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HEALTH EFFECTS ASSESSMENT FOR TRIVALENT CHROMIUM

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with trivalent chromium. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chromium. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-035. NTIS PB 81-117467.

U.S. EPA. 1983b. Health Assessment Document for Chromium. Prepared by the Environmental Criteria and Assessment Office, Research Triangle Park, NC. External review draft. EPA 600/8-83-014A. NITS PB 83-252205.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data are limited concerning the toxicological effects of trivalent chromium salts. Trivalent chromium appears to have a low order of toxicity, presumably due to very poor absorption, especially following oral exposure.

Only one subchronic study adequate for risk assessment was located. Cr_2O_3 was administered in the diet of rats for 90 days at levels of 2% and 5%. The estimated daily consumption of Cr(+3) is 1373 mg/kg for the 5% feeding level. Based on this, an AIS of 979 mg/day was calculated. Adequate subchronic inhalation data were not located.

Again, only one chronic feeding study was found, conducted by the same authors who reported the subchronic investigation. No adverse effects were seen at the highest feeding level, 5%. The daily intake at this level is estimated as 1467 mg Cr(+3)/kg. From these data, an AIC of 103 mg/day is estimated.

Chronic inhalation data were not located. An AIC of 0.357 mg Cr(+3)/day is estimated based on the TLV. All of these estimates should be reviewed as more complete data become available.

Data were not sufficient for derivation of a CS.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Chromium is a metallic element belonging to the First Transitional Series of the periodic table. Elemental chromium has a CAS Registry number of 7440-47-3. The three most stable forms in which chromium occurs in the environment are 0 (metal and alloys), +3 and +6 valence states. In the +3 valence state, the chemistry of chromium is dominated by the formation of stable hexa-coordinated complexes with both organic and inorganic ligands (Hartford, 1979). In the +6 valence state, chromium exists as oxo species such as CrO_3 and CrO_4^{2-} that are strongly oxidizing (Cotton and Wilkinson, 1980).

Chromium in the ambient air occurs from natural sources, industrial and product uses, and burning of fossil fuels and wood. The most important industrial sources of chromium in the atmosphere originate from ferrochrome production. Ore refining, chemical and refractory processing, cement producing plants, automobile brake lining and catalytic converters for automobiles also contribute to the atmospheric burden for chromium (Fishbein, 1981). Chromate chemicals used as mist inhibitors in cooling towers and the mist formed during chrome plating are probably the primary sources of Cr(+6) emitted as mists in the atmosphere (Towill et al., 1978).

Scarce information exists in the literature regarding the nature of the chemical species present in the atmosphere. Under normal conditions, Cr(+3) and Cr(0) in the air should not undergo any reaction (Towill et al., 1978). Cr(+6) in air could eventually react with dust particles or other pollutants to form Cr(+3) (NAS, 1974); however, the exact nature of such atmospheric reactions has not been studied extensively. Chromium is removed from air by atmospheric fallout and precipitation (Fishbein, 1981). The atmospheric half-life for the physical removal mechanism is expected to depend on the

particle size and particle density of atmospheric chromium. Chromium particles of small aerodynamic diameter (<10 μm) may remain airborne for long periods of time and may be transported great distances by wind currents and diffusion forces.

Surface runoff, deposition from air, and release of municipal and industrial wastewaters are the sources of chromium in surface waters. The most significant removal mechanism for Cr(+3) from the aquatic environment will be precipitation as $Cr_2O_3 \cdot xH_2O$ and eventually sedimentation of $Cr_2O_3 \cdot xH_2O$. Cr(+6), however, may exist in aquatic media as a water soluble complex anion and may persist in water for a long time. Cr(+6) is a moderately strong oxidizing agent and will react with organic matter or other reducing agents to form Cr(+3). Eventually, Cr(+3) will be precipitated as $Cr_2O_3 \cdot xH_2O$. Therefore, in surface water rich in organic content, Cr(+6) will exhibit a much shorter lifetime (Callahan et al., 1979).

