EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
**C2 - Management of scientific committees; scientific co-operation and networks**

Brussels, C2/VR/csteeop/Cr/06022003 D(03)

# SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

**Opinion on the results of the Risk Assessment of:**

**Chromium trioxide (CAS No. 1333-82-0)**
**Sodium chromate (CAS No. 7775-11-3)**
**Sodium dichromate (CAS No. 10588-01-9)**
**Ammonium dichromate (CAS No. 7789-09-5)**
**Potassium dichromate (CAS No. 7778-50-9)**

**Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]**

**Adopted by the CSTEE during the 36th plenary meeting of 6 February 2003**

[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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## Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation) and on the basis of the examination of the Risk Assessment Report provided by the European Chemicals Bureau, the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report?

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

## INTRODUCTION

Chromates and chromium trioxide (Chromium$^{VI}$-compounds) are high production volume chemicals and sodium chromate as a precursor for other chromium$^{VI}$-compounds is produced from chromite ore. Chromates are used for a variety of purposes, for example as intermediates in chemical processes, in the manufacture of magnetic tapes and as wood preservatives.

## GENERAL COMMENTS

The document follows the recommendations of the TGD and is comprehensive, well written and clearly structured. The references to the table in the annex (Quantitative risk assessment, page 262) cannot be interpreted since they do not correspond to the numbering in the text.

## SPECIFIC COMMENTS

## HUMAN HEALTH RISK ASSESSMENT

### 1. EXPOSURE ASSESSMENT

For occupational exposure to chromium$^{VI}$-compounds, the inhalation and dermal routes are considered as important pathways. For consumer exposure and exposures from the environment, inhalation, dermal uptake and oral ingestion are considered.

To characterise worker exposure by inhalation, nine different scenarios, where chromium$^{VI}$-compounds are handled, are considered and inhalation exposures are based mainly on measured data from representative workplace environments; due to lack of data, the RAR models dermal exposures at the workplace using EASE and reasonable worst case assumptions. Highest occupational exposures by inhalation occur during the manufacture of chromium$^{VI}$ containing dyes and their application, dermal exposures are generally predicted to be low and may further be

reduced by wearing protective equipment. Human exposure to chromium$^{VI}$-compounds by handling cement, which contains chromates, is not dealt with in the exposure scenarios; the reasons for not including this relevant source of human dermal exposure to chromates are explained in a footnote in the risk characterisation part. The CSTEE has published a recent opinion on the problems associated with dermal exposure of humans to chromates when handling cement.

Consumer and combined exposures are modelled based on reasonable assumption and predicted to be 0.1 and 13 µg/kg bw. Regarding exposure assessment, the information presented on CCA-treated wood is inconclusive since other wood preservatives containing chromium$^{VI}$ are mentioned, but their market share and possible release of chromium$^{VI}$ are not given. What are the expected releases of chromium$^{VI}$ from the wood preservatives others than CCA? If there are major releases expected from these products, this may influence the risk characterisation.

Otherwise, the CSTEE finds the exposure estimates reasonable and agrees with the conclusions based on these estimates.

## 2. EFFECTS ASSESSMENT

### *Acute toxicity*

In experimental animals, chromium$^{VI}$-compounds are comparatively toxic with $LD_{50}$-values below 100 mg/kg bw and a reported $LC_{50}$-value (4 hour exposure) of 217 mg/m$^3$ for chromium trioxide. A number of case reports on human intoxications show that chromium$^{VI}$-compounds are also highly toxic after aerosol inhalation or after ingestion due to their corrosivity. In addition to local effects on the upper respiratory tract or the upper gastrointestinal tract, chromium$^{VI}$-compounds also have been observed to cause damage to the liver and the kidney and deaths in humans have even been reported after skin contact.

### *Irritation, corrosivity and sensitisation*

Highly water soluble chromium$^{VI}$-compounds and aqueous solutions of chromium trioxide are potent irritants to the skin, the eye and the mucous membranes of the upper respiratory tract. They are also skin and respiratory sensitizers based on patch-testing in patients with contact dermatitis, case reports and bronchial challenge experiments. The CSTEE agrees with these conclusions of the rapporteur.

