Chromium and its inorganic compounds

Health-based recommended occupational exposure limit
(revised version)

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Bij brief van 3 december 1993, nr. DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde Minister ingestelde adviescommissie.

Hierbij stuur ik u ter kennisname, een herziene versie van het rapport over chroom en anorganische chroomverbindingen dat verscheen in maart van dit jaar. Deze publicatie heb ik heden aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid aangeboden.

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Report of the Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affaires and Employment

No. 1998/01(R)WGD, Rijswijk, 24 September 1998

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Contents

Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beveelt de Gezondheidsraad gezondheidskundige advieswaarden aan voor beroepsmatige blootstelling aan toxische stoffen in lucht op de werkplek. Deze aanbevelingen worden opgesteld door de Commissie WGD van de Raad, de opvolgster van de Werkgroep van Deskundigen (WGD). Zij vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC waarden).

Het voorliggende rapport is een herziene versie van het rapport over de gezondheidskundige gevolgen van beroepsmatige blootstelling aan chroom en anorganische chroomverbindingen dat in maart van dit jaar verscheen. Dat rapport vormde op zijn beurt een actualisering van een rapport van de Commissie WGD uit 1985. In de herziene versie heeft de Commissie WGD de evaluatie van de toxiciteit van deze stoffen op een aantal punten verduidelijkt.

De conclusies van de commissie, die uitmonden in de presentatie van gezondheidskundige advieswaarden, zijn gebaseerd op wetenschappelijke publicaties die vóór 1995 zijn verschenen. Wetenschappelijke publicaties verschenen tussen 1995 en 1997 gaven de commissie geen reden af te wijken van haar aanbevelingen.

2 Fysische en chemische eigenschappen

Gezien het bestaan van verschillen in zowel fysische en chemische eigenschappen als toxiciteit, acht de commissie het aangewezen om onderscheid te maken tussen de volgende categorieën: chroommetaalstof, chroom(II)verbindingen, oplosbare chroom(III)verbindingen, onoplosbare chroom(III)verbindingen, chroom-(IV)verbindingen en chroom(VI)verbindingen.

3 Monitoring

In het WGD-rapport over chroom en anorganische chroomverbindingen uit 1985 is een methode beschreven voor de bepaling van zowel atmosferische concentraties als concentraties van diverse chroomverbindingen in biologische substraten. De commissie beveelt aan om de biologische monitoring te baseren op de chroomconcentratie in urine.

4 Huidige grenswaarden

Op dit moment vigeren in Nederland de volgende wettelijke grenswaarden voor beroepsmatige blootstelling:

chroommetaalstof	0,5 mg/m^3 gemiddeld over acht uur
oplosbare chroom(VI)verbindingen	0,025 mg/m^3 gemiddeld over acht uur 0,05 mg/m^3 gemiddeld over 15 minuten mét huid-indicatie
chroom(III)verbindingen	0,5 mg/m^3 gemiddeld over acht uur 1,0 mg/m^3 gemiddeld over 15 minuten
calcium-, strontium- en zink-chromaat	0,01 mg/m^3 gemiddeld over 15 minuten
lood- en bariumchromaat	0,025 mg/m^3 gemiddeld over 15 minuten
gecombineerde chroomblootstelling	0,01 mg/m^3 gemiddeld over 15 minuten

5 Effecten

De huid, slijmvliezen, bovenste luchtwegen, nieren, longen en voortplantingsorganen zijn de doelwitorganen bij blootstelling aan chroom of chroomhoudende verbindingen.

Chroomhoudende verbindingen kunnen irriterende en allergische/eczemateuze lesies op de huid veroorzaken. Irriterende lesies ontstaan vooral door toedoen van

chroom(VI), minder door chroom(III). Chroom(IV)verbindingen kunnen verzweringen en doorboringen van het neustussenschot teweegbrengen; naar schatting gebeurt dit bij CrO_3-concentraties vanaf 0,1 mg/m^3.

Oplosbare chroom(VI)verbindingen kunnen bij mensen lesies in de niertubuli veroorzaken. Voor chroom(III)verbindingen zijn geen nefrotoxische effecten gerapporteerd. Met betrekking tot effecten op de nieren lijken er verschillen te bestaan tussen kortdurende hoge en langdurige lage blootstelling. Uit onderzoek bij werkers in een bedrijf dat chromaat en dichromaat produceert, is gebleken dat een chroomconcentratie van 15 µg per gram creatinine in de urine correspondeert met de drempel voor effecten op de tubulaire functies.

Blootstelling aan chroom kan op de longen de volgende niet-carcinogene effecten hebben: pulmonaire fibrose, chronische bronchitis, bronchiale astma en pneumoconiose. In een onderzoek naar langdurige inhalatoire blootstelling van ratten aan chroomdioxide (Cr(IV)) — blootstelling gedurende twee jaar, vijf dagen per week, zes uur per dag — leidde een concentratie van 0,5 mg/m^3 tot een lichte type II-pneumocyte hyperplasie; deze concentratie werd beschouwd als het laagst-waargenomen-ongunstig-effectniveau (LOAEL) voor effecten op de longen. Voor oplosbare chroom(III)verbindingen is bij konijnen een minimaal-waargenomen-ongunstig-effectniveau (MOAEL) van 0,6 mg/m^3 gevonden. Blootstelling aan deze concentratie gedurende vier tot zes weken, vijf dagen per week, zes uur per dag, leidde tot functionele en morfologische veranderingen in de alveolaire macrofagen.

Er zijn niet veel recente gegevens over de kankerverwekkendheid van chroom in de longen van proefdieren. In het hierboven al genoemde langdurige-blootstellingsonderzoek (chroom(IV)verbindingen) ontstonden bij enkele vrouwelijke ratten op kyste lijkende, keratiniserende squameuze celcarcinomen. Bij de mannelijke dieren deed dit zich niet voor. Vermoedelijk is dit tumortype niet relevant voor de mens. Uit een recent verschenen literatuuroverzicht inzake de kankerverwekkendheid van chroomverbindingen bij dieren concludeert de commissie dat er weinig evidentie is voor kankerverwekkende eigenschappen van oplosbare chroom(VI)verbindingen in proefdieren. De carcinogeniteit van calcium-, zink- en strontiumchromaat is daarentegen genoegzaam gebleken. In een groot retrospectief cohort-onderzoek naar de mortaliteit onder mannelijke lassers in negen Europese landen is een significant verhoogde sterfte aan longkanker gevonden, voornamelijk onder lassers die met roestvrij staal omgaan. Overeenkomstige bevindingen zijn verkregen in cohort-onderzoeken in twee Duitse chromaatfabrieken, Japanse plaatwalserijen en onder lassers in 13 Franse bedrijven. In recent verschenen epidemiologische overzichten is geconstateerd dat chroom(VI)verbindingen

beschouwd moeten worden als carcinogeen voor de mens. Er is geen bewijs verkregen voor het bestaan van kankerverwekkende eigenschappen van chroom(III)verbindingen.

Blijkens resultaten van onderzoek naar mutageniteit en genotoxiciteit is chroom(II) niet genotoxisch; chroom(III) induceert in het algemeen geen DNA-schade, genmutatie, 'sister chromatid exchanges' (SCE) of celtransformatie in celkweken van dierlijke of menselijke oorsprong; chroom(VI)verbindingen van uiteenlopende oplosbaarheid zijn consistent actief gebleken in talloze genotoxiciteitsonderzoeken (DNA-schade, genmutatie, SCE, chromosomale afwijkingen, celtransformatie, dominant-lethaal mutatie).

De effecten van chroomhoudende verbindingen op de lever en het centrale of perifere zenuwstelsel bij proefdieren zijn onduidelijk. Hetzelfde geldt voor effecten op de lever bij mensen. Er zijn geen aanwijzingen dat chroom(VI) voor mensen neurotoxisch is.

Chroom(VI) bleek bij mannelijke ratten toxisch te zijn voor de voortplantingsorganen. Zestig dagen na vijf dagelijkse intraperitoneale injecties van 1 mg per kg lichaamsgewicht op vijf opeenvolgende dagen was het relatieve testisgewicht verminderd en was er sprake van atrofie van de zaadbuisjes.

Chroom(III) had geen effect op de voortplantingsorganen van mannelijke ratten. Bij mannelijke lassers met chroomconcentraties tussen 0,08 en 2,18 µg per g creatinine was geen sprake van afwijkingen in de kwaliteit van het semen en van de geslachtshormonen. Er zijn geen gegevens over het effect van chroom op de voortplantingsorganen van vrouwen.

De Wereldgezondheidsorganisatie heeft geconcludeerd dat chroom(III) en chroom(VI) bij proefdieren teratogeen zijn bij parenterale injectie van hoge dosis.

6 Gezondheidskundige advieswaarden

Chroommetaalstof, chroom(II)verbindingen en niet in water oplosbare chroom(III)verbindingen

Wegens gebrek aan wetenschappelijke gegevens kan de commissie voor beroepsmatige blootstelling aan deze stoffen geen gezondheidskundige grenswaarde aanbevelen.

Chroom(III)verbindingen die in water oplosbaar zijn

Voor deze stoffen stelt de commissie de gezondheidskundige advieswaarde voor beroepsmatige blootstelling op 0,06 mg inhaleerbaar stof per m^3 lucht, gemiddeld over acht uur. Deze waarde is afgeleid van een MOAEL van 0,6 mg/m^3 voor effecten op de longen van konijnen bij blootstelling gedurende vier tot zes weken. Zowel voor de interspecies-variatie als de intrapolatie van MOAEL naar NOAEL acht de commissie een veiligheidsfactor van 3 — dus samen een factor 10 — voldoende.

Chroom(IV)verbindingen

De commissie stelt voor beroepsmatige blootstelling van deze stoffen de gezondheidskundige advieswaarde op 0,05 mg inhaleerbaar stof per m^3 lucht, gemiddeld over acht uur. Deze waarde is gebaseerd op een LOAEL van 0,5 mg/m^3 voor effecten op de longen van ratten in een 2-jaars onderzoek. De commissie acht een veiligheidsfactor van 10 voldoende (factor 3 voor zowel de interspecies-variatie als de extrapolatie van LOAEL naar NOAEL).

Chroom(VI)verbindingen

De commissie beschouwt alle chroom(VI)verbindingen als carcinogeen voor de mens. Er wordt een genotoxisch werkingsmechanisme verondersteld. Volgens de commissie zijn er geen redenen om af te wijken van de methode van lineaire extrapolatie.

De commissie schat het extra kankerrisico op:

- 4×10^{-3} bij beroepsmatige blootstelling aan 2 $\mu g/m^3$ inhaleerbaar stof gedurende 40 jaar
- 4×10^{-5} bij beroepsmatige blootstelling aan 0,02 $\mu g/m^3$ inhaleerbaar stof gedurende 40 jaar.

De commissie maakt in de evaluatie van dit rapport nog enkele aanvullende opmerkingen over de vigerende MAC-waarden van chroom metaalstof en de onoplosbare chroom(III)verbindingen.

Executive Summary

1 Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally-binding limit values.

The present report is a revised version of the report, published in March 1998 concerning health effects of occupational exposure to chromium and its inorganic compounds. The latter report was an update of a previous report of the DECOS from 1985. In the revised version, the committee clarifies the health hazard evaluation of these compounds in more detail and recommends health-based occupational exposure limits.

The committee's conclusions are based on scientific publications prior to 1995. Scientific publications between 1995 and 1997 were no reason for the committee to adjust her recommendations.

2 Physical and chemical properties

Due to differences in physical and chemical properties as well as in toxicity, the committee considers speciation of these agents expedient, and the following groups are distinguished: chromium metal dusts, chromium(II) compounds, soluble chromium(III) compounds, insoluble chromium(III) compounds, chromium(IV) compounds and chromium(VI) compounds.

3 Monitoring

A method to determine the atmospheric concentration as well as levels of different chromium compounds in biological media is described in the DECOS document on chromium published in 1985. For biological monitoring the committee recommends the use of chromium concentration in urine.

4 Current limit values

The current legally-binding occupational exposure limits (TWA - time weighted average) in the Netherlands are:

chromium metal dusts	0.5 mg/m^3 TWA - 8h
soluble chromium(VI)compounds	0.025 mg/m^3 TWA - 8h 0.05 mg/m^3 TWA - 15 min with a skin notation
chromium(III)compounds	0.5 mg/m^3 TWA - 8h 1.0 mg/m^3 TWA - 15 min
calcium-, strontium- en zinc-chromate	0.01 mg/m^3 TWA - 15 min
lead- en bariumchromate	0.025 mg/m^3 TWA - 15 min
combined chromium exposure	0.01 mg/m^3 TWA - 15 min

5 Effects

The target organs in occupational exposure to chromium and its compounds are the skin, mucous membranes of the upper respiratory tract, the kidneys, the lungs and the reproductive organs.

Chromium compounds may cause irritative lesions and allergic/eczematous lesions on the skin. Irritative lesions are predominantly caused by chromium(VI), and

less by chromium(III). Chromium(IV) compounds may induce ulceration and perforation of the nasal septum; it is estimated that levels of 0.1 mg CrO_3 per m^3 and above induce lesions.

Soluble chromium(VI) compounds may cause tubular lesions of the kidneys in humans. No nephrotoxic effect has been reported for chromium (III) compounds. There seem to be differences in the effects on the kidneys after short-term high dose and long-term low dose exposure. Studies on workers employed in a chromate and dichromate production plant showed that a chromiumconcentration of 15 µg per g creatinine in the urine may correspond to the threshold for effects on the tubular functions.

The non-carcinogenic effects in the lungs, caused by exposure to chromium are: pulmonary fibrosis, chronic bronchitis, emphysema, bronchial asthma and pneumoconiosis. In a long-term inhalation study on rats exposed to chromium dioxide (Cr(IV)) for two years (6 hours per day, 5 days per week) slight Type II pneumocyte hyperplasia was observed at 0.5 mg/m^3; this concentration was considered to be the lowest observed adverse effect level (LOAEL) for lung effects. For soluble chromium (III) compounds a minimal observed adverse effect level (MOAEL) for lung effects of 0.6 mg/m^3 was found in rabbits. Exposure to this concentration for 6 hours per day, 5 days per week, during 4 to 6 weeks resulted in functional and morphological changes in alveolar macrophages.

