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Zinc and Compounds

CASRN 7440-66-6

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0426

Zinc and Compounds; CASRN 7440-66-6

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 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 and Compounds

File On-Line 02/01/1991

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	10/01/1992
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/1991

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS**I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)**

Substance Name -- Zinc and Compounds
 CASRN -- 7440-66-6
 Last Revised -- 10/01/1992

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.

NOTE: This RfD for the soluble salts of zinc supplies adequate zinc to meet the requirements in adolescents and adults over a lifetime without any concurrent physiological impairment. It does not supply the Recommended Daily Allowance (RDA) to those members of the population who have greater requirements for a short, less-than-lifetime duration, for example, infants, pre-adolescent children, or, possibly, lactating women. For short-term requirements in infants, pre-adolescent children, and lactating females, refer to the RDAs (NRC, 1989).

At a Workshop on the "Risk Assessment of Essential Elements" (Herndon, VA; March 10-12, 1992), several nutritionists commented on the derivation of the zinc RfD. The most relevant comment raised the issue of zinc bioavailability from various media. Dr. Harold Sandstead (1992) summarized this viewpoint and suggested the following values for zinc RfDs from various media: zinc supplements - 0.25 mg/kg/day; "omnivores" - 0.7 mg/kg/day; and vegetarians - 1.7 mg/kg/day. The proposed RfD for individuals consuming supplements, which is roughly comparable to soluble salts of zinc, is quite similar to the RfD verified by EPA's RfD/RfC Work Group. This agreement between the nutritionists and the toxicologists gives the EPA greater confidence in the verified RfD.

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
47% Decrease in erythrocyte superoxide dismutase (ESOD) concentration in adult females after 10 weeks of zinc exposure	NOAEL: None LOAEL = 59.72 mg/day (1.0 mg/kg/day)	3	1	3E-1 mg/kg/day

Human Diet Supplement Study

Yadrick et al., 1989

*Conversion Factors: The dose conversion factors were based on a 60-kg reference female body weight. Total dose was derived from estimations from the FDA Total Diet Study for 1982-1986, plus reported supplemental dose. For example, for the Yadrick et al., 1989 study, the dose is 1.0 mg/kg-day based on 50 mg zinc supplement plus 9.72 mg/day zinc from the diet (total of 60), divided by the assumed average body weight of the participants (60 kg).

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

Yadrick, M.K., M.A. Kenney and E.A. Winterfeldt. 1989. Iron, copper, and zinc status: Response to supplementation with zinc or zinc and iron in adult females. *Am. J. Clin. Nutr.* 49: 145-150.

The oral RfD is based on a clinical study which investigated the effects of oral zinc supplements on copper and iron balance. This study is supported by several other studies which indicate that zinc supplementation can alter copper balance. The effects on copper and iron biochemistry are considered of concern since long-term iron or copper deficiency could result in significant adverse effects. For example, zinc supplementation therapy with megadoses of up to 5 g/day, as well as smaller amounts of 150 mg/day, taken for 1 to 2 years have produced copper deficiency anemia (Fischer et al., 1984). In addition, several studies have investigated the effects of zinc supplementation on the high-density lipoprotein (HDL) levels of adult males. These have been added as supporting studies because the observed change in HDL values in males may be significant since a sustained decrease in HDL concentrations may be associated with increased risk of coronary artery disease when combined with a parallel increase in low-density lipoprotein (LDL) cholesterol.

A 10-week study of zinc supplementation in 18 healthy women given zinc gluconate supplements twice daily (50 mg zinc/day, or 1.0 mg/kg-day, see below) 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 fed copper-deficient or high-zinc diets, in which copper metalloenzyme activity is greater and precedes 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.

No measurements were made of dietary zinc or copper in this study. However, a level of dietary zinc can be estimated at 9.72 mg/day for females (20- to 30-years old) from the results of the FDA Total Diet Study for 1982-1986 (Pennington et al., 1989). The LOAEL of 1.0 mg/kg-day was calculated from the sum of these dietary estimates and the supplemental zinc dose using an assumed body weight of 60 kg for adult females, as shown in the conversion factor section.

