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Concise International Chemical Assessment Document 76

INORGANIC CHROMIUM(III) COMPOUNDS

First draft prepared by Dr Tiina Santonen, Dr Antti Zitting, and Dr Vesa Riihimäki, Finnish Institute of Occupational Health, Helsinki, Finland; and Mr Paul D. Howe, Centre for Ecology and Hydrology, Monks Wood, Huntingdon, Cambridgeshire, England

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). 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.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. 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:

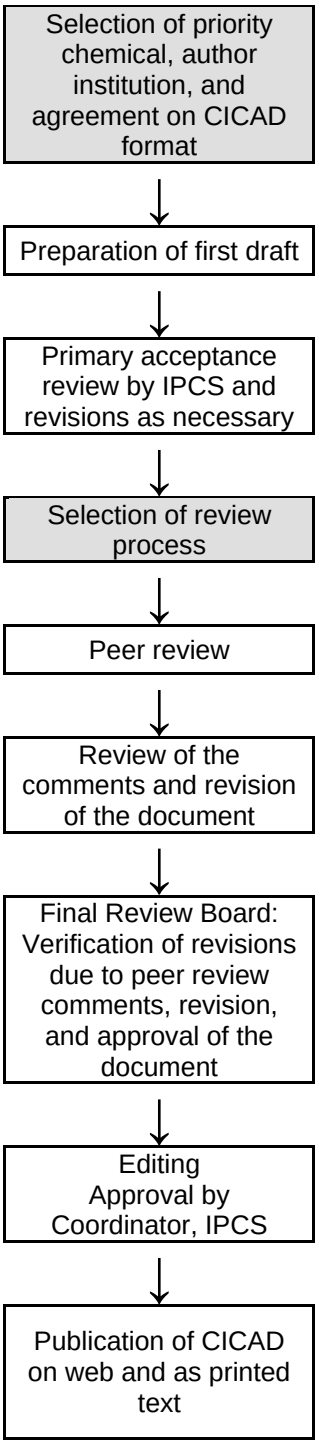
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

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

[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.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

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(III) compounds was prepared jointly by the Finnish Institute of Occupational Health, Helsinki, Finland (human health sections), and the Centre for Ecology and Hydrology, Monks Wood, United Kingdom (environmental sections), based on the *Health Risk Assessment Report for Metallic Chromium and Trivalent Chromium*, prepared by the Finnish Institute of Occupational Health (Riihimäki & Luotamo, 2006), and the Agency for Toxic Substances and Disease Registry's *Toxicological Profile for Chromium* (ATSDR, 2000). The date for the last literature search was December 2004 for the health effects part and December 2005 for the environmental part of the CICAD. Information on the source documents is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD on inorganic chromium compounds was approved as an international assessment at a meeting of the Final Review Board, held in Helsinki, Finland, on 26–29 March 2007. Participants at the Final Review Board meeting are listed in Appendix 4. International Chemical Safety Cards on the most common inorganic trivalent chromium compounds, produced by the International Programme on Chemical Safety (IPCS), have also been reproduced in this document (IPCS, 2002b, 2004a,b,c,d, 2006). This CICAD is restricted to inorganic trivalent chromium compounds, but when additional value can be given, data on organic chromium compounds are also presented. CICAD No. 78 concerning hexavalent chromium is currently in preparation.

Trivalent chromium is thermodynamically the most stable state of chromium. In the environment, almost all naturally occurring chromium is in the trivalent form. There are a wide variety of commercially available trivalent chromium compounds, the most important ones being chromium(III) oxide and basic chromium sulfate.

The general population is exposed to trivalent chromium mainly from the daily diet. Other sources include food supplements containing chromium, ambient air, chrome-tanned leather articles, chromium pigment–based cosmetics, stainless steel articles, prosthetic implants, and orthodontic appliances. Occupational exposure to trivalent chromium may occur in a wide range of industrial activities related to the production, formulation, and use of chromium.

There is a complete chromium cycle, from rocks or soil to plants, animals, and humans, and back to soil. Chromium is emitted into the air, not only by anthropogenic sources, but also by every combustion process, including forest fires. Chromium is present in the atmosphere primarily in particulate form.

Industrial effluents containing chromium, some of which is in the hexavalent form, are emitted into surface waters. Whether the chromium remains hexavalent until it reaches the ocean depends on the amount of organic matter present in the water. If organic matter is present in large quantities, the chromium(VI) may be reduced by, and chromium(III) adsorbed on, the particulate matter. If it is not adsorbed, the chromium(III) will form large, polynucleate complexes that are no longer soluble. The reduction of chromium(VI) to chromium(III) occurs rapidly under anaerobic conditions, and reducing conditions generally exist in deeper groundwaters. Most of the chromium released into water will ultimately be deposited in the sediment. The major dissolved species of chromium(III) are Cr^{3+}, $CrOH^{2+}$, $Cr(OH)_3^0$, and $Cr(OH)_4^-$.

Chromium in soil is present mainly as insoluble oxide and is not very mobile. Chromium(III) is expected to be rapidly and strongly adsorbed onto soil, particularly by iron and manganese oxides, clay minerals, and sand. 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; once absorbed, however, the hexavalent form is reduced to the more stable, trivalent state.

Bioconcentration factors for chromium(VI) in fish are low, at around 1; however, once in the organism, chromium(VI) appears to be reduced to chromium(III), resulting in the accumulation of total chromium in the organisms to a factor of approximately 100 times the water concentration.

The concentrations of atmospheric total chromium in remote areas range from 0.005 to 2.6 ng/m^3, with typically <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 United States of America (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(III) concentrations of up to 2 µg/l have been reported for surface waters. Higher levels of chromium can be related to sources of anthropogenic pollution, with the highest levels of up to 40 mg chromium(III)/l near tannery discharges.

In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The

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

mean total chromium concentration in ocean water is 0.3 µg/l, with a range of 0.2–50 µg/l. Mean chromium(III) concentrations of 2–3 µg/l have been reported for coastal waters. In the suspended materials and sediments 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 in Canada and the USA was 1–2000 mg/kg, with a geometric mean 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.

Trivalent chromium is considered to be an essential trace element in mammals, being involved in lipid and glucose metabolism. Limited amounts (<0.5–2%) of chromium(III) are absorbed from the normal diet—more if the content of chromium in diet is abnormally low, and less when intake is increased. Absorption of water-soluble chromium(III) aerosols of respirable size is more efficient from the respiratory system than from the gastrointestinal tract: approximately 5% may be taken up rapidly within hours, followed by a further slow release into circulation over weeks and months. For insoluble chromium(III) oxide, uptake of deposited and retained particles is a very slow process. Water-soluble trivalent chromium salts are able to penetrate into the skin, but they have not been shown to reach the systemic circulation.

In the blood plasma, 95% of chromium(III) is bound to large molecular mass proteins (e.g. transferrin), but it also associates with an oligopeptide called low-molecular-weight chromium-binding substance (LMWCr). Chromium is distributed predominantly into the liver, kidneys, spleen, and bone. Some administered chromium may reach the interstitium of the testis, and it may accumulate in placenta, but only low amounts cross the placenta. Absorbed chromium(III) is excreted mainly in the urine and to a lesser extent in the faeces.

In rats, the oral acute toxicity of chromium(III) oxide is very low, with median lethal doses (LD_{50} values) above 5 g/kg body weight (bw). The oral LD_{50} for basic chromium sulfate is reported to be 3530 mg/kg bw in rats. Values given for chromium nitrate range from 1540 to 3250 mg/kg bw.

Based on animal studies, chromium(III) oxide and basic chromium sulfate are not skin or eye irritants.

Insoluble chromium(III) oxide does not cause skin sensitization. Trivalent chromium may act as an ultimate haptenic determinant for chromium sensitization in the skin, but the poor skin penetration limits the sensitizing ability of trivalent chromium salts. The sensitizing effects of water-soluble trivalent chromium salts, chromium chloride, and hydrated chromium sulfate have been demonstrated in non-standard tests employing intradermal or subcutaneous injections. Two studies on chromium chloride also showed positive reactions after an epicutaneous challenge. Clinical evidence on skin sensitization relates mainly to the wearing of leather articles. The relationship between trivalent chromium and sensitization induced by leather articles is clouded by the fact that low levels of hexavalent chromium may be present in tanned leather and that the reported cases of foot dermatitis may actually concern elicitation reactions in previously chromium-sensitized people. Skin sensitization among workers handling trivalent chromium salts appears to be a rare event. There is at present no unequivocal evidence to show that exposure to trivalent chromium compounds has induced occupational asthma.

Inhalation of mean chromium concentrations of 3, 10, and 30 mg/m^3 as chromium(III) oxide resulted in very mild inflammatory changes in the lungs of exposed rats at all air levels, whereas dusts of basic chromium sulfate at the same Cr^{3+} air concentrations resulted in more severe and more widespread inflammatory effects and signs of systemic toxicity in middle and high dose groups. Small inflammatory changes seen after chromium(III) oxide inhalation may reflect a nonspecific lung response to accumulated insoluble particles (overload) rather than intrinsic toxicity of chromium(III). The no-observed-adverse-effect concentration (NOAEC) of 3 mg Cr^{3+}/m^3 was identified for basic chromium sulfate for systemic effects; however, since inflammatory changes in the lungs and the respiratory tract were seen even at the lowest level, it was a lowest-observed-adverse-effect concentration (LOAEC) for local effects. The minimal severity of findings at the lowest exposure level suggests that the LOAEC of 3 mg Cr^{3+}/m^3 is near a NOAEC for chromium(III) oxide in rats.

Feeding rats with chromium(III) oxide even at very high doses did not result in any adverse effects. This lack of effects can be explained by the poor oral bioavailability of chromium(III) oxide. In a 20-week oral feeding study with water-soluble chromium chloride, no adverse treatment-related effects were seen in Sprague-Dawley rats even at the highest dose level, corresponding to a chromium intake of 7 mg/kg bw per day.

Although chromium(III) may interact with deoxyribonucleic acid (DNA), the data on in vitro and in vivo genotoxicity studies are conflicting and give no clear evidence on the mutagenicity of trivalent chromium.

Animal studies regarded relevant for the carcinogenicity assessment of chromium(III) did not show an

increased incidence of cancer with trivalent chromium compounds. For some occupations involving trivalent chromium exposure, increased risks for some cancers have been suggested, but the epidemiological data do not permit the discrimination between the simultaneous exposure to trivalent chromium and hexavalent chromium or other carcinogenic agents.

Available data suggest a lack of effects of trivalent chromium on fertility. Based on poor bioavailability and a limited oral developmental toxicity study at high doses, chromium(III) oxide is not a developmental toxicant. No appropriate developmental toxicity studies were available for soluble trivalent chromium salts.

The key end-point considered to be relevant for human exposure to chromium(III) oxide is sustained local irritation and inflammation associated with accumulation of respirable particles in the lungs to the extent that the clearance mechanisms are overloaded. The key end-points relevant for human exposure to basic chromium sulfate, presumed to represent soluble chromium(III) salts as a group, are local respiratory toxicity and sensitization of the skin. Tolerable concentrations (27 µg Cr^{3+}/m^3 for insoluble chromium(III) and 6 µg Cr^{3+}/m^3 for soluble chromium(III) compounds) based on these effects and applicable assessment factors are usually well above the air levels of chromium(III); even in the vicinity of point sources, air levels fall below the tolerable concentrations. Concerning skin sensitization, it is rather unlikely that soluble trivalent chromium salts induce skin sensitization in people using shoes, gloves, or other articles made of chrome-tanned leather, whereas elicitation of chromium allergy in a previously sensitized person is possible owing to small amounts of chromium leached from leather articles.

Chromium(III) is required by some microorganisms for specific metabolic processes, such as glucose metabolism and enzyme stimulation. Chromium(III), in trace amounts, has been reported to be an essential component of animal nutrition and is most notably associated with glucose and fat metabolism. However, whereas chromium has been shown to be essential for glucose metabolism in some laboratory mammals, studies on other animals are equivocal.

The available toxicity data for chromium(III) have been mainly derived using the water-soluble forms (chromium(III) chloride, chromium(III) nitrate, and chromium potassium sulfate). In the environment, chromium(III) is likely to be present in much less soluble forms and hence less bioavailable to aquatic organisms.

Ninety-six-hour median effective concentrations (EC_{50}s) for one freshwater alga, based on growth, ranged from 0.3 to 0.4 mg chromium(III)/l. A 96-h EC_{50}, based on growth, was reported for a marine diatom at 2 mg chromium(III)/l. Median lethal concentrations (LC_{50}s) in freshwater invertebrates ranged from 0.1 mg/l (*Daphnia pulex*) to 442 mg/l (*Asellus aquaticus*), with a life cycle no-observed-effect concentration (NOEC) of 0.047 mg/l for *Daphnia magna.* LC_{50}s ranging from 10 to 100 mg/l have been reported for marine invertebrates. Ninety-six-hour LC_{50}s for freshwater fish ranged from 3.3 mg/l for the guppy (*Poecilia reticulata*) to 151 mg/l for the bighead (*Aristichthys nobilis*), whereas 96-h LC_{50}s of 31.5 and 53 mg/l were reported for marine fish. A 72-day NOEC (survival) of 0.05 mg/l was reported for rainbow trout (*Oncorhynchus mykiss*).

A guidance value for trivalent chromium toxicity in the freshwater environment can be derived using a probabilistic approach, since the data set is sufficiently large to warrant it. A moderate-reliability guidance value of 10 µg chromium(III)/l was derived for the protection of 99% of freshwater species with 50% confidence. There were insufficient toxicity data on marine organisms to allow a guidance value to be calculated using a probabilistic method. A very limited data set was available based on a diatom, aquatic invertebrates, and fish. Therefore, a factor of 1000 was applied to the lowest reliable toxicity value (2 mg/l) to give a low-reliability guidance value of 2 µg chromium(III)/l.

The moderate-reliability guidance value of 10 µg chromium(III)/l for the freshwater environment suggests a low risk for surface waters in general. However, there is a potential risk to organisms when the guidance value is compared with the highest chromium(III) level of around 100 µg/l for surface waters in industrial areas. The higher levels of trivalent chromium in effluent, especially from tanneries, suggest that there is a risk to freshwater organisms in the vicinity of such effluent releases. Comparing the low-reliability guidance value of 2 µg chromium(III)/l for the marine environment with trivalent chromium concentrations in seawater suggests a low risk of toxicity to marine organisms.

The main feature of chromium intoxication in plants is chlorosis. Hexavalent chromium appears to be more toxic to terrestrial plants than is trivalent chromium.

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

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

The oxidation states of chromium range from –2 to +6; the important valences are 0, +3, and +6. The

trivalent state is the thermodynamically most stable. In the environment, almost all chromium exists in trivalent compounds, other forms being mainly of anthropogenic origin.

Identification data for some trivalent chromium compounds of technological importance are given in Table 1, and their physical and chemical properties are given in Table 2.

Commercially, the most important trivalent compounds are chromium(III) oxide and basic chromium sulfate.

3. ANALYTICAL METHODS

Analysis of chromium in air, water, soil, or biological media is performed mainly by atomic absorption spectrometry (AAS) or by inductively coupled plasma atomic emission spectrometry (ICP-AES) or inductively coupled plasma mass spectrometry (ICP-MS), although several chromatographic methods often coupled with AAS, ICP-AES, or ICP-MS have been devised to separate anionic chromium(VI) from cationic chromium(III) species (Urasa & Nam, 1989; Sperling et al., 1992; Gjerde et al., 1993; Byrdy et al., 1995; Inoue et al., 1995; Girard & Hubert, 1996; Goodarzi & Huggins, 2001). The spectrophotometric determination of chromium(VI) as a coloured complex with 1,5-diphenylcarbazide is still widely used for speciation. Trivalent chromium can be similarly measured as the diphenylcarbazide complex after oxidation to the hexavalent state.

In most cases, speciation is based on the determination of hexavalent chromium and total chromium, the difference being trivalent chromium. A major analytical problem in speciation is the instability of hexavalent chromium during sample storage. Although the phenomenon is of fundamental importance, little attention has been given to its quantitative assessment.

3.1 Samples from the general and work environment

The National Institute for Occupational Safety and Health (NIOSH) in the United States of America (USA) has developed a field analytical method to measure hexavalent chromium (chromate) in air (NIOSH Method 7703) (NIOSH, 1994c). The procedure includes ultrasonic extraction from sampling filters, solid-phase extraction of chromate from the previous solution, and the determination of chromium(VI) by spectrophotometry. The method is relatively easy to use, has a low detection limit, and allows analysis before hexavalent chromium can significantly reduce to the trivalent state. For total chromium measurements, it is possible to use atomic absorption with a nitrous oxide–acetylene reducing flame (NIOSH Method 7024) (NIOSH, 1994a) or ICP-AES according to NIOSH Method 7300 (NIOSH, 1994b), which has a detection limit of 20 ng/filter.

A wide variety of methods have been developed for the determination of chromium in water. Analyses of chromium(VI) from groundwater, surface water, raw or potable water, or wastewater, according to International Organization for Standardization (ISO) Standard 18412:2005 (ISO, 2005) or ISO Standard 11083:1994 (ISO, 1994), are based on the spectrophotometric method with 1,5-diphenylcarbazide as a complexing agent. The determination of total chromium can be carried out using AAS with graphite furnace (GAAS) and magnesium nitrate as a recommended modifier (ISO Standard 15586:2003) (ISO, 2003), using ICP-AES (ISO Standard 11885:1996) (ISO, 1996), or using ICP-MS (ISO Standard 17294-2:2004) (ISO, 2004).

3.2 Biological monitoring

Most methods use AAS to measure total chromium in urine, serum, blood, and other human tissues. Chromium in biological samples may also be determined using ICP-MS and neutron activation analysis (NAA) (Nicolaou et al., 1987; Lavi & Alfassi, 1990; Tomlinson et al., 1994; Apostoli et al., 1997). The detection limit in urine measured by AAS is between 0.03 and 0.1 µg/l (Riihimäki & Luotamo, 2006); when measured by NAA, the detection limit in urine is 10 ng chromium per sample (Lavi & Alfassi, 1990). The detection limit in serum measured by GAAS with a background correction lamp is 0.05 µg/l (Randall & Gibson, 1987; Kornhauser et al., 2002); with Zeeman background correction, it varies between 0.02 and 0.2 µg/l (Riihimäki & Luotamo, 2006).

Knowledge of uncertainty has improved the quality of measurements, especially near the detection limit (Ellison et al., 2000; CITAC/Eurachem, 2002), with the paradoxical outcome that detection limits reported in recent publications have become higher. International quality assurance programmes (Interlaboratory Comparison Program for Metals in Biological Matrices, Canada, http://www.inspq.qc.ca/ctq/; German External Quality Assessment Scheme for Analyses in Biological Materials, Germany, http://www.g-equas.de/) provide the opportunity for participants to compare their own results with those from other laboratories.

Determination of chromium in urine is the preferred approach for the biological monitoring of exposure to trivalent chromium. The urine sample is usually diluted

Table 1: Identification data for trivalent chromium compounds (IARC, 1990; Kirk-Othmer, 2003; Ullmann's, 2004; industry information).

Substance name	CAS No.	Synonyms	Chemical formula	Relative molecular mass
Chromite (pure)	1308-31-2	Chromium ore; chromite (mineral); chromite mineral; chromite ore; iron chromite	$FeOCr_2O_3$	223.84
Chromium(III) oxide	1308-38-9	CI 77288; CI pigment green 17; Casalis green; chrome green; chrome ocher; chrome ochre; chrome oxide; chromium acid green; chromium oxide; chromium oxide green; chromium oxide pigment; chromium oxide X1134; chromium oxide greens; chromium sesquioxide; chromium trioxide; Cosmetic hydrophobic green 9409; Cosmetic micro blend chrome oxide 9229; dichromium trioxide; green chrome oxide; green oxide of chromium; green chromium oxide; green cinnabar; green oxide of chromium OC-31; green rouge; leaf green; oil green; oxide of chromium	Cr_2O_3	151.99
Chromium(III) oxide, hydrated	12001-99-9	Chromium hydrate	$Cr_2O_3 \cdot 2H_2O$	188.05
Chromium(III) sulfate	10101-53-8	Dichromium tris(sulfate)	$Cr_2(SO_4)_3$	392.17
Chromium(III) hydroxide sulfate	12336-95-7	Basic chrome sulfate; basic chromium sulfate; chromedol; monobasic chromium sulfate	$Cr(OH)SO_4$	165.06
Chromium(III) potassium sulfate	10141-00-1	Chrome alum; chrome potash alum; chromium potassium sulfate; crystal chrome alum; potassium chromium sulfate; potassium chromium alum; potassium chromium disulfate; potassium chromium(III) sulfate; potassium disulfatochromate(III)	$KCr(SO_4)_2$	283.23
Chromium(III) potassium sulfate, dodecahydrate	7788-99-0		$KCr(SO_4)_2 \cdot 12H_2O$	499.39
Chromium(III) hydroxide, trihydrate	1308-14-1	Chromium(III) hydroxide; chromium hydroxide; chromium oxide gel; chromium oxide, hydrous; chromium trihydroxide	$Cr(OH)_3 \cdot 3H_2O$	163.02
Chromium(III) chloride	10025-73-7	Chromium chloride; chromium trichloride; chromium(III) chloride, anhydrous; puratronic chromium chloride; trichlorochromium	$CrCl_3$	158.36
Chromium(III) chloride, hexahydrate	10060-12-5		$CrCl_3 \cdot 6H_2O$	266.45
Chromium(III) nitrate	13548-38-4	Chromium nitrate; chromium trinitrate; nitric acid, chromium (3+) salt	$Cr(NO_3)_3$	238.03
Chromium(III) nitrate, 7.5 hydrate			$Cr(NO_3)_3 \cdot 7.5H_2O$	373.13
Chromium(III) nitrate, nonahydrate			$Cr(NO_3)_3 \cdot 9H_2O$	400.15
Chromium acetate	1066-30-4	Chromium acetate; chromium(III) acetate; chromium triacetate	$Cr(OCOCH_3)_3$	229.14
Chromium acetate, hydrate			$Cr(OCOCH_3)_3 \cdot H_2O$	247.15
Chromium(III) fluoride, tetrahydrate	7788-97-8	Chromium trifluoride	$CrF_3 \cdot 4H_2O$	181.05
Chromium(III) formate	27115-36-2	Chromium formate; chromium triformate	$Cr(HCOOH)_3$	190.08
Chromium(III) phosphate	7789-04-0	Arnaudon's green; chromium phosphate; chromium monophosphate; chromium orthophosphate; phosphoric acid chromium(III) salt; phosphoric acid, chromium (3+) salt (1:1)	$CrPO_4$	146.97
Chromium(III) phosphate, monohydrate	27096-04-4		$CrPO_4 \cdot H_2O$	164.98
Chromium(III) phosphate, dihydrate			$CrPO_4 \cdot 2H_2O$	183.00

CAS, Chemical Abstracts Service

Table 2: Physical and chemical properties of chromium and chromium(III) compounds (IARC, 1990; Kirk-Othmer, 2003; Ullmann's, 2004; industry information).

Substance name	Physical form	Melting point (°C)	Boiling point (°C)	Solubility in water	Solubility in other solvents
Chromite	Brown-black solid	Depends on composition		Insoluble	Insoluble in organic solvents
Chromium(III) oxide	Light to dark green, fine crystals	2435	4000	Insoluble	Insoluble
Chromium(III) oxide, hydrated	Blue-green powder	–	–	Insoluble	Insoluble
Chromium(III) sulfate, hydrated	Green or violet crystals	90	Decomposes	84–120 g/l00 ml	Insoluble
Chromium(III) potassium sulfate, dodecahydrate	Violet ruby-red to black crystals	89	400	Soluble in water (243.9 g/l) at 25 °C; 500 g/l in hot water	Slightly soluble in dilute acids, insoluble in ethanol
Chromium(III) hydroxide sulfate	Green powder	–	–	Soluble (700 g/l at 30 °C)	–
Chromium(III) hydroxide	Red-brown hexagonal crystals			Insoluble	Soluble in alcohol
Chromium(III) hydroxide, trihydrate	Blue-green powder	Composition varies		Insoluble	Soluble in acids
Chromium(III) chloride	Violet crystalline scales	1152	Sublimes at 1300	Insoluble in cold water, slightly soluble in hot water	Insoluble in ethanol, acetone, methanol, and diethyl ether
Chromium(III) chloride, hexahydrate	Green to violet crystalline powder	83–95	–	Soluble in water (585 g/l)	Soluble in ethanol, slightly soluble in acetone, and insoluble in diethyl ether
Chromium(III) nitrate	Pale green powder	–	–	Soluble	–
Chromium(III) nitrate, 7.5 hydrate	Brown crystals	100	Decomposes	Soluble	–
Chromium(III) nitrate, nonahydrate	Deep-violet crystals	60	Decomposes at 100	Soluble	Soluble in acids, alkali, ethanol, and acetone
Chromium(III) acetate	Grey-green powder	–	–	Soluble	–
Chromium(III) acetate, dihydrate	Red crystals	–	–	Slightly soluble	Slightly soluble in ethanol, soluble in acids
Chromium(III) phosphate	Violet crystalline solid	>1800	–	Insoluble	Soluble in most acids and alkali but not in acetic acid
Chromium(III) phosphate, dihydrate	Violet crystalline solid	–	–	Slightly soluble in cold water	–

with water, nitric acid, Triton X-100, or a combination of these. To normalize for the degree of dilution of the urine sample, the measured chromium concentration can be adjusted for relative density or for creatinine excretion. The control values must be similarly adjusted.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural sources

Chromium is a relatively common element, naturally occurring in rocks, soil, plants, animals, volcanic dust, and gases. Oil and coal contain traces of chromium(III). Chromium is chiefly found as the chromium(III) form in nature (ATSDR, 2000).

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).

4.2 Anthropogenic sources

Approximately 12 million tonnes of chromite ore are mined globally per year. Of this amount, approximately 90% is used for metallurgy, 7% for the manufacture of chemicals, 3% for foundry sands, and 1% for refractories (Keegan, 2001). Chromium(III) is the most stable oxidation state of chromium. This property and the ability of chromium(III) to form coordination complexes with a wide variety of ligands have given chromium(III) compounds diverse industrial applications. The most extensively produced compounds are basic chromium sulfate (global production capacity about 500 000 tonnes per year) and chromium(III) oxide (global production capacity about 88 500 tonnes per year) (Keegan, 2001).

Tanning of leather is by far the most widespread end use of trivalent chromium. The tanning is based on a covalent reaction between the hide proteins, notably collagen, and trivalent chromium salts. Usually the tanning agent is basic chromium sulfate; previously, chromium(III) potassium sulfate was also used.

Chromium(III) oxide pigments are used in paints, plastics, concrete building products, artistic colours, ceramics, and glass. Hydrated chromium oxide pigment is used in cosmetic and personal care products such as eye shadows and soaps. The chromium oxide pigments are used because of their colour, light fastness, stability, and durability. Different grades of chromium oxide–based pigments are used in varying quantities depending on the shade of green required. For example, the concentration of chromium oxide in paint can vary from 8% to 50%.

Some chromium(III) salts (basic chromium(III) sulfate, chromium(III) chloride, chromium(III) sulfate) have found increasing use in decorative chromium plating substituting for hexavalent chromic acid. Decorative plating is common in, for example, faucets, door handles, and furniture.

Chromium(III) oxide, hydroxide, and some salts can be used to make catalysts for the chemical industry. Chromium–iron catalysts are usually made from chromium and iron salts. Iron–chromium catalysts are used in high-temperature shift reactions in the petroleum industry and in the production of hydrogen from methane. Chromium(III) oxide is also used as a raw material in the manufacture of pure chromium metal by the aluminothermic process.

Trivalent chromium compounds (e.g. chromium(III) hydroxide, sulfate, nitrate, acetate) have been used as mordants in textile dyeing to fix dyes to fibres. Chromium(III) complexes are used especially in wool dyes.

Chromite is used as a refractory material because of its high melting point, moderate thermal expansion, inertness, and corrosion resistance. In refractory products, chromium is usually in the form of chromium(III) oxide or chromite. Chromite is used as foundry sand.

Chromium(III) chloride and chromium(III) sulfate have been used as dietary supplements (approved for the manufacture of foods for particular nutritional uses and in food supplements in the European Union), whereas the organic chromium(III) complexes chromium picolinate and nicotinate are not approved in the European Union but find widespread uses (e.g. in the USA) in multivitamin, multimineral products (Riihimäki & Luotamo, 2006). They are also marketed for weight loss purposes and athletic supplements.

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 hexavalent chromium, with by-products going into the water and air. Part of the air chromium 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 every combustion process, 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 the hexavalent state. While suspended in the air, chromium in this 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 by wet and dry deposition. In the case of chromium, the mass median diameter of the ambient atmospheric particle is 0.1 μm (Milford & Davidson, 1985; Ondov et al., 1989), and the dry deposition velocity is 0.5 cm/s (Schroeder et al., 1987). This size and deposition velocity favour 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 the 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 below 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 $\mu g/m^2$ per month, with the largest values occurring during the winter months (Morselli et al., 1999). Golomb et al. (1997) reported a deposition rate (wet plus dry) of 2700 μg chromium/m^2 per year 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, 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 transport from the troposphere to the stratosphere.

5.1.2 Water

Industrial effluents containing chromium, some of which is in the hexavalent form, are emitted into surface waters. Whether the chromium remains hexavalent until it reaches the ocean depends on the amount of organic matter present in the water. If organic matter is present in large quantities, the chromium(VI) may be reduced by, and chromium(III) 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).

Since chromium compounds cannot volatilize from water, transport of chromium from water to the atmosphere is not likely, except by transport in windblown sea sprays. Most of the chromium released into water will ultimately be deposited in the sediment. A very small 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. The major dissolved species of chromium(III) are Cr^{3+}, $CrOH^{2+}$, $Cr(OH)_3^0$, and $Cr(OH)_4^-$. Of these species, Cr^{3+} exists in significant amounts only at pH below about 3.6–3.8; similarly, $Cr(OH)_4^-$ is prevalent only at high pH (pH above about 10–11.5). Between these pH values, $CrOH^{2+}$ is thought to be the dominant species up to around pH 6.3–6.5, and $Cr(OH)_3^0$ is the dominant

species in solution at pHs between 6.3–7 and 10–11.5. Polymeric species such as $Cr_2(OH)_2^{4+}$, $Cr_3(OH)_4^{5+}$, and $Cr_4(OH)_6^{6+}$, although they exist, are never significant in the environment. Overall, chromium(III) species show a minimum solubility between pH 7 and pH 10 (Rai et al., 1987; Richard & Bourg, 1991). At pHs from about 5–6 up to about 12, the solubility of chromium(III) in aqueous systems is limited by the formation of chromium(III) hydroxide. If iron, particularly iron(III), is also present, the chromium(III) can also form insoluble iron complexes. The free energy of formation is lower for the mixed chromium/iron hydroxides than for chromium(III) hydroxide, and so the mixed hydroxides are expected to form preferentially (Rai & Dubey, 1989). The chromium(III) ion readily forms complexes with ligands such as hydroxyl, sulfate, ammonium, cyanide, sulfocyanide, fluoride, and chloride, as well as natural and synthetic organic ligands. In the aquatic phase, chromium(III) occurs mostly as suspended solids adsorbed onto clayish materials, organics, or iron oxide present in water. Approximately 10% of chromium in the aquatic phase of the Amazon and Yukon rivers was in solution, the rest being present in the suspended solid phase (Cary, 1982). The ratio of suspended to dissolved chromium in an organic-rich river in Brazil was 2:1 (Malm et al., 1988).

