Chromium (VI) ; CASRN 18540-29-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Chromium (VI)

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/03/1998
Inhalation RfC (I.B.)	yes	09/03/1998
Carcinogenicity Assessment (II.)	yes	09/03/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Chromium (VI)
CASRN — 18540-29-9
Last Revised — 09/03/1998

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
None Reported **Rat, 1-year drinking water study** **MacKenzie et al., 1958**	NOAEL: 25 mg/L of chromium as K_2CrO_4 2.5 mg/kg-day (adj.) LOAEL: None	300	3	3E-3 mg/kg-day

*Conversion Factors and Assumptions — Drinking water consumption = 0.1 L/kg-day (reported).

I.A.2. Principal and Supporting Studies (Oral RfD)

MacKenzie, RD; Byerrum, RU; Decker, CF, et al. (1958) Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. Am Med Assoc Arch Ind Health 18:232-234.

Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0.45-11.2 ppm (0.45-11.2 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group (10/sex) received distilled water. A second experiment involved three groups of 12 male and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (as K_2CrO_4), a second received 25 ppm chromium in the form of chromic chloride, and the controls again received distilled water. No significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K_2CrO_4) showed an approximate 20% reduction in water consumption. Based on the body weight of the rat (0.35 kg) and the average daily drinking water consumption for the rat (0.035 l/day), this dose can be converted to give an adjusted NOAEL of 2.5 mg/kg-day chromium(VI).

For rats treated with 0-11 ppm (in drinking water), blood was examined monthly, and tissues (livers, kidneys, and femurs) were examined at 6 mo and 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except

that no animals were killed at 6 mo. An abrupt rise in tissue chromium concentrations was noted in rats treated with more than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group. Similar no-effect levels have been observed in dogs. Anwar et al. (1961) observed no significant effects in female dogs (2/dose group) given up to 11.2 ppm chromium(VI) (as K_2CrO_4) in drinking water for 4 years. The calculated doses were 0.012-0.30 mg/kg of chromium(VI).

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 300.

The uncertainty factor of 300 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 3 to compensate for the less-than-lifetime exposure duration of the principal study.

MF = 3.

The modifying factor of 3 is to account for concerns raised by the study of Zhang and Li (1987).

I.A.4. Additional Studies/Comments (Oral RfD)

This RfD is limited to soluble salts of hexavalent chromium. Examples of soluble salts include potassium dichromate ($K_2Cr_2O_7$), sodium dichromate ($Na_2Cr_2O_7$), potassium chromate (K_2CrO_4), and sodium chromate (Na_2CrO_4). Trivalent chromium is an essential nutrient. There is evidence to indicate that hexavalent chromium is reduced in part to trivalent chromium in vivo (Petrilli and DeFlora, 1977, 1978; Gruber and Jennette, 1978).

In 1965, a study of 155 subjects exposed to drinking water at concentrations of approximately 20 mg/L was conducted outside Jinzhou, China. Subjects were observed to have sores in the mouth, diarrhea, stomachache, indigestion, vomiting, elevated white blood cell counts with respect to controls, and a higher per capita rate of cancers, including lung cancer and stomach cancer. Precise exposure concentrations, exposure durations, and confounding factors were not discussed, and this study does not provide a NOAEL for the observed effects. However, the study suggests that gastrointestinal effects may occur in humans following exposures to hexavalent chromium at levels of 20 ppm in drinking water (Zhang and Li, 1987).

Zahid et al. (1990) fed BALB/C albino Swiss mice trivalent (chromium disulfate) and hexavalent (potassium dichromate) chromium at concentrations of 100, 200, and 400 ppm for 35 days in the diet. The author concluded that a small but significant increase of hexavalent chromium in the testes of fed animals induced significant degeneration. The National Toxicology Program (1996a,b, 1997) recently conducted a three-part study to investigate the potential reproductive toxicity of hexavalent chromium in rats and mice. The study included oral administration of potassium dichromate in Sprague-Dawley rats, a repeat of the study of Zahid et al. (1990) using BALB/C mice, and a reproductive assessment by continuous breeding study in BALB/C mice. The reproductive assessment indicated that potassium dichromate administered at 15-400 ppm in the diet is not a reproductive toxicant in either sex of BALB/C mice or Sprague-Dawley rats.

Several reports of possible fetal damage caused by chromium compounds were located in the literature. High doses (250-1,000 ppm) of orally administered chromium (VI) compounds have been reported to cause developmental toxicity in mice (Trivedi et al., 1989). The authors observed significant increases in preimplantation and postimplantation losses and dose-dependent reductions in total weight and crown-rump length in the lower dose groups. Additional effects included treatment-related increases in abnormalities in the tail and wrist forelimbs, and subdermal hemorrhagic patches in the offspring.

