Health Council of the Netherlands

Metallic chromium

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Metallic chromium*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-6873/BvdV/fs/246-N15
Bijlagen : 1
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Geachte staatssecretaris,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan metallisch chroom.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Daarbij heeft de subcommissie op verzoek van uw ministerie de formulering van de categorie waarin metallisch chroom valt, aangepast; niet een numerieke aanduiding maar een standaardzin vormt de hoofdformulering. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb het advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 74 47
E-mail: b.v.d.voet@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

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Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of
the Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2011/34, The Hague, December 2, 2011

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

INAHTA

This report can be downloaded from www.healthcouncil.nl.

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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de Subcommissie Classificatie van carcinogene stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie metallisch chroom onder de loep. Metallisch chroom wordt gebruikt om ijzer en niet-ijzer legeringen met hoge zuiverheid te maken om weerstand te bieden aan oxidatie en corrosie of om microstructuur van de legeringen te regelen.

Op basis van de beschikbare gegevens is de commissie van mening dat die over metallisch chroom niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3).*

* Volgens het nieuwe classificatiesysteem van de Gezondheidsraad (zie bijlage H).

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter the Committee. In this report the Committee evaluated metallic chromium. Metallic chromium is used to prepare ferrous and nonferrous alloys with high purity specifications to confer oxidation and corrosion resistance or to control alloy microstructure.

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of metallic chromium (category 3).*

* According to the new classification system of the Health Council (see Annex H).

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substances in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex H). The criteria used for classification are partly based on an EU-directive (see Annex I). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question.

This report contains the evaluation of the carcinogenicity of metallic chromium.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B.

In 2011 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is standardly based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of metallic chromium, such an IARC-monograph is available, of which the summary and conclusion of IARC is inserted in Annex D.

More recently published data were retrieved from the databases Medline and Toxline and Chemical Abstracts. The last updated online search was in November 2011. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physicochemical properties

Chromium is not found in nature in its metallic form. Chromium is found in nature only in the combined state (mostly chromium(III) and (VI)) and not as a free metal. Chromium salts are present in ore and are produced by man. The salts are, however, not treated in this document.

Chromium metal is used to prepare ferrous and nonferrous alloys with high purity specifications to confer oxidation and corrosion resistance or to control microstructure. Chromium-containing steels are used in general engineering, architectural panels and fasteners, pollution control equipment, chemical equipment, cryogenic uses, hospital equipment, domestic equipment, automotive parts, engine components and food processing. Chromium alloys are used in a large variety of applications, including jet engine parts, nuclear plants, high-temperature reaction vessels, chemical industry equipment, high temperature-resistant equipments, coinage, desalinization plants, ships' propellers, acid-resistant equipment, cutting tools and implants. Occupational exposure to airborne dusts containing chromium metal may occur during production, welding, cutting and grinding of chromium alloys.[1]

Anthropogenic sources release 60-70% of the total emissions of atmospheric chromium. Levels of total chromium in ambient air are <0.01-0.03 μg/m^3 and in

tap water are <1 µg/L. As a result of smoking, indoor air contaminated with chromium can be 10-400 times greater than outdoor air concentrations. Levels of total chromium at the work place range from 10-2500 µg/m^3. No values for chromium (0) alone are available.[1] Chromium(III) is an essential nutrient required for normal energy metabolism.[2]

The identity of metallic chromium and some of its physicochemical properties are given below.[1]

Chemical name	:	chromium
CAS registry number	:	7440-47-3
EC/EINECS number	:	231-157-5
Synonyms	:	chrome
Colour and physical state	:	steel-grey, lustrous metal or powder
Atomic weight	:	51.996
Molecular formula	:	Cr
Crystal structure	:	cubic
Melting/boiling point	:	1,900/2,642 °C
Solubility	:	insoluble in water; soluble in dilute hydrochloric acid and sulphuric acid; insoluble in nitric acid or nitrohydrochloric acid

