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Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
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Cincinnati OH 45268

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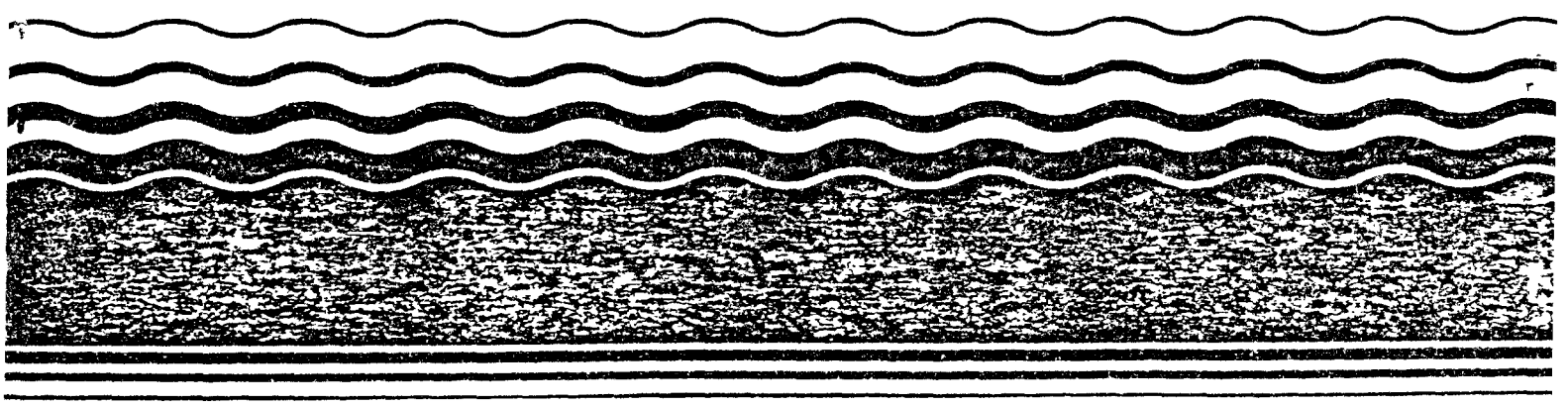
HEALTH EFFECTS ASSESSMENT FOR ZINC (AND COMPOUNDS)



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U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
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Cincinnati, OH 45268

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Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with zinc (and compounds). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Zinc. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-079. NTIS PB 81-117897.

U.S. EPA. 1983b. Reportable Quantity for Zinc (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a

significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

There is a considerable body of information concerning the toxicology of orally administered zinc in both humans and experimental animals. A synthesis of the available human data supported by the experimental animal information resulted in an oral AIS and AIC estimate of 14.9 mg/day. This value represents an estimated additional acceptable increment beyond background dietary exposures. Based on oral studies in humans, a CS of 17.6 was derived.

The data base for inhalation exposure is much more limited. No adequate animal data were located pertinent to either subchronic or chronic inhalation exposures. An AIS of 7.1 mg/day and an AIC of 0.7 mg/day have been estimated based on the TLV for zinc chloride. Zinc chloride is the zinc compound with the lowest TLV except for zinc chromates. Protection from potential carcinogenic effects of zinc chromates is not implied by the AIS and AIC estimates. Data were inadequate to develop suggested exposure limits for the zinc chromates.

ACKNOWLEDGEMENTS

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ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RDA	Recommended daily allowance
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UF	Uncertainty factor

1. ENVIRONMENTAL CHEMISTRY AND FATE

Zinc is a metal belonging to group IIB of the Periodic Table. Elemental zinc has a CAS Registry number of 7440-66-6. It occurs in nature in the zero valence (metal and alloys) and +2 valence (compounds) states. Besides a variety of inorganic compounds, zinc forms a number of compounds with organic ligands. Both organic and inorganic zinc compounds have a variety of uses (Lloyd and Showak, 1984; Lloyd, 1984). Zinc forms simple covalent, ionic and stable covalent complex compounds with other ions, groups or ligands. The element is amphoteric in nature and forms both acidic and basic salts (Lloyd, 1984).

In the atmosphere, zinc is expected to be present as dust and fumes from zinc production facilities, lead smelts, brass works, automobile emissions, fuel combustion, incineration and soil erosion (Lloyd and Showak, 1984). The atmospheric fate of zinc has not been comprehensively studied. Any chemical interaction of zinc compounds in the atmosphere may result in speciation, that is, conversion of zinc into a stable species such as zinc oxide, and not its removal through decomposition as frequently occurs with organic compounds. The atmospheric interactions are minimal for particulates with large aerodynamic diameters because of their short air residence time (Fishbein, 1981). However, zinc is found in the atmosphere at the highest concentrations in smallest particles (<3 μm in aerodynamic diameter) (Fishbein, 1981). Zinc oxide emitted from high-temperature processes (e.g., brass foundries, galvanizing, smelting and welding processes) may have particle sizes in the range of 0.01-0.4 μm (NIOSH, 1975). Therefore, these smaller particles may have a long residence time, although no estimate for the atmospheric lifetime for zinc is available at this time.

Zinc introduced into the aquatic environment is partitioned into sediments through sorption onto hydrous iron and manganese oxides, clay minerals and organic material; a small part may be partitioned into the aquatic phase through speciation into soluble zinc compounds. Precipitation of the sulfide is an important control on the mobility of zinc in reducing environments, and precipitation of hydroxides, carbonate or basic sulfate may occur at high zinc concentration. Formation of complexes with organic and inorganic ligands may increase the mobility of zinc in aquatic media, but these complexes also have a tendency to be absorbed more strongly onto the sediments. Sorption of zinc is probably the dominant fate of zinc in the aquatic environment (Callahan et al., 1979).

Information regarding the fate of zinc in soil is inadequate. However, zinc is likely to be strongly sorbed onto soil. Soil conditions not amenable for the sorption of zinc may lead to the leaching of zinc. The tendency of zinc to be sorbed is affected by the pH and salinity of soils. Decrease of pH (<7) and increase of soil salinity favors desorption (U.S. EPA, 1980b). In a study of groundwater from New Jersey, Page (1981) detected zinc in 100% of the samples. This indicates that leaching of zinc from soil may be prevalent.

The BCFs for zinc in aquatic organisms have been determined by several investigators (U.S. EPA, 1980b). BCFs for zinc in edible portions of aquatic organisms have been found to vary from 43 in soft-shell clam, Mya arenaria, to 16,700 in oyster, Crassostrea virginica (U.S. EPA, 1980b).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

This discussion of oral absorption of zinc and compounds is taken primarily from U.S. EPA (1980b). According to the U.S. EPA (1980b), GI absorption of zinc is dependent in part upon the zinc status of the organism. This is a reasonable conjecture, in that zinc levels in the body are rigidly controlled by various homeostatic mechanisms. Also, it appears that dietary levels of other nutrients may influence the kinetics of zinc absorption. The fact that zinc is excreted, in part, through the GI tract complicates quantitation of zinc uptake. It is also likely that the anion associated with zinc, chelation or other complexing moieties may influence GI absorption.

Spencer et al. (1965) demonstrated that ^{65}Zn as the chloride was rapidly absorbed by human volunteers. Peak plasma values were obtained within 4 hours. Apparent absorption ranged from 20-80% with a mean of 50%. Other early studies (NRC, 1978) also indicated wide variations in absorption rates of ingested zinc. Stokinger (1981), on the other hand, concluded that only very small amounts of zinc are absorbed by laboratory animals.

