Zinc and compounds
CASRN 7440-66-6
00/00/00

Substance code
Zinc; CASRN 7440-66-6; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Zinc

File First On-Line __/__/__

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	On-line	1/31/02
Inhalation RfC Assessment (I.B.)	No data	
Carcinogenicity Assessment (II.)	On-line	1/31/02

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Zinc
CASRN -- 7440-66-6
Last Revised -- 00/00/00

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
Decreases in erythrocyte superoxide dismutase (ESOD) concentration	NOAEL: 0.95 mg/kg-day LOAEL: See below	3	1	0.3 mg/kg-day

Fischer et al., 1984
Yadrick et al., 1989

*Conversion Factors and Assumptions -- The dose conversion factor was based on reference adult body weights for the appropriate gender. Total dose was derived from estimations from the FDA Total Diet Study for 1982-1986, plus reported supplemental dose. For example, for the Fischer et al. (1984) study, the supplemental dose of 50 mg/day was added to the average daily intake of 16.41 mg/day, giving a total intake of 66.41 mg/day. Dividing this by a reference male body weight of 70 kg/day results in a mean zinc intake of 0.95 mg/kg-day.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

A 10-week study of zinc supplementation in 18 healthy women given zinc gluconate supplements twice daily (50 mg supplemental zinc/day, or 0.83 mg supplemental zinc/kg-day) resulted in a decrease of erythrocyte superoxide dismutase (ESOD) activity (Yadrick et al., 1989). ESOD concentrations declined over the 10-week supplementation period and, at 10 weeks, were significantly different ($p<0.05$) from values during the pretreatment period. By 10 weeks, ESOD activity had declined to 53% of pretreatment levels. Change in enzyme activity is considered a better indicator of altered copper status than a measure of metal concentration in tissue or plasma. This has been documented by studies in rats which were fed copper-deficient or high-zinc diets, in which treatment-related changes in copper metalloenzyme activity are greater and precede changes in plasma or tissue levels of copper (L'Abbe and Fischer, 1984a,b). Ceruloplasmin concentrations were not altered. Serum zinc was significantly increased. There was also a significant decline in serum ferritin and hematocrit values at 10 weeks. Such a decrease could pose a significant risk to the iron status of women.

Fischer et al. (1984) instructed groups of 13 healthy adult male volunteers to take capsules containing 0 (cornstarch) or 25 mg supplemental zinc (as zinc gluconate) twice daily for 6 weeks. Nonfasting blood samples were taken at the beginning and at biweekly intervals and tested for measures of copper status. Plasma copper levels and levels of ferroxidase activity did not change during the course of the study. However, erythrocyte superoxide dismutase activity decreased after 4 weeks in the supplement group and was significantly lower than controls by 6 weeks. An inverse correlation between plasma zinc levels and erythrocyte superoxide dismutase activity was also observed at 6 weeks.

The studies of Yadrick et al. (1989) and Fischer et al. (1984) each identified a LOEL for decreased levels of erythrocyte superoxide dismutase (ESOD), an indicator of body copper status. As this effect was not considered adverse of itself, but rather a precursor for more serious effects, it was designated a NOAEL. No measurements were made of dietary zinc or copper in either study. However, a level of dietary zinc was estimated at 9.72 mg/day for females (25-30 years old) and 16.41 mg/day for males (25-30 years old) from the results of the FDA Total Diet Study for 1982-1986 (Pennington et al., 1989). Adding 9.72 mg/day to the NOAEL of 50 mg supplemental zinc/day from the Yadrick et al. (1989) study, and dividing by an assumed body weight of 60 kg for adult females, gives a NOAEL of 0.99 mg zinc/kg-day. Similarly, adding 16.41 mg/day to the 50 mg supplemental zinc/day from the Fischer et al. (1984) study, and dividing by the reference body weight of 70 kg for adult males, gives a NOAEL of 0.95 mg zinc/kg-day. As these NOAEL values for the same endpoint are similar, the Yadrick et al. (1989) and Fischer et al. (1984) studies were selected as co-critical studies for derivation of the RfD. The Yadrick et al. (1989) study was the key study for a previous RfD, which was verified by the RfD/RfC workgroup (U.S. EPA, 1995).

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = An uncertainty factor (UF) of 3 was applied, to account for uncertainties with using a moderate-duration study in humans and consideration of a substance that is an essential dietary nutrient.

