Chromium(III), insoluble salts; CASRN 16065-83-1

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(III), insoluble salts

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/03/1998
Inhalation RfC (I.B.)	qualitative discussion	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(III), insoluble salts
CASRN — 16065-83-1
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
No effects observed **Rat chronic feeding study** **Ivankovic and Preussman, 1975**	NOAEL: 5% Cr_2O_3 in diet 5days/week for 600 feedings (1,800 g/kg bw average total dose) NOAEL(ADJ): 1,468 mg/kg-day LOAEL: none LOAEL(ADJ): none	100	10	1.5E+0 mg/kg-day

*Conversion Factors and Assumptions — 1,800 g Cr_2O_3/kg bw × 1,000 mg/g × 0.6849 g Cr/g Cr_2O_3/600 feeding days × 5 feeding days/7 days = 1,468 mg/kg-day.

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

Ivankovic, S; Preussmann, R. (1975) Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. Food Cosmet Toxicol 13:347-351.

Groups of 60 male and female rats were fed chromic oxide (Cr_2O_3) baked in bread at dietary levels of 0, 1%, 2%, or 5%, 5 days/week for 600 feedings (840 total days). The primary purpose of this study was to assess the carcinogenic potential of Cr_2O_3. Body weight and food consumption were monitored. The average total amounts of ingested Cr_2O_3 were given as 360, 720, and 1,800 g/kg bw for the 1%, 2%, and 5% treatment groups, respectively. The animals were maintained on control diets following termination of exposure until they became moribund or died. All major organs were examined histologically. Other toxicologic parameters were not mentioned explicitly, but may have included some or all of those deSRCibed for the accompanying subchronic study (see below). No effects due to Cr_2O_3 treatment were observed at any dose level.

Ivankovic and Preussmann (1975) also treated rats (both sexes, 12-19 rats/group) at dietary

levels of 0, 2%, or 5% Cr_2O_3 in bread, 5 days/week for 90 days. Food consumption and body weight were monitored. Toxicologic parameters included serum protein, bilirubin, hematology, urinalysis, organ weights, and histopathology. The only effects observed were reductions (12%-37%) in the absolute weights of the livers and spleens of animals in the high-dose group. Organ weights relative to body weight were not reported. The high dose is equivalent to 1,400 mg/kg-day (dose converted using reported data).

Other subchronic oral studies show no indication of adverse effects attributable to trivalent chromium compounds, but dose levels were considerably lower.

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

UF = 100.

The factor of 100 represents two 10-fold decreases in mg/kg bw-day dose that account for both the expected interhuman and interspecies variability to the toxicity of the chemical in lieu of specific data.

MF = 10.

An additional 10-fold modifying factor is applied to reflect database deficiencies including the lack of a study in a nonrodent mammal, lack of unequivocal data evaluating reproductive impacts, and the concern regarding potential reproductive effects raised by the study of Elbetieha and Al-Hamood (1997). The value of the modifying factor has not been changed from the previous IRIS entry. The study of Elbetieha and Al-Hamood (1997) provides strong support for the use of a 10-fold modifying factor to reflect uncertainty regarding potential reproductive effects of Cr(III). The following additional uncertainties relate to the NOAEL derived from the Ivankovic and Preussman (1975) study: 1) the effects observed in the 90-day study were not explicitly addressed in the 2-year study; 2) the effect of the vehicle (baked bread) on absorption of chromium is uncertain, and the relevance of this dosing regimen to exposures in the environment is unclear; 3) animals were allowed to die naturally after feeding stopped (2 years) and only then was histology performed. Application of the 100-fold uncertainty factor and 10-fold modifying factor to the adjusted NOAEL of 1,468 mg/kg-day gives the reference dose of 1.5 mg/kg-day.

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

This RfD is limited to metallic chromium (III) of insoluble salts. Examples of insoluble salts include chromic III oxide (Cr_2O_3) and chromium (III) sulfate ($Cr_2[SO_4]_3$).

Trivalent chromium is an essential element that potentiates insulin action in peripheral tissue and is essential for lipid, protein, and fat metabolism in animals and human beings. Chromium deficiency causes changes in the metabolism of glucose and lipids and may be associated with maturity-onset diabetes, cardiovascular diseases, and nervous system disorders (Anderson, 1993, 1995). The National Research Council has identified an estimated safe and adequate daily dietary intake (ESADDI) for chromium of 50-200 µg/d (NRC, 1989), corresponding to 0.71-2.9 µg/kg/d for a 70 kg adult. FDA has selected a Reference Daily Intake for chromium of 120 µg/d (DHHS, 1995).