2.2 IARC conclusion

In 1990, IARC concluded that there is inadequate evidence for the carcinogenicity of metallic chromium in experimental animals. No conclusion was drawn for the carcinogenicity in humans. Therefore, according to the IARC guidelines, metallic chromium was considered to be not classifiable as to its carcinogenicity to humans (Group 3).[1]

Regarding specifically chromium(III) and chromium(VI), IARC considered chromium(III) to be not classifiable as to its carcinogenicity to humans (Group 3), and chromium(VI) to be carcinogenic to humans (Group 1).[1] IARC reconfirmed chromium(VI) to be carcinogenic to humans in 2009 (IARC monograph 100C, to be published, Straif *et al*. 2009[3]).

Chapter 3

Carcinogenicity

Chromium exists in various oxidation states such as chromium(III) and chromium(VI).

The toxic and carcinogenic potency of chromium are dependent on the oxidation state of the chromium atom, with chromium(VI) more potent that chromium(III).[2] The mechanisms are mediated through reactive intermediates during intracellular reduction of chromium(VI) (via chromium(V) and (IV) to chromium(III) and by chromium(III) itself. The higher redox potential and the greater ability of chromium(VI) to enter cells contributes to the greater toxic and carcinogenic potency of chromium(VI) relative to chromium(III), The lower toxicity and carcinogenicity of chromium(III) may be due to a decreased penetration of chromium into the cells.

Inhalation and skincontact are the most common routes for occupational exposure to chromium. Although most chromium compounds are not absorbed through the skin, caustic chromium(VI) compounds may damage the skin and enhance systemic absorption. Occupational exposure often implies a combined exposure to chromium in various oxidation states. Therefore, in most studies the actual contribution of the separate forms of chromium to toxicity or carcinogenicity cannot be clearly discriminated. In addition, smoking is not only a major source for hexavalent chromium but also a potential confounding factor in these studies.

Overall, very little data is available on metallic chromium(0) as most investigations have focused on chromium(III) and chromium(VI) compounds.

3.1 Observations in humans

No studies with exposure to metallic chromium(0) alone were available. Only the studies that included obvious chromium(0) exposure next to exposure to chromium(III) and chromium(VI), were summarized below (see also Annex E for details).

Axelsson *et al.*[1,2,4] investigated the cause of death and incidence of tumours among 1,876 employees at a ferrochromium plant in Sweden employed for at least one year between 1930 and 1975. Individuals were categorised according to length and place of work in the factory. No significant increase in the incidence of cancer of the stomach, colon, liver, pancreas, prostate, kidney or mulitple myeloma was found when compared to expected rates for the county in which the factory was located. For maintenance workers four cases of respiratory cancer were observed compared to one expected during 1958-75. Two of these had mesotheliomas, which could be connected with asbestos exposure. The estimated levels of chromium metal plus chromium(III) in the work atmosphere ranged from 0 to 2.5 mg/m^3, and those for chromium(VI) from 0 to 0.25 mg/m^3.

Langard *et al.*[1,2,5] studied 325 male workers employed for more than one year at a ferrochromium production plant in Norway between 1928 and 1977. An excess of lung cancer was found in the group whose employment began before 1960 (7 cases; SMR = 2,26; 95% CI 0,91-4,66) when compared to the Norwegian male population (when compared to an internal referent group consisting of all workers except ferrochromium workers: 2 cases; SMR = 8,50; p= 0.026). All workers have been exposed to some extent to asbestos and possibly also to low atmospheric levels of polycyclic aromatic hydrocarbons. In a follow-up cohort (n=379, hired before 1965 and followed through 1985), the rate of lung cancer (10 cases) was not significantly different from the expected rate (SIR 1,54; 95% CI 0,74-2,83) when compared to the Norwegian male population (comparison to internal referent group not reported).[1,2] Workroom monitoring in 1975 indicated that the ferrochromium furnace operators worked in an atmosphere with 0.04-0.29 mg total chromium/m^3, with 11-33% of the total chromium as chromium(VI). The hypothesis that chromium(III) might be carcinogenic to humans was not supported by the results obtained according to the authors, neither a relationship between chromium(0) and carcinogenicity.