Dietary protein levels have been shown to influence uptake of zinc. In studies of zinc-deficient human subjects, zinc uptake was enhanced by simultaneous administration of protein (NRC, 1978). Zinc associated with animal proteins (meat, milk, eggs) seemed to be more easily absorbed, making these foods good sources of dietary zinc. High dietary levels of phytate, a complex organic phosphorus-containing compound in cereal products, have been shown to reduce absorption of zinc, especially if large amounts of calcium are present. Breads and cereal grain food products may, therefore, be less valuable sources of dietary zinc. Arvidsson et al. (1978) added ^{65}Zn to

bread during baking, and in 11 human subjects determined GI absorption to average 25% with a range of 12.2-39.1%. Repeating the experiment 1 month later yielded similar results. In these studies phytate seemed to have little influence on zinc uptake. Sandstead et al. (1978) suggested that dietary fiber content may influence uptake of zinc.

The homeostatic regulators of zinc absorption may involve several proteins and low-molecular-weight compounds. Metallothionein, a low-molecular-weight metal-binding protein in the intestinal mucosa, may bind with zinc and facilitate absorption (Richards and Cousins, 1977). Zinc-binding ligands with molecular weights lower than metallothionein have been found in animals. Evans et al. (1975) proposed that such compounds were produced in the pancreas, and that through the pancreatic secretion, they could complex with zinc in the GI tract and enhance absorption.

That the zinc-binding ligands that facilitate absorption may be species-specific was suggested by Eckhert et al. (1977); these authors showed that zinc in human breast milk was associated with low-molecular-weight fractions, but that in cow's milk, zinc was associated with high-molecularweight fractions, as analyzed by gel chromatography. Presumably, zinc absorption in human infants is enhanced by binding to low-molecular-weight ligands, and in calves by binding to high-molecular-weight ligands. These species differences in zinc-binding ligands were offered as a possible explanation for the occurrence of acrodermatitis enteropathica, a zinc deficiency syndrome, which occasionally appears in human infants after weaning from breast milk.

2.2. INHALATION

No quantitative studies of inhalation absorption of zinc or its compounds could be found in the available literature. The fate of inhaled particles containing zinc depends on particle size and solubility, and on

the functional state of the lungs. Experiments on human subjects (Sturgis et al., 1927; Drinker et al., 1927a) revealed that both zinc oxide fumes and zinc oxide powder with very small particulate size were deposited in the alveoli. Increased serum and plasma levels of zinc were evidence for pulmonary absorption. It should be emphasized, however, that an undetermined amount of inhaled particulate zinc oxide was subjected to GI absorption by ciliary clearance and swallowing.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Zinc is an essential trace element in human and animal nutrition. In the body it is found in high concentrations in male reproductive organs, pancreatic islets, muscle, kidney, liver and bone. It is essential for the activity of some enzymes (U.S. EPA, 1980b). The human RDA of zinc for adults is 15 mg (NAS, 1980). Zinc appears to be toxic only at levels at least an order of magnitude greater than the RDA; toxicity appears to result from an overload of the homeostatic mechanism for absorption and excretion of zinc.

3.1. SUBCHRONIC

3.1.1. Oral. Much of the early research on zinc toxicity was not useful for risk assessment, because the studies were of too short duration or the dose or range of doses used did not result in effects that allowed definitions of NOELs, NOAELs or LOAELs. Only those studies that are useful in risk assessment are presented here.

Acute toxicity has been produced from foods stored in galvanized containers. Brown et al. (1964) reported zinc levels of ~1000 ppm in chicken with tomato sauce and spinach stored ~24 hours in galvanized vats. In another instance (Brown et al., 1964), storage of fruit punch in galvanized containers resulted in zinc levels of 2200 mg/ℓ. Symptoms reported were severe diarrhea, abdominal cramping, nausea and vomiting. The concentration of cadmium, which occurs quite commonly in galvanized surfaces, was not determined.

Lethargy was observed in a 16-year-old boy who ingested 12 g of zinc in peanut butter over a 2-day period in the belief it would accelerate wound

healing (Murphy, 1970). Treatment with dimercaprol resulted in a rapid decrease of blood levels of zinc to subnormal levels and a rapid correction of the boy's lethargic condition.

Anemia was observed in three children who were excreting >1 mg zinc/ℓ of urine (Chunn, 1973). These children reportedly played with toy cars made from a zinc alloy. Placing a toy car in warm water resulted in zinc levels of 1.8 mg/ℓ. It was hypothesized that these children ingested bath water when playing with toy cars in the tub.

Studies of regulated zinc intake in humans are summarized in Table 3-1. Pories et al. (1967) administered 150 mg of zinc as the sulfate to 10 young men for 43-61 days to accelerate wound healing after surgical removal of pilonidal cysts. The subjects complained of some gastric discomfort, but no other ill effects were reported. Wound healing was accelerated, compared with healing in 10 operated and nonsupplemented controls. Assuming a body weight of 70 kg, the administered dose, 2.14 mg/kg/day constituted a LOAEL in this study.

Greaves and Skillen (1970) reported on 18 patients given 150 mg of zinc as zinc sulfate for 16-26 weeks to accelerate healing of venous ulcerations on the legs. Plasma zinc levels were elevated slightly after treatment (0.94 pretreatment versus 1.4 mg/ℓ post-treatment); other clinical laboratory investigations were conducted that indicated no ill effects from supplemented zinc. In this study, 2.14 mg/kg/day appeared to define a NOAEL. Similarly, 135 mg zinc/day as zinc sulfate for 18 weeks, given to 13 patients with leg ulcers, failed to cause alterations in blood counts, liver function tests or urine chemistries (Hallbrook and Lanner, 1972). Placebo treatments were given to 14 patients who served as a control group. Serum levels of zinc in treated patients increased from an average of 0.95 mg/ℓ

TABLE 3-1

Oral Toxicity of Zinc Sulfate in Humans[a]

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Human with non-responsive coeliac disease	F	1	capsules	150 mg Zn/day (220 mg $ZnSO_4 \cdot 7H_2O$ 3x/ day) x 26 months	2.14	Profound hypochromic microcytic anemia, neutropenia, hypocupremia; treatment with transfusion, withdrawal of Zn, and Cu supplementation, returned blood parameters to normal.	Porter et al., 1977
Human with sickle cell anemia age 26	M	1	capsules	150 mg Zn/day (220 mg $ZnSO_4 \cdot 7H_2O$ 3x/ day) x 2 years	2.14	Hypochromic microcytic anemia, neutropenia, hypocupremia, hypoceruloplasminemia; all conditions corrected by Cu supplementation.	Prasad et al., 1978
Humans with sickle cell anemia	NS	13	capsules	150 mg Zn/day (220 mg $ZnSO_4 \cdot 7H_2O$ 3x/ day) x 6 months	2.14	Decreased ceruloplasmin levels in 7 of 13 relative to pretreatment levels and "normal" levels; increasing to normal or high normal when Cu supplements given.	Prasad et al., 1978
Humans with sickle cell anemia and leg ulcers	M,F	17 treated, 17 placebo (double blind)	capsule	150 mg Zn/day as $ZnSO_4 \cdot 7H_2O$ (220 mg 3x/day x 6 months)	2.14	Increase in serum Zn levels, in rate of healing of ulcers, and in incidence of complete healing; patients reported no symptoms of toxicity.	Serjeant et al., 1970
Humans with chronic venous leg ulceration (duration $\geq$2 years)	17F, 3M	20 treated	capsule	150 mg Zn/day (220 mg $ZnSO_4 \cdot 7H_2O$ 3x/ day) $\geq$4 months)	2.14	Complete healing in 13, partial healing in 5, 2 failed to complete study; no effect on blood Hb levels, WBC count (total and differential) or clinical chemistry indicators of hepatic or renal toxicity.	Greaves and Skillen, 1970
Humans with chronic venous ulcers 100-1000 sq mm in size	M,F	treated: 3 M,10 F, age 40-84; placebo: 5 M,9 F, age 43-80	effervescent tablets	200 mg Zn sulfate 3x/day (600 mg/day total) x 18 weeks equivalent to 135 mg Zn/day according to U.S. EPA, 1980b	1.93	Rate and frequency of healing increased by Zn in patients with initial low serum Zn levels; no effect on body weight, blood counts, indicators of liver function or urinalysis values; no symptoms of toxicity.	Hallbook and Lanner, 1972

