EPA-540/1-86-019

Office of Emergency and
Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental
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Environmental Criteria and
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Cincinnati OH 45268

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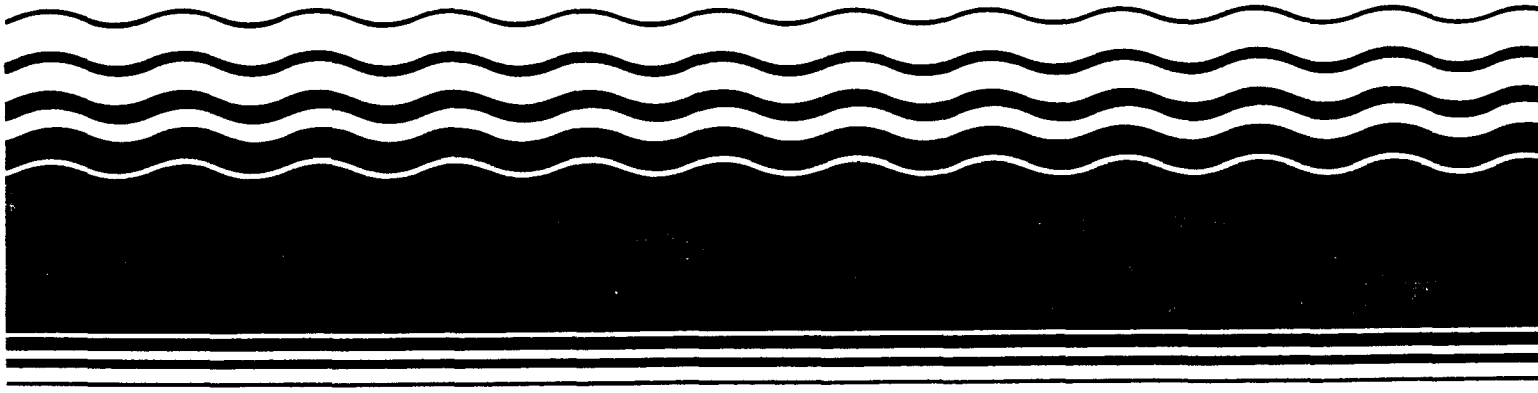
HEALTH EFFECTS ASSESSMENT FOR HEXAVALENT CHROMIUM



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September 1984

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U.S. Environmental Protection Agency
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This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with hexavalent 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. 1983a. Reportable Quantity Document for Chromium (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for Chromium. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-014F. NTIS PB 85-115905.

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 (1983).

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.

Chromium exposure has been shown to contribute to increased incidence of respiratory cancers in occupationally exposed workers. The particular form(s) of chromium responsible is not clear. Increases in cancer incidence in experimental animals following chromium inhalation has not been demonstrated. However, intrapleural and intrabronchial implantation of hexavalent chromium compounds has resulted in tumors at the site of implantation. Hexavalent chromium has been shown to be mutagenic in bacterial systems. Using human epidemiological data, a unit risk of 41 $(mg/kg/day)^{-1}$ has been estimated for inhalation exposure. Data are not available to assess the potential carcinogenicity of hexavalent chromium following oral exposure.

Data are inadequate to consider chromium as a carcinogen by the oral route. Using data from a 1-year rat drinking water exposure study, an oral AIC of 0.35 mg/day is estimated.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

In the hexavalent state, chromium exists as oxo species (such as CrO_3, CrO_4^{2-} and CrO_2Cl_2) that are strongly oxidizing (Cotton and Wilkinson, 1980). The CAS Registry numbers and the solubilities of a few important hexavalent chromium compounds are given in Table 1-1.

In solution, hexavalent chromium exists as hydrochromate ($HCrO_4^-$), chromate (CrO_4^{2-}) and dichromate ($Cr_2O_7^{2-}$) ionic species. The proportion of each ion in solution is pH dependent. In basic and neutral pH, the chromate form predominates. As the pH is lowered (6.0 to 6.2), the hydrochromate concentration increases. At very low pH, the dichromate species predominate (U.S. EPA, 1984).

The primary sources of hexavalent chromium in the atmosphere probably are chromate chemicals used as rust inhibitors in cooling towers and emitted as mists, particulate matter emitted during manufacture and use of metal chromates, and chromic acid mist from the plating industry. Hexavalent chromium in air could eventually react with dust particles or other pollutants to form trivalent chromium (NAS, 1974); however, the exact nature of such atmospheric reactions has not been studied extensively. Both hexavalent and trivalent chromium are 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. Chromium particles of small aerodynamic diameter (<10 μm) may remain airborne for a long period (U.S. EPA, 1984).

Hexavalent chromium may exist in aquatic media as water soluble complex anions and may persist in water for a long time. Hexavalent chromium is a moderately strong oxidizing agent and may react with organic matter or other

TABLE 1-1

CAS Numbers and Aqueous Solubilities of Selected Hexavalent Chromium Compounds*

Compound	CAS No.	Water Solubility
Ammonium chromate $(NH_4)_2\ CrO_4$	7788-98-9	40.5 g/100 mℓ at 30°C
Calcium chromate $CaCrO_4$	13765-19-0	2.23 g/100 mℓ at 20°C
Potassium chromate K_2CrO_4	7789-00-6	62.9 g/100 mℓ at 20°C
Potassium dichromate $K_2Cr_2O_7$	7789-50-9	4.9 g/100 mℓ at 0°C
Sodium chromate Na_2CrO_4	7775-11-3	87.3 g/100 mℓ at 30°C
Chromic acid CrO_3	1333-82-0	61.7 g/100 mℓ at 0°C

*Sources: Weast, 1980; Hartford, 1979

reducing agents to form trivalent chromium. The trivalent chromium will eventually be precipitated as $Cr_2O_3 \cdot xH_2O$. Therefore, in surface water rich in organic content, hexavalent chromium will exhibit a much shorter lifetime (Callahan et al., 1979).

Any hexavalent chromium in soil is expected to be reduced to trivalent chromium by the organic matter in soil. The primary processes by which the converted trivalent chromium is lost from soil are aerial transport through aerosol formation and surface water transport through runoff (U.S. EPA, 1984). Very little chromium is leached from soil because it is present as insoluble $Cr_2O_3 \cdot xH_2O$ (Fishbein, 1981).