Few recent animal data are available on the carcinogenic effect of chromium on the lungs. In the two year study on rats exposed to chromium(IV) compounds mentioned above, some female rats developed cystic keratinized squamous cell carcinomas, but male rats did not. This kind of tumour is allegedly not relevant to man. From a recent review on carcinogenicity of chromium compounds in animals the committee concludes that there is limited evidence in experimental animals for carcinogenicity of soluble chromium(VI) compounds. On the other hand, there is sufficient evidence for the carcinogenicity of calcium-, zinc- and strontium-chromate. In a large retrospective cohort mortality study on male welders in nine European countries a statistical significant excess of mortality due to lung cancer was found, predominantly among welders of stainless-steel. Comparable results were obtained from cohort studies in two German chromate producing factories, in Japanese metal plating plants and among welders from 13 French factories. In recent reviews on epidemiological studies it was concluded that chromium(VI) compounds should be considered carcinogenic to humans. No evidence was found for carcinogenicity of chromium (III) compounds.

From mutagenicity and genotoxicity studies it was found that chromium(II) is non-genotoxic; chromium(III) in general does not induce DNA damage, gene mutation, sister chromatid exchange (SCE) or cell transformation in cultured animal

and human cells; chromium(VI) compounds of various solubility are consistently active in numerous genotoxic studies (DNA damage, gene mutation, SCE, chromosomal aberration, cell transformation, dominant lethal mutation).

The effects of chromium compounds on the liver and central or peripheral nervous system of experimental animals are ambiguous, just as human data on liver effects. There is no evidence that chromium(VI) is neurotoxic to humans.

Chromium(VI) was found to be toxic to the male reproductive system in rats. Sixty days after five intraperitoneal injections of 1 mg per kg bodyweight on consecutive days resulted in reduced relative testicular weights and atrophic seminiferous tubules.

Chromium(III) did not affect the male reproductive system in rats. Male welders with chromium concentrations in urine between 0.08 and 2.18 µg per g creatine did not show aberrations in the quality of semen and sexual hormones. No human data are available on the effect of chromium on female reproduction.

The WHO concluded that chromium(III) and chromium(VI) are teratogenic in experimental animals when injected parentally at high levels.

6 Recommended occupational exposure limit

Chromium metal dusts, chromium(II) compounds and water-insoluble chromium(III) compounds

The committee cannot recommend health-based occupational exposure limits (HBR-OEL) for these compounds due to lack of scientific data.

Water-soluble chromium(III) compounds

The committee recommends a health based occupational exposure limit for water-soluble chromium(III) compounds in the form of inhalable dust of 0.06 mg/m^3, to be interpreted as a time weighted average over 8 hours (TWA - 8 h). This HBR-OEL is derived from a MOAEL of 0.6 mg/m^3 for lung effects in a four to six weeks rabbit study. For both interspecies variations and extrapolation from a MOAEL to a NOAEL a factor of three, thus resulting in an overall safety factor of 10 was considered sufficient by the committee.

Chromium(IV) compounds

The committee recommends a health based occupational exposure limit for these compounds of 0.05 mg/m3 TWA - 8 h (as inhalable dust). The HBR-OEL is derived from a LOAEL of 0.5 mg/m3 for lung effects in a two year rat study. For both

interspecies variations and extrapolation from a LOAEL to a NOAEL a factor of three, thus resulting in an overall safety factor of 10 was considered sufficient by the committee.

Chromium(VI) compounds

The committee considers all chromium(VI) compounds to be carcinogenic in human. A genotoxic mode of action is assumed and the committee has no reason to deviate from the method of a linear exposure response relationships for these compounds.

The committee estimates that the additional cancer risk for chromium(VI) compounds amounts to:

- 4×10^{-3} for 40 years of occupational exposure to 2 $\mu g/m^3$ as inhalable dust.
- 4×10^{-5} for 40 years of occupational exposure to 0.02 $\mu g/m^3$ as inhalable dust.

This report contains some additional considerations of the committee about the present regulatory exposure limits on chromium metaldust and insoluble chromium(III)compounds.

Chapter 1

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if sufficient data are not available or if the toxic action cannot be evaluated using a threshold model. In the latter case an exposure-response relationship is recommended for use in regulatory standard setting.

In the next phase of the three-step procedure the Social and Economic Council advises the minister on the feasibility of using the health based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure the State Secretary of the Ministry of Social Affairs and Employment sets the official Occupational Exposure Limit.

1.2 Committee and procedures

The present document contains the assessment of DECOS, hereafter called the committee, of the health hazard of chromium and inorganic chromium compounds.

The members of the committee are listed in Annex B. The first draft of this report was prepared by dr AAE Wibowo, Coronel Laboratory, Academic Medical Centre, University of Amsterdam, by contract with the Ministry of Social Affairs and Employment.

In 1995 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

This document is a revised version of a report which contained an update of an earlier criteria document of the committee, titled 'Chromium and its compounds' (DECOS, 1985). Only data published after 1985 will be discussed.
In preparing this report the following reviews have been consulted.

- International Agency for Research on Cancer (IARC), monographs on the evaluation of carcinogenic risks to humans. Chromium, Nickel and Welding, IARC) Lyon-France, 1990:49, 49-256 (IARC90).
- World Health Organisation (WHO); International Programme on Chemical Safety (IPCS). Environmental health criteria 61. Chromium. WHO, Geneva, 1988 (WHO88).
- Wibowo AAE. Short evaluation on the carcinogenicity of potassium dichromate, sodium dichromate and ammonium dichromate. Report on behalf of the Directorate-General of Labour, 1993. Report no 93-05 Coronel Laboratorium, Amsterdam (Wib93).
- Langård S. Criteria document for Swedish occupational standards. Arbete och Hälsa 1993:5 (Lan93).
- Environmental Protection Agency. Health assessment document for chromium. Final report,1984. EPA-600/8-83-014F (EPA84).

Chapter 2

Summary of previous recommendations (1985)

In its 1985 report the committee concluded that the hazard of chromium compounds depends on the chemical speciation, and perfomed separate assessments for the following classes of compounds:

- chromium metal
- soluble chromium (VI)-compounds, including chromic acid, sodium-, potassium-, ammonium-, rubidium-(bi)chromate
- chromium (III) compounds, including chromium acetate, oxyde, phosphate and sulphate
- non soluble and/or moderate soluble chromium (VI) compounds particularly calcium, strontium, and zinc chromate
- non soluble and/or moderate soluble chromium (VI) compounds, particularly lead and barium chromate.

Chromium metal

Only very limited scientific data were available at that time. The committee concluded to retain the then existing OEL of 0.5 mg/m^3, TWA - 8 hour. There were no reasons to assume that this agent is carcinogenic.

Soluble chromium (VI) compounds

For chromic acid (CrO_3), irritation of the upper respiratory tract was thought to be of importance leading to the recommendation of a short-term occupational exposure limit. Another target organ for soluble chromium (VI) compounds is the kidney in which aberrations may occur after long-term exposure. The committee recommended HBR-OEL's of 0.025 mg/m^3, TWA - 8 hour, and 0.050 mg/m^3, TWA - 15 min for these compounds. A 'skin' notation was advised.

Given the existence of a biological monitoring method, the committee concluded that a chromium level in urine of 20 μg per g creatinine at the end of workday and workweek should serve as a warning signal for exposure to chromium.

Chromium (III) compounds

In 1985 only very limited animal data were available. Chromium (III) compounds were considered to be less hazardous than chromium (VI) compounds. In short-term exposure the lung was thought to be the target organ. The committee did not object to maintain the existing standard of 0.5 mg/m^3, TWA - 8 hour.

Chromium (VI) compounds: calcium, strontium, and zinc chromate

For these compounds the committee concluded that they are carcinogenic to humans. On the other hand, no dose-response relationship could be established. Quantitative extrapolation from either human or animal data was deemed not possible. The committee recommended to accept the standard advised by the OSHA of 0.01 mg/m^3 chromium (VI), TWA - 15 minutes.

Chromium (VI) compounds: lead and barium chromate

The evidence that these compounds are carcinogenic was not substantial and consistent at the time. The committee concluded that a HBR-OEL of 0.025 mg/m^3, TWA - 15 minutes was appropriate.

Combined exposure irrespective of speciation

For this particular case the committee recommended a health based occupational exposure limit of 0.01 mg/m^3 chromium, TWA - 15 minutes.

Chapter 3

Present guidelines and standards

The table presents occupational exposure limits (OELs) proposed or set in the Netherlands and elsewhere.

country	speciation	OEL (mg/m^3)	comments
Netherlands[a]	Cr metal	0.5	TWA - 8 hour
	soluble Cr(VI)-compounds	0.025	TWA - 8 hour
		0.05	TWA - 15 min
			skin notation
	Cr(III)-compounds	0.5	TWA - 8 hour
		1.0	TWA - 15 min
	Ca-, Sr-, Zn chromate	0.01	TWA - 15 min
	Pb, Ba chromate	0.025	TWA - 15 min
	Combined Cr exposure	0.01	TWA - 15 min
USA-ACGIH[b]	chromite ore processing	0.05	TWA - 8 hour
	(chromate), as Cr		carc., A1
	Cr metal	0.5	
	Cr(II)-compounds	0.5	TWA - 8 hour
	Cr(III)-compounds	0.5	TWA - 8 hour
	water soluble Cr(VI)-compounds	0.05	TWA - 8 hour
	certain water insoluble	0.05	TWA - 8 hour
	Cr(VI)-compounds		carc., A1
Germany[c]	Cr(III)-compounds	-	-
	Cr(VI)-compounds (with exception of insoluble compounds, e.g. lead chromate and barium chromate)	-	carc. group III A2
	chromylchloride	-	carc. group III A2
	chromcarbonyl	-	carc. group III B
Sweden[d]	chromates	0.02	TWA - 8 hour
			C and S notation*
	chromic acid	0.02	TWA - 8 hour
			C and S notation*
		0.06	TWA - short-term
	chromium and other inorganic compounds	0.5	TWA - 8 hour
United Kingdom[e]	chromium	0.5	TWA - 8 hour
	Cr(II)-compounds	0.5	TWA - 8 hour
	Cr(III)-compounds	0.5	TWA - 8 hour
	Cr(VI)-compounds	0.05	TWA - 8 hour

[a] These MAC values of chromium and its inorganic compounds are legally binding since 1994 (Directoraat-Generaal van de Arbeid: Nr. DGA/G/Tos/94/00981; Staatscourant no 245, december 1994). Moreover, some specific chromium compounds, i.e. chromium III chromate and chromium trioxide, are classified as carcinogenic substances according to governmental regulations (Staatsblad van Koninkrijk der Nederlanden, Jaargang 1994, no. 91).

[b] American Conference of Governmental Industrial Hygienists (1993). Threshold Limit Values.

[c] Deutsche Forschungsgemeinschaft. MAK- und BAT-Werte -Liste 1994.

[d] Swedish National Board of Occupational Safety and Health. Occupational Exposure Limit Values (1993).

[e] Health & Safety Executive. Occupational Exposure Limits 1993. The limit for Cr(VI) compounds is listed as confirmed Maximum Exposure Limit and refers to the total inhalable dust fraction.

* C means carcinogen, S means skin notation

Chapter 4

Chemical and physical characteristics

4.1 Chemical and physical properties

The IARC monograph (IARC90) listed the information presented in the table.

chemical name	atomic molecular weight (g/mol)	melting point (°C)	boiling point (°C)	physical description	solubility
metallic chromium (0)					
chromium	51.996	1900	2642	steel-grey, lustrous metal or powder	insoluble in water; soluble in dilute hydrochloric acid and sulfuric acid; insoluble in nitric acid or nitrohydrochloric acid
chromium(III)-compounds					
basis chromic sulfate	165.06	-	-	green powder	soluble in water (approximately 700 g/l at 35 °C)
chromic acetate (hydrate)	229.14 (247.15)	-	-	grey-green powder (blue-violet needles)	slightly soluble in water; insoluble in ethanol; soluble in cold water, acetone (2g/l at 15 °C) and methanol (45.4 g/l at 15 °C)
chromic chloride (hexahydrate)	158.36 (266.45)	1150 (83)	sublimes at 1300	violet crystalline scales	anhydrous form is insoluble in cold water, slightly soluble in hot water, but insoluble in ethanol, acetone, methanol and diethyl ether. The hydrated form is very soluble in water (585 g/l), soluble in ethanol, slightly soluble in acetone and insoluble in diethyl ether

chemical name	atomic/molecular weight	melting point (°C)	boiling point (°C)	typical physical description	solubility
chromium(III)-compounds					
chromic nitrate (7.5 hydrate)	238.03 (373.13)	- (100)	- decomposes	pale-green powder (brouwn crystals)	soluble in water. Both hydrated forms soluble in water; the nonahydrate is soluble in acids, alkali, ethanol and acetone
(nonahydrate)	(400.15)	(60)	decomposes at 100	(deep-violet crystals)	
chromic oxide	151.99	2435	4000	light to dark-green, fine crystals	insoluble in water, acids, alkali and ethanol
chromic phosphate (dihydrate)	147 (183.00)	>1800 °C	-	violet crystalline solid	insoluble in water. Hydrated form is slightly soluble in cold water; soluble in most acids and alkali but not in acetic acid
chromic sulphate	392.16	-	-	violet of red powder	insoluble in water; slightly soluble in ethanol; insoluble in acids
potassium chromic sulphate (dodecahydrate)	283.23 (499.39)	(89)	(400)	(violet ruby-red to black crystals)	hydrated form is 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(VI)-compounds					
ammonium chromate	152.07	180	-	yellow cicular crystals	soluble in water (405 g/l); insoluble in thanol, slightly soluble in ammonia, acotone and methanol
ammonium dichromate	252.06	170 (dec)	-	orange-red crystals	soluble in water (308 g/l at 15 °C; 890 g/l at 30 °C) and ethanol; insoluble in acetone
barium chromate	253.33	-	-	yellow chrystals	very slightly soluble in water (4.4 mg/l at 28 °C); soluble in mineral acids
basic lead chromate	546.37	-	-	red crystalline powder	insoluble in water; soluble in acids and alkali
calcium chromate (dihydrate)	156.09 (192.10)	(200)	-	yellow crystalline powder	slightly soluble in water and ethanol; soluble in acids. Hydrated form is soluble in water (163 g/l at 20 °C; 182 g/l at 45 °C), acids and ethanol
chromium trioxide	99.99	196	decomposes at 250	dark-red crystals, flakes or granular powder	soluble in water (625 g/l at 20 °C; 674.5 g/l at 100 °C), ethanol, diethyl ether and sulfuric and nitric acids
chromyl chloride	154.90	-96.5	117	dark-red volatile liquid	decomposes in water and ethanol; soluble in ether, acetic acid, carbon tetrachloride, carbon disulphide, benzene, nitrobenzene, chloroform and phosphorous oxychloride
lead chromate	323.18	844	decomposes	yelow to orange-yellow crystalline powder	very slightly soluble in water (0.58 mg/l at 25 °C), soluble in most acids and alkali but not in acetic acid or ammonia