Junaid et al. (1996) and Kanojia et al. (1996) exposed female Swiss albino mice and female Swiss albino rats, respectively, to 250, 500, or 750 ppm potassium dichromate in drinking water to determine the potential embryotoxicity of hexavalent chromium during days 6-14 of gestation. The authors reported retarded fetal development and embryo- and fetotoxic effects including reduced fetal weight, reduced number of fetuses (live and dead) per dam, and higher incidences of stillbirths and post-implantation loss in the 500 and 750 ppm dosed mothers. Significantly reduced ossification in bones was also observed in the medium- and high-dose groups. Based on the body weight and the drinking water ingested by the animals in the 250 ppm dose group, the exposure levels in the 250 ppm groups can be identified as 67 mg/kg-day and 37 mg/kg-day in mice and rats, respectively.

The Junaid et al. (1996) and Kanojia et al. (1996) studies utilized doses approximately 10-fold higher than those used in Mackenzie et al (1958), but neither of the reproductive studies identified a clear NOAEL for the embryotoxic effects of hexavalent chromium. On the basis of the body weight and the drinking water ingested by the animals in the low-dose groups (250 ppm), the LOAELs of 67 mg/kg-day and 37 mg/kg-day can be identified from Junaid et al. (1996) and Kanojia et al. (1996) in mice and rats, respectively. Application of 10-fold uncertainty factor to extrapolate from LOAELs to NOAELs in these studies would generate NOAELs of 6.7 mg/kg-day and 3.7 mg/kg-day, respectively. These extrapolated NOAEL values are similar to, and support the use of, the NOAEL of 2.5 mg/kg-day identified from the

study of MacKenzie et al. (1958) for development of the reference dose.

Elbetieha and Al-Hamood (1997) reported impacts on fertility following potassium dichromate exposures in mice; however, many of the observed effects did not occur in a clear dose-dependent fashion. The authors did not indicate the amount of water ingested by the animals, and stated only that water ingestion was reduced in the treatment groups relative to the controls.

Chromium is one of the most common contact sensitizers in males in industrialized countries and is associated with occupational exposures to numerous materials and processes, including chrome plating baths, chrome colors and dyes, cement, tanning agents, wood preservatives, anticorrosive agents, welding fumes, lubricating oils and greases, cleaning materials, and textiles and furs (Burrows and Adams, 1990; Polak et al., 1973). Solubility and pH appear to be the primary determinants of the capacity of individual chromium compounds to elicit an allergic response (Fregert, 1981; Polak et al., 1973). The low solubility chromium (III) compounds are much less efficient contact allergens than chromium (VI) (Spruit and van Neer, 1966).

Dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis (Bruynzeel et al., 1988; Polak, 1983; Cronin, 1980; Hunter, 1974). Primary irritant dermatitis is related to the direct cytotoxic properties of chromium, while allergic contact dermatitis is an inflammatory response mediated by the immune system. Allergic contact dermatitis is a cell-mediated immune response that occurs in a two-step process. In the first step (induction), chromium is absorbed into the skin and triggers an immune response (sensitization). Sensitized individuals will exhibit an allergic dermatitis response when exposed to chromium above a threshold level (Polak, 1983). Induction is generally considered to be irreversible. Concentrations of hexavalent chromium in environmental media that are protective of carcinogenic and noncarcinogenic effects are likely to be lower than the concentrations required to cause induction of allergic contact dermatitis. However, these concentrations may not be lower than concentrations required to elicit an allergic response in individuals who have been induced.

The RfD was updated in 1998. The RfD is similar to the previous value on IRIS but now incorporates a threefold uncertainty factor to account for the less-than-lifetime exposure in the principal study and a threefold modifying factor to account for uncertainties related to reports of gastrointestinal effects following drinking water exposures in a residential population in China.

For more detail on other Hazard Identification Issues, exit to [the toxicological review, Section 4.7](PDF).

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Low
RfD — Low

The overall confidence in this RfD assessment is low. Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured, and the lack of toxic effect at the highest dose tested.

Confidence in the database is low because the supporting studies are of equally low quality and the developmental toxicity endpoints are not well studied.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acetonitrile in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***[To review this appendix, exit to the toxicological review, Appendix A, External Peer Review -- Summary of Comments and Disposition (PDF)](#).***

Other EPA Documentation —

U.S. EPA. (1984) Health effects assessment for hexavalent chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. (1985) Drinking water health advisory for chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Drinking Water, Washington, DC (Draft).