Chromium probably occurs as the insoluble $Cr_2O_3 \cdot xH_2O$ in soil, given that organic matter in soil is expected to convert any soluble chromate to insoluble Cr_2O_3 (U.S. EPA, 1983b). There is no known chemical process that can cause chromium to be lost from soil. The primary processes by which chromium is lost from soil are physical. For example, chromium in soil can be transported to the atmosphere by way of aerosol formation (U.S. EPA, 1983b). Chromium is also transported from soil through runoff. Runoff can remove both chromium ions and bulk precipitates of chromium. In addition, flooding of soils and the subsequent anaerobic decomposition of plant matter may increase dissolution of Cr_2O_3 in soil through complexation (U.S. EPA, 1983b). The water soluble complexes may cause leaching of chromium from soil. Page (1981) reported the detection of a small concentration (1 μg/ℓ mean concentration) of chromium at a frequency of ~100% in groundwater collected from New Jersey.

The BCF for Cr(+6) in fish muscle appears to be <1.0, but values of 125 and 192 were obtained for oyster and blue mussel, respectively (U.S. EPA, 1980b). For Cr(+3), BCF values of 116, 153 and 86 were obtained with the American oyster, soft shell clam and blue mussel (U.S. EPA, 1983b).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Donaldson and Barreras (1966) administered $^{51}CrCl_3$ (chromium chloride) orally to human patients. Based on fecal excretion of ^{51}Cr, absorption was ~0.4%. When $^{51}CrCl_3$ was administered intraduodenally, absorption was not appreciably changed.

In a number of animal studies, gastrointestinal absorption of trivalent chromium (as $CrCl_3$) was estimated to be <3% (Mertz et al., 1965; Visek et al., 1953; MacKenzie et al., 1959; Ogawa, 1976). Furthermore, Mertz et al. (1965) reported that absorption in rats was independent of the administered dose and dietary history (deficient or supplemented in chromium).

2.2. INHALATION

Trivalent chromium is absorbed very slowly by inhalation. Baetjer et al. (1959a) administered $CrCl_3$ to guinea pigs intratracheally. Ten minutes post-treatment, 69% of the administered dose remained in the lungs, while 4% was found in the blood and tissues. Percentages of administered chromium found in the lungs 24 hours, 30 days and 60 days post-treatment were 45, 30 and 12%, respectively. These investigators hypothesized that the slow absorption of trivalent chromium (which is water soluble) is due to the fact that it forms insoluble complexes with macromolecules. Furthermore, gastrointestinal absorption following clearance from the respiratory tract may be a factor when chromium compounds are administered by inhalation. Visek et al. (1953) found similar results when $^{51}CrCl_3$ was instilled intratracheally in guinea pigs. In this study, absorption from the lungs was estimated to be ~5%. There was also evidence of gastrointestinal absorption because 55 and 7% of the administered ^{51}Cr had been recovered from the feces and urine, respectively, within 7 days.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Subchronic studies regarding oral exposure to trivalent chromium are summarized in Table 3-1. The study by Akatsuka and Fairhall (1934) cannot be used for quantitative risk assessment since the dose and duration of exposure were not defined precisely. The study by MacKenzie et al. (1958) suggests a NOEL at 25 ppm $CrCl_3$, equivalent to 8.2 ppm trivalent chromium. Assuming that an average rat weighs 0.35 kg and consumes 0.035 ℓ water/day, 8.2 ppm is adjusted to 0.82 mg trivalent chromium/kg bw/day.

The study by Ivankovic and Preussman (1975) suggests a NOAEL of 5% Cr_2O_3 (50,000 ppm) based on depression of spleen and liver weights. The authors calculated, based on measured food consumption and body weight, that male rats in the 5% feeding group consumed 180 g/kg of Cr_2O_3 total over the 88-day experimental period (discerned from body weight graph). This corresponds to 1399 mg/kg/day of Cr(+3).

