 1946 (n = 144), 1947 (n = 17), 1949–1950 (n = 305) used to characterize cohort average exposure in 1945–1949 and 1950–1959.	Lung	Initial hire, duration of exposure, estimated cumulative exposure in (μg/m^3)·years			Expected numbers from age- and calendar year–adjusted Baltimore rates. Smoking not controlled.	35 death certificates not located. 494 lost to follow-up and assumed alive. Exposure history on assumed cohort average level and duration of exposure. Limited number of measurements, especially for the late entrants.
				1945–1949, <3 years, 670	20/11.42	175 [107–270]		
				1945–1949, ≥3 years, 3647	13/4.28	304 [162–519]		
				1950–1959, <3 years, 354	12/6.7	179 [93–313]		
				1950–1959, ≥3 years, 2930	9/2.63	342 [156–650]		
Gibb et al. (2000b) Chromate production plant in Baltimore, MD, USA, earlier studied in Hayes et al. (1979)	2357 workers first employed in 1950 (after construction of new facilities) for any time followed through 1992. Exclusion of 734 workers in the Hayes et al. (1979) cohort, who began working before the construction of the new facilities. Addition to the Hayes et al. (1979) cohort of workers with <90 days working time. 70 736 person-years, 122 lung cancer deaths.	Lime process under negative pressure. "Very little" non-soluble chromates in air. Job–exposure matrix based on 70 000 contemporary measurements of airborne Cr(VI) spanning the study period in a programme defined to characterize typical exposures.	Lung	Cumulative exposure in (mg Cr(VI)/m^3)·years			Tobacco smoking (data available for 93% of the workers) and exposure to Cr(III) considered as confounders in Cox model.	SMR based on age-, calendar-, race-specific Maryland rates. The Cox model coefficient, relative risk for 10-fold increase in exposure to Cr(VI), and P were 0.509, 1.66 and 0.045. Association with Cr(III) not significant.
				≤0.000 77	26/27.1	96 (63–138)		
				0.000 78–0.0046	28/19.80	142 (95–201)		
				0.0047–0.039	30/9.1	157 (107–220)		
				0.04–2.73	38/17.0	224 (160–303)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Luippold et al. (2003); Crump et al. (2003) Chromate production plant in Painesville, OH, USA	493 workers employed ≥1 year between 1940 and 1972 when the plant closed. Workers who had worked in other company plants earlier were excluded. Follow-up for mortality until 1997. No overlap with Mancuso (1997b).	High-lime process, amount of lime lowered in 1950. Exposure assessed in a job–exposure matrix based on 800 measurements of airborne Cr(VI) in 21 surveys performed in 1943–1971.	Lung	Cumulative exposure in (mg Cr(VI)/m^3)·years			Not adjusted for smoking.	Based on Ohio rates; based on rates in USA, all SMRs were approximately 10% higher. Risk increased with duration of exposure and latency and was higher for workers hired early.
				0.00–0.19	3/4.5	67 (15–196)		
				0.20–0.48	8/4.4	184 (79–362)		
				0.49–1.04	4/4.4	91 (25–234)		
				1.05–2.69	16/4.4	365 (208–592)		
				2.70–23	20/4.3	463 (83–716)		
Luippold et al. (2005) Two chromate production facilities, one of which was in Castle Hayne, NC, USA; for the latter, this is an update of Pastides et al. (1994)	617 workers employed ≥1 year between 1971 and 1989 in two plants but never in the high-lime process. Follow-up for mortality until end of 1998 with a total of 9906 person-years. Average duration of exposure was 12.4 and 7.8 years in the two plants, and average time since first exposure was 20.1 and 10.1 years.	None of the workers had been exposed in the high-lime process. For the period 1971–1974 area samples (no. not given) and for 1974–1989 15 000 personal samples analysed for Cr(VI). For most years, geometric mean of personal sample Cr(VI) remained well below 1.5 µg/m^3. Annual means were 0.36–4.36 µg/m^3.	All causes of death	Cohort vs state	27/46.0	59 (39–85)	Not adjusted for smoking.	Short duration of exposure and short latency period.
			All cancer		9/9.91	91 (41–172)		
			Lung		3/3.59	84 (17–244)		
			Ischaemic heart disease		5/9.08	55 (18–128)		
Mancuso (1997b) Follow-up of Mancuso (1975); partial update of Machle & Gregorius (1948) and USPHS (1953) Chromate production plant in Painesville, OH, USA	332 workers employed 1931–1937 followed through 1993. 283 deaths found; 49 workers "not found". No overlap with Luippold et al. (2003).	High-lime process. Job–exposure matrix based on measurement of personal exposure of every worker in 1949.	Lung	Cumulative exposure in (mg soluble Cr/m^3)·years	No. of deaths	Age-adjusted death rate per 10^5	Not adjusted for smoking. Age adjustment to the person-year distribution of the total cohort.	Death rates not adjusted to the 49 persons lost to follow-up (of 332). Soluble chromium taken to represent Cr(VI). Two nasal sinus cancers (Davies et al.,1991).
				<0.25	5	99.7		
				0.25–0.49	10	503.7		
				0.50–0.99	16	605.3		
				1.0–1.99	19	794.6		
				2.00–3.99	14	1312.8		
				≥4.00	2	2848.3		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Rosenman & Stanbury (1996) Partial update of Machle & Gregorius (1948) and USPHS (1953) Four chromate plants in New Jersey, USA	Eligible were workers employed from 1951 in plants A and B and from 1937 in plants C and D until the closure of the plants: 1954, 1971, 1964 and 1954 in plants A, B, C and D, respectively, and followed through 1991. For workers ever employed, in 1991, 1858 were dead, 1044 alive and 506 unknown. For workers employed for ≥1 year, the figures were 1014, 458 and 53.	Exposure to both Cr(III) and Cr(VI); 8–62% of air samples exceeded 50 µg/m^3.	Lung	Duration of exposure			Not controlled for smoking.	PMR analysis based on figures adjusted for sex, race, age and calendar time. Large proportion of subjects lost to follow-up. Six nasal cavity cancers in white males; greatly in excess.
				<1 year	55/ND	133 (100–173)		
				1–10 years	67/ND	237 (184–301)		
				10–20 years	30/ND	270 (182–385)		
				>20 years	18/ND	283 (168–447)		
Korallus et al. (1982, 1993) Chromate-producing factories in Leverkusen and Uerdingen, Germany	1417 workers employed for ≥1 year during 1903–1987 followed through 1987. 2592.7 person-years in total. 91 lost to follow-up.	The two factories changed over to non-lime process in 1957 and 1964; cohort subdivided into groups employed before and after changeover.	Lung	Pre-change cohort	66/32.27	2.27 (1.78–2.85)	Not corrected for smoking.	SMR corrected for unknown causes of death. Follow-up short for post-change subcohort (maximum 30 and 22 years for the two factories).
				Post-change cohort	9/7.34	1.26 (0.58–2.38)		
Birk et al. (2006) Follow-up of Korallus et al. (1982, 1993) Two German chromate production factories	901 male workers not employed before the changeover to non-lime process (1958 and 1964 in the two plants) followed through 1998. 31 lost to follow-up; they contributed to person-years to last time known to be alive.	12 400 urinary chromium measurements covering the exposure period provided basis for department/time-specific job–exposure matrix.	Lung	Cumulative urinary chromium in (µg/l)·years; 20-year lag			Controlled for smoking ever vs never smoked.	Exposure decreased with time and was lower than in the Korallus et al. (1993) report, in which higher risks were observed among workers also working in the high-lime process.
				0–39.9	14/ND	110 (60–184)		
				40–99.9	2/ND	101 (12–365)		
				100–199.9	2/ND	110 (13–396)		
				≥200	4/ND	274 (75–704)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
De Marco et al. (1988) Chromate plant in northern Italy	540 male workers in a chromate plant with a working history ≥1 year in 1948–1985, follow-up through 1985. Median follow-up 23 years; 7456 person-years, 110 deaths.	Categorization of work–time exposure based on work history and estimated exposure by job title based on expert assessment and series of measurements in 1974.	Lung	Time since first exposure for workers with ≥10 years' exposure			SMR based on national rates.	Three persons lost to follow-up, considered alive at the end of the follow-up.Three tumours of pleura, three of larynx.
				10–20 years	2/0.77	260 [31–938]		
				20+ years	7/2.83	247 [99–510]		
Enterline (1974) Reanalysis of Taylor (1966) Three chromate-producing factories in the USA	1212 from 1319 eligible male workers employed for at least one quarter in 1937 and followed for mortality through 1960.	No information on Cr species or level of exposure. Mortality given by follow-up period.	Respiratory (ICD 160–165)	Follow-up period			Not controlled for smoking.	Figures from Enterline (1974) recalculations. Two of the respiratory cancer cases were maxillary sinus carcinomas; greatly in excess of expected.
				1941–1945	16/0.5	2909 (1663–4623)		
				1946–1950	19/1.2	1570 (945–2452)		
				1951–1955	19/2.4	792 (477–1236)		
				1956–1960	15/3.1	475 (266–783)		
				1941–1945	69/7.3	943 (733–1193)		
Davies et al. (1991) Update of Bidstrup (1951); Bidstrup & Case (1956); Alderson et al. (1981) Three chromate-producing factories in Britain	2298 men working at least a year between 1950 and 1976 and followed through 1988. 133 lost to follow-up. 59 319 person-years; 44.3% ≥10 years of employment. Analysis based on certified cause of death and excludes 13 lung cancer cases (10 deaths from other causes, 3 cases not fatal during the follow-up period).	High-lime process until 1950, then changeover to low-lime and no-lime processes. One factory used high-lime process until closure in 1966, one moved to low-lime process in 1957–1959, one used no-lime process since 1961. Exposure category by job title.	Lung	Pre-change, high exposure	151/67.3	245 (207–287)	Expected numbers from national rates adjusted for social class and area; not controlled for smoking.	Four cases of nasal cancer (0.26 expected, SMRA 1538), all four with >20 years of employment. Workers exposed in no-lime process only also had short exposure duration and follow-up.
				Pre-change, low exposure	21/19.7	107 (66–163)		
				Post-change, high exposure	6/6.07	99 (36–215)		
				Post-change, low exposure	4/3.52	114 (31–291)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Satoh et al. (1981) Chromate-producing factory in Tokyo, Japan	796 men who had worked ≥1 year in chromium chemical production in 1918–1975 followed through 1978. 165 eligible workers excluded because of incomplete data.	No information on exposure or process.	Respiratory	Duration of exposure			Not controlled for smoking. Expected figures for 1918–1950 from data for 1950.	25 respiratory cancers include 5 nasal sinus and 1 nasal cavity cancer.
				1–10 years	5/1.181	423 (137–9889)		
				11–20 years	9/1.204	748 (342–1419)		
				21+ years	17/0.973	1747 (1018–2797)		
				All	31/3.358	923 (627–1310)		
Frentzel-Beyme (1983) Three German and two Dutch chromate-producing factories	1821 workers employed for an unspecified time in one of the five factories followed through 1976. Analysis included only German/Dutch nationals with complete work record and follow-up time ≥10 years; altogether 978 workers and 15 076 person-years.	Production of lead and zinc chromates.	Lung	Cohort	19/9.343	203 (122–318)	Not controlled for smoking.	Expected numbers from district rates, apparently corrected for age, sex, calendar period. Follow-up short, 47% of eligible cohort members excluded from analysis.