Agency consensus date -- 04/28/1998

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Chromium (VI) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Chromium (VI)
CASRN — 18540-29-9
Last Revised — 09/03/1998

The inhalation reference concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (U.S. EPA, 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
(1) Chromic acid mists and dissolved Cr (VI) aerosols:				
Nasal septum atrophy **Human subchronic occupational study Lindberg and Hedenstierna, 1983**	NOAEL: none LOAEL: 2E-3 mg/m^3 7.14 E-4 mg/m^3 (adj.)	90	1	8E-6 mg/m^3
(2) Cr(VI) particulates:				
Lactate dehydrogenase in bronchioalveolar lavage fluid **Rat subchronic study** **Glaser et al., 1990 Malsch et al., 1994**	BMD: 0.016 mg/m^3 0.034 mg/m^3 (adj.)	300	1	1E-4 mg/m^3

*Conversion Factors and Assumptions — Breathing rate for 8-hour occupational exposure = 10 m^3; breathing rate for 24-hour continuous exposure = 20 m^3; occupational exposure = 5 days/week; continuous exposure = 7 days/week. RDDR (regional deposited dose ratio for particulates to account for differences between rats and humans) = 2.16

Nasal mucosal irritation, atrophy, and perforation have been widely reported following occupational exposures to chromic acid mists and dissolved hexavalent chromium aerosols. However, there is uncertainty regarding the relevance of occupational exposures to chromic acid mists and dissolved hexavalent chromium aerosols to exposures to Cr(VI) dusts in the environment. Lower respiratory effects have been reported in laboratory animals following exposures to Cr(VI) dusts. However, these studies have not reported on nasal mucosal effects following the exposures. The uncertainties in the database have been addressed through the development of two RfCs; one based on nasal mucosal atrophy following occupational exposures to chromic acid mists and dissolved hexavalent chromium aerosols, and a second based on lower respiratory effects following inhalation of Cr(VI) particulates in rats.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

(1) Chromic acid mists and dissolved Cr (VI) aerosols

Three studies have focused on nasal mucosal irritation, atrophy, and perforation following occupational exposures to chromic acid mists (Cohen et al., 1974; Lucas and Kramkowski, 1975; Lindberg and Hedenstierna, 1983). Of these, the study of Lindberg and Hedenstierna provides the most information on exposure levels and symptoms reported by exposed workers. Respiratory symptoms, lung function, and changes in nasal septum were studied in 104 workers (85 males, 19 females) exposed in chrome plating plants. Workers were interviewed using a standard questionnaire for the assessment of nose, throat, and chest symptoms. Nasal inspections and pulmonary function testing were performed as part of the study.

The median exposure time for the entire group of exposed subjects (104) in the study was 4.5 years (0.1-36 years). A total of 43 subjects exposed almost exclusively to chromic acid experienced a mean exposure time of 2.5 years (0.2-23.6 years). The subjects exposed almost exclusively to chromic acid were divided into a low-exposure group (8-hr TWA below 0.002 mg/m^3, N=19) and a high-exposure group (8-hr TWA above 0.002 mg/m^3, N=24). Exposure measurements using personal air samplers were performed for 84 subjects in the study on 13 different days. Exposure for the remaining 20 workers was assumed to be similar to that measured for workers in the same area. Nineteen office employees were used as controls for nose and throat symptoms. A group of 119 auto mechanics whose lung function had been evaluated by similar techniques was selected as controls for lung functionmeasurements. Smoking habits of workers were evaluated as part of the study.

At mean exposures below 0.002 mg/m^3, 4/19 workers from the low-exposure group of subjective nasal symptoms. Atrophied nasal mucosa were reported in 4/19 subjects from this group and 11/19 had smeary and crusty septal mucosa, which was statistically higher than controls. No one exposed to levels below 0.001 mg/m^3 complained of subjective symptoms. At mean concentrations of 0.002 mg/m^3 or above, approximately one-third of the subjects had reddened, smeary, or crusty nasal mucosa. Atrophy was seen in 8/24 workers, which was significantly different from controls. Eight subjects had ulcerations in the nasal mucosa and five had perforations of the nasal septum. Atrophied nasal mucosa was not observed in any of the 19 controls, but smeary and crusty septal mucosa occurred in 5/19 controls.

Short-term effects on pulmonary function were evaluated by comparing results of tests taken on Monday and Thursday among exposed groups and controls. No significant changes were seen in the low-exposure group or the control group. Nonsmokers in the high-exposure group experienced significant differences in pulmonary function measurements from the controls, but the results were within normal limits.

The authors concluded that 8-hour mean exposures to chromic acid above 0.002 mg/m^3 may cause a transient decrease in lung function, and that short-term exposures to greater than 0.02 mg/m^3 may cause septal ulceration and perforation. Based on the results of this study, a LOAEL of 0.002 mg/m^3 can be identified for incidence of nasal septum atrophy following exposure to chromic acid mists in chromeplating facilities. At TWA exposures greater than 0.002 mg/m^3, nasal septum ulceration and perforations occurred in addition to the atrophy reported at lower concentrations. The LOAEL is based on an 8-hour TWA occupational exposure. The LOAEL is adjusted to account for continuous exposure according to the following equation:

LOAELc = 0.002 mg/m^3 x (MVho/MVh) x 5 days/7 days

where:

LOAELc is the LOAEL for continuous exposure
MVho is the breathing volume for an 8 hour occupational exposure (10 m^3)
MVh is the breathing volume for a 24 hour continuous exposure (20 m^3)

The LOAEL of 0.002 mg/m^3 based on a TWA exposure to chromic acid is converted to a LOAEL for continuous exposure of 7.14 E-4 mg/m^3. An uncertainty factor of 3 is applied to the LOAEL to extrapolate from a subchronic to a chronic exposure, an uncertainty factor of 3 is applied to account for extrapolation from a LOAEL to a NOAEL, and an uncertainty factor of 10 is applied to the LOAEL to account for interhuman variation. The total uncertainty factor applied to the LOAEL is 90. Application of the uncertainty factor of 90 to the LOAEL of 7.14E-4 mg/m^3 generates an RfC of 8 E-6 mg/m^3 for upper respiratory effects caused by chromic acid mists and dissolved hexavalent chromium aerosols.