chemical name	atomic/molecular weight	melting point (°C)	boiling point (°C)	typical physical description	solubility
chromium-(VI)-compounds					
nickel chromate	174.71	-	-	-	insoluble in water; soluble in nitric acid and hydrogen peroxide
potassium chromate	194.20	968.3	decomposes	lemon-yellow crystals	soluble in water (629 g/l at 20 °C; 792 g/l at 100 °C), insoluble in ethanol
potassium dichromate	294.19	398	decomposes at 500	bright orange-red crystals	soluble in water (49 g/l at 0 °C; 1020 g/l at 100 °C), insoluble in ethanol
sodium chromate	161.97	792	decomposes	yellow crystals	soluble in water (873 g/l at 30 °C) and methanol (3.44 g/l at 25 °C), slightly soluble in ethanol
sodium dichromate (dihydrate)	262.00 (298.00)	356.7	decomposes at 400	reddish to bright-orange crystals	soluble in water (2380 g/l at 0 °C; 5080 g/l at 80 °C) and methanol (513.2 g/l at 19.4 °C), insoluble in ethanol
strontium chromate	203.61	decompose[d]	-	yellow crystalline powder	slightly soluble in water (1.2 g/l at 15 °C; 30 g/l at 100 °C), soluble in hydrochloric, nitric and acetic acids and ammonium salts
zinc chromate	181.37	-	-	lemon-yellow crystals	insoluble in cold water; decomposes in hot water; soluble in acids and liquid ammonia
zinc chromate hydroxide	280.74	-	-	fine yellow powder	slightly soluble in water; soluble in dilute acids, including acetic acid
other chromium compounds					
chromium carbonyl	220.06	decomposes at 110	explodes at 210	colourless crystals or white solid	insoluble in water; slightly soluble in carbon tetrachloride and iodoform; insoluble in ethanol, diethylether and acetic acid
chromium(II) chloride	122.90	824	-	white lustrous needles or fused fibrous mass	soluble in water; insoluble in ethanol and diethyl ether
chromium dioxide	83.99	300	-	brown-black crystalline powder	insoluble in water; soluble in nitric acid

4.2 Monitoring

A method to determine the atmospheric concentration as well as levels of different chromium compounds in biological media is described in the previous DECOS document on chromium. For biological monitoring the committee recommends the use of chromium concentration in urine.

Chapter 5

Effects

5.1 Summary of the effects reported in the previous document (WGD, 1985)

Chromium(III) and chromium(VI) compounds were found to induce local effects on the skin in the form of ulcerations, ortho-ergic and allergic dermatitis.

Zinc chromate(VI) was found to cause ulceration of the nasal septum; the no-observed adverse effect level was estimated at 30 μg/m^3 (as Cr).

Workers in the ferrochroom and ferrosilicium industry who were exposed to 20-190 μg/m^3 total chromium (or 10-160 μg/m^3 insoluble Cr compounds) for long duration, were reported to have aberrations of the lung functions and chronic obstructive lung disease.

Stainless-steel welders with chromium in urine concentrations higher than 13 μg chromium per g creatinine showed effects on the tubular functions of the kidney. Reports on effects on the liver could not be substantiated.

Chromium(VI) compounds were found to be mutagenic, contrary to chromium(III) compounds. Experimental animal studies showed that moderate soluble and insoluble chromium compounds(VI) were carcinogenic agents, although no dose-response relationship could be established. Epidemiological studies also reported higher risks for lung cancer, especially in the chromium chemical industry and to a lesser degree in the metallurgic industry and in stainless-steel welders. A relationship was found between intensity or duration of exposure and increased risk of lung cancer. From these data, the most convincing evidence for carcinogenicity was found for the

moderate soluble chromium(VI) compounds. Carcinogenicity of chromium(III) compounds could not be excluded.

In its earlier report, the committee concluded that people with diminished lung function should be classified as groups at risk with respect to exposure to chromium and its compounds.

5.2 Effects reported in recent studies

The target organs in occupational exposure to chromium and its compounds appear to be: the skin, the mucous membranes of the upper respiratory tract, the kidneys, the lungs and the reproductive organs.

5.2.1 Effects on the skin

Chromium is known to induce two different effects on the skin: irritative lesions and allergic/eczematous lesions.

Chromium(VI) compounds can induce ulceration of the skin, developed from painful crevices, or dryness of the skin to small ulcers, looking like pigeon eyes (Bar92). Whether exposure to chromium(III) induces the same effects is questionable. Von Burg and Liu (Bur93) reported that chromium(VI) as well as chromium(III) compounds are strong skin irritants. On the other hand Baruthio (Bar92) stated that trivalent chromium did not seem to have any effect on the skin. Gad (Gad89) reported minimal effects after contact with chromium(III) as well.

Chromium contact allergies have been observed among workers in numerous industrial activities: electrolyte chromium-plating, leather tanning, manufacturing of pigments and paints, electroforming, offset printing, dry cleaning, mordanting of textiles, ship building and work involving lime. Metallic chromium does not seem to be to allergenic. Trivalent chromium was found allergenic, but to a much lesser degree than the hexavalent form (Bar92). After an initial sensitization to Cr(VI) the subjects studied also reacted to Cr(III), but to a lesser degree.

Hjerpe (Hje86) reported nine cases of chromate dermatitis in an assembly department at a Volvo plant in Sweden since 1976. Yellow chromation was used for corrosion protection in zinc-plated components. About 150 manual assembly workers were diagnosed as having hand eczema and were positive in the patch test with chromate.

Baruthio (Bar92) suggested the following pathogenesis: Cr(III) salts have the property of binding to proteins of the skin after penetrating via the sweat glands and forming stable complexes, contrary to Cr(VI) compounds. Cr(VI) crosses the skin easily, diffuses through the organism and crosses cell membranes. The intracellular

thio-amino acids reduce Cr(VI) to Cr(III), which forms allergenic protein complexes. Sensitization to the trivalent compounds is rare, and only observed with exposure to high concentrations. According to Gochfeld (Goc91) irritation of the skin by chromium increases the likelihood of sensitization. Chromium sensitivity is a so called type IV delayed hypersensitivity. The reaction is stimulated by haptens, which have a molecular weight of usually less than 500 and which combine with proteins in the skin to stimulate the development of the sensitized lymphocytes.

Recently Wass and Wahlberg (Was91) published the results of a study concerning the development of a simple procedure for the determination of leachable Cr(VI) that could be used in industrial applications to check the leakage of Cr from the chromated products and to establish a 'threshold limit value' for such products. Occlusive tests were performed in chromate-sensitive patients using chromate products. Discs representing a release of 0.6 $\mu g/cm^2$ or more elicited positive results in all patients tested. The authors proposed that the mean release of Cr(VI) from chromated parts should not exceed 300 $\mu g/m^2$.

5.2.2 *Effects on the mucous membranes of the upper respiratory tract*

Effects on the mucous membranes of the upper respiratory tract are still frequently observed after chromium exposure. The hexavalent compounds of chromium are found to induce immediate ulceration and then perforation of the nasal septum. The nasal septum appears to be particularly sensitive to the effects of chromium given the very low vascularization of its cartilaginous structure and the causticity of Cr(VI) compounds. Atmospheric levels of chromiumtrioxide of approximately 100 $\mu g/m^3$ were sufficient to induce lesions (Bar92). There were no indications that chromium(III) induced effects on the mucous membrane.

The following upper respiratory tract disorders were also observed:

- inflammation and ulceration of the mucous membranes of the lips, mouth and pharynx
- discoloration of the teeth, a yellowish gingival line
- papillomas on the soft palate.

5.2.3 *Effects on the kidneys*

Trivalent chromium was found to have no nephrotoxic effect. On the other hand, tubular lesions caused by potassium bichromate (Cr VI) were responsible for urinary release of intracellular enzymes, such as ß-glucuronidase, maltase and alkaline phosphatase, and for alterations in the sodium and potassium exchanges (Bar92).

Verschoor *et al.* (Ver88) performed a cross-sectional study of the renal function of chrome-plating workers and welders in the Netherlands. They determined the level of chromium in urine (CrU), chromium clearance and sensitive renal function parameters (creatinine in urine and serum, urea in serum, total protein in urine, albumin in urine, $ß_2$-microglobulin in serum and urine, retinol-binding protein in urine, immunoglobulin in serum and urine, N-acetyl-ß-D-glucosaminidase in urine, ß-galactosidase in urine and lysozyme in urine). The glomerular function parameters of chrome-plating workers (CrU 1-34 µg per g creat.*) and welders (CrU 1-62 µg per g creat.*) appeared to differ from those of boilermakers (CrU 0.3-1.5 µg per g creat.*) and a control group (CrU 0.1-2 µg/g creat.*). This study did not find any aberrations in the tubular function of the kidneys. No environmental exposure levels were determined in this study.

Franchini and Mutti (Fra88) performed a cross-sectional study on 43 male workers employed in a chromate and dichromate production plant in Italy for seven years. Their mean age was 41 years. A control group of 30 subjects with mean age of 39 years was also examined. Chromium concentrations in the plant were usually below 50 µg/m^3 with peaks as high as 1000 µg/m^3. The median chromium levels in the urine of exposed workers was 26 µg per g creat. and about 40% of the concentrations exceeded 30 µg per g.creat. Comparison between the exposed and control groups showed that there was no difference in the albumin levels in urine, but some divergence existed in the retinol binding protein levels. 9 out of 43 samples from the exposed subjects exceeded the upper limit of controls. Further analysis revealed no difference between the controls and those workers with a CrU lower than 15 µg per g creatinine, showing that this level may correspond to the threshold for effects on the tubular functions.

Vyskocil *et al.* (Vys92) recently reported a lack of renal changes in stainless steel welders exposed to chromium and nickel. Biochemical markers were examined in 52 male welders (MMA welding**) and 51 control subjects. The chromium concentration in workroom air as determined by personal air sampling had a geometric mean of 64 µg/m^3 (range 7-161). The chromium levels in urine of the exposed group had a geometric mean of 17.8 µg per g creat. and those of the control group 1.1 µg per g creat. No consistent clinically significant renal impairment was revealed among the welders, however ß2-microglobulin in urine was slightly increased in those welders with a urinary chromium concentration higher than 30 µg per g. creat. ($p < 0.05$). The MMA-welding of stainless steel carried out by these workers is a technique that generated relatively high fume concentrations of soluble chromium. Seventy to ninety percent of chromium in this type of welding fume is present as soluble Cr(VI).

* CrU: chromium concentration in urine; usually per unit mass of creatinine.

** MMA= manual metal are welding

In a recently published review, Wedeen and Qian (Wed91) pointed at the difference in effects on the kidneys between short-term and long-term exposure to chromium. They reported that in contrast to the paucity of evidence on chromium-induced chronic renal disease, massive exposure to hexavalent chromium consistently causes acute tubular necrosis, clinically evident as a marked reduction in urine flow rate, if the patient survives for more than a few hours. Acute renal failure from accidental exposure to Cr(VI) in the workplace is, however, quite rare.

The committee concludes that evidence that long-term low-dose exposure to chromium has adverse effects on the kidneys arises from the finding of low molecular weight proteinuria in chromium workers. Excessive urinary excretion of $ß_2$-microglobulin, a specific proximal tubule brush border protein and an extra-renal enzyme, retinol-binding protein, are reported among some chrome platers and welders.

Standeven and Wetherhahn (Sta91) studied the possible role of glutathione in chromium(VI) toxicity in rats. The acute nephrotoxicity of 30 mg/kg sodium dichromate was potentiated by depletion of renal glutathione. However, depletion of glutathione did not seem to affect the incidence of glucosuria, haematuria or lysozymuria over a range of Cr(VI) doses. Nor did it affect renal uptake of chromium. In their experiment, the estimated NOAEL for acute effects on the kidneys after intraperitoneal injection was 10 mg/kg body weight (as Cr(VI)) This level was obtained irrespective of whether the animals were glutathione depleted or not.

5.2.4 *Effects on the lungs*

The committee makes a distinction between non-carcinogenic and carcinogenic effects on the lungs.

Non-carcinogenic effects on the lungs

The following effects on the lungs have been reported in workers exposed to chromium: pulmonary fibrosis, chronic bronchitis and emphysema, bronchial asthma and pneumoconiosis (Bar92). Pneumoconiosis has been reported in a number of cases in the pigment industry: among chromite workers, in chromates and ferrochromates industries and in the metallurgy. A difficulty in using these data for risk assessment is the simultaneous exposure to various other toxic agents, and the lack of environmental monitoring in most of the cases. Recently animal studies have been performed to investigate whether there are interactions between chromium and other elements.

Animal studies

In 1989, Lee *et al.* (Lee89) reported a study on rats exposed to chromium dioxide (Cr(IV)) dust at concentrations of 0, 0.5 (stabilized and unstabilized, resp.) and 25 mg/m^3 (stabilized) for 6 hours per day, 5 days per week for two years. The dust had an aerodynamic diameter of about 2.7 μm. No exposure related pathological changes were observed other than lung lesions. There were no significant differences in pulmonary response between unstabilized and stabilized CrO_2 at the 0.5 mg/m^3 exposure level. The lungs showed minute dust deposition in the alveoli, but maintained an intact general architecture. The only changes were a slight socalled Type II pneumocytes hyperplasia, which is a non-specific reparative response to damaged Type I pneumocytes. At 25 mg/m^3, dust deposition was confined to the alveoli in the alveolar duct region. Alveolar walls enclosing dust-laden macrophage aggregates were thickened with hyperplastic Type II pneumocytes and slight collagenized fibrosis. The lungs showed minute fibrotic pleuritis. These lesions occurred predominantly in female rats. From this study it can be concluded that a level of 0.5 mg/m^3 dust is the LOAEL for CrO_2 exposure in rats. The critical organ is the lung, although the evidence is limited.