The BCF for hexavalent chromium in fish muscle appears to be <1.0 (U.S. EPA, 1980b), but values of 125 and 192 were obtained for oyster and blue mussel, respectively (U.S. EPA, 1980b).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Absorption of ingested hexavalent chromium is estimated to be <5%. Donaldson and Barreras (1966) fed $Na_2{}^{51}CrO_4$ to rats and humans. Based on mean urinary excretion of ^{51}Cr, absorption was estimated to be 2.1% in humans. In rats, ~2% of the administered dose was absorbed based on fecal excretion of ^{51}Cr. When $Na_2{}^{51}CrO_4$ was administered intraduodenaly (in humans) or intrajejunally (in rats), however, absorption was estimated to ~50 and ~25%, respectively.

MacKenzie et al. (1959) administered $Na_2{}^{51}CrO_4$ to rats by gavage. Based on urinary excretion, absorption was estimated to be 6% in fasted rats and 3% in nonfasted rats.

2.2. INHALATION

A study by Langard et al. (1978) indicates that water-soluble hexavalent chromium is absorbed rapidly by inhalation. Rats were exposed to zinc chromate dust at a level of 7.35 mg/m³. After 0, 100, 250 and 350 minutes of exposure, the concentrations of chromium in the blood (µg/mℓ) were 0.007, 0.024, 0.22 and 0.31, respectively.

In the second part of this study, rats were exposed to the same level for 6 hours on 4 consecutive days. Blood concentrations appeared to peak at the end of the second exposure and then began to decline slowly. Mean blood chromium values measured at the end of each exposure period averaged 0.03, 0.56, 0.46 and 0.34 µg/mℓ for exposures 1-4, respectively. No significant differences in absorption as reflected by blood chromium levels were noted between the sexes or between day and night exposures.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Data from two subchronic studies involving oral exposure to hexavalent chromium are summarized in Table 3-1.

MacKenzie et al. (1958) exposed groups of rats, both male and female, to potassium dichromate (0-25 ppm of hexavalent chromium) in drinking water for 1 year. Since no effects were observed at any level of treatment, a NOEL can be established based on body weight, gross external condition, histopathological analysis and blood chemistry. Converting 25 ppm to mg/kg/day, 25 ppm (mg/ℓ water) is multiplied by the average water consumption/day for a rat (0.035 ℓ/day), and divided by the weight of an average rat (0.35 g), to give a value of 2.50 mg/kg/day.

The study by Gross and Heller (1946), lacking detailed pathological analysis and sufficiently large sample sizes (two animals/treatment level), cannot be used for quantitative risk assessment.

3.1.2. Inhalation. Pertinent data regarding subchronic exposure of animals to hexavalent chromium by inhalation could not be located in the available literature; however, there are many studies regarding occupational exposure of humans to hexavalent chromium.

Bloomfield and Blum (1928) examined 23 men from 6 chromium plating plants in the United States. Fourteen of these workers typically spent 2-7 hours/day over vats of chromic acid, which generated airborne hexavalent chromium ranging from 0.12-5.6 mg/m^3. These men experienced nasal tissue damage, including perforated septum (2), ulcerated septum (3), chrome holes (6), nosebleed (9) and inflamed mucosa (9). In general, the 9 remaining workers examined, not directly exposed to chromium vapors, had only inflamed mucosae.

TABLE 3-1

Subchronic Oral Toxicity of Hexavalent Chromium in Rats

Number of Animals	Dose and Compound	Period of Exposure	Endpoints Monitored and Effect	Reference
9 females, 12 males at 25 ppm 10 males, 10 females at 0 ppm 8 males, 8 females at other treatment levels	0, 0.45, 2.2, 4.5, 7.7, 11, 25 ppm as potassium dichromate in drinking water	1 year	No effect based on body weight, gross external condition, histopathological analysis and blood chemistry.	MacKenzie et al., 1958
1 male, 1 female per level of treatment	0, 0.036, 0.072, 0.143, 0.28% Cr(VI) as zinc chromate or 0, 0.033, 0.067, 0.134 or 0.268% Cr(VI) as potassium chromate in feed	2-3 months	Animals were "subnormal" and sterile at all doses of zinc chromate and at 0.134 and 0.268% potassium chromate.	Gross and Heller, 1946

Several other studies report nasal tissue destruction resulting from hexavalent chromium. The United States Health Public Service conducted a study of workers in seven chromate-producing plants in the early 1950s. The results indicated severe nasal tissue destruction but exposure levels were not measured; hence, the data are of limited usefulness (Federal Security Agency, 1953).

Mancuso (1951) reported on physical examinations of a random sample of 97 workers from a chromate-chemical plant. The results, presented in Table 3-2, indicated that 61 of the 97 workers (63%) had septal perforation. The data suggested to the author that Cr(III) may be partly responsible for the perforations; however, later studies have not provided support for this theory.

The results of examinations of nine workers in a chrome-plating plant are shown in Table 3-3. Analyses of air samples showed chromium concentrations of 0.18-1.4 mg/m^3. Some degree of nasal septal ulceration was seen in 7 of the 9 men, with 4 of 7 demonstrating frank perforations (Kleinfeld and Russo, 1965). The effects of chromium exposure for a specific length of time at a fixed concentration were not studied.

Vigliani and Zurlo (1955) reported nasal septal perforation in workers exposed to chromic acid and chromates in concentrations of 0.11-0.15 mg/m^3. The lengths of exposure were not known. Otolaryngologic examinations of 77 persons exposed to chromic acid aerosol during chrome plating revealed 19% to have septal perforation and 48% to have nasal mucosal irritation. These people averaged 6.6 years of exposure to an air chromium concentration of 0.4 mg/m^3. In 14 persons, papillomas of the oral cavity and larynx were found. The diagnosis of papilloma was confirmed by histologic examination. There were no signs of atypical growth or malignant degeneration (Hanslian et al., 1967).

