Zinc and Compounds; CASRN 7440-66-6

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 Zinc and Compounds

File First On-Line 02/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/03/2005
Inhalation RfC (I.B.)	qualitative discussion	08/03/2005
Carcinogenicity Assessment (II.)	yes	08/03/2005

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Zinc and Compounds
CASRN —7440-66-6
Section I.A. Last Revised — 08/03/2005

The RfD is an estimate of a daily oral exposure to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark dose (BMDL), a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold)

mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Since RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

This RfD replaces the previous RfD of 0.3 mg/kg-day entered on IRIS 02/01/1991. The new RfD is based on additional data from more recent studies using a sensitive endpoint in a variety of human subjects.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Decreases in erythrocyte Cu, Zn-superoxide dismutase (ESOD) activity in healthy adult male and female volunteers **Yadrick et al., 1989** **Fischer et al., 1984** **Davis et al., 2000** **Milne et al., 2001**	NOAEL: NONE LOAEL: 0.91 mg/kg-day	3	0.3 mg/kg-day

* 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 (Pennington et al., 1989), plus reported supplemental dose. For example, for the Yadrick et al. (1989) study, the supplemental dose of 50 mg/day was added to the average daily intake of 9.38 mg/day, giving a total intake of 59.38 mg/day. Dividing this by a reference female body weight of 60 kg results in a mean zinc intake of 0.99 (1.0) mg/kg-day. The principal studies identified effect levels of 0.81 mg Zn/kg-day (Davis et al., 2000; Milne et al., 2001), 0.94 mg Zn/kg-day (Fischer et al., 1984), and 0.99 mg Zn/kg-day (Yadrick et al., 1989). Since the four studies have similar methodologies and outcomes with regard to effects, they were averaged together to obtain the LOAEL (0.81+0.94+0.99=2.74/3=0.91 mg/kg-day).

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

Zinc is an essential element required as part of a healthy diet. The zinc content of a typical mixed diet of North American adults is approximately 10-15 mg/day (IOM, 2001). The FDA's Total Diet Study (Pennington et al., 1989) found zinc intakes of 7.25, 9.74, 15.42, 9.38, and 15.92 mg/day in children (2 years of age), girls (14-16 years), boys (14-16 years), women (25-30 years), and men (25-30 years), respectively. The recommended dietary allowances (RDAs) for zinc for the year 2000 (IOM, 2001) are 11 mg/day for adult males and 8 mg/day for adult females (not pregnant or lactating).

The RfD for zinc is based on human clinical studies to establish daily nutritional requirements. Zinc is an essential trace element that is crucial to survival and health maintenance, as well as growth, development, and maturation of developing organisms of all animal species. Thus, insufficient as well as excessive oral intake can cause toxicity and disease and a quantitative risk assessment must take essentiality into account. The principal studies examine dietary supplements of zinc and the interaction of zinc with other essential trace metals, specifically copper, to establish a safe daily intake level of zinc for the general population, including pregnant women and children, without compromising normal health and development.

A wide range of clinical symptoms have been associated with zinc deficiency in humans (Abernathy et al., 1993; Prasad, 1993; Sandstead, 1994; Walsh et al., 1994). The clinical manifestations of severe zinc deficiency, seen in individuals with an inborn error of zinc absorption or in patients receiving total parenteral nutrition with inadequate levels of zinc, include bullous pustular dermatitis, diarrhea, alopecia, mental disturbances, and impaired cell-mediated immunity resulting in intercurrent infections. Symptoms associated with moderate zinc deficiency include growth retardation, male hypogonadism, skin changes, poor appetite, mental lethargy, abnormal dark adaptation, and delayed wound healing. Neurosensory changes, impaired neuropsychological functions, oligospermia, decreased serum testosterone, hyperammonemia, and impaired immune function (alterations in T-cell subpopulations, decreased natural killer cell activity) have been observed in individuals with mild or marginal zinc deficiency.