Deschamps et al. (1995) Follow-up of Haguenoer et al. (1981) Chromate pigment factory in France	294 male workers employed ≥6 months in 1958–1987 with follow-up to 1987. Average follow-up time 18 years. 16 lost to follow-up.	Lead and zinc chromate production. In 1986, Cr(VI) levels in air were 2–3, 6–165, 6–178 and >2000 µg/m^3 in different departments. Time of employment used as surrogate of exposure.	Lung	Duration of exposure			Not controlled for smoking.	For 8/96 deaths cause unknown, SMR = 237.
				5–10 years	1/0.58	172 (84–961)		
				10–15 years	6/0.83	720 (264–1568)		
				15–20 years	4/0.83	481 (131–1231)		
				>20 years	6/1.59	377 (138–821)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Hayes et al. (1989) Update of Sheffet et al. (1982) Chromate pigment factory in New Jersey, USA	1879 male workers employed for ≥1 months between 1940 and 1969 followed through 1982. 142 lost to follow-up; a total of 50 724 person-years. 453 deaths; for 45, death certificate not available.	Ratio of production of lead chromate/zinc chromate approximately 9:1. During later years, estimated airborne chromium >0.5 mg/m^3 for the exposed and >2 mg/m^3 for the highly exposed.	Lung	Duration of exposure to Cr(VI) dust			Not controlled for smoking.	
				None	17/18.48	92 (53–147)		
				<1 year	7/7.51	93 (37–192)		
				1–9 years	9/5.11	176 (80–334)		
				10+ years	8/4.12	194 (83–383)		
Davies (1979) Three chromate pigment factories in England	1152 workers with ≥1 year of employment by 1975 plus 97 workers employed for 3–11 months entering in 1933–1946 followed through 1981. In one factory, immigrants were excluded; in another, they were included.	Exposure to lead and zinc chromate in two factories, lead chromate only in one. Exposure graded as low or high by tasks performed.	Lung	*High and medium lead and zinc chromate exposure*			No control for smoking. Expected figures based on national rates, not corrected for social class.	No increased risk among those with exposure graded as low. One nasal sinus cancer.
				Time since entry 1–10 years	5/1.25	400 (130–940)		
				Time since entry 10–19 years	12/2.9	415 (210–720)		
				Time since entry 20–29 years	12/3.68	326 (170–570)		
				High and medium lead chromate exposure, non-immigrants				
				Time since entry 1–29 years	4/3.09	129 (35–3319)		
				Time since entry >30 years	0/1.31	0 (0–281)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Langård & Vigander (1983) Update of Langård & Norseth (1975) Zinc chromate factory in Norway	133 workers working in the factory in 1948–1972 followed through 1980. No. of workers exposed >3 years 24; no. of workers exposed >5 years, 18.	Exposure stated to be exclusively to zinc chromate.	Lung	Exposure duration >3 years	6/0.135	3636 (1334–79 159)	Not controlled for smoking.	Cancer incidence studied; figures are for SIR, based on national figures. One nasal sinus cancer.
				Exposure duration >5 years	6/0.10	6000 (2202–13 060)		
Kano et al. (1993) Five chromate pigment plants in Japan	666 workers employed ≥1 year in 1950–1975 in one of the plants followed for mortality through 1989. Average follow-up 24 years; total no. of person-years 16 194; 57 deaths. Five lost to follow-up.	Different factories produced lead chromate, molybdate orange, strontium chromate from sodium dichromate and zinc chromate from potassium dichromate and chromic acid. Geometric mean of air measurements in 1976 in different factories 3–19 µg Cr(VI)/m^3.	Lung	Duration of exposure				Ill-defined and unknown causes of death (n = 4) (SMR 635).
				1–10 years	1/1.63	61 (2–340)		
				11–20 years	1/0.83	120 (3–669)		
				≥21 years	1/0.49	204 (5–1137)		
Franchini et al. (1983) Nine chrome plating plants in Parma province, Italy	124 workers employed ≥1 year in 1951–1972 followed through 1982 to provide a minimum of 10 years of latency. Three lost to follow-up; total no. of person-years 2035.	In hard plating, 10 air CrO_3 measurements averaged 7 (range 1–50) µg/m^3 near the baths and 3 (0–12) µg/m^3 in the middle of the room. Based on urinary chromium concentrations, exposure in bright plating was approximately one third of that in hard plating.	Lung	All	3/0.8	375 (77–1096)	Not controlled for smoking.	
				Hard platers	3/0.6	500 (103–1461)		
				Bright platers	0/ND			
Sorahan et al. (1998) Update of Sorahan et al. (1987) Nickel/chromium plating plant in Midlands, England	1762 chromium platers employed for ≥6 months in 1946–1975 followed through 1995. Workers for whom employment record was not found (660), those who had started work before 1946 (31) and those with no chromium plating work (118) excluded from the final cohort. 752 deaths, 69 emigrated and 114 otherwise lost to follow-up.	Decorative chromium plating with exposure to chromic acid mist. Before 1973, 60 air Cr measurements were available, median “below detection or trace”. From 1973, biweekly measurements of every bath, mostly <50 µg/m^3. Workers grouped as chrome bath workers or other.	Lung	Cumulative duration of chrome bath work				Separate cohort from the same factory exposed to nickel but not to chromium showed an increased risk of lung cancer (Pang et al., 1996). Three nasal cancers, 0.3 expected.
				None	13/ND	100		
				<1 years	32/ND	264 (130–538)		
				1–4 years	14/ND	146 (68–310)		
				≥5 years	10/ND	383 (168–874)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Sorahan & Harrington (2000) Update of Royle (1975) 54 chrome plating plants in Yorkshire, England	1087 chrome platers employed for ≥3 consecutive months by end of 1972 and alive at that time were followed through 1997 with a comparison cohort without chromate exposure. 82 were lost to follow-up and 42 had emigrated; 109 had died by end of 1972.	In 1969, surveys indicated exposure to chromic acid <30 µg/m^3 in 40 of the 42 studied plants; in the remaining 2, concentrations exceeded 100 µg/m^3.	Lung	Duration of work in chrome plating			Expected number of deaths from age-, sex-, period-specific mortality figures for Wales and England.	One nasal sinus cancer (0.15 expected).
				3–11 months	11/5.31	207 (103–371)		
				1–4 years	19/8.90	213 (129–333)		
				≥5 years	19/13.49	141 (85–220)		
				Unknown	11/4.75	232 (116–414)		
				Total	60/32.46	185 (141–238)		
Takahashi & Okubo (1990) Update of Okubo & Tsuchiya (1977, 1979, 1984) 415 chrome plating plants in Japan	626 chrome platers employed for ≥6 months in 1970–1976 alive and <35 years of age in September 1976 followed through 1987; 6622.8 person-years.		Lung	Year first exposed			Not controlled for smoking.	Average follow-up for the shortest follow-up group 11 years.
				<1960	4/1.6	256 (70–565)		
				1960–1969	3/1.7	173 (36–506)		
				1970+	1/1.0	102 (3–568)		
				All	8/4.3	187 (81–369)		
Roberti et al. (2006) A company doing bright chrome plating in Venice region, Italy	127 male workers with ≥6 months of employment in 1968–1994 followed (1 worker lost on follow-up) through 2003. 3012 person-years, 20 deaths, 7 from lung cancer.		Lung	Latency time			Age-, sex-, calendar time–adjusted expected rates for Venice region. Not controlled for smoking.	
				<15 years	2/0.82	245 (30–886)		
				≥15 years	5/1.42	351 (114–819)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Silverstein et al. (1981) Die-casting and electroplating company manufacturing parts for auto industry in Midwest USA	Hourly employees and retirees with ≥10 years of credited pension service who died in 1974–1978.		Lung	Duration of service		PMR		Also exposed to fumes from die-casting.
				<15 years	10/6.06	165 [79–303]		
				≥15 years	18/8.62	209 [124–330]		
Dalager et al. (1980) Two aircraft maintenance bases where zinc chromate spray painting and chromium plating were done	White male decedents who had worked as painters or platers for ≥3 months and terminated work within 10 years before 1959, followed through 1977. Median duration of employment 3.9 years, median latency 1.9 years. Death certificates obtained for 90%.		Respiratory	PMR analysis for spray painters	21/11.4	PMR 1.84	Expected numbers for PMR and PCMR analysis from age- and calendar year–adjusted figures for white males in the USA.	48 deaths among platers; no increased risk for all cancer (10 cases); not further analysed.
Alexander et al. (1996) Aerospace workers in Puget Sound region, Washington State, USA	2426 chromate-exposed workers (painters, paint mixers, sanders, polishers, chrome platers) with ≥6 months of employment between 1974 and 1994, followed to end of 1994.	Job–exposure matrix based on measurements in 1974–1994.	Lung	Cumulative chromate(VI) exposure in ($\mu g/m^3$)·years		SIR	Smoking habits not known.	Median age at end of study 42 years, median years of follow-up 8.9 years. 26.3% lost to follow-up.
				<9.8	10/8.2	120 (60–230)		
				9.8–49.2	0/3.5	0 (0–110)		
				49.3–184.7	4/4.4	90 (20–230)		
				>184.7	1/3.3	30 (10–170)		
Boice et al. (1999) Aircraft manufacturing in Burbanks, CA, USA	77 965 workers employed ≥1 year after 1960 followed to end of 1996. Follow-up 99%, death certificates obtained for 98%. 3634 workers exposed to Cr(VI).	Job–exposure matrix based on routine, intermittent or not likely exposure. Cr(VI) exposure from painting and plating activities.	Lung	All workers	1683/ 1912.9	88 (84–92)	Smoking habits not known.	
				Workers exposed to chromate	87/ND	102 (82–126)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Axelsson et al. (1980) Ferrochromium plant in Trollhättan, Sweden	All workers employed for ≥1 year in 1930–1975 followed for mortality 1951–1975 and incidence 1958–1975.		Lung	Length of employment		SMR	Smoking habits not known.	Figures based on county rates.
				≥1 year	5/7.2	69 [23–162]		
				1–4 years	1/1.7	59 [1–328]		
				5–14 years	1/2.3	43 [1–242]		
				≥15 years	3/3.2	94 [19–274]		
Langård et al. (1990) Follow-up of Langård et al. (1980) Ferrochromium and ferrosilicon plant in Hordaland, Norway	Workers employed for ≥1 year in 1928–1960. Cases identified from the cancer registry in 1953–1985.	Workers employed in ferrochromium plant identified from records.	Lung	Follow-up		SIR		Figures based on national rates.
				1953–1977	7/3.10	226 [91–465]		
				1953–1985	10/6.14	163 [78–300]		
Halašová et al. (2005) Residents of district with ferrochromium industry in Slovakia	Cases of diagnosed lung cancer in district hospital 1984–1999.		Lung		Annual incidence			Derivation of denominator for different exposure groups not clear.
				Residents	79.2×10^{-5}			
				Workers not directly exposed	112.5×10^{-5}			
				Workers directly exposed	320.1×10^{-5}			
Moulin et al. (1990) Ferrochromium and steel mill in France	2269 men employed ≥1 year in 1952–1982 followed through 1982. 137 deaths, 37 persons lost to follow-up.	Work histories were used to classify workers as exposed (worked in stainless steel production) and non-exposed.	Lung			SMR	The exposed group smoked slightly less than the non-exposed group.	Figures based on national rates. Exposure in the "exposed" group also to PAHs.
				Exposed	11/5.40	204 (102–364)		
				Non-exposed	1/3.15	32 (1–177)		