TABLE 3-2

Perforation of Nasal Septum in Chromate Workers*

Ratio of insol Cr^{+3} to sol Cr^{+6}	Chromium concentration, $\mu g/m^3$ (as Cr)	No. Workers Examined	Workers with Septal Perforation	
			No.	%
Workers in plant				
≤1.0:1	≤0.25	4	2	50
	0.26 - 0.51	7	3	43
	≤0.52	8	4	50
1.1 to 4.9:1	≤0.25	9	7	78
	0.26 - 0.51	32	20	63
	≥0.52	15	11	73
≥5.0:1	≤0.25	7	2	29
	0.26 - 0.51	2	1	50
	≥0.52	13	11	85
TOTAL		97	61	63
Office workers	0.06	4	0	0

*Source: Mancuso, 1951

insol = insoluble; sol = soluble

TABLE 3-3

Nasal Lesions in a Chromium-Plating Plant*

Case	Age (yrs)	Duration of Exposure (mos)	Findings
1	30	6	perforated septum
2	19	2	perforated septum
3	19	12	perforated septum
4	18	9	perforated septum
5	47	10	ulcerated septum
6	45	6	ulcerated septum
7	23	1	ulcerated septum
8	20	0.5	moderate injection of septum and turbinates
9	48	9	moderate injection of septum

*Source: Kleinfeld and Russo, 1965

The literature suggests that chromium compounds are also responsible for a wide variety of other respiratory effects. German studies demonstrating mixed results from exposure to chromium compounds were reviewed by the U.S. EPA (1984). Because in all of these studies no correlation between symptomatology, physical signs, length of exposure and dose of chromium compounds was available, they are not useful for risk assessment and are not reviewed here.

In the United States, 897 workers in chromate-producing plants had a higher incidence of severely red throats and pneumonia, but did not show any increase in the incidence of other respiratory diseases when compared with control groups. Although bilateral hilar enlargement was observed, there was no evidence of excessive pulmonary fibrosis in these workers (Federal Security Agency, 1953). The various lung changes described in these workers may represent a nonspecific reaction to irritating material or a specific reaction to chromium compunds. Many of the conditions mentioned occur widely in the general population (NAS, 1974).

Gomes (1972) examined 303 employees who worked in 81 electroplating operations in Sao Paulo, Brazil. Over two-thirds of the workers had mucous membrane or cutaneous lesions, with many of them having ulcerated or perforated nasal septa. The duration of exposure was not stated, but the author mentioned that the harmful effects were noted in <1 year. A direct correlation between workers exposed to a given airborne concentration of chromium (VI) and the development of harmful effects could not be made.

Cohen and Kramkowski (1973) and Cohen et al. (1974) examined 37 workers employed by a chromium-plating plant. Within 1 year of employment, 12 workers experienced nasal ulceration or perforation. The airborne chromium (VI) concentrations ranged from <0.71-9.12 $\mu g/m^3$.

In a chromium plating plant where the maximum airborne chromium (VI) concentration was 3 μg/m³, no ulcerated nasal mucosa or perforated nasal septa were found; however, half of the 32 employees had varying degrees of mucosal irritation (Markel and Lucas, 1973). The authors did not consider this to be significant, because the survey was carried out at the peak of the 1972-1973 influenza epidemic.

Machle and Gregorius (1948) reported an incidence of nasal septal perforation of 43.5% in 354 employees who worked in a chromate-producing plant that manufactured sodium chromate and bichromate. At the time of the study, airborne chromate concentrations ranged from 10 to 2800 μg/m³. The plant had been in operation for at least 17 years, and some employees probably worked in the plant when reverberatory furnaces, a prominent source of high chromate exposure, were used.

In a more recent study, lung function, the condition of the nasal septum and subjective symptoms related to respiratory health (data obtained by questionnaire) were compared in unexposed controls (119) and workers (43) exposed to chromic acid in chrome plating operations (Lindberg and Hedenstierna, 1983). Workers were further divided into low (<2) and high ($\geq$2 μg Cr^{+6}/m^3) exposure groups. Complaints of diffuse nasal symptoms ("constantly running nose," "stuffy nose" or "a lot to blow out") were registered by 4/19 workers in the low group and half of the 24 workers in the high group. Complaints were not registered by workers exposed to <1 μg/m³. The frequency of throat and chest symptoms did not appear to be related to treatment.

Examination of the nasal septum revealed that damage was significantly greater in exposed workers than in unexposed controls and appeared to be somewhat more severe in the high group than the low group. Measurements of

lung function revealed a detrimental effect due to exposure to chromic acid fumes, but significant differences between low and high groups were not observed. There was a tendency for lung function parameters to return to normal over a 2-day weekend.

Various other disease states have been attributed to chromium, but, in most cases, the etiologic relation to chromium is doubtful because of the presence of other chemicals (NAS, 1974). These studies, reviewed by the U.S. EPA (1984), will not be reviewed here.

3.2. CHRONIC

3.2.1. Oral. Only one chronic study pertaining to the oral toxicity of hexavalent chromium was located in the available literature. Anwar et al. (1961) exposed dogs orally to potassium chromate in drinking water for 4 years. Treatment levels were 0, 0.45, 2.25, 4.5, 6.75 and 11.2 ppm potassium chromate; there were two dogs/group. No effects were observed with regard to gross and microscopic analysis of all major organs, urinalysis, and weights of spleen, liver and kidney. The exposure of 11.2 ppm can be converted to units of mg/kg/day by multiplying 11.2 ppm by the average daily water consumption for a dog of average weight (0.0275 ℓ/kg/day) to produce a NOEL of 0.31 mg potassium chromate/kg/day. This is equivalent to 0.089 mg Cr(VI)/kg/day.

3.2.2. Inhalation. Data regarding the chronic toxicity of hexavalent chromium administered by inhalation are summarized in Table 3-4.

Nettesheim et al. (1971) exposed mice to an aerosol of calcium chromate at levels of either 10 mg/m³ (4.33 mg Cr(VI)/m³) or 30 mg/m³ (10 mg Cr(VI)/m³) for 5 hours/day, 5 days/week for life. Based on epithelial necrosis, marked hyperplasia and atrophy of the pulmonary bronchi, emphysema-like changes, and atrophy of the spleen and liver, a LOAEL can be