Support for considering the intake of 50 mg/kg-day supplemental zinc as a threshold LOAEL is provided by Fischer et al. (1984) which also suggests that zinc affects copper balance at doses of 0.95 mg/kg-day in males. Healthy men given 25 mg of zinc as gluconate twice daily for a 6-week period displayed a significant decrease ($p < 0.05$) in erythrocyte superoxide dismutase (ESOD) activity at the end of 6 weeks exposure. There were no differences between serum copper levels or ceruloplasmin activity in the 13 members of the supplement group compared with controls. Serum zinc levels were significantly

increased in the supplement group after 2 weeks.

Prasad et al. (1978) fed a patient with sickle cell anemia supplements of 150 to 200 mg zinc/day for 2 years. The supplement resulted in copper deficiency; serum copper and plasma ceruloplasmin levels were decreased. When copper was administered, the plasma ceruloplasmin levels became normal. In a follow-up study, of 13 patients on zinc therapy, (similar treatment levels assumed), 7 patients had ceruloplasmin levels at the lower limit of normal after 24 weeks of dosing.

In a 9-week study, Festa et al. (1985) fed nine male students diets containing 2.6 mg copper/day and 1.8-20.7 mg zinc/day for 1- to 2-week periods. This study indicated that fecal copper excretion was influenced by the amount of zinc in the diet and the length of time it was administered. Typically, after 1-2 weeks at 18.5 mg/day (just 3.5 mg/day higher than the adult RDA), subjects lost significantly more copper in the feces. Plasma copper concentrations were unchanged.

Groups of 9, 13 or 9 healthy white men were administered 0, 50, or 75 mg/kg-day 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 have a negative impact on 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/day for the groups receiving 0, 50, and 75 mg/kg-day supplement, respectively. Based on the average body weights for each treatment group, these doses correspond to a total zinc intake of 0.16, 0.85, and 1.10 mg/kg-day.

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 ($p > 0.05$) from that for the controls until the 12th week of treatment. Over the 12-week period the HDL values for the 50-mg 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. While it is not absolutely certain that the 50-mg zinc/day supplement represents a clearly biologically significant endpoint, this level, when viewed collectively with other studies investigating effects on HDL-cholesterol, may signify the beginning of the dose-response trend. The significance of this change is unknown in light of an absence of increase in LDLs.

Zinc supplementation (160 mg as zinc sulfate) was found to lower HDL-cholesterol values in 11 healthy men when administered over 5 weeks (Hooper et al., 1980). A control group of eight subjects received a placebo. Fasting cholesterol, HDL-cholesterol, and triglycerides were determined on a weekly basis for 7 weeks and again 11 weeks after the end of supplementation. Dietary zinc levels were not measured, in the FDA Total Diet Study, adult males consumed an average of 16.41 mg/day during 1982-1987 (Pennington et al., 1989). Based on a 70-kg average body weight and 16.41 mg/day dietary zinc, the average dietary zinc intake for those receiving a supplement was 2.52 mg/kg-day.

After an initial HDL increase during the first 2 weeks of supplementation, HDL levels were significantly lower than those for the controls during weeks 4 through 7 ($p = 0.002$ to 0.0001). HDL levels returned to normal 11 weeks after supplementation had ended. The 11 subjects of this study had initial mean HDL

values below average for their age category (23-35 years old). During the first 7 weeks of monitoring, their HDL percentile values fell from the 36th to the 8th population percentile norm. Percentile standings lower than 10 are associated with cardiovascular risk. Serum cholesterol, LDL-cholesterol, and triglycerides did not change significantly during the study; serum zinc levels increased during the supplementation period. Serum cholesterol values were normal.