Johansson *et al.* (Joh86a,b) studied the effects of subacute exposure to chromium(III) and chromium(VI) compounds on the alveolar macrophages of rabbits. The animals were exposed either to 0.9 mg/m^3 Cr(VI) or 0.6 mg/m^3 Cr(III) for 6 hours per day, 5 days per week for 4-6 weeks. In the latter case chromium nitrate was used, which is a soluble Cr(III) compound. The mass median aerodynamic diameter of the aerosols was 1 μm. Macroscopically the controls as well as the exposed animals had all normal lungs. The number of macrophages washed from the lungs was significantly increased in rabbits exposed to Cr(VI). Both Cr(III) and Cr(VI) produced morphological changes in the alveolar macrophages. Although the concentration of Cr(III) was lower than Cr(VI), the former compound produced more conspicuous changes. Most cells had very large lysosomes which contained membranous fragments of different sizes surrounded by a more homogenous matrix. Laminated inclusions similar to the lamellar bodies in the Type II cells increased in number as did the percentage of cells with a smooth cell surface. Only Cr(III) produced functional changes of the macrophages. This study shows that a level of 0.6 mg/m^3 is probably the MOAEL for soluble Cr(III) compounds.

In 1987, Johansson *et al* (Joh87) repeated their study. They exposed rabbits to mean chromium (Cr(III)) concentrations of 0.6 and 2.3 mg/m^3 for about 4 months, 5 days per week, during 6 hours per day. Light microscopic examination of the lungs revealed that both chromium exposures induced a nodular intra-alveolar accumulation of enlarged macrophages with granular, eosinophilic cytoplasm. Some macrophages

were multinucleated and some showed advanced degenerative changes with disruption of cellular borders and nuclear pyknosis. The changes were most prominent in rabbits exposed to the high concentration and were in some areas associated with a mild interstitial infiltration of lymphocytes, neutrophils and eosinophils.

Johansson *et al.* (Joh92a) recently reported the effects of combined exposure to Cr(III) and a soluble cobalt compound on the lungs. Eight rabbits were exposed to 0.7 mg/m^3 cobalt and 1.2 mg/m^3 Cr(III), eight to 0.6 mg/m^3 cobalt only and another eight animals to filtered air for 4 months, 5 days per week during 6 hours per day. All rabbits in the cobalt+chromium group and the cobalt-only group showed nodular aggregation of alveolar Type II cells. In lavage fluid the numbers of macrophages and the percentage of these cells with smooth surface and intracellular surfactant-like inclusions were more increased in the cobalt+chromium group than in the cobalt-only group, as were oxidative metabolic and phagocytic activities of the macrophages. These results imply that it is important to investigate effects of combined exposure of cobalt and chromium in the occupational environment. The experiment indicates, according to the committee, that these two metals act synergistically.

The effect of combined exposure of nickel, cobalt and chromium was reported by Johansson *et al.* (Joh92b). They found that the combined exposure induced more pronounced lung lesions than exposures for each of the metals alone. Chromium potentiated the effects of nickel and cobalt on the Type II cells, which led to secondary effects on the macrophages.

Hilaski *et al.* (Hil92) studied the acute toxicity of chromium in the form of Whetlerite dust in rats. Whetlerite dust is a granular, activated carbon impregnated with compounds of copper, silver and chromium to enhance its ability to absorb and destroy toxic gasses. This dust contains both trivalent and hexavalent chromium. Two groups, both 6 female and 6 male rats, were exposed to base carbon dust and three groups, all 6 female and 6 male rats, were exposed to Whetlerite dust. The exposure was by the nose-only method for a 4-hours period. The exposure concentration was the same for both dusts, 5000 mg/m^3, and the mass median aerodynamic diameter was 3 μm for Whetlerite dust and 4 μm for base carbon dust. Necropsies were performed at 14, 28 and 180 days post exposure. The kidneys, liver and lungs were collected for determination of copper and chromium content. The animals exposed to the Whetlerite dust showed no gross pathological changes. Organ chromium concentrations were below the detection limits of 0.5 μg chromium per g dry tissue in both exposure groups. The auteurs concluded that neither Whetlerite dust nor base carbon dust demonstrated acute inhalation toxicity. The committee agreed with this conclusion.

Human studies

Rastogi *et al.* (Ras91) performed a cross-sectional study of a group of 57 manual welders with ages ranging from 13-60 years in India. The average exposure period was 12.4 years (1-35 years). Comparison was made with a reference group of 131 subjects. The welders showed a significantly higher prevalence of respiratory impairment (28%) than the controls (6.1%). Air concentrations during the welding process varied from: zinc 0.3-1.2 $\mu g/m^3$, copper 0.03-0.89 $\mu g/m^3$, chromium 0.002-0.015 $\mu g/m^3$, nickel 0.002-0.018 $\mu g/m^3$, lead 0.008-0.014 $\mu g/m^3$, and manganese 0.002-0.018 $\mu g/m^3$. It is difficult to determine from this study whether the respiratory impairment was solely or primarily due to exposure to chromium. The results of the pulmonary function tests showed predominantly a restrictive type of pulmonary impairment followed by a mixed ventilatory defect among the welders. A significant correlation was found between the prevalence of respiratory abnormalities and the lenght of exposure.

Srivastava *et al.* (Sri92) studied 78 workers, occupationally exposed to fume and dust in the glass industry in India, for respiratory symptoms. These workers were exposed to products of coal furnaces in which various metal pigments were applied on the hot molten glass to give colour and lustre. Compounds of chromium, copper, manganese and cobalt were used. Other metals, such as nickel and lead were present as impurities. Levels of chromium and nickel in blood were determined, but no environmental monitoring was performed. A statistical significant association was observed between respiratory symptoms and elevated blood nickel and chromium levels. An interaction between nickel and chromium was found in relation to the prevalence of respiratory symptoms. It is difficult to interpret the results of this study. It is known that chromium in blood is a less reliable indicator of exposure than chromium in urine. Furthermore, by determining chromium in blood by atomic absorption spectrometry the speciation is not known.

Carcinogenic effects on the lungs

Animal data

Very few animal data on carcinogenic effects on the lungs have been published. In this respect the situation did not change since the publication of the earlier document of the committee, in which no animal studies on inhalatory exposure to Cr(VI) or Cr(III) compounds were mentioned.

In 1986, Glaser and colleagues (Gla86) reported an inhalation study on male Wistar rats which were continuously exposed to submicron aerosols of sodium dichromate, Cr (VI), and to a pyrolized Cr(VI)/Cr(III) (3:2) oxide mixture. After 18

months of exposure the rats were held under conventional conditions for a further year. The experimental groups consisted of 20 rats and the control group of 40 rats. More than 90% of the rats in each group survived for 2 years.

The concentrations of sodium dichromate equalled 25, 50 and 100 μg chromium/m^3. At the end of the study the mortality in the experimental group was 35%, 45% and 25%, respectively. These values were not significantly different from that of the controls (42.5%). In all exposed rats, no significant effects were found neither clinically nor from hematological and clinical chemical analyses. Three primary lung tumours (2 adenomas and 1 adenocarcinoma) and 1 malignant tumour of the pharynx were found at the highest level of exposure. No primary lung tumours were found in the lower exposure levels and the control group.

One group of rats was exposed to a chromium oxide mixture with a chromium concentration of 100 μg/m^3. The mortality rate at the end of the study was 50%, which was not significantly different from that of the control group. In this group, however, white and red blood cell counts and serum cholesterol were elevated and serum total immunoglobulin levels were decreased at different stages of the study; also a few local lung effects were observed. One primary adenoma of the lung was found in this group. The incidence of treatment-related tumours at other sites was not increased. However, the Working Group of the IARC commented that the number of animals in this study was to small for the results to be conclusive (IARC90).

Also in 1986, Adachi *et al.* (Ada86) reported on an experiment on a group of 50 female ICR/JcI mice which was exposed by inhalation to chromium trioxide mist (Cr VI) (particle size, 84.5% greater than 5 μm) at a chromium concentration of 3.63 mg/m^3 for 30 min per day, 2 days per week for up to 12 months. Mice surviving at that time were maintained for a further six months; two groups of ten mice were killed at 12 and 18 months and served as controls. A single lung adenoma was reported in 1/15 mice that died or were killed between six and nine months. Lung adenomas occurred in 3/14 mice that died between 10 and 14 months, and 1/19 adenoma and 2/19 adenocarcinomas in mice that died at 15 - 18 months. In the control group, no lung tumour was reported in 10 mice killed at 12 months, but 2/10 adenomas occurred in those killed at 18 months. The authors observed nasal perforations in six mice exposed for more than ten months and time-related inflammatory changes, including squamous metaplasia, in the trachea and bronchus of exposed mice. It should be noted that the duration of exposure was rather short for a carcinogenicity study and mice of only one sex (female) was used. The committee considers the results to be inconclusive, but does not interpret the outcome as indicating the effects of chromium exposure as non-carcinogenic.

In a consecutive study by the same research group (Ada87), 43 female C57B1 mice were exposed to chromium trioxide mist (particle size: 85% greater than 5 μm)

generated by a miniaturized electroplating system, during 120 min twice a week for 12 months. The chromium concentration was 1.81 mg/m^3. At the end of the 12 months study period 23 mice were killed. The remaining 20 were killed six months later. Nasal perforation was seen in 3/23 and 3/20 mice killed at 12 and 18 months, respectively; 0/23 and 6/20 nasal papillomas occurred in these groups. A single lung adenoma was reported in the group killed at 18 months. No nasal inflammatory change or lung tumour was seen in a group of 20 untreated control mice. The committee considers the results of this experiment also inconclusive with respect to the nose and lung carcinogenicity of chromium(VI).

Langård (Lan88) has summarised the experimental data on the carcinogenicity of chromium compounds in animals. Surgical implantation of potassium dichromate or sodium dichromate in the left bronchiolus of the rat lung did not increase the incidence rate of lung tumours, but implantation of calcium chromate and zinc potassium chromate did. In an experiment in which rabbits were exposed to mixed chromate dust, potassium dichromate, sodium chromate or pulverized residue dust by inhalation for 4 days per week during 50 months, no increase in tumour rate was found compared to controls.

In 1989, Lee *et al.* (Lee89) reported a study with rats exposed to chromium dioxide (Cr (IV)) dust at concentrations of 0, 0.5 (stabilized and unstabilized, resp.) and 25 mg/m^3 (stabilized) for 6 hours per day, 5 days per week for two years. The dust had an aerodynamic diameter of about 2.7 μm. Of 108 female rats, six developed keratin cysts and two had cystic keratinizing squamous cell carcinoma at 25 mg/m^3. None of the 106 male rats had either a keratin cyst or a carcinoma. This kind of tumour has been reported to be induced in rats by the inhalation of high concentrations of relatively inert materials. They are of benign nature, without invasions or metastases and are different from the type of spontaneous lung tumours generally seen in man or animals. The relevance of this type of lung tumour to man appears to be questionable, especially since no explanation can be forwarded on the sex differences in the induction of tumours. More studies in this case are needed.

Based on an analysis of results from experiments with other exposure routes than inhalation the IARC (IAR90) came to the following conclusions: There is *sufficient evidence* in experimental animals for the carcinogenicity of calcium chromate, zinc chromate, strontium chromate and lead chromate. There is *limited evidence* in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate (soluble chromium(VI) compounds). They used the following arguments. Chromium trioxide has been tested as a mist by inhalation at two dose levels in mice and as a solid by intrabronchial surgical implantation in three studies in rats. In mice, a non-significant number of lung adenocarcinomas was observed at the higher chromium concentration (1810 μg/m^3) and of nasal papillomas at the lower

dose; perforation of the nasal septum was observed at both dose levels. A few lung tumours were seen in two of six studies by intrabronchial administration in rats. Sodium dichromate has been tested in rats by inhalation, and after intratracheal, intrabronchial, intrapleural and intramuscular administration. Lung tumours, benign and malignant, were observed in inhalation studies and after intratracheal administration. Two lung adenomas and one lung adenocarcinoma were induced at the highest dose of three chromium concentrations (25, 50 and 100 $\mu g/m^3$) in inhalation experiments. No increase in the occurrence of local tumours was seen after intrabronchial, intrapleural or intramuscular administration.

There is inadequate evidence in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium(III) compounds.

Human data

In the committee's previous document an extensive assessment was made of the induction of lung cancer in workers occupationally exposed to chromium. Recently Langård (Lan93) reviewed epidemiological studies on respiratory cancer in the chromate manufacturing industry. Table 1 presents a summary of this review.

Worth to be mentioned is the retrospective cohort study performed by Langård and Vigander (Lan83). The prime objective of this study was to re-evaluate the incidence of lung cancer in a working population studied previously. In the previous investigation, the study population was followed from 1948, when chromium pigment production was started, up to December 1972. Three cases of lung cancer were observed in the 24 workers, out of the total number of 133, who had worked in the plant for over three years by the end of 1972. Three years later the same population was updated. No new cases of lung cancer were observed in these three years. The expected numbers of tumours of the respiratory organs were calculated by using the age-specific incidence rates for lung cancer in the whole Norwegian male population for the period 1955 - 1976. The production process in the plant had been altered considerably since the initial study was carried out. Lead chromate was no longer produced since 1956. The dust concentration had been reduced since 1973. The level of zinc chromate dust in this plant had been monitored at regular intervals, and few measurements had exceeded a chromium concentration of 50 $\mu g/m^3$. Most of the routine measurements during the period 1975 - 1980 showed dust concentrations with chromium concentrations between 10 and 30 $\mu g/m^3$. The whole group of workers was followed up to the end of 1980. By the end of 1980, the following malignant tumours had occurred among the 133 workers: lung (7), pancreas (1), stomach (1), large intestine (2), prostate (1) and nasal cavity (1).

Table 1 Review of epidemiological studies on respiratory cancer in chromate manufacturing workers as reported by Langård (1993).

study population	reference population	site	number of cases	estimated relative risk	estimated absolute risk	exposure	ref.
six chromate plants; active employees; 4-17 years before 1948	cancer mortality in an refining company, 1933-1938	bronchial and lung	32	26			Mac48
seven US chromate factories; active workers 1940-1948 included; 5522 person years	US male white black	lung	 10 16	 14.3[a] 80.0			Gaf53
US chromate producing plant; workers employed one or more years 1931-37; all jobs related to exposure to soluble and insoluble chromium	no separate reference group	lung	41	crude rate $37x10^{-4}$	<15 years observation; $9.7x10^{-4}$ to a high of $55x10^{-4}$ after 36 years observation		Lan75
a cohort of 133 of zinc chromate workers in Norway	incidence of cancer in Norway 1953-80	lung	6	44	$150x10^{-4a}$	exposure to 0.01-1.35 mg/m^3 of zinc chromate	Lan83
new Jersey zinc and lead chromate workers employed more than three months between 1940-1969; 1296 white and 650 non-white subjects	standard death rates among US males	lung >3 months employment >10 years employment	 16 9.3	 1.4 ns 1.7[a]		exposure estimated from below 0.1 mg Cr/m^3 to above 2.0 mg/m^3; no specification	She82
UK chromium platers first employed between 1946 and 1975	Compared with mortality rates in England and Wales	Lung males Lung females Nose cavities Larynx (m) (f)	63 6 (2) 3 0	1.6[a] 1.2 ns (10)[a] 3.0 ns -		A few high air concentrations measured before 1973; after 1973 generally less than 50 µg Cr/m^3	Sor87
Same population as Langård et al (1980); also expansion of population to include entries 1960-65; 1235 workers	(A) General population; (B) internal reference with non exposed; (C) local population lung cancer	Lung (ferrochromium workers)	10	A 1.5 ns B 3.0 C 2.6	$9.5x10^{-4}$		Lan89

[a] Significant at 95% level; ns = Non significant

Four new cases of lung cancer had occurred since the initial study was carried out. Three of the four new cases of lung cancer occurred in the above mentioned group of 24 workers who had been employed for more than three years before 1973. The expected number of tumours was 0.135, while the *observed* number of cases was 6. This gave an O/E (Observed/Expected) ratio of 44. The total number of man-years-at-risk in this sub-cohort was 391. It should be noted that five of the six patients smoked. Only one had been exposed to chromates other than zinc chromate.