TABLE 3-1 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Humans with chronic refractory rheumatoid arthritis	NS	12 treated; 12 placebo; both groups received Zn during the 2nd part of the study	capsules	150 mg Zn/day (220 mg $ZnSO_4 \cdot 7H_2O$ 3x/ day) for 12 weeks (double blind), followed by 150 mg Zn/day for 12 weeks	2.14	During both 12-week periods, Zn produced significant improvements in clinical parameters related to arthritis including reduction of soft tissue swelling but no changes in bones (x-ray); no effect on hematocrit, WBC count, clinical chemistry and urinalysis values except slight decrease in serum histidine and increase in serum alkaline phosphatase levels.	Simkin, 1976
Humans, 15-69 years old with sickle cell anemia; some had Zn deficiency and hypogonadism and growth retardation or chronic leg ulcers	M,F	7 M, 2 F	NS	660 mg Zn sulfate/ day for 4-60 weeks	2.14 if heptahydrate	Improvement in condition, including growth, sexual maturation, and healing of ulcers; "no serious toxic side effects"; some had nausea after taking Zn on empty stomach.	Prasad et al., 1975

*Source: Adapted from U.S. EPA, 1983b

Hb = Hemoglobin

NS = Not specified

WBC = White blood cells

Zn = Zinc

to 1.57 mg/ℓ after 6 weeks of treatment, but no further increases were noted. Patients with an initial serum zinc level >1.1 mg/ℓ experienced no increase in serum zinc throughout the 18-week treatment period. This study defined a subchronic oral NOAEL of 1.93 mg/kg/day.

Simkin (1976) subjected 12 human patients with chronic refractory rheumatoid arthritis to 12 weeks of treatment with 150 mg zinc as zinc sulfate. A placebo-treated group of 12 arthritis patients served as a control in this study. After the initial 12 weeks, both groups were put on 150 mg zinc for an additional 12 weeks. Evaluation of clinical parameters of arthritis revealed significant improvement in the patients' conditions, with no effect on hematologic, blood chemistry or urinalysis parameters except for a slight decrease in serum histidine and a slight increase in serum alkaline phosphatase. No toxic manifestations were mentioned, and 2.14 mg zinc/kg/day was a NOAEL in this study.

Serjeant et al. (1970) divided 34 sickle cell anemia patients with leg ulcers into two groups of 17. The treatment group received zinc sulfate capsules 3 times/day (equivalent to 2.14 mg zinc/kg/day for an average human), and the control group received a placebo in this double-blind study that lasted for 6 months. An increase in serum zinc levels, the rate of ulcer healing and the incidence of complete healing were reported. Patients reported no symptoms of toxicity, and 2.14 mg zinc/kg/day constituted a NOAEL in this study. Prasad et al. (1975) reported on the administration of 2.14 mg zinc/kg/day (as the sulfate) for 4-60 weeks to an unspecified number of humans with sickle cell anemia, some of whom also had complications with zinc deficiency, hypogonadism, growth retardation or chronic leg ulcers. Improvement in clinical condition, including growth, sexual maturation and

healing of ulcers without signs of toxicity, was noted. Some patients complained of nausea after taking zinc on an empty stomach. Therefore, 2.14 zinc/kg/day was considered to be a LOAEL in this study.

Studies of subchronic oral exposure of animals to zinc, and its compounds abound in the available literature. Studies between 90 and 365 days in length were considered to be subchronic. Data from these reports are summarized in Table 3-2. Only those studies that affect risk assessment will be discussed in detail here.

Drinker et al. (1927a) administered zinc acetate to 12-week-old male and female rats. Individual rats were given 7.6, 14.4 or a TWA of 25.5 mg zinc/kg/day for 53, 48 or 47 weeks, respectively, and two rats served as untreated controls. Administration was through the drinking water; apparently water consumption was measured to arrive at daily intake. No effects on growth, hematologic parameters, urinalysis or gross or histological appearance of the organs were noted at any dosage level.

Maita et al. (1981) fed diets containing 3000 or 30,000 ppm zinc sulfate to both rats and mice. These diets contributed ~95 or ~950 mg zinc/kg/day to rats and ~188 or ~1880 mg/kg/day to mice, respectively, based on the assumption that a rat weighs 0.35 kg and a mouse weighs 0.03 mg. At 3000 ppm, neither rats nor mice evidenced any effects of treatment; at 30,000 ppm both rats and mice suffered from partial anorexia, retarded growth and hematologic abnormalities. In this study, 3000 ppm (95 mg/kg/day for rats; 188 mg/kg/day for mice) appeared to define a NOEL.

One study of the effects of subchronic administration of zinc chloride was found in the literature. Heller and Burke (1927) added 0, 2500 and 5000 ppm zinc to the diets of 4, 4 and 9 young rats, respectively, for the "full growth period." The only effect reported was high mortality of offspring in

TABLE 3-2

Oral Toxicity Studies of Zinc and Its Compounds[a]

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Mice, Chester Beatly stock, newborn litters (with dams); some weanlings to replace losses	M,F	NS	drinking water; $ZnSO_4$	NS	0, 1000 or 5000 ppm Zn added to drinking water for 1 year	0, 170 or 850[b]	Intercurrent disease (ectromelia) killed some mice in all groups during first 8 weeks; dead and infected mice were replaced with weanlings; Zn had no effect on weight gain, tumor incidence or mortality.	Walters and Roe, 1965
Rats, young	M,F	treated: 2 M, 2 F; control: 3 M, 1 F	diet; $ZnSO_4$	NS	0.25% Zn added to diet for 3 generations, 4 litters (total) (2500 ppm)	125[b]	No effect on growth, reproduction, or gross appearance, weight, and ash content of organs; no signs of toxicity.	Heller and Burke, 1927
Rats, mice	NS	NS	diet; $ZnSO_4$	NS	3000 or 30,000 ppm of $ZnSO_4$ added to diet for 13 weeks dose at 3000 ppm = 230-240 mg/kg/day (rats) or 450-480 mg/kg/day (mice) of $ZnSO_4$	~95 rats, and ~188 mice at 3000 ppm; not estimated at 30,000 ppm	3000 ppm: maximum no-effect level; 30,000 ppm: decreased food intake, retarded growth, hematologic abnormalities (NS).	Malia et al., 1981
Mice, C3H	NS	NS	drinking water; $ZnSO_4$	NS	500 mg Zn/L in water for up to 14 months	85[b]	Microscopic evidence of hypertrophy of adrenal cortex and pancreatic islets and changes characteristic of hyperactivity in pituitary; no change in plasma insulin and glucose levels.	Aughey et al., 1977