(2) Cr (VI) Particulates:

Two studies provide high-quality data on lower respiratory effects following exposures to chromium particulates (Glaser et al., 1985, 1990). Glaser et al. (1990) exposed 8-week-old male Wistar rats to sodium dichromate at 0.05 - 0.4 mg Cr(VI)/m^3 22 hr/day, 7 days/wk for 30-90 days. Chromium-induced effects occurred in a strong dose-dependent manner. The authors observed obstructive respiratory dyspnea and reduced body weight following subacute exposure at the higher dose levels. The mean white blood cell count was increased at all doses (p < 0.05) and was related to significant dose-dependent leukocytosis following subacute exposures. Mean lung weights were significantly increased at exposure levels of 0.1 mg/m^3 following both the subacute and subchronic exposures. Accumulation of macrophages was seen in all of the exposure groups and was postulated to be a chromium-specific irritation effect that accounted for the observed increases in lung weights. Focal inflammation was observed in the upper airways following the subchronic exposure, and albumin and lactate dehydrogenase (LDH) in

bronchioalveolar lavage fluid (BALF) were increased following the exposure. The authors concluded that chromium inhalation induced pneumocyte toxicity and suggested that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of Cr(VI) compounds.

Glaser et al. (1985) exposed 5-week-old male Wistar rats to aerosols of sodium dichromate at concentrations ranging from 0.025 to 0.2 mg Cr(VI)/m^3, 22 hr/day in subacute (28 day) or subchronic (90 day) protocols. Chromium-induced effects occurred in a dose-dependent manner. Lung and spleen weights were significantly increased (p < 0.005) after both subacute and subchronic exposures at concentrations greater than 0.025 mg/m^3. Differences in the mean total serum immunoglobulin were also significant at exposures above 0.025 mg/m^3, while exposures to aerosol concentrations greater than 0.1 mg/m^3 resulted in depression of the immune system stimulation. The immune stimulating effect of subchronic exposure was not reversed after 2 mo of fresh air regeneration. Bronchoalveolar lavage (BAL) cell counts were significantly decreased following subchronic exposure to levels above 0.025 mg/m^3 chromium. The number of lymphocytes and granulocytes showed a slight but significant increase in the lavage fluids of the subacute and subchronically exposed groups. At subacute exposure concentrations up to 0.05 mg/m^3 the phagocytic activity of the alveolar macrophages increased; however, subchronic exposure at 0.2 mg/m^3 decreased this function significantly. The spleen T-lymphocyte subpopulation was stimulated by subchronic exposure to 0.2 mg/m^3 chromium, and serum contents of triglycerides and phospholipids differed significantly from controls (p < 0.05) at this concentration.

Together, these studies provide useful information on chromium exposure-related impacts including lung and spleen weight, LDH in BALF, protein in BALF, and albumin in BALF. The cellular content of BALF is considered representative of initial pulmonary injury and chronic lung inflammation, which may lead to the onset of pulmonary fibrosis (Henderson, 1988). While these studies present dose-dependent results on sensitive indicators of lower respiratory toxicity, potential upper respiratory impacts resulting from the exposures were not addressed. Glaser et al. (1990) state that the upper respiratory tract was examined, but these data were not reported.

One approach for development of an RfC using the data of Glaser et al. (1985, 1990) was offered by Malsch et al. (1994), who generated an inhalation RfC for chromium dusts using a benchmark concentration (BMC) approach. The Agency developed its RfC for particulates based on this approach. After excluding exposures for periods of less than 90 days from the BMC analysis, Malsch et al. (1994) developed BMCs for lung weight, LDH in BALF, protein in BALF, albumin in BALF, and spleen weight. The Malsch et al. (1994) analysis defined the benchmark concentration as the 95% lower confidence limit on the dose corresponding to a 10% relative change in the endpoint compared to the control. Dose-effect data were adjusted to account for discontinuous exposure (22 hr/day) and the maximum likelihood model was used to fit

continuous data to a polynomial mean response regression, yielding maximum likelihood estimates of 0.036 - 0.078 mg/m^3 and BMCs of 0.016 - 0.067 mg/m^3. Malsch et al. (1994) applied dosimetric adjustments and uncertainty factors to determine a RfC based on the following equation:

RfC =
BMC x RDDR

UF$_A$ x UF$_F$ x UF$_H$

where:

