EVALUATION OF THE HEALTH ASPECTS OF CERTAIN ZINC SALTS AS FOOD INGREDIENTS

NOVEMBER, 1973

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

Contract No. FDA 72-85
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I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using certain zinc salts as food ingredients, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents, including current literature citations obtained through Toxline* and Medline*, available as of November, 1973. Certain zinc salts are food substances that have been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101 revised April 1, 1973).

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the requirement of premarketing clearance for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health, and realizes that a conclusion, based on such reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's conclusions, based as they are on the information now available, cannot anticipate and be guided by experiments

* Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.
not yet done or by the results of tests that may be reconduted, using new technologies that are continually being evolved. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on certain zinc salts and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Zinc is an essential element in the nutrition of man, animals, and plants (2). It is an integral component of a number of metalloenzymes, including carbonic anhydrase, alcohol dehydrogenase, carboxypeptidase, glutamic dehydrogenase, lactic dehydrogenase, and alkaline phosphatase (3). The manifestations of inadequate intake in humans include stunted growth and delayed sexual maturation (2). Zinc has been reported as necessary for normal mobilization of vitamin A from the liver (4). Widespread interest in the biological role of zinc and its nutritional importance has stimulated the development of a variety of analytical methods (5, 6). As little as 0.5 ppb can be detected by x-ray and neutron activation techniques.

Zinc compounds are added to foods and animal feeds chiefly as nutritional supplements. The sulfate and the oxide are the principal zinc compounds used for this purpose in foods (7). Other zinc compounds listed as GRAS for use in foods, feeds, or food packaging materials are zinc acetate, zinc carbonate, zinc chloride, zinc gluconate, zinc hydrosulfite, and zinc stearate (8). Three of these compounds - the chloride, gluconate and stearate - were proposed for removal from the GRAS list in April, 1973 (9) because of an apparent lack of use in foods, but the proposal was withdrawn in July, 1973 (10) when evidence of some use in foods was provided to the Food and Drug Administration.

The Food Chemicals Codex (11) lists specifications for food grade zinc sulfate only, requiring that it assay no less than 99.0 percent and not more than 108.7 percent ZnSO₄·7H₂O, and that it contain not more than the following amounts of impurities: arsenic, 3 ppm; heavy metals as lead, 10 ppm; and selenium, 30 ppm.
A comprehensive survey conducted by a National Research Council subcommittee (7) indicates that zinc sulfate is added to foods to provide supplemental zinc in amounts ranging from 0.03670 to 0.03799 percent in infant formulas and at a level of 0.00004 percent in nonalcoholic beverages. Zinc oxide is used in amounts ranging from 0.0002 to 0.00025 percent in reconstituted vegetable protein and at a level of 0.006 percent in imitation dairy products (7).

Zinc salts were first added to food in the United States in 1961; there has been a fivefold increase in the total amount used annually since that time (7). However, the Select Committee has no information to indicate the extent to which the zinc content of the foregoing food categories has changed within the past decade.

III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee (7) has provided information on the possible daily human intake of zinc sulfate and zinc oxide in the total diet, as shown in the following table for individuals in various age groups. The Select Committee has converted these figures to possible intakes of elemental zinc per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th>Zn per kg body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>ZnO</td>
</tr>
<tr>
<td></td>
<td>ZnSO₄·7H₂O</td>
<td>ZnO</td>
</tr>
<tr>
<td></td>
<td>Av Max mg</td>
<td>Av Max mg</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>123.20 225.70</td>
<td>0.00 5.59</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>25.10 119.60</td>
<td>0.08 0.72</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>8.10 8.38</td>
<td>0.05 0.17</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>0.04 0.11</td>
<td>0.05 &lt;0.01</td>
</tr>
</tbody>
</table>

*Figures represent Zn consumed as the sulfate plus the oxide. Calculations are also based on an average weight of 60 kg for an adult (12) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (13).
The daily intakes indicated in the table should be considered in relation to the reported total use of zinc salts in foods. Other NRC data (7), assumed by them to represent 60 percent of total usage, recalculated to equal 100 percent, indicate that a total of approximately 35,467 pounds (16,121 kg) of zinc sulfate heptahydrate was used in the United States as a food supplement in 1970. The total use of zinc oxide in foods in 1970 was reported to be approximately 30 pounds (13.6 kg). Based on the total poundage of zinc sulfate reported to be used in foods, and excluding the relatively insignificant amounts of zinc oxide and the several other zinc compounds reported to be used, enough could be present in foods to supply about 0.22 mg of zinc sulfate heptahydrate per capita per day. Even if only 10 percent of the population consumed all the foods and beverages to which zinc sulfate is added, their per capita consumption would be of the order of only 2.2 mg of the hydrated sulfate, or about 0.50 mg of elemental zinc per person per day.

In light of these considerations, the Select Committee regards the figures given in the foregoing table as overestimates of the daily intake of zinc, particularly by the younger age groups*. The table does, however, make it apparent that infants are the primary consumers of products containing added zinc sulfate.