TABLE 3-4

Chronic Toxicity of Hexavalent Chromium to Animals Exposed by Inhalation

Species	Number of Animals	Dose and Compound	Period of Exposure	Endpoints Monitored and Effect	Reference
Mice	136 total (male and female); unspecified number of controls	13 or 30 mg calcium chromate aerosol/m³ [4.33 or 10 mg Cr(VI)/m³, respectively]	5 hours/day, 5 days/week for life	At 6-month intervals, bacteriological, parasitological, virological and histopathological analyses were performed. 10 mg/m³ level: early death, rapid weight loss, fatty liver, distended and atrophic intestines 4.33 mg/m³ level: epithelial necrosis, marked hyperplasia and atrophy of pulmonary bronchi, alveolar scarring after 6 months; after 2 years, atrophy of spleen and liver	Nettesheim et al., 1971
Rats	100	2 mg calcium chromate aerosol/m³ [0.67 Cr(VI)/m³]	589/891 days	Laryngeal hyperplasia (2) and laryngeal metaplasia (3) were found upon examination immediately after treatment was stopped.	Laskin, 1972
Hamsters	100			Squamous metaplasia (8) and laryngeal hyperplasias (8) were found immediately after treatment was stopped. No other details were provided.	

established at 4.33 mg Cr(VI)/m³. Adjusting to units of mg/kg/day, 4.33 mg/m³ is multiplied by the product of 5 hours/24 hour day times 5 days of exposure/week times the average inhalation rate/day for a mouse (0.05 m³/day). This value is subsequently divided by the average body weight of a mouse (0.03 kg) to yield a value of 1.07 mg CR(VI)/kg/day.

Laskin (1972) exposed rats and hamsters to calcium chromate aerosol at a level of 2 mg/m³ (0.67 mg Cr(VI)/m³) for 589 of 891 days. Although some laryngeal hyperplasias and metaplasias were observed in both species tested, details pertaining to controls were not given in the available review.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

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

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

3.4. TOXICANT INTERACTIONS

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

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent human data regarding the carcinogenicity of ingested hexavalent chromium could not be located in the available literature.

4.1.2. Inhalation. Occupational exposure to chromium compounds via inhalation has been studied in the chromate, chrome-plating and chrome pigment industries.

Workers in the chromate industry are exposed to both trivalent and hexavalent compounds of chromium. Epidemiological studies of chromate production plants in Japan, Great Britain, West Germany and the United States have revealed a correlation between occupational exposure to chromium and lung cancer, but the specific etiological agent was not identified (Machle and Gregorius, 1948; Brinton et al., 1952; Baetjer, 1950a,b; Mancuso and Hueper, 1951; Mancuso, 1975; Taylor, 1966; Enterline, 1974; Hayes et al., 1979; Hill and Ferguson, 1979; Bidstrup, 1951; Bidstrup and Case, 1956; Alderson et al., 1981; Todd, 1962; Watanabe and Fukuchi, 1975; Ohsaki et al., 1978; Sano and Mitohara, 1978; Satoh et al., 1981; Korallus et al., 1982). Of these, the studies by Mancuso and Hueper (1951) and Mancuso (1975) are of interest, since they were used by the Carcinogen Assessment Group to derive a cancer-based criterion for lifetime exposure to chromium (U.S. EPA, 1984).

Mancuso and Hueper (1951) analysed the vital statistics of a cohort of chromate workers (employed for >1 year from 1931-1949 in a Painesville, OH chromate plant) in order to investigate lung cancer associated with chromate production. Of the 2931 deaths of males in the county where the plant was located, 34 (1.2%) were due to respiratory cancer. Of the 33 deaths among the chromate workers, however, 6 (18.2%) were due to respiratory cancer.

The difference between these groups is significant at $p<0.01$. Furthermore, two of these workers exposed primarily to insoluble chromite had ~390 and 250 μg chromium/10 g of lung tissue, respectively. By contrast, chromium levels in the lungs of nonexposed individuals were nearly zero.

In an update of the Mancuso and Hueper (1951) study, Mancuso (1975) followed 332 of the workers employed from 1931-1951 until 1974. By 1974, >50% of this cohort had died. Of these men, 63.6, 62.5 and 58.3% of the cancer deaths for men employed from 1931-1932, 1933-1934 and 1935-1937, respectively, were due to lung cancer. Mancuso (1975) reported that these lung cancer deaths were related to insoluble (trivalent), soluble (hexavalent) and total chromium exposure, but the small numbers involved make this relationship questionable (U.S. EPA, 1984).

In two studies derived from the chrome pigment industry, workers were exposed only to hexavalent chromium. In both studies, exposure to chromium was correlated with lung cancer (Langard and Norseth, 1975; Davies, 1978, 1979).

Studies from the chrome-plating industry either demonstrated a correlation between lung cancer and exposure to chromium compounds (Royle, 1975), or were inconclusive (Silverstein et al., 1981; Okubo and Tsuchiya, 1979).

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenicity of orally administered hexavalent chromium in animal systems could not be located in the available literature.

4.2.2. Inhalation. To date, it has not been possible to induce tumors in laboratory animals by exposing them to chromium (either trivalent or hexavalent) via inhalation.

Baitjer et al. (1959) chronically exposed three strains of mice (Strain A, Swiss, C57B1) and mixed-breed rats to ~1 mg chromium dust/m^3, and reported no increase in the incidence of lung tumors with respect to untreated controls. Similar results were obtained by Steffee and Baetjer (1965) for Wistar rats, rabbits and guinea pigs exposed to chromium dust.

Nettesheim et al. (1971) exposed C57B1 mice to 4.33 mg calcium chromate dust/m^3, 5 hours/day, 5 days/week for life, and reported an increase in the number of lung tumors with respect to controls. Since statistical analysis was not performed, however, the significance of these results is unclear. In a review of this study, IARC (1980) concluded that a significant excess of treatment-related tumors was not observed.

There is some evidence that hexavalent chromium may be carcinogenic following intrapleural implantation of calcium chromate (Hueper and Payne, 1962) or intrabronchial implantation of strontium chromate, calcium chromate or zinc chromate (Levy and Martin, 1983). These tumors, however, were observed at the site of implantation. In addition, Steinhoff et al. (1983) have shown that intratracheal administration to rats both $Na_2Cr_2O_7$ and $CaCrO_4$ produced increased incidences of lung tumors following 30 months of administration.

In contrast, zinc chromate was not carcinogenic following intratracheal implantation (Steffee and Baetjer, 1965; Baetjer et al., 1959), nor were barium chromate, chromium dust, lead chromate, chromite ore, powdered chromium metal, potassium chromate and sodium dichromate following intrabronchial, intrapleural or intratracheal implantation (Steffee and Baetjer, 1965; Baetjer et al., 1959; Hueper, 1955, 1958; Payne, 1960; Hueper and Payne, 1962; Levy and Venitt, 1975).