A third study of the effects of zinc supplementation was conducted by Chandra (1984) in 11 adult men (ages not given). Zinc sulfate tablets were administered twice daily for a total zinc supplement intake of 300 mg/day. Average dietary zinc during the supplementation period was 10.1 mg/day, based on 24-hour recall data and 11.2 mg/day in the pre-test period. Thus, the daily zinc intake was 4.43 mg/kg-day for a 70-kg male during supplementation. Fasting serum cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were measured biweekly for 6 weeks; a final measurement of these parameters was conducted at 16 weeks. Total lymphocytes, T-lymphocytes, and B-lymphocytes were also measured. Lymphocyte activity was monitored through polymorphonuclear migration response to chemotactic phytohemagglutinin (PHA) stimulation and phagocytosis of opsonized bacteria.

There was a significant decrease in serum HDL values during weeks 4 and 6 ($p < 0.1$ and $p < 0.01$, respectively) with a return to baseline levels at week 16 (Chandra, 1984). LDL-cholesterol levels were significantly increased ($p < 0.05$) at week 6, but there were no significant changes in serum cholesterol and triglycerides. During the 6-week supplement administration period, the HDL percentile values fell from the 43rd to the 6th percentile, as estimated from the population percentile norms for 30- to 35-year-old males (Simko et al., 1984).

There were no significant changes in lymphocyte counts during the period of zinc supplementation, but polymorphonuclear response to PHA stimulation (chemotactic migration) and phagocytosis were impaired (Chandra, 1984). Plasma zinc values increased during the supplement administration.

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

UF -- An uncertainty factor of 3 was used, based on a minimal LOAEL from a moderate-duration study of the most sensitive humans and consideration of a substance that is an essential dietary nutrient.

MF -- None

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

Zinc is an essential nutrient with RDA values ranging from 5 to 15 mg/day for different age and sex categories (NRC, 1989). The RDA is an estimate of the zinc needed for growth, development, metabolism and tissue maintenance for over 98% of the healthy American population. 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. It neither induces a nutritional deficiency in healthy, non-pregnant, adult humans consuming the average American diet nor causes undesirable inhibition of normal lipid transport.

When the three studies monitoring HDL-cholesterol are considered as a group, they show a consistent lowering of HDL-cholesterol levels in response to the addition of zinc to the diet, an effect which is reversed with cessation of the zinc supplementation. The data of Black et al. (1988) indicate that the depressed HDL values can persist for up to 12 weeks. Data are available from all 3 studies at 6 weeks. However, in the Hooper et al. (1980) study, the 6-week data represent HDL status 1 week after supplement administration ended. Additional data will be needed to clarify whether or not this change is significant with longer exposure.

Supplemental zinc does not appear to have the same effect on females that it has on males. Healthy adult females were given supplemental zinc doses of 0, 15, 50 or 100 mg/day zinc as zinc acetate for 60 days (Freeland-Graves et al., 1982). Plasma cholesterol, HDL-cholesterol, and zinc were monitored at biweekly intervals. A transitory decrease in HDL values was noted at 4 weeks, but only in the group receiving the 100-mg/day supplement (1.8 mg/kg-day based on a 60-kg body weight and 8.1 mg/day zinc in the diet [from diet records]). This decrease in HDL values was not apparent at 6 and 8 weeks. Serum zinc levels were also highest in these subjects at 4 weeks.

A very slight but statistically significant ($p = 0.04$) 2-mg/dL increase in HDL cholesterol was seen in a group of 22 elderly male and female subjects (sex ratio unknown) 8 weeks after they ceased using zinc supplements (Goodwin et al., 1985). Serum zinc values fell from 92 to 86 $\mu\text{g/dL}$ during the same period. The average supplement intake was 29.1 mg/day with a range of 17.5 to 52.2 mg/day. The increase in HDL value seemed to be greatest for the subjects with the highest ratings for physical activity. Although the data in this study are far from conclusive with regard to the relationship between zinc and HDL values, they do add to the weight of evidence which suggests that the impact of supplemental zinc on HDL levels is real.

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium
Data Base -- Medium
RfD -- Medium

The level of confidence in the studies is medium since they are well-conducted clinical studies with many biochemical parameters investigated but only few numbers of humans were tested. The confidence in the overall database is medium since these studies are all of short duration. Medium confidence in the RfD follows.