As reviewed by Mahomed et al. (1989), severe zinc deficiency in animals has been associated with reduced fertility, fetal nervous system malformations, and growth retardation in late pregnancy. In humans, labor abnormalities, congenital malformations, and preterm labor have been reported in otherwise healthy women with low maternal serum zinc concentrations. Numerous studies have examined pregnancy outcomes following zinc supplementation. For example, Simmer et al. (1991) found significant intrauterine growth retardation and fewer inductions of labor (generally associated with poor fetal growth), and non-statistically significant increases in birth weight and placental weights in zinc-deficient women receiving a

supplement containing 100 mg zinc citrate (22.5 mg zinc) (these women were receiving the supplement because they were determined to be at risk of delivering small-for-gestational age babies). However, Mahomed et al. (1989) did not find any statistically significant differences in gestation duration, details of labor and delivery, fetal development, or neonatal health among 246 randomly selected pregnant women receiving 20 mg Zn/day as zinc sulfate tablets beginning before the 20th week of pregnancy as compared to 248 women receiving placebo tablets. While the zinc supplement and placebo group had marginal zinc intake (approximately 10 mg/day) prior to supplementation, the zinc supplementation did not appear to influence pregnancy outcome.

Reduced copper status has been associated with increased zinc intake. In studies in which the interactions of excess zinc with copper were measured, there was a consistent decrease in erythrocyte Cu, Zn-superoxide dismutase (ESOD) activity. Thus, copper status and ESOD activity are considered a sensitive measure of the effects of high levels of zinc exposure. The study of Yadrick et al. (1989) exposed a group of healthy adult women to 50 mg supplemental Zn/day; adding in an average daily dietary consumption of 9.38 mg/day (from the FDA Total Diet Study from 1982-1986 [Pennington et al., 1989]), the total exposure level from the Yadrick et al. (1989) study was 59.38 mg Zn/day, or 0.99 mg/kg-day assuming a reference female body weight of 60 kg. ESOD activity declined over the 10-week supplementation period and, at 10 weeks, was 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. Adding in an average daily dietary consumption of 15.92 mg Zn/day (from the FDA Total Diet Study from 1982-1986 [Pennington et al., 1989]), the total exposure level from Fischer et al. (1984) was 65.92 mg Zn/day, or 0.94 mg/kg-day assuming a reference male body weight of 70 kg. 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, ESOD 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 ESOD activity was also observed at 6 weeks.

Davis et al. (2000) and Milne et al. (2001) have reported the results of exposure of a group of postmenopausal women (aged 50-76, mean of 64.9 ± 6.7 years) to varying concentrations of zinc and copper in the diet. Average height was 159.6 ± 7.6 cm, and mean body weight was 65.1 ± 9.5 kg. These studies were conducted in a hospital metabolic ward where patients or human volunteers are maintained under strict environmental and dietary control to monitor dietary intake with collection of biological samples for metabolic studies. Subjects were kept in a metabolic ward for a 200 day period, and fed a controlled basal diet that contained 0.6 mg Cu/day and 3 mg Zn/day. For the first ten days, all subjects consumed an equilibration diet, which consisted of the basal diet supplemented with 1.4 mg Cu/day (2 mg total) and 6 mg Zn/day (9 mg total). Following the initial 10-day equilibration, one group (n=12) was exposed to a diet containing basal diet supplemented with 0.4 mg Cu/day (1.0 mg Cu/day total) and the other group (n=13) was fed the basal diet supplemented with 2.4 mg Cu/day (3.0 mg Cu/day total). The remaining 190 days were divided into two 90-day study periods for both groups: the Cu-supplemented basal diet with no zinc supplement was fed for the first 90-day period and the Cu-supplemented basal diet supplemented with 50 mg Zn/day (for a total of 53 mg Zn/day; a total average daily dose of 0.81 mg Zn/kg-day using a mean body weight of 65.1 kg provided in the manuscripts) was fed for the second 90-day period. The two 90-day periods were separated by an additional equilibration period, identical to the one performed at the beginning of the study.