### *Toxicokinetics*

As with many other metal ions, chromium$^{VI}$-compounds are poorly absorbed after administration by the oral route (< 5% of dose) and through the skin (< 1 to 4 % of applied dose in water), absorption of chromium$^{VI}$-compounds from the lungs into the bloodstream after inhalation is more effective and may reach 20 – 30 % of inhaled dose. Absorbed chromium$^{VI}$-compounds are rapidly reduced to chromium$^{III}$ after uptake by erythrocytes and are retained by erythrocytes. Excretion of chromium$^{VI}$-compounds occurs with urine and feces, mainly after metabolic reduction. The CSTEE agrees with the rapporteur that the kinetic behaviors of the substances under review in this RAR are expected to be very similar due to high water solubility and dissociation to chromate and dichromate ions in water.

***Repeated dose toxicity***

Only limited animal testing data are available for chromium$^{VI}$-compounds, the CSTEE agrees with the rapporteur that thresholds or NOAELs for skin and respiratory effects of chromium$^{VI}$-compounds in animals cannot be defined based on the available data. The NOAEL for testicular effects of sodium dichromate is supported. Experience with workplace exposure to chromium$^{VI}$-compounds in humans has clearly shown that irritation of the respiratory tract and the skin and skin corrosion are the major toxicities associated with repeated human exposure to chromium$^{VI}$-compounds.

***Genotoxicity***

Chromium$^{VI}$-compounds are mutagenic and clastogenic in a wide variety of standard in vitro test systems and in somatic cells in vivo. Genotoxicity is particularly found in the absence of chromium$^{VI}$-reducing agents such as glutathione, ascorbate, sulphite or tissue S9- or S12 fractions.

After parenteral administration of chromium$^{VI}$-compounds to laboratory animals, increases in chromosome aberrations and micronucleated cells in the bone marrow, DNA single strand breaks, interstrand cross-links and DNA protein cross-links in the liver, kidneys and lung were found. A mouse spot test with intraperitoneal administration of potassium chromate was positive.

Toxicokinetics and data from a dominant lethal assay with potassium dichromate indicate the potential of these compounds to also act as germ cell mutagens.

In limited or poorly reported studies, some evidence of genotoxicity was found in chromium exposed workers, whereas no such activity was reported from a few, but well conducted studies.

The CSTEE agrees with the rapporteur that the highly water soluble chromium$^{VI}$-compounds under review in this RAR should be considered as in vivo somatic and germ cell mutagens.

***Carcinogenicity***

Animal carcinogenicity studies were conducted on sodium dichromate and chromium trioxide. Sodium dichromate aerosols were carcinogenic in rats, producing lung tumours when administered by inhalation. In rats and mice, inhalation or intrabronchial implantation studies using chromium trioxide produced lung tumours.

Chromium$^{VI}$-compounds have not been tested by the oral or dermal routes for carcinogenic potential. Though poor absorption and reduction to Cr(III) may limit the carcinogenicity of chromium$^{VI}$-compounds on repeated dermal or oral exposure, the potential activity at the site of contact still raises concern.

A number of epidemiology studies in chromium exposed workers are available, but there is no study of workers that were exclusively exposed to the highly soluble chromium$^{VI}$-compounds under review in this RAR. An increased mortality from lung cancer was reported by several investigators, and IARC concluded in 1990 that there is sufficient evidence of carcinogenicity of chromium$^{VI}$-compounds in the chromate production, the chromate pigment production and chrome plating industries. Although only limited or no information on smoking habits was available in most studies, the magnitude of the risk and its relationship to duration of exposure is such that it cannot be explained by smoking alone. In chrome plating workers, the acidic nature of the chromium trioxide mists might have significantly contributed to tumour development.

From the available data it is not possible to relate the excess in lung cancer mortality in a reliable way to particular levels of chromium$^{VI}$-compounds in the atmosphere.

Results from a recently published study on lung cancer incidence in 1,087 chrome platers from 54 plants in Yorkshire are not discussed in the RAR. In this study, mortality from lung cancer between 1972 and 1997 was investigated in relation to the working histories before 1972 (Sorahan and Harrington, 2000). A significantly increased mortality from lung cancer was observed in male chrome platers (observed 60, expected 32.5, SMR 185, CI 141-238, $p< 0.001$). Information on duration of chrome work and smoking habits collected for a cross-sectional survey carried out in 1969-1972 was available for 84.3% of the chrome platers. This study should be discussed in the RAR.