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

Source Document -- U.S. EPA, 1990

The Drinking Water Health Advisory for Zinc has received internal Office of Water review.

Other EPA Documentation -- None

Agency Work Group Review -- 09/21/1989, 08/15/1991, 09/11/1991, 11/06/1991

Verification Date -- 11/06/1991

IA.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).

IB. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 02/01/1991

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 ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing 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 CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on inadequate evidence in humans and animals.

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.

Case reports of chronic therapeutic exposure for approximately 2 years of two patients, a 59-year-old female and a 26-year-old homozygous sickle-cell male, to 100-150 mg/day zinc as zinc sulfate or zinc acetate, respectively, have reported a profound anemia associated with hypoceruloplasminemia and hypocupremia (Porter et al., 1977; Prasad et al., 1978). The conditions were corrected by copper supplementation and, in one case, withdrawal of zinc.

Habib et al. (1976) reported that average zinc concentrations in normal and hypertrophic prostate tissues were similar, approximately 6.8 $\mu\text{mol/g}$, but the average zinc concentration was lower in carcinomatous prostate tissues (2.6 $\mu\text{mol/g}$). These tissue samples were obtained as follows: normal prostate tissues were obtained at autopsy from 9 men 25-58 years old (average age 36); and both hyperplastic and carcinomatous prostate tissues were obtained from the biopsies of 23 men 58-87 years old (average age 70) and from 9 men 64-91 years old (average age 73), respectively. Several other studies have also shown lower average zinc concentrations in cancerous vs. normal or hypotrophic prostate tissue (U.S. EPA, 1987). NRC (1978) and U.S. EPA (1987) have reviewed other studies which have noted both high and low zinc levels in other cancerous and noncancerous tissues with no definite pattern. From these studies it could not be concluded whether zinc was a carcinogen.

Several occupational studies have been conducted on workers exposed to zinc compounds (Batchelor et al., 1926; Chmielewski et al., 1974a,b; Bobrishchev-Pushkin et al., 1977). No increase in the incidence of cancer was noted; however, the studies were designed to evaluate other endpoints and did not specifically address cancer. Other symptoms such as slight leukocytosis, occurrences of metal fume fever, respiratory disease and hypocalcemia were some of the findings noted in exposed workers. Batchelor et al. (1926) extensively investigated workers exposed to zinc in a smelter. A total of 24 workers whose exposure ranged from 2-35.5 years were selected. In most work areas the mean zinc concentrations were generally below 35 mg/cu.m, except in the zinc dust plant where concentrations of up to 130 mg/cu.m were measured. The average level of zinc in whole blood of the 24 exposed workers was 458 $\mu\text{g}/100\text{ mL}$, compared with 387 $\mu\text{g}/100\text{ mL}$ in 10 control measurements. No information was given about the control subjects. Klucik and Koprda (1979) found that exposure levels to zinc oxide dust in a zinc oxide factory were on average 0.5 mg/cu.m for zinc melters and 2.44-7.15 mg/cu.m for zinc oxide packers; it was not indicated how these values were obtained. Chmielewski et al. (1974a,b) examined a group of workers who were exposed to zinc oxide in a shipyard; this included 20 ship smiths, 20 electric welders, 20 ship's pipeline fitters, and 20 zincifying workers. High concentrations of zinc oxide were found at the stands of the electric welders, who worked in containers (maximum 58 mg/cu.m, mean 18 mg/cu.m), and the ship smiths, who worked in a superstructure (maximum 50 mg/cu.m, mean 12 mg/cu.m). These workers were also exposed to other hazardous compounds, such as nitrogen oxides. Bobrishchev-Pushkin et al. (1977) studied 1018 workers in the casting shops of three copper alloy production facilities in the USSR. Four hundred and fifty-one workers from the rolling shops were used as controls. The average level of zinc oxide exposure in the casting shop was 2.1 mg/cu.m (range of 0.2-5.1 mg/cu.m), well below the USSR's maximally allowable concentration of 6 mg/cu.m. Workers were also exposed to other metals such as

copper, lead and nickel.