Sediment–water partition coefficients of approximately 30 000 l/kg have been reported for chromium(III) in both fresh water and seawater at pH 8 and 2–3% organic matter (Young et al., 1992; Wang et al., 1997). Soluble forms and suspended chromium can undergo intramedia transport. Chromium(VI) in water will eventually be reduced to chromium(III) by organic matter in the water. It has been estimated that the residence time of total chromium 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, 1984) and is not very mobile. A leachability study was conducted to study the mobility of chromium in soil. Owing to 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 (Lin et al., 1996). These results are 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 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 matters may increase the mobilization of chromium(III) in soils owing to the formation of soluble complexes (Stackhouse & Benson, 1989). This complexation may be facilitated by a lower soil pH. A smaller 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 iron oxide and the organic content of soil. Chromium that is irreversibly sorbed onto soil—for example, in the interstitial lattice of geothite (FeOOH)—will not be bioavailable to plants or animals under any conditions (Calder, 1988; Hassan & Garrison, 1996). Chromium(III) appears to be much more strongly adsorbed to soils than is chromium(VI) (Hassan & Garrison, 1996).

Organic matter in soil is expected to convert soluble chromate, chromium(VI), to insoluble chromium(III) oxide (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. On the other hand, 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 the hexavalent form in preference to the trivalent form; once absorbed, however, the hexavalent form is reduced to the more stable, trivalent state (IPCS, 1988). Chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary, 1982).

5.2 Environmental transformation

5.2.1 Air

In the atmosphere, chromium(VI) may be reduced to chromium(III) by vanadium (V^{2+}, V^{3+}, and VO^{2+}), Fe^{2+}, HSO_3^-, and As^{3+}. Conversely, chromium(III), if present as a salt other than chromium(III) oxide, may be oxidized to chromium(VI) in the atmosphere in the presence of at least 1% manganese oxide (ATSDR, 2000). However, this reaction is unlikely under most environmental conditions. The estimated atmospheric half-life for chromium(VI) reduction to chromium(III) was reported to be in the range of 16 h 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 is fast, and reduction half-lives range from instantaneous to a few days. 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 more rapid under anaerobic than under aerobic conditions. The reduction half-life of chromium(VI) in water with soil and sediment ranged from 4 to 140 days (Saleh et al., 1989). Dissolved oxygen by itself in natural waters did not cause any measurable oxidation of chromium(III) to chromium(VI) in 128 days (Saleh et al., 1989). 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 at 50 mg/l accelerated the process, decreasing the oxidation half-life to around 2 years (Saleh et al., 1989). Therefore, this oxidation process would not be important in most natural waters except in the presence of naturally occurring manganese oxides (Rai & Dubey, 1989; Richard & Bourg, 1991). The oxidation of chromium(III) to chromium(VI) during chlorination of water was highest in the pH range of 5.5–6.0 (Saleh et al., 1989). 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 to free available chlorine (USEPA, 1988). In chromium(III)-contaminated wastewaters with pHs ranging from 5 to 7, chlorination may convert chromium(III) to chromium(VI) in the absence of chromium(III) complexing and free chlorine reducing agents (ATSDR, 2000).

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 species in the trivalent oxidation state. This species and other chromium(III) species will predominate at more acidic pHs, whereas $Cr(OH)_3$ and $Cr(OH)_4^-$ predominate in more alkaline waters (Calder, 1988). In seawater, chromium(VI) is generally stable (Fukai, 1967).

5.2.3 Soil

The fate of chromium in soil is greatly 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 deeper soil, where anaerobic conditions exist, chromium(VI) will be reduced to chromium(III) by S^{2-} and Fe^{2+} present in 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; ATSDR, 2000). 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 soil, and the process is enhanced by pH values higher than 6 (Bartlett, 1991). Because most chromium(III) in soil is immobilized as a result of 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. Owing to 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 favourable pH conditions (Barth et al., 1965; 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 as possible remediation strategies 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 for chromium(VI) in fish are low, at around 1; however, once in the organism, chromium(VI) appears to be reduced to chromium(III), resulting in the accumulation of total chromium in the organisms to a factor of approximately 100 times the water concentration. Uptake of chromium(III) directly from water is likely to be very low owing to the limited water solubility of trivalent chromium compounds found in the environment and strong adsorption to sediment under most conditions in the environment.

The uptake of chromium(III) potassium sulfate, chromium(III)–ethylenediaminetetraacetic acid (EDTA) complex and chromium(III)–glycine complex by the freshwater alga *Chlorella pyrenoidosa* was studied by Meisch & Schmitt-Beckmann (1979). Bioconcentration factors ranged from 558 to 580, from 11 to 12, and from 224 to 254 for the three compounds, respectively, following 5 days of exposure to chromium concentrations of 0.5 and 1 mg/l.

In bottom-feeding bivalves, such as the oyster (*Crassostrea virginica*), blue mussel (*Mytilus edulis*), and soft shell clam (*Mya arenaria*), the bioconcentration factors for chromium(III) were found to range from 86 to 192 (USEPA, 1980, 1984; Fishbein, 1981; Schmidt & Andren, 1984). 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. Stackhouse & Benson (1989) reported that the accumulation of chromium was significantly reduced by the presence of humic acid. The bioconcentration factor for chromium(III) in 96-h exposures (10 mg/l) of *Daphnia magna* was reduced from 10 000 to 3000 by the presence of 50 mg humic acid/l.

Chromium is not expected to biomagnify in the aquatic food-chain.

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 aboveground parts of plants is unlikely (Petruzzelli et al., 1987).

Van Gestel et al. (1993) reported low bioconcentration factors for chromium(III) in earthworms (*Eisenia andrei*). Chromium nitrate was added to artificial soil; after 3 weeks, bioconcentration factors of 0.03–0.05 were determined at exposure concentrations ranging from 10 to 100 mg chromium(III)/kg dry soil. The elimination half-life for total chromium was estimated to be 51–109 days.

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

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Chromium occurs naturally in the Earth's crust. Continental dust is the main source of exposure to natural chromium present in the environment (Fishbein, 1981). As a result of human activities, however, chromium is released into the environment in larger amounts. 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.

6.1.1 Air

The atmospheric total chromium concentration in the USA is typically <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 United States Environmental Protection Agency's (USEPA) National Aerometric Data Bank (USEPA, 1984; ATSDR, 2000). 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 total arithmetic mean chromium concentrations were in Steubenville, Ohio, in 1977 (525 ng/m^3) and in Baltimore, Maryland, in 1980 (226 ng/m^3) (ATSDR, 2000). Arithmetic mean total chromium concentrations were above 100 ng/m^3 in only 8 of 173 sites monitored in 1984 (ATSDR, 2000). During the period 1978–1982, the maximum level of total chromium in ambient air samples in Corpus Christi, Texas, a site of chromate manufacture, was 5500 ng/m^3.

The annual average concentration of chromium in Corpus Christi ambient air was 400 ng/m^3 during the same period (Wiersema et al., 1984). The USEPA monitored two locations in Corpus Christi in 1981 and reported an arithmetic mean chromium concentration of 100 ng/m^3 (ATSDR, 2000).

The concentrations of atmospheric chromium in remote areas range from 0.005 to 2.6 ng/m^3 (Cary, 1982; Barrie & Hoff, 1985; Schroeder et al., 1987; Sheridan & Zoller, 1989). 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 National Air Sampling Network in the USA in 1964 gave the national average concentration for chromium in the ambient air as 15 ng/m^3, varying from non-measurable levels to a maximum 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.

Kieber et al. (2002) reported a volume-weighted annual average dissolved chromium(III) concentration of 0.04 µg/l for rainwater collected at Wilmington, North Carolina, USA (1999–2001).

6.1.2 Surface water

Total chromium concentrations in river water in the USA usually range from <1 to 30 µg/l (USEPA, 1984; Malm et al., 1988), with a median value of 10 µg/l (Smith et al., 1987; Eckel & Jacob, 1988). In Europe, a median concentration of 0.38 µg total chromium/l (<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 <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) composing 67% of the total (Riedel & Sanders, 1998). In March 1992, these concentrations decreased to 0.03–0.2 µg/l. 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 concentration of 1.57 µg chromium/l for post-treatment wastewater from a metal recycling plant. The river water samples contained about 60% chromium(III), and the wastewater contained about 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)/l and 3 µg chromium(VI)/l 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)/l and 0.1 µg chromium(VI)/l 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 for 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, around 50% of chromium(VI) concentrations.

Higher levels of chromium(III) have been found in industrial effluents. Ding et al. (2005) reported a concentration of 1 mg chromium(III)/l in industrial effluents, whereas wastewater from an electroplating plant contained around 4 mg/l (Kiptoo et al., 2004). Mean chromium(III) and chromium(VI) concentrations in wastewater 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)/l and 296 µg chromium(VI)/l 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). The highest chromium(III) concentrations have been reported in tannery effluents, with mean concentrations ranging from 1 to 44 mg/l (Prasada Rao et al., 1998; Dominguez & Arcos, 2002; Dominguez Renedo et al., 2004).

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 (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 chromium(VI)/chromium(III) ratios; 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 from 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). They noted that chromium(VI) is not detected in seawater samples that have been preserved for more than 4 h. In samples analysed immediately after collection, chromium(III) and chromium(VI) concentrations were found to be 0.04 and 0.05 µg/l, respectively. Yalçin & Apak (2004) reported a chromium(III) concentration of 2 µg/l for coastal waters in Avcilar, Turkey (Marmara Sea). Likewise, mean chromium(III) concentrations of 2–3 µg/l have been reported for coastal seawater in China (Yu et al., 2001; Tang et al., 2004).

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 sediments of water bodies, total chromium levels ranged from 1 to 500 mg/kg (USEPA, 1984; 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; for floodplain sediment, chromium concentrations were 59 mg/kg (5–2731 mg/kg) and 23 mg/kg (3–1596 mg/kg) after the two extractions, 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 concentration of 93 mg chromium/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).

6.1.4 Soil

Total chromium levels in soil 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 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 total chromium in 1319 samples of soils and other surficial materials collected in the conterminous USA was 1–2000 mg/kg, with a geometric mean of 37 mg/kg (USGS, 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 a mean chromium 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, which was a site listed on the National Priorities List in the USA (ATSDR, 2000). Hu & Deming (2005) found the mean "bioavailable" (EDTA extractable) total chromium concentration in soil samples to be 0.053 mg/kg dry weight (dw), 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, 1984).

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 dw, respectively (Ramelow et al., 1987).

Chromium levels in shellfish vary from <0.1 to 6.8 mg/kg dw (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 dw. Mean chromium concentrations ranging from 5 to 7.6 mg chromium/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, contained <0.3–2.7 mg chromium/kg wet weight (ww) (Greig & Jones, 1976).

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

Mean chromium concentrations in birds' eggs from a variety of geographical areas range from <0.2 to 1 mg/kg dw (Hothem et al., 1995; Hui et al., 1998; Burger et al., 1999), and mean liver concentrations range from 0.1 to 4.4 mg/kg dw (Hui et al., 1998; Burger & Gochfeld, 1999, 2000). Mean concentrations of chromium in bird feathers collected between 1988 and 1997 from the USA, China, and the Pacific basin ranged from 0.5 to 49.1 mg/kg dw. 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, 1995a; Burger et al., 1994, 2000).

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

6.2 Human exposure

6.2.1 General population exposure

The general population is exposed to trivalent chromium mainly orally from the daily diet. Use of chromium supplements can multiply the oral intake. Orthodontic appliances made of stainless steel may leach minimal amounts of chromium into the oral cavity. Small amounts of chromium enter the respiratory system in inhaled ambient air. Dermal exposure will result from the use of chrome-tanned leather in shoes and gloves, from cosmetic products containing chromium pigments, and from stainless steel articles lying on the skin, such as watches. Prosthetic implants made of chromium-containing alloys may degrade and release chromium internally.

6.2.1.1 Diet

The chromium content in most Finnish foods was below 100 µg/kg. In staple foods, particularly cereals and milk, concentrations were very low, 10 µg/kg or less. Processing may increase the concentration in food significantly. For example, meat grinding using stainless steel equipment almost doubled the chromium content in the meat (Kumpulainen, 1992). In basic Spanish foods, the ranges of chromium concentrations were 4–79 µg/kg in seafood, 7–456 µg/kg in cereals and vegetables, not detectable to 625 µg/kg in dairy products, and not detectable to 40 µg/kg in olive oil (Lendinez et al., 2001). In Austria, high levels were found in spices (59–4530 µg/kg) and cocoa and cocoa products (152–1840 µg/kg) (Wilplinger et al., 1995). Whole meal products contained 20–171 µg/kg, and fruits, vegetables, and meat, <15–44 µg/kg. High levels of chromium in some spices and aromatic herbs were confirmed in Spain (Garcia et al., 2000). In that country, chromium concentrations varied between non-detectable and 17.6 µg/l in fruit juices and between 3.6 and 60.5 µg/l in soft drinks (Garcia et al., 1999). The highest levels were analysed in orange soft drinks, possibly as a result of releases from stainless steel during production. Beer samples contained chromium at concentrations ranging from 0.5 to 56 µg/l (Anderson et al., 1992). The higher levels were attributed to external sources (e.g. during processing, preparation, or storage).

The concentration of chromium in uncontaminated water is low. Garcia et al. (1999) found that the chromium level in 15 samples of tap water in Spain was below the detection limit (i.e. <0.1 µg/l), whereas in 15 samples of commercial bottled water, the concentration varied between 4.2 and 11.8 µg/l. Total concentrations in drinking-water in the USA were reported to range from 0.4 to 8 µg/l, with a mean of 1.8 µg/l (ATSDR, 2000).

To estimate the dietary intake in the USA, Anderson et al. (1992) analysed the chromium content of 22 prepared daily diets designed by nutritionists. As all individual food items were analysed as eaten, the potential release of chromium from kitchenware and utensils was included. The intake ranged from 2.0 to 5.6 µg/MJ, with a mean of 3.2 ± 0.3 µg/MJ. Based on the mean caloric intake by adult men and women of 9.0 and 7.7 MJ/day, respectively (Anderson et al., 1993), the corresponding

dietary intakes were 18–51 and 15–43 µg/day. Similar assessments of the daily dietary intake gave a mean of 34.4 µg/day (range 28.5–44.7 µg/day) in Austria (Wilplinger et al., 1996), a mean ± standard deviation of 58 ± 31 µg/day in Belgium (Van Cauwenbergh et al., 1996), and a range from 16 to 117 µg/day in Spain (Garcia et al., 2001). Kumpulainen (1992) concluded that the dietary intake of chromium in Finland, Sweden, and Switzerland was 50 µg/day or lower, whereas in many developing countries, such as Brazil, Sudan, and Iran, the corresponding intakes were 2 times higher.

In the USA and Finland, the average chromium content of human milk was reported to be below 0.5 µg/l, which would result in a low average intake of 0.3 µg chromium/day by breastfed infants (Kumpulainen, 1992). However, ICP-MS analysis of chromium in milk samples collected from 27 healthy mothers in Austria gave higher concentrations, ranging from <0.8 to 163 µg/l (mean 24.3 µg/l) (Krachler et al., 2000).

6.2.1.2 Food supplements

Under legislation in the European Union, chromium(III) chloride and chromium(III) sulfate can be used in the manufacture of food for particular nutritional uses and in food supplements. Apart from these salts, more bioavailable organic chromium complexes (chromium picolinate, nicotinate) are widely used as supplements and as weight loss agents (e.g. in the USA). Recommended daily regimens of chromium supplements available on the market contain 200–600 µg trivalent chromium, and multivitamin supplements contain up to 100 µg chromium in a daily serving unit (EVM, 2003).

6.2.1.3 Orthodontic appliances

Orthodontic bands, brackets, and wires made of stainless steel contain 17–22% chromium (Kocadereli et al., 2000). Studies investigating the release of chromium from orthodontic appliances into saliva have provided conflicting results (Kerosuo et al., 1997; Kocadereli et al., 2000; Agaoglu et al., 2001). A large variation was observed in chromium concentrations in saliva in two studies, and there was no increase in chromium concentrations in samples taken before and after insertion of the appliances. The amount of chromium potentially ingested as a result of release from orthodontic appliances is probably negligible compared with the dietary intake.

6.2.1.4 Ambient air

Levels of chromium in air are summarized in section 6.1.1. Generally, chromium concentrations in air vary with location, being very low in unpolluted regions. A typical range of <0.01–0.03 µg chromium/m^3 in ambient air was used by the United States Department of Health and Human Services (ATSDR, 2000) to estimate the exposure to chromium via inhalation (i.e. <0.2–0.6 µg/day).

6.2.1.5 Consumer goods

About 80% of leather products are currently tanned with chromium(III) salts, notably basic chromium sulfate (Graf, 2001). Tanned leather contains about 3% chromium (Nygren & Wahlberg, 1998). It has been reported that chrome-tanned leather products may also contain low concentrations of chromium(VI) (Nygren & Wahlberg, 1998; Hansen et al., 2002), but its true occurrence is still debated because of analytical complications. Human sweat may extract soluble, unbound chromium from chrome-tanned leather. Higher levels of unbound chromium(III) may occur in the leather if washing has not been done properly after tanning. In an old study, specimens of shoe leather immersed in human sweat were reported to release 20–300 µg total chromium/ml sweat (Samitz & Gross, 1960). Fregert & Gruvberger (1979) measured both total chromium and chromium released from seven samples of industrial leather gloves into synthetic sweat at pH 6.5 during 1 week. Total chromium ranged from 11 000 to 36 000 µg/g, and the chromium released ranged from 100 to 1300 µg/g. A more recent study measured the amount of free chromium(III) capable of migrating from the upper of baby shoes to an aqueous solution of hydrochloric acid with a pH of 1–1.5 during 2 h at 37 °C and found 370 and 560 µg/g leather for two shoes, respectively (Hansen et al., 2002). Unfortunately, no accurate data are available regarding the actual chromium(III) concentrations at the surface of the skin derived from wearing leather shoes or gloves.

Insoluble green chromium pigments (chromium hydrates) are used in soaps and cosmetics (e.g. eye shadows). Chemical analysis of some eye shadow colours on the market revealed a total chromium concentration above 2000 mg/kg (Sainio et al., 2000). A typical amount of "eye make-up powder" per application is 0.01 g (European Commission, 2003), and the typical frequency of use is once daily. Thus, the daily topical dose of (insoluble) chromium could be up to 20 µg.

There are no data available on the release of chromium from stainless steel articles such as watches, jewellery, and fasteners of clothing that lie in direct contact with skin.

6.2.1.6 Orthopaedic implants

Total hip and knee replacements made of cobalt–chromium alloy or stainless steel can corrode and release metal debris from wear (Case et al., 1994; Merritt & Brown, 1996). Loosening of the implant and local inflammation are expected to aggravate the release of

metals (Hennig et al., 1992). Black et al. (1983) estimated that dissolution of metals from a total hip replacement could be 0.15–0.30 µg/cm^2 per day, or 30 µg/day and 11 mg/year. There are reports of increased tissue chromium in patients carrying especially metal on metal total hip replacements. More recent advancements in implant design and composition and surgical techniques reduce the likelihood and magnitude of internal exposure to chromium in patients.

6.2.2 Occupational exposure

A wide variety of exposures to trivalent chromium compounds may occur in activities related to production, formulation, and uses (Kirk-Othmer, 2003; Riihimäki & Luotamo, 2006). Some of the processes or applications involve intentional or unintentional transformation of trivalent chromium to hexavalent chromium. The former applies to the manufacture of chromium chemicals from chromite ore, whereby sodium dichromate is produced as a chemical intermediate. Hexavalent chromium is inadvertently generated from trivalent chromium under oxidizing and alkaline conditions, such as in the use of refractories.

The following text deals with meaningful exposures to trivalent chromium, where the more toxic hexavalent compounds are excluded because of their likely overriding health significance.

6.2.2.1 Chromium(III) oxide

Exposure to chromium oxide occurs in chromite mining and processing, ferrochrome production, and the production of chromium oxide, chromium carbide, and chromium refractories. Other sources of occupational exposure derive from the uses of chromite sand, ferrochrome slag, and chromium oxide pigments and catalysts. Metallic chromium exposed to air is immediately oxidized and covered with chromium(III) oxide. Therefore, processes and applications dealing with chromium metal or its alloys also involve exposures to oxide. The smaller the airborne particles generated, the greater the mass fraction of chromium oxide. An important area of potential exposure is the manufacture and tooling of products made of chromium alloys, especially stainless steel.

Workers are exposed to airborne dusts of chromium(III) oxide. The highest measured or estimated levels were found in chromite ore mining (1 mg chromium/m^3), bagging of refractory materials (3.5 mg chromium/m^3), use of chromite sand (1.5 mg chromium/m^3), handling of chromium oxide pigments or catalysts (0.6–0.7 mg chromium/m^3), and polishing of stainless steel (1.2 mg chromium/m^3) (Riihimäki & Luotamo, 2006).

6.2.2.2 Inorganic chromium(III) salts

The most common trivalent chromium salt is basic chromium sulfate, which is used for leather tanning. Other chromium(III) compounds (e.g. chlorides, fluorides, phosphates, nitrates, and hydroxides) are found in miscellaneous applications, such as catalysts, hardeners, mordants, and crosslinking and binding agents (Kirk-Othmer, 2003). For most of these compounds, information on the processes and use conditions is scarcely available. In addition to leather tanning, basic chromium sulfate is used for electroplating. Chromium chloride is also used for trivalent electroplating.

Inhalation exposure to basic chromium sulfate in the tanning process was low (about 0.03 mg chromium/m^3) (Riihimäki & Luotamo, 2006). According to one report, some tannery workers had remarkably increased chromium levels in urine, which the authors attributed to probable entrance of airborne droplets of the tanning liquor into the mouth and ingestion (Aitio et al., 1984). Polishing (buffing) of tanned leather is dusty, and airborne levels up to 0.3 mg chromium/m^3, mainly in non-respirable large particles, have been measured (Stupar et al., 1999). Airborne chromium levels in trivalent electroplating are presumed to be very low (Riihimäki & Luotamo, 2006).

6.3 Levels in humans

6.3.1 General population

Trivalent chromium is considered to be an essential trace element in mammals (see section 9.1), which implies that endogenous chromium is homeostatically maintained.

Chromium occurs at very low levels in the human body. Concentrations less than 0.2 µg/l in serum and plasma and slightly higher levels in whole blood and urine (<0.5 µg/l) are currently considered as normal (Brune et al., 1993; Kumpulainen, 1995; Fagliano et al., 1997). However, since urinary excretion depends on the daily intake, which may vary considerably (processed meats, whole grain products, pulses, spices, and beverages such as beer contain higher amounts), urinary chromium in successive spot samples may vary considerably (Gargas et al., 1994). Intake of chromium supplements caused a still more marked (at least 10-fold) but transient increase in urinary concentrations (Gargas et al., 1994).

Lung chromium concentrations measured in accidental or violent cases of death in Germany were 133–277 ng/g ww (Raithel et al., 1993), whereas corresponding concentrations measured in Belgium were 32–181 ng/g (Vanoeteren et al., 1986). Chromium levels in the lungs were higher in subjects living in polluted areas (250–7070 ng/g dw) than in those living in an unpolluted

area of Germany (60–150 ng/g dw) (Kollmeier et al., 1990), and the concentrations were usually higher in older people (Vanoeteren et al., 1986). (Note that dry weight concentrations are approximately 3.5 times higher than wet weight concentrations.)

In Finnish infants and children under the age of 9, chromium concentrations in the liver ranged from 4 to 15 ng/g dw and in the spleen from 7 to 29 ng/g dw (Vuori & Kumpulainen, 1987). In four elderly persons who died of non-diabetic causes in Germany, concentrations in the liver, spleen, and kidney were <14 ng/g dw, 134 ± 117 ng/g dw, and <39 ng/g dw, respectively (Michels et al., 1991).

Orthopaedic patients carrying (especially total hip or knee) implants made of chromium alloys have sometimes had markedly increased chromium concentrations in serum, urine, and tissues due to corrosion or wear of the implant. In some cases, chromium concentrations in serum and urine were found to be increased by 10-fold or more compared with the normal levels (Jacobs et al., 1996; Schaffer et al., 1999), and corresponding findings have been made in tissues surrounding the implant (Hennig et al., 1992) as well as in distant organs (Michels et al., 1991; Case et al., 1994). With recent developments in the composition and design of implants, such internal exposures to released chromium are expected to have become less frequent.

Thermally induced sweat was found to contain about 0.7 µg chromium/l (Stupar et al., 1999). The mean chromium concentration in human milk samples from Finland and the USA was reported to be <0.5 µg/l (Kumpulainen, 1992), whereas the corresponding levels in 27 samples in Austria varied from <0.8 to 163 µg/l (mean 24.3 µg/l) (Krachler et al., 2000).

Conflicting evidence has been provided on the relationship between serum or urinary chromium and age. Recent observations from over 40 000 ambulatory patients indicated a steady decline of chromium levels in serum, sweat, and hair from childhood into old age, and concentrations in the three tissues correlated with each other (Davies et al., 1997). At old age, the concentration in serum had decreased by 42%.

The total body reservoir of chromium was estimated as 0.4–6 mg and, relative to body size, may be higher in neonates than in adults (Dubois & Belleville, 1991). The upper-range value was, however, based on old measurements, and the true body burden in normal adults may be an order of magnitude lower (Lim et al., 1983). It has been noted that chromium levels in serum, urine, or hair are not reliable indicators of body stores of chromium (Offenbacher & Pi-Sunyer, 1988; Mertz, 1993; Jeejeebhoy, 1999; Gunton et al., 2001).

6.3.2 Occupationally exposed populations

Urinary chromium among ferrochromium production workers exposed to trivalent chromium oxide and among unexposed clerks was studied (Foa et al., 1988). Urinary chromium concentrations were stable among unexposed clerks (0.60–0.58 µg/g creatinine) during the work day and over the work week. Production workers had significantly increased urinary concentrations, ranging from 0.94 to 1.21 µg/g creatinine during the work shift and to 1.25 µg/g creatinine at the end of the working week. Subcontractors also showed an increase in urinary chromium concentrations from 0.77 to 0.96 µg/g creatinine over the shift and to 1.05 µg/g creatinine over the work week (Foa et al., 1988).

In Finland, production of ferrochromium covers the whole chain from chromite mining to stainless steel manufacture. The mean urinary chromium concentrations varied from 0.5 µg/l in miners to 2.1 µg/l in steel smelters. In the mine, no hexavalent chromium was found in personal air samples; in the steel melting shop, the highest concentration of hexavalent chromium was 6.6 µg/m^3 (Huvinen et al., 1993).

Tannery workers exposed to basic chromium sulfate or chromium(III) in leather dust exhibited 4 µg chromium/g in hair, 1.7 µg chromium/g creatinine in urine, and 25 µg chromium/l in sweat; these concentrations were significantly higher than those in the control group (0.16 µg/g in hair, 0.13 µg/g creatinine in urine, and 0.7 µg/l in sweat) (Stupar et al., 1999). In the buffing department, the mean chromium level in the urine of workers, 2.35 µg/g creatinine, was clearly higher than that measured in the chrome tanning process, 1.11 µg/g.

In a tannery, Kornhauser et al. (2002) measured the chromium body burden in workers from the tanning and retanning departments, in workers from the dyeing, drying, and finishing departments, and in control subjects. Both serum and urine samples were collected, and the highest concentrations were in workers from the tanning and retanning departments: 0.43 µg/l in serum and 1.78 µg/l in urine. The mean values in controls were 0.13 µg/l in serum and 1.35 µg/l in urine.

A week's follow-up of tannery workers who were exposed to chromium(III) from basic chromium sulfate in four different tanneries was performed by Randall & Gibson (1987). The Monday morning urinary chromium concentration, 0.51–1.16 µg/l, was clearly lower than that of Friday afternoon, 0.56–2.57 µg/l. Also, the median serum (0.49 µg/l) and urinary concentrations (0.96 µg/l) were significantly higher in tannery workers than in the control population (serum, 0.15 µg/l; urine, 0.24 µg/l).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The toxicokinetics of trivalent chromium species strongly depend on physical-chemical properties, particle characteristics (mainly size), and the route of administration (Visek et al., 1953; Sayato et al., 1980; Anderson et al., 1996; O'Flaherty et al., 2001).

7.1 Absorption, distribution, and excretion

7.1.1 Chromium(III) oxide

The toxicokinetics of chromium oxide have been investigated primarily after administration into the respiratory system.

Chromium oxide particles are insoluble in water and organic solvents. Consequently, absorption is strongly limited during passage through the gastrointestinal tract or from the skin. Particle size–dependent deposition and clearance processes with mucociliary clearance and phagocytosis are the main toxicokinetic features in the respiratory system. Little is known of pure chromium oxide, but studies with fine chromite particles and fumes from welding of stainless steel with the metal inert gas method may provide helpful information.

A suspension of chromium oxide particles with a mean geometric mean diameter of 0.45 μm was instilled into the tracheal lobe of sheep (Perrault et al., 1995). Bronchoalveolar lavage samples taken over 30 days showed the half-time of elimination to be about 11 days. According to transmission electron microscopy analysis and the surface composition and valency analyses, the size of chromium oxide particles remained unchanged over the 30 days, and the state of oxidation did not show any measurable change.

Swensson (1977) injected 40 mg of chromite particles ground to less than 5 μm in diameter in saline into the trachea of rats. Rats were killed at intervals over 8 months, and the mass of the remaining particles in the lungs was determined with emission spectrophotometry. From the decay curve, the half-time of elimination was calculated to be about 6 months.

Nose-only exposure of rats to metal inert gas/stainless steel welding fumes characterized as long chains and agglomerates of submicrometre particles containing 4–15% chromium mainly in trivalent or metallic form and iron, manganese, nickel, and silicon for 1 h/day, 5 days/week, over up to 4 weeks resulted in a gradual increase in lung chromium content with exposure duration (Kalliomäki et al., 1983). Clearance of chromium was slow, with an estimated half-time of approximately 240 days. However, in a further study, when metal inert gas/stainless steel welding fumes collected on filters were neutron activated, suspended in saline, and instilled into the trachea of anaesthetized rats, practically no decrease in the pulmonary content of chromium, iron, nickel, or cobalt was noted over the first 2 months after exposure (Kalliomäki et al., 1986). In the first study, clearance functions varied for the different elements, suggesting that the particles were gradually dissolved, whereas in the second study, all the metal components of the suspended welding fume had a similar slow clearance from the respiratory system, indicating different toxicokinetic behaviour of de novo metal inert gas/stainless steel welding fumes from the "aged" particles.

Plasma cutting of stainless steel generates fumes containing the alloyed metals, including chromium, which is mainly in trivalent and metallic form. A plasma cutter exposed to these fumes for 7 years had elevated concentrations of chromium in serum (10.3 μg/l) and urine (10 μg/g creatinine), with a very slow decrease, with half-times of 40 months in serum and 129 months in urine (Petersen et al., 2000).