During each of the equilibration periods, and twice monthly during the exposure periods, blood was drawn from the subjects after an overnight fast, and evaluated for changes in cells and cell elements (erythrocytes, platelets, mononuclear cells, neutrophils), plasma and blood levels of copper and zinc, and a variety of blood proteins and factors (alkaline phosphatase activity, superoxide dismutase activities [ESOD and extracellular Cu, Zn-superoxide dismutase (EC-SOD)], 5'-nucleotidase activity, triiodothyronine, thyroxine, and thyroid-stimulating hormone levels, and amyloid precursor protein levels). Copper and zinc levels were determined for urine, feces, and diet. Alcohol tolerance tests were performed at the end of the first equilibration period and at the end of the low- and high-zinc exposures. Data were analyzed by a two-way (dietary zinc and copper) repeated-measures analysis of variance (ANOVA), and Tukey's contrasts were used to test for differences among means.

Plasma zinc concentrations were significantly lower, relative to the equilibration levels, and platelet zinc concentrations tended to be lower, though not significantly, in subjects fed 3 mg Zn/day than in those fed 53 mg Zn/day; plasma zinc was not lowered from equilibration levels when subjects were fed 3 mg Zn/day, but was elevated in those fed 53 mg Zn/day. Zinc supplementation increased Zn levels in the feces and urine, but did not appear to affect plasma

Cu levels. Neither erythrocyte zinc levels nor erythrocyte membrane zinc concentrations were significantly altered by changes in dietary zinc. High-zinc subjects showed significant increases in bone-specific alkaline phosphatase activity, relative to the equilibration period, but not in plasma alkaline phosphatase or erythrocyte membrane alkaline phosphatase. Zinc supplementation significantly increased mononuclear white cell 5'-nucleotidase activity and decreased plasma 5'-nucleotidase activity; the difference in 5'-nucleotidase activity was apparent when subjects were fed the high-copper diet, but not when they were fed the low-copper diet. EC-SOD activity, but not ESOD activity, was significantly increased by zinc supplementation; this was more apparent in the low-copper group. ESOD activity was significantly decreased relative to equilibration levels in low-copper subjects and significantly increased in high-copper subjects; in both cases, zinc supplementation caused a statistically insignificant decrease in ESOD activity. Erythrocyte glutathione peroxidase activity was increased by low dietary zinc and decreased by high dietary zinc; however, the decrease did not result in a return to initial equilibration activity. Plasma free thyroxine concentrations, but not total thyroxine concentrations, were significantly increased in the zinc-supplemented groups; no other effects on thyroid-related endpoints were noted. During the low-zinc period, there was an increase in total cholesterol; this increase was reversed with high-zinc treatment, resulting in lower total cholesterol. LDL-cholesterol changes were similar to the total cholesterol changes, while HDL-cholesterol, very low density lipoprotein-cholesterol, and triglycerides were not affected. Zinc supplementation significantly decreased platelet amyloid precursor protein expression in subjects fed the low-copper diet; however, technical concerns prevented many of these samples from being properly analyzed, so the sample size for amyloid precursor protein expression was very small. Most indicators of iron status were not affected by the changes in dietary zinc or copper; the exception was a small drop in hemoglobin levels, which the investigators attributed to the effects of accumulated blood loss from phlebotomy.

As the four studies identified physiological changes on similar, sensitive endpoints (indicators of body copper status) at similar dose levels (0.81-0.99 mg Zn/kg-day) in a variety of human subject groups (postmenopausal females, adult females, and adult males), the studies of Yadrick et al. (1989), Fischer et al. (1984), Davis et al. (2000) and Milne et al. (2001) were selected as co-principal studies.[1]

[1]The studies by Davis et al. (2000) and Milne et al. (2001) were approved by the Institutional Review boards of the University of North Dakota and the US Department of Agriculture and followed Guidelines of the Department of Health and Human Services and the Helsinki Declaration regarding the use of human subjects. The study by Yadrick et al. (1989) was approved by the Institutional Review Board of Oklahoma State University and informed consent was obtained from each participant. Finally, the study by Fischer et al. (1984) was

approved by the Human Studies Committee of the Health Protection Branch, Health and Welfare Canada, and a consent form was signed by all participants.

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

UF=3

In selecting the point of departure for the RfD, the effect levels from the co-principal studies (Yadrick et al. 1989; Fischer et al. 1984; Davis et al. 2000 and Milne et al. 2001) were averaged (0.81+0.94+0.99=2.74/3=0.91 mg/kg-day), since they have similar methodologies and outcomes with regards to effects.