TABLE 3-2 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Rats, 12 weeks old at start; ~250 g M and 200 g F plateau weight	M,F	1/dose level and 2 controls	drinking water; Zn acetate	NS	1.9 mg/day for 53 weeks (M), 3.6 mg/day for 48 weeks (M), 4.4 mg/day for 29 weeks plus 6.3 mg/day for 18 weeks (F) (5.1 mg/day TWA)	M: 7.6 or 14.4 F: 25.5 (TWA)	No effect on growth, blood Hb levels, RBC or WBC counts, urinary excretion of albumin or sugar, or gross or histological appearance of organs.	Drinker et al., 1927a
Rats, 200-325 g plateau weight	M,F	Parents: treated, 3 M, 3 F; control, 3 M, 3 F. Offspring: treated, 4 M, 1 F; control, 9 M, 12 F	drinking water; Zn acetate	NS	3 F given Zn acetate or citrate for 29 weeks before mating and Zn acetate or malate after mating through rearing of 2 litters; 3 M given Zn malate or acetate as for female above; all parents received Zn acetate either before or after mating; 5 offspring (M and F) received Zn acetate until 60 days of age	Parents: 1.75-16.5 mg Zn/day[b]; 5.4-47 mg/kg/day. Offspring: NS	No overt signs of toxicity; no effect on body weight or reproduction of parents or on growth of offspring.	Thompson et al., 1927
Rats, young	M,F	0.25% Zn: 2 M, 2 F; 0.5% Zn: 2 M, 7 F control 3 M, 1 F	diet; Zn chloride	NS	0.25% Zn added to diet for 3 generations through "full growth" of each	0, 125 or 250[b]	No effect on growth, reproduction, or gross appearance, weight, and ash content of organs; no signs of toxicity; high mortality of offspring at high dose only, not specifically attributed by authors to Zn treatment.	Heller and Burke, 1927

TABLE 3-2 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Rats, young, 40-50 g	M,F	ambiguous; ≥3 F and 2 M/dose level	diet; Zn carbonate	Impurities <0.024%	0.1, 0.5 or 1.0% Zn in diet for 39 weeks (1000, 5000 or 10,000 ppm)	50, 250 or 500[c]	0.1%: no effect on growth, reproduction, blood Hb levels, RBC count. 0.5%: no effect on growth or RBC count, but Hb level decreased below normal and as compared with controls by 30 weeks; some pups in first litter were stillborn and no live young were born after this; no pregnancies after 5 months (Hb and fertility returned to normal when $ZnCO_3$ no longer given). 1%: most animals failed to grow and some died within 4 weeks; Hb and RBC count markedly decreased starting at ~3 weeks; abnormal RBC; no reproduction occurred.	Sutton and Nelson, 1937
Rats, young	M,F	treated: 4 M, 4 F; control: 5 M, 3 F	diet; metallic	NS	0.25% Zn added to diet for 3 generations; through "full growth" of each	125[c]	No effect on growth, reproduction, or gross appearance, weight, ash content of organs; no signs of toxicity.	Heller and Burke, 1927
Rats, 200 g (parents)	M,F	parents: treated, 3 M, 1 F; control 3 M, 3 F; offspring: treated, 3 M, 3 F; from Zn malate parents; control, 9 M,12 F	suspended in 3% gum acacia solution (drinking water); ZnO	NS	1 F given Zn citrate for 29 weeks before mating and ZnO through rearing of 2 litters, 2 M given ZnO given ZnO and 1 M given Zn malate before mating as above and ZnO through siring of 2nd litter; offspring received ZnO through 60 days of age	parents: 6.5-38 mg Zn/day[c]; 32.5-190 mg/kg/day; offspring NS	No overt signs of toxicity, no effect on body weight or reproduction of parents but 1 male given ZnO before mating was sterile and 19 of 20 offspring from Zn-treated parents did not survive through weaning[d]; growth of offspring (from Zn malate parents) unaffected by ZnO.	Thompson et al., 1927

TABLE 3-2 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Rats, young	M,F	treated: 2 M, 3 F; control: 3 M, 1 F	diet; ZnO	NS	0 or 0.5% Zn added to diet for 3 generations through "full growth" of each	250[b]	Slight depression of growth, food consumption NS, no effect on reproduction or gross appearance, weight, and ash content of organs; no signs of toxicity.	Heller and Burke, 1927
Rats, 5-7 weeks old, plateau weight 200-250 g	M	treated: total of 11, 1/dose level except 3 at highest dose; control: 6	suspended in 3.5% gum acacia solution (drinking water); ZnO	NS	2.7-34.4 mg Zn/day[c] x 34-36 weeks	12-153	No effect on growth; decreased water consumption at higher dosages; no effect on blood Hb levels, RBC or WBC counts, urinary excretion of albumin or sugar, or gross histological appearance of organs; slight but not significant increase in tissue but not blood Zn levels.	Drinker et al., 1927a
Cats, 2.8-4.8 kg at start	5 M, 5 F	10 treated; apparently no controls; compared with values from the literature, pretreatment urinalysis values, and Zn levels in 7 normal cats	food; ZnO	99.799%	200-858 mg ZnO/day (TWA) mixed with food x 10-53 weeks (actual range = 175-1000 mg/day)	33.8-223.8 (TWA)	No signs of toxicity; 7 cats receiving <76.4 mg Zn/kg/day gained weight, 3 cats receiving $\geq$132.7 mg Zn/kg/day (16-21 weeks) lost 14% of their body weight and ate less; RBC and WBC counts, blood Hb levels and urinalysis findings were normal; the 3 high-dose cats had fibrotic pancreas glands, no other gross or microscopic evidence of Zn damage in tissues of any treated cat; dose-related increase in Zn levels of liver, pancreas and kidney and uniform increase in Zn levels; increase in blood Zn levels in higher dose group only.	Drinker et al., 1927b

TABLE 3-2 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Dogs, 10 kg average weight during experiment	1M, 1F	2 treated, apparently no controls; compared with values from the literature, pretreatment urinalysis values, and Zn levels in 9 normal dogs	food; ZnO	99.799%	1M: 500 mg ZnO/day x 19 weeks; 1F: 1000 mg ZnO/day x 15 weeks mixed with food; 1M: 500 mg ZnO/day x 3 weeks (died of distemper)	M: 36.1 F: 76.5	No signs of toxicity, slight weight gain; RBC and WBC counts and urinalysis findings were normal; no gross or microscopic evidence of Zn damage in tissues; average of Zn levels from all 3 dogs was increased in liver, kidney, pancreas, bone and bone marrow but not in blood and other tissues.	Drinker et al., 1927b
Dogs, beagle skeletally mature, 15-16 months old at start	M	4 treated; 22 control (possibly not concurrent)	drinking water acidified to pH 5 with HCl; ZnO	NS	0 ppm Zn x 7 months, then 100 ppm Zn in drinking water x 9 months	0 or 2.5	No signs of toxicity; clinical chemistry and hematologic values unaffected as compared with controls; blood immunoreactive parathyroid hormone within "normal" range and unchanged from pretreatment values; rib biopsies had no significant differences ($p<0.05$) in parameters of Haversian bone remodeling from pretreatment levels except those attributable to normal aging, which recurred also in control dogs; no significant increase ($p<0.05$) in bone Zn as compared with pretreatment levels or levels in controls.	Anderson and Danylchuk, 1979

TABLE 3-2 (cont.)

Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg Zn/kg/day)	Response	Reference
Pigs, Yorkshire 4 weeks old, 7.5 kg at start	M,F	3/group	diet containing 0.7% or 1.1% Ca; ZnO	NS	0 or 0.4% Zn added to low- or high-Ca diet x 9-13 weeks	185 (low-Ca diet), 170 (high-Ca diet)	No signs of toxicity; weight gain and feed efficiency decreased by Zn when diet low in Ca ($p<0.05$); weight gain (but not feed efficiency) increased by Zn when diet high in Ca ($p<0.05$); serum Ca and alkaline phosphatase levels were increased and serum P levels were decreased by Zn ($p<0.05$) when diet low in Ca; slight but not significant decrease in specific gravity, % ash, and ash/cc in humerus and femur of pigs fed Zn and low Ca diet.	Hsu et al., 1975

[a]Source: Adapted from U.S. EPA, 1983b

[b]Assuming that rats and mice consume the equivalent of 5% and 13%, respectively, of their body weight as food/day or that mice drink water equivalent to 17% of their body weight/day.

[c]According to Thompson et al. (1927), who calculated these values from observed food or water consumption.

[d]According to the author, deaths from all causes (including offspring killed and eaten by parents) were included in this number, and therefore it is not an index of health of the offspring.

NS = Not specified; Zn = Zinc; Cu = Copper; Fe = Iron; Ca = Calcium; Hb = Hemoglobin; RBC = Red blood cells; WBC = White blood cells

Doses are shown as reported by authors or were calculated from actual food consumption and body weight values if these values were given by authors. When authors did not provide necessary information, doses were calculated as indicated by superscripts and footnotes.

rats in the high-dose group. No other effects of treatment were noted, and the authors did not specifically attribute high mortality of offspring to zinc treatment. Although the size of this study was too small to be considered in risk assessment, a NOEL of 2500 ppm (125 mg/kg/day) appeared to be defined.

Of a number of studies investigating the toxicity of zinc carbonate, the study by Sutton and Nelson (1937) seemed to define the highest NOEL. About five rats were fed diets fortified with 1000, 5000 or 10,000 ppm zinc (50, 250 or 500 mg/kg/day) for 39 weeks. At the lowest dose level, no effects on growth, reproduction, hemoglobin concentration or erythrocyte count were observed. At higher-dose levels, depression in hemoglobin concentration and a high frequency of interference with reproductive performance occurred. Mortality occurred after 4 weeks on the high-dose diet.

The toxicity of zinc oxide has been examined in greater detail than has the toxicity of other zinc compounds. Several studies on the toxicity of zinc oxide are summarized in Table 3-2. Drinker et al. (1927a,b) investigated the toxicity of zinc oxide in several species. These authors suspended zinc oxide in 3.5% gum acacia solution in drinking water, which supplied 0 or 12-153 mg zinc/kg/day to 6 control or 14 exposed rats for 34-36 weeks. It was impossible to discern from this report exactly which rats received exactly how much zinc. No adverse effects of any kind were noted except for decreased water consumption at "higher dosages." Very conservatively, then, a dose of 12 mg zinc/kg/day in drinking water defined a NOEL for rats in this study.

Drinker et al. (1927b) incorporated zinc oxide into the diet of 10 cats for 10-53 weeks, which resulted in TWA zinc intakes of 33.8-223.8 mg/kg/day. No signs of toxicity were observed in cats receiving $\leq$76.4 mg/kg/day, and

this level constitued a NOEL in cats in this study. Cats receiving ≥132.7 mg/kg/day experienced finicky appetites and loss of 14% of their body weight. Cats receiving 223.8 mg zinc/kg/day showed fibrotic pancreas glands.

3.1.2. Inhalation. Subchronic oral inhalation in humans is almost exclusively due to occupational exposure to the fumes or dusts of zinc or its compounds. Since zinc oxide is the compound used most in industry, it has been examined in most detail. Inhalation of vapors or dust of zinc or its compounds leads to a condition called metal fume fever. Although subchronic or even acute exposure to zinc oxide dust can cause metal fume fever, it is discussed in connection with chronic toxicity in Section 3.2., since occupational inhalation exposure is usually considered in relation to chronic toxicity.

Few reports of subchronic inhalation exposure in animals were found in the available literature. Pistorius (1976) exposed unspecified numbers of rats to a concentration of 15 mg zinc oxide/m³ for 1, 4 or 8 hours/day, presumably for 84 days (U.S. EPA, 1980b). Zinc oxide particulate size was reportedly <1 μ. "A number of lung function tests" were performed after 2, 4 and 7 weeks and at the end of the experiment. No differences in lung function were observed between control and treatment groups, except for a significant decrease in specific conductance and difference volume at the end of 2 weeks. Continued exposure resulted in apparent recovery of these parameters in treated animals. It was hypothesized that increasing exposure caused an increase in pulmonary macrophages, which accelerated, clearing the lung tissue of zinc oxide.

In another experiment, Pistorius et al. (1976) exposed an unspecified number of male and female rats for 1, 14, 28 or 56 days to zinc oxide dust at a level of 14 mg/m³ for 4 hours/day, 5 days/week. Animals were killed

24 hours after the last exposure, and zinc levels in lungs, liver, kidneys, tibia and femur were measured. A single exposure resulted in pulmonary levels of 46 and 49 μg zinc in male and female rats, respectively. Pulmonary levels of zinc were highest after 1 and 14 days of treatment (1 and 10 exposures). No changes in hepatic, renal or skeletal levels of zinc were noted, but control rats were not used in this study. After 28 and 56 days of treatment (20 and 40 exposures), inflammatory changes in the lungs, including infiltration of leukocytes and macrophages, were observed. Frank effects were observed at all levels of exposure.

3.2. CHRONIC

3.2.1. Oral. In humans, two case reports of chronic exposure to 150 mg zinc/day for therapeutic reasons illustrate the intimate relationship between zinc and copper (see Table 3-1). A profound hypochromic microcytic anemia associated with hypoceruloplasminemia, hypocupremia and neutropenia developed in two patients given 150 mg zinc/day as the sulfate for ~2 years. Discovery of this condition prompted Prasad et al. (1978) to assay ceruloplasmin levels in all 13 of their sickle cell anemia patients who were receiving zinc therapy. The mean ceruloplasmin level in these patients was ~50% what it had been before initiation of zinc therapy. In seven of these patients, ceruloplasmin was less than the lower limit of the normal range. This clinical syndrome was rapidly reversed by discontinuing zinc therapy and administering copper.

Only four studies of chronic exposure of animals to zinc were found in the available literature (summarized in Table 3-2). In the first, Heller and Burke (1927) added 0 or 5000 ppm zinc oxide to diets fed to two male and three female rats for three generations through the "full growth" of each generation. No effect on reproductive performance, gross appearance, weight

or ash content of organs was noted. No manifestations of toxicity occurred except for a "slight" depression of food intake and growth rate of F_1, F_{1b} and F_{1c} offspring. The dosage employed, 250 mg zinc/kg/day, appeared to constitute a NOAEL in this study.