7.1.2 Inorganic chromium(III) salts and complexes

The main body of available data concerns water-soluble chromium(III) salts: hydrated forms of chromium chloride and chromium potassium sulfate (chrome alum), basic chromium sulfate, and chromium nitrate. It is generally considered that trivalent chromium is poorly absorbed and taken up by cells when not in organic complexes, such as in the glucose tolerance factor, which is a material isolated from porcine kidney (Schwarz & Mertz, 1957, 1959). During and after absorption, chromium(III) is expected to form various, so far poorly characterized, coordination complexes with low molecular weight ligands, which may enhance absorption and enable the element to enter tissues and traverse cell membranes. There is no evidence of a change in valency during the metabolism of trivalent chromium.

7.1.2.1 Oral exposure

Sayato et al. (1980) administered $^{51}CrCl_3$ (0.1 mg chromium/kg bw) by a stomach tube to rats and measured the radioactivity in the whole body, urine, and faeces daily for 30 days. Retention of ^{51}Cr after 2 days was less than 1% of the dose, and on day 30, it was 0.3%. After the first 6 days, the elimination of radioactive chromium in the body had a half-time of about 92 days. Over 20 post-administration days, 99% of the oral dose was excreted in faeces and 0.8% in the urine. Similar findings were made with rats given 1 ng of $^{51}CrCl_3$ in saline by a stomach tube: the excretion of the

radiolabel over 7 days in faeces and urine was 98% and 1.4%, respectively (Donaldson & Barreras, 1965).

Similar oral bioavailability levels have been observed in humans. Donaldson & Barreras (1965) gave $^{51}CrCl_3$ at a dose of 20 ng orally to six fasting subjects; for two patients, the dose was administered through a tube placed in the duodenum. Urine was collected for 24 h and faeces for 6 days, and both were assayed for radioactive chromium. After oral administration, the mean recovery of faecal radioactivity was 99.6%, and the recovery in urine was 0.5%. After duodenal administration, the corresponding figures were 93.7% and 0.6%. Anderson & Kozlowsky (1985) demonstrated the dependence of the degree of absorption on intake. They noted that when the intake was low (10–15 µg/day), absorption was about 2%, gradually decreasing with increasing intake. At intake levels of about 40 µg/day or higher, absorption was only 0.4%. The finding is in support of a regulatory mechanism in the human intestine to ensure relatively constant amounts of absorbed chromium.

Other factors also modify gastrointestinal absorption of chromium(III). In rats, co-administration of $^{51}CrCl_3$ with phytate and with oxalate significantly decreased and markedly increased, respectively, chromium absorption (Nelson et al., 1973). Experiments with rats given $^{51}CrCl_3$ showed that ascorbic acid and a prostaglandin inhibitor, aspirin, enhanced intestinal absorption of chromium, whereas an antacid containing aluminium and magnesium hydroxide reduced it (Davis et al., 1995). Sullivan et al. (1984) demonstrated that ^{51}Cr as chromium chloride was absorbed 10 times more efficiently from the gastrointestinal tract of 2-day-old rats than from the intestine of the adult rat.

In humans, ascorbic acid enhanced chromium chloride absorption (Offenbacher, 1994). Offenbacher (1994) proposed that ascorbate chelated chromium and made it more soluble and more readily absorbed. In a study by Kerger et al. (1996), the toxicokinetics of a chromium(III) complex that was derived from prior reduction of potassium dichromate with orange juice (chromium(III)–OJ) were investigated with volunteers, with chromium chloride as a reference. The estimated bioavailability of chromium chloride was lower than that of chromium(III)–OJ, 0.13% and 0.6%, respectively, and the elimination half-time of chromium chloride in urine was shorter than that of chromium(III)–OJ, ~10 h and ~17 h, respectively. Although chromium(III)–OJ exhibited 4-fold higher bioavailability than chromium chloride, it showed clearly lower plasma concentrations, suggesting a more rapid clearance from plasma to tissues, which is also in keeping with slower elimination via the urine. The authors proposed that ingested ionic chromium(III) may not be able to form bioavailable chromium(III) complexes as readily because of lower solubility and tissue permeability.

Oral bioavailability and tissue distribution studies on chromium chloride and organic chromium complexes with rats employing single gavage or dietary administration for 3 weeks showed that whereas bioavailability did not vary significantly among the different chromium species, incorporation into tissues, especially the kidney, was highly dependent on the species (Olin et al., 1994; Anderson et al., 1996). Among inorganic chromium compounds, incorporation in the kidney after 3 weeks of dietary exposure was high for chromium potassium sulfate (407 ng/g) and chromium acetate (397 ng/g) compared with chromium chloride (74 ng/g). Control rats had chromium levels of 23 ng/g in kidney. Liver chromium content was significantly increased from control levels with chromium acetate, but not with chromium chloride or chromium potassium sulfate (Anderson et al., 1996).

Mertz et al. (1969) administered radiolabelled chromium chloride hexahydrate ($^{51}CrCl_3 \cdot 6H_2O$) orally to pregnant rats 5 days/week and counted the radioactivity of the litter after the birth. According to the results, the radioactivity of the whole litter accounted only for 0.45–1.57% of that of the mother. However, administration of chromium in a complex with glucose tolerance factor resulted in high accumulation of chromium in the litters (Mertz et al., 1969).

In in vitro studies on gastrointestinal absorption, it has been shown that the absorption of trivalent chromium occurs by passive diffusion (Dowling et al., 1989). However, dietary amino acids may enhance chromium absorption and reduce the retention in the intestinal wall. It has been hypothesized that amino acids act as chromium ligands, resulting in rapidly diffusing chromium complexes of low molecular weight (Dowling et al., 1990). An organic complex, chromium picolinate, has demonstrated higher permeability through rat jejunum compared with inorganic chromium compounds. Measurements by the rat everted gut sac technique indicated that the permeability of picolinate across the rat jejunum was more than 10 times greater than that of chromium chloride or nitrate, whereas there was no difference between the latter two (Gammelgaard et al., 1999).

7.1.2.2 Inhalation exposure

Rats were exposed to aerosols (particle size 1.5–1.8 µm) of aqueous solutions of chromium chloride at 10.7 mg/m^3 for 2 h or at 8 mg/m^3 for 6 h (Suzuki et al., 1984). Chromium was analysed in the blood components, kidney, liver, heart, spleen, and testis at intervals over 7 days after the 2-h exposure using AAS. Retention and elimination of chromium in the lung were estimated

from chromium measurements in the context of both 2- and 6-h exposures. The lung concentrations immediately after exposure were nearly proportional to the product of exposure concentration and time, and the concentrations declined linearly, with an elimination half-time of 164 h (6.8 days). In the 2-h exposure group, the chromium concentration in the blood cells was about half of the concentration in plasma immediately after exposure and about the same as the concentration in plasma in later samples. The tissue concentrations relative to the lung at later time points were slightly above 1% for the kidney and slightly below 1% for the spleen (in both cases with an increasing tendency over time), about 0.5% for the liver and heart, slightly less than 0.5% for the testis, and about 0.25% for the whole blood.

Syrian hamsters were exposed to nebulized liquid aerosols (median particle diameter 1.2 µm) of chromium chloride labelled with ^{51}Cr at 2.8 or 77 mg/m^3 for 30 min (Henderson et al., 1979). At 2 h, the labelled chromium lung burdens were 0.71 µg and 20.4 µg at the low and high exposure levels, respectively (i.e. directly proportional to the exposure concentrations). Labelled chromium in the liver and kidney at 2 h was 4% of the lung burden; lower levels were found at day 1. The lung burden decreased by 60% during the subsequent 3 weeks. The corresponding elimination rate of ^{51}Cr in the liver was similar to that in the lung and somewhat faster than that in the kidney.

Intratracheal instillation has been used as a surrogate of inhalation exposure. An early study by Visek et al. (1953) with ^{51}Cr-labelled chromium chloride in rats showed that 55% of the intratracheally administered chromium was excreted in the faeces and 7% in the urine in 7 days. Apparently, most of the dose had been cleared from the respiratory tract to the oral cavity. The authors estimated that probably less than 5% was absorbed from the lungs.

In a study by Baetjer et al. (1959), after the intratracheal injection of 200 µg of chromium chloride hexahydrate to guinea-pigs, 69% of the dose was recovered from the lungs and 4% in the blood (mainly in plasma) and other tissues immediately after injection. At 24 h, 45% was retained in the lungs, 6% was excreted in urine, and small amounts were found in the liver and spleen. At day 30 post-injection, 30% of the dose was still present in the lung; at day 60, 12% of the dose remained in the lung.

Edel & Sabbioni (1985) injected four male Sprague-Dawley rats intratracheally with either 0.1 µg or 10 µg of ^{51}Cr-labelled chromium(III) as chromium chloride. In the former case, the animals were killed after 24 h, in the latter case, after 7 days. At the termination of the 24-h study, about 5% of the dose was recovered in lung lavage; the lungs and trachea still contained 23% of the radiotracer dose per gram of tissue (lungs and trachea constitute about 0.5% of body weight, or about 1 g), whereas other tissues contained trace amounts, and none was detected in the pancreas, brain, heart, thymus, skin, fat, or muscle. In the blood, 85% of the label was in plasma, and 15% was in the cells. Analysis of the subcellular distribution of ^{51}Cr in the lung homogenate indicated that 42% was in the nuclear fraction, 24% in the mitochondria, 21% in lysosomes, and 10% in cytosol, of which 33% was dialysable. In the 7-day study, 3.6% of the administered chromium was excreted via urine, whereas more than 36% was eliminated via faeces, mainly during the first 2 days.

Similar results on absorption and distribution pattern have also been obtained with rabbits treated intratracheally with $^{51}CrCl_3$ (Wiegand et al., 1984). A study with chromium acetate hydroxide in male rats (Gao et al., 1993) also demonstrated higher concentrations of chromium in plasma compared with whole blood. No chromium was found in lymphocytes. Peak concentrations in all specimens were obtained at 6 h, and the levels did not return to control values within 72 h. Urine contained remarkably high concentrations, with a peak at 6 h after exposure. From the urinary excretion curve, it was estimated that about 7% of the dose was excreted in urine during the first 24 h. After a rapid drop in blood and urinary chromium during the first 24 h, the rate of decrease of concentration in plasma and urine had slowed down to approximately 20% over the 3rd day of follow-up.

Compared with intratracheal instillation, the previously described inhalation experiments (Henderson et al., 1979; Suzuki et al., 1984) likely resulted in more effective chromium deposition in the lung, which enhanced pulmonary absorption and decreased the likelihood of mucociliary clearance. Nevertheless, both types of administration indicated that a fraction of the deposited chromium(III) was absorbed rapidly, followed by slow elimination, consistent with extensive binding in the lung and airway mucosa.

In a tannery, two workers fed soaking wet hides into a press, and four workers received the hides on the other side of the press (Aitio et al., 1984). The tanning liquid was reported to contain 7 g chromium(III)/l. The absence of chromates was verified by the diphenylcarbazide reaction. Airborne chromium levels (inhalable fraction) were always below 30 µg/m^3. However, feeding the hides to the press generated a visible cloud of large droplets, and splashes to the face were not uncommon. The operators of the press had high levels of chromium in blood and urine, whereas the receivers generally showed concentrations at the limit of detection. Among two press operators, whole blood chromium reached 6.8 and 11 µg/l, and plasma chromium, 13 and 22 µg/l, respectively. Thus, chromium was

confined to the plasma. One of the operators showed occasional, transient high peaks (up to 62 µg/l) in urinary chromium, whereas the basal levels in both operators towards the end of the week and during the exposure-free weekend ranged from 10 to 15 µg/l. After an interval of 10 days without exposure, the two operators both had 10 µg chromium/l in urine; after a vacation of 40 days, the concentrations were 4.8 and 6.2 µg/l, respectively. Assuming that the basal level at the end of work had been 10–15 µg/l, the half-time of chromium in urine was about 30 days. The investigators assumed that absorption of basic chromium sulfate among the press operators actually took place in the gastrointestinal tract.

In another study of tannery workers (Randall & Gibson, 1987), chromium in urine significantly increased from the first to the last day of the work week. Concentrations in serum and urine correlated with each other, but neither of them correlated with the length of employment in the tanning industry. Thus, long-term accumulation did not seem to occur, which was also demonstrated in a subsequent study in the same laboratory among five men whose employment in a tannery had ceased 9 months earlier and among two men who had retired 15 or 33 months earlier (Simpson & Gibson, 1992). Similar results were also obtained in a study by Stupar et al. (1999), who measured chromium in hair samples obtained from six ex-workers of a tannery who had been on retirement for 2–5 years. The retired workers exhibited chromium levels in hair similar to those of the controls.

7.1.2.3 Dermal exposure

No relevant animal studies on skin absorption of chromium(III) compounds were located.

Mali et al. (1963) performed skin penetration experiments on chromium chloride and chromium sulfate (1.2% chromium labelled with ^{51}Cr) with skin chambers glued to the skin of normal volunteers. Chambers were removed at 6, 12, or 24 h, and radioactive chromium was analysed in the stratum corneum of the chamber site as well as in the underlying epidermis and dermis cut out with a punch biopsy. As no label was found in the dermis, the authors concluded that chromium(III) salts did not permeate through the intact epidermis. Some blood samples and 24-h urine were also examined, and no radioactive chromium was detected.

An experiment was performed in which one male volunteer held his hand in a tanning solution containing 7 g chromium/l as basic chromium sulfate for 1 h (Aitio et al., 1984). The concentrations of chromium in blood and urine were monitored for 24 h. No increases in chromium levels were detected in the samples, and no difference in chromium concentration was found in the cubital venous blood drawn from the exposed side compared with the contralateral sample. The sensitivity of the method, however, was not sufficient to detect slight deviations from endogenous baseline levels of chromium.

Wahlberg & Skog (1965) explored the percutaneous penetration of chromium chloride in guinea-pigs using a disappearance technique and ^{51}Cr-labelled compound. The maximum penetration rate was 330 µmol chromium/cm per hour, and the mean relative absorption in 5 h was 2% from 0.239–0.261 mol/l solutions. Sodium chromate exhibited 2 times higher penetration. The method provides information on substance transfer and binding in the skin, but it is not informative on the amounts that are ultimately absorbed into the systemic circulation.

An in vitro skin penetration study on chromium chloride hexahydrate (0.034 or 0.17 mol chromium/l, pH buffered to 3.0), chromium nitrate nonahydrate (0.034 mol chromium/l, pH buffered to 2.8), and potassium dichromate (0.034 mol chromium/l) was conducted employing a modern gas diffusion cell and full-thickness human abdominal skin (Gammelgaard et al., 1992). After the test duration of 190 h (when the skin barrier was still found intact), no chromium was detected in the recipient phase after exposure to chromium chloride or chromium nitrate. Moreover, the chromium concentrations in the skin layers were about 10 times lower after chromium chloride application and about 15–30 times lower after nitrate application than the corresponding concentrations after application of potassium dichromate. A 5-fold increase in the applied chromium chloride concentration did not increase chromium levels in the skin.

7.1.2.4 Intravenous studies

Several studies employing intravenous administration have been conducted. The intravenous route is unnatural and can lead to artefacts due to the formation of colloids or complexes of trivalent chromium, which are trapped by the reticuloendothelial system (Visek et al., 1953). However, these studies of intravenously administered chromium(III) support findings from oral and inhalation studies on chromium distribution in various organs, the most prominent organs of chromium distribution being liver, kidneys, spleen, and bone (Hopkins, 1965; Onkelinx, 1977; Sayato et al., 1980). Growing bone in particular takes up chromium (Hopkins, 1965).

Regarding chromium transfer to reproductive organs, an increase in chromium(III) levels has been seen in testicular tissue after intravenous, intraperitoneal, or subcutaneous administration of chromium(III) chloride (Hopkins, 1965; Sipowicz et al., 1997). An autoradiographic study on testis showed that after an

intravenous injection of radiolabelled chromium chloride, the label is taken up in the interstitial compartment of the testis (Danielsson et al., 1984). Danielsson et al. (1982) studied chromium distribution in fetuses 1 h after the intravenous injection of radioactive chromium chloride on gestational day 11, 13, or 16. An accumulation of chromium was seen in the visceral yolk sac placenta. No detectable levels of chromium were found in embryonal tissues on day 11; even on gestational day 16, only low levels were detected in the calcified areas of the fetal skeleton. When pregnant rats were treated with an intravenous injection of radioactive trivalent chromium on gestational day 17 and sacrificed 3 days after the treatment, chromium was found to accumulate in the placenta. On average, 11.4% of the total dose was found in the pregnant rat uteri containing 10–16 placento-fetal units (Wallach & Verch, 1984).

Studies dealing with toxicokinetic models are presented in section 7.3.

7.2 Association of chromium(III) with blood components

Chromium(III) binds in plasma to transferrin (Hopkins, 1965; Sayato et al., 1980) and albumin. The distribution of ^{51}Cr(III) in the plasma from a healthy individual was characterized with fast protein liquid chromatography (Cornelis et al., 1992). The major part (85%) was associated with transferrin and 8% with albumin, and about 6% was spread over other proteins. Harris (1977) isolated transferrin from pooled human serum and showed with electron paramagnetic spectra that trivalent chromium binds under in vitro conditions to both sites A and B, but iron added to dichromium transferrin selectively displaces chromium from site A. Chromium was found to bind competitively with iron or aluminium to human apotransferrin in the presence, but not in the absence, of bicarbonate, citric acid, or oxalic acid (Moshtaghie et al., 1992). A study with a haemochromatosis patient showed that excessive iron burden displaces chromium from transferrin, and a larger share of chromium is unbound (Lim et al., 1983). Chromium could thus interfere with iron metabolism, and vice versa.

Trivalent chromium binds to an oligopeptide called low-molecular-weight chromium-binding substance (LMWCr), with a molecular mass of about 1500 daltons, which has been found in the liver and many other organs (Wada et al., 1983; Yamamoto et al., 1989; Vincent, 1999). LMWCr is believed to be central in the endogenous metabolism of chromium (see section 9.1). Wada et al. (1983) studied urinary excretion and renal clearance of LMWCr and chromium chloride in Japanese White rabbits following an intravenous injection of 500 µg chromium/kg bw as each of the two compounds. The chromium dose in LMWCr was excreted more rapidly than chromium chloride: 66% versus 25% in 6 h. LMWCr may play an important role in chromium excretion in mammals.

The distribution of chromium chloride in blood components in vitro was studied by Lewalter et al. (1985). Blood was spiked to 50 or 500 µg chromium/l and incubated for 10 min; after centrifugation, chromium in plasma and erythrocytes was measured with GAAS. At the lower concentration, plasma contained 48 µg chromium/l and red blood cells less than 1 µg chromium/l. At the higher concentration, the corresponding levels were 455 and 36 µg/l. Addition of ascorbic acid had no effect on chromium distribution. Dialysis of the erythrocytes from blood spiked to 500 µg chromium/l reduced the red blood cell chromium content to a low level in four dialysis steps. The authors' interpretation of the results was that at a very high concentration, chromium ion may penetrate the red cell membrane and that it then associates reversibly with the biomolecules.

7.3 Toxicokinetic models

7.3.1 Rats

Metabolism of $^{51}CrCl_3 \cdot 6H_2O$ after a single intravenous injection (0.76 µg chromium) was assessed from measurements of radiochromium in blood, urine, and faeces in rats of different ages (Onkelinx, 1977). Samples were taken for counting from 1 h to 11 days post-injection. A computerized iterative curve fitting of the measured plasma ^{51}Cr concentrations suggested three elimination components with first-order kinetics (the last one with an approximate half-time of 53 h). The authors proposed a three-compartment model, where the central compartment includes plasma from which elimination takes place. The other two were hypothetical pools that are connected to the central compartment by processes of reversible exchange. The total clearance of ^{51}Cr was divided into urinary clearance, faecal clearance (based on measured data), and the clearance not accounted for by the previous two, which was thought to correspond to deposition into very slowly exchangeable body reservoirs (body sink). Of the total clearance, more than half took place via the urine, and less than 10% in the faeces, whereas clearance into the body sink was as high as 30–40%. The authors noted that their third exponential elimination rate was clearly less than that earlier reported for the whole body by Mertz et al. (1965) (half-time of 83 days) and thus did not correspond to the terminal slope, which is related to the body sink. Analysis of data in the different age groups indicated that the main feature was a decrease by age of the functions of excretory clearance and clearance by the body sink.

A repeated-dose experiment with rats given 100 mg chromium(VI)/l as potassium chromate via drinking-water for 6 weeks provided information on chromium

that is likely relevant, because by the oral route, hexavalent chromium is efficiently reduced to trivalent species before tissue distribution (Thomann et al., 1994). Chromium assays at the end of the 20-week study and after the 42-day exposure showed that the main part (about 87%) of the body burden was in the carcass and bone and that it was eliminated slowly, such that the half-time for chromium label in bone exceeded 100 days. Elimination from the liver was biphasic, whereas it was monophasic in the spleen, kidney, and bone. A three-compartment model was devised, assuming that diffusion limited chromium uptake. Compartment 1 was blood, from which plasma exchanged chromium with compartment 2 (storage in bone and carcass) as well as with compartment 3 (liver, kidney, spleen), from which chromium was lost by excretion. A set of kinetic parameters was found to adequately describe post-exposure chromium elimination in the whole body (half-time of about 80 days), bone plus carcass (half-time over 100 days), and liver, kidney, and spleen (half-time about 10 days). The observations suggested that chromium is sequestered and released by the storage compartment over an extended period of time.

7.3.2 Humans

Lim et al. (1983) injected a single dose of 100–200 µg chromium(III) as $^{51}CrCl_3 \cdot 6H_2O$ into the antecubital vein of three subjects. The radiochromium was monitored for 6 months in the whole body and up to 60 days in blood plasma. Since the relative radiochromium clearance rates showed only three major clearance components, the authors devised a functional kinetic model characterized by the fast, medium, and slow compartments and the central compartment composed of bound and free chromium in plasma. Rate constants were calculated for each subject by feeding 13 data points each from the whole-body retention and for plasma clearance. The fast compartment with half-times of 12.1 and 5.2 min for transfer in and out of the pool was found to the greatest extent in adipose and muscle tissue. The medium compartment showed half-times of 0.8 and 2.2 days in and out of the pool. In this compartment, the radiochromium was rather evenly distributed between adipose and muscle tissue, the spleen, and the liver. In the slow compartment, the influx half-time was 4.2 days, and the efflux half-time was 315 days. This storage function was relatively greater in the liver and spleen. From the determined transfer rates and normal plasma chromium (0.1 µg/l), the authors estimated the compartment sizes in normal individuals at steady state: in total plasma, 0.3 µg chromium, in the fast compartment, 0.13 µg, in the medium compartment, 0.8 µg, and in the slow compartment, 24.4 µg chromium. The limitations of the study were that it utilized a single dose and the intravenous route of administration; as well, the difficulty measuring some tissues (e.g. bone) must be borne in mind when one tries to evaluate the overall toxicokinetics of chromium(III) in humans from these observations.

O'Flaherty et al. (2001) reviewed human toxicokinetics studies involving oral ingestion of chromium(III) or chromium(VI) compounds and, from the blood and urinary chromium data, elaborated a comprehensive computer program for a physiologically based toxicokinetic model. By the oral route, chromium kinetics were shown to be essentially independent of the oxidation state of the administered chromium except for the fraction absorbed from the intestine. Modelled absorption for chromium(III) species among seven subjects ranged from 0.7% to 2% (optimized absorption rate constant was 0.25/day). The authors noted that the body conserved nearly all renally filtered chromium in the background plasma concentration range of 0.05–0.15 µg/l but allowed relatively much greater excretion at higher plasma concentrations. For modelling chronic oral exposures to chromium at ambient or somewhat higher than ambient levels, the authors recommended setting urinary clearance to 1–2 l/day. If clearance is expressed for the ultrafilterable chromium (about 5% of total serum chromium) that is handled by the kidneys after glomerular filtration, the clearance is 20 times higher (20–40 l/day).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

8.1.1 Chromium(III) oxide

Five male and five female Wistar rats were given a single intragastric chromium oxide dose of 5000 mg/kg bw. Two female rats showed a reduced weight gain during the second study week. There was no effect on weight gain in the male rats. None of the animals died during the 14-day observation period. Postmortem pathological examination showed no effects. The median lethal dose (LD_{50}) was higher than 5000 mg/kg bw (Bayer, 1988).

Male Wistar II rats (10 animals per group) were given by gavage 10 or 15 g/kg bw of a chromium oxide preparation in distilled water. None of the animals died during the study period of 14 days, and the only symptom reported was ruffled hair. The LD_{50} was higher than 15 g/kg bw (Bayer, 1972).

Low oral toxicity can be expected from chromium oxide because the compound is insoluble in water and poorly absorbed. There are no acute toxicity studies available by other routes of administration.

8.1.2 Inorganic chromium(III) salts

Male Wistar II rats (10 animals per group) were given by gavage one dose of basic chromium sulfate at 1.0, 3.1, 3.5, 4.0, 4.5, or 5.0 g/kg bw. The rats were followed up for 14 days. The signs observed were weight loss, bleeding eyes and nose, and weakening of their general condition. The calculated LD_{50} was 3.53 g/kg bw (Bayer, 1978).

Smyth et al. (1969) presented oral (rat) LD_{50} values for chromium acetate nonahydrate and chromium nitrate of 11.26 g/kg bw and 3.25 g/kg bw, respectively. Vernot et al. (1977) reported that the oral LD_{50} of chromium nitrate nonahydrate in male rats was 1540 mg/kg bw (range 1270–3010 mg/kg bw).

The acute toxicities of several chromium(III) compounds (nitrate, chloride, sulfate) by the intraperitoneal route were studied in male NZC mice by Bryson & Goodall (1983). The LD_{50}s obtained were as follows: chromium chloride, 17.3 mg chromium/kg bw; chromium nitrate, 17.8 (8.6–36.9) mg chromium/kg bw; and hydrated chromium sulfate, 28.1 (19.5–39.2) mg chromium/kg bw.

Two millilitres of an aqueous solution of 0.239 mol chromium chloride/l (dose about 339 mg/kg bw) was administered intraperitoneally to guinea-pigs. Within 7 days, 6 of 10 animals died, compared with none of the control animals given only distilled water (Wahlberg, 1965).

Male Sprague-Dawley rats (4–6 per dose group) were injected intravenously with 10, 15, or 20 mg chromium/kg bw as chromium potassium sulfate, and 0/4, 2/6, and 3/4 rats died, respectively. Lethal doses usually caused convulsions and death within a few minutes following the injection (Mertz et al., 1965).

The previous studies indicate that inorganic chromium(III) salts have fairly low toxicity by the oral route, whereas by the parenteral routes (intraperitoneal or intravenous), they are acutely toxic at dose levels that are 2–3 orders of magnitude lower than those for the oral route. No acute toxicity data were available for the inhalation or dermal routes of administration.

8.2 Irritation and sensitization

8.2.1 Chromium(III) oxide

8.2.1.1 Skin irritation

Skin irritation and corrosion by chromium oxide (500 mg moistened with water) were examined in two studies with rabbits, the more recent one employing Good Laboratory Practice (GLP) and Organisation for Economic Co-operation and Development (OECD) Test Guideline 404 (Bayer, 1977, 1988). No irritation was observed.

8.2.1.2 Eye irritation

Eye irritation and corrosion by chromium oxide were examined in two studies with rabbits. The more recent study was conducted according to GLP and OECD Test Guideline 405 (Bayer, 1977, 1988). No reactions meeting the criteria for eye irritancy were observed.

8.2.1.3 Respiratory irritation

Swensson (1977) studied the lung reaction to a single intratracheal instillation of chromite dust in rats. Chromite contains about 50% chromium oxide, with the remainder consisting of oxides of iron, aluminium, and magnesium. Male Sprague-Dawley rats were administered 40 mg of chromite particles (33% Cr^{3+} and only 0.7% silicon dioxide, ground to less than 5 μm in diameter) in 1 ml of saline, and groups of 7–10 rats were killed at 1, 2, 4, or 8 months. Quartz served as a positive control. The post-injection follow-up assays included a macroscopic examination of the lungs, lung weights (absolute and relative), lung collagen content and concentration, lung histopathology, macroscopic examination of the regional lymph nodes, weight of lymph nodes, lymph node histopathology, and lymph node collagen content. In comparison with the severe tissue reaction caused by quartz, the reaction caused by chromite was minimal. The histological picture of the lung was characterized by the occurrence of particle-bearing phagocytic cells without any fibroblast reaction. The same applied to the hilar lymph nodes. No indication of fibrogenesis was detected by 8 months of follow-up. The author likened chromite particles to other mineral particles considered to be "inert", such as iron silicate or titanium dioxide.

8.2.1.4 Sensitization

No sensitization studies on chromium oxide were available.

8.2.2 Inorganic chromium(III) salts

8.2.2.1 Skin irritation

An industry summary report on skin irritation by a preparation of basic chromium sulfate was the only available document on skin irritation studies with chromium(III) salts. The substance was applied under an adhesive patch to the inside of an ear of two rabbits for 24 h, and the condition of the application site was followed up for 7 days (Bayer, 1979). The report concludes that the basic chromium sulfate preparation was not irritating.

8.2.2.2 Eye irritation

An industry summary report concluded that a preparation of basic chromium sulfate was not a primary irritant in the eye after application of 50 mg of the substance in the conjunctival pouch. Symptoms and signs were followed up over 7 days (Bayer, 1979).

8.2.2.3 Respiratory irritation

The respiratory irritancy of chromium chloride was studied by exposing Syrian hamsters to nebulized liquid aerosols of chromium(III) chloride at 2.8 or 77 mg/m^3 for 0.5 h (Henderson et al., 1979). The median diameter of the aerosol particles was 1.2 µm. Enzymatic and cytological profiles of lung lavage fluids were examined. At the higher exposure concentration, a slight increase in lysosomal enzymes was found 1 day after exposure, and a slight increase in acid phosphatase was found throughout the study (i.e. for 21 days). Histopathological examination at day 1 after exposure showed focal accumulations of macrophages, and the alveolar capillaries were diffusely congested. The authors considered these responses to be minimal.

8.2.2.4 Sensitization

To investigate the sensitizing potency of a trivalent and a hexavalent chromium salt, and cross-reactivity between them, Siegenthaler et al. (1983) exposed guinea-pigs by five injections of 0.2 ml each of an emulsion containing either 2 mg chromium chloride/ml or 1 mg potassium dichromate (hexavalent chromium)/ml in Freund's complete adjuvant (FCA) into the footpad and nape of the neck. The animals were restimulated once a week by intradermal injections of 25 µg of either chromium chloride or potassium dichromate. Simultaneously, 0.02 ml of either 0.5% chromium chloride or potassium dichromate in 1% Triton X-100 was applied epicutaneously to the skin of the opposite flank. The boosting was continued weekly until a positive reaction was observed. Four to six weeks after the positive skin reaction had emerged, the animals were challenged epicutaneously with both haptens, and skin inflammation was evaluated 24 h later. Seven out of 10 guinea-pigs sensitized and boosted with chromium chloride responded to an epicutaneous challenge with chromium chloride. In the same group, 3 of the 10 animals responded to a challenge with potassium dichromate. In the three guinea-pigs that responded to both haptens, no difference in the intensity of skin reactions could be observed. Essentially the same results were observed in guinea-pigs sensitized and boosted with the potassium dichromate. From the 11 animals that responded to the epicutaneous challenge with potassium dichromate, 7 responded also to chromium chloride, whereas 4 guinea-pigs responded only to potassium dichromate (Siegenthaler et al., 1983).