An ecological study[2] (Halasova *et al.*) examined the distribution of lung cancer cases in a ferrochromium production facility in Dolny Kubin in the Slovak Replublic. Cases were stratified into three groups (males): ferrochromium workers (n=59), workers (n=106) thought not to have been exposed to chromium, and residents (n=409). Lung cancer rates were higher in the chromium workers (320 per 1000 per year, 95% CI 318-323) compared to workers (112, 95% CI 109-113) and residents (79, 95% CI 76-80) who were not thought to have been exposed to chromium (relative risk = 4.04 for chromium workers compared to residents). Mean work shift air concentrations in the smelter were 0.03-0.19 mg/m^3 for total chromium and 0.018-0.03 mg/m^3 for chromium(VI). However, it was argued that smoking was an important risk factor in these chromium workers that might have contributed to the lung cancer rates.

IARC summarized[1] a Russian study (Pokrovskaya, 1973) investigating a cohort of male and female factory workers engaged in chromium ferroalloy production between 1955 and 1969 in the USSR. Workers were reported to be exposed to chromium(VI) and chromium(III) compounds as well as benzo[a]pyrene. Male chromium workers aged 50-59 experienced significant ($p = 0.001$) increases in death rates in all malignancies, from lung cancer and from oesophageal cancer, as compared with death rates in the municipal population. The relative risk for lung cancer in men was reported to range from 4.4 in the 30-39-year age group to 6.6 ($p = 0.001$) in the 50-59-year age group. A large proportion of the cases of lung cancer among workers was exposed to high concentrations of dust (cinder pit workers, metal crushers, smelter workers), including workers who were not exposed to benzo[a]pyrene in areas of furnace charge and finished products preparation. Numbers of workers and numbers of cancer by specific site were not reported.

3.2 Carcinogenicity studies in animals

A number of animal studies with chromium(0) are available.[1,2,6] However, the routes of exposure used (intrapleural, intramuscular, intraperitoneal, intravenous and intrafemoral) are not representative for human exposure. Moreover, exposure was short, number of animals was low, doses were low, no control group used and/or reporting was limited. For completeness all animal studies are presented in Annex F.

Only one intratracheal study (summary and Tables in English)[1,7] was available. Groups of 35-62 female Wistar rats were administered 10 mg powdered chromium in combination with 1 or 5 mg 20-methylcholanthrene (MC; polycyclic aromatic hydrocarbon) or MC alone in saline once. Rats were killed at vari-

ous intervals up to 12 weeks. Squamous-cell carcinomas of the lung developed 12 weeks after treatment in 6/12 rats given Cr + 5 mg MC, in 1/12 given Cr + 1 mg MC, in 2/7 given 5 mg MC alone, in 0/8 given 1 mg MC alone and in 0/12 given Cr alone. The Committee is aware that this is a very short combination study which makes extrapolation to the human situation difficult.

Chapter 4

Genotoxicity

Genotoxicity data are summarized below, and are presented in Annex G.

4.1 *In vitro* assays

No data on mutagenic or genotoxic activity is available. Metallic chromium was assayed for the ability to induce cell transformation (anchorage-independent growth) in Syrian hamster BHK fibroblasts. Although chromium particles were phagocytized by cells, no significant increase in the number of cell foci growing in soft agar was observed. Due to technical and interpretative difficulties with this assay the result is not considered to evaluate the mutagenicity of metallic chromium as indicated by IARC.[1]

4.2 *In vivo* assays

As reported in an abstract[8], male Sprague-Dawley rats were exposed to chromium fumes generated from powders of chromium metal by a plasma flame sprayer at concentrations of 1.84 ± 0.55 mg/m^3 or 0.55 ± 0.07 mg/m^3 fume for 5 hours/day on five days a week for one week or two months, respectively. Significant increases in the frequencies of sister chromatid exchange and of chromosomal aberrations were observed in peripheral blood lymphocytes, whereas chromosomal aberration frequencies in bone-marrow cells were unchanged. Par-

tial oxidation of the metallic chromium to chromium(III) and/or (VI) may have played a role.

