ZINC METABOLISM
Compiled and Edited by
ANANDA S. PRASAD, M.B., B.S., Ph.D. (MINN.)
CHARLES C THOMAS, PUBLISHER
Springfield, Illinois, U.S.A.

Chapter 23

ZINC TOXICITY IN MAN AND EXPERIMENTAL SPECIES*†

ROBERT VAN REEN

INTRODUCTION

IT HAS BEEN KNOWN for some time that many of the metals or metal salts exert a degree of toxicity when ingested, inhaled or placed on the skin surfaces. Naturally, the level of a metal which causes a toxic reaction varies tremendously with the mineral. Zinc salts are not particularly toxic in comparison to some of the other metal salts such as those of copper, molybdenum or mercury; however, studies on zinc toxicity have revealed rather interesting interrelationships which are worthy of our attention.

In the present review, zinc toxicity in man, rats and in swine

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In the present review, zinc toxicity in man, rats and in experimental species other than rats will be discussed. Several review articles and discussions on zinc toxicity were consulted in preparing this manuscript (1-4). These may be of value to those desiring further reading into the problem.

ZINC TOXICITY IN MAN

Zinc poisoning in man has been studied in regard to three distinct avenues of exposure to salts of the metal: (a) Ingestion of toxic amounts of zinc with food or drink; (b) inhalation and retention of dusts and fumes of zinc in fairly high concentrations, and (c) direct contact of zinc or zinc salts with the skin.

Our interest here will be primarily with the first avenue of exposure, that is through food and drink, although documentation will be provided concerning the second and third pathways for those who may be interested. No attempt has been made to provide an exhaustive literature survey, since much of the early work

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and indeed some of the more recent observations are confused by the possibility that other metals were involved.

Toxicity due to Inhalation of Zinc Oxide Fumes

Vallee (5) has presented a brief review of zinc toxicity due to the inhalation of zinc oxide fumes (also called metal fume fever, galvo, brass founders ague, brass chills, zinc shakes and spelter shakes). A review of zinc toxicity in man can also be found in a recent article by Stokinger (6). The inhalation of zinc oxide fumes causes fever, malaise and depression, coughing which might induce vomiting, excessive salivation and headache. In regard to the inhalation of zinc oxide, the studies of Sturgis, Drinker, and Thompson (7) are interesting in that two healthy subjects were exposed to fumes and their reactions measured. The average concentration of zinc oxide calculated as zinc was 600 mg/m³ (Table LXXII). One subject breathed vapors for 10.5 minutes and inspired 48 mg of zinc, while the second subject breathed the vapors for twelve minutes inspiring 74 mg of zinc. Both developed moderate symptoms of zinc toxicity. The actual concentration of zinc in the air appears to be a factor in determining the toxicity of zinc oxide since Batchelor, Fehnel, Thompson, and Drinker (8) found no acute or chronic illness in their examinations of twenty-four men who had been exposed during working hours to zinc oxide fumes at levels of about 3 to 15 mg zinc/m³ for from two to thirty-five years. According to Stokinger (6), the American Conference of Government Industrial Hygienists accepts a limit of 15 mg zinc/m³ of air.

In spite of our knowledge of metal-fume fever, cases are still reported (9), and the problem really revolves about prevention through reducing fume concentration, limiting exposure time,

TABLE LXXII
METAL FUME FEVER STUDIES*

Concentration in Air	*600 mg zinc/m³*
Zinc inhaled	
Subject 1	48 mg/10.5 min
Subject 2	74 mg/12.0 min
Zinc retained	
Subject 1	24 mg
Subject 2	37 mg

*Observations of Sturgis, Drinker, and Thompson (7).

maintaining adequate ventilation or using mechanical-filter respiratory devices.

Toxicity due to Contact with Metal Salts

In regard to zinc toxicity in man due to contact of metal salts with the skin, it can be said that zinc oxide ointments have been used for many years. Turner has indicated that, while zinc oxide is a relatively nontoxic substance, the material may block the sebaceous gland ducts and give rise to a papulopustular eczema in men engaged in packing the substance (10).