The same authors also studied, by the technique of positive or negative in vitro and in vivo selection of chromium-specific lymphocytes, whether one common determinant or different determinants are formed by sensitization with trivalent or hexavalent chromium compounds (Siegenthaler et al., 1983). Their observations and rationale suggested the hypothesis that there is a common determinant, which is chromium(III): 1) chromium(III)-modified macrophages exerted a better stimulatory capacity on lymphocytes than chromium(VI)-modified macrophages, 2) trivalent chromium compounds are capable of forming covalent bonds with proteins, which is the mechanism by which metals form allergens, and 3) hexavalent chromium is transformed to trivalent chromium in the skin.

Thirteen guinea-pigs were given chromium chloride hexahydrate by three subcutaneous injections in the nape 1 week apart (Gross et al., 1968). The sensitizing injections contained 0.5 ml of FCA with 0.5 ml of 3.4×10^{-2} mol chromium chloride hexahydrate/l. Three weeks later, the animals were tested with an intradermal injection into clipped or epilated skin. The eliciting dose was 0.1 ml of 4.2×10^{-4} mol chromium chloride hexahydrate/l. After 48 h, this produced moderate positive responses in 10 of the 13 animals, whereas the control animals (injected only with FCA) showed no reactions. In the same study, sensitization to hexavalent chromium was achieved by intradermal injections of potassium dichromate with 10-fold lower concentrations than required for sensitization to chromium chloride. Of 26 guinea-pigs sensitized to potassium dichromate, all reacted to intradermally applied chromium chloride. Of the 10 guinea-pigs sensitized to chromium chloride, 3 elicited weaker cross-reactions after intradermal injection of chromium nitrate (9.6×10^{-4} mol/l) and sulfate (2.4×10^{-4} mol/l). Using the same study method, the authors also attempted to sensitize guinea-pigs with chromium acetate and chromium oxalate, but without success (Gross et al., 1968).

Polak et al. (1973) sensitized 21 guinea-pigs with 2 mg chromium chloride in FCA by a combined method in which chromium chloride was injected intramuscularly into the thighs and the neck, intradermally into the clipped skin of the right flank, and epicutaneously with a non-ionic surfactant (Triton X-100) to the left flank. Subsequently, the animals were epicutaneously (weekly) and intradermally (every 2 weeks) challenged with chromium chloride. With this treatment protocol, it took about 6–8 weeks for the positive reactions to occur. Chromium chloride produced positive reactions in the epicutaneous test in 38% of the animals and in the intradermal test in 74% of the animals. A corresponding study with an equivalent amount of hexavalent chromium (potassium dichromate) produced positive reactions in an epicutaneous test in 95% of the animals and in an intradermal test in 100% of the animals. The

authors thought that the lower rate of elicitation with chromium chloride compared with potassium dichromate was understandable, because the former is a poorer skin penetrant than the latter.

Van Neer (1963) sensitized guinea-pigs with three intradermal injections, given every 2nd or 3rd day, of 0.1 ml of a 0.04% chromium sulfate solution and found that the sensitized state was detectable only through epicutaneous tests with potassium dichromate (nearly 60% of the animals showed a positive reaction), not with chromium sulfate.

Jansen & Berrens (1968) indicated in guinea-pigs not only that two weekly subcutaneous injections of hydrated chromium sulfate and potassium dichromate (hexavalent chromium), both with FCA, sensitized equally well, but also that the intradermal tests 18 days later with both compounds yielded equally intense skin reactions.

The previous animal experiments show that trivalent chromium salts can sensitize the guinea-pig skin by intradermal or subcutaneous injections. When a positive allergic skin reaction was achieved intradermally, subsequent elicitation in an epicutaneous test (with chromium chloride) was demonstrated in two studies; in both cases, not all of the sensitized animals reacted. The low potency of trivalent chromium salts compared with hexavalent potassium dichromate has been attributed to the poor penetration of the compounds into the skin. However, in some studies, intradermally injected chromium chloride elicited fewer positive reactions in sensitized guinea-pigs than an equivalent amount of potassium dichromate, suggesting that other factors may also play a role. Toxicokinetic differences among the trivalent chromium salts may underlie the observed variation in cross-reaction sensitivity.

8.3 Short- and medium-term exposure

8.3.1 Chromium(III) oxide

8.3.1.1 Inhalation exposure

Derelanko et al. (1999) conducted a guideline-based 13-week inhalation toxicity study with chromium(III) oxide by exposing 15 male and 15 female CDF rats 6 h/day, 5 days/week, to chromium(III) oxide aerosols at dose levels of 4.4 ± 0.23, 15 ± 1.2, and 44 ± 3.7 mg/m^3. This corresponds approximately to 3, 10, and 30 mg Cr^{3+}/m^3. The mean mass median aerodynamic diameters (MMADs) of particles were approximately 1.8–1.9 µm, and the particles can be regarded as largely respirable. Two thirds of the animals were sacrificed immediately after the exposure period, and one third were followed up for an additional 13-week recovery period. An additional satellite group of 10 rats was exposed to chromium(III) oxide for 5 days in order to evaluate the changes in bronchoalveolar lavage parameters.

No chromium(III) oxide–related mortality or clinical signs of toxicity occurred at any exposure level. Also, the weight gain of the exposed animals was comparable to the weight gain of the control group. Absolute and relative lung weights were increased in males in the high exposure group, and the mean weights of mediastinal lymph nodes were increased in high-dose animals. In macroscopic examination, green discoloration of the lungs and mediastinal lymph nodes was observed in all exposed animals. In microscopic examination, an accumulation of randomly distributed foci or aggregates of alveolar macrophages filled with dense black pigment was observed within the alveolar spaces. Black pigment was also present at tracheal bifurcation, in the peribronchial lymphoid tissue, and within the mediastinal lymph nodes. The black pigment correlated with the macroscopic green discoloration of lungs and was presumed to represent the test article. Trace to mild chronic inflammation and septal hyperplasia were observed in alveolar septa surrounding the aggregates of pigmented macrophages in mid- and high-exposure animals, and lymphoid hyperplasia was present in all exposure groups. Pigment deposits and slight inflammatory changes or septal hyperplasia were also observed after the recovery period at a similar or increased incidence and severity. Also, some low-dose males exhibited slight inflammatory changes in alveolar septa. No other treatment-related changes in macroscopic or microscopic pathology, sperm evaluation, clinical biochemisty, urinalysis, or haematology were observed. In a satellite group examined for bronchoalveolar lavage parameters, no differences in cellular composition or biochemical parameters of bronchoalveolar lavage fluid between the control and exposed groups were observed.

Thus, the effects of repeated inhalation of water-insoluble chromium(III) oxide in rat are restricted to the lungs and include pigment deposition in the lower respiratory tract and peribronchial and mediastinal lymphoid tissue. The accumulation of the pigment was accompanied by mild interstitial inflammation and septal hyperplasia, especially in the middle and high exposure groups, but some very slight changes were also seen in low-dose males sacrificed after the recovery period. The clearance of the pigment seemed to be low and was most likely to occur via the lymphatic system, which was demonstrated by the presence of the pigment in the lungs and surrounding lymph nodes, also after the recovery period. A lowest-observed-adverse-effect concentration (LOAEC) of 4.4 mg/m^3 was set for chromium(III) oxide in rats.

8.3.1.2 Oral exposure

In a study by Ivankovic & Preussman (1975), chromium(III) oxide was baked into bread at concentration levels of 2% and 5%, and this bread was fed to BD rats of both sexes (n = 12–19) on 5 days/week for a period of 90 days. Based on the reported food consumption, these chromium(III) oxide levels corresponded to a Cr^{3+} uptake of 568 mg/kg bw per day for males and 547 mg/kg bw per day for females in the 2% group and 1368 mg/kg bw per day for males and 1216 mg/kg bw per day for females in the 5% group. Regardless of the high Cr^{3+} doses, chromium(III) oxide did not cause any significant treatment-related changes in the general condition of animals, body weights, clinical biochemistry, haematology, or pathological examination. The lack of toxicity of chromium(III) oxide can be explained by the poor bioavailability of this water-insoluble chromium compound. Faeces of treated animals showed an intense green discoloration, indicating significant excretion of the substance into faeces.

8.3.2 Inorganic chromium(III) salts

8.3.2.1 Inhalation exposure

A comparable 13-week inhalation toxicity study with the same test protocol as described above in section 8.3.1.1 was also conducted with basic chromium sulfate (Derelanko et al., 1999). The mean aerosol concentrations were 17 ± 4.3, 54 ± 4.2, and 168 ± 25.3 mg basic chromium sulfate/m^3, approximating to 3, 10, and 30 mg Cr^{3+}/m^3, respectively. The mean MMAD of the particles ranged from 4.2 to 4.5 µm.

No clinical signs of toxicity were observed, except for sporadic cases of laboured breathing in females of the high exposure group. Mean body weights of males in the middle and high exposure groups and of females of the high exposure group were statistically significantly lower than among controls during the exposure period. During the recovery period, males from the middle and high exposure groups continued to exhibit significantly lower body weights than controls, and males in the low exposure group continued to exhibit slightly lower body weights than controls, but the body weight gains were similar. Among females, mean body weights in all exposure groups were not different from those of controls at the recovery sacrifice. The exposures did not seem to have an impact on food consumption. In haematological assays, total leukocytes and neutrophils were increased in both sexes in the middle and high exposure groups. In clinical chemistry parameters, high-exposure females had elevated alkaline phosphatase levels, and mid- and high-exposure females had decreased cholesterol levels.

Mean absolute and relative lung weights were significantly and dose-dependently increased in both sexes and in all treatment groups sacrificed at the end of exposure, as well as after the recovery period. Macroscopically, the lungs of the mid- and high-exposure group animals exhibited grey discoloration in animals sacrificed both at the end of the exposure period and after the recovery period. Microscopic evaluation revealed chronic inflammation of the lungs at all exposure levels, consisting of alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris. Chronic interstitial inflammation was usually multifocally distributed and consisted of thickened alveolar walls caused by inflammatory cell infiltration and hyperplasia of type II pneumocytes. Areas of granulomatous inflammation characterized by infiltration of macrophages and multinucleated giant cells were observed in the lungs at all exposure levels. Microscopic changes correlated with lung weights and grey discoloration of the lungs. In peribronchial and mediastinal lymph nodes, histiocytosis (macrophage hyperplasia) and lymphoid hyperplasia correlated with lymph node enlargement. At the recovery sacrifice, foreign material persisted in the lungs of some animals, but with decreased incidence. The incidence and severity of chronic inflammation of the alveoli and chronic interstitial or granulomatous inflammation were similar in the middle and high exposure groups and slightly reduced in the low exposure group, when compared with the animals sacrificed at the end of exposure. Peribronchial histiocytosis continued to be observed in mid- and high-exposure animals of the recovery groups, with an increased incidence among the high-exposure animals.

Nasal cavity mucosa of the exposed animals exhibited acute inflammation with suppurative or mucoid exudate, which had largely disappeared at the recovery sacrifice. In the larynx, green refractile material in the lamina propria and submucosa associated with an infiltration of macrophages and multinucleated giant cells (granulomatous inflammation) was seen in the animals from all treatment groups. After the recovery period, these changes were no longer detected in the low dose group and in males in the middle exposure group and were markedly reduced in incidence and severity in the females in the middle exposure group and in both sexes in the high exposure group.

In other organs observed to have small exposure-related increases in absolute or relative organ weights, the histopathological findings were unremarkable. No exposure-related effects were noted for sperm motility, morphology, or concentration or for testicular and ovarian weights or histopathology.

In the satellite group sacrificed after the 5-day exposure period, bronchoalveolar lavage samples showed a dose-dependent increase in the number of

neutrophiles and mononuclear cells. Total protein and lactate dehydrogenase levels were also slightly (but not statistically significantly) increased.

The lowest basic chromium sulfate exposure level of 17 mg/m^3 (3 mg Cr^{3+}/m^3, corresponding to an inhaled dose of 0.7 mg chromium/kg bw) was a no-observed-adverse-effect concentration (NOAEC) for systemic effects (decreased body weight, changes in haematology). However, in the respiratory system, clear, dose-dependent inflammatory changes were seen at the lowest exposure level. Therefore, no NOAEC for the local respiratory effects could be determined.

Johansson and co-workers (Johansson et al., 1986a,b, 1987) exposed male rabbits to mean concentrations of 0.6 or 2.3 mg chromium/m^3 as chromium(III) nitrate nonahydrate, 5 days/week, 6 h/day, for 4–6 weeks or 4 months. Only lung effects were evaluated. Main findings included increased accumulation of test material–filled macrophages in lungs and morphological changes in macrophages, including an increased size of lysosomes and an accumulation of laminated structures in lysosomes. In some areas, intra-alveolar accumulation of enlarged macrophages was accompanied by a mild interstitial inflammation, mainly at the highest dose level. Increased oxidative metabolic activity of macrophages and decreased phagocytic activity were also demonstrated. Apart from slight inflammatory reactions, many of the changes observed in this study can be regarded as a physiological response to the foreign material rather than as an adverse effect.

8.3.2.2 Oral exposure

Four-week-old male Harlan Sprague-Dawley rats (eight per group) were fed a diet supplemented with 0, 5, 25, 50, or 100 mg Cr^{3+}/kg as chromium chloride for a period of 20 weeks (Anderson et al., 1997). Daily Cr^{3+} intakes can be estimated to correspond to 0.35–7 mg/kg bw (estimated on the basis of default reference values given in Appendix VI of European Commission [2003]). The authors calculated the highest dose to correspond to a chromium intake of 15 mg/kg bw. However, in calculations, they used a rat body weight of only 100 g, which seems exceptionally low, because the normal weight of adult Sprague-Dawley rats is between 200 and 300 g. If 200 g is used as a mean body weight, the highest dose corresponds to 7 mg chromium/kg bw. Effects on body weights, selected organ weights, and the histology of liver and kidneys were evaluated. Histopathological examination was performed on four high-dose and four control rats. Haematology and biochemical analyses of blood (serum glucose, cholesterol, triglycerides, liver enzymes, blood urea nitrogen, total protein, and creatinine) were performed on animals at 11, 17, and 24 weeks of age. No changes in body or organ weights, no general signs of toxicity, and no changes in liver or kidney histopathology were seen. Toxicokinetic evaluation showed a dose-dependent increase in liver and kidney chromium concentrations. Some sporadic, statistically significant changes were seen in some clinical chemistry parameters (lactate dehydrogenase, aspartate aminotransferase, serum creatinine levels), but because these changes did not show any dose or time dependency, they were not considered to be treatment related. Based on these results, the authors suggested the highest dose level as a no-observed-adverse-effect level (NOAEL) for trivalent chromium (7 mg/kg bw using 200 g as a mean body weight). However, because the study was limited only to a small number of animals and to a limited number of end-points, this conclusion should be regarded with reservation.

A similar study was also performed with organic chromium picolinate. Although the estimated Cr^{3+} intake was similar to that of chromium chloride, the chromium picolinate treatment resulted in a significantly more pronounced increase in liver and kidney chromium levels compared with the chromium chloride treatment (Anderson et al., 1997). However, no differences attributable to the treatment were observed in clinical evaluation, body or organ weights, selected organ histopathology, haematological parameters, or clinical chemistry.

8.4 Long-term exposure and carcinogenicity

8.4.1 Chromium(III) oxide

Several studies from the 1950s, 1960s, and 1970s tried to evaluate the carcinogenicity of trivalent chromium compounds, but had different shortcomings in study designs. A description of all of these studies can be found in IARC (1990) or Riihimäki & Luotamo (2006).

Laskin et al. (1970) developed an intrabronchial pellet technique to study bronchial carcinogenicity in rats. Pellets prepared from molten cholesterol carrier mixed with an equal quantity of chromium oxide were put inside a cylindrical box of stainless steel wire mesh and placed in the left bronchus. The exposure duration was up to 136 weeks. None of the 98 chromium oxide–treated rats had lung tumours. Among rats similarly exposed to calcium chromate, bronchial carcinomas were found.

The study was repeated by Levy & Venitt (1986) with the same methodology. A group of 48 male and 52 female rats received a bronchial pellet containing 2 mg of chromium(III) oxide mixed with an equal amount of cholesterol. The animals were kept for

2 years, and a postmortem study was performed on the 94 remaining rats. None of them exhibited local squamous carcinomas or carcinomas in situ, and the occurrence of squamous metaplasia was not increased compared with the stainless steel wire mesh controls.

Groups of 60 male and 60 female BD rats were fed 1, 2, or 5% chromium(III) oxide baked in bread on 5 days/week for 2 years (600 feeding days) (Ivankovic & Preussman, 1975). Male and female rats, 60 animals per group, served as untreated controls. The total consumption of chromium(III) oxide (in 600 days) in the dosed groups ranged from 360 to 1800 g/kg bw. After the feeding period, animals were maintained on the control diet until they died or became moribund. Body weight gains in the dosed groups showed no differences from those of the controls, and the median survival times in all three dose groups were comparable with that of the controls. No macroscopic or histological postmortem findings could be related to the treatment. Regarding tumours, no gastrointestinal tumours were reported in any group. Low rates of mammary fibroadenomas, mammary carcinomas, or hypophyseal adenomas were found in all groups (including controls), without a dose–response. The occurrence of these tumours was characteristic of the BD strain of rats. It should be noted that owing to the insolubility of the chromium oxide powder used in the study, very little is expected to become absorbed.

8.4.2 Inorganic chromium(III) salts and complexes

Levy & Venitt (1986) conducted a study in which groups of 48 male and 52 female rats received a bronchial pellet containing 2 mg of chromium chloride hexahydrate or chrome tan (basic chromium sulfate), each mixed with an equal amount of cholesterol. The animals were kept for 2 years, and a postmortem study was performed on the 83 (chromium chloride) or 95 (basic chromium sulfate) remaining rats. None of the rats in either group exhibited local squamous carcinomas or carcinomas in situ, and the occurrence of squamous metaplasia was not increased compared with the stainless wire mesh controls.

Trivalent chromium was not found to be carcinogenic in a study in which 5 mg chromium acetate/l in drinking-water was given for life to 54 male and 50 female white Swiss mice of the Charles River strain. The experiment continued until all animals had died; the total elapsed time was 36 months, but only 60% of the males survived more than 18 months (Schroeder et al., 1964).

Groups of at least 50 male and 50 female Long-Evans rats were given 5 mg chromium acetate/l in drinking-water from weaning until death. Mortality due to an intercurrent pneumonia in chromium-fed animals was 26.7% for males and 7.8% for females, compared with 27.3% and 25.6% in control groups, respectively. The incidences of tumours (in either males or females) were not significantly different from those in controls. The total numbers of autopsied animals with tumours were as follows: 16/39 treated males, 18/35 treated females, 9/35 male controls, and 15/35 female controls (Schroeder et al., 1965).

The strain A mouse lung tumour system, once proposed to screen carcinogenic potential, was used to examine a series of metal compounds, including chromium sulfate. Strain A/Strong mice, 20 animals (10 males and 10 females) per dose group, received intraperitoneal injections of chromium(III) sulfate (tricaprylin as vehicle) at three dose levels (480, 1200, or 2400 mg/kg bw) 3 times per week, for a total of 24 injections. The animals were killed 30 weeks after the first injection. Chromium(III) sulfate did not induce any increase in the lung tumour frequency compared with the vehicle and untreated controls, whereas urethane (20 mg) as a positive control was clearly carcinogenic (Stoner et al., 1976).

Chromium chloride hexahydrate was studied, among other metal salts, for a promoting effect on rat renal tumorigenesis. Fifteen male F344 rats were given 500 mg *N*-ethyl-*N*-hydroxyethylnitrosamine/l in drinking-water for 2 weeks and thereafter chromium chloride at 600 mg/l in drinking-water for a subsequent 25 weeks. Statistically significant increases in the mean number of dysplastic foci per square centimetre of renal tubules were found in rats treated with the five metal compounds, including chromium chloride. The incidence of renal cell tumours was, however, significantly higher only in rats treated with nickel chloride (Kurokawa et al., 1985).

Trivalent chromium has also been suggested to have the capability to cause paternally mediated transgenerational carcinogenesis (Anderson et al., 1994; Yu et al., 1999). This is based on two studies employing single high-dose (52 mg Cr^{3+}/kg bw) intraperitoneal treatment of male rats with chromium(III) chloride and showing increases either in lung tumours (Anderson et al., 1994) or in adrenal, thyroid, and Harderian gland tumours, as well as in reproductive organ tumours (Yu et al., 1999) in offspring.

8.5 Genotoxicity and related end-points

8.5.1 In vitro studies

There are a huge number of in vitro genotoxicity studies available on chromium(III) compounds. Studies published before the year 1990 have been reviewed comprehensively by De Flora et al. (1990). All genotoxicity studies available before December 2004 are summarized in Riihimäki & Luotamo (2006).

In acellular systems, water-soluble chromium(III) compounds, such as chromium(III) chloride and chromium(III) nitrate, have been shown to induce genotoxic effects, including deoxyribonucleic acid (DNA) adducts, DNA strand breaks, DNA–DNA interstrand crosslinks, DNA–protein crosslinks, DNA–amino acid crosslinks, DNA–glutathione crosslinks, gene mutations after transfection of treated DNA into cells, and 8-oxodeoxyguanosine in DNA in the presence of hydrogen peroxide (De Flora et al., 1990; Singh et al., 1998). The electropositive chromium(III) ion interacts with the negatively charged phosphate groups in the DNA backbone and with guanine bases, forming phosphate–chromium–phosphate or guanine–chromium–guanine interstrand crosslinks (Singh et al., 1998). Consequently, interstrand crosslinks can result in functional disturbances in DNA and ribonucleic acid (RNA) polymerases and inhibition of DNA and RNA synthesis. Whereas chromium(III)-induced low-level DNA damage stimulates DNA synthesis of reduced fidelity, at higher concentrations, crosslinks result in DNA polymerase arrest and inhibition of DNA replication and RNA polymerase arrest and transcriptional inhibition (Snow, 1994). In acellular systems, chromium(III) compounds have usually been more reactive towards DNA than have chromium(VI) compounds (Dayan & Paine, 2001), reflecting the fact that chromium(III) can readily interact with DNA, whereas chromium(VI) acts by reduction products such as reactive oxygen species, chromium(VI) esters, chromium(V), chromium(IV), and chromium(III), which are formed in cells but not in acellular systems (Singh et al., 1998).

In bacterial tests, inorganic chromium(III) compounds have shown mainly negative results. De Flora et al. (1990) summarized the results of 25 bacterial genotoxicity studies on chromium chloride, 11 studies on chromium(III) nitrate, 11 studies on chromium(III) acetate, 7 studies on chromium(III) sulfate, 14 studies on chromium(III) potassium sulfate, and 2 studies on basic chromium sulfate. The assays included various types of tests with *Escherichia coli*, *Salmonella typhimurium*, and *Bacillus subtilis* with and without metabolic activation systems. With few exceptions, these studies showed negative results. Positive doses were generally very high. Water-insoluble chromium(III) phosphate, chromium(III) oxide, and chromium(III) hydroxide were studied in a single study by Yagi & Nishioka (1977) in *E. coli*, and no DNA damage was seen.

In older studies in cultured mammalian cells, chromium(III) chloride gave negative results when tested for DNA damage (measured by alkaline elution) or interference with DNA synthesis (De Flora et al., 1990). However, in one recent study, DNA damage (single strand breaks and abasic sites) measured as an increase in comet tail moment was demonstrated at concentrations of 0.5–1 mmol chromium(III) chloride/l (Blasiak & Kowalik, 2000). Gene mutations (6-thioguanine-resistant mutants) were not seen in human fibroblasts at 0.5–1 mmol/l concentrations of chromium(III) chloride (Biedermann & Landolph, 1990). Basic chromium sulfate did not cause any increase in DNA mutations in Chinese hamster V79 cells at 0.2–0.8 mmol/l concentrations (Bianchi et al., 1983).

Eleven out of 14 studies on the induction of sister chromatid exchanges (SCEs) by chromium(III) chloride in cultured mammalian cells were negative (De Flora et al., 1990). Some of these negative studies were performed using very low chromium(III) chloride concentrations and may thus have been inconclusive. The three positive studies utilized Chinese hamster cell lines. The clearest effect was seen in Chinese hamster V79 cells, where up to a 3.4-fold increase in SCEs and a delay in cell cycle progression were observed (Elias & Schneider, 1984), with a clear dose- and time-related increase in SCE induction by prolongation of treatment time from 24 h to 36 h and 48 h. It was suggested that the longer incubation time and higher concentrations allowed an increased chromium ion accumulation through slow transportation into the cell. Venier et al. (1985) observed that chromium(III) chloride induced a slight, but statistically significant, increase in SCEs in Chinese hamster ovary cells when the incubation time was 44–52 h to cover two generation cycles. An increase in SCEs by chromium(III) chloride was also observed in Chinese hamster Don cells (Ohno & Hanaoka, 1982). Chromium(III) nitrate, chromium(III) sulfate, basic chromium sulfate, and chromium(III) potassium sulfate have shown negative or equivocal results in the SCE assay (De Flora et al., 1990). Chromium(III) acetate increased SCEs in mouse macrophage cells, human lymphocytes, and skin fibroblasts (Nakamuro et al., 1978; Andersen, 1983), but not in Chinese hamster ovary cells (Levis & Majone, 1979).

There are also several studies on the induction of chromosomal aberrations by inorganic chromium(III) compounds. Chromium(III) chloride has increased chromosomal aberrations in mouse fetal tertiary cells at low concentrations, but not in Syrian hamster embryo primary cells (Raffetto & Parodi, 1977; Tsuda & Kato, 1977). Both negative and positive results have been observed in Chinese hamster ovary cells (Levis & Majone, 1979, 1981; Majone & Rensi, 1979; Bianchi & Dal Toso, 1980; Stearns et al., 1995). Although two studies with human lymphocytes did not show any positive effect (Nakamuro et al., 1978), three other studies showed a positive response (Kaneko, 1979; Stella et al., 1982; Friedman et al., 1987). Concentrations up to the millimole per litre range were used in two of these positive studies (Kaneko, 1979; Stella et al., 1982), whereas one showed a 1.6- to 4.3-fold increase in chromosomal aberrations in six out of seven human

donors after in vitro exposure to a very low concentration of chromium(III) chloride (2.5 µg/ml) for 68–72 h (Friedman et al., 1987). Various antioxidants reduced the incidence of chromosomal aberrations.

In human diploid MRC-5 fibroblasts, chromium(III) chloride (1–5 µmol/l, 24–26 h treatment) induced an 11- to 22.5-fold increase in the frequency of micronuclei (Seoane & Dulout, 2001). The majority of the induced micronuclei were kinetochore positive and thus probably contained whole chromosomes, indicating an aneugenic effect. However, a significant increase was also seen in kinetochore-negative micronuclei, suggesting a clastogenic influence as well. In primary cultures of human fibroblasts treated for one cell cycle (21 h) with chromium(III) chloride, a 2.2-fold increase in aberrant cell division patterns (studied by a differential staining technique for chromosomes and spindles) was observed at a concentration of 100 µmol/l (Nijs & Kirsch-Volders, 1986).

Other soluble chromium(III) compounds have also shown variable results in chromosomal aberration tests. Chromium(III) acetate induced chromosomal aberrations in Chinese hamster ovary cells and human lymphocytes (Nakamuro et al., 1978; Levis & Majone, 1979; Bianchi & Dal Toso, 1980), whereas chromium(III) sulfate induced chromosomal aberrations in Chinese hamster ovary and 237-21 cells (Levis & Majone, 1981; Rossner et al., 1981), but not in mouse mammary carcinoma cells (Umeda & Nishimura, 1979) or Syrian hamster embryo cells (Tsuda & Kato, 1977) (the latter study involved low concentrations only). Both basic chromium(III) sulfate and chromium(III) potassium sulfate induced chromosomal aberrations in Chinese hamster ovary cells (Levis & Majone, 1979, 1981), but chromium(III) nitrate was negative in both Chinese hamster ovary cells and human lymphocytes (Nakamuro et al., 1978; Levis & Majone, 1979; Bianchi & Dal Toso, 1980).

Water-insoluble chromium(III) oxide has given mainly positive results in the few studies available. It has induced 6-thioguanine-resistant mutants in Chinese hamster V79 cells and human fibroblasts (Elias et al., 1986; Biedermann & Landolph, 1990), SCEs and chromosomal aberrations in Chinese hamster V79 cells (Elias et al., 1983; Elias & Schneider, 1984), morphological transformation in Syrian hamster embryo cells (Elias & Schneider, 1984), and anchorage-independent growth in human fibroblasts (Biedermann & Landolph, 1990). It did not, however, induce SCEs in mouse macrophage P388D1 cells (Andersen, 1983) or anchorage independence in Syrian hamster BHK cells (Hansen & Stern, 1985). In Chinese hamster V79 cells, prolongation of the treatment time from 24 h to 36 h and 48 h resulted in a progressive dose- and time-related enhancement in SCE frequencies (Elias et al., 1983). Lower concentrations of chromium(III) oxide, which had no effect after the 28-h treatment, induced an increase of SCEs at the prolonged exposure time. The penetration of the crystalline chromium(III) oxide into the cells appeared to occur by phagocytosis. Chromium(III) oxide particles were usually observed in the cytoplasm, around the nucleus. It was suggested that the effect of chromium(III) oxide was due to the slow solubilization of the particles to yield chromium(III).

8.5.2 In vivo studies

There are only a few studies on the genotoxic effects of chromium(III) in experimental animals in vivo.

In an internal report of Bayer AG (Herbold, 1992), chromium oxide green (in corn oil), consisting of 98.9% chromium(III) oxide, did not induce micronuclei in bone marrow polychromatic erythrocytes of male and female NMRI mice at a very high dose single intraperitoneal administration (10 g/kg bw), with sampling 16, 24, and 48 h after the administration. The chromium(III) oxide treatment was associated with toxicity seen as a decrease in the ratio of polychromatic to normochromatic erythrocytes, which indicates a cytotoxic effect on bone marrow.

Chromium(III) chloride has been negative in the wing somatic mutation and recombination test in *Drosophila melanogaster* in several studies (Graf et al., 1992; Ogawa et al., 1994; Amrani et al., 1999; Katz et al., 2001). Results obtained with chromium(III) nitrate in the *D. melanogaster* wing somatic mutation and recombination test were inconclusive (Yesilada, 2001).

No DNA strand breaks, DNA interstrand crosslinks, or DNA–protein crosslinks were observed by alkaline elution of DNA in kidneys of Sprague-Dawley rats 1 h after an intraperitoneal injection of chromium(III) chloride at 80 mg/kg bw (Tsapakos et al., 1983).