Hayes *et al.* (Hay89) studied the mortality among 1879 male workers employed in a Baltimore chromium pigment factory; they were followed from 1940 up to 1982. The vital status of 1737 (92%) of the eligible cohort members was determined. For all malignant neoplasms, 101 deaths were observed while 108.8 were expected (US national rates), SMR* = 93. For the entire study group, no significant excess was observed for respiratory cancer (SMR for lung cancer was 116 with a 95% confidence interval of 83 - 158), nor for cancer at other sites. However, the total number of years of employment in the factory and the total number of years of exposure to chromate dusts were both statistical significantly ($p < 0.05$, for trend) associated with an increased risk of lung cancer. The excess risk of lung cancer was associated with duration of exposure to chromate dusts. This was, however, only clearly apparent for subjects followed for 30 years or more after initial employment. For this group, the SMRs were 81, 139, 201 and 321 for the subjects with 0 years, less than 1 year, 1 - 9 years, and 10+ years of exposure to chromate dusts ($p < 0.01$, for trend), respectively. The risk of digestive cancer was only weakly associated with exposure to chromate dusts. Although detailed environmental data were not available, the ratio of lead to zinc chromate concentrations in the study plant was reported to be approximately nine to one. The smoking habits of the cohort were not taken into consideration in this study.

Korallus *et al.* (Kor93) studied the mortality of 1417 workers who had been employed for at least one year between 1948 and 1988 (a total of 25982.7 man-years) in two German chromate producing factories in the North Rhein Westphalia region. The main objective of the study was to establish whether the change-over to a production process using lime-free conversion of chromite ore, thus eliminating the formation of calcium chromate, had resulted in the reduction of lung cancer among the workers (the change was effectuated in 1958 in one and in 1964 in the other factory). In the earlier period, the exposure was characterized as 'high'; between 1977 to 1987 the mean annual chromium concentrations were between 12 and 73 $\mu g/m^3$. The results showed that in a group of 739 workers exposed before the process change, the SMR for lung cancer was 2.27 (95% CL 1.78-2.85). On the other hand, the SMR for lung

* SMR - standardized mortality ratio

cancer of the 678 workers exposed after the process change-over, was 126 (95% confidence interval 58-238). Confounding factors in this study were: smoking which was more common in the industrial cohorts than in the general population, additional exposure to asbestos, a short latency period.

In 1990, Moulin *et al.* (Mou90) reported a mortality study with 2269 male workers of a plant producing ferrochromium and stainless steel in France. Their vital status was recorded between 1952 and 1982, and smoking habits of 67% of cohort members were registered. The cohorts were divided into two groups based on administrative data: the exposed (N = 1717) and the unexposed (N = 552) groups. There were no levels of exposure reported in this paper. It was surmised that the 'exposed' workers were exposed to chromium, nickel and polycyclic aromatic hydrocarbons (PAH). Among the exposed group, a significant excess of lung cancer mortality was observed (SMR 204, 95% CI* 102-364), which was not found in the unexposed group (SMR 32, 95% CI 1-177). A nested case-control analysis performed on the cohort showed that the excess of mortality due to lung cancer was associated with former PAH exposures in the ferrochromium production workshops rather than with exposures in the stainless steel manufacturing areas.

In 1991, Simonato *et al.* (Sim91) published a report on a retrospective cohort mortality study which was the result of an extensive co-operation between the IARC, WHO Europe and the Danish Welding Institute. It is a multicentre cohort study of 11092 male welders from 135 companies located in nine European countries with a total of 164 077 person-years. The aim was to investigate the relation of potential cancer risk, lung cancer in particular, to occupational exposure. The observation period and the criteria for inclusion of welders varied from country to country. Follow-up was successful for 96.9% of the cohort. The observed numbers of deaths were compared with expected numbers, calculated from national reference rates. Mortality and cancer incidence ratios were analyzed by disease category, time since first exposure, duration of employment and estimated cumulative exposure to total fumes, chromium, Cr(VI) and nickel. Overall, a statistical significant excess for mortality due to lung cancer was reported (116 observed v. 86.81 expected deaths, SMR = 134; 95% CI: 110-160). An increase with time since first exposure was present for both mild steel and stainless steel welders, which was more noticeable for the subcohort of predominantly stainless steel welders. On the other hand no clear association was apparent between mortality from lung cancer and estimated duration of cumulative dose of nickel or chromium. The confounding effect of smoking habits had not been taken into account. Also a statistically significant excess of bladder cancer was observed (SMR=191; 95% CI: 107-315). However, no association was found with time since first exposure, nor with

* CI - confidence interval

duration of employment. These data suggest a possible role of occupational exposure to stainless steel welding fumes in the occurrence of lung cancer mortality.

Takahashi and Okubo (Tak90) performed a prospective cohort mortality study of workers employed in 415 small-scale chromeplating plants in Japan between 1970 and 1976. A group of 1193 male metal platers was identified in 1976 and divided into a chromium platers subgroup (N = 626) and a non-chromium plater subgroup (N = 567). Both subgroups were followed from 1976 to December 1987. For the entire period of follow-up a total of 12606 person-years was enumerated. The observed number of deaths (all causes) was slightly below the expected value, particularly in the chromium plater subgroup. Among specific causes of deaths, only the observed number of cancer of the lung was found to be significantly higher than the expected number for all platers (SMR 179, 95% CI 102 -290). However, the SMR in either of the two plater subgroups did not differ significantly from 100. In the chromium plater subgroup, the highest SMR was observed for leukaemia; this value was based on two cases only. Smoking history was not obtained in this study.

A cohort mortality study was performed by Moulin *et al.* (Mou93). This study included a group of 2721 welders (34 131 person years) and a control group of 6683 manual workers (84 429 person years) employed in 13 factories in France. The mortality of the two cohorts was studied from 1975 to 1988. Data on smoking habits were collected from medical records. The smoking habits of 87% of the study population were known. The expected number of deaths was based on national rates after adjustments for age, sex and calendar time. There were no data on levels of exposures to metals in the past. The main welding techniques initially used in most factories, were MMA welding and oxyacetylene welding to a lesser extent. SMR for lung cancer was 124 (95% CL 75-194) for welders; the corresponding value for the controls was lower (SMR 94, 95% CI 68-126). For the subgroup of stainless-steel welders, the SMR was 92 (95% CL 19-269).

Raithel *et al.* (Rai89) studied the levels of chromium and nickel in the pulmonary tissues of lung cancer patients and in a control group. They examined 34 deceased persons, 21 men and 13 women; in 15 cases death resulted from lung cancer and in the other 19 cases there was no indication of a malignant disease of the airways. There was no difference in the levels of nickel, but on the other hand, the concentration of chromium in patients who had died of lung cancer and who had all been smokers, were significantly higher than in the non-smokers or in those with healthy lungs. An accumulation of nickel or chromium in the tumour matrix could not be detected.

A similar study was reported by Antilla *et al.* (Ant89). These authors examined the chromium content of the lungs of 53 lung cancer and 43 control patients. They found that the levels of chromium in the lung cancer patients were higher than those in (smoking and non-smoking) control patients. A positive correlation between the

pulmonary chromium concentration and smoking time and the severity of emphysema was found in the control but not in the cancer patients. This group of lung cancer patients included subjects with occupational exposure to chromium.

Akslen *et al.* (Aks90) also found increased concentrations of chromium in lung tissues from patients with bronchial carcinoma. In this study, central and peripheral lung tissue, bronchial tissue and hilar lymph nodes were collected from 20 patients with bronchial carcinoma and 21 control individuals. Lung tissue concentration of chromium was doubled, compared to the level in control individuals. Smokers showed a dose-related increase in the deposition of chromium. Furthermore, in cancer patients an inverse relationship between smoking and the tissue concentration of chromium in regional lymph nodes was found, possibly indicating a decrease on pulmonary clearance mechanisms by smoking.

More recently, Adachi *et al.* (Ada91) analyzed the concentrations of nine metals (iron, calcium, magnesium, zinc, copper, cobalt, nickel, lead and chromium) in lung tissues from 224 lung cancer cases in Japan. Comparisons were made with controls. There were no significant differences in the chromium, nickel and lead concentrations between lung cancers and other cases, although these values were lower in lung cancers.

Since 1985 a few reviews have published epidemiological evidence of the carcinogenicity of chromium in particular branches of the industry. Langård (Lan90) wrote an extensive review on "one hundred years of chromium and cancer". He concluded that all Cr(VI) compounds should be considered as carcinogenic, and that no evidence has been presented indicating that human exposure to Cr(III) is associated with increased cancer risk. Lees (Lee91) in his review on chromium and disease observed that the relationship between employment in industries producing chromium compounds from chromite ore and lung cancer has been well established in numerous studies. The relationship between exposure to certain chromium-based pigments and chromic acid and lung cancer, although not strong, is well accepted. The data concerning emissions from stainless-steel manufacturing are contradictory. Hypotheses about the carcinogenicity of specific chromium compounds generally relate to their *solubility* in body fluids. These hypotheses, however, have generally been determined from toxicological, not epidemiological, investigations. Well designed epidemiological studies, with detailed assessments of exposure of the workers, have the potential to help to elucidate causality, to identify specific carcinogenic compounds, and to quantify risk in humans eliminating the need to extrapolate from animal data. Although the need for exposure data crucial to this effort was identified in the earliest epidemiologic studies of chromium, such studies have not been conducted.

Recently Marini *et al.* (Mar95) wrote a comment on a 'Letters to Editor' column stating their disagreement in the interpretation that welding of stainless steel is an activity with potentially a carcinogenic risk. It was based on a study performed by the IARC and reported by Simonato *et al.* (Sim92), in which a comparison was made between mild steel welding, predominantly stainless steel welders, stainless steel and shipyard welders. Marini *et al.* (Mar95) concluded that mild steel welders in this cohort were at higher risk for lung cancer than stainless steel welders; other conclusions could not be drawn from this material. Langård (Mar95) replied to this letter, stating that the existence of confounding factors like smoking habits and asbestos pointed to the need for further clarification of the significance of exposure to hexavalent chromium as a determinant of respiratory cancer among stainless steel welders. There was also a need to elucidate whether the different methods of welding may contribute differently to the risk of cancer in the respiratory organ of welders.

In a recent Symposium on Epidemiology in Occupational Health in September 1995 in the Netherlands, Lees *et al.* (Lee95) presented their preliminary results on a retrospective cohort mortality study of chromate production workers (Letter from Gibb from EPA to Swaen, January 1996). This study has been performed by a co-operative agreement between John Hopkins University and the US Environmental Protection Agency. The cohort studied by Dr Richard Hayes which had been published in his disertation in 1976 was used, and the vital status was updated till 1992 and employment records till 1985. Exposure data were available in the form of 200,000 industrial hygiene measurements, most of them by personal sampling. The population characteristics were as follows: cohort size 2357 males, dates first employed 1950 - 1974, ethnic background 51% white and 49% non-white, smoking information 57%, total deaths 857, lung cancer deaths 122 and observation time 70,736 person-years, through 1992. The SMR for respiratory cancer was 154 (95% CI 129 - 183), for lung cancer 156 (95% CI 129 - 186) and for all cancers combined 107 (95% CI 94 - 122). When the exposure was expressed as a concentration times exposure period (mg/m^3 x years) and grouped into quartiles, there was a positive exposure - response (SMR) relationship. From a logistc regression analysis the following relationship between odds ratio (OR) and cumulative exposure was obtained: OR = exp(cumulative exposure x 0.744). The final results of this study are not yet published.

Sjogren *et al.* (Sjo94) performed a meta-analysis of five case-referent studies of stainless steel welders and the risk of lung cancer. Stainless steel welding is associated with exposure welding fumes, including airborne chromium and nickel. Between 50% and 90% of the chromium generated in manual metal arc welding is hexavalent. The five studies originated from Canada, Denmark, France, Norway and Sweden. The relative risk (RR) was computed, weighting the estimates of the individual studies with their reciprocal variance. The variances were calculated from the 95% CIs published

by the authors of the original studies. Asbestos exposure and smoking habits had been taken into account. The resulting value was 1.94 with a 95% confidence interval of 1.28 - 2.93. This result suggests an association between exposure to stainless steel welding fumes and lung cancer.

Mancuso (Man75) studied 332 white male workers who were employed in a chromate plant in the US between 1931 and 1937, and who were followed to 1974; In his study Mancuso reported lung cancer death rates by levels of exposure to soluble, insoluble, and total chromium concentrations. His results have been assessed by the US Environmental Protection Agency (EPA84). According to the EPA, a life-time (75 years) exposure to 0.001 mg/m^3 total chromium dust entailed an additional lung cancer mortality risk of 1.4×10^{-2}.

5.2.5 *Genotoxicity / Mutagenicity*

Most short-term tests to study the genotoxicity of chromium(VI) compounds are carried out using soluble compounds, *i.e.* potassium, sodium and ammonium chromates or dichromates. This is not surprising because for a chromium compound to interact with the test cells it must be soluble in biological fluid. Occasionally, tests were performed with moderate and poorly soluble chromium compounds like calcium, zinc, strontium and lead chromates.

In the present document only the more recent data are listed.