4.3. OTHER RELEVANT DATA

Hexavalent chromium has been shown to be mutagenic in bacterial systems in the absence of a mammalian activating system (Venitt and Levy, 1974; Nishioka, 1975; Nakamuro et al., 1978; Green et al., 1976; Kanematsu et al., 1980; Lofroth and Ames, 1978; Newbold et al., 1979; Bonatti et al., 1976; Fukanaga et al., 1982), and not mutagenic when a mammalian activating system is present (Lofroth, 1978; Petrilli and Deflora, 1977, 1978a,b). Hexavalent chromium is also mutagenic in eucaryotic test systems (Bonatti et al., 1976; Newbold et al., 1979; Fukanaga et al., 1982) and clastogenic in cultured mammalian cells (Raffetto, 1977; Levis and Majone, 1979; Umeda and Nishimura, 1979; Tsuda and Kato, 1977; Newbold et al., 1979; Nakamuro et al., 1978; Stella et al., 1982; Ohno et al., 1982; Gomez-Arroyo et al., 1981; Wild, 1978; Sarto et al., 1982).

4.4. WEIGHT OF EVIDENCE

IARC (1980) has concluded that there is sufficient evidence of respiratory carcinogenicity in men occupationally exposed during chromate production; however, the epidemiological data do not allow elucidation of the relative contributions to carcinogenic risk of metallic chromium, trivalent chromium, hexavalent chromium, or of soluble versus insoluble chromium compounds. Furthermore, the animal studies using non-natural routes of administration have provided sufficient evidence that certain compounds of hexavalent chromium (sintered calcium chromate, lead chromate, strontium chromate, sintered chromium trioxide and zinc chromate) are carcinogenic. Therefore, IARC (1982) classified chromium and chromium compounds as Group I chemicals. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), hexavalent chromium is most appropriately designated a Group A - Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Recommended standards for occupational exposure to hexavalent chromium compounds are summarized in Table 5-1.

The U.S. EPA (1980b) has recommended a criterion of 0.05 mg/ℓ for the concentration of hexavalent chromium in water. They also established an interim ADI of 0.175 mg/man/day for chronic ingestion of hexavalent chromium based on the study of MacKenzie et al. (1958). These levels are not intended to protect against potential carcinogenic effects of chromium VI compounds. The considered opinion when these levels were suggested was that Cr(VI) would potentially be reduced in the gastrointestinal tract to Cr(III). Although this is a plausible assumption, conclusive data are not available.

TABLE 5-1

Standards for Occupational Exposure to Cr(VI)

Compound	Standard (mg/m^3)	Reference
Noncarcinogenic chromium VI*	0.025 TWA 0.050 ceiling	NIOSH, 1975
Carcinogenic chromium	0.001 TWA	NIOSH, 1975
Soluble chromic or chromous salt	0.500 TWA	OSHA, 1978
Insoluble salts	1.000 TWA	OSHA, 1978
Water soluble compounds of chromium (VI) (noncarcinogenic)	0.05 TWA	ACGIH, 1983
Insoluble compounds of chromium (VI) (carcinogenic potential)	0.05 TWA	ACHIH, 1983

*Monochromates and dichromates of hydrogen, lithium, potassium, rubidium, cesium, ammonium and chromic oxide

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. A 1-year oral study has established a NOEL for hexavalent chromium in rats of 2.5 mg/kg/day (MacKenzie et al., 1958) (see Section 3.1.1.). Applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability) and assuming a 70 kg body weight results in an estimated oral AIS of 1.75 mg/day.

6.1.2. Inhalation. Hexavalent chromium has been shown to be a human carcinogen by the inhalation route for which data are sufficient for computation of a q_1*. It is inappropriate, therefore, to calculate an inhalation AIS for hexavalent chromium.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Using the oral AIS of 1.75 mg/day and applying an additional uncertainty factor of 5 to adjust for a study which is of intermediate duration between subchronic and chronic results in an estimated oral AIC of 0.35 mg/day. This is the approach recommended by U.S. EPA (1985).

6.2.2. Inhalation. Hexavalent chromium has been shown to be a human carcinogen for which data are sufficient for computation of a q_1*. It is inappropriate, therefore, to calculate an inhalation AIC for hexavalent chromium.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. The lack of data regarding the carcinogenicity of orally administered hexavalent chromium precludes assessment of carcinogenic risk.

6.3.2. Inhalation. Based on the epidemiological study of Mancuso (1975), the Carcinogen Assessment Group has derived a cancer-based criterion for exposure to chromium by inhalation (U.S. EPA, 1984). Assuming a lifetime

exposure to 1 μg elemental chromium/m^3, the upper limit unit carcinogenic risk was estimated to be 1.16×10^{-2} $(\mu g/m^3)^{-1}$ in units of lifetime risk per 1 $\mu g/m^3$ exposure for humans. This unit risk may be transformed to units of $(mg/kg/day)^{-1}$ as follows: the concentration of 1 $\mu g/m^3$ is equivalent to 20 μg/day or 0.02 mg/day assuming a human respiratory rate of 20 m^3/day. Assuming an average human weighs 70 kg, the dosage becomes 2.857×10^{-4} mg/kg/day. The unit risk of 1.16×10^{-2} $(\mu g/m^3)^{-1}$ ÷ 2.857×10^{-4} mg/kg/day results in an expression of unit risk of 41 $(mg/kg/day)^{-1}$.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. p. 15.

Alderson, M.R., N.S. Rattan and L. Bidstrup. 1981. Health of workmen in the chromate-plating industry in Britain. Br. J. Ind. Med. 38: 117-124. (Cited in U.S. EPA, 1984)

Anwar, R.A., C.F. Langham, C.A. Hoppert, B.V. Alfredson and R.U. Byerrum. 1961. Chronic toxicity studies. III. Chronic toxicity of cadmium and chromium in dogs. Arch. Environ. 3: 456. (Cited in U.S. EPA, 1984)

Baetjer, A.M. 1950a. Pulmonary carcinoma in chromate workers. I. A review of the literature and report of cases. Arch. Ind. Hyg. Occup. Med. 2: 487-504. (Cited in U.S. EPA, 1984)

Baetjer, A.M. 1950b. Pulmonary carcinoma in chromate workers. II. Incidence on basis of hospital records. Arch. Ind. Hyg. Occup. Med. 2: 505-516. (Cited in U.S. EPA, 1984)