The most recent IARC-evaluation (1997) of the carcinogenicity of chromium$^{VI}$ also identified an excess of cancers of the sinonasal cavity in workers occupationally exposed to chromates. The RAR should comment on this issue more extensively. In the present version, an association of chromate exposure and nasal cancer is not explicitly mentioned.

For the group of highly soluble chromium$^{VI}$-compounds, evidence of carcinogenicity exists for chromium trioxide (chromic acid) and sodium dichromate after inhalation exposure. In animal studies, the carcinogenicity of different chromium$^{VI}$-compounds differed markedly, and the carcinogenic potency of the highly soluble chromium$^{VI}$-compounds was comparatively low. Elevated lung cancer risks have been consistently observed in chromate production workers with inhalation exposures mainly to Cr(III) and water-soluble chromium$^{VI}$-compounds, in chromate pigment production workers with main inhalation exposures to water-soluble and water-insoluble chromates, and in chrome plating workers using chromium trioxide.

The CSTEE therefore agrees with the rapporteur that the chromium$^{VI}$-compounds in this RAR should be considered to have carcinogenic potential by the inhalation route. The CSTEE also agrees with the view that based on the available data and the genotoxicity of these chemicals, a dose-response relationship or threshold levels cannot be deduced.

### *Reproductive and developmental toxicity*

A number of studies on effects of chromium$^{VI}$-compounds on reproduction and development after drinking water administration of potassium dichromate to mice are reported, but no data are available after skin application or inhalation, which are more relevant pathways of human exposure to chromium$^{VI}$-compounds. Regarding fertility, a NOAEL of 60 mg chromium$^{VI}$/day was defined for male mice and of 20 mg chromium$^{VI}$/day for female mice, a NOAEL for developmental toxicity could not be defined based on the available data.

## 3. RISK CHARACTERISATION

### *Acute and repeated-dose toxicity*

Regarding acute toxicity over the whole workshift, conclusion ii) is reached and supported by the CSTEE. The CSTEE also supports conclusion iii) regarding short-term exposures to high concentrations of chromium$^{VI}$-compounds due to possible local effects. The CSTEE also supports conclusion iii) regarding skin, eye, and respiratory irritation and skin and respiratory sensitisation since dose-response relationships cannot be defined for these endpoints. Conclusion iii) regarding occupational asthma is also supported for workplace exposures.

Due to lack of adequate data to determine a MOS regarding repeated dose toxicity, conclusion i) is reached since further data on exposure-response relationships are required for a proper risk characterisation regarding these endpoints. This is supported by the CSTEE.

Regarding consumer and indirect exposure to chromium$^{VI}$-compounds, the calculated MOS-values for worst-case exposure scenarios are high and conclusion ii) is supported by the CSTEE for all endpoints except carcinogenicity and mutagenicity (see below).

***Genotoxicity and Carcinogenicity***

Chromium$^{VI}$-compounds can produce significant mutagenic activity *in vitro* and in somatic cells *in vivo*. Toxicokinetic data and results from a dominant lethal test suggest that these compounds have also the potential to be *in vivo* germ cell mutagens.

Chromium$^{VI}$-compounds have been shown in animal studies and through epidemiological studies to be carcinogenic in the respiratory tract by the inhalation route.

From the available information and taking into account the mutagenic properties of these compounds, it is not possible to identify a dose-response relationship or thresholds for mutagenicity and carcinogenicity. Thus, it is not therefore possible to calculate a toxicologically valid margin of safety.

The CSTEE generally agrees with the conclusion (iii) for workers, consumers, indirect exposure via the environment and combined exposure. However, specific reference to conclusion (iii)a and (iii)b should be removed. Instead, the magnitude of the risk should be described not only for workers, but also for consumers.

***Reproductive and developmental toxicity***

Conclusion iii) is reached regarding effects on development and fertility after workplace exposure to chromium$^{VI}$-compounds due to low calculated MOS (< 50) and issues of route of exposure and interspecies extrapolation with high degrees of uncertainty. The RAR explains the basis for these conclusions, which are supported by the CSTEE.

***Reference:***

Sorahan T, Harrington JM (2000): Lung cancer in Yorkshire chrome platers, 1972-97. Occup Environ Med 57(6): 385-389 (http://oem.bmjjournals.com/cgi/content/full/57/6/385)