Reference(s), location of study	Cohort description	Exposure/exposure assessment	Organ site	Exposure metric	No. of observed/ expected deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Gérin et al. (1993) 135 companies active in welding operations in a multicentre European cohort	Welders with ≥5 years of welding experience and 20 years of latency. 20 lung cancer deaths among predominantly stainless steel welders. Follow-up successful for 96.7% of the total cohort (11 062 welders in nine countries).	Individual welding profile (mild or stainless steel, MMA/MIG/TIG/other) and expert assessment of process-specific Cr(VI) exposure.	Lung	Predominantly stainless steel welders, cumulative exposure in $(mg/m^3)\cdot$years			National reference rates.	
				<0.05	0/0.13	0		
				0.05–0.5	3/1.40	214 (44–626)		
				0.5–1.5	4/1.55	258 (70–661)		
				≥1.5	4/1.02	133 (36–339)		

CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; MIG, metal inert gas; MMA, manual metal arc; ND, no data; PAHs, polycyclic aromatic hydrocarbons; PCMR, proportionate cancer mortality ratio; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SMRA, adjusted standardized mortality ratio; TIG, tungsten inert gas

[a] Figures in square brackets [..] calculated by the working group using Fisher's exact test.

LEAD CHROMATE

ICSC: 0003

Peer-Review Status: 08.06.2012 Validated

Plumbous chromate
Chromic acid, lead (II) salt (1:1)

CAS #: 7758-97-6 RTECS #: GB2975000
UN #: 2291
EC #: 082-004-00-2
EINECS #: 231-846-0

Formula: $PbCrO_4$
Molecular mass: 323.2

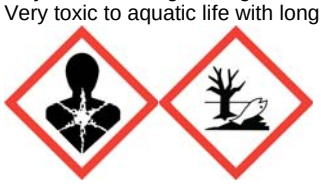
TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION	Risk of fire and explosion on contact with: See Chemical Dangers.	NO contact with incompatible materials: See Chemical Dangers	
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	
Inhalation	Cough.	Use local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves. Protective clothing.	Rinse and then wash skin with water and soap.
Eyes	Redness.	Wear safety goggles or eye protection in combination with breathing protection if powder.	Rinse with plenty of water (remove contact lenses if easily possible).
Ingestion	See Effects of short-term exposure	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink.

SPILLAGE DISPOSAL

Personal protection: particulate filter respirator adapted to the airborne concentration of the substance. Do NOT let this chemical enter the environment. Vacuum spilled material with specialist equipment. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations.

PACKAGING & LABELLING

Unbreakable packaging.
Put breakable packaging into closed unbreakable container.
Do not transport with food and feedstuffs.
EC Classification
Symbol: T, N; R: 45; R: 61-62-33-50/53; S: 53-45-60-61
UN Classification
UN Hazard Class: 6.1; UN Pack Group: III
GHS Classification
Signal: Danger
May cause cancer
May damage fertility or the unborn child if inhaled
May cause damage to organs through prolonged or repeated exposure
Very toxic to aquatic life with long lasting effects



EMERGENCY RESPONSE

SAFE STORAGE

Separated from food and feedstuffs and incompatible materials. See Chemical Dangers. Store in an area without drain or sewer access. Provision to contain effluent from fire extinguishing.

IMPORTANT DATA

Physical State; Appearance
YELLOW-TO-ORANGE-YELLOW CRYSTALLINE POWDER.

Physical dangers

Chemical dangers
Decomposes on heating. This produces toxic fumes including lead oxides.

Routes of exposure
The substance can be absorbed into the body by inhalation of dust and by ingestion.

Inhalation risk
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly on spraying or when dispersed, especially if powdered.

Reacts violently with many substances such as combustible substances, amines, bases and metals. This generates fire and explosion hazard.

Occupational exposure limits
TLV: 0.01mg/m³ as TWA; A1 (confirmed human carcinogen); BEI issued; (ACGIH 2011).
MAK: Carcinogen category: 1; Germ cell mutagen group: 2; (DFG 2011).

Effects of short-term exposure
The substance is irritating to the respiratory tract.

Effects of long-term or repeated exposure
The substance may have effects on the blood, bone marrow, central nervous system, peripheral nervous system, kidneys and lungs. This may result in anaemia, peripheral nerve disease, abdominal cramps and kidney impairment. This substance is carcinogenic to humans. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes
Melting point: 844°C
Density: 6.3 g/cm³
Solubility in water at 25°C: none

ENVIRONMENTAL DATA

Bioaccumulation of this chemical may occur along the food chain. The substance is very toxic to aquatic organisms. It is strongly advised not to let the chemical enter into the environment.

NOTES

Chromates are classified as human carcinogens, but evidence for this substance is limited.
Lead chromate pigments may contain appreciable quantities of water-soluble lead compounds.
Toxic fumes (lead and chromium compounds) are also liberated during welding, cutting and heating of material treated with lead chromate.
Depending on the degree of exposure, periodic medical examination is indicated.
Do NOT take working clothes home.
Lead chromate occurs in nature as the minerals crocoite, phoenicochroite.
NEVER use a domestic-type vacuum cleaner to vacuum the substance, only use specialist equipment.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

ZINC CHROMATE

ICSC: 0811

Peer-Review Status: 08.06.2012 Validated

Chromium zinc oxide
Zinc tetraoxychromate
Chromic acid, zinc salt (1:1)

CAS #: 13530-65-9 RTECS #: GB3290000
UN #: 3288
EC #: 024-007-00-3
EINECS #: 236-878-9

Formula: $ZnCrO_4$
Molecular mass: 181.4

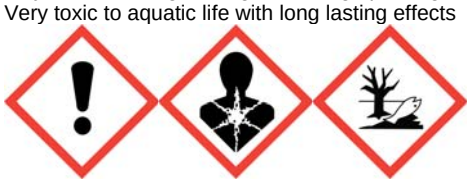
TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION	Risk of explosion on contact with reducing agents or organic materials.	NO contact with incompatible materials: See Chemical Dangers	
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	
Inhalation	Cough. See Effects of long-term or repeated exposure.	Use local exhaust or breathing protection.	Fresh air, rest.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness.	Wear safety goggles or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	See Effects of long-term or repeated exposure.	Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL

Personal protection: particulate filter respirator adapted to the airborne concentration of the substance. Do NOT let this chemical enter the environment. Do NOT absorb in saw-dust or other combustible absorbents. Vacuum spilled material with specialist equipment. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: T, N; R: 45-22-43-50/53; S: 53-45-60-61; Note: A, E
UN Classification
UN Hazard Class: 6.1; UN Pack Group: II
GHS Classification
Signal: Danger
Causes mild skin irritation
May cause an allergic skin reaction
May cause cancer
May damage fertility or the unborn child
May cause damage to organs through prolonged or repeated exposure
Very toxic to aquatic life with long lasting effects



EMERGENCY RESPONSE

SAFE STORAGE

Well closed. Separated from food and feedstuffs, reducing agents and organic compounds. Store in an area without drain or sewer access. Provision to contain effluent from fire extinguishing.

IMPORTANT DATA

Physical State; Appearance
YELLOW CRYSTALLINE POWDER.

Physical dangers

Routes of exposure
The substance can be absorbed into the body by inhalation of dust and by ingestion.

Inhalation risk
Evaporation at 20°C is negligible; a harmful concentration of airborne

Chemical dangers
Decomposes on heating above 440°C . The substance is a strong oxidant. It reacts violently with reducing agents and organic compounds.

Occupational exposure limits
TLV: 0.01mg/m³ as TWA; A1 (confirmed human carcinogen); (ACGIH 2011).
MAK: Carcinogen category: 1; Germ cell mutagen group: 2; Sensitization of skin (SH); (DFG 2011).

particles can, however, be reached quickly when dispersed.

Effects of short-term exposure
The substance is irritating to the eyes, skin and respiratory tract.

Effects of long-term or repeated exposure
The substance may have effects on the blood, bone marrow, central nervous system, peripheral nervous system and kidneys. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. Repeated or prolonged contact may cause skin sensitization. This substance is carcinogenic to humans. May cause toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Melting point: 316°C
Density: 3.4 g/cm³
Solubility in water: none

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. Bioaccumulation of this chemical may occur along the food chain. It is strongly advised not to let the chemical enter into the environment.

NOTES

NEVER use a domestic-type vacuum cleaner to vacuum the substance, only use specialist equipment.
Depending on the degree of exposure, periodic medical examination is suggested.
Do NOT take working clothes home.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

STRONTIUM CHROMATE

ICSC: 0957

Peer-Review Status: 12.04.2013 Validated

C.I. Pigment yellow 32
Chromic acid strontium salt

CAS #: 7789-06-2 RTECS #: GB3240000
UN #: 3288
EC #: 024-009-00-4
EINECS #: 232-142-6

Formula: $SrCrO_4$
Molecular mass: 203.6

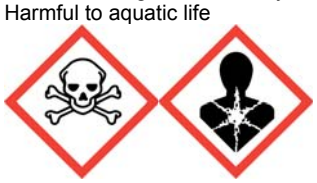
TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible.		In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	
Inhalation	Cough. Sore throat. Wheezing.	Use closed system or ventilation.	Fresh air, rest. Refer for medical attention.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention .
Eyes	Redness.	Wear safety goggles, face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Diarrhoea.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Refer for medical attention .

SPILLAGE DISPOSAL

Personal protection: chemical protection suit including self-contained breathing apparatus. Sweep spilled substance into covered containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: T, N; R: 45-22-50/53; S: 53-45-60-61; Note: E
UN Classification
UN Hazard Class: 6.1; UN Pack Group: II
GHS Classification
Signal: Danger
Harmful if swallowed
Fatal if inhaled
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
Suspected of damaging fertility or the unborn child
Causes damage to the kidneys through prolonged or repeated exposure
Harmful to aquatic life



EMERGENCY RESPONSE

SAFE STORAGE

Separated from food and feedstuffs.

IMPORTANT DATA

Physical State; Appearance
YELLOW CRYSTALLINE POWDER.

Physical dangers

Chemical dangers

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Occupational exposure limits
TLV (as Cr): 0.01mg/m³ as TWA; A1 (confirmed human carcinogen); (ACGIH 2012).
MAK: Carcinogen category: 1; Germ cell mutagen group: 2; Sensitization of skin (SH); (DFG 2012).

Effects of short-term exposure
The substance is irritating to the respiratory tract.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. The substance may have effects on the kidneys. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes
Density: 3.9 g/cm³
Solubility in water, g/100ml at 15°C: 0.12 (poor)

ENVIRONMENTAL DATA

This substance may be hazardous to the environment. Special attention should be given to aquatic organisms. It is strongly advised not to let the chemical enter into the environment because it is persistent.