Sensitivity to zinc oxide appears to be quite rare, although Freeman (11) has reported a dermatitis in a family resulting from exposure to zinc salts. Some of the salts of zinc such as the chloride have a caustic action and may result in ulceration of the fingers, hands, or forearm of those who use it as a flux in soldering or in other occupations. In cases of such ulceration, we cannot attribute the action to a sensitivity or allergy to the zinc ion, since continued exposure to any strong acid or alkali will eventually cause skin damage.

Toxicity due to the Ingestion of Zinc Salts

Zinc is present in the various tissues of man and other vertebrates in concentrations varying from 10 to 200 μg/gm (1, 12, 13). An extensive study on the mineral composition of whole human bodies on a fat-free basis by Widdowson, McCance and Spray (14) indicated that a 70 kg man contains from 1.36 to 2.32 gm of zinc. This compares with values of 4.2 to 6.1 gm of iron and 81 to 230 mg of copper.

The normal zinc intake by man has been estimated by McCance and Widdowson (15) to be about 10 to 15 mg/day. From 5.1 to 10.3 mg/day is excreted in the stool, according to the level of intake and about 440 $\pm$ 120 μg/day excreted in the urine. Losses via other routes such as sweat, skin, milk, etc. must also be considered in a zinc balance study.

According to Hinman (16) the threshold concentration of zinc for taste in drinking water is about 15 ppm, with 40 ppm producing a definite metallic taste and also imparting a milky ap-

pearance to the water (Table LXXIII). The emetic concentration range in water is 675 to 2280 ppm. Sollman (17) lists the emetic dose of zinc sulfate to be 1 to 2 gm, which is approximately equivalent to 225 to 450 mg of zinc. Since this is the amount which would cause immediate vomiting, the amount that could be retained in the stomach and cause subsequent illness would be somewhat less. The usual symptoms of toxicity are fever, nausea, vomiting, stomach cramps and diarrhea in three to twelve hours following ingestion, although some cases have been reported within twenty minutes of drinking contaminated liquids without the ingestion of foods.

TABLE LXIII
TOXICITY OF ZINC

Threshold for taste	15 ppm (water)
Definite taste	40 ppm (water)
Emetic concentration	675-2280 ppm (water)
Emetic dose ($ZnSO_4.7H_2O$)	1 - 2 gm
Equivalent in Zn^{++}	225-450 mg

The fact is well known that poisonous amounts of zinc can be brought into solution when fruit juices are placed in galvanized iron utensils or when vegetables and meats are cooked in them. Numerous reports of zinc poisoning can be found in the public health and medical literature, and essentially all of them relate the illness to the type of pots or cooking utensils used in the preparation of foods. A difficulty in interpretation arises, however, from the fact that the specificity of the toxicity generally could not be established. Metal poisoning by minerals other than zinc could have contributed to the illnesses. As an example, Callender and Gentzkow (18) have reported on episodes with two companies of soldiers in which about 80 per cent of the personnel were ill with gastrointestinal distress and diarrhea of varying intensity. The poisoning was apparently the result of drinking limeade prepared in galvanized iron garbage cans. To establish this, a fruit drink was prepared in a similar fashion and then analyzed for heavy metals (Table LXXIV). The average dose of zinc was estimated to be 495 mg and 468 mg per man for the two companies. The average doses of antimony was calculated to be 10.5

mg and 10.0 mg per man, respectively, or 29.0 mg and 27.6 mg, calculated as antimonyl-potassium tartrate. The emetic dose of the latter compound is about 30 mg. Thus, the experimental studies indicated that poisonous amounts of zinc and antimony were present in the limeade and that these were responsible for the symptoms, but the relative importance of the two metals could not be stated.

TABLE LXXIV
CONTAMINATION OF LIMEADE BY STORAGE IN GALVANIZED CANS*

Zinc	730 mg/liter
Antimony	15.6 mg/liter
Arsenic	trace
Cu, Hg, Pb	none
Iron	considerable

*From Callender and Gentzkow (18).