DNA damage induced by exposure to potassium dichromate (K_2CrO_4) in *in vitro* experiments have been reported. Wolf *et al.* (Wol89) studied the occurrence of DNA strand breaks induced *in vitro* by chromium (VI), which was reduced by gluthation to different chromium species. Using DNA agarose gel electrophoresis and nick translation assay, strand breaks were detected only when chromium(VI) was reduced by hydrogen peroxide. The reduction of chromium(VI) by an excess of glutathione led to no alteration in the DNA agarose gel electrophoresis pattern of the double-stranded plasmid pBR322 DNA and in the nick translation assay, indicating that no strand breaks had occurred under these conditions. Borges *et al.* (Bor91) also studied the ability of the thiols in glutathione, cysteine, ß-mercaptoethanol and dithiothreitol (DTT) to effect chromium(VI)-induced DNA damage *in vitro*, using supercoiled plasmid DNA pBR322 (form 1) isolated from Escherichia coli HB101. Chromium(VI) in the form of potassium dichromate was used. Reaction of pBR322 DNA with chromium(VI) in the presence of the thiols led to the formation of chromium(V) and chromium-DNA adducts. Transmission electromicroscopy of chromium-DNA complexes revealed aggregates of several plasmids, as well as condensation of individual plasmids into compact kinked forms. These effects may be due to

cross-linking of DNA induced by chromium complexes. Witmer and Park (Wit89) reported that 5-20 μM chromium(VI) (potassium dichromate and sodium dichromate) caused single strand breaks as well as DNA-protein crosslinks in A549 lung cells when studied by alkaline elution, while with L1210 mouse leukaemia cells only DNA-protein crosslinks were found. This means that the DNA lesions are different in different cells.

Data on the genotoxicity of potassium dichromate on Escherichia Coli was reported by Gaur and Bhattacharjee (Gau91). Concentrations potassium dichromate of 50 and 80 μg/ml lead to respectively 56 and 69% loss of plasmid born resistance. Sugden *et al.* (Sug90) reported that potassium dichromate required the presence of oxygen to revert the Salmonella typhimurium strain TA102 but induced a moderate reversion frequency in TA2638 under anaerobic conditions. These data support a role of oxygen radicals in chromium-mediated mutagenesis and suggests at least two pathways by which chromium compounds can induce mutations.

The mutational specificity of chromium(VI) compounds in the hprt locus of Chinese hamster ovary-K1 cells was studied by Tang *et al.* (Tan92). Among the effects of potassium dichromate on the mutants, single base substitutions, two base substitutions, four base substitutions, splicing mutations and single base pair insertions or deletions were shown. All the base substitutions and most of the frameshift mutations observed were located at the A/T-rich sequences.

De Marco *et al.* (Mar88) reported that potassium dichromate significantly increases the frequency of micronucleated cells in Vicia faba root tips with a clear dose-effect relationship. On the same experiments, potassium chromate also induces increased lagging chromosomes/chromatids and chromatid bridges or acentric fragments by 24 hours treatment. Chorvatovicova *et al.* (Cho91) studied the effects of simultaneous pretreatment with vitamins C and E on the toxicity and mutagenicity of potassium dichromate in rats and guinea pigs by using the micronucleus test in bone marrow. The results showed that vitamin C caused an antimutagenic effect against bichromate. The effect of vitamin E was demonstrated only in an increase of the ratio of NCE (normochromatic erythrocytes) to PCE (polychromatic erythrocytes), *i.e.*, in a decrease of the cytotoxic but not the mutagenic effects of hexavalent chromium.

It should be noted that the above mentioned experiments have been performed to study the interaction between the kinetics and the dynamics of the carcinogenicity of some hardly soluble hexavalent chromium compounds, e.g. calcium, zinc and strontium chromates. An 'uptake-reduction' model explaining the carcinogenicity of these compounds has been forwarded, which also explains the lack of carcinogenicity of Cr(III) compounds. The model takes into account that Cr(VI) readily enters cells by diffusion through a non-specific anion channel, whereas cells are relatively impermeable to Cr(III). Some factors appear to facilitate Cr(VI) uptake by reducing

Cr(VI) to Cr(III) after it enters the cell, presumably keeping intracellular Cr(VI) concentration low and allowing for further Cr(VI) uptake. Cr(VI), once reduced intracellularly, produces various forms of DNA damage including DNA interstrand crosslinks, DNA-protein crosslinks, DNA strand breaks and Cr-DNA adducts (Sta89; Wet89a,b; Gib89). Recently, De Flora *et al.* (Flo90) have published a comprehensive review on the genotoxicity of chromium compounds, including potassium-, sodium- and ammonium dichromate.

Gennart *et al.* (Gen93) studied the sister-chromatid exchange (SCE) in blood lymphocytes, serum tumour markers, carcinoembryonic antigen (CEA) and tissue polypeptide antigen (TPA), and urinary excretion of chromium, cobalt and nickel in 26 male workers occupationally exposed to chromium, cobalt and nickel dust and in 25 control subjects matched for age and smoking habits. An analyses of variance on the SCE rank values revealed that both exposure status and smoking habits had a statistically significant effect. The tumour markers did not reveal a significant difference between exposed and control groups. However, CEA serum levels were significantly correlated not only with smoking habits but also with duration of exposure. Popp *et al.* (Pop91) investigated the frequency of DNA strandbreakage and cross-linking and of SCE in the lymphocytes of 39 electric welders exposed to chromium and nickel with 18 controls standardized for age, smoking habits and sex. The study on the DNA was performed by using the alkaline filter elution technique and the results were expressed as relative elution rates based on the elution of V79 cells (hamster fibroblasts). The SCE determination was carried out by examining 25 complete second metaphases per subject and the proliferation index was determined based on a total of 100 metaphases. The mean levels of chromium and nickel in the urine of the welders were 28.4 (SD* 19.8) and 11.7 (SD 7.82) µg/l, respectively. The results surprisingly showed that the welders exhibited significantly lower SCE frequency than did the controls. On the other hand, a significant correlation was found between the frequency of SCE, the frequency of individual DNA strand breakage and the concentration of chromium in urine. In the case of welders less DNA was eluted through the two filter types used than in the case of the control group, which according to the authors must be interpreted as resulting from the presence of DNA-protein cross-links. Nagaya *et al.* (Nag91) studied the SCE in lymphocytes from 12 male chromium-platers in a 5-year follow-up study in Japan. Multiple regression of SCE frequency on age, urinary chromium and smoking habits was analyzed. It was found that neither age nor urinary chromium was a significant predictor for SCE frequency. It was concluded that although urine analysis revealed that workers were exposed to

* SD - standard deviation

chromium, this exposure did not influence the SCE frequency: on the other hand smoking habits were a highly significant positive predictor for this effect.

The following conclusions were drawn by IARC (IARC90):

Chromium(VI) compounds of various solubilities in water are consistently active in numerous studies covering a wide range of tests for genetic and related effects. In particular, potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate, chromium trioxide, calcium chromate, strontium chromate and zinc yellow induced a variety of effects (including DNA damage, gene mutation, sister mutation, sister chromatid, exchange chromosomal aberrations, cell transformation and dominant lethal mutation) in a number of targets, including animal cells *in vivo* and animal and human cells *in vitro*. Potassium chromate induced aneuploidy in insects, while chromium trioxide did not. Various compounds induced gene mutation in insects. Potassium dichromate produced recombination, gene mutation and aneuploidy in fungi. All of these chromium(VI) compounds induced DNA damage and gene mutation in bacteria. Similar patterns were observed with zinc chromate, barium chromate, lead chromate and the derived pigments chromium organ, chromium yellow and molybdenum orange, which, however, often required preliminary dissolution in alkali or acids. A liquid chromium(VI) compound (chromyl chloride) and its vapours induced gene mutation in bacteria.

Although *chromium(III)* compounds are generally more reactive than chromium (VI) compounds with purified DNA and isolated nuclei, 12 chromium(III) compounds of various solubilities (chromic chloride, chromic acetate, chromic nitrate, chromic sulphate, chromic potassium sulphate, chromium alum, neochromium, chromic hydroxide, chromic phosphate, chromic oxide, chromite ore and cupric chromite) gave positive results in only a minority of studies using cellular test systems, often under particular treatment conditions or at very high concentrations, which were generally orders of magnitude higher than those needed to obtain the same effect with chromium(VI) compounds. Some of the positive results could be ascribed to contamination with traces of chromium(VI) compounds. In particular, no DNA damage was observed in cells of animals treated *in vivo* with chromic chloride, and no micronuclei were seen in cells of animals given chromic nitrate. The chromium(III) compounds tested generally did not produce DNA damage, gene mutation, sister chromatid exchange or cell transformation in cultured animal and human cells. Chromosomal aberrations were often observed with high concentrations of chromium(III) compounds. Weak effects on gene mutation and mitotic gene conversion were observed in fungi. Negative results were obtained in the large majority of tests for DNA damage and gene mutation in bacteria. Certain complexes of

chromium(III) with organic ligands, which favour the penetration of chromium(III) into cells, were reported to induce DNA damage and gene mutation in bacteria and in cultured mammalian cells.

A *chromium(II)* compound (chromous chloride) gave negative results in *in vitro* tests with animal cells (DNA damage, chromosomal aberrations and aneuploidy). 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 of the IARC.

5.2.6 *Effects on the reproduction*

The following conclusions were drawn by the IARC (IARC90) on the effects of chromium on reproduction. Chromium(VI) compounds cross the placental barrier in greater amounts than chromium(III) compounds. Chromium trioxide increases fetal death rate, causes growth retardation and increases the frequency of skeletal deformaties and cleft palate in rodents. Developmental effects have also been reported in mice exposed to chromic chloride.

More recent data are listed below.

Male reproduction

Ernst (Ern90) studied the toxicity of Cr(VI) and Cr(III) compounds on the testes of rats after short-term exposure. Groups of 8 male rats were injected intra-peritoneally daily for 5 consecutive days with 1, 2 or 4 mg/kg Cr(III) doses (as chromium chloride) or Cr(VI) doses (as sodium chromate). The animals were sacrificed 7 and 60 days after administration of the last dose. 7 days after the last dose, testicular effects were not seen in any of the groups. When investigated after 60 days, a significant reduction in relative testicular weight was seen in the groups injected with Cr(VI). Histological examination revealed a dose-dependent increase in the number of atrophic seminiferous tubules with a loss of spermiogenetic epithelium. In the group receiving 4 mg Cr (VI)/kg the cellular organization was lost. Complete degeneration was observed in almost every seminiferous tubule and the Leydig cells appeared to be atrophic. In addition, a substantial loss of epididymal spermatozoa was observed. From this study the committee concludes that the NOAEL of Cr(VI) on the male reproduction is far lower than 1 mg/kg body weight. No significant treatment-related alterations, either in testicular histopathology or in epididymal sperm number, were

seen after Cr(III) administration. No clinical signs of toxicity were observed in any experimental animal during the study.

More recently, Ernst and Bonde (Ern92) reported on the effects of Cr(VI) after subchronic treatment on rats. The rats were injected intraperitoneally with a Cr(VI) dose of 0.5 mg/kg (as sodium chromate), 5 days per week, for 8 weeks. The authors found a significant reduction in epididymal sperm motility at the end of exposure period. The reduction was reversed after an unexposed period of a further 8 weeks. Furthermore, the percentage of abnormal spermatozoa was similar between the groups of animals. A decrease in serum testosterone and an increase in FSH were found at the end of exposure period. The results indicate that a number of mechanisms may be involved in the deleterious effects of chromate on male rat fertility. Since the effect is reversible the committee concludes that a Cr(VI) dose of 0.5 mg/kg body weight is the MOAEL for male rat reproduction.

In 1992, Bonde and Ernst (Bon92) published a cross-sectional study on the spermatotoxic effects of water soluble hexavalent chromium in welders. They examined the relationship between semen quality and chromium in urine and blood of a population of 30 tungsters inert gas (TIG) stainless steel welders, 30 mild steel welders and 47 non-welding workers (controls). For each subject, the semen volume, sperm concentration, total sperm count, proportion of normal sperm forms, proportion of motile sperm and linear penetration rate in chicken egg white were determined. In addition, the serum concentration of testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) were analyzed. A spot urine sample was delivered at end of the semen sample collection period for determination of chromium. Information on occupational exposure, personal habits and urogenital disorders was gathered by interview. No environmental monitoring was performed. The concentration of chromium in blood was determined in a blood sample obtained before the start of a workshift. The chromium concentrations in urine ranged from 0.08 to 2.18 μg per g creatinine and the chromium concentration in blood from 0.3 to 2.4 μg/l. This study did not reveal any association between the level of chromium in biological fluids and the quality of semen or male sexual hormones. However, after adjustments for confounding factors, the serum concentration of testosterone showed a borderline significant decrease with a corresponding increase in urinary chromium ($p=0.05$). By separate regression analysis this negative regression coefficient was found only on the stainless steel welders.

Female reproduction

Ratnasooriya and Balasuriya (Rat92) reported antigestational effects of Cr(VI) in the rat. Groups of pregnant rats were given sodium chromate doses of either 1, 4 or 8

mg/kg (as sodiumchromate) per day by intraperitoneal injections from day 1 through day 7 of pregnancy. Another three groups were given the same doses but between day 7 and day 14 of pregnancy. With each group a control group was associated, that was given saline by i.p. injections. Laparotomy was done on day 11 and 15 of the pregnancy and the numbers of uterine implants, resorption and corpora lutea were counted. Pre- and post-implantation losses were also computed. The results showed no significant effect on any of the reproductive parameters studied when given the lowest and the highest doses, either during days 1-7 or days 7-14 of pregnancy. On the other hand, the intermediate dose altered the number of uterine implants and post-implantation losses, when administered during days 7-14 of pregnancy. None of the chromium treatments had any effect on fetal size. The absence of a dose-response relationship makes interpretation of the results difficult.

In 1988, the WHO cited a report from Glaser *et al.* (Gla84) to the Umweltbundesamt, Germany. An inhalation study was performed to investigate the effects of sodium dichromate on the reproduction and teratogenicity in three generations of rats. The animals were exposed to aerosols of this compound in the atmosphere at a level of 200 $\mu g/m^3$ during 130 days per generation. No effects on reproduction were found. All teratogenicity tests were negative, and there was no increase in fetal chromium content. However, from generation to generation, there was an increase in immunosuppression and hyperplasia of organs (especially in the lungs) and changes in haematological variables.

The WHO drew the following conclusion on the teratogenicity of chromium (WHO88): "Both chromium oxidation states, when injected at high levels parentally into animals, are teratogenic, with the hexavalent form accumulating in the embryos to much higher concentrations than the trivalent. The Task Group was not aware of any report indicating teratogenicity in human populations".