NOTES

Do NOT take working clothes home.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

CHROMIUM(VI) OXIDE

ICSC: 1194

Peer-Review Status: 12.04.2013 Validated

Chromic trioxide
Chromic acid
Chromic anhydride

CAS #: 1333-82-0 RTECS #: GB6650000
UN #: 1463
EC #: 024-001-00-0
EINECS #: 215-607-8

Formula: CrO_3
Molecular mass: 100.0

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible but enhances combustion of other substances. Many reactions may cause fire or explosion.	NO contact with combustible substances or reducing agents.	NO water. In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Sore throat. Cough. Wheezing. Laboured breathing.	Use closed system or ventilation.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	Remove contaminated clothes. First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Refer for medical attention .
Eyes	Redness. Pain. Blurred vision. Severe burns.	Wear face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Burning sensation. Diarrhoea. Shock or collapse.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Give one or two glasses of water to drink. Do NOT induce vomiting. Refer immediately for medical attention.

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Do NOT let this chemical enter the environment. Sweep spilled substance into sealable containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Do NOT absorb in saw-dust or other combustible absorbents.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: O, T+, N; R: 45-46-9-24/25-26-35-42/43-48/23-62-50/53; S: 53-45-60-61; Note: E
UN Classification
UN Hazard Class: 5.1; UN Subsidiary Risks: 6.1 and 8; UN Pack Group: II
GHS Classification
Signal: Danger
May intensify fire; oxidizer
Toxic if swallowed
Fatal in contact with skin or if inhaled
Causes severe skin burns and eye damage
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
May damage fertility or the unborn child
Causes damage to the kidneys through prolonged or repeated exposure
Causes damage to the nose through prolonged or repeated exposure if inhaled
Very toxic to aquatic life with long lasting effects

EMERGENCY RESPONSE

NFPA Code: H3; F0; R1; OX.

SAFE STORAGE

Provision to contain effluent from fire extinguishing. Separated from combustible substances, reducing agents, bases and food and feedstuffs. Well closed. Store in an area without drain or sewer access.

IMPORTANT DATA

Physical State; Appearance
ODOURLESS DARK RED DELIQUESCENT CRYSTALS, FLAKES OR GRANULAR POWDER.

Physical dangers
No data.

Chemical dangers
Decomposes above 250°C . This produces chromic oxide and oxygen. This increases fire hazard. The substance is a strong oxidant. It reacts violently with combustible and reducing materials. This generates fire and explosion hazard. The solution in water is a strong acid. It reacts violently with bases and is corrosive.

Occupational exposure limits
TLV (as Cr): 0.05mg/m³ as TWA; A1 (confirmed human carcinogen); (ACGIH 2012).
MAK: Carcinogen category: 1; Germ cell mutagen group: 2; Skin absorption (H); Sensitization of skin (SH); (DFG 2012).
EU OEL (selected): SCOEL recommendation available.

Routes of exposure
The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure
The substance is corrosive to the eyes, skin and respiratory tract. Corrosive on ingestion. The substance may cause effects on the kidneys and liver. This may result in tissue lesions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes at 250°C
Melting point: 197°C
Density: 2.7 g/cm³
Solubility in water, g/100ml: 61.7 (good)

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.

NOTES

Do NOT take working clothes home.
Rinse contaminated clothing with plenty of water because of fire hazard.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
Depending on the degree of exposure, periodic medical examination is suggested.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

AMMONIUM DICHROMATE

ICSC: 1368

Peer-Review Status: 12.04.2013 Validated

Diammonium dichromate (VI)
Dichromic acid, diammonium salt
Ammonium bichromate

CAS #: 7789-09-5 RTECS #: HX7650000
UN #: 1439
EC #: 024-003-00-1
EINECS #: 232-143-1

Formula: $(NH_4)_2Cr_2O_7$
Molecular mass: 252.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible but enhances combustion of other substances.	NO contact with combustible substances.	In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION	Risk of fire and explosion on contact with combustible substances.		In case of fire: keep drums, etc., cool by spraying with water. Combat fire from a sheltered position.
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Sore throat. Cough. Wheezing. Laboured breathing.	Use closed system or ventilation.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Refer for medical attention .
Eyes	Redness. Pain. Blurred vision. Severe deep burns.	Wear face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Burning sensation. Diarrhoea. Shock or collapse.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention .

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Sweep spilled substance into covered non-combustible containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Do NOT absorb in saw-dust or other combustible absorbents. Do NOT let this chemical enter the environment.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: E, T+, N; R: 45-46-60-61-2-8-21-25-26-34-42/43-48/23-50/53; S: 53-45-60-61; Note: E, 3
UN Classification
UN Hazard Class: 5.1; UN Pack Group: II
GHS Classification
Signal: Danger
May intensify fire; oxidizer
Toxic if swallowed
Harmful in contact with skin
Fatal if inhaled
Causes severe skin burns and eye damage
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
May damage fertility or the unborn child
Causes damage to kidneys
Causes damage to the nose through prolonged or repeated exposure if inhaled
Very toxic to aquatic life with long lasting effects

EMERGENCY RESPONSE

NFPA Code: H2; F1; R1; OX.

SAFE STORAGE

Fireproof. Provision to contain effluent from fire extinguishing. Separated from organic solvents, combustible substances and reducing agents. Well

	closed. Store in an area without drain or sewer access.

IMPORTANT DATA

Physical State; Appearance
ORANGE-TO-RED CRYSTALS.

Physical dangers

Chemical dangers
May explode on heating. The substance is a strong oxidant. It reacts with combustible and reducing materials. The solution in water is a weak acid. Reacts violently with organic solvents.

Occupational exposure limits
TLV (as Cr): 0.05mg/m³ as TWA; A1 (confirmed human carcinogen); BEI issued; (ACGIH 2012).
MAK (inhalable fraction): Carcinogen category: 1; Germ cell mutagen group: 2; Skin absorption (H); Sensitization of skin (SH); (DFG 2012).
EU OEL:.
EU OEL:.
EU OEL:.
EU OEL (as Cr): SCOEL recommendation available.

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure
The substance is corrosive to the eyes, skin and respiratory tract. Corrosive on ingestion. The substance may cause effects on the kidneys and liver. This may result in tissue lesions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes at 180°C
Density: 2.15 g/cm³
Solubility in water, g/100ml at 20°C: 36 (good)

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.

NOTES

Do NOT take working clothes home.
Rinse contaminated clothing with plenty of water because of fire hazard.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.
Depending on the degree of exposure, periodic medical examination is suggested.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SODIUM DICHROMATE (ANHYDROUS)

ICSC: 1369

Peer-Review Status: 12.04.2013 Validated

Disodium dichromate (VI)
Dichromic acid, disodium salt
Disodium dichromium heptaoxide

CAS #: 10588-01-9 RTECS #: HX7700000
UN #: 3288
EC #: 024-004-00-7
EINECS #: 234-190-3

Formula: $Na_2Cr_2O_7$
Molecular mass: 262

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible but enhances combustion of other substances.	NO contact with combustible substances.	In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION	Risk of fire and explosion on contact with combustible substances.		
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Sore throat. Cough. Wheezing. Laboured breathing.	Use closed system or ventilation.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Refer for medical attention .
Eyes	Redness. Pain. Blurred vision. Severe deep burns.	Wear face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Burning sensation. Diarrhoea. Shock or collapse.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention .

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Sweep spilled substance into covered non-combustible containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Do NOT absorb in saw-dust or other combustible absorbents. Do NOT let this chemical enter the environment.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: T+, N, O; R: 45-46-60-61-8-21-25-26-34-42/43-48/23-50/53; S: 53-45-60-61; Note: E
UN Classification
UN Hazard Class: 6.1; UN Pack Group: II
GHS Classification
Signal: Danger
May intensify fire; oxidizer
Toxic if swallowed
Fatal if inhaled
Harmful in contact with skin
Causes severe skin burns and eye damage
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
May damage fertility or the unborn child
Causes damage to kidneys
Causes damage to the nose through prolonged or repeated exposure if inhaled
Very toxic to aquatic life with long lasting effects

EMERGENCY RESPONSE

NFPA Code: H3; F0; R0; OX.

SAFE STORAGE

Dry. Provision to contain effluent from fire extinguishing. Separated from combustible substances, reducing agents and food and feedstuffs. Well closed. Store in an area without drain or sewer access.

IMPORTANT DATA

Physical State; Appearance
RED-TO-ORANGE HYGROSCOPIC CRYSTALS.

Physical dangers

Chemical dangers
The substance is a strong oxidant. It reacts with combustible and reducing materials. The solution in water is a weak acid.

Occupational exposure limits
TLV (as Cr): 0.05mg/m³ as TWA; A1 (confirmed human carcinogen); BEI issued; (ACGIH 2012).
MAK (inhalable fraction): Carcinogen category: 1; Germ cell mutagen group: 2; Skin absorption (H); Sensitization of skin (SH); (DFG 2012).

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure
The substance is corrosive to the eyes, skin and respiratory tract. Corrosive on ingestion. The substance may cause effects on the kidneys and liver. This may result in tissue lesions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes at 400°C
Melting point: 357°C
Density: 2.5 g/cm³
Solubility in water, g/100ml at 20°C: 236 (very good)

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.

NOTES

Do NOT take working clothes home.
Rinse contaminated clothing with plenty of water because of fire hazard.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SODIUM CHROMATE

ICSC: 1370

Peer-Review Status: 12.04.2013 Validated

Disodium chromate (VI)
Chromic acid, disodium salt
Disodium chromium tetraoxide

CAS #: 7775-11-3 RTECS #: GB2955000
UN #: 3288
EC #: 024-018-00-3
EINECS #: 231-889-5

Formula: Na_2CrO_4
Molecular mass: 162

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible but enhances combustion of other substances.	NO contact with combustible substances.	In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Sore throat. Cough. Wheezing. Laboured breathing.	Use closed system or ventilation.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Refer for medical attention .
Eyes	Redness. Pain. Blurred vision. Severe deep burns.	Wear face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Burning sensation. Diarrhoea. Shock or collapse.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention .

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Sweep spilled substance into covered containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Do NOT let this chemical enter the environment.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: T+, N; R: 45-46-60-61-21-25-26-34-42/43-48/23-50/53; S: 53-45-60-61; Note: E, 3
UN Classification
UN Hazard Class: 6.1; UN Pack Group: II
GHS Classification
Signal: Danger
May intensify fire; oxidizer
Toxic if swallowed
Harmful in contact with skin
Fatal if inhaled
Causes severe skin burns and eye damage
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
May damage fertility or the unborn child
Causes damage to kidneys
Causes damage to the nose through prolonged or repeated exposure if inhaled
Very toxic to aquatic life with long lasting effects

EMERGENCY RESPONSE

SAFE STORAGE

Provision to contain effluent from fire extinguishing. Separated from combustible substances, reducing agents and food and feedstuffs. Dry. Well closed. Store in an area without drain or sewer access.

IMPORTANT DATA

Physical State; Appearance
YELLOW HYGROSCOPIC CRYSTALS.

Physical dangers

Chemical dangers
The solution in water is a weak base. The substance is a strong oxidant. It reacts with combustible and reducing materials.