After an intraperitoneal injection of Sprague-Dawley rats with chromium(III) chloride (80 mg/kg bw), chromium entered liver and kidney tissues at a slow rate and bound to liver and kidney chromatin and DNA (Cupo & Wetterhahn, 1985). Chromium binding to liver chromatin from chromium(III) chloride was observed to increase through 40 h (later sampling times were not examined). In the kidney, the level of chromium in chromatin after the chromium(III) chloride treatment increased with time until 24 h, but decreased thereafter. Alkaline elution indicated no increase in DNA–protein crosslinks, DNA interstrand crosslinks, and DNA strand breaks in liver or kidney 4, 24, or 40 h after the chromium(III) chloride injection.

In female Sprague-Dawley rats, a single oral dose of chromium(III) chloride hexahydrate (895 mg/kg bw)

resulted in an increased excretion of the urinary lipid metabolites formaldehyde, acetaldehyde, and acetone 48, 72, and 96 h after the dosing and malonaldehyde 72 h after the dosing, indicating oxidative stress (Bagchi et al., 2002). No effect on these urinary metabolites was evident 24 h after the treatment. An increase was also seen in the production of superoxide anion by peritoneal macrophages and hepatic mitochondrial and microsomal lipid peroxidation 48 h after the treatment.

Chromium(III) chloride (62.5, 125, or 250 mg/kg bw) given intraperitoneally once a day for 2 consecutive days did not induce micronuclei in Slc:ddY mouse bone marrow polychromatic erythrocytes examined 24 h after the last injection (Itoh & Shimada, 1996).

In a study by Fabry (1980), chromium(III) nitrate was not observed to induce micronuclei in bone marrow polychromatic erythrocytes of BALB/c mice after intraperitoneal injection (250–500 mg/kg bw). Further experimental details were not available.

Although this document does not assess the risks of organic chromium(III) complexes, the data from studies performed with these compounds may provide some additional relevant information. Chromium picolinate and chromium picolinate monohydrate were tested by the United States National Toxicology Program in the in vivo micronucleus test. Chromium picolinate administered at dose levels of 156, 312, 625, 1250, or 2500 mg/kg bw by gavage 3 times, 24 h apart, and sampled 24 h after the last treatment was negative in the bone marrow micronucleus test in male Fischer 344 rats (NTP, 2004). Chromium picolinate monohydrate (80–50 000 mg/kg in feed for 90 days; sampling 24 h after exposure cessation) was tested in the peripheral blood erythrocyte micronucleus assay in male and female B6C3F1 mice. It was considered to be "negative (male)" and "equivocal (female)" (NTP, 2004), since in female mice, the highest dose of chromium picolinate monohydrate was associated with a 1.6-fold increase in the mean number of micronucleated normocytes (P = 0.0396).

8.6 Reproductive and developmental toxicity

8.6.1 Effects on fertility

8.6.1.1 Chromium(III) oxide

In conjunction with a 13-week rat inhalation toxicity study with chromium(III) oxide (Derelanko et al., 1999), effects on ovarian and testicular weights, histopathology, and sperm parameters were evaluated. Chromium(III) oxide did not cause any changes in testicular or ovarian weights or histopathology or in any sperm parameters, even at the highest dose level of 30 mg/m^3 (which corresponds to an inhaled dose of 6.6 mg Cr^{3+}/kg bw).

In the study by Ivankovic & Preussman (1975) described in section 8.3.1.2, nine male and nine female rats were paired after 60 days of exposure to chromium(III) oxide. All females became pregnant.

8.6.1.2 Inorganic chromium(III) salts

In a 13-week rat inhalation toxicity study with basic chromium sulfate (Derelanko et al., 1999), no statistically significant changes in absolute testicular weights were seen at any basic chromium sulfate dose, but the relative testicular weights increased at the highest dose level of 30 mg Cr^{3+}/m^3, corresponding to an inhaled dose of 6.6 mg Cr^{3+}/kg bw. This finding was not associated with microscopic pathology and was most probably attributed to the decreased body weight of animals. No exposure-related effects were noted in sperm parameters. In females, no effects on ovarian weights were seen.

Sexually mature male and female Swiss mice were exposed for 12 weeks to chromium chloride hexahydrate dissolved in drinking-water at concentrations of 2000 or 5000 mg/l (Elbetieha & Al Hamood, 1997). Daily chromium(III) doses were estimated to be 82 and 204 mg Cr^{3+}/kg bw for males and 85 and 212 mg Cr^{3+}/kg bw for females. Effects of chromium chloride hexahydrate on fertility were evaluated by mating the treated animals with untreated counterparts. Main findings included a decrease in the number of pregnant females when untreated females were mated with high-dose males and a decrease in the number of implantations and viable fetuses when treated females were mated with untreated males. No mortality or clinical signs of toxicity were seen in treated animals. The water consumption of mice in the highest exposure group was lower than that in the control group. In the group of animals killed after a 12-week exposure, some changes in the relative weights of reproductive organs (decreased relative seminal vesicle and preputial gland weights in males; increased relative uterine weight and decreased relative ovarian weights in females) were seen either at both doses or at the higher dose level. In the absence of a clear dose–response and any histopathological data, the relevance of these changes remains unclear.

In a subsequent study by the same group, 25 pregnant mice were exposed to 1000 mg chromium chloride hexahydrate/l in the drinking-water from day 12 of pregnancy to the weaning of the pups on postnatal day 20 (Al Hamood et al., 1998). Estimated doses were 36 and 31 mg Cr^{3+}/kg bw per day during the gestation and lactation periods, respectively. Main findings included reduced body weights and the relative weights of testes, seminal vesicles, and preputial glands in treated male offspring, changes in body weights, relative ovarian

weights, and uterine weights in a subgroup of female offspring studied (n = 8), and delayed time of vaginal opening in another subgroup of female offspring (n = 10). When prenatally and postnatally exposed F_1 males (n = 9) were mated with untreated females (1:2), no statistically significant changes in fertility were seen. Mating a group of 16 F_1 females with untreated males resulted in a statistically significant reduction in the number of pregnant females and an increase in the number of resorptions, although the number of implantations and number of viable fetuses per female remained unchanged.

When a group of 10 male rats was treated with 1000 mg chromium chloride/l in drinking-water for 12 weeks and mated with virgin females (1:2), no significant changes in the number of pregnant females, the number of implantations per female, or the number of viable fetuses per female were seen (Bataineh et al., 1997). The estimated daily intake of Cr^{3+} was 24 mg/kg bw, assuming that chromium chloride was in the form of hexahydrate. The body weights of treated males, absolute but not relative testes weights, as well as the absolute and relative seminal vesicle and preputial gland weights were significantly reduced. A significant increase in the post-ejaculatory latency, a reduction in the number of males ejaculating during the observation period, and decreased aggressivity of treated males were also observed (Bataineh et al., 1997). None of these three studies (Bataineh et al., 1997; Elbetieha & Al Hamood, 1997; Al Hamood et al., 1998) included histopathology of reproductive organs or any sperm analysis.

In an oral fertility study in mice, effects of trivalent chromium on testicular histology and on the number of spermatogenic cells and epididymal sperm were suggested (Zahid et al., 1990). However, owing to apparent methodological deficiencies and the uncertainty concerning the compound used in this study, the relevance of these findings remains unclear (Riihimäki & Luotamo, 2006).

No effects on testicular weights were seen when chromium chloride or chromium picolinate was given to rats for 20 weeks at four concentrations ranging from 5 to 100 mg Cr^{3+}/kg diet (at the highest concentration, the approximate intake of chromium was 7 mg Cr^{3+}/kg bw per day) (Anderson et al., 1997).

In an intraperitoneal study, rats were injected with 1, 2, or 4 mg chromium chloride/kg bw for 5 consecutive days, and no changes in histology or in epididymal sperm counts were seen (Ernst, 1990). Hexavalent chromium (as sodium chromate) at the same dose levels induced atrophy of the seminiferous tubules and a decrease in epididymal sperm numbers.

8.6.2 Developmental toxicity

According to the study by Ivankovic & Preussman (1975), no obvious malformations were seen in the offspring of the female rats eating chromium(III) oxide–containing bread throughout pregnancy. The average chromium intake was 547 or 1216 mg/kg bw per day, and the number of animals per group was nine.

In high-dose intraperitoneal developmental toxicity studies, embryotoxic, fetotoxic, and teratogenic effects have been seen (Matsumoto et al., 1976; Iijima et al., 1983). However, because of the very high doses, approaching LD_{50} levels, and intraperitoneal administration, these studies cannot be used in the developmental risk assessment of trivalent chromium.

9. EFFECTS ON HUMANS

9.1 Essentiality

The primary biological effect attributed to endogenous chromium(III) is potentiation of the action of insulin, which has an impact on carbohydrate, lipid, and protein metabolism. In humans, glucose intolerance, insulin resistance, and impaired lipid profile (increased serum free fatty acids, cholesterol, and triglycerides) have been related to chromium deficiency (Mertz, 1993; Anderson, 1997). However, states of true chromium deficiency rarely occur because of the trace amounts required, whereas some room remains for speculation concerning relative deficiencies due to poor nutrition and chromium losses in old age or higher chromium needs among specific populations, such as Type II diabetics (Mertz, 1993; Anderson, 1997; Jeejeebhoy, 1999).

Homeostatic mechanisms involving regulation of absorption, excretion, and tissue retention, which enable adaptation to varying nutrient intakes, are typical for essential trace elements (IPCS, 2002a). In the case of chromium, homeostatic mechanisms were found to operate in the gastrointestinal tract, such that absorption of chromium(III) from normal diets was inversely related to daily dietary intakes (Anderson & Kozlowsky, 1985). In humans, renal clearance appears to function as a regulatory mechanism for the removal of excessive chromium in plasma (O'Flaherty et al., 2001). This is possibly mediated by LMWCr (Wada et al., 1983), which is an oligopeptide found mainly in the liver, although appreciable quantities also occur in the kidney, spleen, intestine, testis, and the brain, and probably it is the major form of chromium(III) in urine (Vincent, 2000). In the normal state of health, there also seems to be a homeostatic metabolic control of chromium in

insulin-sensitive cells that involves LMWCr. This chromium homeostasis is disturbed in Type I and Type II diabetes (Morris et al., 1999).

It has been shown that LMWCr isolated from rabbit liver enhances glucose oxidation and lipogenesis from glucose in rat adipocytes, whereas the activity is lost in chromium-depleted LMWCr (Yamamoto et al., 1989). LMWCr occurs in the apo form in insulin-sensitive cells and tightly binds four chromium ions to make holoLMWCr, the active form of the oligopeptide (Vincent, 1999, 2000; Clodfelder et al., 2001). Using isolated rat insulin receptor, LMWCr was shown to bind to insulin-activated insulin receptor, resulting in an increase of its tyrosine protein kinase activity (Davis & Vincent, 1997). LMWCr is believed to be part of an insulin signal amplification mechanism. In response to increases in the concentration of blood insulin, the chromium concentration in blood was found to decrease, presumably due to uptake of the element by insulin-dependent cells, where it binds to generate the active LMWCr. LMWCr was proposed to stabilize the active conformation of insulin receptor, thus resulting in increased insulin signalling and subsequent cellular actions.

9.2 Acute effects

A woman ingested 400 ml of a leather tanning solution containing 48 g of basic chromium sulfate and died of cardiogenic shock 36 h after admission to the hospital, in spite of intensive care, including haemodialysis treatment. At postmortem, haemorrhagic erosive gastroenteritis of the entire gut, severe haemorrhagic pancreatitis, pulmonary congestion and oedema, peritonitis, ascites in the abdominal cavity, and widespread petaechial haemorrhages were found (Van Heerden et al., 1994).

9.3 Irritation and sensitization

9.3.1 Chromium(III) oxide

No human studies were located concerning irritation (skin and eyes) or sensitization by chromium(III) oxide.

9.3.2 Inorganic chromium(III) salts

9.3.2.1 Irritation

No studies were found that reported skin or eye irritation in humans exposed to inorganic chromium(III) salts.

9.3.2.2 Sensitization

Skin sensitization among workers handling trivalent chromium salts appears to be a rare event. Two workers handling wet hides tanned with basic chromium sulfate developed work-related dermatitis of the hands, arms, and legs and were found to be sensitized to chromium (positive patch test to chromium chloride and potassium dichromate) as well as to a polyfunctional aziridine, another recognized contact allergen (Estlander et al., 2000). It is possible that one of the sensitizers had enhanced the sensitization reaction to the other. Overall, although skin sensitization by basic chromium sulfate may occur in tanneries, the few cases reported in the open literature indicate that the risk is low.

Clinical evidence pointing to the potential of allergic skin reactions by soluble trivalent chromium salts mainly relates to the wearing of leather articles tanned with chromium (Oumeish & Rushaidat, 1980; Zachariae et al., 1996; Freeman, 1997). In a typical clinical report, the development of foot dermatitis linked with a positive skin reaction in a standard epicutaneous test performed with potassium dichromate (hexavalent chromium) in a patient not known to be previously sensitized to chromium suggests the causal inference that chromium leached from the leather shoe had caused sensitization. The cases reported over the last few decades involve a substantial number of persons, many of them having worn shoes in direct contact with the skin, such as sandals, and less frequently workers using wet gloves (Nygren & Wahlberg, 1998). The issue is, however, clouded by the fact that in a number of instances, low levels of hexavalent chromium may have been present in the leather (Hansen et al., 2002), which is a more likely cause than trivalent chromium, or that the reported cases of dermatitis may actually concern elicitation reactions in previously chromium-sensitized people.

Hansen et al. (2003) recently determined the minimum elicitation threshold (MET) concentrations for trivalent chromium chloride hexahydrate and potassium dichromate (hexavalent chromium) in chromium(VI)-sensitive patients with mainly a leather-related history of previous chromium dermatitis but no active eczema. Dilution series of chromium(III) and chromium(VI) were applied on the skin of 18 patients using the standard Finn Chamber patch test method. The patches were left for 2 days, and readings were done on days 2, 3, and 7. The concentration of either chromium(III) or chromium(VI) that resulted in 10% or 50% of the patients with a positive reaction was calculated from dose–response curves. According to the study, for chromium chloride, the $MET_{10\%}$ was approximately 0.18 µg/cm^2 per 48 h, and the $MET_{50\%}$ was approximately 2.7 µg/cm^2 per 48 h. For potassium dichromate, the $MET_{10\%}$ and the $MET_{50\%}$ were around 0.03 µg/cm^2 per 48 h and 0.15 µg/cm^2 per 48 h, respectively. The study showed that both chromium(III) and chromium(VI) are capable of eliciting dermatitis at low concentrations in the same patient. The MET concentrations found by Hansen et al. (2003) for chromium(III)

were much lower than those found in earlier studies by Allenby & Goodwin (1983) and Nethercott et al. (1994). This difference might be explained by variation in the test methods or, possibly, by a change in the sensitivity of patients due to changes in exposure patterns over the years.

Park et al. (1994) reported on four workers with asthma caused by chromium. Two patients were exposed to chromium in metal plating (chromium compounds not specified, but most likely chromium(VI)), one in the cement industry (exposure to chromium(VI)), and one in construction work (exposure to chromium(VI)). Two of the patients (one of the metal plating workers and the cement industry worker) showed positive skin prick tests to 10 mg chromium sulfate/ml in saline, indicating immediate-type immunological reactivity to trivalent chromium compounds. The former worker, but not the latter, was also found to be an atopic. The remaining two patients, both with atopy, showed positive responses to 0.5% potassium dichromate in a patch test, but none of the four patients exhibited contact dermatitis. A bronchial provocation test was carried out by administering chromium sulfate solutions at increasing concentrations of 0.1, 1, and 10 mg/ml in saline, each for 10 min, with a nebulizer. Asthmatic responses developed in all cases. When the same bronchial provocation tests were performed in two patients with intrinsic asthma as well as in two healthy controls without any history of exposure to chromium, none of them showed a positive response after the inhalation of chromium sulfate up to 10 mg/ml.

There is at present no unequivocal evidence to show that exposure to trivalent chromium compounds has induced occupational asthma, whereas exposure to the fumes of hexavalent chromium (e.g. in electroplating) may induce occupational asthma, possibly by an immunoglobulin E (IgE)-mediated reaction (Shirakawa & Morimoto, 1996). However, among four persons with clinical asthma from occupational exposure to hexavalent chromium, a bronchial provocation test with nebulized chromium sulfate hydrate solution elicited clear asthmatic responses. Thus, trivalent chromium compounds cannot be regarded as respiratory sensitizers.

9.4 Chronic toxicity

9.4.1 Mortality and morbidity studies

Mortality has been investigated in worker cohorts from different areas of industrial activity involving exposure to chromium alloys, chromium oxide, or trivalent chromium salts. Although the investigators have primarily been interested in the occurrence of cancer (see section 9.6), other causes of death by organ system have been reported as well. No increased standardized mortality rates for diseases of the circulatory system, ischaemic heart disease, or diseases of the respiratory system were found in ferrochromium and stainless steel production workers (Moulin et al., 1990, 1993), among workers grinding, brushing, and polishing stainless steel articles (Svensson et al., 1989), or among tannery workers (Puntoni et al., 1984; Stern et al., 1987; Costantini et al., 1989; Mikoczy et al., 1994; Stern, 2003).

Korallus et al. (1974a) described the circumstances of exposure to chromium compounds and gave a retrospective overview (since the late 1940s) on the causes of death, and health reasons for shifting to other jobs, among workers engaged in chromium oxide production (54 workers) and basic chromium sulfate production (74 workers) in a German plant. Some measured exposure data were provided in a different publication (Korallus et al., 1974c). Basic chromium sulfate production workers also rotated to work occasionally at the chromic acid plant, which thus implied exposure to hexavalent chromium. The authors reported on the types of tumours and numbers of cases found in the workforce and provided crude descriptions of the causes of death and the causes of sickness-related pensioning or sickness-related shifts to other jobs, with the numbers of cases involved. No conclusions about risks or etiological factors can be drawn from the descriptive data. However, the authors noted that in the spectrum of illnesses, there was no emphasis on the occurrence of chronic obstructive pulmonary disease and that no cases of skin sensitization to chromium(III) ("allergic reactions") were found.

Another report from the same plant (Korallus et al., 1974b) analysed the occurrence of unfitness to work based on medical (sick leave) documents registered in the company health insurance scheme. The data suggested higher representation of the diagnoses of asthma, bronchitis, and acute illnesses of the upper airways in the sick leaves among basic chromium sulfate workers when compared with chromium oxide workers. The paper did not make reference to the fact that the basic chromium sulfate workers occasionally worked at the chromic acid plant.

The third report involving the same plant concerned clinical examinations of 106 workers from the two above-mentioned work areas (Korallus et al., 1974c). The paper provides summary data on symptoms, smoking habits, physical examination, lung function (forced vital capacity [FVC], forced expiratory volume in 1 s [$FEV_{1.0}$]), haematological and clinical chemical examinations, chromium measurements in blood and urine (by AAS), and chest radiography. The authors concluded from their investigations that the prevailing exposures to chromium oxide or basic chromium sulfate in the plant caused no serious health impairment, even after exposure for years. In the report, one may note that five workers exhibited nasal septum perforation.

Inadequate methodologies used in these investigations and mixed exposure to chromic acid among basic chromium sulfate workers do not, however, allow any certain conclusions to be drawn about health risks due to chromium(III) compounds.

9.4.2 Respiratory effects

Cross-sectional worker surveillance studies focused on the respiratory system were conducted involving exposures to chromium oxide in the mining and concentration of chromite ore and in the production of ferrochromium and stainless steel (Ballal, 1986; Huvinen et al., 1996, 2002a,b). A similarly oriented study concerned polishers in a tannery with exposure to trivalent chromium salts (Bulikowski & Tyras, 1985).

Chromite ore is up to 50% chromium oxide. In Finnish chromite mine dust, one third was chromite, one third talc, and one third chlorite serpentine, part of which can be classified as fibres (Huvinen et al., 1996). Chromite miners in Sudan exposed to extremely high dust levels (up to 224 mg/m^3) exhibited an increased prevalence of chronic bronchitis or asthma (Ballal, 1986), whereas their Finnish counterparts exposed to low or moderate dust levels (mean of 1 mg/m^3 in the mine and up to 4.9 mg/m^3 in the crushing plant) showed an increased prevalence of some respiratory symptoms and decreased values in some lung function parameters (Huvinen et al., 1996, 2002b). However, the complex exposures involved do not allow any conclusions to be drawn about the potential respiratory toxicity of chromium oxide.

Exposures more focused on chromium oxide–containing dust are involved in certain parts of ferrochromium production. Huvinen et al. (1996) explored respiratory health in ferrochromium workers exposed to chromium(III)–containing dust in grinding, pelletizing, and sintering of concentrated chromite and crushing of cooled ferrochromium castings and repeated the study after a 5-year follow-up (Huvinen et al., 2002b). The average duration of the work history was 21 years (range 9–27 years). A group of 95 workers from the stainless steel cold rolling mill served as controls. The workers involved were specifically exposed to dusts containing chromium(III) (Cr^{3+} group), since their work areas were separated from the smelting furnaces where some hexavalent chromium was generated. In the sintering and crushing departments, the average total dust exposure was 2.4 mg/m^3. No data on the particle size distribution were given. The dust was estimated to contain 10–20% chromium, which would give approximately 240–480 µg Cr^{3+}/m^3. The frequencies of smokers, ex-smokers, and non-smokers were 39%, 32%, and 29%, respectively; current smoking was somewhat less frequent than among the controls. Compared with the control group, work-related cough or dyspnoea, production of phlegm, and shortness of breath when hurrying on level ground occurred significantly more frequently in the Cr^{3+} group. The lung function variables did not differ from the controls except for FVC, which was lower among smokers than in the smoking controls. In the radiographs of the chest, the frequency of small opacities was not significantly different between the Cr^{3+} group and the control group, and their occurrence increased with age in both groups. However, there were more individuals with more severe findings in the Cr^{3+} group.

In the 5-year follow-up study (Huvinen et al., 2002b), 68 persons of the original Cr^{3+} group were re-examined, as well as 81 workers from the original control group. There was a slightly lower fraction of current smokers in both groups compared with the original study groups. The Cr^{3+} group still exhibited a higher frequency of shortness of breath (non-smokers) and phlegm (current and ex-smokers) than corresponding groups of controls. Lung functions, smokers plus ex-smokers and non-smokers separated, did not show any differences between workers in the Cr^{3+} group and the controls. Thus, the changes over the preceding 5-year period had been parallel. In one Cr^{3+} worker, the profusion of small opacities in the chest radiograph had progressed. Because the same pattern of symptoms in the Cr^{3+} group occurred consistently in both the original and the follow-up study and could not be explained by smoking habits, the authors proposed that the reason for the symptoms was irritation, although they could not identify an obvious causative agent.

In a separate study, 14 workers of the sintering and crushing departments (Cr^{3+} group) and 39 referents from the stainless steel cold rolling mill were examined for nasal symptoms, appearance of nasal mucosa, mucociliary clearance (saccharine test), and nasal cytology (Huvinen et al., 2002a). There were no remarkable findings in nasal cytology and no indication of impaired mucociliary clearance. In anterior rhinoscopy, infected and atrophic mucous membranes tended to occur more frequently in the Cr^{3+} group than among the referents, but without statistical significance.

A pilot health study in a Polish tannery (Bulikowski & Tyras, 1985) concerned 24 polishers (12 men and 12 women) of chrome-tanned dried leather with 2–20 years of employment in this job. The authors used 21 office workers as a control group. The average concentration of the leather dust was reported as 2 mg/m^3, and the geometric mean particle size was 2.2 µm. The leather dust contained 5.8% chromium; that is, airborne chromium levels were about 0.1 mg/m^3 (only trivalent chromium was mentioned). Among the polishers, the mean post-shift urinary chromium concentration at the end of the work week, measured with a photocolorimetric method, was given as 0.030 mg/l. Epicutaneous tests showed that

none of the workers had been sensitized to chromium. In a laryngological examination, 14 of the 24 polishers were reported to exhibit chronic tonsillitis, 5 had chronic hypertrophic rhinitis, and 1 had atopic rhinitis as well as chronic bronchitis. No laryngological findings were reported for the controls. In haematological examinations of the peripheral blood, eosinophils were found to occur in significantly higher concentrations among the polishers than in control subjects. In blood samples obtained from the nasal turbinate and the fingertip, there was a significant difference (direction of change not given) in the concentration of monocytes between the exposed and the controls. Furthermore, the polishers frequently experienced a slight rise in body temperature on the 1st day of the work week, which the authors attributed to airborne bacteria. The findings suggested that chrome-tanned leather dust caused chronic inflammation in the upper airways, especially in the pharynx. Although the reported airborne chromium concentration was rather low (average about 0.1 mg/m^3), the authors attributed the observed effect to airborne trivalent chromium, but failed to show evidence to exclude other potential causes (e.g. finishing chemicals in the leather, airborne microbes, or microbial toxins).

9.5 Genotoxicity

Studies of the genotoxicity of trivalent or metallic chromium in humans in vivo have concerned workers occupationally exposed to chromium in leather tanneries, ferrochromium works, chromite mines, metal workshops, and dental laboratories, residents living near chromium dumpsites, and patients exposed to chromium released from prostheses. In most cases, the exposure has been complex (Riihimäki & Luotamo, 2006).

Iraqi tannery workers (n = 17) handling chrome alum (chromium potassium sulfate) did not show an increase in (total) chromosomal aberrations in cultured peripheral lymphocytes in comparison with unexposed control subjects (n = 13) (Hamamy et al., 1987). When smoking tannery workers (n = 9) were compared with smoking controls (n = 7), a statistically significantly higher (2.19-fold) frequency of chromosome-type aberrations was noted.

Italian workers employed in the drum workshop of the tanning process (n = 19) and in the finishing department (n = 17) of tanneries and two control groups (n = 19 and n = 17) of unexposed administrative office staff were studied for the frequency of chromosomal aberrations and micronuclei in cultured peripheral lymphocytes (Sbrana et al., 1990; Migliore et al., 1991). The drum workshop workers showed a 3.2-fold statistically significant increase in the mean frequency of cells with chromosomal aberrations, and the finishing department workers showed a statistically non-significant increase in chromosomal aberrations. No increase in micronucleated cells was observed in the drum workshop workers or the finishers. The influence of chromium(III) is, however, difficult to assess as a result of the other exposures involving genotoxic compounds (Riihimäki & Luotamo, 2006).

The same problem with complex exposures also applies to studies performed in Turkey and Portugal showing an increased incidence of markers of genotoxic damage in leather tannery workers when compared with controls (González Cid et al., 1991; Medeiros et al., 2003).

In ferrochromium production, a slight (statistically non-significant) increase in the frequency of chromosomal aberrations in cultured peripheral lymphocytes was observed in 28 workers of a furnace sector of an Italian ferrochromium plant, in comparison with 14 matched control persons and 7 general controls (Sbrana et al., 1990). However, the furnace workers may have also been exposed to chromium(VI). Workers from crushing and milling departments (n = 7), expected to be exposed to trivalent chromium, and workers in a machine shop (n = 8) did not differ from the controls in frequencies of cells with chromosomal aberrations.

Finnish workers (all non-smokers) exposed to chromium(III) in a chromite ore mine (n = 5) and in sintering and crushing departments of a ferrochromium works (n = 14) showed no increase in nasal cells with micronuclei, in comparison with unexposed referents (n = 39) (Huvinen et al., 2002a). The average dust content in the air of the chromite ore mine was 1 mg/m^3, and the median personal level of exposure to total chromium was 22 µg/m^3. Chromium(VI) was not detected in the samples. At the sintering and crushing departments, the average dust level in the air was 2.4 mg/m^3, and the average exposure to total chromium was 248 µg/m^3. Chromium remains in a trivalent state in these steps of the process.

Residents of Hudson County, USA, living near large chromium dumpsites of waste from mine slags and chromite ore processing residues used as landfill and in construction of roads and buildings, with urinary chromium levels ≥0.5 µg/l, were found to have a statistically significantly higher mean level of DNA–protein cross-links (1.3%; n = 33) in their mononuclear leukocytes compared with unexposed controls (0.8%; n = 49) (Taioli et al., 1995).

Three studies have suggested that patients with hip replacements or fracture fixation devices containing metallic chromium, among other components, have an increased frequency of various types of chromosomal damage (Case et al., 1996; Savarino et al., 2000; Doherty et al., 2001). Although these patients often show elevated levels of serum chromium, it is unclear if

the increased incidence of cytogenetic alterations is due to chromium, other metals, or other substances released as particles or ions from the prostheses, or the inflammatory reaction associated with the released particles.

9.6 Carcinogenicity

Epidemiological carcinogenicity studies that may be relevant to trivalent chromium concern occupational exposures in ferrochromium production, leather tanning, and chromate production. In ferrochromium operations, insoluble trivalent chromium as concentrated chromite and chromium oxide predominates, but soluble hexavalent chromium species also occur at smelting furnaces (Huvinen et al., 1996). Leather tanning with chromium is currently based on trivalent basic chromium sulfate, but hexavalent chromium was used in the two-bath process before the Second World War. Moreover, it must be noted that tanneries have also used a wide variety of biocides, dyes, pigments, and solvents, including recognized carcinogens (Stern et al., 1987; Costantini et al., 1989; Mikoczy et al., 1994). In chromate production, although the starting material is trivalent chromium (chromite), further stages of the process deal with hexavalent chromium in the form of chromate and dichromate, and separation of the effects for tri- and hexavalent chromium species will be problematic, if not impossible. Chromium electroplating is currently performed with both hexavalent chromium (the predominant process) and trivalent chromium. The latter found use only about 20 years ago and is still not widely applied. Therefore, cancer risks observed in past research among electroplating workers cannot be directly associated with trivalent chromium.

A cancer mortality and morbidity study in a population of male workers employed for at least 1 year between 1930 and 1975 at a Swedish plant producing ferrochromium alloys from chromite ore showed no increased death rate or an increase in the incidence of cancer (Axelsson et al., 1980). Levels of chromium exposure were based on estimations; no measured data existed.

A Norwegian study (Langård et al., 1990) that included all male workers employed in ferrochromium and ferrosilicon production for at least 1 year from 1928 onwards showed a significant excess of lung cancer risk in the ferrochromium subgroup when using all non-ferrochromium workers as a reference group. However, measurements conducted in ferrochromium production in 1975 indicated that hexavalent chromium constituted 11–33% of total chromium in the work atmosphere. Hence, the study could not address the question of whether exposure to chromium(III) was carcinogenic in humans.

In a French study (Moulin et al., 1990), among workers producing ferrochromium and stainless steel, lung cancer mortality was in excess, but the link was stronger for polycyclic aromatic hydrocarbons than for chromium exposure. A further study (Moulin et al., 1993) was aimed at assessing the potential risk of lung cancer related to occupational exposures when producing stainless steel. No significant excess of lung cancer was found in the manufacture of ferroalloys and in the melting and casting of stainless steel, whereas a significant excess was observed among workers with more than 30 years of employment in the foundry area. However, Moulin et al. (1993) could not point at a specific causal factor because of the many simultaneously occurring exposures (chromium, nickel, silica, asbestos, and polycyclic aromatic hydrocarbons) in the industry.

The previous French study cohort of 4900 workers was followed up until 1992 (Moulin et al., 2000), and the workers' exposures were carefully assessed. An induction period of 10 years for lung cancer was assumed. All potential confounders (i.e. smoking and known occupational exposures), which in a univariate analysis seemed to have an effect, were adjusted for using a conditional logistic regression analysis. In a case–referent study nested in the cohort, no excess mortality from lung cancer was observed. The authors concluded that the study failed to demonstrate any relationship between lung cancer and exposure to chromium (predominantly chromium(III)) or its compounds.