- **RfC** is the inhalation reference concentration
- **BMC** is the benchmark concentration (lower 95% confidence limit on thedose corresponding to a 10% relative change in the endpoint compared to the control)
- **RDDR** is the regional deposited dose ratio to account for pharmacokineticdifferences between species
- **UF$_A$** is a threefold uncertainty factor to account for pharmacodynamicdifferences not addressed by the RDDR
- **UF$_F$** is a threefold uncertainty factor to account for extrapolating from subchronic to chronic exposures; and
- **UF$_H$** is a 10-fold uncertainty factor to account for the variation in sensitivity among members of the human population

The RDDR factor is incorporated to account for differences in the deposition pattern of inhaled hexavalent chromium dusts in the respiratory tract of humans and the Wistar rat test animals (Jarabek et al., 1990). The RDDR of 2.1576 was determined based on the mass median aerodynamic diameter (0.28 µm for dose levels of 0.05-0.1 mg/m^3 and 0.39 for dose levels of 0.1-0.4 mg/m^3) and the geometric standard deviation (1.63 for dose levels of 0.05-0.1 mg/m^3 and 1.72 for dose levels of 0.1-0.4 mg/m^3) of the particulates reported in Glaser et al. (1990). A 3.16-fold uncertainty factor (midpoint between 1 and 10 on a log scale) was incorporated to account for the pharmacodynamic differences not accounted for by the RDDR. An additional 3.16-fold uncertainty factor was incorporated to account for the less-than-lifetime exposure in Glaser et al. (1990), and a 10-fold uncertainty factor was applied to account for variation in the human population. A total uncertainty factor of 100 was applied to the BMC in addition to the RDDR.

Glaser et al. (1990) reported that LDH in BALF increased in a dose-dependent fashion from 0.05 to 0.4 mg/m^3 sodium dichromate, and this endpoint generated the lowest BMC (0.016 mg/m^3) and RfC (3.4 E-4 mg/m^3). LDH in BALF is considered the among the most sensitive indicators of potential lung toxicity (Henderson, 1984, 1985, 1988; Beck et al., 1982; Venet et

al., 1985), as LDH is found extracellularly after cell damage and BALF is the closest site to the original lung injury. LDH in BALF may also reflect chronic lung inflammation, which may lead to pulmonary fibrosis through prevention of the normal repair of lung tissue (Henderson, 1988).

Several uncertainties must be addressed with regard to the BMC and RfC developed by Malsch et al. (1994). Potentially important endpoints, including upper airway effects and potential renal or immunological toxicity, were not addressed in the Glaser et al. (1985, 1990) studies and could not be included in the BMC analysis. While LDH in BALF resulted in the lowest BMC and RfC, all of the effects noted in Glaser et al. (1985, 1990) can be considered indicative of an inflammatory response, and might be equally suited to development of the RfC. LDH in BALF did not generate the best fit on the regression curve of the endpoints considered in the BMC analysis. In addition, the threefold uncertainty factor accounting for the use of a subchronic study may not be sufficiently protective for long-term effects. While the analysis acknowledged the importance of particle size and airway deposition in the development of the RDDR, the potential impact of different particle sizes in respiratory toxicity by hexavalent chromium particulates was not addressed.

Several of these uncertainties were conservatively addressed in the analysis of Malsch et al. (1994). LDH in BALF generated the lowest estimate of the BMC from the effects noted by Glaser et al. (1985, 1990). This effect can be considered to be indicative of cell damage that occurs prior to fibrosis, as LDH appears in BALF following cell lysis. While the Malsch et al. (1994) analysis demonstrated a relatively poor curve fit for this endpoint, the model generated a conservative fit in the data that is unlikely to overestimate the BMC. LDH in BALF as reported in Glaser et al. (1990) is considered to be an acceptable endpoint for development of an RfC for inhalation of hexavalent chromium particulates, and Malsch et al. (1994) used a reasonable approach for development of a BMC based on this endpoint.

The threefold uncertainty factor used by Malsch et al. (1994) to account for the subchronic study is insufficient for development of the RfC for inhalation of chromium particulates. Glaser et al. (1985) demonstrated that at the end of the 90-day exposure period, chromium was still accumulating in the lung tissue of the test animals, suggesting that lower long-term exposures might lead to accumulation of a critical concentration in the lung. Subchronic studies also may not adequately predict the presence of inflammatory effects from lower long-term exposures. The Agency has therefore determined that a 10-fold uncertainty factor accounting for the use of a subchronic study is more appropriate in this case for the development of an RfC for inhalation of chromium particulates.

Selection of a threefold uncertainty factor to account for the pharmacodynamic differences not accounted for by the RDDR, an additional 10-fold uncertainty factor to account for the less-

than-lifetime exposure in Glaser et al. (1990), and a 10-fold uncertainty factor to account for variation in the human population generates a total uncertainty factor of 300. Application of the total uncertainty factor of 300 and the RDDR of 2.1576 to the BMC generated by Malsch et al. (1994) based on LDH in BALF (Glaser et al., 1990) results in an RfC of 1 E-4 mg/m^3 for inhalation of hexavalent chromium particulates.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

See discussion above.