4.3 Carcinogenic mechanism of action

No data on the mechanism for possible carcinogenicity on chromium(0) is available. The most likely route of occupational exposure is via inhalation and dermal. The absorption of inhaled chromium(0) depends on physical and chemical properties, predominantly the particle size as it is insoluble in water, and the activity of alveolar macrophages. Chromium has been identified in the tissues of occupationally-exposed humans, suggesting that chromium can be absorbed from the lungs.[2] Chromium containing alloys, like stainless steel, that are used in implants form chromium oxide films.[6] Chromium-cobalt alloys appear to release chromium(VI) after intramuscular implantations in rats. Chromium metal powder released chromium(VI) when incubated in aerated phosphate buffer, Ringer's solution, phosphate buffer with added bicarbonate and Locke's physiological buffer.[1]

From the above it can be deduced that chromium(VI), which is regarded as carcinogenic to humans, might be formed from chromium(0) in the body.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Human epidemiological studies with obvious metallic chromium(0) exposure are available. However, as also exposure to other forms of chromium occurred results were inconclusive for metallic chromium. Although some animal studies showed an increased incidence of neoplasms, no conclusion could be drawn on the chromium-related induction of these neoplasms. The animal studies were poorly executed and/or described, and the route of exposure was not relevant to occupational exposure. Overall, the Committee concludes that epidemiological and animal data are insufficient to evaluate the carcinogenic potency of metallic chromium.

Chromium(0) did not induce cell transformations in hamster fibroblasts *in vitro* or chromosomal aberrations in rat bone marrow *in vivo*, but it did induce sister chromatid exchange and chromosomal aberrations in rat peripheral blood lymphocytes *in vivo*. The data do not allow a conclusion on a genotoxic mechanism.

5.2 Recommendation for classification

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of metallic chromium (category 3)*.

The Committee is aware that conversion of metallic chromium into ionic chromium(III) or chromium(VI) may not be excluded in every occupational situation.

* According to the new classification system of the Health Council (see Annex H).

References

1 Chromium and chromium compounds. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans 1990; 49: 49-256.

2 Toxicological profile for chromium (draft). US Department of Health and Human Services; Public Health Service; Agency for Toxic Substances and Disease Registry; 2008.

3 Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El GF et al. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol 2009; 10(5): 453-454.

4 Axelsson G, Rylander R, Schmidt A. Mortality and incidenc of tumours among ferrochromium workers. Br J Ind Med 1980; 37: 121-127.

5 Langard S, Andersen A, Gylseth B. Incidence of cancer among ferrochromium and ferrosilicon workers. Br J Ind Med 1980; 37: 114-120.

6 Surgical implants and other foreign bodies. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans 1999; 74.

7 Mukubo K. Studies on experimental lung tumor by the chemical carcinogens and inorganic substances. III. Histopathological studies on lung tumour in rats induced by pertracheal vinyl tube infusion of 20-methylcholanthrene combined with chromium and nickel powders. J Nara Med Assoc 1978; 29: 321-340.

8 Koshi K, Serita F, Sawatari K, Suzuki Y. Cytogenetic analysis of bone marrow cells and peripheral blood lymphocytes from rats exposed to chromium fumes by inhalation (Abstract no 21). Mutat Res 1987; 181: 365.

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10-4 and 10-6 per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologix Pathologist, TNO Quality of Life; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemicals NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- G.B. van der Voet, *scientific secretary*
  Toxicologist, Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not

necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2011 for public review. The following organisations and persons have commented on the draft document:

- National Institute of Occupational Safety and Health, Cincinnati, USA

Annex **D**

IARC Monograph

VOL: 49 (1990, update 1997)

Summary of Data Reported and Evaluation

Exposure data

Chromium in the form of various alloys and compounds has been in widespread commercial use for over 100 years. Early applications included chrome pigments and tanning liquors. In recent decades, chromium has also been widely used in chromium alloys and chrome plating.