Occupational exposure limits
TLV (as Cr): 0.05mg/m³ as TWA; A1 (confirmed human carcinogen); BEI issued; (ACGIH 2012).
MAK (inhalable fraction): Carcinogen category: 1; Germ cell mutagen group: 2; Skin absorption (H); Sensitization of skin (SH); (DFG 2012).

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure
The substance is corrosive to the eyes, skin and respiratory tract. Corrosive on ingestion. The substance may cause effects on the kidneys and liver. This may result in tissue lesions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Melting point: 762°C
Density: 2.7 g/cm³
Solubility in water, g/100ml at 20°C: 53 (good)

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.

NOTES

Do NOT take working clothes home.
Rinse contaminated clothing with plenty of water because of fire hazard.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.
The recommendations on this Card also apply to sodium chromate tetrahydrate (CAS No. 10034-82-9).

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

POTASSIUM DICHROMATE

ICSC: 1371

Peer-Review Status: 12.04.2013 Validated

Dipotassium dichromate (VI)
Dichromic acid, dipotassium salt
Potassium bichromate

CAS #: 7778-50-9 RTECS #: HX7680000
UN #: 3288
EC #: 024-002-00-6
EINECS #: 231-906-6

Formula: $K_2Cr_2O_7$
Molecular mass: 294.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible but enhances combustion of other substances.	NO contact with combustible substances.	In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION	Risk of fire and explosion on contact with combustible substances.		
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Sore throat. Cough. Wheezing. Laboured breathing.	Use closed system or ventilation.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Refer for medical attention .
Eyes	Redness. Pain. Blurred vision. Severe deep burns.	Wear face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Nausea. Vomiting. Abdominal pain. Burning sensation. Diarrhoea. Shock or collapse.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention .

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Sweep spilled substance into covered non-combustible containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Do NOT absorb in saw-dust or other combustible absorbents. Do NOT let this chemical enter the environment.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification
Symbol: T+, N, O; R: 45-46-60-61-8-21-25-26-34-42/43-48/23-50/53; S: 53-45-60-61; Note: E, 3
UN Classification
UN Hazard Class: 6.1; UN Pack Group: II
GHS Classification
Signal: Danger
May intensify fire; oxidizer
Toxic if swallowed
Harmful in contact with skin
Fatal if inhaled
Causes severe skin burns and eye damage
May cause allergy or asthma symptoms or breathing difficulties if inhaled
May cause an allergic skin reaction
May cause genetic defects
May cause cancer
May damage fertility or the unborn child
Causes damage to kidneys
Causes damage to the nose through prolonged or repeated exposure if inhaled
Very toxic to aquatic life with long lasting effects

EMERGENCY RESPONSE

SAFE STORAGE

Provision to contain effluent from fire extinguishing. Separated from combustible substances, reducing agents and food and feedstuffs. Well closed. Store in an area without drain or sewer access.

IMPORTANT DATA

Physical State; Appearance
ORANGE-TO-RED CRYSTALS.

Physical dangers

Chemical dangers
The substance is a strong oxidant. It reacts with combustible and reducing materials. The solution in water is a weak acid.

Occupational exposure limits
TLV (as Cr): 0.05mg/m³ as TWA; A1 (confirmed human carcinogen); BEI issued; (ACGIH 2012).
MAK (inhalable fraction): Carcinogen category: 1; Germ cell mutagen group: 2; Skin absorption (H); Sensitization of skin (SH); (DFG 2012).
EU OEL (selected): SCOEL recommendation available.

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure
The substance is corrosive to the eyes, skin and respiratory tract. Corrosive on ingestion. The substance may cause effects on the kidneys and liver. This may result in tissue lesions.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes at 500°C
Melting point: 398°C
Density: 2.7 g/cm³
Solubility in water, g/100ml at 20°C: 12 (moderate)

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.

NOTES

Do NOT take working clothes home.
Rinse contaminated clothing with plenty of water because of fire hazard.
Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.
The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

BARIUM CHROMATE

ICSC: 1607

Peer-Review Status: 05.04.2006 Validated

Barium chromate (VI)
Barium chromate (1:1)
Chromic acid, barium salt 1:1
C.I. 77103
C.I. Pigment Yellow 31

CAS #: 10294-40-3 RTECS #: CQ8760000
EINECS #: 233-660-5

Formula: $BaCrO_4$
Molecular mass: 253.3

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE-FIGHTING
FIRE	Not combustible.		In case of fire in the surroundings, use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!**	
Inhalation	Cough. Sore throat.	Use local exhaust or breathing protection.	Fresh air, rest.
Skin	Redness.	Protective gloves. Protective clothing.	Rinse and then wash skin with water and soap.
Eyes	Redness. Pain.	Wear safety goggles.	Rinse with plenty of water for several minutes (remove contact lenses if easily possible).
Ingestion	Burning sensation.	Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL

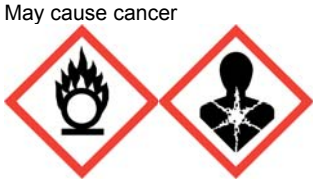
Personal protection: particulate filter respirator adapted to the airborne concentration of the substance. Sweep spilled substance into covered containers. If appropriate, moisten first to prevent dusting. Then store and dispose of according to local regulations.

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EC Classification

UN Classification

GHS Classification
Signal: Danger
May intensify fire; oxidizer
Causes damage to the nose through prolonged or repeated exposure if inhaled
May cause cancer



EMERGENCY RESPONSE

SAFE STORAGE

Separated from strong reducing agents and food and feedstuffs.

IMPORTANT DATA

Physical State; Appearance
YELLOW CRYSTALS.

Physical dangers

Chemical dangers
Reacts with reducing agents.

Occupational exposure limits
TLV: 0.01mg/m³ as TWA; A1 (confirmed human carcinogen); (ACGIH 2006).

Routes of exposure
The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

Inhalation risk
A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

Effects of short-term exposure
The substance is irritating to the eyes, skin and respiratory tract.

Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation may cause asthma. Repeated or prolonged inhalation may cause nasal ulceration. This may result in perforation of the nasal septum. The substance may have effects on the kidneys. This may result in kidney impairment. This substance is carcinogenic to humans.

PHYSICAL PROPERTIES

Melting point: 1380°C
Density: 4.5 g/cm³
Solubility in water, g/100ml at 20°C: 0.00026 (none)

ENVIRONMENTAL DATA

NOTES

Do NOT take working clothes home.
Card has been partially updated in January 2008: see GHS classification.

ADDITIONAL INFORMATION

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

RÉSUMÉ D'ORIENTATION

Le présent CICAD (Concise International Chemical Assessment Document / Document concis d'évaluation chimique internationale)[1] relatif aux composés minéraux du chrome (VI) s'inspire pour l'essentiel d'un document de l'Agency for Toxic Substances and Disease Registry des États-Unis intitulé *Profil toxicologique du chrome* (ATSDR, 2000) qui a été mis à jour afin de prendre en compte les informations figurant dans la première version d'un profil toxicologique actualisé que l'ATSDR avait publié en vue de recueilllir les observations du public (ATSDR, 2008)[2]. Des informations sur l'examen par des pairs et la disponibilité des sources bibliographiques sont données à l'appendice 2. Le Secrétariat a effectué des recherches bibliographiques remontant jusqu'à décembre 2008 en vue de repérer toute référence relative à la santé humaine qui aurait été publiée postérieurement à celles qui sont prises en compte dans les documents de base. On a également consulté un document préparé par l'United States Environmental Protection Agency et intitulé *Toxological review of hexavalent chromium (CAS No. 18540-29-9) in support of summary information on the Integrated Risk Information System (IRIS)* (USEPA, 1998). Les sections 10 (Effets sur les autres organismes au laboratoire et dans leur milieu naturel) et 11.2 (Évaluation des effets environnementaux) s'appuient sur un rapport d'évaluation des risques préparé par l'Union européenne (UE) et portant sur le trioxyde de chrome, le chromate et le bichromate de sodium, le bichromate d'ammonium et le bichromate de potassium (UE, 2005). Des renseignements sur la nature et la disponibilité des documents de l'USEPA (1998) et de l'UE (2005) figurent également à l'appendice 2. Des informations sur l'examen par des pairs du présent CICAD sont données à l'appendice 3. Un premier examen de ce CICAD en tant qu'évaluation internationale a été effectué lors de la réunion du Comité d'évaluation finale qui s'est tenue à Helsinki (Finlande) du 26 au 29 mars 2007. La liste des participants à cette réunion figure à l'appendice 4. À la suite de la décision de mettre à jour la section consacrée à la cancérogénicité, la version préliminaire du CICAD a été communiquée à un groupe consultatif de l'Organisation mondiale de la Santé (OMS), qui s'est réuni à l'Université de Bradford (Angleterre) les 1er et 2 novembre 2010. L'appendice 5 donne la liste des participants à ce groupe consultatif. Une fois modifiée par le groupe consultatif, cette version préliminaire du CICAD a été rendue publique sur le site Internet du Programme international sur la Sécurité chimique (IPCS/PISC) et soumise à un examen par des pairs. À la suite de cet examen, le Secrétariat a procédé à la révision du document. Il a décidé de maintenir à décembre 2008 la date des dernières données bibliographiques à prendre en considération dans le CICAD. Les membres du Comité d'évaluation finale ont approuvé le CICAD en tant qu'évaluation internationale au cours de la période allant de juin à octobre 2012 (par courrier). Des précisions au sujet des membres du Comité d'évaluation finale qui ont participé à cet exercice sont données à l'appendice 6. Les fiches internationales sur la sécurité chimique du chromate de plomb (ICSC 0003), du chromate de zinc (ICSC 0811), du chromate de strontium (ICSC 0957), de l'oxyde de chrome (VI) (ICSC 1194), du bichromate d'ammonium (ICSC 1368), du bichromate de sodium (anhydre) (ICSC 1369), du chromate de sodium (ICSC 1370), du bichromate de potassium (ICSC 1371) et du chromate de baryum (ICSC 1607), établies par l'OMS en collaboration avec l'Organisation internationale du travail, sont également reproduites dans le présent document.

Le chrome est présent à l'état naturel dans les roches, le sol, chez les animaux et les végétaux ainsi que dans les poussières et les gaz volcaniques. Les formes les plus stables sont le chrome métallique (0), le chrome trivalent ou chrome (III) et le chrome hexavalent ou chrome (VI).

Le présent CICAD est consacré au chrome (VI) mais d'autres états d'oxydation peuvent être mentionnés au sujet de la spéciation du chrome dans l'environnement ou l'organisme, dont la connaissance est essentielle pour comprendre le mode d'action. Un CICAD distinct consacré aux composés minéraux du chrome (III) a été publié (CICAD 76; IPCS, 2009).

Les dérivés du chrome (VI) produits par l'industrie chimique ont des applications très diverses, notamment pour le chromage, la fabrication de teintures et de pigments, d'agents de protection du bois, de revêtements de surface et d'inhibiteurs de corrosion.

Du chrome est libéré dans l'atmosphère, non seulement à partir de sources anthropogéniques (utilisation de combustibles, métallurgie), mais aussi à partir de sources naturelles, comme les feux de forêt, par exemple. Dans l'atmosphère, le chrome est principalement présent sous la forme de particules.