3.1.2. Inhalation. Only one subchronic animal study regarding exposure to trivalent chromium by inhalation was located in the available literature. Akatsuka and Fairhall (1934) exposed two cats to chromium carbonate dust at a level that varied from 3.3-83 mg/m³ (average = 58.3 mg/m³) for 86 sessions. Each session varied from 10-60 minutes, averaging 28 minutes for one cat and 57 minutes for the other. No effects in terms of gross or microscopic pathology were observed upon termination of the experiment. Examination of control animals, if there were any, was not reported.

No human data that could be used in quantitative risk assessment of inhalation exposure to trivalent chromium were located in the available literature.

TABLE 3-1

Subchronic Oral Toxicity of Trivalent Chromium

Species	Number	Compound	Vehicle	Dose	Duration	Effects	Reference
Rat	12 males, 9 females	$CrCl_3$	drinking water	0, 25 ppm	12 months	No change in body weight. No changes in macroscopic or microscopic pathology, or clinical chemistry variables.	MacKenzie et al., 1958
Rat	6 males, 6 females/ control; 14 males, 5 females/2%; 5 males, 10 females/5%	Cr_2O_3	bread	0, 2, 5%	5 days/week for 90 days	No effect on body weight, urological or hematological variables, or food intake. Slight reduction in spleen and liver weights at 2 and 5% levels.	Ivankovic and Preussman, 1975
Cat	10	chromium carbonate, chromium phosphate	feed	50-100 mg/cat/day	1-3 months	No effect on weights or gross or microscopic pathology of major organs.	Akatsuka and Fairhall, 1934

3.2. CHRONIC

3.2.1. Oral. Only one chronic study regarding oral exposure to trivalent chromium was located. Ivankovic and Preussman (1975) fed 60 male and female rats (per dose group) 0, 1, 2 or 5% Cr_2O_3, baked in bread on 5 days/week for 600 feeding days (120 weeks). The authors estimated, based on measures of food consumption and body weight, that rats consumed 360 g/kg bw, 720 g/kg bw and 1800 g/kg bw of total Cr_2O_3 over the duration of the study in the 1, 2 and 5% Cr_2O_3 feeding groups, respectively. The highest dose level (5%), which represented a total Cr_2O_3 consumption for 600 days of feeding of 1800 g/kg bw, corresponds to a total Cr (+3) intake of 1232 g/kg or 1467 mg/kg/day, expanding exposure over 840 days (600 days at 5 days/week = 120 weeks or 840 days). Adverse effects were not noted at any feeding level.

3.2.2. Inhalation. Exposure to vapors of chromium salts have been suspected as a cause of asthma in occupationally-exposed workers. Until recently, chromium specific immunoglobulin E antibodies had not been found in affected workers to confirm the connection between chromium and asthma. Recently, however, Novey et al. (1983) identified chromium specific antibodies in a 32-year-old white male worker who experienced a productive cough, wheezing and dyspnea within 2 weeks of beginning a new job electroplating with chromium. Laboratory testing of this individual was performed with placebo, nickel and chromium solutions vaporized by heat. The nickel and chromium solutions precipitated asthmatic symptoms identical to those experienced on the job. The authors concluded that the affected individual developed an acquired sensitivity to chromium and nickel vapors.

Pertinent data regarding chronic exposure of animals to trivalent chromium by inhalation could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of orally administered trivalent chromium could not be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled trivalent chromium could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding toxicant interactions of trivalent chromium with other compounds could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of orally administered trivalent chromium could not be located in the available literature.

4.1.2. Inhalation. Occupational exposure to trivalent chromium and other chromium compounds by inhalation has been studied in the chromate manufacturing and ferrochromium industries; however, exposures all include mixed exposures to both Cr(+3) and Cr(+6). The Cr(+6) species is the likely etiological agent in reports of excess cancer risk in chromium workers. Data addressing exposures to Cr(+3) alone are not available.