A very recent report by Brown, Thom, Orth, Cova and Juarez (19) about two situations of mass food poisoning indicated that they were due to zinc contamination and not to other metals. The first episode involved 300 to 350 ill people out of 400 attending a celebration for which food was stored in galvanized tubs. Rinsing the tubs used for food storage with acid rinses resulted in a solution containing zinc in a concentration over 2,500 ppm. No other metals were found in any but trace amounts other than iron. Some of the ill patients showed zinc levels in their stools as high as 1200 ppm. on a dry weight basis. In the second episode, forty-four subjects of fifty-one who drank a punch stored in a galvanized container became ill. It was found that a 5 oz. portion of the punch contained 525 mg of zinc, an amount which is within the emetic dose of the metal.

Because of the difficulties inherent in studying the cause of food poisoning, in some cases days after the occurrence, a number of investigators have turned to experimental animals for more basic information on the mechanism of toxicity.

ZINC TOXICITY IN RATS

Some of the early studies with experimental animals were initiated in order to elucidate the contradictory findings concern-

ing the toxicity of zinc to man. A review of the early pharmacological studies on zinc can be found in an article by Salant (20). Reports can be found in the literature of the beginning of the twentieth century which suggest that food poisoning can result from storage of a variety of edibles in zinc-lined or galvanized containers. Heller and Burke (21) studied the concentration of zinc in buttermilk stored in galvanized pails and found up to 33 mg zinc/liter after forty-eight hrs. of storage. The same investigators fed young rats a basal diet consisting of natural materials with and without 0.25 per cent zinc provided as zinc dust, zinc chloride, zinc carbonate or zinc sulfate. This level of zinc did not cause reduced growth, and the general appearance of the animals as to the eyes, smoothness of coat and ease of movement did not indicate any deleterious effect. Three generations were maintained on the same ration with the same vigor in growth and reproduction and without any obvious changes of the internal organs.

In a series of reports (22, 23), findings were presented concerning the absorption, storage and excretion of zinc and on the physiological and pathological action of zinc in rats, cats and dogs. The latter reference also provides a good review of earlier papers on zinc toxicity. The results of the above investigations demonstrated that the ingestion of 0.5 to 34.4 mg of zinc per day by rats was not toxic and that only a small fraction of the ingested zinc is excreted in the urine, the major fraction by far appearing in the feces.

Later studies by Sutton and Nelson (24) established the toxic level of zinc ions for young rats to be between 0.5 and 1.0 per cent of the ration. Below this level growth, reproduction and hemoglobin levels were normal. After 39 weeks on toxic levels of zinc administered as zinc carbonate, hemoglobin levels dropped to 10.2 and 6.1 gm/100 ml for rats receiving 0.5 and 1.0 per cent zinc, respectively. The anemia was of the hypochromic, microcytic type. The establishment of toxicity at 0.5 to 1.0 per cent zinc appears quite valid in that the investigators used purified salts, and it is unlikely that other elements were involved. As indicated previously, the cases of poisoning in man through the use of

galvanized containers were complicated by the fact that materials other than zinc could have contributed to the toxicity.

In spite of the low toxicity of zinc salts, some interesting observations have been made concerning the mechanism of toxicity. Smith and Larson (25) used rations containing 0.7 per cent zinc and studied the effects of various supplements on the toxicity. They observed that 0.2 mg copper as cupric sulfate per day was effective in alleviating the anemia associated with zinc toxicity, whereas a combination of 2 mg iron as ferric pyrophosphate and 0.2 mg cobalt as cobaltous chloride was not. These investigators also demonstrated that 1 per cent liver extract powder produced significantly better growth when incorporated into the toxic diets. Thus, two of the effects of zinc toxicity in rats can be partially mitigated, namely, the anemia with copper salts and the growth depression with liver extract. As a working hypothesis, it might be possible to assume that excessive dietary zinc in the rat induces a copper deficiency. If this is true, then the biological systems involving copper would be expected to be affected.