There are few studies on cancer risk in tannery workers available. In a retrospective study involving 9365 chrome leather tannery workers in two tanneries in the USA, mortality from all causes and deaths from cancers were lower than expected (Stern et al., 1987). In a follow-up of this cohort for an additional 11 years with data on vital status and work histories and 1153 new deaths, no elevation in any primary cause of death was seen, with the exception of lung cancer in one tannery when state death rates were used as a standard (Stern, 2003). However, in an Italian tannery study, no excess of cancers of all sites was seen, but slight, statistically non-significant increases were shown in deaths from cancers of the lung, bladder, kidney, and pancreas and leukaemia (Costantini et al., 1989). In a Swedish cohort of 2026 workers, a significantly increased incidence of soft tissue sarcomas based on only five cases was found among tannery workers. Non-significant excesses were also found in multiple myelomas and sinonasal cancer (Mikoczy et al., 1994). Because of the exposure to multiple carcinogens in tanneries, these studies are inconclusive regarding trivalent chromium. In the Swedish study (Mikoczy et al., 1994), the researchers hypothesized that the increased risk of soft tissue

sarcomas could be related to chlorophenols, which had been used in all three plants investigated.

Mancuso (1997) and Gibb et al. (2000) addressed the question of whether chromium(III) exposure, like chromium(VI) exposure, is associated with an excess lung cancer risk in chromate production workers. Mancuso (1997) followed up successive cohorts by year of hire (1931–1937) at the same chromate manufacturing plant, 332 workers in total, through 1993. There were no smoking data available. Based on measured atmospheric concentrations in 1949, an exposure index was formed as a weighted average of exposure to total insoluble (mainly trivalent) and total soluble (essentially hexavalent) chromium in the departments where the worker was assigned during his work history. Lung cancer death rates increased by gradient level of exposure to insoluble (trivalent) and soluble (hexavalent) chromium. To investigate whether the relationship was due to one form of chromium compound, either chromium(III) or chromium(VI), the age-adjusted death rates for the two compounds were cross-classified by the level of total chromium. Mancuso (1997) concluded that all forms of chromium were carcinogenic. However, from tabled data of the exposure distributions, it is evident that chromium(III) and chromium(VI) are highly correlated. Even an appropriate statistical analysis might not be able to discriminate the separate effects of these compounds when collinearity is high (Nurminen, 2005).

Gibb et al. (2000) studied the mortality experience in a cohort of 2357 workers first employed between 1950 and 1974 at a chromate production plant. The follow-up lasted until the end of 1992. Annual average exposure estimates, based on historical exposure measurements for each job title in the plant for the years 1950–1985, were made to construct a job–exposure matrix, and cumulative chromium(VI) exposures for each member of the study population were calculated. Following closure of the plant, settled dust samples were collected and analysed for hexavalent and trivalent chromium. The trivalent/hexavalent concentration ratios in each plant area were combined with historic air sampling data to estimate cumulative chromium(III) exposure for each individual in the study cohort. Smoking status and clinical signs of potential chromium irritation were identified from company records. A lag period of 5 years was assumed for the illnesses. Using Cox models for three different exposure measures, cumulative hexavalent chromium exposure, cumulative trivalent chromium exposure, and work years were found to be roughly equivalent in predictive ability when smoking was included in the model, and each of these exposure measures was significantly associated with increased lung cancer risk. There was a strong correlation between the log of cumulative chromium(VI) exposure and the log of chromium(III) exposure (correlation coefficient = 0.95). The authors utilized two proportional hazard models, one incorporating the log of cumulative hexavalent chromium exposure, the log of cumulative trivalent chromium exposure, and smoking, the other incorporating the log of cumulative hexavalent chromium exposure, work duration, and smoking. The inclusion of the three exposure variates as risk factors in the same model resulted in cumulative chromium(VI) exposure remaining statistically significant, although at a lower significance level, whereas the other measures lost statistical significance. Thus, although cumulative hexavalent chromium exposure was associated with an increased lung cancer risk, cumulative trivalent chromium exposure was not. The authors concluded that their study provided no evidence that trivalent chromium is carcinogenic, and if it is indeed carcinogenic, it is much less so than hexavalent chromium (Gibb et al., 2000).

9.7 Sensitive subpopulations

There are no data available on subpopulations being at extra risk for health hazards caused by inorganic trivalent chromium.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Essentiality

Chromium(III) is required by only some microorganisms for specific metabolic processes, such as glucose metabolism and enzyme stimulation (Hughes & Poole, 1989). Huffman & Allaway (1973) demonstrated that chromium was not an essential component of plant nutrition.

Chromium(III), in trace amounts, has been reported to be an essential component of animal nutrition and is most notably associated with glucose and fat metabolism (Mertz, 1969). However, whereas NAS (1997) reported that chromium has been shown to be essential for glucose metabolism in some laboratory mammals, studies on other animals are equivocal. The literature does not support a general recommendation for chromium supplementation of commercial ruminant diets. However, two situations have been identified in which chromium supplementation might be beneficial: following the transportation of cattle, and first-lactation dairy cattle during the transition period (NAS, 1997). Although responses of pigs to supplemental chromium are inconsistent, there is an increasing amount of evidence indicating that chromium may favourably alter metabolism of pigs under some circumstances, with resultant improvements in growth rate, carcass traits, and reproductive performance (NAS, 1997). Chromium

deficiency in rabbits has not been demonstrated, but positive effects of chromium on cholesterol metabolism and sucrose utilization have been reported (NAS, 1997). Investigations concerning the influences of dietary chromium on fish are limited. Some studies reported no effect on growth or tissue chromium distribution, whereas others showed that chromium supplementation of diets, especially those containing glucose, caused significant increases in weight gain, energy deposition, and liver glycogen and altered postprandial plasma glucose concentrations (NAS, 1997). Research with poultry has shown that supplemental dietary chromium can be used to alleviate some of the toxic effects of vanadium in growing chicks and laying hens. Evidence has also been obtained that supplemental chromium at 20 mg/kg diet as chromium(III) chloride increases the rate of glucose utilization by livers of chicks and poults in vivo and in vitro. However, the results from experiments to determine the effect of added dietary chromium on growth rate and feed efficiency of growing poultry are inconsistent (NAS, 1997).

10.2 Aquatic organisms

The available toxicity data for chromium(III) have been mainly derived using the water-soluble forms (chromium(III) chloride, chromium(III) nitrate, and chromium potassium sulfate). In the environment, chromium(III) is likely to be present in much less soluble forms and hence less bioavailable to aquatic organisms.

The toxicity of trivalent chromium to aquatic organisms is summarized in Table 3. Ninety-six-hour median effective concentrations (EC_{50}s) for one freshwater alga, based on growth, ranged from 0.3 to 0.4 mg chromium(III)/l. A 96-h EC_{50}, based on growth, was reported for a marine diatom at 2 mg chromium(III)/l. Median lethal concentrations (LC_{50}s) in freshwater invertebrates ranged from 0.1 mg/l (*Daphnia pulex*) to 442 mg/l (*Asellus aquaticus*), with a 21-day no-observed-effect concentration (NOEC) (reproduction) of 0.7 mg/l and a life cycle NOEC of 0.047 mg/l for *Daphnia magna.* LC_{50}s ranging from 10 to 100 mg/l have been reported for marine invertebrates. Ninety-six-hour LC_{50}s for freshwater fish range from 3.3 mg/l for the guppy (*Poecilia reticulata*) to 151 mg/l for the bighead (*Aristichthys nobilis*), whereas 96-h LC_{50}s of 31.5 and 53 mg/l were reported for marine fish. A 72-day NOEC (survival) of 0.05 mg/l was reported for rainbow trout (*Oncorhynchus mykiss*).

Trivalent chromium is generally less toxic than hexavalent chromium in algae and aquatic invertebrates. In both aquatic invertebrates and fish, chromium(III) is more toxic in soft waters than in hard waters (Pickering & Henderson, 1966; US EPA, 1985). Stackhouse & Benson (1989) found a decrease in chromium(III) toxicity with increasing humic acid levels. The main features of trivalent chromium toxicity to algae are inhibition of growth (Nollendorf et al., 1972) and inhibition of various metabolic processes, such as photosynthesis and protein synthesis (USEPA, 1978). The high deposition of chromium(III) in fish gills leads to tissue damage, including hyperplasia, clubbing of lamellae and necrosis, and the impairment of the ability to osmoregulate and respire (Moore, 1991).

Walsh et al. (1994) studied the effect of chromium(III) effluent from a tannery on marine grey mullet (*Chelon labrosus*). Fish exposed for 2 months to contaminated sediment (46 mg chromium/kg dw) and food (*Enteromorpha intestinalis* [9.4 mg/kg] and *Mytilus edulis* [6 mg/kg]) showed no adverse effects on growth, mortality, or gross tissue damage. Significant bioaccumulation was measured in livers of exposed fish; however, chromium levels in liver samples from fish at the contaminated site were not significantly higher than those of controls.

10.3 Terrestrial organisms

The toxicity of chromium to soil bacterial isolates was studied by measuring the turbidity of liquid cultures supplemented with trivalent chromium. Gram-negative bacteria were more affected by hexavalent chromium (1–12 mg/kg) than were Gram-positive bacteria. Toxicity due to trivalent chromium was not observed at similar levels (Ross et al., 1981).

The results of short-term tests indicate that a variety of effects are induced in soil microbes at concentrations ranging from 25 to 100 mg chromium(III)/kg dw, such as changes in species abundance, respiration, nitrogen transformation, and enzyme activities (Tabatabal, 1977; Drucker et al., 1979; Chang & Broadbent, 1981, 1982; Ross et al., 1981). In long-term tests, the addition of 10 mg chromium(III)/kg dw affected the arylsulfatase activity, whereas soil respiration was affected at 150 mg/kg and phosphatase activity at 280 mg/kg (IPCS, 1988). Crommentuijn et al. (1997) reviewed the toxicity of chromium(III) to soil processes. The results of 51 determinations were reported, covering arylsulfatase, nitrification, nitrogen mineralization, phosphatase, respiration, and urease. The test results (mainly expressed as lowest-observed-effect concentrations [LOECs]) ranged from 1 to 3332 mg/kg dw (both values being for arylsulfatase). All studies used soluble chromium(III) compounds, largely chromium(III) chloride. Data were selected from this survey, taking values where a NOEC was obtained directly or where the LOEC related to an effect level of 20% or less (and using LOEC/2 as the NOEC), in the European Union Risk Assessment Report (EU, 2005). A total of 37 values were obtained, and a further selection was made, giving preference to longer exposure times in the same

Table 3: Toxicity of trivalent chromium to aquatic species.[a]

Organism	End-point	Chromium salt	Concentration (mg chromium/l)	Reference
Microorganisms				
Freshwater				
Green alga (*Selenastrum capricornutum*)	24-h EC_{50}	–	>1	Turbak et al. (1986)
	96-h EC_{50} (growth)	Chloride	0.4	USEPA (1985)
	96-h EC_{50} (biomass)	Chloride	0.3	Greene et al. (1988)
	14- to 21-day EC_{50} (biomass)	–	0.6	Turbak et al. (1986)
Protozoan (*Tetrahymena pyriformis*)	9-h IC_{50} (growth)	Chloride	50	Sauvant et al. (1995)
Marine				
Diatom (*Ditylum brightwellii*)	96-h EC_{50}	Chloride	2	Canterford & Canterford (1980)
Invertebrates				
Freshwater				
Snail (*Amnicola* sp.)	96-h LC_{50}	–	8.4	Rehwoldt et al. (1973)
Annelid worm (*Nais* sp.)	96-h LC_{50}	–	9.3	Rehwoldt et al. (1973)
Water flea (*Daphnia magna*)	48-h LC_{50}	Nitrate	17–59[b]	USEPA (1985)
	24-h EC_{50} (immobilization)	Chloride	22	Kühn et al. (1989)
	21-day NOEC (reproduction)	Chloride	0.7	Kühn et al. (1989)
	21-day LC_{50}	Chloride	2	Biesinger & Christensen (1972)
	21-day EC_{50} (reproductive impairment)	Chloride	0.6	Biesinger & Christensen (1972)
	Life cycle NOEC	Nitrate	0.047 and 0.129[c]	USEPA (1985)
Water flea (*Daphnia pulex*)	96-h LC_{50}	Chloride	0.1–6[d]	Stackhouse & Benson (1989)
Water hoglouse (*Asellus aquaticus*)	96-h LC_{50}	Chloride	442	Martin & Holdich (1986)
Amphipod (*Gammarus* sp.)	96-h LC_{50}	–	3.2	Rehwoldt et al. (1973)
Amphipod (*Crangonyx pseudogracilis*)	96-h LC_{50}	Chloride	291	Martin & Holdich (1986)
Crayfish (*Austropotamobius pallipes*)	96-h LC_{50}	Chloride	3.4	Boutet & Chaisemartin (1973)
Crayfish (*Orconectes limosus*)	96-h LC_{50}	Chloride	6.6	Boutet & Chaisemartin (1973)
Mayfly (*Ephemerella subvaria*)	96-h LC_{50}	Chloride	2	Warnick & Bell (1969)
Caddis fly (*Hydropsyche betteni*)	96-h LC_{50}	Chloride	64	Warnick & Bell (1969)
Caddisfly (unidentified)	96-h LC_{50}	–	50	Rehwoldt et al. (1973)
Stonefly (*Acroneuria lycorias*)	7-day LC_{50}	Chloride	32	Warnick & Bell (1969)
Damsel fly (unidentified)	96-h LC_{50}	–	43.1	Rehwoldt et al. (1973)
Midge (*Chironomus* sp.)	96-h LC_{50}	–	11	Rehwoldt et al. (1973)
Marine				
American oyster (*Crassostrea virginica*)	48-h LC_{50}	Chloride	10.3[e]	Calabrese et al. (1973)
Polychaete (*Ophryotrocha diadema*)	48-h LC_{50}	–	100	Parker (1984)
Polychaete (*Neanthes arenaceodentata*)	293-day NOEC (behaviour and reproduction)	Chloride	50.4	Oshida et al. (1981)
Brown mussel (*Perna perna*)	1-h EC_{50} (filtering rate)	Chloride	2	Watling & Watling (1982)
Crab (*Sesarma haematocheir*) zoea	96-h LC_{50}	–	56	USEPA (1985)

Table 3 (continued)

Organism	End-point	Chromium salt	Concentration (mg chromium/l)	Reference
Fish				
Freshwater				
Rainbow trout (*Oncorhynchus mykiss*)	96-h LC_{50}	Nitrate	24.1	Hale (1977)
	96-h LC_{50}	–	11.2	Bills & Marking (1977)
	96-h LC_{50}	Nitrate	4.4	Stevens & Chapman (1984)
	72-day NOEC (survival)[f]	Nitrate	0.05	Stevens & Chapman (1984)
Goldfish (*Carrasius auratus*)	96-h LC_{50}	Potassium sulfate	4.1	Pickering & Henderson (1966)
	96-h LC_{50}	–	98	Wong et al. (1982)
Common carp (*Cyprinus carpio*)	96-h LC_{50}	–	14.3[g]	Rehwoldt et al. (1972)
Fathead minnow (*Pimephales promelas*)	96-h LC_{50}	Potassium sulfate	5.1–67.4[h]	Pickering & Henderson (1966)
Bluegill (*Lepomis macrochirus*)	96-h LC_{50}	Potassium sulfate	7.5–71.9[h]	Pickering & Henderson (1966)
Pumpkinseed (*Lepomis gibbosus*)	96-h LC_{50}	–	17[g]	Rehwoldt et al. (1972)
Banded killifish (*Fundulus diaphanous*)	96-h LC_{50}	–	16.9[g]	Rehwoldt et al. (1972)
Striped bass (*Roccus saxatilis*)	96-h LC_{50}	–	17.7[g]	Rehwoldt et al. (1972)
White perch (*Roccus americanus*)	96-h LC_{50}	–	14.4[g]	Rehwoldt et al. (1972)
Bighead (*Aristichthys nobilis*)	96-h LC_{50}	–	151	Wong et al. (1982)
Guppy (*Poecilia reticulata*)	96-h LC_{50}	Potassium sulfate	3.3	Pickering & Henderson (1966)
American eel (*Anguilla rostrata*)	96-h LC_{50}	–	13.9[g]	Rehwoldt et al. (1972)
Marine				
Mummichog (*Fundulus heteroclitus*)	96-h LC_{50}	Chloride	31.5[i]	Dorfman (1977)
Yellow eye mullet (*Aldrichetta forsteri*)	96-h LC_{50}	Nitrate	53	Negliski (1976)

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

[a] All freshwater tests conducted at a hardness of <100 mg calcium carbonate/l unless otherwise stated.
[b] Hardness ranging from 52 to 215 mg calcium carbonate/l.
[c] Hardness 52 and 100 mg calcium carbonate/l.
[d] Humic acid concentration ranging from 0 to 50 mg/l.
[e] Visible precipitate.
[f] Newly fertilized eggs to 30-day post-swim-up.
[g] Temperature = 28 °C (not significantly different from tests performed at 15 °C).
[h] Hardness ranging from 20 to 360 mg calcium carbonate/l.
[i] Salinity 6–24‰.

studies, resulting in a final data set of 30 values. The statistical extrapolation method was then used to derive an $HC_5(50)$ value (the hazardous concentration for 5% of species, with a 50% confidence level) of 5.9 mg/kg dw.

Although chromium is present in all plants, it has not been proved to be an essential element for plants. Chromium can be absorbed through either the root or the leaf surface. Several factors affect the availability of chromium for the plant, including the pH of the soil, interactions with other minerals or organic chelating compounds, and carbon dioxide and oxygen concentrations (Black, 1968; IPCS, 1988). The main feature of chromium intoxication is chlorosis, which is also caused by iron deficiency. Although both chromium(III) and chromium(VI) are equally available to plants grown in nutrient solutions (NRCC, 1976), the results of most studies indicate that chromium(VI) is consistently more toxic than chromium(III) (IPCS, 1988). Whereas the toxic properties of hexavalent chromium originate from its action as an oxidizing agent, trivalent chromium causes toxic effects in plants as a result of its ability to coordinate various organic compounds, resulting in inhibition of some metalloenzyme systems. At high concentrations, chromium(III) can generate reactive oxygen species (Shanker et al., 2005). Levels of 200 mg chromium(III)/kg dw in soils resulted in a significant (23–36%) reduction in the yields of grass, lettuce, and

radish (Sykes et al., 1981). Janus & Krajnc (1990) reported that levels of 150 mg chromium(III)/kg dw or more in soil can inhibit the growth of sensitive plant species, depending on the nature of the soil. Wheat (variety Florence-Aurore) and tomatoes (variety John Moran) were grown in soil spiked with various concentrations of chromium(III) (10–500 mg chromium/kg soil for wheat; 20–1000 mg chromium/kg soil for tomatoes). Chromium(III), in the form of chromium sulfate, was shown to reduce the yields of wheat at concentrations of 200 mg chromium/kg and greater in the acid soil and about 100 mg chromium/kg soil and greater in the alkaline soil. No effects were seen with chromium(III) in the form of the insoluble chromium oxide (Moulinier & Mazoyer, 1968).

In 8-week toxicity tests using activated sludge, no significant effect on the growth of earthworms (*Eisenia foetida*) was observed at the highest concentration tested (46 000 mg chromium(III)/kg, as chromium(III) oxide) (Hartenstein et al., 1981). Sivakumar & Subbhuraam (2005) reported 14-day LC_{50}s for chromium(III) ranging from 1656 to 1902 mg/kg for *E. foetida*. Statistical analysis of the results predicted that the clay content of the soils accounted for 92% of the variation in toxicity. Van Gestel et al. (1993) found a significant reduction in reproduction of earthworms (*Eisenia andrei*) exposed to ≥100 mg chromium(III)/kg dry artificial soil in 3-week tests; however, growth was significantly reduced only at the highest concentration tested (1000 mg/kg). The NOEC from the study was 32 mg/kg dry soil.

Tatara et al. (1998) reported the 24-h LC_{50} for total trivalent chromium at 967 mg/l (18.6 mmol/l) and for the free ion at 946 mg/l (18.2 mmol/l) for the free-living soil nematode *Caenorhabditis elegans* exposed to chromium nitrate.

Controlled studies on the toxicity of chromium to wild mammals and birds are very limited. Turkey hens fed 10 µg chromium(III)/g ww in their diet produced significantly fewer eggs than controls; however, egg fertility and hatchability were unaffected (Frobish, 1980). Eisler (1986) and Outridge & Scheuhammer (1993) reviewed an unpublished study by Haseltine et al. (1985) in which juvenile American black ducks (*Anas rubripes*) fed 10 µg chromium(III)/g dw in the diet had increased concentrations of uric acid and reduced growth and survival. In adults administered 10 and 50 µg/g in the diet, there were no effects on survival, reproduction, or blood chemistry.

Significant adverse effects on growth and behaviour of herring gull (*Larus argentatus*) chicks were observed following a single intraperitoneal injection of chromium nitrate (25 mg/kg bw) (Burger & Gochfeld, 1995b). In 5-day dietary tests with Japanese quail (*Coturnix coturnix japonica*), LC_{50}s were >5000 mg chromium(III)/kg for chromium sulfate and chromium potassium sulfate and 2476 mg chromium(III)/kg for chromium acetylacetonate (Hill & Camardese, 1986). In further tests, a 5-day LC_{50} for mallard ducks (*Anas platyrhynchos*) of >5000 mg chromium(III)/kg was reported for chromium acetylacetonate (Hill et al., 1975).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

Human studies concerned with inorganic species of trivalent chromium are restricted to some experimental or occupational investigations dealing with toxicokinetics and clinical health outcomes. The latter do not provide sufficient data for dose–response assessments. The key toxicological end-point for chromium(III) oxide is respiratory toxicity associated with substance accumulation and overload in the lungs on repeated inhalation exposure. The key toxic end-points for basic chromium sulfate, presumably representing soluble inorganic chromium(III) salts as a group, are chronic respiratory toxicity on inhalation and contact sensitization of the skin.

Absorbed chromium(III) is excreted mainly in the urine and to a lesser extent in the faeces.

In rats, the oral acute toxicity of chromium(III) oxide is low, with LD_{50} values above 5 g/kg bw. Similarly, acute oral toxicities of soluble chromium(III) salts are low. An oral LD_{50} for basic chromium sulfate of 3530 mg/kg bw is reported (Bayer, 1978). In the case of chromium nitrate, values range from 1540 to 3250 mg/kg bw (Smyth et al., 1969; Vernot et al., 1977). By parenteral routes (intraperitoneal or intravenous), chromium(III) salts have lethal effects in rats and mice at doses 2–3 orders of magnitude lower than those for the oral route. No acute toxicity data were available for inhalation or dermal exposure to any of the inorganic trivalent chromium compounds.

Based on animal studies, chromium oxide and basic chromium sulfate are not skin or eye irritants. Liquid aerosols of chromium chloride at a high concentration have caused slight irritancy in Syrian hamsters. On repeated exposure, inhaled dusts of basic chromium sulfate have caused irritation and inflammation in the respiratory system of rats, whereas the corresponding reaction to chromium oxide inhalation was mild.

Water-insoluble chromium(III) oxide, which normally covers the surface of metallic chromium, does not cause skin sensitization.

Among trivalent chromium salts, chromium chloride and hydrated chromium sulfate have been sensitizing to guinea-pig skin in non-standard tests employing intradermal or subcutaneous injections, whereas chromium nitrate, chromium sulfate (hydrate), chromium acetate, and chromium oxalate have given negative responses (Van Neer, 1963; Gross et al., 1968; Jansen & Berrens, 1968; Polak et al., 1973; Siegenthaler et al., 1983). Chromium chloride has also given positive reactions after an epicutaneous challenge in guinea-pigs (Polak et al., 1973; Siegenthaler et al., 1983). Trivalent chromium acts as the ultimate haptenic determinant for chromium sensitization in the skin; however, especially because of their lower penetration into the skin, trivalent chromium compounds are less potent sensitizers than hexavalent chromium compounds.

Clinical evidence pointing to the potential of soluble trivalent chromium to cause allergic skin reactions relates mainly to the wearing of leather articles tanned with chromium. Case-studies of more than 100 sensitized patients, many of them having worn shoes in direct contact with the skin, such as sandals, and less frequently having used wet gloves, have been reported over the last few decades. The issue is, however, clouded by the fact that, in addition to the higher levels of mobile trivalent chromium in the leather, even low levels of hexavalent chromium may have been present, or the reported cases of foot dermatitis may actually be elicitation reactions in previously chromium-sensitized people.

Skin sensitization among workers handling trivalent chromium salts appears to be a rare event.

There is currently no evidence to show that exposure to trivalent chromium compounds (unlike exposure to hexavalent chromium) has induced occupational asthma. However, in a study of four persons with clinical asthma from occupational exposure to hexavalent chromium, a bronchial provocation test with nebulized chromium sulfate elicited asthmatic responses.

Only a few studies have addressed chronic respiratory effects of occupational exposure to chromium(III) compounds. Main findings have included an increased prevalence of respiratory symptoms indicative of sustained irritation. However, in view of the complexity of the dust exposures in occupational settings, the sustained respiratory irritation found in the workforce cannot be attributed exclusively to trivalent chromium.

In a 90-day toxicity study with rats, no adverse effects were seen when the animals were fed with chromium(III) oxide baked in bread at dose levels as high as 1368 mg Cr^{3+}/kg bw per day (Ivankovic & Preussman, 1975). This lack of effects can be explained by the poor oral bioavailability of chromium(III) oxide. In a 20-week oral feeding study with water-soluble chromium chloride, no adverse effects were seen in Sprague-Dawley rats, even at the highest dose level, corresponding to a chromium intake of 7 mg/kg bw per day (Anderson et al., 1997).

In a 13-week inhalation toxicity study, no systemic adverse effects were seen in chromium(III) oxide–exposed rats. However, in the lungs, the retention of chromium(III) oxide caused mild inflammatory changes, especially in mid- and high-dose animals (10 and 30 mg Cr^{3+}/m^3), but also at the lowest exposure level (3 mg Cr^{3+}/m^3; Derelanko et al., 1999). These small inflammatory changes may reflect a nonspecific lung response to accumulated insoluble particles rather than intrinsic toxicity of chromium(III), which is slowly liberated. The minimal severity of findings at the lowest exposure level suggests that the LOAEC of 3 mg Cr^{3+}/m^3 is near a NOAEC for chromium(III) oxide in rats.

In a similar 13-week inhalation toxicity study with rats, dusts of basic chromium sulfate induced more severe and more widespread inflammatory effects in the respiratory tract and lungs than did chromium(III) oxide (Derelanko et al., 1999). Signs of systemic toxicity were also seen: body weights of mid- and high-dose (10 and 30 mg Cr^{3+}/m^3) males and high-dose females were decreased. Histopathological findings were unremarkable in organs other than the respiratory system. The lowest exposure level of 3 mg Cr^{3+}/m^3 (17 mg basic chromium sulfate/m^3) was a NOAEC for systemic effects. However, since inflammatory changes in the lungs and the respiratory tract were seen even at the lowest level, it was a LOAEC for local effects.

Although chromium(III) may interact with DNA, the data on in vitro and in vivo genotoxicity studies are conflicting and give no clear evidence on the mutagenicity of trivalent chromium.

Chromium(III) oxide did not cause local bronchial tumours (Levy & Venitt, 1986) in a well conducted 2-year rat study using the intrabronchial pellet technique or any increased occurrence of any tumours when administered orally in feed (Ivankovic & Preussman, 1975).

Chromium sulfate did not induce tumours in a 30-week strain A mouse lung tumour system, which involved administration of 24 intraperitoneal injections (Stoner et al., 1976). In a 2-year study with rats, intrabronchial administration of basic chromium sulfate

(chrome tan) or chromium chloride hexahydrate from a cholesterol pellet in a stainless steel wire mesh did not cause any local tumours or an increased frequency of squamous metaplasia (Levy & Venitt, 1986).

Although conventional inhalation carcinogenicity studies are lacking, intrabronchial studies on chromium(III) oxide, basic chromium sulfate, and chromium chloride hexahydrate are relevant for the evaluation of carcinogenicity. These studies did not provide any evidence of a local carcinogenic effect on the bronchial epithelium, whereas hexavalent chromium compounds caused local squamous metaplasia with or without local tumours.

For some occupations involving trivalent chromium exposure, increased risks for some cancers have been suggested, but the epidemiological data do not permit discrimination between effects due to trivalent chromium and those due to hexavalent chromium or other carcinogenic agents in simultaneous exposures. A study on chromate production workers found that trivalent chromium showed no association with an increased risk of lung cancer when adjusted for hexavalent chromium exposure and smoking (Gibb et al., 2000). Studies of other occupations exposed to hexavalent and trivalent chromium found increased risks of lung cancer, but the studies did not discriminate between hexavalent and trivalent exposure. Chromium and trivalent chromium compounds have been evaluated by IARC (1990), with the conclusion that there is *inadequate evidence* in humans and animals for the carcinogenicity of metallic chromium and chromium(III) compounds (Group 3).

In a 13-week inhalation toxicity study with rats, no compound-related effects on sperm parameters or testicular and ovarian weights were seen after inhalation exposure to chromium(III) (Derelanko et al., 1999). Also, a limited 90-day oral feeding study at two very high dose levels of chromium(III) oxide did not show any adverse effects on the reproductive performance of rats (Ivankovic & Preussman, 1975).

No compound-related effects on sperm parameters and testicular or ovarian weights were seen after a 13-week inhalation exposure of rats to basic chromium sulfate for 6 h/day at concentrations up to 30 mg Cr^{3+}/m^3 (Derelanko et al., 1999). Other studies on fertility effects of trivalent chromium salts suffer from several deficiencies and cannot be used for the fertility assessment of chromium(III).

No malformations were seen in the offspring of female rats given chromium(III) oxide in a 90-day feeding study at two dose levels (about 560 or 1300 mg Cr^{3+}/kg bw per day) (Ivankovic & Preussman, 1975). The study was limited to only a small number of animals and provided no quantitative data.

No appropriate developmental toxicity studies were available for soluble trivalent chromium salts.

11.1.2 Criteria for setting tolerable intakes/ concentrations

Among inorganic trivalent chromium compounds, insoluble species, typically chromium(III) oxide, must be distinguished from water-soluble salts. The key end-point considered to be relevant for human exposure to chromium(III) oxide is sustained local irritation and inflammation associated with accumulation of respirable particles in the lungs to the extent that the clearance mechanisms are overloaded. The key end-points relevant for human exposure to basic chromium sulfate, presumed to represent soluble chromium(III) salts as a group, are local respiratory toxicity and sensitization of the skin.

Data on the speciation of chromium in ambient air would be required for an accurate evaluation of respiratory effects in the general population by airborne trivalent chromium compounds. In reality, it is expected that the speciation is variable, depending on the sources of chromium emissions. Transport from soil to air, weathering of rocks, and many industrial point sources are expected to release mainly chromium(III) oxide to the environment, but combustion processes may also oxidize a proportion of the element to the hexavalent state. It is less likely that the general population is exposed via air to aerosols of soluble chromium(III) salts. However, in the following evaluation, both types of trivalent chromium species are considered.