Heller and Burke (1927) also administered 2500 ppm zinc dust in the diet to rats through the full growth of three generations. Assuming that a rat consumes food equivalent to 5% of its body weight, this dietary level corresponds to an intake of 125 mg/kg/day. Initially, the treatment group consisted of two males and two females, and the control group consisted of three males and one female. Zinc-treated rats did not differ from controls in growth, reproduction, or the gross appearance, weight or ash content of heart, lungs, liver, spleen, kidneys or testicles. Histopathological examinations were not performed. No overt signs of toxicity were observed. The dose level of 125 mg/kg/day was a NOEL in this study.

Walters and Roe (1965) exposed unspecified numbers of Chester Beatty mice to 0, 1000 or 5000 ppm zinc as the sulfate in drinking water for 1 year. Concurrent infection with mouse pox virus caused mortality in all groups during the first 8 weeks. Affected mice were replaced with weanlings. At these levels, corresponding to 0, 170 and 850 mg/kg/day, no effect on weight gain, tumor incidence or mortality occurred.

More recently, however, Aughey et al. (1977) administered 500 mg zinc/ℓ as the sulfate in drinking water to mice for ~14 months. Assuming 6 mℓ of water intake and a body weight of 0.03 kg, zinc intake of 100 mg/kg/day is calculated. Necropsy revealed microscopic evidence of hypertrophy of adrenal cortex and pancreatic islets, and changes in the pituitary characteristic of hyperactivity.

3.2.2. Inhalation. Chronic exposure to zinc stearate, a fine powder used in the plastic and rubber industries, may have been responsible for the death of a factory worker exposed for 29 years (Votila and Noro, 1957). Necropsy revealed cause of death to be a diffuse pulmonary fibrosis containing deposits of zinc. No quantitative determination of pulmonary zinc content was made. Weber et al. (1976) discussed the necropsy findings of a man employed for the last 8 years of his life in a rubber factory. These authors found fibrosis associated with a zinc content of 62 mg/kg dry lung tissue. That this level is within the normal limit for zinc indicates the ability of pathologic lesions to persist, even though zinc is cleared.

The most common syndrome in humans exposed to atmospheric zinc is known as metal fume fever. This syndrome is described by NIOSH (1975) and is briefly summarized here. After 4-12 hours of exposure to fumes of zinc or finely divided zinc oxide dust, a metallic taste is noted. This is followed by dryness and irritation of the throat, coughing, dyspnea, weakness, fatigue, aching muscles and joints, and a general malaise, similar to the prodromal syndrome of influenza. Fever then develops, typically associated with chills. Body temperature usually reaches 38.9-40.0°C. The patient may suffer from febrile shivering or rigors, which may become malaria-like in intensity. Profuse sweating follows, accompanied by a drop in body temperature and frequently by convulsions. Severe chest pains have also been reported. Recovery is usually complete within 24-48 hours (Drinker, 1922; Kehoe, 1948; Rohrs, 1957; Fishburn and Zenz, 1969; Anseline, 1972.)

A remarkable feature of metal fume fever is the rapid development of tolerance, to which the term "tachyphylaxia" was given by McCord (1960). The author stressed that this "immunity" was both quickly gained and quickly lost. The practical consequence of the phenomenon is the greater likelihood

of experiencing metal fume fever following a weekend or vacation than during midweek exposure; hence, the term "Monday-morning fever." This phenomenon may be related to more rapid pulmonary clearance of zinc particles resulting from enhanced phagocytosis by macrophages, following continued exposure to zinc oxide particles.

One group of investigators studied the quantitative aspects of metal fume fever in considerable detail. Sturgis et al. (1927) exposed two male subjects with a history of metal fume fever to amounts of zinc oxide fumes that, based on their history, should precipitate the disease. Exposure for 10-12 minutes resulted in the retention of 24 and 37 mg of zinc followed by onset of the syndrome in 7 and 4 hours, respectively, in the two subjects. The white blood cell count of each subject peaked (~17,000 cells/mm^3) at about the same time that peak body temperature was obtained. Vital capacity, measured every 4 hours, declined synchronously with the rise in body temperature, reaching a declination of 18 and 54% in the two subjects.

Drinker et al. (1927c) later exposed these same two subjects to workroom levels of zinc oxide fume for 2 or 3 consecutive days. Initial exposures resulted in typical onset of metal fume fever. Subsequent exposures resulted in milder attacks or no attacks at all, indicating that "acquired resistance" had occurred.

Subsequently, Drinker et al. (1927c) subjected five men and three women to zinc oxide fumes in order to determine threshold levels that trigger zinc fume fever. The exposure data were not specified in the document (NIOSH, 1975) from which this report was taken. The authors concluded, from measuring zinc content of inhaled and exhaled air, that ~50% of inhaled zinc oxide

is retained in the lungs. They further postulated that slower and deeper breathing resulted in a greater depth of penetration of zinc oxide into the alveoli and decreased the time to onset of zinc fume fever.

In continuing experiments, Drinker et al. (1927c) subjected seven male and three female volunteers to different concentrations of zinc oxide in the air for varying lengths of time. Although the treatment protocol was not presented in the NIOSH (1975) document, these authors determined a dose-response relationship and suggested that 15 mg zinc/m^3 be established as the threshold limit for an 8-hour workday.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The U.S. EPA (1980b) stated that Cox et al. (1969) found increased concentrations of zinc and reduced concentrations of copper in the liver and other tissues of fetuses from rats fed diets containing 4000 ppm zinc during gestation. Ketcheson et al. (1969) fed diets containing up to 5000 ppm zinc to rats during gestation and observed reduced copper content in fetal livers. No malformations were observed in the fetuses in either of these studies. Detailed information on protocol was lacking.

Kumar (1976) stated that in "a small group" of women in the third trimester of pregnancy supplemented their diets with 100 mg zinc sulfate (23 mg zinc)/day, three experienced premature deliveries and one delivered a stillborn infant. This author (Kumar, 1976) then supplemented rats with "100 ppm zinc orally" (experimental protocol and calculation of dosage not given). Zinc-supplemented rats manifested a "significant increase" in the number of fetal resorptions. Zinc supplementation for pregnant women has been recommended, but because of the known interaction between zinc and copper,

excessive zinc supplementation for prolonged times could have an adverse effect on the fetus. It is also well-documented that zinc deficiency during pregnancy may have an adverse effect on the fetus (NRC, 1978).

3.3.2. Inhalation. No reports of teratogenicity or fetotoxicity in man or animals associated with inhalation of zinc or its compounds have been found in the available literature.

3.4. TOXICANT INTERACTIONS

Zinc has been shown to interact with other metals in the body. These interactions have been presented in detail in U.S. EPA (1980b), to which the reader is referred, and only a brief summary will be presented here. Interactions between cadmium and zinc have been discussed extensively in NRC (1978). In general, exposure to cadmium may cause changes in the distribution of zinc, with accumulation occurring in the liver and kidney. Elevation of dietary cadmium can precipitate zinc deficiency in some organs by causing accumulation of zinc in the liver and kidney, particularly if the diet level of zinc is marginal. A case in point is the report of Lal (1976), who found that oral exposure to cadmium could cause testicular and pulmonary lesions in rats on a marginal (5 ppm) but not an adequate (40 ppm) zinc-fortified diet.

