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

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# HEALTH EFFECTS ASSESSMENT FOR HEXAVALENT CHROMIUM

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# 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

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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<br>10 males, 10 females at 0 ppm<br>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, histo-pathological 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/m³. 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/m³. 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/m³. 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 | | | | |
| $\leq$1.0:1 | $\leq$0.25 | 4 | 2 | 50 |
| | 0.26 - 0.51 | 7 | 3 | 43 |
| | $\leq$0.52 | 8 | 4 | 50 |
| 1.1 to 4.9:1 | $\leq$0.25 | 9 | 7 | 78 |
| | 0.26 - 0.51 | 32 | 20 | 63 |
| | $\geq$0.52 | 15 | 11 | 73 |
| $\geq$5.0:1 | $\leq$0.25 | 7 | 2 | 29 |
| | 0.26 - 0.51 | 2 | 1 | 50 |
| | $\geq$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 $Cr^{+6}$/m³) 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/m$^3$ (4.33 mg Cr(VI)/m$^3$) or 30 mg/m$^3$ (10 mg Cr(VI)/m$^3$) 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.<br>10 mg/m³ level: early death, rapid weight loss, fatty liver, distended and atrophic intestines<br>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, C57Bl) 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 C57Bl 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<br>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 $\mu g$ elemental chromium/$m^3$, the upper limit unit carcinogenic risk was estimated to be $1.16 \times 10^{-2}$ $(\mu g/m^3)^{-1}$ 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 $\mu g$/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 $2.857 \times 10^{-4}$ mg/kg/day. The unit risk of $1.16 \times 10^{-2}$ $(\mu g/m^3)^{-1}$ $\div$ $2.857 \times 10^{-4}$ mg/kg/day results in an expression of unit risk of 41 $(mg/kg/day)^{-1}$.

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APPENDIX

Summary Table for Hexavalent Chromium

| Carcinogenic Potency | Species | Experimental Dose/Exposure | Effect | $q_1^*$ | Reference |
|---|---|---|---|---|---|
| | | | **Carcinogenicity** | | |
| Inhalation | human | 1 μg/m³ | 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