Trivalent chromium is an essential element at very low dietary doses (some tens of micrograms per day), and human experience from the widespread use of mainly organic chromium(III) complexes (chromium picolinate, chromium nicotinate) as a food supplement at 10-fold or even higher dose levels has not brought to light any consistent toxic effects. Animal studies also show that orally administered trivalent chromium has low toxicity.

11.1.2.1 Chromium(III) oxide inhalation

In a 13-week rat inhalation toxicity study on chromium(III) oxide with a 13-week recovery period, mild, sustained inflammatory changes in the lungs were produced, with a dose–response at concentrations ranging from 3 to 30 mg Cr^{3+}/m^3 (Derelanko et al., 1999). The study identified a LOAEC of 3 mg Cr^{3+}/m^3. In Riihimäki & Luotamo (2006), a tolerable concentration for occupational exposure was set. Since the observed LOAEC was judged to be close to a NOAEC and because the effect was slight and probably non-specific, no assessment factor was used for extrapolation from the LOAEC to a NOAEC. For extrapolation from

rats to humans, an assessment factor of 2 was used, as interspecies variation is not expected to be high because of the local type of effect and because the rat is a sensitive species for lung overload–related injury. An assessment factor of 3 was used to cover interindividual differences, resulting in an occupational exposure level of 0.5 mg Cr^{3+}/m^3.

In Riihimäki & Luotamo (2006), no tolerable concentration for continuous exposure was set. However, the LOAEC of 3 mg Cr^{3+}/m^3 is equivalent to 0.54 mg Cr^{3+}/m^3 for continuous exposure (3 mg × 6/24 h/day × 5/7 days/week). Following the same principles as in the setting of the tolerable concentration for occupational exposure, no assessment factor is used for extrapolation from the LOAEC to a NOAEC, and an assessment factor of 2 is used to cover interspecies variation. However, for interindividual differences in the general population, an assessment factor of 10 is used. Application of the overall assessment factor of 20 to the LOAEC of 0.54 mg Cr^{3+}/m^3 generates a tolerable concentration of 27 µg Cr^{3+}/m^3.

11.1.2.2 Basic chromium sulfate inhalation

In a 13-week rat inhalation study on basic chromium sulfate with a 13-week recovery period, dose-dependent chronic inflammation of the alveoli and chronic interstitial or granulomatous inflammation of the lungs and respiratory tract were produced at all three exposure concentrations: 3, 10, and 30 mg Cr^{3+}/m^3. These inflammatory changes found in the airways largely reverted during the 13-week recovery period. For local respiratory effects, the study identified a LOAEC of 3 mg Cr^{3+}/m^3. In Riihimäki & Luotamo (2006), a tolerable concentration for occupational exposure was set. For extrapolation from the LOAEC to a NOAEC, an assessment factor of 3 was used. An assessment factor of 3 was also used for interspecies extrapolation, because interspecies variation was not expected to be large owing to the local type of effect. To cover interindividual variation in occupational exposure, an assessment factor of 2 was used. This results in an occupational exposure level of 0.2 mg Cr^{3+}/m^3.

In Riihimäki & Luotamo (2006), no tolerable concentration for continuous exposure was set. However, the LOAEC of 3 mg Cr^{3+}/m^3 is equivalent to 0.54 mg Cr^{3+}/m^3 for continuous exposure (3 × 6/24 × 5/7). This concentration was a NOAEC for impaired weight gain as a systemic effect, which was presumably secondary to respiratory toxicity. Local respiratory system toxicity is the critical effect for basic chromium sulfate. For extrapolation from the LOAEC to a NOAEC, an assessment factor of 3 is used. An assessment factor of 3 is also used for interspecies extrapolation, because interspecies variation is not expected to be large owing to the local type of effect. An additional assessment factor of 10 is used for interindividual differences. Application of the overall assessment factor of 90 to the LOAEC of 0.54 mg Cr^{3+}/m^3 generates a tolerable concentration of 6 µg Cr^{3+}/m^3 for continuous environmental exposure.

Concerning skin sensitization, it is rather unlikely that soluble trivalent chromium salts induce skin sensitization in a person wearing shoes, gloves, or other articles made of chrome-tanned leather, whereas it is more likely that mobile trivalent chromium leached from the leather article can elicit chromium allergy in a previously sensitized person. Recently, the MET level for trivalent chromium has been determined in chromium(VI)-sensitive patients (Hansen et al., 2003). According to the study by Hansen et al. (2003), 10% of patients reacted to the skin application dose of 0.18 µg chromium(III)/cm^2 per 48 h as chromium chloride.

11.1.3 Sample risk characterization

The concentrations of total atmospheric chromium in the USA and Europe are very low in rural areas (<10 ng/m^3), are about 10–30 ng/m^3 in urban areas, and may reach 0.1–1 µg/m^3 around polluting point sources. Thus, the concentrations in ambient air are generally several orders of magnitude lower than the tolerable concentrations; even in the vicinity of point sources, they fall below the tolerable concentrations.

There are no reliable data for the setting of tolerable daily intake for oral exposure; therefore, no sample risk characterization for oral exposure can be done.

11.1.4 Uncertainties in the hazard characterization

Some uncertainty exists regarding the ability of trivalent chromium to induce contact allergy. Elicitation of skin allergy (induction of allergic reaction in a person previously sensitized to chromium(VI)) by trivalent chromium has been demonstrated. Developmental toxicity of trivalent chromium is not adequately studied. No reliable data exist for the setting of tolerable daily oral intake.

11.2 Evaluation of environmental effects

Chromium(III) is required by only some microorganisms for specific metabolic processes, such as glucose metabolism and enzyme stimulation. Chromium(III), in trace amounts, has been reported to be an essential component of animal nutrition and is most notably associated with glucose and fat metabolism. However, although chromium has been shown to be essential for glucose metabolism in rats under highly controlled experimental conditions in which body stores of chromium were depleted, studies on other animals are more equivocal.

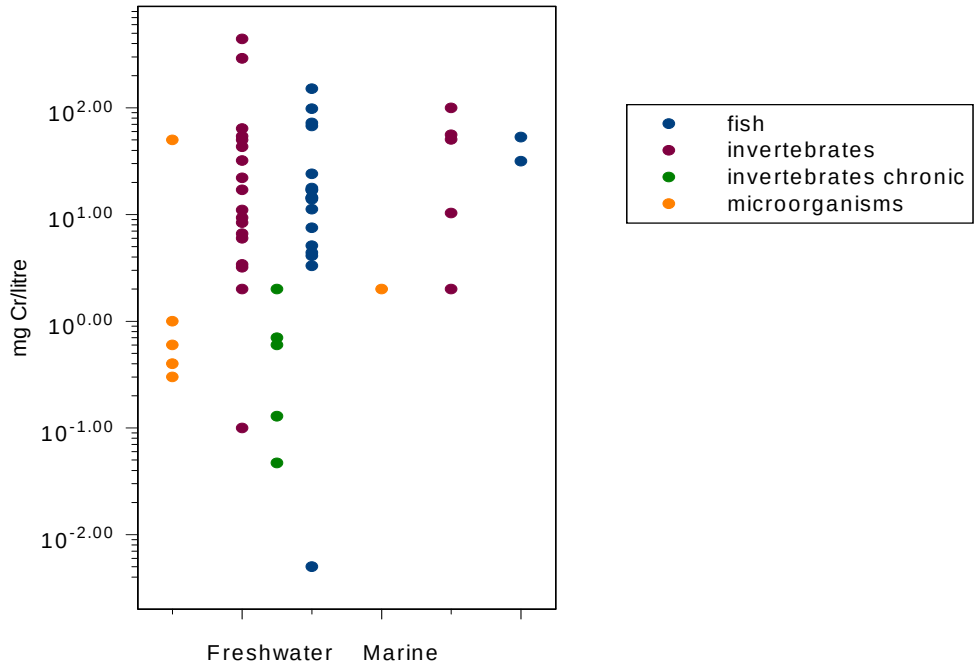


Figure 1: Toxicity of trivalent chromium to aquatic organisms.

The available toxicity data for chromium(III) have been derived mainly using the water-soluble forms (chromium(III) chloride, chromium(III) nitrate, and chromium potassium sulfate). In the environment, chromium(III) is likely to be present in much less soluble forms and hence less bioavailable to aquatic organisms.

The toxicity data for aquatic organisms are summarized in Figure 1. Ninety-six-hour EC_{50}s for one freshwater alga, based on growth, ranged from 0.3 to 0.4 mg chromium(III)/l. A 96-h EC_{50}, based on growth, was reported for a marine diatom at 2 mg chromium(III)/l. LC_{50}s in freshwater invertebrates ranged from 0.1 mg/l (*Daphnia pulex*) to 442 mg/l (*Asellus aquaticus*), with a life cycle NOEC of 0.047 mg/l for *Daphnia magna*. LC_{50}s ranging from 10 to 100 mg/l have been reported for marine invertebrates. Ninety-six-hour LC_{50}s for freshwater fish ranged from 3.3 mg/l for the guppy (*Poecilia reticulata*) to 151 mg/l for the bighead (*Aristichthys nobilis*), whereas LC_{50}s of 31.5 and 53 mg/l were reported for marine fish. A 72-day NOEC (survival) of 0.05 mg/l was reported for rainbow trout (*Oncorhynchus mykiss*).

A guidance value for trivalent chromium toxicity in the freshwater environment can be derived using a probabilistic approach (ANZECC/ARMCANZ, 2000), since the data set is sufficiently large to warrant it. Appendix 5 details the methodology used as an example. For the freshwater environment, 28 toxicity values were chosen to derive a moderate-reliability guidance value. The criteria for choosing the toxicity values and the values are presented in Appendix 5. Acute and chronic toxicity values have been converted to estimates of NOEC using the factors described in Appendix 5 (see Table A5-1, Appendix 5). A moderate-reliability guidance value of 0.01 mg chromium(III)/l (10 µg chromium(III)/l) was derived for the protection of 99% of freshwater species with 50% confidence, based on tests performed at a hardness of <100 mg calcium carbonate/l (see Figure A5-1, Appendix 5). In comparison, if a deterministic approach is carried out using the toxicity data for freshwater organisms, this would be based on long-term NOEC values of 0.05 mg/l for fish, 0.047 mg/l for invertebrates, and a 96-h EC_{50} (growth) of 0.4 mg/l for algae. The fish and invertebrate values relate to hardness levels of 26 and 52 mg/l, respectively. Applying an assessment factor of 10 to the lowest available NOEC gives a tentative predicted no-effect concentration (PNEC) for chromium(III) of 5 µg/l for soft water, about half that obtained using the probabilistic method.

There were insufficient toxicity data on marine organisms to allow a guidance value to be calculated using a probabilistic method. A very limited data set was available based on a diatom, aquatic invertebrates, and fish. Therefore, a factor of 1000 was applied to the lowest reliable toxicity value (2 mg/l) to give a low-reliability guidance value of 0.002 mg chromium(III)/l (2 µg chromium(III)/l).

The moderate-reliability guidance value of 10 µg chromium(III)/l for the freshwater environment suggests a low risk for surface waters in general. However, there is a potential risk to organisms when the guidance value is compared with the highest chromium(III) level of around 100 µg/l for surface waters in industrial areas, especially for softwater regions. The higher levels of trivalent chromium in effluent, especially from tanneries, suggest that there is a risk to freshwater organisms in the vicinity of such effluent releases. Comparing the low-reliability guidance value of 2 µg chromium(III)/l for the marine environment with trivalent chromium concentrations in seawater suggests a low risk of toxicity to marine organisms.

There are more limited data for terrestrial organisms. The NOEC for chromium(III) to plants is of the order of 100 mg chromium/kg soil, with a NOEC of 32 mg chromium/kg dry artificial soil being reported for earthworms and a NOEC/LOEC of ~100–330 mg chromium/kg soil also being reported. Applying an assessment factor of 10 to the lowest of these NOECs gives a PNEC for chromium(III) of approximately 3.2 mg chromium/kg dry soil, which is equivalent to a PNEC of around 2.8 mg/kg on a wet weight of soil basis. Total chromium levels in soil vary greatly, with levels ranging from <1 to >6000 mg/kg, depending on the underlying geology and localized industrial contamination. However, both the PNEC for earthworms and most of the monitoring data for soils are reported as total chromium and do not give any indication of the bioavailability of trivalent chromium. Therefore, in the absence of more data on the bioavailability of chromium in soils, it is difficult to assess the risk of chromium(III) to soil organisms.

12. PREVIOUS EVALUATIONS BY INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS (IOMC) BODIES

The International Agency for Research on Cancer (IARC) evaluated chromium and chromium compounds in 1990 and concluded that metallic chromium and chromium(III) compounds are not classifiable as to their carcinogenicity to humans (Group 3).

A World Health Organization (WHO) study group (WHO, 1996) evaluated the normative requirements for chromium. Their conclusion was that the available data were too limited to determine the basal and normative requirements for chromium. Their best guess at the time was that the minimum population mean intake likely to meet normative needs might be approximately 33 µg chromium/day.

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APPENDIX 1 — ACRONYMS AND ABBREVIATIONS

AAS	atomic absorption spectrometry
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CAS	Chemical Abstracts Service
CICAD	Concise International Chemical Assessment Document
DNA	deoxyribonucleic acid
dw	dry weight
EC_{50}	median effective concentration
EDTA	ethylenediaminetetraacetic acid
FCA	Freund's complete adjuvant
$FEV_{1.0}$	forced expiratory volume in 1 s
FIOH	Finnish Institute of Occupational Health
FVC	forced vital capacity
GAAS	graphite furnace atomic absorption spectrometry
GLP	Good Laboratory Practice
HC_5	hazardous concentration for 5% of species
IARC	International Agency for Research on Cancer
IC_{50}	median inhibitory concentration
ICDA	International Chromium Development Association
ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
Ig	immunoglobulin
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standardization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LMWCr	low-molecular-weight chromium-binding substance
LOAEC	lowest-observed-adverse-effect concentration
LOEC	lowest-observed-effect concentration
MET	minimum elicitation threshold
MMAD	mass median aerodynamic diameter
NAA	neutron activation analysis
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
OECD	Organisation for Economic Co-operation and Development
OJ	orange juice
PNEC	predicted no-effect concentration

RNA	ribonucleic acid
SCE	sister chromatid exchange
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
ww	wet weight

APPENDIX 2 — SOURCE DOCUMENTS

Riihimäki V, Luotamo M, eds (2006) *Health risk assessment report for metallic chromium and trivalent chromium*. Paris, International Chromium Development Association (http://www.icdachromium.com/).

The *Health Risk Assessment Report for Metallic Chromium and Trivalent Chromium* (Riihimäki & Luotamo, 2006) was prepared by the Finnish Institute of Occupational Health (FIOH) for the Commission of the International Chromium Development Association (ICDA) and the International Stainless Steel Forum. The report was published by ICDA in 2006. Copies can be obtained from the ICDA Secretariat (see http://www.icdachromium.com/).

The following scientists from FIOH contributed to the development of the *Health Risk Assessment Report for Metallic Chromium and Trivalent Chromium*: Dr Vesa Riihimäki (principal investigator), Dr Kerstin Engström, Dr Riitta Jolanki, Dr Mirja Kiilunen, Dr Kimmo Louekari, Dr Marita Luotamo, Dr Hannu Norppa, Dr Markku Nurminen, Ms Hanna Paananen, Dr Tiina Santonen, and Dr Antti Zitting. The document went through a peer review by the project steering group, which consisted of representatives of academia, FIOH scientists, and the chromium industry.

ATSDR (2000) *Toxicological profile for chromium*. Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

The *Toxicological Profile for Chromium* was prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) through a contract with the Syracuse Research Corporation. The profile was published in final form in September 2000. Copies of the profile can be obtained from:

Division of Toxicology
Agency for Toxic Substances and Disease Registry
Public Health Service
United States Department of Health and Human Services
1600 Clifton Road NE, Mailstop E-32
Atlanta, Georgia 30333
USA

Ms Sharon Wilbur, ATSDR, Division of Toxicology and Environmental Medicine, and Drs Lisa Ingerman, Mario Citra, Mark Osier, and David Wohlers, Syracuse Research Corporation, contributed to the development of the toxicological profile as chemical manager and authors. 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 update profile for chromium. The panel consisted of the following members: Dr William Berndt, University of Nebraska Medical Center; Dr Max Costa, The George Washington University Medical School and School of Public Health; and Dr Elizabeth Snow, New York University Medical Center. 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.

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

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

APPENDIX 3 — CICAD PEER REVIEW

The draft CICAD on inorganic chromium(III) compounds was sent for review 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, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

G. Darrie, International Chromium Development Association, Paris, France

H. Gibb, Sciences International Inc., Alexandria, VA, USA

R. Hertel, Federal Institute for Risk Assessment (BfR), Berlin, Germany

J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

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, United Kingdom

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

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

APPENDIX 4 — CICAD FINAL REVIEW BOARD

Helsinki, Finland
26–29 March 2007

Members

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

Professor H. Bouwman, School of Environmental Sciences and Development, North-West University, Potchefstroom, South Africa

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Devotta, National Environmental Engineering Research Institute, Nagpur, India

Dr S. Dobson, Centre for Ecology and Hydrology, Monks Wood, United Kingdom

Dr L. Fructengarten, Centro de Controle de Intoxicacoes de Sao Paulo, Sao Paulo, Brazil

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R. Hertel, Federal Institute for Risk Assessment (BfR), Berlin, Germany

Mr P. Howe, Centre for Ecology and Hydrology, Monks Wood, United Kingdom

Dr S. Keith, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Ms M.E. Meek, Health Canada, Ottawa, Ontario, Canada

Dr T. Santonen, Finnish Institute of Occupational Health, Helsinki, Finland

Dr B. Sonawane, National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, USA

Dr J. Stauber, CSIRO Centre for Environmental Contaminants Research, Sydney, Australia

Dr M. Sweeney, Division of Surveillance, Hazard Evaluations & Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr P. Watts, BIBRA Information Services Ltd, Sutton, United Kingdom

Ms D. Willcocks, Australian Department of Health and Ageing, Sydney, Australia

Dr K. Ziegler-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission), Munich, Germany

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

APPENDIX 5 — OUTLINE OF THE SPECIES SENSITIVITY DISTRIBUTION METHOD (DUTCH STATISTICAL EXTRAPOLATION METHOD) USED TO DERIVE GUIDANCE VALUES FOR TRIVALENT CHROMIUM FOR THE PROTECTION OF AQUATIC SPECIES

Introduction

The traditional approach to using single-species toxicity data to protect field ecosystems has been to apply standardized assessment factors, safety factors, or application factors to the lowest toxicity figure for a particular chemical. The magnitude of these safety factors depends on whether acute or chronic toxicity figures are available and the degree of confidence that one has in whether the figures reflect the field situation. Most of the factors are multiples of 10, and larger factors are applied where there is less certainty in the data. For example, a factor of 1000 is generally used for acute data.

Concerns have often been raised as to the arbitrary nature of assessment factors (Chapman et al., 1998) and the fact that they do not conform to risk assessment principles. OECD (1992) recommended that assessment factors be used only when there are inadequate data to allow statistical extrapolation methods to be used.

The following sections briefly outline the statistical extrapolation method used to derive the trivalent chromium guidance values for the protection of freshwater aquatic organisms for this CICAD. Much of the text is taken directly from the *Australian and New Zealand Guidelines for Fresh and Marine Water Quality* (ANZECC/ARMCANZ, 2000).

Use of statistical extrapolation methods

New methods using statistical risk-based approaches have been developed over the last decade for deriving guideline (trigger) values. These are based on calculations of a statistical distribution of laboratory ecotoxicity data and attempt to offer a predetermined level of protection, usually 95%. The approach of Aldenberg & Slob (1993) has been adopted in the Netherlands, Australia, and New Zealand for guideline derivation and is recommended for use by the OECD. It was chosen because of its theoretical basis, its ease of use, and the fact that it has been extensively evaluated. Warne (1998) compared in detail the risk-based and assessment factor approaches used in various countries.

The Aldenberg & Slob (1993) method uses a statistical approach to protect 95% of species with a predetermined level of confidence, provided there is an adequate data set. This approach uses available data from all tested species (not just the most sensitive species) and considers these data to be a subsample of the range of concentrations at which effects would occur in all species in the environment. The method may be applied if toxicity data, usually chronic NOEC values, are available for at least five different species from at least four taxonomic groups. Data are entered into a computer program and generally fitted to a log-logistic distribution. A hazardous concentration for *p* per cent of the species (HC_p) is derived. HC_p is a value such that the probability of selecting a species from the community with a NOEC lower than HC_p is equal to *p* (e.g. 5%, HC_5). HC_5 is the estimated concentration that should protect 95% of species. A level of uncertainty is associated with this derived value, and so values with a given confidence level (e.g. 50% or 95%) are computed in the program by attaching a distribution to the error in the tail. The ANZECC/ARMCANZ (2000) guidelines use the median of 50% confidence.

HC_5 is estimated by dividing the geometric mean of the NOEC values for *m* species by an extrapolation factor *T* (OECD, 1995), where:

$$T = \exp^{(s_m \times k)}$$

and where s_m is the sample standard deviation of the natural logarithm of the NOEC values for *m* species; and *k* is the one-sided tolerance limit factor for a logistic or normal distribution (from computer simulations).

The Aldenberg & Slob (1993) extrapolation method is based on several critical assumptions, outlined below. Many of these are common to other statistical distribution methods:

- The ecosystem is sufficiently protected if theoretically 95% of the species in the system are fully protected.
- The distribution of the NOECs is symmetrical (not required in the ANZECC/ARMCANZ [2000] modification).
- The available data are derived from independent random trials of the total distribution of sensitivities in the ecosystem.
- Toxicity data are distributed log-logistically, i.e. a logistic distribution is the most appropriate to use.
- There are no interactions between species in the ecosystem.
- NOEC data are the most appropriate data to use to set ambient environmental guidelines.
- NOEC data for five species are a sufficient data set.

Modification of the Aldenberg & Slob (1993) approach

The Aldenberg & Slob (1993) approach assumes the data are best fitted to a log-logistic distribution. For some data sets, however, a better fit is obtained with other models. By using a program developed by CSIRO Biometrics, the data are compared with a range of statistical distributions called the Burr family of distributions, of which the log-logistic distribution is one case. The program determines the distribution that best fits the available toxicity data and calculates the HC_5 with 50% confidence (ANZECC/ARMCANZ, 2000); this method has been used to calculate the HC_5 for trivalent chromium.

Application to the data set for trivalent chromium

For the freshwater risk assessment, acute LC_{50} values were converted to chronic NOEC values using an acute to chronic ratio of 10 following ANZECC/ARMCANZ (2000) guidelines. Chronic EC_{50}s and LC_{50}s were converted to chronic NOECs by applying a factor of 5, according to ANZECC/ARMCANZ (2000) guidelines. It would have been better to use experimentally derived acute to chronic conversion factors; however, these were not available for trivalent chromium.

Freshwater guidance value

Twenty-nine freshwater data were used from Table 3 (see section 10.2), and from these data were calculated chronic NOECs (see Table A5-1). Non-standard test end-points or end-points of uncertain significance were not included.

Using the calculated chronic NOECs, the $HC_5(50)$, i.e. the hazardous concentration to protect 95% of species with 50% confidence—a "safe" value to ensure protection against chronic

Table A5-1: Toxicity end-points and calculated chronic NOECs used in the derivation of a freshwater guidance value for trivalent chromium.[a]

Organism	End-point	Chromium concentration (mg Cr/l)	Calculated chronic NOEC (mg Cr/l)
Microalgae			
Green alga (*Selenastrum capricornutum*)	96-h EC_{50}	0.4	0.08
Protozoa			
Ciliated protozoan (*Tetrahymena pyriformis*)	9-h IC_{50}	50	5
Invertebrates			
Snail (*Amnicola* sp.)	96-h LC_{50}	8.4	0.8
Annelid worm (*Nais* sp.)	96-h LC_{50}	9.3	0.9
Water flea (*Daphnia magna*)	Life cycle NOEC	0.047	0.047
Water flea (*Daphnia pulex*)	96-h LC_{50}	0.6[b]	0.06
Water hoglouse (*Asellus aquaticus*)	96-h LC_{50}	442	44.2
Amphipod (*Gammarus* sp.)	96-h LC_{50}	3.2	0.3
Amphipod (*Crangonyx pseudogracilis*)	96-h LC_{50}	291	29.1
Crayfish (*Austro-potamobius pallipes*)	96-h LC_{50}	3.4	0.3
Crayfish (*Orconectes limosus*)	96-h LC_{50}	6.6	0.7
Mayfly (*Ephemerella subvaria*)	96-h LC_{50}	2	0.2
Caddis fly (*Hydropsyche betteni*)	96-h LC_{50}	64	6.4
Caddisfly (unidentified)	96-h LC_{50}	50	5
Stonefly (*Acroneuria lycorias*)	7-day LC_{50}	32	6.4
Damsel fly (unidentified)	96-h LC_{50}	43.1	4.3
Midge (*Chironomus* sp.)	96-h LC_{50}	11	1.1

Table A5-1 (continued)

Organism	End-point	Chromium concentration (mg Cr/l)	Calculated chronic NOEC (mg Cr/l)
Fish			
Rainbow trout (*Oncorhynchus mykiss*)	72-day NOEC	0.05	0.05
Goldfish (*Carrasius auratus*)	96-h LC_{50}	20[b]	2
Common carp (*Cyprinus carpio*)	96-h LC_{50}	14.3	1.4
Fathead minnow (*Pimephales promelas*)	96-h LC_{50}	5.1	0.5
Bluegill (*Lepomis macrochirus*)	96-h LC_{50}	7.5	0.75
Pumpkinseed (*Lepomis gibbosus*)	96-h LC_{50}	17	1.7
Banded killifish (*Fundulus diaphanous*)	96-h LC_{50}	16.9	1.7
Striped bass (*Roccus saxatilis*)	96-h LC_{50}	17.7	1.8
White perch (*Roccus americanus*)	96-h LC_{50}	14.4	1.4
Bighead (*Aristichthys nobilis*)	96-h LC_{50}	151	15.1
Guppy (*Poecilia reticulata*)	96-h LC_{50}	3.3	0.3
American eel (*Anguilla rostrata*)	96-h LC_{50}	13.9	1.4

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

[a] Tests conducted at a hardness of <100 mg calcium carbonate/l.

[b] Geometric mean of LC_{50} values for this species for the same time period.

toxicity for most freshwater species—was 0.06 mg chromium(III)/l. However, the moderate-reliability guidance value of 0.06 mg/l is not protective of chronic toxicity to *D. magna* (NOEC: 0.047 mg/l) and rainbow trout (NOEC: 0.05 mg/l), and so a protection level of 99% should be applied. Therefore, a moderate-reliability guidance value for the protection of 99% of freshwater species with 50% confidence was derived at 0.01 mg chromium(III)/l (Figure A5-1).

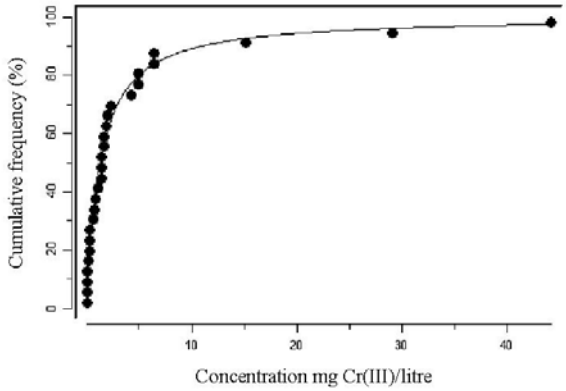

Fig. A5-1: Probability curve for trivalent chromium in the freshwater environment using actual and derived data from Table A5-1.

INTERNATIONAL CHEMICAL SAFETY CARDS

RÉSUMÉ D'ORIENTATION

Le présent CICAD[1] (Concise International Chemical Assessment Document/Document concis d'évaluation chimique internationale) relatif aux composés minéraux du chrome (III) a été préparé conjointement par l'Institut finlandais de la santé publique dont le siège se trouve à Helsinki (Finlande) pour les sections portant sur la santé humaine, et par le Centre d'écologie et d'hydrologie de Monks Wood (Royaume Uni) pour les sections traitant de l'environnement. Il s'inspire d'un rapport intitulé *Health Risk Assessment Report for Metallic Chromium and Trivalent Chromium* (Rapport d'évaluation des risques pour la santé imputables au chrome métallique et aux dérivés du chrome trivalent) rédigé par l'Institut finlandais de la santé publique (Riihimäki & Luotamo, 2006) et d'un document de l'Agency for Toxic Substances and Disease Registry intitulé *Profil toxicologique du chrome* (ATSDR, 2000). Les dernières recherches bibliographiques remontent à décembre 2004 pour la partie du présent CICAD relative aux effets sanitaires et à décembre 2005 pour la partie relative à l'environnement. L'appendice 2 donne des renseignements sur les sources bibliographiques. Des informations sur l'examen par des pairs du présent CICAD figurent à l'appendice 3. Ce CICAD relatif aux dérivés minéraux du chrome a été approuvé en tant qu'évaluation internationale lors 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. Les fiches internationales sur la sécurité chimique des composés courants du chrome trivalent sont également reproduites dans ce document (IPCS, 2002,b, 2004a,b,c,d, 2006). Ce CICAD ne concerne que les composés minéraux du chrome trivalent, mais chaque fois qu'il a été possible d'en étendre la portée, des données relatives aux dérivés organiques du chrome y ont été également ajoutées. Le CICAD No 78 consacré au chrome hexavalent est en cours de préparation.

C'est à l'état trivalent que le chrome est le plus stable du point de vue thermodynamique. Dans l'environnement, le chrome est presque toujours présent à l'état naturel sous cette forme. Il existe dans le commerce toute une gamme de dérivés du chrome (III), dont les plus importants sont l'oxyde de chrome (III) et le sulfate de chrome basique.

L'exposition de la population générale au chrome trivalent trouve principalement son origine dans le régime alimentaire de tous les jours. Parmi les autres sources d'exposition on peut citer certains suppléments alimentaires contenant du chrome, l'air ambiant, les articles en cuir qui ont subi un tannage au chrome, les produits cosmétiques contenant des pigments à base de chrome, certains articles en inox, les implants prothétiques et les appareils orthodontiques. Les nombreuses activités industrielles liées à la production, à la préparation et à l'utilisation du chrome et de ses dérivés entraînent également une exposition professionnelle à ces substances.

Le chrome accomplit un cycle complet qui part des roches ou du sol, se poursuit chez les végétaux, les animaux et l'Homme pour revenir ensuite dans le sol. Du chrome est libéré dans l'atmosphère, non seulement à partir de sources anthropogéniques mais aussi chaque fois qu'une combustion se produit, par exemple lors de feux de forêt. Dans l'atmosphère, le chrome est principalement présent sous la forme de particules.