Hart, Steenbock, Waddell and Elvehjem (26) have demonstrated the need of copper for hemoglobin formation, and this helps explain the anemia of zinc toxicity. Furthermore, Schultze (27, 28) reported that feeding rats a copper-deficient diet results in decreased activities of cytochrome oxidase in the livers, heart and bone marrow. In another report, Schultze and Kuiken (29) indicated that rat liver catalase activity was also decreased in copper deficiency. In a series of experiments, Van Reen and Pearson (30) and Van Reen (31) showed that a dietary level of 500 to 700 mg per cent zinc administered to rats as zinc carbonate resulted in a marked reduction in liver catalase and cytochrome oxidase activities. Copper fed as copper sulfate, along with the toxic zinc levels, resulted in an increase in liver catalase and cytochrome oxidase activities to normal values. In these latter studies, while copper supplementation influenced the liver enzymes, it had no effect in correcting the growth inhibition produced by zinc. Similar findings in regard to hemoglobin and heart cytochrome oxidase activities were reported simultaneously by Duncan, Gray and Daniel (32) while confirmation of the effect of copper supple-

mentation on liver cytochrome oxidase has been provided by Witham (33).

Effects of zinc feeding to rats other than the aforementioned have been reported in a series of papers by Sadasivan (34-36). In this work, levels of zinc oxide of 0.5 and 1.0 per cent caused a reduction in the weight and the fat content of the livers and also adversely affected the femurs resulting in lower calcium/phosphorus ratios than in normal rats. Other changes included increased excretion of urinary and fecal nitrogen, lowered urinary excretion of phosphorus and sulfur, but increased fecal excretion, increased urinary uric acid and creatinine and increased liver and kidney alkaline phosphatase activities. The influence of dietary zinc on calcium and phosphorus and its relationship to bone development has been studied in considerable detail by Stewart and Magee (37). These investigators have presented data which indicate that zinc has an antagonistic effect on the normal deposition of calcium and phosphorus in the bones of young rats, an effect which can be alleviated with dietary calcium and phosphorus supplements. Dietary zinc also caused an increase in fecal and urinary calcium and phosphorus resulting in decreased retention. It appears that an antagonism exists between zinc and calcium from the work of Newland, Ullrey, Hoefer and Luecke (38) who indicated that increased fecal excretion of zinc occurs in pigs given supplements of calcium. The earlier observations of Hoekstra, Lewis, Phillips and Grummer (39) also support this concept.

In view of the ameliorating effect of copper salts on zinc toxicity, a number of studies have been undertaken to determine the fate of copper and copper storage during toxicity. Duncan, Gray and Daniel (32) reported that the copper content of the normal rat heart was 27 μg/gm, whereas that of the zinc-toxic animal was 10 μg/gm on the dry weight basis. In a time study designed to determine whether liver copper or iron was reduced first in the rat, Cox and Harris (40) studied the effects of 0.4 per cent zinc over a forty-two-day period. Anemia was evident after fourteen days; however, the iron content of the livers dropped to about 50 per cent of controls after only seven days. A consistent decrease in liver copper stores did not develop until between

twenty-one and twenty-eight days on the zinc-toxic diet. The study also showed that the buildup of liver zinc is very rapid, being found in the livers in high concentrations after only one day on the diet. Unfortunately, the concentrations of minerals in the liver may not be related to their availability. McCall, Mason and Davis (41) have also reported a decrease in the iron content of livers of rats given zinc. Evidence was also presented indicating that the severity of symptoms of zinc toxicity depends upon the type and level of dietary protein. Rats fed 20 or 30 per cent soybean protein were more resistant to zinc toxicity than rats fed casein diets.

The actual fraction of liver iron lost under the influence of zinc feeding has been investigated by Cox and Harris (42). They reported that 0.4 per cent zinc as zinc oxide in the diet of rats reduced liver iron, ferritin, hemosiderin and hemoglobin. Of the total iron lost, approximately 77 per cent was from ferritin iron and 20 per cent from hemosiderin iron.