The interactions of copper and zinc were alluded to in the discussions of the studies of Prasad et al. (1978) and Porter et al. (1977), where zinc was given therapeutically to sickle cell anemia patients. Murthy and Petering (1976) administered 0, 2.5, 5.0, 10.0, 20 or 40 mg zinc acetate/ℓ of drinking water to Carworth rats for 60 days. The diet was "artificially low" in both zinc and copper. Hematocrit and hemoglobin levels varied inversely with zinc dosage and directly with copper level in the diet. Although these data were significant ($p<0.05$), all values remained within

normal ranges. Klevay and Forbush (1976) suggested that the ratio of copper and zinc in the American diet contributes to coronary heart disease. The probability that copper nutrition in the typical American diet is suboptimal may have been responsible for this suggestion. Klevay (1973) found a direct relationship between hypercholesterolemia in rats and the zinc:copper ratio in the diet. It has been shown (Petering et al., 1977, Murthy and Petering, 1976) that copper status is a factor with regard to serum cholesterol levels.

NRC (1978) suggested that calcium in the diet may interfere with zinc uptake in the diet. Underwood (1977) reviewed the relationship between zinc and calcium, and concluded that, unless zinc status is marginal, calcium did not interfere with zinc uptake.

Within the body, an interesting relationship exists between zinc and calcium. Beginning on the first day of gestation, female rats were given zinc deficient (0.4 ppm) diets with or without calcium deficient (15 ppm) diets (Hurley and Tao, 1972). Gravida were examined on the 21st day of gestation. Females deficient in both calcium and zinc had a larger number of live fetuses/litter than those deficient in zinc only. Of fetuses from zinc-deficient/calcium adequate females, 83% exhibited malformations; from the zinc- and calcium-deficient females, only 57% of fetuses showed malformation. Analysis of maternal femurs showed reduction of total ash, zinc and calcium in females from the zinc- and calcium-deficient groups. These findings were interpreted to suggest that calcium deficiency triggered maternal osteolysis to meet fetal demands for calcium. Bony resorption also returned zinc to the maternal circulation, which partially protected fetal rats from teratogenicity induced by zinc deficiency.

Hamilton et al. (1978) studied the intestinal absorption of zinc in iron-deficient mice, and found that zinc uptake from the gut was inhibited by adding iron to the duodenal loop system used. These authors concluded that zinc and iron share mucosal binding sites.

Cerklewski and Forbes (1976) fed diets containing 8, 35 or 200 ppm zinc to rats challenged with 50 or 200 ppm lead in the diet. Rats on higher dietary levels of zinc experienced a milder syndrome of lead toxicity, had lower tissue levels of lead and showed a lesser magnitude of hematological changes associated with lead toxicity. These authors concluded that dietary zinc had a protective effect against toxicity to ingested lead and that the site of activity was probably within the gut.

Since oral progestational contraceptives have been associated with altered zinc metabolism, Hess et al. (1977) measured urinary zinc output in women using and not using oral contraceptives. During the latter course of this study, these women received about 0.17 mg zinc/day in their diet, compared with ~10 mg/day before the study began. Urinary zinc excretion decreased 83% in women using oral contraceptives and 62% in women not using oral contraceptives. At the beginning of this study, urinary excretion of zinc was about 0.36 and 0.4 mg, respectively, in women using and not using oral contraceptives. These authors concluded that oral contraceptives probably have little effect on zinc metabolism during adequate zinc intake, but may have a more pronounced effect if zinc intake is low or marginal.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data associating cancer in humans with zinc could not be located in the available literature. Attempts have been made, however, to relate zinc levels in tumorous tissue to the development of the tumors. Most such attempts have met with frustration (NRC, 1978). In the prostate gland, an organ ordinarily high in zinc, neoplasia has been shown to result in a zinc level <50% of normal (Habib et al., 1976).

4.2. BIOASSAYS

No bioassays of zinc or its compounds for carcinogenicity could be located in the available literature. The effect of dietary levels of zinc upon development of cancer has been investigated. Wallenius et al. (1979) exposed groups of female rats to diets containing 15, 50 or 200 ppm zinc. The palatal mucosa was then painted with 4-nitro-quinoline-n-oxide 3 times/ week to induce cancer. The animals were killed after cancer of the palate became grossly visible. Animals exposed to 200 ppm dietary zinc developed macroscopically detectable cancer earlier than rats exposed to the two lower doses. Mathur et al. (1979) applied an identical protocol to rats on diets containing 5.9, 50 or 260 ppm zinc. Palatal mucosa was sampled at 3, 9, 13 and 23 weeks after exposure, at which time all rats were killed and examined. After 3 weeks the animals on the zinc-deficient diet showed most advanced histologic changes. After 20 weeks, cancers were found in both the zinc-deficient and zinc-supplemented groups. Rats on the adequate (50 ppm zinc) diet only evidenced moderate dysplasia.

One group of compounds, the zinc chromates, are suspected carcinogens. Since the suspected carcinogenicity of these compounds is associated with the chromate moiety rather than the element zinc, these compounds will not be discussed in this document.

4.3. OTHER RELEVANT DATA

Pertinent data regarding mutagenicity of zinc or its compounds could not be located in the available literature.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to zinc or its compounds. Using criteria for evaluating the overall weight of evidence of carcinogenicity in humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), zinc compounds are most appropriately classified as Group D - Not Classified compounds.

5. REGULATORY STANDARDS AND CRITERIA

A summary of regulatory standards and criteria for zinc and its compounds is presented in Table 5-1. The ACGIH (1980) has recommended a TLV of 1 mg/m³ for zinc chloride, based apparently on its corrosive and "harmful" nature. An STEL of 2 mg/m³ is suggested. For zinc chromates, a TLV of 0.05 mg/m³ is recommended, primarily based on the suspicion that these compounds are carcinogenic. The suggested TLV of 0.05 mg/m³ is identical to the TLV for lead chromate. No STEL is given. For zinc oxide fumes, a TLV of 5 mg/m³ and a STEL of 10 mg/m³ are suggested, so that "the incidence of metal fume fever will be low and any attacks which may occur will be mild." For zinc stearate, a TLV of 10 mg/m³ and a STEL of 20 mg/m³ are suggested, putting zinc stearate dust in the category of a nuisance dust rather than a toxic compound.

The U.S. EPA (1980b) has recommended a level of 7.5 mg/ℓ as the ambient water quality criterion, primarily because consumption of 2 ℓ of water would provide 15 mg of zinc, an amount felt to be "well tolerated" on the basis of long-term administration of zinc to patients to accelerate wound healing. NAS (1974) recommended a drinking water standard of 5 mg/ℓ based on organoleptic effects.

TABLE 5-1

Regulatory Standards and Criteria for Zinc

Standard or Criterion	Value	Reference
Zinc chloride		
TLV	1 mg/m³	ACGIH, 1980
STEL	2 mg/m³	
Swedish limit	1 mg/m³	
Zinc chromates*		
TLV	0.05 mg/m³	ACGIH, 1980
Zinc oxide, fume		
TLV	5 mg/m³	ACGIH, 1980
STEL	10 mg/m³	
USSR, Czechoslovakia, East Germany, West Germany	5 mg/m³	
Zinc stearate		
TLV	10 mg/m³	ACGIH, 1980
STEL	20 mg/m³	
Zinc oxide	5 mg/m³	NIOSH, 1975
TWA	5 mg/m³	
Ceiling	15 mg/m³	
Ambient water quality criterion	7.5 mg/ℓ	U.S. EPA, 1980b
Drinking water criterion	5 mg/ℓ	NAS, 1974

*Based on suspected carcinogenicity of chromate moiety

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Several studies of subchronic oral administration of various compounds of zinc to animals and of the administration of zinc sulfate to humans have been examined in Section 3.1. The human data are case reports of the therapeutic use of zinc to accelerate normal or ulcer healing, to relieve the suffering of arthritis victims or to aid recovery of sickle cell anemia patients. These authors (Pories et al., 1967; Greaves and Skillen, 1970; Simkin, 1976; Serjeant et al., 1970; Prasad et al., 1975) used oral encapsulated doses of zinc, ~2.14 mg/kg/day (assuming a human body weight of 70 kg), often divided into 3 doses/day. Essentially, no adverse effects were noted in any of these studies, except for mild nausea in some patients who took their dosage on an empty stomach (Pories et al., 1967; Prasad et al., 1975). Moderately elevated serum or plasma levels of zinc were reported (Greaves and Skillen, 1970; Hallbrook and Lanner, 1972; Serjeant et al., 1970), but only if pretreatment zinc serum levels were <1.1 mg/ℓ (Hallbrook and Lanner, 1972), indicating the possibility of suboptimal zinc nutrition before treatment.