There are data on the natural zinc content of foods and the nutritional needs for this mineral. Schlettwein-Gsell and Mommsen-Straub (14) have assembled the results of many foodstuff analyses for zinc. With some exceptions, relatively less zinc occurs in fruits, vegetables, and milk (generally less than 1 mg per 100 g) than in meats and cereals. These investigators also report that samples of prepared hospital and other institutional meals contained from about 2.3 to 7.9 mg zinc per 100 g. Analyses of human milk from 13 mothers in Ohio, and of local market samples of infant formula foods such as evaporated milk, modified milk, and formulas containing lamb and soybean flour, showed the presence of zinc in the range 1.34 to 8.60 ppm (0.13 to 0.86 mg per 100 g) (15). Surveys of food consumption and data on the zinc content of various adult foods indicated that consumption of zinc from these sources could be of the order of 5 to 22 mg per day (2). A workshop conducted by the

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*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (7). The Select Committee finds this explanation reasonable and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
Food and Nutrition Board of the National Academy of Sciences (16), concluded that while the daily zinc requirement for humans has not been established, a daily intake of 9 to 10 mg in a mixed hospital diet resulted in equilibrium or a slightly positive balance. The Food and Drug Administration has established for the United States the following recommended daily allowances (USRDA) for zinc, representing an adaptation of the 1968 RDA's proposed by the Food and Nutrition Board: 4.0 - 12.0 mg for children under 4 years, 7.5 - 22.5 mg for adults and children over 4 years, and 7.5 - 30.0 mg for pregnant and lactating women (17). The Food and Nutrition Board has since revised its recommended dietary allowances for zinc as follows: infants 0 to 0.5 years, 3 mg and 0.5 to 1.0 years, 5 mg; children 1 to 10 years, 10 mg; men and women 11 to 51+ years, 15 mg; pregnant women, 20 mg; and lactating women, 25 mg (60). A recent report of a World Health Organization expert committee (61) also provides estimates of zinc distribution in foods and the daily zinc requirements of various age groups based on retention and excretion data.

IV. BIOLOGICAL STUDIES

Zinc is absorbed largely from the duodenum (18). The degree of absorption is substantially affected by the nutritive status with respect to zinc (19), dietary phytate (20), and calcium, and phosphorus (21). Usually about 8 to 10 percent of the zinc ingested by rats, cats, and dogs is absorbed and the rest is excreted in the feces (22, 23). Retention may be higher in bone and skin than in some other tissues (24) but the element is present in every cell. The average biological half-life of zinc in adult man is 154 days (24).

As is the case with other metallic salts, zinc salts ingested in large amounts cause a variety of metabolic changes, including the inhibition of intestinal alkaline phosphatase (25, 26), xanthine oxidase (27, 28), liver catalase and cytochrome oxidase (28, 29, 30) and succinic dehydrogenase (31); also, they modify the excretion of nitrogen, phosphorus, and sulfur (32). For example, feeding up to one percent of zinc oxide in the diet of rats resulted in increased urinary excretion of nitrogen, while phosphorus and sulfur excretion was reduced. However, fecal excretion was also increased resulting in decreased net retention. Urinary excretion of both uric acid and creatinine was increased (32).

In general, the most important effect of feeding excess zinc appears to be a specific microcytic hypochromic anemia, probably related to changes in iron and copper utilization. For example, decreases in iron storage proteins were observed when rats were fed a diet containing 0.4
percent zinc as zinc oxide (27). In other studies, diets containing 0.75 percent zinc (salt not indicated) resulted in decreased red cell life spans and increasing iron excretion in rats (33). Finally, feeding an excess of zinc oxide (up to 0.6 percent as zinc) to rats resulted in a decrease in both iron and copper levels of all tissues (34), explaining most of the enzyme changes. This effect of zinc excess on iron and copper metabolism appears to be the result of interference with iron and copper utilization at the cellular level and by increasing the excretion of copper (35). Evidence for this interaction is observed in studies in which iron and copper supplementation can reverse the anemia caused by excess zinc feeding (29, 36, 37).

A similar interaction has been found with calcium. For example, increasing dietary calcium increased the loss of zinc in rats and resulted in decreasing absorption and decreasing turnover (38). In other studies, high calcium and phosphorus intakes appeared to increase the zinc requirement of rats (21). On the other hand, feeding an excess (0.75 percent zinc as zinc carbonate) in the diet of young rats for one week resulted in a marked decrease in bone calcium and phosphorus (39). The mechanism of this interaction remains unknown.

In the rat the oral LD$_{50}$ of zinc sulfate has been reported to be 1374 mg per kg; of zinc sulfate heptahydrate, zinc acetate heptahydrate, and zinc chloride, 750 mg per kg (1). Values of similar magnitude have been reported for mice and rabbits (1). One human fatality has been reported; the death of an adult female was attributed to zinc sulfate poisoning following the accidental consumption of about 30 g of the salt (40). This intake amounted to about 500 mg per kg of body weight, a value similar to that found to be a lethal dosage in animal studies.