5.2.7 *Miscellaneous effects*

The reports on effects of chromium exposure on the *liver* are ambiguous. Baruthio (Bar92) mentioned hepatocellular deficiency, and Anonymus (Ano88) liver damage. These effects probably occurred at very high doses in which case general toxicity was induced. The WHO (WHO88) reported that statistics on liver disease are usually included in the group of diseases of the digestive system and seldomly published separately. The rate of diseases of the digestive system for chromate industry workers was reported to be similar to that in many other industries. In an epidemiological study a low rate of cirrhosis of the liver in chromium workers was reported, and liver function test results that did not differ significantly from those of controls (WHO88).

The effects of chromium on the *central and peripheral nervous system* are also vague. There is no evidence that Cr(VI) is neurotoxic to humans. But Von Burg and Liu (Bur93) cited a report from 1977, claiming that intraperitoneal injections of 2 mg/kg Cr(VI) every day for 3 or 6 weeks in rabbits resulted in neuronal degeneration of the cerebral cortex, marked chromolysis and meningeal congestion. No more recent data are available.

5.3 Summary of effects

The committee summarizes its findings as follows:

- The target organs in occupational exposure to chromium and its compounds are the skin, mucous membranes of the upper respiratory tract, the kidneys, the lungs and the reproductive organs.
- Chromium exposure of the skin may cause irritative lesions and allergic/eczematous lesions. Irritative lesions are mostly caused by Cr(VI), and to a much lesser extent by Cr(III). Chromium sensitivity is a type IV delayed hypersensitivity. Cr(VI) and Cr(III) compounds are allergenic, but the latter compound to a much lesser degree. Chromium(III & VI) contact allergies haven been observed among workers in numerous industrial activities.
- The hexavalent chromium compounds may induce ulceration and perforation of the nasal septum after inhalatory exposure. The nasal septum is particularly sensitive because of the very low vascularisation of its cartilaginous structure in combination with the causticity of Cr(VI). It is estimated that CrO_3 concentrations as low as 100 $\mu g/m^3$ can induce lesions.
- No nephrotoxic effect has been reported for trivalent chromium. Soluble Cr(VI) compounds may cause tubular lesions of the kidneys. The committee concludes that the NOAEL in rats for acute effects on the kidneys corresponds to a chromium(VI) dose of 10 mg/kg body weight after intraperitoneal injections. The critical effects are changes in the serum urea nitrogen and relative kidney weight.
- Cross-sectional studies on workers employed in a chromate and dichromate production plant showed that a concentration of 15 µg chromium per g creatinine in the urine corresponds to the threshold for effects on the tubular functions. In these studies the most sensitive kidney variable was the retinol-binding protein level in urine. A different study on stainless-steel welders, however, showed that $ß_2$-microglobulin in urine was slightly increased in workers with a urinary chromium concentration exceeding 30 µg per g creatinine. There appear to be differences in the effects on the kidneys after short-term high dose and long-term low dose exposure.

- The non-carcinogenic effects with respect to aberrations of the lung of workers caused by exposure to chromium and its components are: pulmonary fibrosis, chronic bronchitis, emphysema, bronchial asthma and pneumoconiosis. A long-term inhalation study with rats exposed to CrO_2 (CrIV !) for two years showed the lungs to be the critical organ. The estimated LOAEL is 0.5 mg/m^3. In another study in which rabbits were exposed to soluble chromium (Cr(III)) compounds for 4-6 weeks, a MOAEL of 0.6 mg/m^{3}was found.
- Experiments have been performed in rabbits to study the effects of administrating two different compounds simultaneously. It was found that the combination of Cr(III) and a soluble cobalt compound produces a stronger effect on the lung than would expected from the effects of the exposure to the single compounds. The effects of combined exposure to nickel, cobalt and chromium have also been reported. Cross-sectional epidemiological studies on a group of manual welders exposed to various metals (zinc, copper, chromium, nickel, lead and manganese) showed a predominantly restrictive type of pulmonary impairment followed by a mixed ventilatory defect. However, it is not possible to deduce the contribution of chromium to these aberrations.
- Few recent animal data are available on the carcinogenic effect of chromium on the lungs. In a two-year study on rats exposed to a Cr(IV) compound, some female rats, developed cystic keratinized squamous cell carcinomas in the lungs. Such tumours were not induced in male rats. This kind of tumour is allegedly not significant to man. There is limited evidence in experimental animals for the carcinogenicity of soluble chromium(VI) compounds (chromium trioxide and sodium dichromate). On the other hand the commitee deems that there is sufficient evidence for the carcinogenicity of the slight soluble calcium, zinc and strontium chromate (Cr(VI)).
- In a large retrospective cohort mortality study consisting of 11092 male welders from 135 companies in nine European countries, a statistical significant excess of mortality due to lung cancer was found. When analyzed according to the type of welding, the excess lung cancer mortality was predominantly noticeable in the subcohort of stainless-steel welders. In another cohort mortality study, on workers of chromeplating plants in Japan, a significant excess mortality was observed for lung cancer and not for other causes of deaths. Few studies have reported on the levels of chromium in the pulmonary tissue of lung cancer patients. The chromium levels were elevated in the lungs of the lung cancer patients.
- For the mutagenicity and genotoxicity of chromium compounds the committee concludes the following:
  · Metallic chromium: no relevant studies are available.
  · Chromium(II): non-genotoxic.

- Chromium(III): *in vivo* experiments show no DNA damage. In general these Cr(III) compounds did not induce DNA damage, gene mutation, SCE or cell transformation in cultured animal and human cells.
- Chromium(IV): no tests have been performed on Cr(IV).
- Chromium(VI): compounds of various solubilities in water were consistently active in numerous studies (including DNA damage, gene mutation, SCE, chromosomal aberrations, cell transformation and dominant lethal mutation).

- Chromium(III) compounds do not affect the male reproductive system. On the other hand Cr(VI) is toxic to the male reproductive system in a dose-dependent manner. From a study on rats the committee estimates that the NOAEL of Cr(VI) for effects the male reproductive system should be much lower than a dose of 1 mg/kg body weight by intraperitoneal injection per day. In a more recent study on rats, a MOAEL of 0.5 mg/kg body weighy per day after intraperitoneal injection was found. The effect found was a reversible reduction of epididymal sperm motility.
- The results of a cross-sectional study on welders demonstrated that workers with urinary chromium concentrations between 0.08 and 2.18 μg per g creatinine did not show aberrations in the quality of semen or sexual hormones like testosterone, follicle stimulating hormone and luteinizing hormone, although after adjustments of confounding factors a slight decrease of testosterone levels in serum was found.
- No human data are available on the effect of chromium on the female reproductive system. Cr(III) and Cr(VI) compounds are teratogenic in experimental animals when injected parentally at high levels, the latter compounds being more toxic than the former. In a three generation study on rats exposed to aerosols of sodium dichromate with chromium concentrations 0.2 mg/m^3 (as Cr) showed no effects on the reproduction. However, comparisons between successive generations disclosed an increase of the immunosuppression, hyperplasia of especially the lungs and changes in haematological variables. This implies that a chromium(VI) concentration of 0.2 mg/m^3 Cr(VI) in ambient air cab be considered as a MOAEL of this compound.
- The effects of chromium on the liver and the central or peripheral nervous system of experimental animals are ambiguous. Human data are limited.

Chapter 6

Previous evaluation by other national and international bodies

Dutch Expert Committee on Occupational Standards (1985)

The earlier report op the committee was summarized in chapter 2.

Health Council of the Netherlands (1991)

In 1991, another committee of the Health Council assessed a criteria document on chromium. That committee did not take speciation of chromium(VI) compounds into account, as it is most often impossible to determine the chemical form of chromium(VI) compounds in the ambient environment. Chromium(VI) compounds were classified as genotoxic carcinogens in case of inhalatory exposure, and consequently a linear extrapolation method was used for risk assessment. The other Health Council committee concluded that chromium(III) compounds are not carcinogenic to humans.

American Conference of Governmental Industrial Hygienists (ACGIH) (1986)

The recommended TLV's are listed in chapter 3.

The TLV* for water soluble Cr(VI) compounds is considered adequate in protecting against irritation of the respiratory tract and possible kidney and liver

* Treshold limit value

damage. For certain water insoluble Cr(VI) compounds, a classification in class A1a (confirmed human carcinogen) is recommended. A TLV of 0.05 mg/m^3 is recommended because monitoring data on exposures associated with an increased respiratory risk are scarce. This value should provide an adequate safety margin.

For exposures to mixtures of soluble and insoluble hexavalent chromium compounds a TLV of 0.05 mg/m^3 as Cr(VI) is recommended.

For chromite ore processing and chromate pigment manufacture the ACGIH proposed a TLV of 0.05 mg/m^3 (as chromium concentration) with inclusion in Class A1a.

National Institute for Occupational Health and Safety (1973)

The NIOSH in the US recommended an Ocuppational Exposure Limited of 0.05 mg/m^3, TWA - 8 h for chromic acid, and a ceiling value of 0.1 mg/m^3, TWA - 15 min. These limits are based on prevention of nasal ulceration and chronic effects, such as lung cancer and liver damage.

Deutsche Forschungsgemeinschaft (1992)

The DFG does not recommend MAK values for any chromium compounds, as these compounds were classified as carcinogenic agents: zinc chromate - class A1 (confirmed human carcinogen); Cr(VI) compounds in the form of dust and aerosols (with the exception of those water insoluble compounds such as lead chromate and barium chromate) - class A2 (confirmed animal carcinogen); lead chromate - class B (confirmed suspected carcinogen).

Swedish Criteria Group for Occupational Standards (1993)

The most recent report of the SCG concluded that only those subjects who are exposed to hexavalent chromium compounds are at higher risk of developing cancer, and that the excess cancer risk is mainly related to cancer of the respiratory organs. Water soluble compounds are more potent human carcinogens than are those with low solubility. This report does not recommend a occupational exposure limit for chromium compounds. Of interest is the estimation of cancer risk based on a cohort of Norwegian workers exposed to zinc chromates, with 15 cases of lung cancer in 1000 man-years at risk. This is equivalent to a unit risk of 1.3×10^{-1} (1 case per 100000 per 1 µg Cr VI). It is not clear whether the risk is calculated for one year or the whole 40 years of work-life. The method of estimation of exposure is not reported.

European Union - Scientific Expert Group (1993)

The SEG recommended an occupational exposure limit (OEL) of 0.5 mg/m^3 TWA - 8 hours for chromium (III) compounds based on the same data that the committee had used in its former report, *i.e.* the results of a rabbit study of Johansson *et al.* (Joh86, 87). The SEG concluded that the exposure at the level of 0.5 mg/m^3 did not result in adverse effects on the lungs (which means the NOAEL). The DECOS concluded differently on this experiment.

The same value of 0.5 mg/m^3 TWA - 8 h was recommended with respect to chromium(II) compounds and chromium metal based on the assumption that the biological activities of chromium(II) compounds are similar with that of chromium(III) compounds, and chromium metal would be less biologically active.

The SEG did not recommend an occupational exposure limit for Cr(VI) compounds.

USA - Environmental Protection Agency (1984)

In 1984, the US EPA drew the following conclusion: From epidemiological studies of chromate production workers there is, using the IARC criteria, sufficient evidence of carcinogenicity. Using the same criteria, there is sufficient evidence of carcinogenicity of hexavalent chromium in animal bioassay studies. The results in animals appear to be determined to some extent by the solubility of hexavalent chromium compounds. Trivalent chromium has not been found to be carcinogenic in animal studies. Hexavalent chromium is mutagenic, and this supports the findings that hexavalent chromium is carcinogenic in animal bioassays.

Chapter 7

Evaluation of human health risk

7.1 Groups at extra risk

Chromium skin contact allergies have been observed among workers in numerous industrial activities. Sensitized subjects to chromium are at extra risk and should not be placed in jobs where skin contact with chromium and chromium compounds can occur. In contrast with the previous document, the committee concluded that it is inappropriate to consider people with a dimished lungfunction at extra risk.

7.2 Assessment of health risk

Chromium trioxide is used in chrome plating, copper stripping, aluminium anodizing, as a catalyst, refractories, in organic synthesis and photography. Occupations in which exposure may occur include: anodizers, copper etchers, electro-platers, glass workers, lithographers, metal workers, oil purifiers, photoengraphers, photographers, process engravers, stainless steel workers, textile workers, painters and welders (Sit79).

Theory and practice show that the kinetics and toxic effects induced by chromium compounds depend on the valency of the chromium ion and the water solubility of the compounds.

Chromium metal dust (Cr^0)

There are almost no toxicological data on chromium metal dust. Given this lack of scientific data the committee can not establish a HBR-OEL*, see however 7.4.

Chromium(II) compounds (chromium dichloride)

Limited relevant data are available on these compounds. It has been shown that chromium(II) is non-genotoxic. No human data are available. The committee can not recommend a HBR-OEL* due to the lack of scientific data.

Soluble chromium(III) compounds (chromic acetate, chromic nitrate, chromic chloride hexahydrate, potassium chromic sulphate dodecahydrate)

The target organ of chromium(III) compounds after inhalatory exposure are the lungs. A MOAEL of 0.6 mg/m^3 was found in rabbits exposed to soluble chromium(III) compounds by inhalation for six hours per day, five days per week during four to six weeks. At this concentration morphological as well as functional changes in the alveolar macrophages were found. Human data are lacking. Chromium(III) compounds have been shown to be not mutagenic, nor clastogenic, nor carcinogenic. The committee considers chromium(III) compounds to be non nephrotoxic.

In establishing a HBR-OEL a large safety factor for the extrapolation of animal data to humans is not indicated since chromium(III) compounds induce only local effects. The committee recommends a HBR-OEL of 0.06 mg/m^3 for soluble chromium(III) compounds, TWA - 8 hour by dividing the MOAEL value of 0.6 mg/m^3 in rabbits by a factor of 10. This safety factor is the product of a factor of 3 for interspecies variations and 3 for using a MOAEL as starting point resulting in a safety factor 10 . The HBR-OEL should be applied to inhalable dusts.

Insoluble chromium(III) compounds (chromic oxide, chromic phosphate, chromic sulphate)

There are almost no recent toxicological data on insoluble chromium(III) compounds. No human data are available. Given this lack of data the committee can not recommend a HBR-OEL for insoluble chromium(III) compounds, see however 7.4.