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 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 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 pooled). The hepatoma incidence in the control, low-dose drinking water, high-dose drinking water, and test-diet group was 3/24 (12.5%), 3/28 (10.7%), 3/22 (13.6%), and 7/23 (30.4%), respectively. Incidence of malignant lymphoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups was 3/24 (12.5%), 4/28 (14.3%), 2/22 (9%), and 2/23 (8.7%), respectively. Incidence of lung adenoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups was 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 this data performed by the EPA. In a 14-month study conducted with 150 C3H mice (sex not reported), administration of 500 mg/L zinc sulfate (approximately 100 mg/kg/day) in the drinking water resulted in hypertrophy of the adrenal cortex and pancreatic islets (Aughey et al., 1977). No tumors were noted; however, only the adrenal, pancreas and adenohypophysis were examined. Accurate consumption data could not be obtained due to spillage during drinking. No instances of adrenal or pancreatic hypertrophy were seen in a control group (number of animals not stated) that received only distilled water.

After an intratesticular injection of zinc, Guthrie observed seasonally-related testicular tumors in fowl (Guthrie, 1964) but no tumors in rats (Guthrie, 1956). Guthrie (1964) administered zinc chloride, zinc acetate or zinc stearate to groups of white leghorn chickens by intratesticular injection (approximately 0.01 g/injection); groups of chickens were sacrificed from 3 weeks to 11 months. Eight of the 111 chickens injected with zinc chloride in January and February developed testicular testoma, while none of the 48 chickens injected with zinc chloride in March developed tumors. None of the 36 chickens injected with zinc acetate in March and none of the 14 chickens injected with zinc stearate in January and February developed tumors; no conclusions about the carcinogenicity of these two compounds could be made because an insufficient number of chickens were tested. No control group was described.

Guthrie injected 0.15-0.20 mL of 10% zinc sulfate into the testis of nineteen 4-month-old rats and 0.15 mL of 5% zinc chloride into the testis of twenty-nine 3-month-old rats (strain not specified) (Guthrie 1956). No testicular tumors were observed in either group at sacrifice 15 months after injection. No controls were described. Riviere et al. (1959) injected 5% zinc chloride in distilled water into the testicles of 100 Wistar rats. The rats were subdivided into several groups; some rats were unilaterally castrated and some rats received an injection of 200 units serum gonadotrophin and a subcutaneous implantation of a 25 mg pellet of distilbene or 100 mg testosterone. The number of rats in each of the four groups (unilateral castration +/- hormone treatment and untreated +/- hormone treatment was not stated. No control group was described. Testicular tumors (including

interstitial tumors, a seminoma and an embryoma) became apparent 15 months after inoculation (tumor incidence not specified). There are no specific data on the effects of hormones in this experiment.

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. The spontaneous tumor frequency for this strain of mice was 0.0004%. The tumor frequencies in the generations were: 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 tumor-type 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 adenocarcinomas. The numbers of specific tumor types were not reported. The 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

In a short-term, in vivo assay, Stoner et al. (1976) injected strain A/Strong mice (20/sex/dose) intraperitoneally with zinc acetate 3 times/week for a total of 24 injections (total doses were 72, 180, or 360 mg/kg). Controls (20/sex/group) consisted of an untreated group, a vehicle control group administered 24 injections of saline and a positive control group administered a single injection of urethan (20 mg/mouse). Mice were sacrificed 30 weeks after the first injection; survival was comparable for all groups. There was no increase in number of lung tumors per mouse in treated animals relative to the pooled controls. While four thymomas were observed in zinc acetate-treated groups and none in controls, the occurrence of these tumors was not statistically significantly elevated.

Urine samples from subjects occupationally exposed in the rubber industry to a variety of compounds, including zinc oxide, were not found to be mutagenic in the microtitre fluctuation assay with *Salmonella typhimurium* strains TA1535, TA98 and TA100 (Crebelli et al., 1985).