Grant-Frost and Underwood (43) undertook to determine whether the effects of zinc toxicity in rats was due to reduced food intake. From a series of studies, they have concluded that the depressing effect of zinc on growth is caused largely by reduced food intake, but that the anemia is caused by a zinc-induced copper deficiency in the animals. They further consider that zinc lowered tissue copper but also antagonized copper absorption.

Under certain conditions, zinc salts may be more toxic than indicated in the previous discussion. Thus, Brinkman and Miller (44) have demonstrated that rats receiving 200 ppm molybdenum and 0.05 per cent zinc oxide had a weight gain of only 52 per cent of that of rats fed molybdenum alone. Similarly, rats fed 200 ppm molybdenum gained less weight and showed lower hemoglobin levels when maintained in galvanized rather than stainless steel cages. It is thus apparent that since zinc interferes with copper metabolism, any other dietary factor which influences copper levels may be expected to affect the tolerance of the rat to zinc salts.

In summary, it may be said that the feeding of zinc to rats has many and varied effects (Table LXXV). The best documented

observations are in regard to growth depression, which can be alleviated by liver extract and an induced copper deficiency, which results in anemia and lowered activities of several iron-containing enzymes. These latter effects can be mitigated by providing supplemental copper and, in some cases, iron. Zinc may also interfere with the utilization or absorption of other divalent minerals, such as calcium.

TABLE LXXV
ZINC TOXICITY IN RATS

Effects Observed	*Investigator*
0.25% zinc is non-toxic level.	Heller and Burke (21)
Up to 34.4 mg zinc/day non-toxic. (35-53 wks)	Drinker *et al.* (22)
0.5-1.0% zinc—reduced growth, anemia, poor reproduction.	Sutton and Nelson (24)
0.7% zinc—anemia modified by copper—poor growth improved by liver extract.	Smith and Larson (25)
0.5% zinc reduces liver catalase and cytochrome oxidase—reversed by copper.	Van Reen (31)
0.5% zinc reduces weight and fat of liver, lowers Ca/P of femurs, increases urinary and fecal nitrogen, reduces urinary phosphate and sulfate.	Sadasivan (34)
1.0% zinc—anemia and reduced heart cytochrome oxidase—reversed by copper.	Duncan *et al.* (32)
0.4 - 0.6% zinc reduces liver iron and copper.	Cox and Harris (40)
0.5% zinc less toxic on soybean than casein protein diet.	McCall *et al.* (41)
0.4% zinc reduces liver ferritin and hemosiderin.	Cox and Harris (42)
0.75% zinc decreases bone calcium. Calcium phosphorus reduce bone uptake of zinc.	Stewart and Magee (37)
0.5% zinc depresses food intake and therefore weight. Inhibits copper and causes anemia.	Grant-Frost and Underwood (43)

ZINC TOXICITY IN EXPERIMENTAL SPECIES OTHER THAN RATS

Very brief mention has already been made of the work of Drinker, Thompson, and Marsh (22) on zinc toxicity in cats and dogs. No further information will be provided here, since it appears that the toxicity is similar to that in rats.

Sastry, Murty, and Sarma (45, 46) have reported the results of investigations on zinc toxicity in the lepidopterous insect *Corcyra cephalonica St.* This organism was utilized, since, in many ways, its nutritional requirements and metabolism are similar to higher organisms. It was shown that the larvae of the rice moth were resistant to as much as 800 ppm zinc given as zinc chloride or zinc