Du chrome (VI) peut être présent dans les effluents domestiques ou industriels qui sont déchargés dans les eaux de surface. En présence d'une grande quantité de matières organiques, le chrome (VI) peut être réduit en chrome (III) qui sera ensuite adsorbé à la surface des

[1] La liste complète des acronymes et abréviations utilisés dans le présent rapport se trouve à l'appendice 1.

[2] Pendant que l'on préparait le présent CICAD en vue de sa publication, la mise à jour du *Profil toxicologique du chrome* a été rédigée sous sa forme définitive et publiée par l'ATSDR en 2012. Toutes les informations tirées des documents de l'ATSDR (2000, 2008) ont été vérifiées par rapport à la version définitive de ce profil toxicologique.

particules. La réduction du chrome (VI) en chrome (III) est un processus rapide dans les conditions réductrices et anaérobies qui règnent généralement dans les eaux souterraines profondes. La majeure partie du chrome déchargé dans l'eau va finir par se déposer dans les sédiments.

Dans le sol, le chrome est essentiellement présent sous forme d'oxyde insoluble et sa mobilité est réduite. On constate que le chrome (VI) est beaucoup moins fortement adsorbé sur les sols que le chrome (III). Dans le sol, la mobilité du chrome soluble va dépendre des caractéristiques de sorption de ce sol. Les organismes vivants (plantes et animaux) absorbent le chrome (VI) plus volontiers que le chrome (III), mais une fois absorbé, le chrome (VI) est réduit en chrome (III), plus stable.

Le facteur de bioconcentration du chrome (VI) dans les poissons d'eau douce est faible, autour de 1, car dans l'organisme, le chrome (VI) est réduit en chrome (III) ce qui entraîne une accumulation de chrome total dans une proportion qui représente environ 100 fois la concentration dans l'eau.

Dans les zones reculées, la concentration atmosphérique du chrome total va de 0,005 à 2,6 ng/m^3, avec une valeur habituellement égale à moins de 10 ng/m^3 en milieu rural et comprise entre 10 et 30 ng/m^3 en milieu urbain. On a fait état de concentrations plus élevées (> 500 ng/m^3) au voisinage de sources anthropogéniques de chrome. Aux États-Unis d'Amérique, la concentration en chrome total dans les cours d'eau est généralement comprise entre moins de 1 et 30 µg/l, avec une valeur médiane de 10 µg/l. En Europe, on indique une concentration médiane en chrome total de 0,38 µg/l (<0,01 - 43,3 µg/l) dans les eaux de surface. Dans l'eau des lacs, la concentration en chrome total ne dépasse généralement pas 5 µg/l. Des concentrations moyennes en chrome (VI) allant jusqu'à 3 µg/l ont été relevées dans les eaux de surface. La présence de teneurs élevées en chrome – pouvant atteindre 648 µg de chrome (VI) par litre dans des effluents industriels – peut être attribuée à une pollution par des sources anthropogéniques.

La concentration du chrome dans les eaux océaniques est généralement beaucoup plus faible que dans les lacs ou les cours d'eau. En effet, la concentration moyenne en chrome total dans les eaux océaniques est de 0,3 µg/l, avec une fourchette de 0,2 à 50 µg/l. Dans les étendues d'eau, on a constaté que les matières en suspension et les sédiments présentaient des teneurs en chrome total allant de 1 à 500 mg/kg. Dans le sol, la concentration en chrome total est très variable et dépend de la composition des roches à partir desquelles tel ou tel sol s'est formé. En Amérique du Nord, les relevés de concentration du chrome total dans le sol et autres matériaux de surface donnent une fourchette de 1 à 2000 mg/kg, avec une moyenne géométrique d'environ 40 mg/kg. En Europe, la concentration médiane du chrome dans la couche superficielle du sol s'est révélée égale à 60 mg/kg (< 3 - 6230 mg/kg) après extraction à l'acide fluorhydrique et à 22 mg/kg (< 1 - 2340 mg/kg) après extraction à l'acide nitrique. Des valeurs plus élevées ont été observées sur des sites contaminés.

L'exposition de la population générale trouve son origine dans l'inhalation de l'air ambiant et dans l'ingestion d'aliments et d'eau contenant du chrome. L'exposition cutanée de cette même population au chrome peut provenir d'un contact de la peau avec certains produits de consommation.

C'est sur les concentrations du chrome dans l'air ambiant (< 0,01- 0,03 µg/m^3) et dans l'eau du robinet (< 2 µg/l) que l'on s'est basé pour estimer l'apport journalier de chrome par l'air inhalé (< 0,2 - 0,6 µg) et par l'eau du robinet (< 4 µg). La teneur en chrome des aliments varie dans d'importantes proportions. L'exposition cutanée journalière des travailleurs qui procèdent à l'emballage de produits contenant des chromates ou de ceux qui pèsent les ingrédients secs et les chargent dans des mélangeurs pour la fabrication de pigments à base de chrome (VI) est respectivement estimée à 0 - 0,1 et 0,1 - 1 mg/cm^2.

Autrefois, les travailleurs des industries produisant ou utilisant du chrome étaient exposés à des concentrations de chrome beaucoup plus élevées que ce n'est le cas actuellement; dans beaucoup de ces industries, l'exposition était de l'ordre de plusieurs centaines de microgrammes par mètre cube. Dans les installations modernes, l'exposition est habituellement inférieure à 20 µg/m^3.

La toxicocinétique d'un composé donné du chrome dépend de l'état d'oxydation de l'atome de chrome et de la nature de ses ligands. Les dérivés du chrome (VI) sont davantage absorbés que ceux du chrome (III) et ce, quelle que soit la voie d'exposition. Cela tient au fait que l'anion chromate peut pénétrer dans les cellules en empruntant les canaux anioniques de la membrane cellulaire, alors que la l'absorption des dérivés du chrome (III) s'effectue par diffusion passive et phagocytose. Une fois inhalés, les composés du chrome sont absorbés soit au niveau du poumon par passage à travers la membrane cellulaire, soit au niveau des voies digestives à partir des particules évacuées par les poumons. Chez l'être humain, l'absorption consécutive à une exposition par voie orale est d'environ 2 à 8 % dans le cas du chrome (VI) sous forme de chromate ou de bichromate. Après exposition au chrome (VI) par voie orale, l'absorption diminue par suite de la réduction en chrome (III) sous l'effet de l'acidité gastrique.

Une fois passés dans le sang, les composés du chrome se répartissent dans l'ensemble des organes. Après une exposition professionnelle, des particules contenant du chrome peuvent être retenues pendant des années au niveau pulmonaire. Dans l'organisme, le chrome (VI) est instable et il est successivement réduit en chrome (V), en chrome (IV) puis finalement en chrome (III) par de nombreuses substances, notamment l'acide ascorbique et le glutathion. On pense que la toxicité des composés du chrome (VI) s'explique par les dommages causés aux constituants cellulaires au cours de ce processus (par ex. en raison de la production de radicaux libres). Il y a également possibilité d'une interaction avec l'acide désoxyribonucléique (ADN) entraînant des dommages structuraux.

Une fois absorbé, le chrome est principalement excrété dans l'urine avec une demi-vie d'excrétion que l'on estime à environ 40 h après absorption par voie orale chez l'Homme. Les cheveux et les ongles constituent des voies d'excrétion secondaires.

Chez des animaux exposés par voie orale à de très fortes doses de dérivés du chrome (VI), on a observé des effets gastrointestinaux, hépatiques, rénaux, immunologiques, hématologiques, neurologiques, développementaux et reprotoxiques. L'exposition d'animaux à des dérivés du chrome (VI) par contact avec la peau a provoqué des ulcères cutanés et une réaction allergique.

Au nombre des effets observés chez des rats et des souris exposés par voie orale pendant 13 semaines ou 2 ans à une eau de boisson contenant du chrome (VI) figuraient une anémie passagère, des lésions de la cavité buccale et des intestins, une inflammation du foie, des ganglions lymphatiques et du pancréas ainsi que des tumeurs de la cavité buccale chez les rats et de l'intestin grêle chez les souris.

Chez l'Homme, de graves effets respiratoires, cardiovasculaires, hématologiques, hépatiques, rénaux et neurologiques ont été observés à la suite de l'ingestion accidentelle ou intentionnelle de fortes doses de composés du chrome (VI).

Chez des sujets humains exposés de par leur profession à des composés du chrome (VI) sous forme aéroportée, on peut avoir des effets au niveau des voies respiratoires ainsi qu'une irritation des yeux; ces effets peuvent conduire à une ulcération et à une perforation de la cloison nasale et se traduire également par une incidence accrue de cancers des voies respiratoires. L'exposition à des composés du chrome (VI) peut également provoquer de l'asthme.

Il existe une relation de cause à effet entre l'exposition au chrome (VI) par inhalation et l'augmentation de l'incidence des cancers pulmonaires. Plusieurs études révèlent également qu'il y a un lien entre l'exposition au chrome (VI) et les cancers des fosses nasales et des sinus paranasaux. On ne possède en revanche que des données très limitées concernant l'existence d'un lien entre certains cancers chez l'Homme et la présence de chrome (VI) dans l'eau de boisson. L'exposition d'animaux de laboratoire à du chrome (VI) soit par inhalation, soit par administration intrabuccale ou intratrachéale a provoqué des cancers chez ces animaux.

Une exposition professionnelle par contact cutané peut provoquer une ulcération profonde de la peau. Le chrome (VI) est une cause fréquente de dermatite allergique de contact qui peut conduire à une invalidité importante et prolongée.

On a observé des aberrations chromosomiques et des lésions de l'ADN chez certains sujets humains professionnellement exposés à des dérivés du chrome (VI). Des tests effectués *in vivo* et *in vitro* montrent que le chrome (VI) est également génotoxique.

On a obtenu une valeur de 0,005 µg de chrome (VI) par mètre cube pour la concentration tolérable de trioxyde de chrome/acide chromique en se basant sur la concentration la plus faible provoquant un effet observable (LOAEC), qui est égale chez l'Homme à 2 µg de chrome (VI) par mètre cube dans le cas d'effets sur les voies respiratoires supérieures à l'exclusion du cancer.

Pour ce qui est des effets sur les voies respiratoires à l'exclusion du cancer, on a obtenu une concentration tolérable de 0,03 µg de chrome (VI) par mètre cube dans le cas d'une exposition par inhalation à des sels de chrome (VI) en procédant à une analyse comparative basée sur la dose repère (BMD) qui provoque l'augmentation de l'activité de la lactate-déshydrogénase dans le liquide de lavage alvéolaire de rats exposés à ces composés, ce paramètre étant utilisé comme indicateur de la présence de lésions pulmonaires. Cette valeur de la dose tolérable est corroborée par l'observation de cas d'irritation nasale chez des travailleurs employés à la production de chromate.

En se basant sur l'hyperplasie épithéliale diffuse du duodénum observée chez des souris femelles après exposition à du bichromate de sodium dihydraté dissous dans leur eau de boisson, on a obtenu la valeur de 0.9 µg de chrome (VI) par kg de poids corporel pour la dose journalière tolérable dans le cas d'effets non cancérogènes. Pour ce calcul, on a utilisé la limite inférieure de l'intervalle de confiance de la dose repère correspondant à une réponse de 10 % ($BMDL_{10}$) qui est égale à 0,094 mg/kg de poids corporel par jour et on a appliqué un facteur d'incertitude de 100.