Several million workers worldwide are exposed to airborne fumes, mists and dust containing chromium or its compounds. Of the occupational situations in which exposure to chromium occurs, highest exposures to chromium (VI) may occur during chromate production, welding, chrome pigment manufacture, chrome plating and spray painting; highest exposures to other forms of chromium occur during mining, ferrochromium and steel production, welding and cutting and grinding of chromium alloys.

Data on exposure levels are available for several specific industries and job categories covering several decades. In the past, exposures to chromium(VI) in excess of 1 mg/m^3 were found repeatedly in some processes, including chro-

mium plating, chromate production and certain welding operations; exposures to total chromium have been even higher. Modern control technologies have markedly reduced exposures in some processes, such as electroplating, in recent years.

Occupational exposure has been shown to give rise to elevated levels of chromium in blood, urine and some body tissues, inhalation being the main route. Nonoccupational sources of exposure to chromium include food, air and water, but the levels are usually several orders of magnitude lower than those typically encountered in occupational situations.

Experimental carcinogenicity data

Studies in rats by intratracheal, intramuscular and intrafemoral administration, in mice and rats by intrapleural and intraperitoneal administration and in mice, rats and rabbits by intravenous injections were inadequate to evaluate the carcinogenicity of chromium metal as a powder.

Human carcinogenicity data

In three reports, from Norway, Sweden and the USSR, in which ferrochromium workers were studied, the overall results with regard to lung cancer were inconclusive. The major exposure in this industry is to chromium(III) compounds and to metallic chromium, although exposure to chromium(VI) may also occur. No epidemiological study addressed the risk of cancer from exposure to metallic chromium alone.

Other relevant data

A water-insoluble chromium(0) compound (chromium carbonyl) did not induce DNA damage in bacteria. No relevant study on the genetic and related effects of metallic chromium was available to the Working Group.

Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of metallic chromium. There is *inadequate evidence* in experimental animals for the carcinogenicity of metallic chromium.

Overall evaluation

Metallic chromium is not classifiable as to its carcinogenicity to humans (Group 3).

In addition IARC concludes that chromium(VI) is carcinogenic to humans (Group 1) (see IARC 49[1] en 100C, Straif[3]) and that chromium(III) compounds are not classifyable as to their carcinogenicity to humans (Group 3).

Annex **E**

Human data

Study type, Population,, Follow up	Total dose or atmospheric concentration, Exposure duration	Effect	Relative Ratio (95% Conf. Interval)	Reference
Cohort of 1876 workers in ferrochromium plant in Sweden exposed employed between 1930 and 1975 (control: county population)	Cr(0) + Cr(III) = 0-2.5 mg/m^3; Cr(VI) = 0-0.25 mg/m^3 (estimates) Exposure ≥ 1 y between 1930 and 1975	No increase in incidence of cancer of the stomach, colon, liver, pancreas, prostate, kidney or multiple myeloma; maintenance workers: 4 respiratory cancer (2 mesotheliomas) and 1 in control	-	Axelsson 1980[4]; IARC1999[6], ATSDR 2008[2]
Cohort of 325 male workers in ferrochromium plant in Norway employed between 1928 and 1977(control: national mortality rates)	Near furnace: 0.04-0.29 mg Cr/m^3 with 11-33% Cr(VI) (in 1975) Exposure > 1 y between 1928 and 1977	Hired before 1960: lung cancer: 7 observed; 3.1 expected (national mortality) When compared to internal referent: Hired before 1965 (followed through 1985): 10/379 lung cancer	SMR 226 (91-466) SMR 850 (p = 0.026) SIR 154 (74-283)	Langard 1980[5] IARC1999[6], ATSDR 2008[2]