Baetjer, A.M., J.F. Lowney, H. Steffee and V. Budacz. 1959. Effect of chromium on incidence of lung tumors in mice and rats. Arch. Ind. Health. 20: 124-135. (Cited in IARC, 1980; U.S. EPA, 1984)

Bidstrup, P.L. 1951. Carcinoma of the lung in chromate workers. Br. J. Med. 8: 302-305. (Cited in U.S. EPA, 1984)

Bidstrup, P.L. and R.A.M. Case. 1956. Carcinoma of the lung in workmen in the bichromates-producing industry in Great Britain. Br. J. Ind. Med. 13: 260-264. (Cited in U.S. EPA, 1984)

Bloomfield, J.J. and W. Blum. 1928. Health hazards in chromium plating. Public Health Rep. 43: 2330-2351. (Cited in U.S. EPA, 1984)

Bonatti, S., M. Meini and A. Abbondandolo. 1976. Genetic effects of potassium dichromate in Schizosaccharomyces pombe. Mutat. Res. 38: 147-150. (Cited in U.S. EPA, 1984)

Brinton, H.P., E.S. Rasier and A.L. Koven. 1952. Morbidity and mortality experience among chromate workers. Public Health Rep. 67: 835-847. (Cited in U.S. EPA, 1984)

Callahan, M.A., M.W. Slimak and N.W. Bagel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. II. U.S. EPA, Office of Water Planning and Standards, Office of Water and Waste Management, Washington, DC. EPA 440/4-79-029.

Cohen, S.R. and R.S. Kramkowsi. 1973. Health Hazard Evaluation Determination, Report No. 72-118-104. Cincinnati, OH, U.S. DHEW, NIOSH. (Cited in U.S. EPA, 1984)

Cohen, S.R., D.M. Davis and R.S. Kramkowski. 1974. Clinical manifestations of chromic acid toxicity -- Nasal lesions in electroplate workers. Cutis. 13: 558-568. (Cited in U.S. EPA, 1984)

Cotton, F.A. and G. Wilkinson. 1980. Advanced Organic Chemistry. A Comprehensive Test, 4th ed. John Wiley and Sons, NY. p. 719-736.

Davies, J.M. 1978. Lung-cancer mortality of workers making chrome pigments. Lancet. 1: 384. (Cited in U.S. EPA, 1984)

Davies, J.M. 1979. Lung cancer mortality in workers in chromate pigment manufacture: An epidemiological survey. J. Oil Chem. Assoc. 62: 157-163. (Cited in U.S. EPA, 1984)

Donaldson, R.M. and R.F. Barreras. 1966. Intestinal absorption of trace quantities of chromium. J. Lab Clin. Med. 68: 484-493. (Cited in U.S. EPA, 1984)

Enterline, P.E. 1974. Respiratory cancer among chromate workers. J. Occup. Med. 16: 523-526. (Cited in U.S. EPA, 1984)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. Federal Register. 49: 46294-46299.

Federal Security Agency. 1953. Health of Workers in Chromate Producing Industry. A Study. U.S. Public Health Service Publication No. 192. Washington, DC. U.S. Government Printing Office. 131 p. (Cited in U.S. EPA, 1984)

Fishbein, L. 1981. Source, transport and alterations of metal compounds: An Overview. I. Arsenic, beryllium, cadmium, chromium and nickel. Environ. Health Perspect. 40: 43-64.

Fukanaga, M., Y. Kurachi and Y. Mizuguchi. 1982. Action of some metal ions on yeast chromosomes. Chem. Pharm. Bull. 30: 3017-3019. (Cited in U.S. EPA, 1984)

Gomes, E.R. 1972. Incidence of chromium-induced lesions among electroplating workers in Brazil. Ind. Med. 41: 21-25. (Cited in U.S. EPA, 1984)

Gomez-Arroyo, S., M. Altamirano and R. Villalobos-Pietrini. 1981. Sister-chromatid exchanges induced by some chromium compounds in human lymphocytes in vitro. Mutat. Res. 90: 425-431. (Cited in U.S. EPA, 1984)

Green, M.H.L., W.J. Muriel and B.A. Bridges. 1976. Use of a simplified fluctuation test to detect low levels of mutagens. Mutat. Res. 38: 33-42. (Cited in U.S. EPA, 1984)

Gross, W.G. and U.G. Heller. 1946. Chromium in animal nutrition. J. Ind. Hyg. Toxicol. 28: 52. (Cited in U.S. EPA, 1984)

Hanslian, L., J. Nauratil, J. Jurak and M. Kotrle. 1967. Upper respiratory tract lesions from chromic acid aerosols. Pracovni. Lekar. 19:294-298. (Czech., English Abstr.) (Cited in U.S. EPA, 1984).

Hartford, W.H. 1979. Chromium Compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 6, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 82-120.

Hayes, R.B., A.M. Lilienfield and L.M. Snell. 1979. Mortality in chromium chemical production workers: A prospective study. Internat. J. Epidemiol. 8: 365-374.

Hill, W.J. and W.S. Ferguson. 1979. Statistical analysis of epidemiological data from chromium chemical manufacturing plant. J. Occup. Med. 21: 103-106. (Cited in U.S. EPA, 1984)

Hueper, W.C. 1955. Experimental studies in metal carcinogenesis. VII. Tissue reactions to parenterally introduced powdered metallic chromium and chromite ore. J. Natl. Cancer Inst. 16(2): 447-469. (Cited in U.S. EPA, 1984)

Hueper, W.C. 1958. Experimental studies in metal cancerogenesis. X. Cancerogenic effects of chromite ore roast deposited in muscle tissue and pleural cavity of rats. Am. Med. Assoc. Arch. Ind. Health. 18: 284-291. (Cited in U.S. EPA, 1984)

Hueper, W.C. and W.W. Payne. 1962. Experimental studies in metal carcinogenesis -- Chromium, nickel iron arsenic. Arch. Environ. Health. 5: 445-462. (Cited in IARC, 1980; U.S. EPA, 1984)

IARC (International Agency for Research on Cancer). 1980. Chromium and Chromium Compounds. In: Some Metals and Metallic Compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyon, France. 23: 205-323.

IARC (International Agency for Research on Cancer). 1982. Results and Conclusions. In: Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyon, France. 1-29 (Suppl. 4): 18.