MF = 1.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

In a double-blind crossover trial, Samman and Roberts (1987, 1988) gave zinc sulfate tablets (150 mg supplemental zinc/day in three divided doses at mealtimes) to healthy adult volunteers (21 men and 26 women) for 6 weeks; identical capsules containing lactose were given to the same group of volunteers for 6 weeks as the placebo. Using the reported average body weights, the zinc doses averaged 2 mg Zn/kg-day for the men and 2.5 mg Zn/kg-day for the women. Adverse symptoms, including abdominal cramps, vomiting, and nausea, occurred in 84% of the women and 18% of the men. Five females withdrew from the trial because of gastric irritation. A dose-related increase in clinical symptoms was observed when doses were expressed on a mg/kg-day basis. Ingestion of zinc tablets alone (contrary to instructions) or with small meals increased the incidence of adverse effects. Zinc administration for six weeks had no effect on plasma levels of copper, total cholesterol or HDL-cholesterol in males or females, but significantly decreased the plasma level of LDL-cholesterol in females only. An apparent inverse linear relationship between plasma zinc levels and LDL-cholesterol levels was found in the females. Hematocrit values were unaffected by zinc ingestion in males and females and specific measures of copper status (ferroxidase activity of serum ceruloplasmin, antioxidant activity of erythrocyte superoxide dismutase, and Zn/Cu-dependent erythrocyte superoxide dismutase activity) were apparently unaffected in males. However, females, who received

higher mg/kg-day doses of zinc than males, exhibited significantly reduced activity levels of two copper metalloenzymes: serum ceruloplasmin and erythrocyte superoxide dismutase.

Hale et al. (1988) carried out an epidemiological study of the effect of zinc supplements on the development of cardiovascular disease in elderly subjects who were participants in an ongoing longitudinal geriatric health screening program. Noninstitutionalized, ambulatory subjects between the ages of 65 and 91 (average 78) years were evaluated using questionnaire, electrocardiogram, hematological, and drug-use data. A group of subjects (38 women and 31 men) which had ingested zinc supplements (20 to 150 mg supplemental zinc/day) for at least one year was compared to a control group (1195 women and 637 men) from the same screening program. Approximately 85% of the study group reported taking <50 mg supplemental zinc/day; for the 15% that reported an average intake of 60-150 mg supplemental zinc/day, the average duration was 8 years. The overall duration of zinc usage by the study group was: $\leq$2 years, 30%; >2$\leq$10 years, 55%; and >10 years, 15%. Based on the results of the questionnaire, the incidence of anemia was reported to have decreased with an increase in zinc dose. There were no differences between zinc and control groups with respect to electrocardiographic results or the incidence of adverse cardiovascular events (heart attack, heart failure, hypertension, or angina). The zinc group had a lower mean serum creatinine, lower total serum protein, lower serum uric acid, and a higher mean corpuscular hemoglobin. Red blood cell counts were significantly lower in the women, but not in the men, in the zinc group.

Groups of 9, 13, or 9 healthy white men were administered 0, 50, or 75 mg/day supplemental zinc as zinc gluconate, respectively, for 12 weeks (Black et al., 1988). The subjects were given instructions to avoid foods high in calcium, fiber and phytic acid, dietary constituents that are known to decrease zinc absorption. Subjects were also told to restrict their intake of zinc-rich foods in order to minimize the variation in daily dietary zinc. Three-day dietary records were collected on a biweekly basis. These records indicated that the dietary zinc intakes of the three treatment groups were 12.5, 14.0, and 9.5 mg zinc/day for the groups receiving the 0, 50, and 75 mg/day supplements, respectively. Based on the average body weights for each treatment group, total zinc intakes were 0.16, 0.85, and 1.10 mg zinc/kg-day for the 0, 50, and 75 mg/day groups, respectively. Biweekly blood samples were collected from all subjects and analyzed for total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, zinc, and copper. Urinary zinc and copper values were also determined. There was a general decline in the mean serum HDL-cholesterol for the 75-mg supplement group between weeks 6 and 12. HDL values for this group were significantly lower than those for the placebo group at weeks 6 and 12 ($p < 0.05$). When the mean HDL-cholesterol level of these subjects was compared to population percentile norms, there was a decline from the 92nd to the 77th percentile (Simko et al., 1984) in 6 weeks, followed by a relative stabilization of HDL values for the remaining 6-week test period. There was also a decline in the HDL values for the 50-mg group between weeks 8 through 12; however, this decline was not significantly different from that for the controls until the 12th week of treatment. Over the 12-week period, the HDL values for the 50-mg supplemental zinc group declined from the 90th to the 77th population percentile norms. Serum zinc, copper, total cholesterol, LDL-cholesterol, and triglycerides did not appear to be affected by treatment.