Cohort including male and female workers in ferrochromium production (control: municipal population) no data on follow up	Exposed to Cr(VI), Cr(III) and benzo[a]pyrene Exposure between 1955-1969	Male workers aged 30-39: excess lung cancer Male workers aged 50-59: increased lung and oesophageal cancer	RR 4.4 RR 6.6 (p = 0.001)	Pokrovskaya, 1973, IARC1999[6]
Case-control study including 59 ferrochromium workers , 106 not exposed workers and 409 residents) no data on follow up	Smelter: 0.03-0.19 mg Cr/m^3; 0.018-0.03 mg $Cr(VI)/m^3$ No data on exposure duration	Excess lung cancer	RR 4.04 (CI not specified)	ATSDR, 2008[2]

Annex **F**

Animal data

Abbrevations used:
freq = frequency
X_{po} = duration of exposure
X_{pe} = duration of the experiment
bw = body weight
no. = number
y = year

Purity is not specified unless stated otherwise. The age of the animals is only given if it deviates from the normal age of starting administration.

Species sex (no./ group)	Dose, frequency	X_{po} /X_{pe}	No. survivors	No. animals with tumours	Comments/specified tumours	Reference
Chromium powder						
Intrapleural						
Mouse C57B1 Male (50)	10 µg in 0.2 ml 2.5% gelatin-saline 6 times, 1x/2 weeks	12 weeks/ 14 months	32	none	-	IARC49[1]/74[6]
Rat Osborne-Mendel 4 months old Female (17) M ale (8)	16.8 mg in 50 µl lanolin 6 times, 1x/month	6 months/ lifetime	19-24 months: 6 (sex not specified)	3 Female 2 other (group not specified)	3 adenofibromas of the thoracic wall; 1 retro-peritoneal haemangioma	IARC49[1]/74[6]
Rat Wistar 4 months old Male (25; control 12)	0 or 0.5 mg in 0.1 ml 2.5% gelatin-saline 6 times, 1x/month	6 months/ lifetime	25-30 months:12	another (group not specified) Wistar gelatin control: 3/12	1 haemangioma; 1 angiosarcoma 1 intra-abdominal round-cell sarcoma intra-abdominal round-cell sarcoma	
Intramuscular						
Rat Fischer Male (24)	2 mg Cr dust[a] in 0.5 ml penicillin G procaine once	Once/ 24 months	22	-	No local tumours	IARC49[1]/74[6]
Rat Fischer-344 Male (18 and 20)	4.4 mg Cr dust[b] in 0.2 ml penicillin G procaine	--/ 2 years	13/18; 0/20	-	Low survival in second group due to pulmonary pneumonia; no local tumours	IARC49[1]/74[6]
Rat Fischer-344 Male/Female (25/sex)	100 mg (99.9% pure) in 0.2 ml tricaprylin, monthly until nodule at injection site (not specified)	not specified/ 644 days	not specified	Male:1 Female: 0 control Male/Female: 0	Local fibrosarcoma	IARC49[1]/74[6]

Intraperitoneal						
Mouse C57B1 Male (50)	10 µg[c] in 0.2 ml 2.5% gelatin-saline weekly	4 weeks/ 21 months	40	1	Myeloid leukaemia	IARC49[1]/74[6]
Rat Wistar 3-4 months, Male (25)	50 µg in 0.1 ml 2.5% gelatin-saline weekly	6 weeks/--		5; no vehicle control reported	1 scirrhous carcinoma of caecal submucosa; 2 intra-abdominal round-cell sarcomas, 1 sarcoma of cartilaginous osteoid origin of the leg + insulinoma of the pancreas, 1 insulinoma; the authors stated that round-cell sarcomas also occurred in controls, insulinomas not	IARC49[1]/74[6]
Intravenous						
Mouse C57B1, sex unspecified (25)	2.5 µg[d] in 0.05 ml 2.5% gelatin-saline into tail vein weekly	6 weeks/ 18 months	12 months: 6 18 months: 0	none		IARC49[1]/74[6]
Rat Wistar 7 months, Male (25)	90 µg in 0.18 ml 2.5% gelatin-saline into left vena saphena, weekly	6 weeks/ 2 years	1 y: 15 2 y: 13	7 (vehicle control not reported)	4 round-cell sarcoma (3 ileocaecal, 1 intra-thoracic), 1 haemangioma of renal medulla, 2 papillary adenoma of lung (1 extensive squamous-cell carcinomatous changes); author stated: round-cell sarcomas also occurred in control rats, lung adenomas not in the series of studies	IARC49[1]/74[6]
Rabbit albino 6 months, sex unspecified (8); control (4)	0, 25 mg/kg bw in 0.5 ml 2.5% gelatin-saline into ear vein weekly	6 weeks; same treatment 4 months later and 3 y after first injection/ > 3 y	3 y: 3/8 control not specified	0, 1	Tumour of uncertain origin (apparently immature carcinoma) involving various lymph nodes	IARC49[1]/74[6]
Intrarenal						
Rat Sprague-Dawley, Female (18 or 20); control (16)	5 mg in glycerine into each pole of right kidney (10 mg/ rat) , once	Once/ 12 months	not specified	none	Positive control (nickel subsulfide): 1/20 rhabdomyosar-coma in injected kidney and mesentery; 7/20 renal carcinoma	IARC74[6]