Kanematsu, N., M. Hara and T. Kada. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat. Res. 77: 109-116. (Cited in U.S. EPA, 1984)

Kleinfeld, M. and A. Russo. 1965. Ulcerations of the nasal septum due to inhalation of chromic acid mist. Ind. Med. Surg. 34: 242-243. (Cited in U.S. EPA, 1984)

Korallus, V., H. Lange, A. Ness, E. Wuestefeld and T. Zwingers. 1982. Relationships between precautionary measures and bronchial carcinoma mortality in the chromate-producing industry. Arbeitsmedizin, Social Medizin Preventivmedizin. 17(7): 159-167. (Cited in U.S. EPA, 1984)

Langard, S. and T. Norseth. 1975. A cohort study of bronchial carcinomas in workers producing chromate pigments. Br. J. Ind. Med. 32: 62-65. (Cited in U.S. EPA, 1984)

Langard, S., NJ. Gundersen, D.L. Tsalev and B. Glyseth. 1978. Whole blood chromium level and chromium execretion in the rat after zinc chromate inhalation. Acta. Pharmacol. Toxicol. 42:142-149. (Cited in U.S. EPA, 1984)

Laskin, S. 1972. Research in Environmental Sciences, Washington, DC., Institute of Environmental Medicine. p. 92-97. (Cited in IARC, 1980)

Levis, A.G. and F. Majone. 1979. Cytotoxic and clastogenic effects of soluble chromium compounds on mammalian cell cultures. Br. J. Cancer. 40: 523-533. (Cited in U.S. EPA, 1984)

Levy, L.S. and P.A. Martin. 1983. The effects of a range of chromium-containing materials on rat lung. Dye Color Manufacturers Assoc.

Levy, L.S. and S. Venitt. 1975. Carcinogenic and mutagenic activity of chromium containing materials. Br. J. Cancer. 32: 254-255. (Cited in IARC, 1980)

Lindberg, E. and G. Hedenstierna. 1983. Chrome plating: Symptoms, finding in the upper airways, and effects on lung functions. Arch. Environ. Health. 38(6): 367-374.

Lofroth, G. 1978. The mutagenicity of hexavalent chromium is decreased by microsomal metabolism. Naturwissenschaften. 65: 207-208. (Cited in U.S. EPA, 1984)

Lofroth, G. and B.N. Ames. 1978. Mutagenicity of inorganic compounds in Salmonella typhimurium: Arsenic, chromium and selenium. Am. Environ. Mut. Soc. 8th Meeting, February 13-17, 1977, Colorado Springs. Mutat. Res. 53: 65-66. (Cited in U.S. EPA, 1984)

Machle, W. and F. Gregorius. 1948. Cancer of the respiratory system in the United States chromate-producing industry. Public Health Rep. 63(35): 1114-1127. (Cited in U.S. EPA, 1984)

MacKenzie, R.D., R.U. Byerrum, C.F. Decker, C.A. Hoppert and F.L. Langham. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. Am. Med. Assoc. Arch. Ind. Health. 18: 232-234. (Cited in U.S. EPA, 1984)

MacKenzie, R.D., R.A. Anwar, R.U. Byerrum and C.A. Hoppert. 1959. Absorption and distribution of ^{51}Cr in the albino rat. Arch. Biochem. Biophys. 79: 200-250. (Cited in U.S. EPA, 1984)

Mancuso, T.F. 1951. Occupational cancer and other health hazards in a chromate plant: A mdeical appraisal. I. Lung cancer in chromate workers. Ind. Med. Sing. 20: 358-363. (Cited in U.S. EPA, 1984)

Mancuso, T.F. 1975. International Conference on Heavy Metals in the Environment, Ioronto, Canada, Oct. 27-31. (Cited in Towill et al., 1978; U.S. EPA, 1984)

Mancuso, T.F. and W.C. Hueper. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal. I. Lung cancer in chromate workers. Ind. Med. Surg. 20: 358-363. (Cited in NIOSH, 1975; U.S. EPA, 1984)

Markel, H.L., Jr. and J.B. Lucas. 1973. Health Hazard Evaluation Report 72-106. Cincinnati, OH, U.S. DHEW, NIOSH, Division of Technical Services, Hazard Evaluation Services Branch. (Cited in NIOSH, 1975; U.S. EPA, 1984)

Nakamuro, K., K. Yoshikawa, Y. Sayato and H. Kurata. 1978. Comparative studies of chromosomal aberration and mutagenicity of trivalent and hexavalent chromium. Mutat. Res. 58: 175-181. (Cited in U.S. EPA, 1984)

NAS (National Academy of Sciences). 1974. Medical and Biological Effects of Environmental Pollutants: Chromium. National Academy Press, Washington, DC. (Cited in U.S. EPA, 1984)

Nettesheim, P., M.G. Hanna, Jr., D.G. Doherty, R.F. Newell and A. Hellman. 1971. Effect of calcium chromate dust, influenza virum, and 100 R whole-body X-radiation on lung tumor incidence in mice. J. Natl. Cancer Inst. 47: 1129-1144. (Cited in IARC, 1980; U.S. EPA, 1984)

Newbold, R.F., J. Amos and J.R. Connell. 1979. The cytotoxic, mutagenic and clastogenic effects of chromium-containing compounds on mammalian cells in culture. Mutat. Res. 67: 55-63. (Cited in U.S. EPA, 1984)

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185-189. (Cited in U.S. EPA, 1984)

NIOSH (National Institute for Occupational Safety and Health). 1975. Criteria for a Recommended Standard...Occupational Exposure to Chromium (VI). U.S. DHEW, PHS, CDC, Rockville, MD.