4.2. BIOASSAYS

4.2.1. Oral. The results of several studies indicate that trivalent chromium is not carcinogenic in mice or rats.

Schroeder et al. (1965) exposed 54 male and 54 female Swiss mice to drinking water that contained 5 ppm chromium (as chromium acetate) for life. No increase in the incidence of tumors was seen in the treated animals with respect to controls. Similar results were obtained by Schroeder et al. (1965) for Long-Evans rats.

Ivankovic and Preussman (1975) fed chromium trioxide in bread to 60 male and female rats at levels of 1, 2 or 5%, 5 days/week for 2 years. No difference was seen between controls and treated animals with respect to tumor incidence.

4.2.2. Inhalation. Several animal studies indicate that trivalent chromium compounds are not carcinogenic when administered by inhalation, either by natural routes (Baetjer et al., 1959a), intrapleural injection (Baetjer et al., 1959b; Hueper and Payne, 1962) or intrabronchial implantation (Levy and Venitt, 1975; Levy and Martin, 1983).

4.3. OTHER RELEVANT DATA

In general, trivalent chromium was not mutagenic in bacterial assays when tested with or without a mammalian activation system (Venitt and Levy, 1974; Petrilli and Deflora, 1977, 1978a,b). In one study, trivalent chromium was mutagenic in Bacillus subtilis, but this activity was low compared with compounds of hexavalent chromium (Nakamuro et al., 1978).

There is conflicting information with regard to the ability of trivalent chromium to interact with DNA. Compounds of trivalent chromium were found to be clastogenic in BALB/c cells as $CrCl_3$ (Raffetto, 1977), CHO cells as $CrCl_3$, $Cr(NO_3)_3$, $KCr(SO_4)_2$ or $Cr(CH_3COO)_3$ (Levis and Majone, 1979), Don Chinese hamster cells as hydrated $CrCl_3$ (Ohno et al., 1982) and in cultured human leukocytes as $Cr(CH_3COO)_3$ (Nakamuro et al., 1978), but not in mouse FM3A cells as $Cr_2(SO_4)_3$ (Umeda and Nishimura, 1979), cultured human leukocytes as $CrCl_3$ or $Cr(NO_3)_3$ (Nakamuro et al., 1978) or Don Chinese hamster cells as $Cr_2(SO_4)_3$ (Ohno et al., 1982).

4.4. WEIGHT OF EVIDENCE

IARC (1980) concluded that animal data are inadequate for the evaluation of the carcinogenicity of Cr(+3) compounds. Furthermore, although there is sufficient evidence of respiratory carcinogenicity associated with exposure to chromium, the relative contributions of Cr(+3), Cr(+6), metallic chromium or soluble versus insoluble chromium to carcinogenicity cannot be elucidated.

Applying the criteria for evaluating the overall weight of evidence for carcinogenicity to man proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), trivalent chromium is most appropriately designated a Group D - Not Classified material.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1983) has recommended a TLV-TWA of 0.5 mg/m³ for occupational exposure to trivalent chromium. This level was established in order to minimize toxic effects and to protect against pulmonary disease.

The U.S. EPA (1982) has established a criterion of 59 mg/ℓ for trivalent chromium in water. This is derived from the interim ADI of 125 mg/man/day (see Section 3.1.1.) (Ivankovic and Preussman, 1975).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Based on the study by Ivankovic and Preussman (1975), the NOAEL of 1399 mg trivalent chromium/kg bw/day for depression of spleen and liver weights in rats can be used to calculate an AIS. Dividing 1399 mg/kg/day by an uncertainty factor of 100 (10 to account for the range of sensitivities in the human population, 10 for extrapolating from animal data to humans), an AIS of 13.99 mg/kg/day is established for ingestion of trivalent chromium. Assuming an average human weighs 70 kg, this is equivalent to 979 mg/man/day.