(1) Chromic acid mists and dissolved Cr (VI) aerosols:
UF = 90.
MF = 1.

(2) Chromium (VI) particulates:
UF = 300.
MF = 1

I.B.4. Additional Studies/Comments (Inhalation RfC)

There is considerable uncertainty with regard to the relevance of the nasal septum atrophy endpoint observed in the chromeplating industry to exposure to hexavalent chromium in the environment. The effects were observed in chromeplaters who were exposed to chromic acid mists near the plating baths. Environmental exposures would most likely occur through contact with hexavalent chromium dusts, and exposures to chromic acid mists in the environment is considered to be unlikely. An additional uncertainty is related to the determination of dose in the Lindberg and Hedenstierna study. Nasal septum atrophy in this study was related to TWA exposures to chromic acid. The most significant effects (nasal septum perforation) were observed in workers who experienced peak excursions to levels considerably greater than the TWA. It is uncertain whether the peak excursion data or the TWAs are more appropriate for the determination of dose in this study. The RfC based on the data of Lindberg and Hedenstierna (1983) should only be used to address exposures to chromic acid and dissolved hexavalent chromium aerosols.

Nasal mucosal irritation, atrophy, and perforation have been widely reported following occupational exposures to chromic acid mists and dissolved hexavalent chromium aerosols. Glaser et al. (1990) did not report on upper respiratory effects following exposure of rats to sodium dichromate. The RfC based on the data of Glaser et al. should only be used to address inhalation of Cr(VI) particulates.

The RfCs in this IRIS Summary were added in 1998. The previous RfC section for hexavalent chromium in IRIS was empty.

For more detail on other Hazard Identification Issues, exit to [the toxicological review, Section 4.7](#) (PDF).

I.B.5. Confidence in the Inhalation RfC

(1) Chromic acid mists and dissolved Cr (VI) aerosols:

Study — Low
Database — Low
RfC -- Low

The overall confidence in this RfC assessment is low. Confidence in the chosen study is low because of uncertainties regarding the exposure characterization and the role of direct contact for the critical effect. Confidence in the database is low because the supporting studies are equally uncertain regarding the exposure characterization.

(2) Chromium (VI) particulates:

Study — Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. Confidence in the chosen study is medium because of uncertainties regarding upper respiratory, reproductive, and renal effects resulting from the exposures.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acetonitrile in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). *[To review this appendix, exit to the toxicological review, Appendix A,](#)*

External Peer Review -- Summary of Comments and Disposition (PDF).

Agency Consensus Date — 04/28/1998

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Chromium (VI) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name: Chromium (VI)
CASRN: 18540-29-9
Last Revised — 09/03/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m3 air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the current guidelines (EPA, 1986), Cr(VI) is classified as Group A - known human carcinogen by the inhalation route of exposure. Carcinogenicity by the oral route of exposure cannot be determined and is classified as Group D.

Under the proposed guidelines (EPA, 1996), Cr(VI) would be characterized as a known human carcinogen by the inhalation route of exposure on the following basis.

Hexavalent chromium is known to be carcinogenic in humans by the inhalation route of exposure. Results of occupational epidemiologic studies of chromium-exposed workers are consistent across investigators and study populations. Dose-response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both Cr(III) and Cr(VI) compounds. Because only Cr(VI) has been found to be carcinogenic in animal studies, however, it was concluded that only Cr(VI) should be classified as a human carcinogen.

Animal data are consistent with the human carcinogenicity data on hexavalent chromium. Hexavalent chromium compounds are carcinogenic in animal bioassays, producing the following tumor types: intramuscular injection site tumors in rats and mice, intrapleural implant site tumors for various Cr(VI) compounds in rats, intrabronchial implantation site tumors for various Cr(VI) compounds in rats, and subcutaneous injection site sarcomas in rats.

In vitro data are suggestive of a potential mode of action for hexavalent chromium carcinogenesis. Hexavalent chromium carcinogenesis may result from the formation of mutagenic oxidatitive DNA lesions following intracellular reduction to the trivalent form. Cr(VI) readily passes through cell membranes and is rapidly reduced intracellularly to generate reactive Cr(V) and Cr(IV) intermediates and reactive oxygen species. A number of potentially mutagenic DNA lesions are formed during the reduction of Cr(VI). Hexavalent chromium is mutagenic in bacterial assays, yeasts, and V79 cells, and Cr(VI) compounds decrease the fidelity of DNA synthesis in vitro and produce unscheduled DNA synthesis as a consequence of DNA damage. Chromate has been shown to transform both primary cells and cell lines.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

For more detail on other Hazard Identification Issues, exit to [the toxicological review, Section 4.7](#) (PDF).