Very limited data suggest that Cr(III) may have respiratory effects on humans (see Section I.B). No data on chronic or subchronic effects of inhaled Cr(III) in animals can be found. Adequate developmental toxicity data do not exist, and there are inadequate data on reproductive effects.

Elbetieha and Al-Hamood (1997) reported impacts on fertility following high doses (2,000-5,000 ppm in the drinking water) of chromium chloride 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 only stated that water ingestion was reduced in the treatment groups relative to the controls. Zahid et al. (1990) fed mice trivalent chromium at concentrations of 100, 200, and 400 ppm for 35 days in food and reported ambiguous levels of degeneration in the outermost cellular layers of the seminiferous tubules, reduced spermatogonia per tubule, reduced sperm count, and increased percentage of morphologically abnormal sperms at all dose levels. Serious questions have been raised regarding the design and conduct of this study (Finley et al., 1993; NTP, 1996a,b, 1997). The methods utilized by Zahid et al. were considered to be insufficient to identify spermatogonia, likely generated nonreproducible counts of epididymal sperm, and resulted in the biologically implausible conclusion of reduction in spermatogonia numbers concurrent with unchanged spermatocyte and spermatid numbers. Additional questions have been raised with regard to the groupings of animals used and the statistical analysis of the data. The uncertainties preclude the use of the Elbetieha and Al-Hamood (1997) and Zahid et al. (1990) studies in the risk assessment for trivalent chromium.

The 1998 IRIS assessment updates the previous RfD of 1E+0 mg/kg-day.

For more details 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. The principal study is rated low because of the lack of explicit detail on study protocol and results. Low confidence in the database reflects the lack of high-dose supporting data. The low confidence in the RfD reflects the foregoing, but also reflects the lack of an observed effect level. Thus, the RfD, as given, should be considered conservative, since the MF addresses only those factors that might lower the RfD.

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 Trivalent Chromium in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Other EPA Documentation — U.S. EPA, 1984

Agency Consensus Date — 4/28/98

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(III), insoluble salts, conducted in November 2001 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(III), insoluble salts
CASRN — 16065-83-1
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

Not available.

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

Not available.

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

Not available.

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

Data are considered to be inadequate for development of an RfC due to the lack of a relevant toxicity study addressing respiratory effects of Cr(III). Data from animal studies have identified the respiratory tract as the primary target of chromium toxicity following inhalation of hexavalent chromium and these data have been used for development of an RfC for hexavalent chromium particulates. However, these data do not demonstrate that the effects observed following inhalation of hexavalent chromium particulates are relevant to inhalation of trivalent chromium, and these data are considered to be inappropriate for development of an RfC for trivalent chromium. The following discussion of issues related to development of an RfC for Cr(III) has been added in 1998.

Occupational exposure to trivalent chromium and other chromium compounds by inhalation has been studied in the chromate manufacturing and ferrochromium industries; however, exposures all include mixed exposures to both Cr(III) and Cr(VI). A number of epidemiological studies have demonstrated an association between inhalation of Cr(VI) and noncarcinogenic endpoints, including upper respiratory irritation and atrophy, changes in lung function, and renal toxicity. These studies have been used to support the development of an RfC for chromic acid mists (VI) and soluble chromates (VI). Data addressing exposures to Cr(III) alone are not available, and the occupational studies are considered to be unsuitable for development of an RfC for Cr(III).

Several animal studies have been performed to assess the carcinogenic potential of Cr(III) by inhalation, either by natural routes, intrapleural injection, or intrabronchial implantation (Baetjer et al., 1959; Hueper and Payne, 1962; Levy and Venitt, 1975; Levy and Martin, 1983). These studies did not provide detailed reports of noncarcinogenic effects associated with inhalation exposure to Cr(III).

Data from subchronic animal studies identify the respiratory tract as the primary target of chromium toxicity following inhalation. Johansson et al. (1986) exposed rabbits to aerosols of hexavalent (0.9 mg/m^3 Na_2CrO_4) or trivalent (0.6 mg/m^3 $Cr(NO_3)_3$) chromium for 5 days/week, 6 hours/day for 4 to 6 weeks. The number of macrophages obtained from the lungs of the rabbits exposed to Cr(VI) was significantly increased. While the numbers of macrophages from rabbits exposed to Cr(III) were not increased, striking morphological changes were observed, including round dark chromium-rich inclusions in the cytoplasm, an increased number of cells with a smooth inactive cell surface, enlarged Golgi apparatus, and a tendency toward elongated cell shape. The macrophages from rabbits exposed to Cr(VI) showed less marked morphological changes than those exposed to Cr(III). This study did not focus on endpoints that are considered suitable for development of an RfC for Cr(III).