Many short-term feeding tests with high levels of zinc salts fed to a number of experimental animal species have shown no adverse effects at levels below 100 mg of the salt per kg per day. At higher levels a variety of observations have been reported depending on the salt used. At these levels, the most injurious salts were the chloride (41, 42) and the acetate (43, 44) with the latter apparently the more toxic. On the other hand, extensive studies indicate that feeding zinc oxide (26, 45) or zinc sulfate (46, 47) at levels in excess of 500 mg of the salt per kg has no consistently adverse effects (23, 46, 48). It would appear that the nature of the compound plays a significant role in the toxicology of zinc. Unfortunately, all four compounds have not been compared under the same experimental conditions.

Limited studies of zinc sulfate intake have been conducted in man. In general, there was no evidence of toxicity at levels of up to 660 mg per
day of the heptahydrate (about 10 mg of the salt per kg per day) for up to 3 months (49).

Long-term exposures have been carried out in rats with zinc chloride, oxide, carbonate, and sulfate (50). These studies, extending for one year and over three generations, showed no effect at levels up to 0.25 percent of the diet. However, in other investigations, zinc sulfate, fed at dietary levels of about 100 ppm to rats and dogs, was reported to cause hematological changes including microcytosis, coupled with polychromasia in some animals and hyperchromomasia in others; in addition, more rapid turnover of red blood cells was observed (33, 51).

No evidence of carcinogenicity of the several zinc salts was noted in rat studies over three generations (50) or in the feeding to rats of zinc oxide (equivalent to 34.4 mg of zinc daily for 29 weeks), zinc acetate (equivalent to up to 6.3 mg of zinc daily for 29 weeks), or zinc carbonate (equivalent to up to 1 percent zinc in the diet for 39 weeks) (52, 53).

Two studies with evidence of carcinogenicity from zinc have been reported (54, 55). These observations were made on mice given zinc chloride in drinking water at different levels and under different conditions, but the concentrations of greatest interest to the investigators were 10 to 20 mg of the salt per liter. Treatment schedules, or precise evaluation of tumors and sites were not reported. No controls were used in some of the experiments, and in others it is apparent that the controls were used in a different time sequence. No statistical evaluation of the data was given. Therefore, it is impossible to draw definite conclusions.

In another study mice were given up to 5,000 ppm of zinc as zinc sulfate in drinking water (56). No significant carcinogenic differences between the treated and control groups were observed. These findings, the comprehensive critical analyses of the literature by experienced investigators, and recent reviews by two laboratories specializing in experimental carcinogenesis (57, 58), make it evident that zinc salts taken orally should not be considered a carcinogenic hazard.

Reproduction studies performed through several generations have revealed no evidence of any adverse effect on fertility, gestation, and the health of the fetus from feeding up to 0.25 percent zinc chloride, zinc oxide, zinc carbonate, or zinc sulfate to rats (50). In addition, specific studies of the effect of excess dietary zinc, fed as the oxide, malate, acetate, citrate, or sulfate on the chemical composition and enzymic activities of maternal and fetal tissues, have not revealed adverse effects (28, 52, 53).
Teratologic tests on three species of animals were negative (59). Daily oral administration of up to 30 mg of zinc sulfate per kg of body weight in mice (day 6 through day 15 of gestation), up to 42.5 mg per kg in rats (day 6 through day 15 of gestation), and up to 88 mg per kg in hamsters (day 6 through day 10 of gestation) had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities observed either in soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

V. OPINION

The available information indicates that a wide margin exists between present intake levels of zinc salts and those that have been reported to produce noticeably harmful effects. Similarly, the suggestion that zinc chloride is carcinogenic has not been supported in carefully controlled animal studies.

However, because of the central role of zinc as either an activator of certain enzymes or as a coenzyme in many metabolic reactions, it has been demonstrated that relatively large excesses of zinc salts in the diet can lead to metabolic dysfunctions. In particular, the interaction of zinc with several other mineral nutrients, notably iron, copper, and calcium, suggests that major modification of this nutritional balance might lead to significant metabolic disturbances. In consideration of this and the currently wide nutritional use of zinc sulfate and zinc oxide in infant formulas, it would be desirable, in due course, to expand our knowledge of the interaction of zinc salts in association with dietary levels of other essential mineral nutrients. It would also be desirable to establish maximum limits for the levels of zinc salts in foods, particularly in formulas for infants, since this segment of the population may now consume the highest level of zinc salts when calculated on a daily or body weight basis.

In view of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on zinc sulfate, zinc oxide, zinc acetate, zinc carbonate, and zinc chloride that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public
when they are used at levels that are now current and in the manner now practiced. However, without additional data, it is not possible to determine whether a significant increase in consumption would constitute a dietary hazard.
VI. REFERENCES CITED


7. Subcommittee on Review of the GRAS List (Phase II). 1972. A comprehensive survey of industry on the use of food chemicals generally recognized as safe (GRAS). Prepared under DHEW contract FDA 70-22 by Committee on Food Protection, Division of Biology and Agriculture, National Research Council, Washington, D.C.


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