L'excès de risque cumulé de cancer du poumon sur toute la durée de la vie par suite d'une exposition professionnelle à une dose de 1 µg de chrome (VI) par mètre cube est égal à 6×10^{-3}, cette détermination étant basée sur l'étude épidémiologique donnant la meilleure information sur l'exposition des travailleurs employés à la production de chromate. Pour cette estimation, on a supposé que l'activité professionnelle commençait à l'âge de 20 ans avec les conditions de travail suivantes : 8 heures par jour, 5 jours par semaine, pendant une durée de 45 ans. En ce qui concerne le risque de cancer du poumon sur toute la durée de la vie consécutif à une exposition environnementale à une concentration de 0,001 µg de chrome (VI) par mètre cube (24 h/jour, 365 jours/an, sur une durée de 70 ans), on arrive à un chiffre de 4×10^{-5}.

Après exposition à du bichromate de sodium présent dans de l'eau de boisson, on a constaté une augmentation de l'incidence des tumeurs bénignes et malignes de la cavité buccale chez des rats et de l'intestin grêle chez des souris. S'agissant du lien entre risque cancérogène et exposition humaine au chrome (VI) par voie orale, il existe une incertitude importante.

Il existe des données écotoxicologiques à court et à long terme sur les effets des composés du chrome (VI) pour une large gamme d'organismes, de stades du cycle évolutif, de paramètres biologiques et de conditions expérimentales. D'une façon générale, la toxicité du chrome (VI) augmente lorsqu'il y a diminution du pH (en l'occurrence de 8,0 à 6,0), augmentation de la température (en l'occurrence de 15 à 25 °C) et diminution de la dureté ou de la salinité de l'eau. Lorsque on étudie des organismes vivant habituellement en eau salée dans de l'eau de faible salinité (< 2 pour mille) leur sensibilité se révèle comparable à celle des organismes dulçaquicoles.

La concentration prédite sans effet (PNEC) pour les organismes dulçaquicoles calculée sur la base de la limite inférieure de confiance à 95 % de la concentration dangereuse pour la protection de 95 % des espèces ($5^{\text{ième}}$ percentile de la sensibilité des espèces), à savoir la HC_5-95 %, est égale à 4 µg/l. Dans l'eau salée, le chrome (VI) devrait être moins toxique, sauf peut-être lorsque la salinité est très faible.

La plupart des étendues d'eau naturelles présentent des teneurs en chrome total plus faibles que la PNEC pour les eaux douces; même lorsque la PNEC est dépassée, les valeurs qui sont données représentent le chrome total et il est probable que la biodisponibilité du chrome naturel serait très faible. Toutefois, de plus fortes teneurs en chrome et plus particulièrement en chrome (III) et en chrome (VI) ont été relevées à proximité de points d'émissions anthropogéniques. Ainsi, dans un rayon de 80 m autour d'une tannerie désaffectée, on a relevé une concentration de chrome (VI) libre égale à 63 µg/l dans un cours d'eau. Le risque pour les organismes aquatiques en général est donc faible, mais ces organismes sont néanmoins exposés au risque au voisinage de certains points où se produisent des rejets anthropogéniques de chrome (VI). Les résultats des tests toxicologiques ont tendance à indiquer que les organismes marins ne sont pas plus sensibles que les organismes dulçaquicoles. Cela donne à penser que la valeur de 4 µg/l obtenue pour la PNEC dans le cas des espèces d'eau douce devrait également assurer la protection des espèces marines. La conclusion à laquelle on est parvenu au sujet des organismes dulçaquicoles (à savoir que le chrome (VI) ne devrait pas représenter un risque pour ces organismes en l'absence de sources locales de pollution) vaut donc également pour les organismes marins.

Faute de données plus abondantes au sujet de la disponibilité du chrome dans les sols, il est difficile d'évaluer le risque que le chrome (VI) représente pour les organismes terricoles.

RESUMEN DE ORIENTACIÓN

Este Documento abreviado de evaluación internacional de productos químicos (CICAD)[1] sobre compuestos inorgánicos de cromo(VI) se basó principalmente en el *Perfil toxicológico del cromo*, preparado por la Agencia para el Registro de Sustancias Tóxicas y Enfermedades (ATSDR, 2000), de los Estados Unidos, y posteriormente actualizado para incluir la información que figuraba en un borrador de puesta al día del Perfil que dicha Agencia dio a conocer para que el público hiciera observaciones[2] (ATSDR, 2008). La información sobre el carácter del examen pericial y la disponibilidad de los documentos originales se presenta en el Apéndice 2. La Secretaría efectuó una búsqueda bibliográfica, con fecha límite en diciembre de 2008, para identificar cualquier referencia sobre salud humana que hubiera sido publicada con posterioridad a las que figuran en los documentos originales. También se consultó el *Examen toxicológico del cromo hexavalente (CAS No. 18540-29-9) en apoyo al resumen del Sistema Integrado de Información sobre Riesgos (IRIS)*, preparado por la Agencia de Protección Ambiental de Estados Unidos (USEPA, 1998). Los apartados 10 (Efectos sobre otros organismos en el laboratorio y sobre el terreno) y 11.2 (Evaluación de los efectos sobre el medio ambiente) se basan en el Informe de evaluación del riesgo para la salud del trióxido de cromo, cromato de sodio, dicromato de sodio, dicromato de amonio y dicromato de potasio, de la Unión Europea (UE, 2005). Los detalles sobre el carácter y la disponibilidad de los documentos de la USEPA (1998) y la UE (2005) también se proporcionan en el Apéndice 2. La información sobre el examen pericial de este CICAD se presenta en el Apéndice 3. Este CICAD se examinó por primera vez, en tanto que documento de evaluación internacional, en una reunión de la Junta de Evaluación Final, celebrada en Helsinki (Finlandia) del 26 al 29 de marzo de 2007. La lista de participantes en dicha reunión aparece en el Apéndice 4. Tras tomar la decisión de actualizar el apartado sobre carcinogenia, el borrador del CICAD se remitió a un Grupo Consultivo de la Organización Mundial de la Salud (OMS), que se reunió en la Universidad de Bradford (Bradford, Inglaterra) del 1 al 2 de noviembre de 2010. Los participantes en la reunión del Grupo Consultivo se enumeran en el Apéndice 5. Después de la reunión del Grupo Consultivo, el borrador del documento modificado se publicó en el sitio web del Programa Internacional de Seguridad de las Sustancias Químicas (IPCS) para que el público y los expertos lo examinaran. La Secretaría revisó el borrador del documento después de que lo examinaran los expertos y tomó la decisión de mantener la fecha de finales de 2008 como fecha final para la inclusión de datos en este CICAD. El CICAD fue aprobado como documento de evaluación internacional por los miembros de la Junta de Evaluación Final (por correspondencia) entre junio y octubre de 2012. Los detalles sobre los miembros de la Junta de Evaluación Final que participaron en este proceso se presentan en el Apéndice 6. También se han reproducido en este documento las Fichas internacionales de seguridad química sobre el cromato de plomo (ICSC 0003), el cromato de cinc (ICSC 0811), el cromato de estroncio (ICSC 0957), el óxido de cromo(VI) (ICSC 1194), el dicromato de amonio (ICSC 1368), el dicromato de sodio (anhidro) (ICSC 1369), el cromato de sodio (ICSC 1370), el dicromato de potasio (ICSC 1371) y el cromato de bario (ICSC 1607), elaboradas por la OMS en colaboración con la Organización Internacional del Trabajo.

El cromo es un elemento natural, que se encuentra en rocas, suelos, animales, plantas y cenizas y gases volcánicos. Las formas más estables son el cromo metálico, o «cromo(0)», el cromo trivalente, o «cromo(III)», y el cromo hexavalente, o «cromo(VI)».

Aunque este CICAD se centra en el cromo(VI), también se refiere a otros estados de valencia cuando se trata de la especiación en el mebio ambiente y dentro del organismo, que es esencial para comprender el modo de acción. Se ha publicado un CICAD separado (CICAD 76; IPCS, 2009) sobre compuestos inorgánicos de cromo(III).

Los compuestos de cromo(VI) producidos por la industria química tienen una gran variedad de aplicaciones, como el cromado, la fabricación de colorantes y pigmentos, conservantes de madera, recubrimientos de superficies y anticorrosivos.

El cromo es emitido al aire por fuentes antropógenas (p. ej., debido a la combustión de materiales o procedente de industrias metalúrgicas) y también por fuentes naturales, como los incendios forestales, y está presente en la atmósfera principalmente en forma de partículas.

Los efluentes domésticos e industriales que contienen cromo(VI) se vierten en las aguas superficiales. El cromo(VI) puede reducirse a cromo(III) y luego adsorberse a partículas en presencia de una gran cantidad de materia orgánica. La reducción de cromo(VI) a cromo(III) ocurre rápidamente en las

[1] En el Apéndice I, se proporciona una lista completa de los acrónimos y las abreviaturas que se utilizaron en este documento.

[2] Durante la preparación de este CICAD para publicación, la ATSDR finalizó el Perfil toxicológico actualizado del cromo y lo publicó en 2012. Toda la información procedente de la ATSDR (2000, 2008) fue cotejada con la versión final de 2012 del perfil toxicológico.

condiciones anaerobias y reductoras que suelen existir en las aguas freáticas más profundas. Con el tiempo, la mayor parte del cromo que se libera en el agua acabará depositándose en el sedimento.

El cromo está presente en el suelo fundamentalmente como óxido insoluble y su movilidad es baja. Aparentemente, el cromo(VI) se adsorbe menos a los suelos que el cromo(III). La movilidad del cromo soluble en el suelo dependerá de las características de sorción de dicho suelo. Las plantas y los animales vivos absorben mejor la forma hexavalente que la trivalente, pero, una vez absorbida, la forma hexavalente se reduce al estado trivalente, que es más estable.

Los factores de bioconcentración del cromo(VI) en los peces de agua dulce son bajos, de alrededor de 1, debido a que el cromo(VI) se reduce a cromo(III) dentro del organismo, de modo que la acumulación de cromo total puede equivaler a un factor unas 100 veces mayor que la concentración en el agua.

La concentración atmosférica de cromo total en zonas remotas oscila entre 0,005 y 2,6 ng/m^3, siendo normalmente inferior a 10 ng/m^3 en las zonas rurales y de 10 a 30 ng/m^3 en las urbanas. Se han notificado concentraciones más elevadas (> 500 ng/m^3) cerca de fuentes antropógenas. La concentración total de cromo en las aguas fluviales de los Estados Unidos suele variar entre menos de 1 y 30 µg/l, con un valor mediano de 10 µg/l. En Europa, se ha notificado, en aguas superficiales, una concentración de cromo total mediana de 0,38 µg/l (< 0,01–43,3 µg/l). La concentración total de cromo en aguas lacustres no suele sobrepasar los 5 µg/l. En aguas superficiales se han notificado concentraciones medias de cromo(VI) de hasta 3 µg/l. Las concentraciones más elevadas de cromo pueden estar vinculadas a fuentes de contaminación antropógenas: se han registrado concentraciones de hasta 648 µg de cromo(VI) por litro en aguas residuales industriales.