Ohno, H., F. Hanaoka and M. Yanada. 1982. Inducibility of sister-chromatid exchanges by heavy-metal ions. Mutat. Res. 104: 141-145. (Cited in U.S. EPA, 1984)

Ohsaki, Y., S. Abe, K. Kimura, Y. Tsunita, H. Mikami and M. Murao. 1978. Lung cancer in Japanese chromate workers. Thorax. 33: 372-374. (Cited in U.S. EPA, 1984)

Okubo, T. and K. Tsuchiya. 1979. Epidemiological study of chromium plater in Japan. Biol. Trace Element Res. 1: 35-44. (Cited in U.S. EPA, 1984)

OSHA (Occupational Safety and Health Administration). 1978. Air contaminents. 29 CFR. 1910.1000. p. 99-100. (Cited in U.S. EPA, 1984)

Payne, W.W. 1960. Production of trace elements in whole blood by photon-induced x-ray fluorescence. Eur. J. Nucl. Med. 2: 277-279. (Cited in IARC, 1980)

Petrilli, F.L. and S. DeFlora. 1977. Toxicity and mutagenicity of hexavalent chromium on Salmonella typhimurium. Appl. Environ. Microbiol. 33: 805-809. (Cited in U.S. EPA, 1984)

Petrilli, F. and S. DeFlora. 1978a. Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. Mutat. Res. 58: 167-178. (Cited in U.S. EPA, 1984)

Petrilli, F.L. and S. DeFlora. 1978b. Metabolic deactivation of hexavalent chromium mutagenicity. Mutat. Res. 54: 139-147. (Cited in U.S. EPA, 1984)

Raffetto, G. 1977. Direct interaction with cellular targets as the mechanism for chromium carcinogenesis. Tumorigenesis. 63: 503-512. (Cited in U.S. EPA, 1984)

Royle, H. 1975. Toxicity of chromic acid in the chromium plating industry (2). Environ. Res. 10: 141-163. (Cited in U.S. EPA, 1984)

Sano, T. and I. Mitohara. 1978. Occupational cancer among chromium workers. Jap. J. Chest Disorders. 37: 90-101. (Cited in U.S. EPA, 1984)

Sarto, F., I. Ceminato, V. Bianihi and A.G. Lewis. 1982. Increased incidence of chromosomal aberrations and sister chromatid exchanges in workers exposed to chromic acid (CrO3) in electroplating factories. Carcinogenesis (London). 3: 1011-1016. (Cited in U.S. EPA, 1984)

Satoh, H., Y. Fukuda, K. Terii and N. Chika Katsuno. 1981. Epidemiologic study of workers engaged in the manufacturing of chromium compounds. J. Occup. Med. 23(12: 835-838. (Cited in U.S. EPA, 1984)

Silverstein, M., F. Mirer, D. Kotelchuck, B. Siverstein and M. Bennett. 1981. Mortality among workers in a die-casting and electroplating plant. Scand. J. Work Environ. Health. 7(4): 156-165. (Cited in U.S. EPA, 1984)

Stella, M., A. Mentaldi, R. Rossi, G. Rossi and A.G. Levis. 1982. Clastogenic effects of chromium on human lymphocytes in vitro and in vivo. Mutat. Res. 101: 151-164. (Cited in U.S. EPA, 1984)

Steffee, C.H. and A.M. Baetjer. 1965. Histopathological effects of chromate chemicals. Report of studies in rabbits, guinea pigs, rats and mice. Arch. Environ. Health. 11: 66. (Cited in U.S. EPA, 1984)

Steinhoff, S., C. Gud, G.K. Hatfield and U. Mohr. 1983. Listing sodium dichromate and soluble calcium chromate for carcinogenicity in rats. Bayer AG Institute of Toxicology. (Sept., Unpublished) (Cited in U.S. EPA, 1984)

Taylor, F.H. 1966. The relationship and duration of employment as reflected by a cohort of chromate workers. Am. J. Public Heath. 56: 218-229. (Cited in U.S. EPA, 1984)

Todd, G.E. 1962. Tobacco manufacturer's standing committee research papers. No. 1. Statistics of Smoking in the United Kingdom, 3rd ed. Tobacco Research Council, London. (Cited in U.S. EPA, 1984)

Towill, L.E., C.R. Shriner, J.S. Drury, A.S. Hammons and J.W. Holleman. 1978. Reviews of the environmental effects of pollutants: III. Chromium. Prepared for Health Effects Research Laboratory, Office of Research and Development, U.S. EPA, Cincinnati, OH. Report No. ORNL/EIS-80 and EPA 600/1-78-023. (Cited in U.S. EPA, 1984)

Tsuda, H. and K. Kato. 1977. Chromosomal aberrations and morphological transformation in hamster embryonic cells treated with potassium dichromate. Mutat. Res. 46: 87-94. (Cited in U.S. EPA, 1984)

Umeda, M. and M. Nishimura. 1979. Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. Mutat. Res. 67: 221-229. (Cited in U.S. EPA, 1984)

U.S. EPA. 1980a. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45: 79347-79357.

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. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for Chromium. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-014F. NTIS PB 85-115905.

U.S. EPA. 1985. Acceptable Daily Intakes for Volatile Organic Chemicals, Inorganic Chemicals and Synthetic Organic Chemicals. Criteria and Standards Division, Office of Drinking Water. (Federal Register Draft)

Venitt, S. and L.S. Levy. 1974. Mutageniticy of chromates in bacteria and its relevance to chromate carcinogenesis. Nature. 250: 493-495. (Cited in U.S. EPA, 1984)

Vigliani, E.C. and N. Zurlo. 1955. Efahrung der Clinica del Lavoro mit einigen maximalen Arbitsplatzkonzentrationen (MAk) von Industriegiften. Arch. Gewerbepath. Gewerbhyg. 13:528-534. (Ger.) (Cited in U.S. EPA, 1984)

Watanabe, S. and Y. Fukuchi. 1975. An epidemiological survey on lung cancer in workers of a chromate-producing industry in Hokkaido, Japan. Presented at International Congress on Occupational Health. (Cited in U.S. EPA, 1984)

Weast, R.C., Ed. 1980. Handbook of Chemistry and Physics, 61st ed. CRC Press, Boca Raton, FL. p. B73-166.

Wild, D. 1978. Cytogenetic effects in the mouse of 17 chemical mutagens and carcinogens evaluated by the micronucleus test. Mutat. Res. 56: 319-327. (Cited in U.S. EPA, 1984)

APPENDIX

Summary Table for Hexavalent Chromium

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
			Carcinogenicity		
Inhalation	human	1 $\mu g/m^3$	lung tumors	41 $(mg/kg/day)^{-1}$	U.S. EPA, 1984; Mancuso, 1975
Oral				ND	

Route	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
			Systemic Toxicity		
Inhalation					
AIS				ND	
AIC				ND	
Oral					
AIS	rat	0-25 ppm in drinking water for 1 year (2.5 mg/kg)	none	1.75 mg/day	MacKenzie et al., 1958
AIC	rat	0-25 ppm in drinking water for 1 year (2.5 mg/kg)	none	0.35 mg/day	MacKenzie et al., 1958

ND = Not derivable