Certaines industries déchargent dans les eaux de surface des effluents contenant du chrome, dont une partie se trouve à l'état hexavalent. Quant à savoir dans quelle mesure le chrome demeure sous forme hexavalente jusqu'à ce qu'il parvienne à l'océan, cela dépend de la quantité de matières organiques présentes dans l'eau. Si ces matières sont présentes en grande quantité, il est possible qu'elles réduisent le chrome (VI) en chrome (III) qui sera ensuite adsorbé à la surface des particules. S'il n'est pas adsorbé, le chrome (III) va former de gros complexes polynucléaires qui ne sont plus solubles. En anaérobiose, la réduction du chrome (VI) en chrome (III) est un processus rapide et des conditions réductrices existent généralement dans les eaux souterraines profondes. La majeure partie du chrome déchargé dans l'eau va finir par se déposer sur les sédiments. A l'état dissous, le chrome (III) est principalement présent sous les formes suivantes : Cr^{3+}, $CrOH^{2+}$, $Cr(OH)_3^0$ et $Cr(OH)_4^-$.

Dans le sol, le chrome est essentiellement présent sous forme d'oxyde insoluble et sa mobilité est réduite. On estime que le chrome (III) est rapidement et fortement adsorbé par le sol, notamment par les oxydes de fer et de manganèse, les minéraux argileux et le sable. La mobilité des espèces solubles présentes dans le sol va dépendre des propriétés sorbantes du sol. Les végétaux et les animaux absorbent la forme hexavalente de préférence à la forme trivalente mais une fois résorbé, le chrome (VI) est réduit à l'état de chrome (III), qui est plus stable.

Dans le cas du chrome (VI), le facteur de bioconcentration pour les poissons est à peu près égal à 1; toutefois, une fois présent dans leur organisme, le chrome (VI) est apparemment réduit en chrome (III) avec, pour résultat, une accumulation de chrome total quelque 100 fois supérieure à la concentration dans l'eau.

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

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 Etats-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 (III) allant jusqu'à 2 µg/l ont été relevées dans des eaux superficielles. La présence de teneurs élevées en chrome peut être attribuée à une pollution par des sources anthropogéniques, les valeurs les plus élevées – pouvant atteindre 40 mg de chrome (III) par litre – étant observées à proximité des points de décharge des tanneries.

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). Une concentration moyenne en chrome (III) de 2 à 3 µg/l a été relevée dans les eaux littorales. 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. Au Canada et aux Etats-Unis, la fourchette de concentration du chrome total dans les différents sols et autres matériaux de surface est 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. On a fait état de valeurs plus élevées sur des sites contaminés.

Le chrome (III) est considéré comme un oligoélément essentiel pour les mammifères, car il intervient dans le métabolisme des lipides et des glucides. Une proportion limitée de chrome (III) est absorbée à partir d'une ration alimentaire normale (<0,5 à 2 %) – davantage si la teneur en chrome de la ration est anormalement faible et moins si l'apport de chrome est plus important. Les aérosols hydrosolubles de chrome (III) que leur granulométrie rend respirables sont plus efficacement absorbés par l'appareil respiratoire que par les voies digestives : ils peuvent être rapidement résorbés dans une proportion d'environ 5 % en l'espace de quelques heures, mais il leur faut ensuite des semaines ou des mois pour passer dans le courant sanguin. Dans le cas de l'oxyde de chrome (III) qui est insoluble, la résorption des particules déposées et retenues est un très long processus. Les sels hydrosolubles de chrome (III) peuvent pénétrer dans le revêtement cutané mais on ne les retrouve pas dans la circulation générale.

Dans le plasma sanguin, le chrome (III) est lié à 95 % à des protéines de masse moléculaire élevée (par ex. la transferrine), mais on le trouve également associé à la chromoduline, un oligopeptide appelé également substance de liaison au chrome de faible masse moléculaire (LMWCr). Le chrome se répartit principalement dans le foie, le rein, la rate et les os. Après administration, une partie du chrome peut atteindre le tissu interstitiel testiculaire et il peut également s'accumuler dans le placenta, mais il ne peut traverser la barrière placentaire qu'en petite quantité. Une fois absorbé, le chrome (III) est principalement excrété par la voie urinaire et dans une moindre mesure par la voie fécale.

Chez le rat, la toxicité aiguë de l'oxyde de chrome (III) est très faible par voie orale, la dose létale médiane (DL_{50}) étant supérieure à 5 g par kg de poids corporel (p.c.). En ce qui concerne le sulfate de chrome basique, on indique une DL_{50} par voie orale de 3530 mg/kg de poids corporel pour le rat. Pour le nitrate de chrome, la valeurs vont de 1540 à 3250 mg/kg de p.c.

D'après les résultats de l'expérimentation animale, l'oxyde chrome (III) et le sulfate de chrome basique ne sont irritants ni pour la peau ni pour les yeux.

L'oxyde chrome (III), insoluble, ne provoque pas de sensibilisation cutanée. Le chrome trivalent pourrait se comporter comme un déterminant hapténique extrême de la sensibilisation cutanée par le chrome, mais la faible pénétration tégumentaire des dérivés du chrome (III) limite leur pouvoir sensibilisateur. Des tests non classiques comportant des injections intradermiques ou sous-cutanées de sels hydrosolubles de chrome trivalent comme le chlorure de chrome ou le sulfate de chrome hydraté ont mis en évidence les effets sensibilisateurs de ces sels. Deux études sur le chlorure de chrome ont également permis d'observer une réaction positive lors d'une épreuve de sensibilisation épicutanée. Les données cliniques relatives à la sensibilisation cutanée mettent principalement en cause le port d'articles en cuir. Il est malaisé de définir le rôle exact du chrome trivalent dans la sensibilisation cutanée due au port d'articles de maroquinerie du fait que du chrome hexavalent peut être présent à faible concentration dans le cuir tanné et que les cas de dermatite du pied dont on a connaissance peuvent correspondre en fait à des réactions d'élicitation chez des sujets déjà sensibilisés au chrome. Chez les travailleurs qui manipulent des sels de chrome trivalent,

il semble que les cas de sensibilisation cutanée soient rares. Actuellement, rien ne prouve de façon indubitable que l'exposition professionnelle à des composés du chrome (III) puisse provoquer de l'asthme.

L'inhalation de chrome (III) sous forme d'oxyde à des concentrations moyennes de 3, 10 ou 30 mg/m^3 a provoqué de très légères modifications de nature inflammatoire au niveau des poumons chez des rats exposés à toutes ces concentrations dans l'air, mais à des concentrations identiques de Cr^{3+} dans l'air, des poussières de sulfate de chrome basique ont provoqué des effets inflammatoires et fait apparaître des signes de toxicité générale plus sévères et plus disséminés chez les animaux des groupes soumis aux doses intermédiaire et élevée. Les légères modifications de nature inflammatoire observées après inhalation d'oxyde de chrome (III) pourraient être imputables à une réaction non spécifique du tissu pulmonaire à l'accumulation de particules insolubles (surcharge) plutôt qu'à la toxicité intrinsèque du chrome (III). La concentration sans effet nocif observé (NOAEC) a été trouvée égale à 3 mg de Cr^{3+}/m^3 en ce qui concerne les effets généraux du sulfate de chrome basique; toutefois, comme des modifications de nature inflammatoire ont été observées au niveau des voies respiratoires et du poumon en particulier, même à la concentration la plus faible, on a considéré que cette valeur représentait la concentration la plus faible provoquant un effet nocif observable localement (LOAEC). La gravité minime des anomalies observées après exposition à la concentration la plus faible incite à penser que, chez le rat, cette LOAEC de 3 mg de Cr^{3+}/m^3 est proche de la NOAEC de l'oxyde de chrome (III).

L'administration à des rats de rations alimentaires contenant de l'oxyde de chrome (III), même à forte dose, n'a provoqué aucune effet nocif. Cette absence d'effets peut s'expliquer par la faible biodisponibilité de cette substance par voie orale. Lors d'une étude de 20 semaines comportant l'administration de chlorure de chrome hydrosoluble par voie orale à des rats Sprague-Dawley, on n'a pas observé d'effet nocif imputable à ce traitement, même à la dose la plus élevée, qui correspondait à l'ingestion journalière de 7 mg de chrome par kg de poids corporel.

Des interactions sont possibles entre le chrome (III) et l'acide désoxyribonucléique (ADN), mais les résultats des études de génotoxicité in vitro et in vivo sont contradictoires et ne fournissent aucune preuve manifeste d'une mutagénicité du chrome trivalent.

Les études sur des animaux de laboratoire qui seraient susceptibles de permettre une évaluation de la cancérogénicité du chrome (III) ne mettent en évidence aucune augmentation de l'incidence des cancers après exposition à ses composés. On a avancé qu'il existerait un risque accru de certains cancers chez les sujets exerçant des professions qui les exposent à des composés du chrome (III), mais les données épidémiologiques ne permettent pas de faire la distinction entre les effets respectifs du chrome trivalent, du chrome hexavalent ou d'autres substances cancérogènes en cas d'exposition simultanée à ces diverses substances.

A la lumière des données disponibles, il semble que le chrome trivalent n'ait aucun effet sur la fécondité. Si l'on se base sur sa faible biodisponibilité et sur les résultats d'une étude limitée de ses effets toxiques à forte dose, il apparaît que l'oxyde de chrome (III) n'a pas d'effets nocifs sur le développement. Il n'existe pas d'étude convenable relative aux effets nocifs des sels solubles de chrome (III) sur le développement.

En ce qui concerne l'exposition de sujets humains à l'oxyde de chrome (III), on considère que son effet essentiel consiste en une irritation et une inflammation locales durables liées à l'accumulation intrapulmonaire de particules respirables dans une proportion qui provoque la saturation de l'ascenseur mucociliaire. Dans le cas de l'exposition humaine au sulfate de chrome basique, qui est censé représenter l'ensemble de sels solubles de chrome (III), les effets considérés comme essentiels sont une toxicité respiratoire locale et la sensibilisation cutanée. Les concentrations tolérables (27 µg de Cr^{3+}/m^3 pour les composés insolubles du chrome (III) et 6 µg de Cr^{3+}/m^3 pour ses composés solubles) établies sur la base de ces effets compte tenu des facteurs d'évaluation appropriés, sont en général largement supérieures aux concentrations de chrome (III) présentes dans l'air; même à proximité de sources ponctuelles, la concentrations atmosphérique est inférieure aux concentrations tolérables. Pour ce qui est de la sensibilisation cutanée par des sels solubles de chrome trivalent, s'il est assez peu probable que les personnes portant des chaussures, des gants et autres articles en cuir tanné au chrome puissent en souffrir, il est possible, en revanche, que les petites quantités de chrome libérées par des articles en cuir déclenchent une réaction allergique chez des sujets déjà sensibilisés.

Il y a des microorganismes qui ont besoin de chrome (III) pour assurer certains de leurs processus métaboliques et stimuler leurs enzymes. A l'état de traces, le chrome (III) est un oligoélément essentiel pour la nutrition animale et il intervient tout particulièrement dans le métabolisme du glucose et des lipides. A noter toutefois que si le chrome se révèle essentiel pour le métabolisme du glucose chez certains mammifères de laboratoire, les études portant sur d'autres animaux donnent des résultats ambigus.

Les données toxicologiques relatives au chrome (III) sont principalement tirées d'études portant sur des dérivés hydrosolubles (chlorure et nitrate de chrome (III)

et sulfate double de chrome et de potassium). Dans l'environnement, il est probable que le chrome (III) est présent sous des formes beaucoup moins solubles et par conséquent moins biodisponibles pour les organismes aquatiques.

Dans le cas d'une algue d'eau douce, on a trouvé, pour la concentration effective médiane à quatre-vingt seize heures (CE_{50}), des valeurs allant de 0,3 à 0,4 mg de chrome (III) par litre. Pour une diatomée marine, on a déterminé, sur la base de la croissance, une CE_{50} à 96 h de 2 mg de chrome (III) par litre. Chez les invertébrés aquatiques, les valeurs de la concentration létale médiane (CL_{50}) vont de 0,1 mg/l (*Daphnia pulex*) à 442 mg/l (*Asellus aquaticus*), la concentration sans effet observé (NOEC) sur l'ensemble du cycle évolutif étant égale à 0,047 mg/l pour *Daphnia magna*. En ce qui concerne les invertébrés marins, les valeurs de la CL_{50} qui ont été relevées vont de 10 à 100 mg/l. Dans le cas des poissons d'eau douce, les valeurs de la CL_{50} à 96 h qui sont rapportées vont de 3,3 mg/l pour le guppy (*Poecilia reticulata*) à 151 mg/l pour la carpe marbrée (*Aristichthys nobilis*), les valeurs de cette même CL_{50} à 96 h oscillant entre 31,5 et 53 mg/l pour les poissons de mer. Pour la truite arc-en-ciel (*Oncorhynchus mykiss*), on fait état d'une concentration sans effet observé à 72 jours (NOEC) égale à 0,05 mg/l.

Il est possible de calculer une valeur-guide pour la toxicité du chrome trivalent en utilisant une méthode probabiliste, étant donné que la somme de données est suffisamment importante pour justifier cette démarche. C'est ainsi que pour une protection de 99 % des espèces d'eau douce, on a obtenu une valeur-guide modérément fiable égale à 10 µg de chrome trivalent par litre avec un taux de confiance de 50 %. Les données toxicologiques relatives aux organismes marins sont insuffisantes pour que l'on puisse déterminer une valeur-guide selon une méthode probabiliste. On ne dispose que d'un ensemble très limité de données concernant une diatomée, des invertébrés aquatiques et des poissons. On a donc appliqué un facteur de sécurité de 1000 à la donnée toxicologique fiable ayant la valeur la plus basse (2 mg/l), ce qui donne une valeur-guide de faible fiabilité égale à 2 µg de chrome trivalent par litre.

Avec une valeur-guide modérément fiable égale à 10 µg de chrome (III) par litre, on peut estimer que le risque est faible pour les eaux de surface en général. Toutefois, si l'on compare la valeur-guide à la concentration la plus élevée de chrome (III) relevée dans les eaux de surface des zones industrielles (environ 100 µg/l), on voit qu'il existe un risque potentiel pour les êtres vivants présents dans ces zones. Les valeurs élevées de la concentration en chrome trivalent mesurées dans les effluents industriels, notamment ceux qui proviennent de tanneries, indiquent qu'il peut y avoir un risque pour les organismes d'eau douce qui vivent à proximité des points de décharge de ces effluents. Si l'on compare maintenant la valeur-guide de faible fiabilité qui a été fixée, pour le milieu marin, à 2 µg de chrome (III) par litre, aux concentrations de chrome trivalent relevées dans l'eau de mer, on peut penser que le risque reste faible pour les organismes marins.

Chez les végétaux, une intoxication par le chrome se traduit principalement par une chlorose. Le chrome (VI) se révèle plus toxique que le chrome (III) pour les plantes terrestres.

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

RESUMEN DE ORIENTACIÓN

Este Documento abreviado de evaluación internacional de productos químicos (CICAD)[1] sobre compuestos inorgánicos de cromo (III), preparado conjuntamente por el Instituto Finlandés de Salud Ocupacional de Helsinki (Finlandia) (secciones relativas a la salud humana) y el Centro de Ecología e Hidrología de Monks Wood (Reino Unido) (secciones relativas al medio ambiente), se basó en el *Informe de evaluación del riesgo para la salud del cromo metálico y el cromo trivalente*, preparado por el Instituto Finlandés de Salud Ocupacional (Riihimäki & Luotamo, 2006), y el *Perfil toxicológico del cromo,* de la Agencia para el Registro de Sustancias Tóxicas y Enfermedades (ATSDR, 2000). La última búsqueda bibliográfica sobre los efectos en la salud se hizo en diciembre de 2004 y sobre el medio ambiente en diciembre de 2005. La información sobre los documentos originales se presenta en el apéndice 2. La información sobre el examen colegiado de este CICAD figura en el apéndice 3. Este CICAD sobre compuestos inorgánicos de cromo se aprobó como 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 esta reunión aparece en el apéndice 4. También se reproducen en este documento las Fichas internacionales de seguridad química para los compuestos inorgánicos comunes de cromo trivalente (IPCS, 2002b, 2004a,b,c,d, 2006). Aunque este CICAD se limita a los compuestos inorgánicos de cromo trivalente, también contiene datos sobre compuestos orgánicos de cromo cuando pueden aportar algún valor adicional. En este momento se está preparando el CICAD Nº 78 sobre el cromo hexavalente.

El estado trivalente es la forma más estable del cromo desde el punto de vista termodinámico. Casi todo el cromo presente en el medio ambiente se encuentra en ese estado. Hay una gran variedad de compuestos de cromo trivalente disponibles en el comercio, siendo los más importantes el óxido de cromo (III) y el sulfato básico de cromo.

La población general está expuesta al cromo trivalente fundamentalmente a partir de la alimentación diaria. Otras fuentes son los complementos alimenticios que contienen cromo, el aire ambiente, los artículos de piel curtida con cromo, los cosméticos fabricados con pigmentos de cromo, los artículos de acero inoxidable, los implantes protésicos y los aparatos de ortodoncia. Se puede producir exposición profesional al cromo trivalente en una gran variedad de actividades industriales relacionadas con la producción, formulación y uso del cromo.

[1] La lista completa de las siglas y abreviaturas utilizadas en este informe figura en el apéndice 1.

Hay un ciclo completo del cromo, desde las rocas o el suelo a las plantas, los animales y las personas y su vuelta al suelo. Se libera en el aire, no sólo a partir de fuentes antropogénicas, sino también por los procesos de combustión, incluidos los incendios forestales. El cromo está presente en la atmósfera sobre todo en forma de partículas.

En las aguas superficiales se vierten efluentes industriales que contienen cromo, parte del cual está en forma hexavalente. La posibilidad de que se mantenga hexavalente hasta llegar al mar depende de la cantidad de materia orgánica presente en el agua. En presencia de una cantidad grande de materia orgánica, la materia particulada puede reducir el cromo (VI) y adsorber el cromo (III). Si no se produce la adsorción del cromo (III), éste formará grandes complejos polinucleados que dejan de ser solubles. La reducción del cromo (VI) a cromo (III) es rápida en condiciones anaerobias, y suelen ser éstas las condiciones que existen en las aguas freáticas más profundas. La mayor parte del cromo que se libera en el agua con el tiempo se acaba depositando en el sedimento. Las principales especies de cromo (III) disueltas son Cr^{3+}, $CrOH^{2+}$, $Cr(OH)_3^0$ y $Cr(OH)_4^-$.

El cromo está presente en el suelo fundamentalmente como óxido insoluble y su movilidad es baja. Para el cromo (III) se prevé una adsorción rápida e intensa en el suelo, en particular por los óxidos de hierro y manganeso, los minerales de arcilla y la arena. La movilidad en el suelo del cromo soluble depende 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 son bajos, de alrededor de 1; sin embargo, una vez en el organismo parece que el cromo (VI) se reduce a cromo (III), dando lugar a una acumulación de cromo total hasta alcanzar un factor de unas 100 veces la concentración en el agua.

Las concentraciones de cromo total en la atmósfera de zonas remotas oscilan entre 0,005 y 2,6 ng/m^3, siendo normalmente <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 antropogénicas. Las concentraciones totales de cromo en las aguas fluviales de los Estados Unidos de América suelen ser de <1 a 30 µg/l, con un valor mediano de 10 µg/l. En Europa se ha notificado para aguas superficiales una concentración mediana de cromo total de 0,38 µg/l (<0,01–43,3 µg/l). Las concentraciones totales de cromo en las aguas lacustres no suelen rebasar los 5 µg/l. Se han notificado para aguas superficiales concentraciones medias de cromo (III) de hasta 2 µg/l. Los

niveles más elevados de cromo pueden estar relacionados con fuentes de contaminación antropogénicas, alcanzando los niveles máximos, de hasta 40 mg de cromo (III)/l, cerca de los efluentes de curtidurías.

La concentración de cromo en el agua marina suele ser mucho más baja que en la de lagos y ríos. La concentración total media de cromo en el agua marina es de 0,3 µg/l, con un intervalo de 0,2 a 50 µg/l. Se han notificado en aguas costeras concentraciones medias de cromo (III) de 2 a 3 µg/l. En los materiales en suspensión y los sedimentos de las masas de agua, los niveles totales de cromo oscilaron entre 1 y 500 mg/kg. Los niveles totales de cromo en el suelo varían considerablemente y dependen 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 del Canadá y los Estados Unidos era de 1 a 2000 mg/kg, con una media geométrica de unos 40 mg/kg. En Europa, las concentraciones medianas de cromo en la superficie del suelo tras la extracción con ácido fluorhídrico eran de 60 mg/kg (<3–6230 mg/kg) y de 22 mg/kg (<1–2340 mg/kg) con ácido nítrico. En lugares contaminados se han notificado niveles más altos.

Se considera que el cromo trivalente es un oligoelemento esencial en los mamíferos, puesto que interviene en el metabolismo de los lípidos y la glucosa. Se absorben cantidades limitadas (<0,5–2%) de cromo (III) de la alimentación normal, más si el contenido de cromo en los alimentos es anormalmente bajo y menos si la ingesta es más elevada. La absorción de aerosoles hidrosolubles de cromo (III) de tamaño respirable es más eficaz a partir del sistema respiratorio que del aparato digestivo: alrededor del 5% se puede absorber con rapidez en unas horas, y sigue una liberación más lenta en la circulación durante semanas y meses. Para el óxido de cromo (III) insoluble, la absorción de las partículas depositadas y retenidas es un proceso muy lento. Si bien las sales de cromo trivalente hidrosolubles pueden penetrar en la piel, no se ha observado que lleguen a la circulación sistémica.

El 95% del cromo (III) presente en el plasma sanguíneo está unido a proteínas de peso molecular elevado (por ejemplo, la transferrina), pero también se asocia con un oligopéptido denominado sustancia fijadora de cromo de bajo peso molecular. El cromo se distribuye fundamentalmente en el hígado, los riñones, el bazo y los huesos. Parte del cromo administrado puede alcanzar el intersticio testicular; también se puede acumular en la placenta, pero sólo la atraviesan cantidades pequeñas. El cromo (III) se excreta sobre todo en la orina y en menor grado en las heces.

En las ratas, la toxicidad aguda por vía oral del óxido de cromo (III) es muy baja, con dosis letales medianas (valores de la DL_{50}) superiores a 5 g/kg de peso corporal. Se ha notificado una DL_{50} del sulfato básico de cromo por vía oral de 3530 mg/kg de peso corporal. Los valores obtenidos para el nitrato de cromo varían entre 1540 y 3250 mg/kg de peso corporal.

En los estudios realizados en animales se ha observado que el óxido de cromo (III) y el sulfato básico de cromo no son irritantes cutáneos ni oculares.

El óxido de cromo (III) insoluble no provoca sensibilización cutánea. El cromo trivalente puede actuar como un auténtico determinante hapténico de la sensibilización cutánea, pero su escasa penetración limita la capacidad de sensibilización de sus sales. Se ha demostrado el efecto sensibilizador de las sales de cromo trivalente, el cloruro de cromo y el sulfato de cromo hidratado, que son hidrosolubles, en pruebas no normalizadas utilizando inyecciones intradérmicas o subcutáneas. En dos estudios sobre el cloruro de cromo también se observaron reacciones positivas tras una aplicación epicutánea. Las pruebas clínicas relativas a la sensibilización cutánea se refieren en particular al uso de artículos de cuero. La relación entre el cromo trivalente y la sensibilización inducida por los artículos de cuero se ve empañada por el hecho de que el cuero curtido puede contener niveles bajos de cromo hexavalente y de que los casos notificados de dermatitis de los pies pueden deberse en realidad a que se producen reacciones en personas previamente sensibilizadas al cromo. La sensibilización cutánea en los trabajadores que manipulan sales de cromo trivalente parece ser un fenómeno raro. No hay en este momento ninguna prueba inequívoca que demuestre que la exposición a los compuestos de cromo trivalente ha inducido asma profesional.

La inhalación de concentraciones medias de cromo de 3, 10 y 30 mg/m^3 en forma de óxido de cromo (III) provocó cambios inflamatorios muy leves en los pulmones de ratas expuestas a todos los niveles en el aire, mientras que el polvo de sulfato básico de cromo con las mismas concentraciones de Cr^{3+} en el aire dio lugar a efectos inflamatorios más graves y generalizados y a signos de toxicidad sistémica en los grupos expuestos a dosis medias y altas. Los cambios inflamatorios leves observados tras la inhalación de óxido de cromo (III) pueden reflejar una respuesta pulmonar no específica a la acumulación de partículas insolubles (sobrecarga) más que a la toxicidad intrínseca del cromo (III). Para los efectos sistémicos del sulfato básico de cromo se identificó una concentración sin efectos adversos observados (NOAEC) de 3 mg Cr^{3+}/m^3; sin embargo, dado que se observaron cambios inflamatorios en los pulmones y el sistema respiratorio incluso con el nivel más bajo, se la consideró como la concentración más baja con efectos adversos observados (LOAEC) para los efectos locales. La gravedad mínima observada en las ratas con el nivel de exposición más

bajo parece indicar que para el óxido de cromo (III) la LOAEC de 3 mg Cr^{3+}/m^3 se acerca a la NOAEC.

La administración a ratas de óxido de cromo (III) con los alimentos incluso en dosis muy elevadas no produjo ningún efecto adverso. Esta falta de efectos se puede explicar por la escasa biodisponibilidad oral del óxido de cromo (III). En un estudio de administración oral de cloruro de cromo hidrosoluble a ratas Sprague-Dawley durante 20 semanas, no se observaron efectos adversos relacionados con el tratamiento incluso con las dosis más elevadas, correspondientes a una ingesta de cromo de 7 mg/kg de peso corporal al día.

Aunque puede haber una interacción del cromo (III) con el ácido desoxirribonucleico (ADN), los datos de los estudios de genotoxicidad *in vitro* e *in vivo* son contradictorios y no demuestran de manera clara la mutagenicidad del cromo trivalente.

En los estudios en animales considerados pertinentes para la evaluación de la carcinogenidad del cromo (III) no se observó una incidencia mayor de cáncer con los compuestos de cromo trivalente. Para algunas ocupaciones relacionadas con la exposición al cromo trivalente se ha indicado que es posible un mayor riesgo de algunos tipos de cáncer, pero los datos epidemiológicos no permiten distinguir entre la exposición simultánea al cromo trivalente y hexavalente y a otros agentes carcinogénicos.

Los datos disponibles parecen indicar una falta de efectos del cromo trivalente en la fecundidad. Teniendo en cuenta la escasa biodisponibilidad y los resultados de un estudio limitado de la toxicidad en el desarrollo por vía oral a dosis elevadas, el óxido de cromo (III) no es tóxico en el desarrollo. No se dispone de estudios apropiados de toxicidad en el desarrollo para las sales de cromo trivalente solubles.

Los efectos finales fundamentales que se considera que son pertinentes para la exposición humana al óxido de cromo (III) se basan en la irritación y la inflamación locales asociadas con la acumulación de partículas respirables en los pulmones, en la medida en que los mecanismos de limpieza están sobrecargados. Los efectos finales fundamentales para la exposición humana al sulfato básico de cromo, como supuesto representante de las sales de cromo (III) solubles como grupo, son la toxicidad respiratoria local y la sensibilización cutánea. Las concentraciones tolerables (27 µg de Cr^{3+}/m^3 para el cromo (III) insoluble y 6 µg de Cr^{3+}/m^3 para los compuestos de cromo (III) solubles) basadas en estos efectos y los factores de evaluación aplicables suelen estar muy por encima de los niveles de cromo (III) en el aire; incluso en la proximidad de fuentes puntuales, los niveles en el aire están por debajo de las concentraciones tolerables. Con respecto a la sensibilización cutánea, es bastante poco probable que las sales de cromo trivalente solubles la induzcan en personas que utilizan zapatos, guantes u otros artículos de cuero curtido con cromo, mientras que es posible la aparición de alergia al cromo en una persona previamente sensibilizada debido a la filtración de pequeñas cantidades de cromo de los artículos de cuero.

Algunos microorganismos necesitan cromo (III) para procesos metabólicos específicos, como el metabolismo de la glucosa y la estimulación enzimática. Se ha informado de que el cromo (III), en cantidades minúsculas, es un componente esencial de la nutrición animal y está fuertemente asociado con el metabolismo de la glucosa y las grasas. No obstante, si bien se ha demostrado que el cromo es esencial para el metabolismo de la glucosa en algunos mamíferos de laboratorio, hay estudios en otros animales que son ambiguos.

Los datos disponibles de la toxicidad del cromo (III) se han obtenido en particular utilizando formas hidrosolubles (cloruro de cromo (III), nitrato de cromo (III) y sulfato de cromo y potasio). Es probable que el cromo (III) se encuentre en el medio ambiente en formas mucho menos solubles, y por consiguiente con menor biodisponibilidad para los organismos acuáticos.

Las concentraciones efectivas medianas a las 96 horas (CE_{50}) para un alga de agua dulce, basándose en el crecimiento, fueron de 0,3 a 0,4 mg de cromo (III)/l. Se notificó una CE_{50} a las 96 horas para una diatomea marina, basándose en el crecimiento, de 2 mg de cromo (III)/l. Las concentraciones letales medianas (CL_{50}) en los invertebrados de agua dulce iban de 0.1 mg/l (*Daphnia pulex*) a 442 mg/l (*Asellus aquaticus*), con una concentración sin efectos observados (NOEC) en el ciclo biológico de 0,047 mg/l para *Daphnia magna*. Para los invertebrados marinos se han notificado valores de las CL_{50} que oscilan entre 10 y 100 mg/l. Las CL_{50} a las 96 horas para los peces de agua dulce estaban entre 3,3 mg/l para el "guppy" (*Poecilia reticulata*) y 151 mg/l para la carpa cabezona (*Aristichthys nobilis*), mientras que en los peces marinos se notificaron CL_{50} a las 96 horas de 31,5 y 53 mg/l. Se informó de una NOEC a las 72 horas (supervivencia) de 0,05 mg/l para la trucha arco iris (*Oncorhynchus mykiss*).

Se puede obtener un valor guía para la toxicidad del cromo trivalente en un entorno de agua dulce utilizando un método probabilístico, puesto que el conjunto de datos disponibles es suficientemente amplio para justificarlo. Se derivó un valor guía de fiabilidad moderada de 10 µg de cromo (III)/l para la protección del 99% de las especies de agua dulce con una confianza del 50%. Los datos de la toxicidad no fueron suficientes para poder calcular un valor guía utilizando un método probabilístico.

El valor guía de fiabilidad moderada de 10 µg de cromo (III)/l asignado al entorno de agua dulce parece indicar un riesgo bajo para las aguas superficiales en general. Sin embargo, hay un riesgo potencial para los organismos cuando dicho valor guía se compara con el nivel más elevado de cromo (III), de unos 100 µg/l, en las aguas superficiales de zonas industriales. Los niveles más altos de cromo trivalente en los efluentes, sobre todo de las curtidurías, parecen indicar que hay un riesgo para los organismos de agua dulce en las proximidades de las descargas de dichos efluentes. La comparación del valor guía de fiabilidad baja de 2 µg de cromo (III)/l del entorno marino con las concentraciones de cromo trivalente en el agua del mar parece indicar un riesgo bajo de toxicidad para los organismos marinos.

La característica principal de la intoxicación de las plantas por cromo es la clorosis. El cromo hexavalente parece ser más tóxico para las plantas terrestres que el trivalente.

En ausencia de más datos sobre la biodisponibilidad del cromo en el suelo, es difícil evaluar el riesgo del cromo (III) para los organismos presentes en él.

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