* HBR-OEL - Health Based Recommended Occupational Exposure Limit

Chromium(IV) compounds (chromium dioxide)

A long-term inhalation study in rats showed the lungs to be the target organ. A LOAEL of 0.5 mg/m^3 was found in a two year study in rats. Exposure to this concentration resulted in slight Type II pneumocyte hyperplasis. At higher levels of exposure, hyperplastic Type II pneumocytes and slightly collagenized fibrosis were found. The lungs showed minute fibrotic pleuritis. The committee recommends a HBR-OEL of 0.05 mg/m^3 for chromium(IV) compounds, TWA - 8 hour. This value is derived by dividing the LOAEL value in rats of 0.5 mg/m^3 by a factor of 10. This safety factor is the product of a factor of 3 for the interspecies variations and 3 using a LOAEL as the starting point. The HBR-OEL should be applied to inhalable dusts.

Chromium(VI) compounds Includes: soluble chromium(VI) compounds (e.g. ammonium dichromate, chromium trioxide, potassium dichromate, sodium dichromate); slightly soluble chromium(VI) compound (e.g. calcium chromate, strontium chromate, zinc chromate); very slightly soluble chromium(VI) compounds (e.g. barium chromate, lead chromate)

Several epidemiological studies of workers mainly exposed to zinc chromate (a slightly soluble chromium(VI) compound) report a clear excess of lung cancer mortality. The same holds for lead chromate (a very slightly soluble chromium(VI) compound). No cohort studies of workers that were exclusively exposed to soluble chromium(VI) compounds were found in the literature. However, there are some series of lung cancer cases that provide circumstantial evidence for the carcinogenicity of sodium dichromate and potassium dichromate (soluble chromium(VI) compounds). These lung cancer cases were listed by Langård (Lan90).

Carcinogenicity studies with experimental animals are scarce and of limited value for human risk estimation, due to limitations in the experimental design. Nevertheless, most of these studies point to a carcinogenic effect of chromium(VI) compounds in the lungs. In any case these studies can certainly not be considered as 'negative' with respect to carcinogenesis. It appears that the carcinogenicity of chromium(VI) compounds in animals varies with the solubility of the compound. Moreover, all chromium(VI) compounds are mutagenic, irrespective of their solubility. How the solubility interferes with the carcinogenic potential of chromium(VI) compounds is not known.

The committee draws the following conclusions. Epidemiological studies provide clear and unambiguous evidence for the carcinogenicity of slightly soluble and very slightly soluble chromium(VI) compounds and circumstantial evidence for the carcinogenicity of soluble chromium(VI) compounds. Experimental animal studies indicate that chromium(VI) compounds possess carcinogenic potential and that there are quantitative differences between soluble, slightly soluble and very slightly soluble chromium(VI) compounds. Therefore, the committee considers *all* chromium(VI) compounds as carcinogenic. It considers a worst case approach warranted and has therefore selected the study of Mancuso (Man75) on slightly soluble chromium(VI) compounds as a basis for human risk assessment.

The committee decided to adopt the data from the EPA as starting point for the estimation of the additional life time cancer risk. The EPA risk assessment was based on the results of the Mancuso study (Man75) complemented with additional exposure data and follow-up. In agreement with the EPA the committee prefers to use the Mancuso study because of the availability of reliable historic exposure data and the availability of a substantial number of observed lung cancer deaths. The EPA used a low-dose linear extrapolation model for the estimation of the cancer risk. A life time (75 years) exposure of 1 $\mu g/m^3$ chromium(VI) total dust entails an additional lung cancer risk of 1.4×10^{-2}. This risk is calculated on the basis of the total chromium concentration in the chromate plant. The EPA noted that the use of total chromium as a surrogate for hexavalent chromium could result in an underestimate of the risk by no more than 7 times; on the other hand, underestimation of plant exposures and of smoking habits in the workers could lead to a overestimation of the risk by roughly 4 times. Overall, the EPA found the Mancuso study was the best possible estimate of the risk (EPA84).

For the occupational situation the analysis implies that exposure to 8 $\mu g/m^3$ total dust may result in an additional cancer mortality risk of 1.4×10^{-2}. The committee is of the opinion that in the type of industry involved in the Mancuso study, exposure to 8 $\mu g/m^3$ measured as total dust will not differ considerably from an identical exposure measured as inhalable dust, since particulates in these type of industries have relatively small aerodynamic diameters.

Therefore for the chromium(VI) compounds the committee derives an:

- additional cancer mortality risk of 4×10^{-3} after 40 years of occupational exposure to 2 $\mu g/m^3$ as inhalable dust.
- additional cancer mortality risk of 4×10^{-5} after 40 years of occupational exposure to 0.02 $\mu g/m^3$ as inhalable dust.

7.3 Recommended Occupational Exposure Limits

The recommendations of the committee with respect to health based occupational exposure limit can be summarized as:

speciation	occupational exposure limit
chromium metal dust	not possible to determine, see however 7.4
chromium(II) compounds	not possible to determine
soluble chromium(III) compounds	0.06 mg/m^3, TWA - 8 h (as inhalable dust)
insoluble chromium(III) compounds	not possible to determine, see however 7.4
chromium(IV) compounds	0.05 mg/m^3, TWA - 8 h (as inhalable dust)
chromium(VI) compounds	additional cancer mortality risk of 4 x 10^{-3} after 40 years of occupational exposure to 2 µg/m^3 inhalable dust additional cancer mortality risk of 4 x 10^{-5} after 40 years of occupational exposure to 0.02 µg/m^3 inhalable dust

7.4 Additional considerations

Chromium metal dust (Cr°)

The committee concluded that it is not possible to determine a health based occupational exposure limit for chromium metal dust because of a lack of scientific data. However, taking all data into account and until more pertinent data are available, the committee does not object to maintain the present regulatory exposure limit (MAC-value*) of 0.5 mg/m^3, TWA - 8 hours.

Insoluble chromium(III) compounds (chromic oxide, chromic phosphate, chromic sulphate)

As stated above, given the lack of scientific data, the committee cannot recommend a health-based occupational exposure limit for insoluble chromium(III)compounds. However, the committee has reason to believe that the insoluble chromium(III) compounds are probably less toxic than the soluble chromium(III)compounds. Therefore, in line with the recommendation in its 1985 report, the committee is of the opinion that applying the occupational exposure limit of 0.5 mg/m^3, TWA 8-hours, for

* MAC - Maximal Accepted Concentration, see chapter 1

the soluble chromium(III)compounds in case of the insoluble chromium(III) compounds is justifiable.

Rijswijk, 24 September 1998
For the committee,

dr ASAM van der Burght,
scientific secretary

prof. dr VJ Feron,
chairman

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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

- VJ Feron, *chairman*
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik,
  epidemiologist; Agricultural University, Wageningen
- PTh Henderson
  professor of toxicology; Maastricht University, Maastricht
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- G de Mik
  toxicologist; National Institute of Public Health and the Environment, Bilthoven
- J Molier-Bloot
  occupational physician; Academic Medical Centre (AMC), Amsterdam
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Rijswijk

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam.
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen, Switzerland
- AAE Wibowo
  toxicologist; Coronel Institute, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Rijswijk.
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Rijswijk.

The first draft of the present advisory report was prepared by dr AAE Wibowo, Coronel Institute, Academic Medical Centre, University of Amsterdam, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance was provided by E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in 1995 for public review. The following organisations and persons have commented on the draft document:

- W ten Berge, Th Scheffers
  DSM, The Netherlands
- Dr HD Brommer
  The European Manufacturers of Lead Chromate and Lead Molybdate Pigments E.V., Germany
- G Darrie
  International Chromium Development Association (ICDA), United Kingdom (through ECETOC)
- Dr L Erkens, E Claeys
  Ciba - Geigy Maastricht BV, The Netherlands
- dr S Fairhurst
  Health and Safety Executive, United Kingdom
- dr AO Gamer
  BASF Aktiengesellschaft, Germany
- CJ Halm
  FME, The Netherlands
- dr Hochgeschender
  Bayer AG, Germany (through ECETOC)
- mr CW van der Horst
  BASF Nederland BV, The Netherlands

- dr EC Rietveld
  AKZO Nobel, The Netherlands
- dr Scherhag
  Bayer AG, Germany
- R Schmitt
  European Catalysts Manufacturers Association, Belgium (through ECETOC)
- dr B Sjögren,
  Swedisch National Institute for Working Life, Sweden

Annex **D**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion $(v/v)10^{-9}$
ppm	parts per million $(v/v)10^{-6}$
RD_{50}	dose at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit

STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Association (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration

MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

CI	confidence interval
GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

CrU	chromium in urine
Cr	chromium
CAE	carcinoembryonic antigen
TPA	tissue popypeptide antigen

Annex **E**

DECOS-documents

DECOS has produced documents on the following substances.
To be ordered from the Health Council of the Netherlands:

Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Bisphenol A and its diglycidylether	1996/02WGD
Butanol (1,2- and t-)	1994/10
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
1,2-Dichloroethane	1997/01WGD
Diphenylamine	1997/05WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Formamide and dimethylformamide	1995/08WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Isopropyl acetate	1997/04WGD
Man made mineral fibers	1995/02WGD
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
Propanol (1- and 2-)	1994/24

Propylene oxide	1997/02WGD
Thrichloroethane (-1,1,1)	1995/03WGD
Trichloropropane (1,2,3-)	1994/25

The following documents, that were published before 1994, can be ordered from the Sdu Uitgeverij Den Haag.

Acetaldehyde	RA 6/92
Acrylaten	RA 13/87
Aflatoxine B1, B2, G1 en G2	RA 6/87
Allylglycidylether	RA 1/92
Amyl acetate	RA 4/90
Aniline	RA 2/89
Anorganisch Lood	RA 2/80
Anorganische Kwikzouten	RA 3/82
Arc welding fume particles not containing chromium and nikkel	RA 1/93
Arseenverbindingen (anorganische)	RA 2/84
Asbest	RA 1/84
Asbest, Evaluatie van risico op kanker bij beroepshalve blootstelling aan (aanvullend op RA 1/84)	RA 9/89
Benzeen	RA 5/89
Beryllium and beryllium compounds	RA 4/88
Blootstelling, Gezondheidskundige aspecten van het begrip en van het meten/schatten ervan	RA 8/90
Butadiene (1,3-)	RA 5/90
Cadmium	RA 5/80
Caprolactam	RA 4/84
Carbon monoxide	RA 7/92
Carbonylfluoride and PTFE pyrolysis products	RA 3/88
Carcinogene stoffen	RA 3/80
Chloor	RA 6/80
Chloroform	RA 7/87
ß-Chloroprene	RA 4/93
Chroom en chroomverbindingen	RA 6/85
Cyclohexane	RA 15/90
Cyclohexanol	RA 3/90
Cyclohexanone	RA 9/93
Dibroomethaan	RA 5/87
Dichloorethaan (1,1-)	RA 8/87
Diisocyanates	RA 3/91
Dimethyl- en diethylsulfaat	RA 12/90
Dimethylamine	RA 10/90
Dimethylbutane (2,2- & 2,3-)	RA 7/93
Dimethylhydrazine	RA 2/87
Dinitro-*ortho*-cresol (4,6-)	RA 4/87
Dioxaan (1,4-)	RA 1/87
Epichloorhydrine	RA 1/86

Ethylacrylate	RA 6/90
Ethylacetate	RA 10/91
Ethyl Methanesulphonate (EMS)	RA 4/89
Ethylamine	RA 7/90
Ethylbenzene	RA 9/91
Ethyleenoxide	RA 6/89
Fenylhydrazine	RA 2/87
Fluorcarbons (except FC11)	RA 15/87
Fluorine compounds (inorganic)	RA 1/89
Fluorine	RA 1/89
Formaldehyde	RA 3/87
Fosfine	RA 1/80
Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989	RA 9/90
Gasoline	RA 3/92
Heptaan (n-)	RA 1/81
Heptane (n-)	RA 6/93
Hexaan (n-)	RA 11/87
Hexachlorobenzene	RA 2/88
Hexanone (2-)	RA 2/90
Hydrazine	RA 2/87
Hydrogenfluoride	RA 1/89
Hydroxyethylhydrazine	RA 12/87
Isopropylglycidylether	RA 1/92
Isopropoxyethanol (2-)	RA 2/87
Koolmonoxide (Carbon monoxide)	RA 2/79 (7/92)
Kwikalkylverbindingen - Korte keten	RA 5/82
Kwikverbindingen (Organische)	RA 4/82
Lachgas (Nitrous oxide)	RA 2/85 (2/92)
Lasrook (Arc welding fume.....nickel)	RA 1/93
Mangaan	RA 1/82
Metallisch Kwik	RA 5/81
1-Methoxypropanol-2	RA 5/93
2-Methoxypropanol-1	RA 5/93
1-Methoxypropylacetate-2	RA 5/93
2-Methoxypropylacetate-1	RA 5/93
Methylacrylate	RA 1/90
Methyleenchloride (Methylene chloride)	RA 1/83 (8/92)
Methyl ethyl ketone	RA 16/90
Methyl isobutyl ketone	RA 4/91
Methyl Methanesulphonate (MMS)	RA 4/89
Methylbromide	RA 13/90
Methylpentane (2- & 3-)	RA 7/93
Monochloorethaan	RA 2/82
Monoketones (7/8 carbon chain aliphatic)	RA 14/90
Nikkel en nikkelverbindingen	RA 3/85
Nitropropaan (2-)	RA 1/85
Nitrous oxide	RA 2/92

Ozone	RA 4/92
para-Dichloorbenzeen	RA 1/88
Pentaan	RA 2/81
Phthalate esters	RA 8/93
Phthalic anhydride	RA 3/89
Piperazine	RA 7/91
Polyvinyl chloride (PVC) dust	RA 2/93
Propoxyethanol (2-)	RA 12/87
Propoxyethylacetate (2-)	RA 12/87
Pyridine	RA 3/93
Selenium en -verbindingen	RA 7/89
Silicon dioxide, crystalline forms of	RA 5/92
Stikstofdioxide (Nitrogen dioxide)	RA 5/85
Styreen	RA 8/89
Talc dusts	RA 6/91
Tetrahydrofuran	RA 1/91
Thiourea	RA 11/90
Tolueen diisocyanaat	RA 4/80
Tolueen	RA 2/91
Trichloorethaan (1, 1, 1-)	RA 3/81
Trichloorethyleen	RA 3/83
Trichlorofluoromethane	RA 14/87
Triethylamine	RA 2/83
Trimethylamine	RA 9/87
Vadium metaal en anorganische verbindingen	RA 10/87
Wood dust	RA 8/91
Xylene	RA 5/91
Zwaveldioxide (sulphur dioxide)	RA 4/85