In another study, 12 healthy men (23 to 35 years) with normal serum cholesterol levels received a zinc sulfate capsule twice a day with meals (160 mg supplemental zinc/day or ~2 mg supplemental zinc/kg-day, assuming a 70 kg reference body weight) for 5 weeks and 8 subjects received placebo capsules (Hooper et al., 1980). Fasting lipid levels were measured weekly for 7 weeks and at week 16 in the zinc group, and biweekly for six weeks in the control group. There were no statistically significant differences in total serum cholesterol, triglyceride, and LDL-cholesterol between the zinc and control groups. After 5 weeks of zinc ingestion, serum HDL-cholesterol had been reduced by 17%; although no further zinc was administered, the serum HDL-cholesterol level continued to decline and was reduced by 26% at week 7, relative to the values for the placebo group. The rise in plasma zinc concentration did not correlate with the fall in HDL-cholesterol. Serum HDL-cholesterol returned to near baseline levels 11 weeks after the end of zinc supplementation.

In a study by L'Abbe and Fisher (1984a), groups of 10 weanling male Wistar rats were fed a basal diet supplemented with 15, 30, 60, 120, or 240 ppm zinc as zinc sulfate for 6 weeks; the 30 ppm group served as the control group. Using a reference (U.S. EPA, 1988) body weight of 0.217 kg and food intake of 0.020 kg/day, daily doses of 1.4, 2.8, 5.5, 11, and 22 mg supplemental zinc/kg-day were estimated. Although a linear relationship between zinc intake and serum ceruloplasmin levels was not established, the number of animals with abnormal ceruloplasmin levels increased with increasing doses. Abnormal ceruloplasmin levels were observed in 0, 0, 11, 30, and 100% of the animals in the 15, 30, 60, 120, and 240 ppm groups, respectively. The study authors estimated that the ED_{50} for low ceruloplasmin levels was approximately 125 ppm. Dose-related decreases in liver erythrocyte superoxide dismutase and heart cytochrome c oxidase were observed at dietary zinc levels greater than 30 ppm, reaching statistical significance in the 120 and 240 ppm groups. Heart erythrocyte superoxide dismutase and liver cytochrome c oxidase levels were not affected.

In a second study, L'Abbe and Fisher (1984b) fed groups of 10 weanling male Wistar rats diets containing normal (30 mg zinc/kg diet) or supplemented (240 mg zinc/kg diet) zinc (as zinc sulfate) and normal (6 mg copper/kg diet) or deficient (0.6 mg copper/kg diet) copper for up to 6 weeks. Groups of rats were sacrificed at 2, 4, and 6 weeks. Blood, heart, and liver samples were collected for analysis. No significant differences in body weight or food consumption were noted among treated groups. Similarly, no differences were seen in hemoglobin levels. Both increased zinc and deficient copper resulted in significant decreases in serum, heart, and copper levels. In both the high zinc and copper-deficient groups, serum ceruloplasmin, liver and heart Cu-Zn superoxide dismutase, and liver and heart cytochrome c oxidase were significantly reduced relative to control animals by 2 weeks of exposure, and remained reduced throughout the study.

According to a recent report by the National Academy of Sciences, the average daily intake for zinc among the U.S. population is 10-15 mg/day. Based on an average human body weight of 70 kg, this equates to 0.14-0.21 mg/kg-day. The recently-derived recommended dietary allowances (RDA; NRC, 2000) are 11 mg/day for men and 8 mg/day for women; using reference body weights of 70 kg for men and 60 kg for women, these equate to 0.16 mg/kg-day for men and 0.13 mg/kg-day for women. Therefore, recommendation of a risk value below the

range of 0.13-0.21 mg/kg-day, which represent both the daily intake levels necessary for normal health and the average daily intake of the U.S. population, is contraindicated.

For 79% of a 70-year lifetime (55 years), the proposed RfD of 0.3 mg/kg-day supplies adequate zinc to meet these requirements in adolescents and adults without any concurrent physiological impairment. It does not supply the RDA for infants, preadolescent children or, possibly, for lactating women. The RfD of 0.3 mg/kg-day is expected to be without adverse effects when consumed on a daily basis over an extended period of time.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study – Medium
Data Base – Medium
RfD -- Medium

The level of confidence in the key studies is medium since they are well-conducted clinical studies with relevant biochemical parameters investigated in both males (Fischer et al., 1984) and females (Yadrick et al., 1989), but had a limited number of study subjects. The confidence in the overall database is medium since the available suitable human studies are all of moderate duration and chronic animal data are limited. Medium confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- _____

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 _____.

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Zinc
CASRN -- 7440-66-6
Last Revised -- 00/00/00

Not available at this time.

Available data are not suitable for the derivation of an RfC for zinc.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Zinc
CASRN -- 7440-66-6
Last Revised -- 00/00/00

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/cu.m 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 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), zinc is classified in Group D, *Not Classifiable as to Human Carcinogenicity*, based on inadequate evidence of carcinogenicity in humans and animals. Under the proposed guidelines (U.S. EPA, 1999), *data are inadequate for an assessment of human carcinogenic potential* of zinc, because studies of humans occupationally-exposed to zinc are inadequate or inconclusive, adequate animal bioassays of the possible carcinogenicity of zinc are not available, and tests of the genotoxic effects of zinc have been equivocal.