Intrafemoral						
Rat Wistar 5 months, Male (25)	0.2 ml of ~45 mg in 20% gelatin-saline, once	Once/ 24 months	1 y: 19	none	No tumour at injection site	IARC49[1]/74[6]
Rat Osborne-Mendel 5 months, Male (25)	~45 mg in 0.2 ml lanolin, once	Once/ 24 months	1y: 14	1	Fibroma at injection site	IARC49[1]/74[6]
Rabbit strain, sex, age unspecified, (15-20)	Cr dust (particle size unspecified) implant in femoral cavity, Once	Once/ 6 years	3 y: 11 up to 6 y: not specified	none (X-ray) 3	Sarcoma	IARC74[6]
Intratracheal co-administration with, methylcholantrene (MC), a known carcinogen						
Rat Wistar , Female (35-62)	10 mg (purity9..4%; diameter 1-3 µm) + 1 or 5 mg 20-methylcholanthrene (MC) or MC alone in saline, once	Once/ intervals up to 12 weeks		6/12 In group Cr + 5 mg MC: 1/12 in group Cr + 1 mg 1/12 in group MC 2/7 in Group 5 mg MC 0/8 in group 1 mg MC: 0/8 0/12 in group Cr	Squamous-cell carcinoma of the lung	Mukubo, 1978[7]; IARC49[1]

[a] Elemental Cr, 65%; chromium oxides as Cr2O3, 35%; Ni, Al, Cu, Mn and Co, <0.1%; mean particle diameter, 1.6 µm).
[b] Cr, 76%; O_2, 24%; Mn, 0.2%; median particle diameter, 1.4 µm).
[c] Diameter > 100 µm to colloidal particle size.
[d] Particle size, ≤ 4 µm.

Annex **G**

Genotoxicity data

Test system	Dose[a] (LED or HID)	Result [b]		Reference
		exogenous metabolic activation		
		without	with	
In vitro assays				
Cell transformation, Syrian hamster BHK fibroblasts	Not specified	-	NT	Hansen & Stern, 1985; IARC49[1]
In vivo assays				
SCE and chromosomal aberrations, rat peripheral blood lymphocytes	5 x 1.84 mg/m^3 x 0.55 mg/m^3; 5 h/d inhalation[c]	+		Koshi, 1987[8]
Chromosomal aberrations, rat bone marrow	5 x 1.84 mg/m^3 x 0.55 mg/m^3; 5 h/d inhalation[c]	-		Koshi, 1987[8]

a LED, lowest effective dose; HID, highest ineffective dose.
b +, Positive; –, negative; NT, not tested.
c Partial oxidation of metallic chromium.

Annex **H**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GRGHS)	Comparable with EU Category	
		67/584/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	1	1A
1B	The compound is presumed to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	Not applicable	Not applicable
(4)	The compound is probably not carcinogenic to man.	Not applicable	Not applicable

Source: Health Council of the Netherlands. Guidline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.