II.A.2. Human Carcinogenicity Data

Occupational exposure to chromium compounds has been studied in the chromate production, chromeplating and chrome pigment, ferrochromium production, gold mining, leather tanning, and chrome alloy production 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 form of chromium responsible for the induction of cancer was not identified (Machle and Gregorius, 1948; Baejter, 1950a,b; Bidstrup, 1951; Mancuso and Hueper, 1951; Brinton et al., 1952; Bidstrup and Case, 1956; Todd, 1962; Taylor, 1966; Enterline, 1974; Mancuso, 1975; Ohsaki et al., 1978; Sano and Mitohara, 1978; Hayes et al., 1979; Hill and Ferguson, 1979; Alderson et al., 1981; Haguenor et al., 1981; Satoh et al., 1981; Korallus et al., 1982; Frentzel-Beyme, 1983; Langard and Vigander, 1983; Watanabe and Fukuchi, 1984; Davies, 1984; Mancuso, 1997).

Mancuso and Hueper (1951) conducted a proportional mortality study of a cohort of chromate workers (employed for > l year from 1931-1949 in a Painesville, OH chromate plant) in order to investigate lung cancer associated with chromate production. Of the 2,931 deaths of males in the county where the plant is 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. Within the limitations of the study design, this report strongly suggested an increased incidence of respiratory cancer in the chromate-production plant.

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. Lung cancer death rates increased by gradient of exposure to total chromium, and significant deposition of chromium was found in the lungs of workers long after the exposure ceased. 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 identification of the specific form of chromium responsible for the lung cancer uncertain.

Mancuso (1997) recently updated this study, following the combined cohort of 332 workers until 1993. Of 283 deaths (85% of the cohort identified), 66 lung cancers were found (23.3%

of all deaths and 64.7% of all cancers). Lung cancer rates clearly increased by gradient level of exposure to total chromium. The relationship between gradient level of exposure and lung cancer rates is less clear for trivalent and hexavalent chromium. The rates of lung cancer within the cohort are consistent with those reported in Mancuso (1975), and provide further support for the cancer risk assessment based on those data.

Studies of chrome pigment workers in the United States (Hayes et al., 1989), England (Davies, 1984, 1979, 1978), Norway (Langard and Vigander, 1983; Langard and Norseth, 1975), and in the Netherlands and Germany (Frentzel-Beyme, 1983) have consistently demonstrated an association between occupational chromium exposure (predominantly to Cr [VI]) and lung cancer.

Several studies of the chromeplating industry have demonstrated a positive relationship between cancer and exposure to chromium compounds (Royle, 1975; Franchini et al., 1983; Sorahan et al., 1987).

II.A.3. Animal Carcinogenicity Data

Animal data are consistent with the findings of human epidemiological studies of hexavalent chromium. Hexavalent chromium compounds were carcinogenic in animal assays producing the following tumor types: lung tumors following inhalation of aerosols of sodium chromate and pyrolized Cr(VI)/Cr(III) oxide mixtures in rats (Glaser et al., 1986), lung tumors following intratracheal administration of sodium dichromate in rats (Steinhoff et al., 1983), intramuscular injection site tumors in Fischer 344 and Bethesda Black rats and in C57BL mice (Furst et al., 1976; Maltoni, 1974, 1976; Payne, 1960a; Hueper and Payne, 1959); intrapleural implant site tumors for various Cr(VI) compounds in Sprague-Dawley and Bethesda Black rats (Payne, 1960b; Hueper 1961; Hueper and Payne, 1962), intrabronchial implantation site tumors for various Cr(VI) compounds in Wistar rats (Levy and Martin, 1983; Laskin et al., 1970; Levy, as quoted in NIOSH, 1975), and subcutaneous injection site sarcomas in Sprague-Dawley rats (Maltoni, 1974, 1976). Inflammation is considered to be essential for the induction of most chromium respiratory effects and may influence the carcinogenicity of Cr(VI) compounds (Glaser et al., 1985).

II.A.4. Supporting Data for Carcinogenicity

Metabolism and genotoxicity. Hexavalent chromium is rapidly taken up by cells through the sulfate transport system (Sugiyama, 1992). Once inside the cell, Cr(VI) is quickly reduced to the trivalent form by cellular reductants, including ascorbic acid, glutathione and flavoenzymes (cytochrome P-450 and glutathione reductase), and riboflavin (De Flora et al., 1989; De Flora et al., 1990; Sugiyama, 1992). The intracellular reduction of Cr(VI) generates

reactive Cr(V) and Cr(IV) intermediates as well as hydroxyl free radicals (OH) and singlet oxygen ($^1O_2$) (Kawanishi et al., 1986). A variety of DNA lesions are formed during the reduction of Cr(VI) to Cr(III), including DNA strand breaks, alkali-labile sites, DNA-protein and DNA-DNA crosslinks, and oxidative DNA damage, such as 8-oxo-deoxyguanosine (Klein et al., 1992; Klein et al., 1991; De Flora et al., 1990). The relative importance of the different chromium complexes and oxidative DNA damage in the toxicity of Cr(VI) is unknown.