6.1.2. Inhalation. Only one study (Akatsuka and Fairhall, 1934) regarding the effects of subchronic inhalation of trivalent chromium was located in the available literature. Only two cats were exposed, however, and neither the doses nor the durations of exposure were precisely defined; therefore, these data cannot be used in quantitative risk assessment.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The NOEL of 5% Cr_2O_3 [1467 mg Cr(+3)/kg bw/day calculated from measured food and body weight factors] derived from the chronic study by Ivankovic and Preussman (1975) on rats can be used as the basis for the calculation of an AIC. Dividing the NOEL of 1467 mg/kg/day by an uncertainty factor of 1000 (10 to account for the range of sensitivities in the human population; 100 for extrapolating from animal studies to humans and because effects seen in the subchronic study were not specifically addressed in the chronic study), an AIC of 1.467 mg/kg bw/day is established for trivalent chromium. Assuming an average human body weight of 70 kg, this is equivalent to 103 mg/man/day.

This value differs from the ADI of 125 mg/man/day derived by the U.S. EPA (1982) from the Ivankovic and Preussman (1975) study because the U.S. EPA (1980b) did not convert ppm Cr_2O_3 to ppm trivalent chromium, and used standard reference values for the rat for food consumption and body weight in lieu of figures reported in Ivankovic and Preussman (1975).

6.2.2. **Inhalation.** Since quantitative chronic exposure studies regarding inhalation of trivalent chromium were not located in the available literature, an AIC may be calculated from the TLV of 0.5 mg/m³ established by the ACGIH (1983). Adjusting to units of mg/man/day, 0.5 mg/m³ x 5/7 days/week x the average work day human inhalation rate (10 m³/day) = 3.57 mg/man/day. Dividing 3.57 mg/man/day by an uncertainty factor of 10 (to account for the range of sensitivities in the human population), an AIC of 0.357 mg/man/day is established for chronic inhalation of trivalent chromium.

6.2.3. **Composite Score.** U.S. EPA (1983c) calculated CSs for chromium and compounds using data from two inhalation and two oral studies. These experiments were conducted with hexavalent forms of chromium. U.S. EPA (1983c) also reviewed the study in rats in which a slight reduction in spleen and liver weights was observed in animals fed bread containing Cr_2O_3 for 90 days (Ivankovic and Preussman, 1975). Since similar signs did not appear in rats treated with Cr_2O_3 containing bread for 2 years (Ivankovic and Preussman, 1975), the toxicological significance of the apparent effects on liver and spleen weights in the subchronic study was questionable and a CS was not derived from these data (U.S. EPA, 1983c). No other studies with trivalent chromium were found from which a CS could be calculated. Therefore, in their review of the data base for trivalent chromium, U.S. EPA (1983a) calculated no CSs based on studies with trivalent chromium.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. IARC (1980) has concluded that animal data are inadequate for the evaluation of the carcinogenicity of Cr(+3) compounds. The two oral studies located in the available literature (Schroeder et al., 1965; Ivankovic and Preussman, 1975) reported negative results for rats and mice.

6.3.2. Inhalation. Data are inadequate for the evaluation of the carcinogenicity of Cr(+3) compounds. Animal studies have been negative (Baetjer et al., 1959a,b; Hueper and Payne, 1962; Levy and Venitt, 1975; Levy and Martin, 1983).

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APPENDIX

Summary Table for Trivalent Chromium

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS				ND	
AIC	human	TLV-TWA = 0.5 mg/m³	none	0.357 mg/man/day	ACGIH, 1983
Oral					
AIS	rat	5% Cr_2O_3 = NOAEL	slight reduction in liver and spleen weights	979 mg/man/day	Ivankovic and Preussman, 1975
AIC	rat	5% Cr_2O_3 = NOEL	none	103 mg/man/day	Ivankovic and Preussman, 1975
Maximum composite score				ND	U.S. EPA, 1983a

ND = Not derived