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are no reports on the possible carcinogenicity of zinc and compounds per se in humans. Case studies have been used to evaluate the effects of zinc administered for therapeutic reasons. There are reports which compare zinc levels in normal and cancerous tissue. Studies of occupational exposure to zinc compounds have also been conducted, but have limited value because they do not correlate exposure with cancer risk.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In a 1-year study, an unspecified number of newborn Chester Beatty stock mice (sex not reported) were administered 0, 1000, or 5000 ppm zinc (approximately 0, 170, or 850 mg/kg/day) as zinc sulfate in drinking water (Walters and Roe, 1965). A separate group of mice received zinc oleate in the diet at an initial dose of 5000 ppm supplemental zinc; this dose was reduced to 2500 ppm after 3 months and to 1250 ppm after an additional 3 months because of mortality due to anemia. An epidemic of ectromelia caused the deaths of several mice during the first 8 weeks; consequently, additional control and test-diet groups were established. There was no difference in body weight gain between control and treated groups, except for the dietary zinc group which became anemic. Survival was not reported in treated compared with control groups. An apparent increase in the incidence of hepatomas was observed in treated mice surviving for 45 weeks or longer relative to controls (original and replacement mice were pooled). The hepatoma incidences in the control, low-dose drinking water, high-dose drinking water, and test-diet groups were 3/24 (12.5%), 3/28 (10.7%), 3/22 (13.6%), and 7/23 (30.4%), respectively. Incidences of malignant lymphoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups were 3/24 (12.5%), 4/28 (14.3%), 2/22 (9%), and 2/23 (8.7%), respectively. Incidences of lung adenoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups were 10/24 (41.7%), 9/28 (32.1%), 5/22 (22.7%), and 9/23 (39.1%), respectively. None of these were significantly elevated in a statistical analysis of these data performed by the EPA.

Halme (1961) exposed tumor-resistant and tumor-susceptible strains of mice to zinc in drinking water. In a 3-year, 5-generation study, zinc chloride was added to the water of tumor-resistant mice (strain not specified); the groups received 0, 10, 20, 50, 100, or 200 mg Zn/L. The spontaneous tumor frequency for this strain of mice was 0.0004%. The tumor frequencies in the generations were reported as: F0=0.8%, F1=3.5%, F1 and F2=7.6% and F3 and F4=25.7%. Most of the tumors occurred in the 10- and 20-mg Zn dose groups. No statistical analyses and no individual or group tumor incidence data were reported. In the tumor- susceptible mice, strains C3H and A/Sn received 10-29 mg Zn/L in their drinking water for 2 years; 33/76 tumors were observed in the C3H strain (31 in females) and 24/74 tumors were observed in the A/Sn strain (20 in females). Most of the tumors were reported to be adenocarcinomas, but the tissues in which they occurred were not reported. The numbers of specific tumor types were not reported. The overall tumor frequencies (43.4% for C3H and 32.4% for A/Sn; both sexes combined) were higher than the spontaneous frequency (15% for each strain), although no statistical analyses were reported.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Either zinc deficiency or excessively high levels of zinc may enhance susceptibility to carcinogenesis, whereas supplementation with low to moderate levels of zinc may offer protection (Mathur, 1979; Woo et al., 1988). For example, zinc deficiency enhanced carcinomas of the esophagus induced by methylbenzylnitrosoamine (Fong et al., 1978) but retarded the development of cancer of the oral cavity induced by 4-nitroquinoline-N-oxide (Wallenius et al., 1979). Thus, zinc's modifying effect on carcinogenesis may depend both on the dose of zinc and the identity of the carcinogen being affected. The genotoxicity of zinc, particularly in *S. typhimurium*, appears to depend greatly on the chemical form (e.g., inorganic or organic salt).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- _____

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 _____.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Zinc
CASRN -- 7440-66-6
Last Revised -- 00/00/00

__VI.A. ORAL RfD REFERENCES

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None.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Zinc
CASRN -- 7440-66-6

Date	Section	Description
__/__/__		
__/__/__		
__/__/__		
__/__/__		

_VIII. SYNONYMS

Zinc
CASRN -- 7440-66-6
Last Revised -- __/__/__

7440-66-6
Zinc
Asarco L 15
Blue powder
Cinc [Spanish]
EMANAY ZINC DUST
GRANULAR ZINC
HSDB 1344
JASAD
Lead refinery vacuum zinc
Merrillite
UN 1436
Zinc
ZINC DUST
ZINC POWDER

ZINC, ashes
ZINC, powder or dust, non-pyrophoric
ZINC, powder or dust, pyrophoric