Por lo general, la concentración de cromo en el agua marina es mucho menor que en la de lagos y ríos. La concentración total media de cromo en el agua marina es de 0,3 µg/l (varía entre 0,2 y 50 µg/l). En las partículas en suspensión y los sedimentos de las masas de agua, la concentración total de cromo oscila entre 1 y 500 mg/kg. La concentración total de cromo en el suelo varía considerablemente y depende de la composición de la roca que dio origen al suelo. La gama de concentraciones de cromo total en el suelo y en otros materiales superficiales analizadas en América del Norte era de 1–2000 mg/kg, siendo su media geométrica de unos 40 mg/kg. En Europa, la concentración mediana de cromo en la capa superficial del suelo tras la extracción con ácido fluorhídrico era de 60 mg/kg (< 3–6230 mg/kg) y de 22 mg/kg (< 1–2340 mg/kg) tras la extracción con ácido nítrico. En lugares contaminados se han notificado cifras más altas.

La exposición de la población general se produce por inhalación del aire ambiental y la ingestión de alimentos y de agua potable que contienen cromo. La exposición dérmica al cromo del público en general puede darse por contacto de la piel con ciertos productos de consumo.

La concentración de cromo en el aire ambiental (< 0,01–0,03 µg/m^3) y el agua del grifo (< 2 µg/l) se ha utilizado para estimar el consumo diario de cromo por inhalación (< 0,2–0,6 µg) o por ingestión del agua del grifo (< 4 µg). El contenido de cromo de los alimentos varía considerablemente. La exposición dérmica estimada del personal encargado de envasar productos a base de cromato o de pesar ingredientes en polvo y cargarlos en las mezcladoras durante la fabricación de pigmentos de cromo(VI) es de 0–0,1 o de 0,1–1 mg/cm^2 por día, respectivamente.

En el pasado, el personal de las industrias relacionadas con el cromo estaba expuesto a concentraciones mucho mayores de cromo que los trabajadores de hoy día; en muchas industrias, el nivel de exposición era de varios cientos de microgramos por metro cúbico. En las instalaciones modernas, la exposición suele ser inferior a 20 µg/m^3.

La toxicocinética de un determinado compuesto de cromo depende del estado de valencia del átomo de cromo y de la naturaleza de sus ligandos. La absorción de los compuestos de cromo(VI) es mayor que la de los compuestos de cromo(III), cualquiera que sea la vía de exposición. Ello se debe a que el anión cromato puede ingresar en la célula a través de los canales aniónicos presentes en la membrana plasmática, mientras que la absorción de los compuestos de cromo(III) ocurre por difusión pasiva y fagocitosis. La absorción de los compuestos de cromo inhalados se produce tanto en los pulmones, a través de la membrana plasmática, como en el tubo digestivo a partir de partículas que se eliminan de los pulmones. En el ser humano, la absorción del cromo(VI) tras su ingestión en forma de cromato o dicromato de potasio es de 2–8% aproximadamente. En las condiciones ácidas del estómago dicha absorción es más baja debido a la reducción a cromo(III).

Una vez en la sangre, los compuestos de cromo se distribuyen por todos los órganos del cuerpo. Las partículas que contienen cromo pueden quedar retenidas en el pulmón durante años tras una exposición laboral. El cromo(VI) es inestable en el organismo y es reducido a cromo(V), cromo(IV) y, en última instancia, a cromo(III) por muchas sustancias, como el ascorbato y el glutatión. Se cree que la toxicidad de los compuestos de cromo(VI) obedece a lesiones de componentes

celulares durante este proceso (por ejemplo, debido a la formación de radicales libres). También existe la posibilidad de interacción con el ácido desoxirribonucleico (ADN), que le causa daños estructurales.

El cromo absorbido se excreta principalmente en la orina; en el ser humano, se ha calculado que la semivida de eliminación del cromo administrado por vía oral en forma de dicromato de potasio es de unas 40 horas. El cabello y las uñas son vías minoritarias de eliminación.

La exposición oral de animales a dosis muy elevadas de compuestos de cromo(VI) ha traído aparejados efectos gastrointestinales, hepáticos, renales, inmunitarios, hemáticos, neurales y en el desarrollo y la reproducción. La exposición dérmica de animales a dichos compuestos ha provocado úlceras y reacciones alérgicas en la piel.

Entre los efectos de la exposición oral de ratas y ratones a agua de bebida que contenía cromo(VI) durante 13 semanas o 2 años había anemias transitorias, lesiones en la cavidad bucal y los intestinos, inflamación del hígado, los nódulos linfáticos y el páncreas y tumores en la cavidad bucal de las ratas y en el intestino delgado de los ratones.

La ingestión fortuita o deliberada de dosis elevadas de compuestos de cromo(VI) por el ser humano ha causado efectos respiratorios, cardiovasculares, gastrointestinales, hemáticos, hepáticos, renales y neurales graves.

Uno de los efectos de los compuestos de cromo(VI) presentes en el aire, en los seres humanos expuestos laboralmente a ellos, puede ser la irritación de las vías respiratorias y de los ojos, que a su vez puede causar ulceración y perforación del tabique nasal y una mayor incidencia de cáncer en las vías respiratorias. La exposición a compuestos de cromo(VI) también puede provocar asma.

La exposición laboral al cromo(VI) por inhalación guarda una asociación causal con una mayor incidencia de cáncer de pulmón. Varios estudios han revelado asimismo que la exposición al cromo(VI) se asocia a cáncer de la nariz y de los senos nasales. Se dispone de muy escasa información sobre la asociación entre la exposición al cromo(VI) presente en el agua potable y el cáncer en el ser humano. El cromo(VI) ha provocado cáncer en animales de experimentación expuestos a dicho elemento por vía oral, intratraqueal o inhalatoria.

La exposición laboral por contacto dérmico puede generar úlceras cutáneas profundas. El cromo(VI) es una causa frecuente de dermatitis alérgica por contacto, que puede ser un trastorno incapacitante grave y duradero.

Se han observado aberraciones cromosómicas y lesiones en el ADN de algunas personas expuestas laboralmente a compuestos de cromo(VI). El cromo(VI) también ha demostrado ser genotóxico en ensayos *in vivo* e *in vitro*.

Con respecto a los efectos no cancerígenos en las vías respiratorias del ser humano, se ha calculado una concentración tolerable de cromo(VI) de 0,005 µg/m^3 para el ácido crómico o el trióxido de cromo, con base en la concentración más baja con efectos adversos observados (LOAEC) de 2 µg de cromo(VI) por metro cúbico.

Con respecto a los efectos no cancerígenos en las vías respiratorias, se ha estimado una concentración tolerable de cromo(VI) de 0,03 µg/m^3 para la exposición por inhalación al cromo(VI) en forma de sales de cromo(VI), tomando como base un análisis de referencia de la actividad elevada de lactato-deshidrogenasa que se detecta en el líquido del lavado broncoalveolar de ratas expuestas al cromo(VI) y que se utiliza como indicador de daño pulmonar. Esta concentración tolerable está avalada por las manifestaciones de irritación nasal que se han observado en el personal a cargo de la producción de cromatos.

Con respecto a los efectos no cancerígenos, se ha calculado una ingesta diaria tolerable de 0.9 µg de cromo(VI) por kilogramo de peso corporal al día a partir de los signos de hiperplasia epitelial difusa observados en el duodeno de ratones hembra expuestas al dicromato de sodio dihidratado a través del agua de bebida. El cálculo se basó en un $BMDL_{10}$ (límite inferior de la dosis que origina un 10% de incremento de un efecto o una respuesta medible en la población) de 0,094 mg/kg de peso corporal al día y en la aplicación de un factor de incertidumbre de 100.

El riesgo adicional acumulado durante toda la vida de cáncer de pulmón resultante de una exposición laboral a 1 µg de cromo(VI) por metro cúbico es de 6×10^{-3}, a juzgar por el estudio epidemiológico que brindaba la mejor información en materia de exposición (realizado en trabajadores a cargo de la producción de cromatos). Esta estimación presupone que se ha empezado a trabajar a los 20 años, con jornadas laborales de 8 horas/día durante 5 días/semana, y que se ha trabajado durante 45 años. Una estimación del riesgo vitalicio de cáncer de pulmón resultante de una exposición ambiental a 0,001 µg de cromo(VI) por metro cúbico (24 horas/día, 365 días/año, durante 70 años) es de 4×10^{-5}.

Después de la exposición a dicromato de sodio a través del agua de bebida, se observó una mayor incidencia de tumores malignos y benignos en la cavidad bucal de las ratas y el intestino delgado de los ratones

expuestos. Hay gran incertidumbre con respecto al riesgo de carcinogenia que los compuestos de cromo(VI) entrañan para los seres humanos expuestos a ellos por vía oral.

Se dispone de datos procedentes de estudios ecotoxicológicos de corta y larga duración sobre los efectos de los compuestos de cromo(VI) en una gran variedad de organismos, etapas de vida, criterios de valoración y condiciones experimentales. Por lo general, la toxicidad del cromo(VI) aumenta a medida que disminuye el pH (es decir, de 8,0 a 6,0), aumenta la temperatura (es decir, de 15 °C a 25 °C) y desciende la dureza o la salinidad del agua. Dondequiera se han evaluado organismos de agua salada en aguas de baja salinidad (< 2‰), su sensibilidad parecía ser comparable a la de los organismos de agua dulce.

La concentración sin efectos previstos (PNEC) para los organismos de agua dulce, basada en el límite inferior del intervalo de confianza del 95% de la concentración peligrosa para la protección del 95% de las especies (el percentil 5 de la distribución de la sensibilidad por especies), HC_5-95%, es de 4 µg/l. En agua salada, cabe esperar que el cromo(VI) sea menos tóxico, salvo, quizás, cuando la salinidad es muy baja.

La mayor parte de las aguas naturales contienen concentraciones totales de cromo inferiores a la PNEC de agua dulce; aun en los casos en que se sobrepase la PNEC, los valores se proporcionan en cifras de cromo total y es probable que la biodisponibilidad del cromo natural sea muy baja. Sin embargo, se han notificado concentraciones mayores de cromo y, más concretamente, de cromo(III) y cromo(VI), cerca de fuentes de emisiones antropógenas. Por ejemplo, en un radio de 80 m de una curtidoría abandonada, se determinó una concentración de cromo(VI) libre de 63 µg/l en el agua fluvial. Puede decirse entonces que el riesgo para los organismos acuáticos es generalmente bajo, pero que existe un riesgo en la vecindad de algunas emisiones antropógenas de cromo(VI). Los datos de los estudios de toxicidad tienden a indicar que los organismos marinos no son más sensibles que los de agua dulce. Ello sugiere que la cifra de 4 µg/l derivada de las especies de agua dulce debería ser protectora de las especies marinas. Así pues, la misma conclusión a la que se llegó para los organismos de agua dulce (esto es, que el cromo(VI) no representará un riesgo significativo para los organismos a menos que exista una fuente de contaminación local) vale para el medio marino.

En ausencia de más datos sobre la biodisponibilidad del cromo en los suelos, es difícil evaluar el riesgo que entraña el cromo(VI) para los organismos de los suelos.

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