An interspecies uncertainty factor (UF_A) was not necessary for extrapolation from an animal study to the human population. The principal studies were conducted in human volunteers.

An uncertainty factor to account for extrapolation from a subchronic study to estimate chronic exposure conditions (UF_S) was not necessary. Zinc is an essential element and therefore, chronic exposures of zinc are required for proper nutrition. The RfD is expected to be without adverse effects when consumed on a daily basis over the life-span of the individual, neither inducing nutritional deficiency nor resulting in toxic effects in healthy non-pregnant adult humans consuming an average American diet.

A database uncertainty factor (UF_D) to account for uncertainties due to lack of information in the database was not necessary. The database contains a considerable number of well-conducted human studies in a diverse group of human subjects. There are numerous reproductive and developmental toxicity studies performed in different species. Animal studies demonstrate that effects on reproductive and/or developmental endpoints are observed at doses higher than the zinc supplemental dosages associated with ESOD activity and copper homeostasis.

An uncertainty factor for extrapolation from a minimal LOAEL to a NOAEL (UF_L) was determined not to be necessary. The RfD was based on a minimal effect level for a sensitive biological indicator, decreased ESOD activity, which is a measure of zinc associated alterations in copper homeostasis that could lead to oxidative tissue damage.

A threefold intraspecies uncertainty factor (UF_H) was used to account for variability in susceptibility in human populations. For zinc, and other nutritionally required elements, it is important that the RfD not be set at a value that would suggest that people should consume diets with insufficient zinc. Nutritional studies have established a baseline and the use of a

greater UF would place some sensitive humans in the possible position of either exceeding the RfD or not obtaining sufficient zinc. Therefore, a UF_H of 3 was applied, based on four different studies with moderate duration in the most sensitive humans and consideration of a substance which is an essential dietary nutrient.

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

Zinc is essential for the function of more than 300 enzymes, including alkaline phosphatase, alcohol dehydrogenase, Cu, Zn-superoxide dismutase, carboxypeptidase, delta-aminolevulinic acid dehydratase, carbonic anhydrase, ribonucleic acid polymerase, and reverse transcriptase (Vallee and Falchuk, 1993; Sandstead, 1994). Zinc is also involved in DNA and RNA synthesis and cell proliferation. Zinc coordinates with cysteine and histidine residues of certain peptides and produces a tertiary structure which has an affinity for unique segments of DNA in promoter gene regions, including zinc finger protein domains, the most common zinc motif, and the zinc thiolate cluster (Prasad and Nath, 1993; Walsh et al., 1994). Other physiological roles of zinc include enhancement of the affinity of growth hormone for its binding receptors, modulation of synaptic transmissions by interacting with specific sites on ionotrophic neurotransmitter receptor proteins, and induction of metallothionein (Walsh et al., 1994).

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 men and 2.5 mg Zn/kg-day for women. Adverse symptoms, including abdominal cramps, vomiting, and nausea, occurred in 84% of women and 18% of 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 recommended instructions) or with small meals increased the incidence of adverse effects. Zinc administration for 6 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 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 ESOD) were apparently unaffected in males. However, females, who received higher mg/kg-day doses of zinc than males, exhibited a significant reduction in the activity of two copper metalloenzymes: serum ceruloplasmin and ESOD. Possible explanations for the discrepancy between these results for the male subjects and those reported by Fischer et al. (1984) may be differences in the composition of the diets

of test subjects (e.g., high phytic acid content), decreased zinc absorption with higher doses, body weight, etc.

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: <=2 years, 30%; >2<=10 years, 55%; and >10 years, 15%. Based on the results of the questionnaire, the incidence of anemia was reported to decrease with increasing zinc dose. There were no differences between zinc-treated and control groups with respect to electrocardiogram 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 women, but not in men, in the zinc-treated 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. The records indicated that the dietary zinc intakes of the three treatment groups were 12.5, 14.0, and 9.5 mg Zn/day for the groups receiving the 0, 50, and 75 mg/day supplements, respectively. Thus, 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 6 weeks in the control group. There were no statistically significant differences in total serum cholesterol, triglycerides, 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 Fischer (1984a), groups of 10 weanling male Wistar rats were fed a basal diet supplemented with 0, 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 body weight of 0.217 kg and food intake of 0.020 kg/day (U.S. EPA, 1988), daily doses of 1.4, 2.8, 5.5, 11, and 22 mg supplemental Zn/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 0, 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 the activities of liver Cu, Zn-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 Cu, Zn-superoxide dismutase and liver cytochrome c oxidase activities were not affected.