Johansson et al. (1980) exposed groups of four rabbits to chromium dust at concentrations of 3.1 mg/m^3 and 0.6 mg/m^3 for 5 days/week, 6 hours/day for 4 weeks. Macrophages collected from rabbits exposed to the higher concentration of chromium phagocytized significantly more chromium particles than the controls, though the number of nonviable macrophages was less than 3%. This study utilized small groups and did not focus on endpoints that are considered to be suitable for development of an RfC for Cr(III).

Akatsuka and Fairhall (1934) exposed cats to chromium carbonate dust and found no effects in terms of gross or microscopic pathology upon termination of the experiment. Only two cats were exposed, however, and neither the doses nor the durations of exposure were precisely defined; therefore, these data cannot be used in quantitative risk assessment.

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

I.B.5. Confidence in the Inhalation RfC

Not available

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 Trivalent Chromium in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

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(III), insoluble salts, conducted in November 2001 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

Chromium(III), insoluble salts
CASRN — 16065-83-1
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 $\mu g/m^3$ 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 (U.S. EPA, 1986) 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 (U.S. EPA, 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

The following discussion of issues related to potential Cr(III) carcinogenicity has been updated in 1998.

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

Applying the criteria for evaluating the overall weight-of-evidence for carcinogenicity to humans outlined in EPA's guidelines for carcinogen risk assessment (U.S. EPA, 1986), trivalent chromium is most appropriately designated a Group D -- Not classified as to its human carcinogenicity. Using the Proposed Guidelines for Carcinogen Risk Assessment

(EPA, 1996), there are inadequate data to determine the potential carcinogenicity of trivalent chromium, as discussed below. However, the classification of hexavalent chromium as a known human carcinogen raises a concern for the carcinogenic potential of trivalent chromium.

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

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

II.A.2. Human Carcinogenicity Data

Occupational exposure to trivalent chromium and other chromium compounds by inhalation has been studied in the chromate manufacturing and ferrochromium industries; however, exposures all include mixed exposures to both Cr(III) and Cr(VI). The Cr(VI) species is the likely etiological agent in reports of excess cancer risk in chromium workers. Data addressing exposures to Cr(III) alone are not available, and data are inadequate for an evaluation of human carcinogen potential. Two oral studies located in the available literature (Schroeder et al., 1965; Ivankovic and Preussman, 1975) reported negative results for rats and mice. Several animal studies have been performed to assess the carcinogenic potential of Cr(III) by inhalation. These studies have not found an increased incidence of lung tumors following exposure either by natural routes, intrapleural injection, or intrabronchial implantation (Baetjer et al., 1959; Hueper and Payne, 1962; Levy and Venitt, 1975; Levy and Martin, 1983).

II.A.3. Animal Carcinogenicity Data

The data from oral and inhalation exposures of animals to trivalent chromium do not support determination of the carcinogenicity of trivalent chromium. IARC (1990) concluded that animal data are inadequate for the evaluation of the carcinogenicity of Cr(III) compounds. Furthermore, although there is sufficient evidence of respiratory carcinogenicity associated with exposure to chromium, the relative contributions of Cr(III), Cr(VI), metallic chromium, or soluble versus insoluble chromium to carcinogenicity cannot be elucidated. In general, trivalent chromium was not mutagenic in bacterial assays when tested with or without a mammalian activation system (Venitt and Levy, 1974; Petrilli and Deflora, 1977, 1978a,b). In one study, trivalent chromium was mutagenic in *Baccillus subtilis*, but this activity was low compared with compounds of hexavalent chromium (Nakamuro et al., 1978). Taken together, these studies do not provide adequate data to support determination of the carcinogenicity of Cr(III), and a quantitative estimate of potential Cr(III) carcinogenicity has not been generated.

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

Not available.

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

Not available.

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 Trivalent Chromium in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

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

Not available.

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(III), insoluble salts, conducted in November 2001 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(III), insoluble salts
CASRN — 16065-83-1

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VII. Revision History

Chromium(III), insoluble salts
CASRN — 16065-83-1

Date	Section	Description
09/03/1998	I., II., VI.	Revised RfD, RfC, carcinogenicity sections, refs.
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Chromium(III), insoluble salts
CASRN — 16065-83-1
Last Revised — 09/03/1998

- 16065-83-1
- 7440-47-3
- Chromic ion
- Chromium
- Chromium (III)
- Chromium (III) ion
- Chromium, ion