A large number of chromium compounds have been assayed with in vitro genetic toxicology assays. In general, hexavalent chromium is mutagenic in bacterial assays whereas trivalent chromium is not (Lofroth, 1978; Petrilli and DeFlora, 1977, 1978). Likewise Cr(VI), but not Cr(III), was mutagenic in yeasts (Bonatti et al., 1976) and in V79 cells (Newbold et al., 1979). Cr(III) and (VI) compounds decrease the fidelity of DNA synthesis in vitro (Loeb et al., 1977), while Cr(VI) compounds inhibit replicative DNA synthesis in mammalian cells (Levis et al., 1978) and produce unscheduled DNA synthesis, presumably repair synthesis, as a consequence of DNA damage (Raffetto, 1977). Chromate has been shown to transform both primary cells and cell lines (Fradkin et al., 1975; Tsuda and Kato, 1977; Casto et al., 1979). Chromosomal effects produced by treatment with chromium compounds have been reported by a number of authors; for example, both Cr(VI) and Cr(III) salts were clastogenic for cultured human leukocytes (Nakamuro et al.,1978).

In dogs (2/group) exposed to potassium dichromate in drinking water at concentrations up to 11.2 ppm for 4 years, gross and microscopic examination of all major organs revealed no treatment-related lesions (Anwar et al., 1961). The small number of animals and the relatively short exposure duration relative to the lifespan of the dog precludes a conclusion regarding a possible carcinogenic response. There are no other long-term studies of ingested Cr(VI). Cr(VI) is readily converted to Cr(III) in vivo, but there is no evidence that Cr(III) is oxidized to Cr(VI) in vivo. Cr(III) is an essential trace element.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

The oral carcinogenicity of Cr(VI) cannot be determined. No data were located in the available literature that suggested that Cr(VI) is carcinogenic by the oral route of exposure.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

II.C.1.1. Air Unit Risk — 1.2E-2 per (µg/cu.m)

Source: Mancuso, 1975

II.C.1.2. Extrapolation Method — Multistage, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E-3 (μg/m^3)
E-5 (1 in 100,000)	8E-4 (μg/m^3)
E-6 (1 in 1,000,000)	8E-5 (μg/m^3)

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor type -- lung cancer
Test animals — human
Route — inhalation, occupational exposure
Source -- Mancuso, 1975

Subject age (years)	Exposure Level midrange (μg/m^3)	Deaths From Lung Cancer	Person-Years
50	5.66	3	1,345
	25.27	6	931
	46.83	6	299
60	4.68	4	1,063
	20.79	5	712
	39.08	5	211
70	4.41	2	401
	21.29	4	345

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Mancuso (1997) recently updated the study of Mancuso (1975), following the combined cohort of 332 workers until 1993. Of 283 deaths (85% of the cohort identified), 66 lung cancers were found (23.3% of all deaths and 64.7% of all cancers). Lung cancer rates clearly increased by gradient level of exposure to total chromium. The relationship between gradient level of exposure and lung cancer rates is less clear for trivalent and hexavalent chromium. The rates of lung cancer within the cohort are consistent with those reported in Mancuso (1975), and provide further support for the cancer risk assessment based on those data.

The cancer mortality in Mancuso (1975) was assumed to be due to Cr(VI), which was further assumed to be no less than one-seventh of total chromium. It was also assumed that the smoking habits of chromate workers were similar to those of the U.S. white male population.

Trivalent chromium compounds have not been reported as carcinogenic by any route of administration.

The unit risk should not be used if the air concentration exceeds 8E-1 µg/m3, since above this concentration the unit risk may not be appropriate.

The carcinogenicity section of this IRIS Summary was updated in 1998; however, the quantitative results have not been modified.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Results of studies of chromium exposure are consistent across investigators and countries. A dose relationship for lung tumors has been established. Theassumption that the ratio of Cr(III) to Cr(VI) is 6:1 may lead to a sevenfold underestimation of risk. The use of 1949 hygiene data (Bourne and Yee, 1950), which may underestimate worker exposure, may result in an overestimation of risk. Further overestimation of risk may be due to the implicit assumption that the smoking habits of chromate workers were similar to those of the general white male population, since it is generally accepted that the proportion of smokers is higher for industrial workers than for the general population.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acetonitrile in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). *To review this appendix, exit to the toxicological review, Appendix A, External Peer Review -- Summary of Comments and Disposition (PDF)*.

Other EPA Documentation — U.S. EPA. (1984) Health assessment document for chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-83-014F.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency consensus date -- 04/28/1998

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Chromium (VI) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Chromium (VI)
CASRN — 18540-29-9

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VII. Revision History

Chromium (VI)
CASRN —18540-29-9

Date	Section	Description
09/03/1998	I., II., VI.	Revised RfD, RfC, carcinogenicity assessment, refs.
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Chromium (VI)
CASRN —18540-29-9
Last Revised — 03/31/1987

- 18540-29-9
- 7440-47-3
- Chromic ion

- Chromium
- Chromium, ion
- Chromium (VI)
- Chromium (VI) ion