In a second study, L'Abbe and Fischer (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. Serum and heart copper levels were significantly decreased in rats fed either zinc-supplemented or copper-deficient diets. In both the high-zinc and copper-deficient

groups, the activities of 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.

The recently-derived recommended dietary allowances (IOM, 2001) are 11 mg/day for men and 8 mg/day for women (not pregnant or lactating). 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 more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium-to-high
Data Base — High
RfD — Medium-to-high

The overall confidence in this RfD assessment is medium-to-high because the principal studies are well-conducted clinical studies with relevant biochemical parameters investigated in both males (Fischer et al., 1984) and females (Davis et al., 2000; Milne et al., 2001; Yadrick et al., 1989), but had a limited number of study subjects. The confidence in the overall database is high because there are several available suitable human studies that are of moderate duration. Chronic animal data are limited. Medium-to-high confidence in the RfD follows.

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 (2005)

This assessment was peer reviewed by external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Zinc and Compounds (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A: External Peer Review-Summary of Comments and Disposition (PDF)***.

Agency Completion Date -- 7/29/2005

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 (email address).

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

Zinc and Compounds
CASRN — 7440-66-6
Section I.B. Last Revised — 08/03/2005

The RfC is an estimate of a daily inhalation exposure to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark concentration (BMCL), a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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 at this time.

Available data are not suitable for the derivation of an RfC for zinc. A number of case reports of metal fume fever have been reported in humans; however, exposure levels are not known.

The data in animals are limited to a few studies of acute duration; no subchronic or chronic inhalation studies of zinc are available at this time.

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

Not applicable.

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

Not applicable.

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

Not applicable.

I.B.5. Confidence in the Inhalation RfC

Not applicable.

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

Source Document — U.S. EPA (2005)

This assessment was peer reviewed by external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Zinc and Compounds (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A: External Peer Review-Summary of Comments and Disposition (PDF)***.

Agency Completion Date — 7/29/2005

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 (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Zinc and Compounds
CASRN — 7440-66-6
Section II. Last Revised — 08/03/2005

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is an upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. Evidence for Human Carcinogenicity

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

Under the *Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is inadequate information to assess 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 results of genotoxic tests of zinc have been equivocal.

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

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

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, a natural mouse pathogen and an orthopoxvirus, 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 groups compared with control groups. In mice administered zinc oleate in the diet, no statistically significant increases in liver tumors were observed. 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 performed by the EPA.

Halme (1961) exposed tumor-resistant and tumor-susceptible strains of mice to zinc in drinking water. In a 3-year, five-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. Most of the tumors occurred in the 10- and 20-mg Zn/L 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). However, this study provided no support for carcinogenicity since no statistical analyses were performed and no individual or group tumor incidence data 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 methylbenzylnitrosamine (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 mutagenicity of zinc, particularly in *Salmonella typhimurium*, appears to depend greatly on the chemical form.

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

Not applicable.

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

Not applicable.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA (2005)

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 in Appendix A of the Toxicological Review of Zinc and Compounds (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A: External Peer Review-Summary of Comments and Disposition (PDF)***.

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

Agency Consensus Date — 7/29/2005

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 (email address).

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

VI. Bibliography

Zinc and Compounds
CASRN — 7440-66-6

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

Not Applicable.

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Zinc and Compounds
CASRN — 7440-66-6
File First On-Line — 02/01/1991

Date	Section	Description
02/01/1991	II.	Carcinogenicity assessment on-line
10/01/1992	I.A.	Oral RfD summary on-line
08/03/2005	I., II., VI.	RfD, RfC, and cancer sections updated.

VIII. Synonyms

Zinc and Compounds
CASRN — 7440-66-6
Section VIII. Last Revised — 08/03/2005

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