Several studies have been conducted using other zinc compounds (acetate, chloride carbonate and oxide, as well as sulfate) in laboratory animals. These data, summarized in Table 3-2, indicate that NOELs ranged from 25.5 mg zinc/kg/day as the acetate (Drinker et al., 1927a) to 95-188 mg zinc/kg/day as the chloride (Heller and Burke, 1927). It is possible that administration in drinking water may result in greater toxicity than administration through the diet. Many of these studies used small numbers of experimental animals, often without controls; thus, these studies were not ideally suited for risk assessment. Since none of the animal studies demonstrated adverse

effects at zinc dosage levels lower than the human dose of ~2.14 mg/kg/day, and since this dose in humans appeared to be very near an MED, this commonly used therapeutic level of 2.14 mg/kg/day was chosen as a human MED from which to derive an AIS. A UF of 10 is introduced to protect especially sensitive populations, such as those with faulty copper nutrition. The human AIS can be calculated by the formula AIS (mg/day) = MED (mg/kg/day) x 70 kg ÷ UF. AIS = 14.9 mg/day. Rather than representing a total acceptable intake, this value is suggested as an additional allowable increment beyond that representing a baseline from dietary intake.

The calculated AIS, 14.9 mg/day, is well within the NAS (1974) recommendations that adults should have a daily intake of 15 mg zinc/day, pregnant women should have an intake of 20 mg/day, lactating women should receive 25 mg/day and pre-adolescent children should receive 10 mg zinc/day. As mentioned in Section 3.3., Kumar (1976) associated premature delivery in women with zinc supplementation of ~23 mg/day. This author then reported fetal absorption in rats associated with supplementation with "100 ppm zinc." Unfortunately, no definitive diagnosis of the cause of the premature deliveries was mentioned. Furthermore, the nutritional competency of the diets of the women who suffered premature delivery, or of the rats used in the study, was not mentioned. If supplementation with zinc can be expected to result in fetal loss, one would have expected the studies by Cox et al. (1969) and Ketcheson et al. (1969) to point up this phenomenon, as they fed diets containing 4000-5000 ppm zinc, respectively, to gestating rats. No mention of reduced litter size was made by either of these studies.

Zinc supplements containing 15 mg zinc/tablet have been available over the counter to the general public for several years. Zinc is a nutrient that has been associated with improved wound healing and fertility, and by

some with improved resistance to cancer. It seems reasonable that if it existed, an association between zinc supplementation and premature delivery would have surfaced by this time. The NRC currently recommends 40 ppm zinc in the diet (dry matter basis) for many classes of livestock (Underwood, 1977). Many private consultants and livestock nutritionists have routinely formulated rations containing 50-200 ppm zinc, either for therapeutic reasons or to improve herd fertility. Fertility and reproductive performance are constantly monitored in livestock operations, as these are major factors that determine the economic well-being of livestock husbandmen. It seems reasonable to assume that had reproductive performance suffered because of zinc supplementation, this phenomenon would have been speedily identified and remedial action promptly taken. For these reasons, the report by Kumar (1976), associating zinc supplementation with premature delivery, is not considered in selecting the factors used to derive either an AIS or an AIC for zinc.

6.1.2. Inhalation. No pertinent reports on subchronic inhalation toxicity of zinc and its compounds could be located in the available literature that lend themselves to risk assessment. However, the TLV for zinc chloride could be used to estimate an AIS (see Section 6.2.2.). Since the TLV is designed to protect workers on a chronic basis, it should be adequate to protect the general population on a subchronic basis. The TLV for zinc chloride of 1 ppm would convert to an AIS value of 7.1 mg/day by applying an uncertainty factor of 1.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Few studies of chronic oral exposure of laboratory animals to zinc or its compounds were found in the available literature. The two studies discussed in Section 3.2.1. indicated only a slight depression in

food intake and growth of rats exposed to 250 mg zinc/kg/day (as the oxide) in the diet (Heller and Burke, 1927), and no evidence of toxicity in mice exposed to 850 mg/kg/day (as the sulfate) in drinking water (Walters and Roe, 1965). The case reports of Porter et al. (1977) and Prasad et al. (1978) strongly indicated that chronic human exposure to 2.14 mg/kg/day for a prolonged period may result in a severe hypochromic microcytic anemia, hypoceruloplasminemia and neutropenia. Copper nutrition of these patients before treatment is not known. The fact that cessation of zinc therapy followed by supplemental copper brought about a rapid reversal of these undesired effects emphasized the intimate relationship between zinc and copper nutrition. Since no data from experimental animals suggested a lower MED than the data on humans generated by Porter et al. (1977) and Prasad et al. (1978), their dosage of 2.14 mg/kg/day was chosen as the starting point from which to derive an AIC. Again, a UF of 10 is chosen to protect especially sensitive populations, primarily those with inadequate copper nutrition. As in Section 6.1.1., an AIC of 14.9 mg/day is obtained. This value represents an additional increment beyond background dietary exposures.

The U.S. EPA (1983b) calculated a CS for zinc based on the hypochromic microcytic amenia observed by two separate research teams (Porter et al., 1977; Prasad et al., 1978) in humans treated with zinc sulfate to supply zinc at 150 mg/day. This human MED corresponds to an RV_d of 2.2. The hypochromic microcytic anemia is assigned an RV_e of 8. A CS of 17.6 results as the product of RV_e and RV_d.

6.2.2. Inhalation. Pertinent data regarding the chronic inhalation studies of zinc or its compounds in humans or animals that lend themselves to risk assessment coulds not be located in the available literature. An AIC for chronic inhalation exposure can be derived in humans, based on the

TLV recommendations set forth by the ACGIH (1980). The TLV for zinc chloride was chosen because the ACGIH (1980) considered zinc chloride to be the most damaging zinc compound of those tested. A TLV for zinc chloride of 1 mg/m³ would result in a daily intake of 7.1 mg/day, assuming that a workman inhales 10 m³/day and works 5 days/week. A UF of 10 is applied to protect especially sensitive populations. Division by 10 results in an AIC of 0.7 mg/day.

6.3. UNIT CARCINOGENIC RISK (q_1^*)

No bioassays of zinc by either oral or inhalation exposure have been performed. No reports of cancer in humans induced by zinc or its compounds could be located in the available literature. It is therefore not possible to calculate a q_1^* or a 10^{-5} risk level for zinc or its compounds by either oral or inhalation intake.

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