sulfate. Higher levels of zinc reduced survival to barely one week. Further studies showed that vitamin B_{12} and liver extract reduced the mortality due to lethal doses of zinc with the liver preparation being the more effective. With these high, lethal doses of zinc, none of the supplements protected against the growth inhibition. At toxic, but not lethal, levels of zinc, growth protection was afforded by liver extract and by DNA and RNA. Dietary DNA did not influence the uptake of zinc-65 from the diet, and the precise action of DNA and RNA are unknown. Sastry *et al.* (46) in further studies demonstrated that the intake of toxic amounts of zinc by rice moth larvae brings about not only an inhibition of growth but also a pronounced fall in tissue catalase activity. Copper sulfate added to the zinc toxic meal restored the enzyme level to normal without improving growth. These findings are quite similar to those reported by Van Reen and Pearson (30) and Van Reen (31) for the rat and suggest a similar mechanism of zinc toxicity, that is, via inhibition of copper metabolism. Adiga *et al.* (47) further showed that iron supplementation restored the growth of *Corcyra larvae* given toxic levels of zinc. This compares with the observation of Cox and Harris (40), who noted that in rats the zinc-iron antagonism manifests itself in altered tissue iron levels which can be partially brought to normal by additional iron.

MacLeod (48) has investigated the toxicity of zinc for *Lactobacillus arabinosus* and *Lactobacillus pentosus* and has reported that toxicity is markedly decreased as the pH of the medium is reduced from 6.5 to 5.0. He has suggested that zinc ions exert their toxicity by forming an inactive complex with metabolically active components of the cell. Lower pH's would affect the formation of a complex, thus the metal ions would demonstrate reduced toxicity.

The toxicity of zinc to *Aspergillus niger* was studied by Adiga *et al.* (49), who have shown that 1,000 μg zinc/10 ml of culture medium reduces the growth of mold to about 40 per cent of controls. Interestingly enough, magnesium salts appear to reverse the toxicity. Only 200 μg magnesium were able to counteract 1.000 μg of zinc in a 10 ml culture. From these results, it is possible to

conclude that zinc toxicity in *A. niger* is equivalent to a conditioned magnesium deficiency, whereas, in the rat it is a zinc-copper relationship. Iron also counteracts the growth suppression in *A. niger* but is not as effective as magnesium.

Investigations have also been made utilizing the yeast, *Saccharomyces carlsbergensis* (50). Toxic levels of zinc in the culture medium caused reduced oxygen uptake and reduced aerobic and anaerobic fermentation. Cytochrome oxidase activity was also markedly reduced in the toxic state. This corresponds to the observations in rat tissues but leaves unexplained the zinc-magnesium relationship observed in *A. niger*.

The toxicity of zinc to aquatic animals has been recently reviewed by Skidmore (51), who has indicated that the toxicity can be modified by several environmental factors, particularly the hardness of the water, the dissolved oxygen concentration and temperature. Apparently, a different mechanism of zinc toxicity must be operative in trout and other fish than in higher animals, since zinc and copper salts exert a synergistic action on one another. The synergism holds only at relatively high concentrations, whereas at concentrations of zinc less than 1.8 ppm and copper 0.3 ppm, the effect of the salts are additive.

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13. ABSTRACT

Many of the metals or metal salts exert a degree of toxicity when ingested, inhaled or placed on the skin surfaces. The level of a metal which causes a toxic reaction varies tremendously with the mineral. Zinc salts are not particularly toxic in comparison with salts of copper, molybdenum, mercury, etc.

In man, the inhalation of air containing from 3 to 15 mg zinc/m³ during working hours over a period of many years apparently exerts no toxic manefestations. Skin sensitivity to zinc appears to be relatively rare, although salts such as zinc chloride have a caustic action and can cause damage to the skin. The action in this case cannot be attributed to the zinc ion. Many cases of poisoning due to the ingestion of zinc salts have been reported. These cases usually occur through the use of galvanized containers to store acid foods or drinks. The emetic dose of zinc sulfate has been reported to be 1 to 2 gm which would be equivalent to 225 to 450 mg of zinc.

Zinc toxicity in rats has been shown to result in growth depression and anemia. Some evidence is presented to indicate that the anemia produced in this manner can be overcome by simultaneous copper administration. Zinc toxicity in other species of experimental animals is discussed.

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