The results of short-term genotoxicity assays for zinc are equivocal. Zinc acetate and/or zinc 2,4-pentanedione have been analyzed in four short-term mutagenicity assays (Thompson et al., 1989). In the *Salmonella* assay (with or without hepatic homogenates), zinc acetate was not mutagenic over a dose range of 50-7200 ug/plate but zinc 2,4-pentanedione was mutagenic to strains TA1538 and TA98 at 400 ug/plate. The addition of hepatic homogenates diminished this response in a dose-dependent manner. In the mouse lymphoma assay, zinc acetate gave a dose-dependent positive response with or without metabolic activation; the mutation frequency doubled at 10 ug/mL. In the CHO in vitro cytogenetic assay, zinc acetate gave a dose-dependent positive response with or without metabolic activation, but the presence of hepatic homogenates decreased the clastogenic effect. Neither zinc acetate nor zinc 2,4-pentanedione were positive in the unscheduled DNA synthesis assay in rat hepatocytes over a dose range of 10-1000 ug/mL.

Zinc chloride is reported to be positive in the *Salmonella* assay (Kalinina et al., 1977), negative in the mouse lymphoma assay (Amacher and Paillet, 1980), and a weak clastogen in cultured human lymphocytes (Deknudt and Deminatti, 1978). Zinc sulfate is reported to be not mutagenic in the *Salmonella* assay (Gocke et al., 1981), and zinc acetate is reported to not induce chromosomal aberrations in cultured human lymphocytes (Gasiorek and Bauchinger, 1981). Crebelli et al. (1985) found zinc oxide (99% purity) (1000-5000 ug/plate) to be not mutagenic for *Salmonella* in the reversion assay.

Responses in mutagenicity assays are thought to depend on the form (e.g., inorganic or organic salt) of the zinc tested. For example, inorganic salts tend to dissociate and the zinc becomes bound with culture media constituents. Salts that dissociate less readily tend to be transported into the cell and are postulated to cause a positive response (Thompson et al., 1989). Zinc is an essential trace element involved in numerous biological functions including growth, taste and spermatogenesis. It is a cofactor for several enzymes such as those involved in the metabolism of proteins and nucleic acids. Zinc may be a modifier of the carcinogenic response; 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 (Woo et al., 1988). Zinc deficiency enhanced carcinomas of the esophagus induced by methylbenzyl nitrosoamine (Fong et al., 1978) but retarded the development of cancer of the oral cavity induced by 4-nitroquinoline-N-oxide (Wallenius et al., 1979). In a study that examined both zinc deficiency and supplementation, Mathur (1979) found that animals with a deficient diet (5.9 mg/kg) and animals diet supplemented with excessively high levels of zinc in the diet (200-260 mg/kg) had fully developed carcinomas of the palatial mucosa. While the rats were on the specific diets, the palatial mucosa was painted with 4 nitroquinoline 3 times/week for 20 weeks. In the zinc deficient group 2/25 rats developed cancer of the palatial mucosa; 2/25 rats in the excessive zinc group also developed this form of cancer. Animals supplemented with moderate levels of zinc in the diet (50 mg/kg) developed only moderate dysplasia. Thus, zinc's modifying effect on carcinogenesis may be dose-dependent.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSUR

None.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION E

None.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASS

II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1980, 1984, 1987, 1988

The 1984 Health Effects Assessment for Zinc (and compounds), the 1987 Health Issue Assessment and the 1980 and 1988 Ambient Water Quality Criteria Documents have received Office of Health Effects Assessment review.

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 11/08/1989, 06/15/1990

Verification Date -- 06/15/1990

II.D.3. U.S. 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).

VI. BIBLIOGRAPHY

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 10/01/1992

VI.A. ORAL RfD REFERENCES

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None

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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VII. REVISION HISTORY

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Date	Section	Description
02/01/1991	II.	Carcinogenicity assessment on-line
02/01/1991	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory Action section on-line
10/01/1992	I.A.	Oral Rfd summary on-line
10/01/1992	VI.A.	Oral Rfd references on-line

VIII. SYNONYMS

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 02/01/1991

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



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