EVALUATION OF THE HEALTH ASPECTS OF STANNOUS CHLORIDE
AS A FOOD INGREDIENT

October, 1974

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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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
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NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances being made by the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB

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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 stannous chloride as a food ingredient. The evaluation has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1970.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally recognized as available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register of September 23, 1974 (39 FR 34218) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using stannous chloride as a food ingredient. The Select Committee received no requests for such a hearing on stannous chloride.

Stannous chloride is a food substance that has been generally recognized as safe (GRAS) under the provisions of the Code of Federal Regulations (21 CFR 121.101, revised April 1, 1974). As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarking clearance that is required 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. FDA recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 accordance 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, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconducted, using new technologies. 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 stannous chloride and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Tin is very widely distributed. It is present in municipal drinking waters in amounts ranging from 0.0008 to 0.03 ppm (2). Tin in fish for market is reported to range from 0.1 ppm for flounder to 0.63 for halibut (3). Fresh vegetables in the United States usually contain less than 1 ppm. Tin in canned goods is reported to range from 2.8 to 11.8 ppm (2). Analyses conducted in 1963, of a typical institutional diet for one person per day contained 3.6 mg of tin (2).

It has been claimed that most infants in this country as well as some adults in non-industrialized countries have no readily detectable amounts of tin in their tissues. However, the element is deposited rapidly in persons who reside in industrialized countries during the first decade of their lives without apparent further accumulation with age (2).

In mammals, tin is accumulated selectively by many different tissues (2). In beef, the concentration in the mucous membrane of the tongue may reach as high as 18.65 mg per kg of fresh tissue (4). Typical concentrations of tin in normal human tissues in mg per kg of wet tissue are: long bone, 0.80; liver, 0.60; rib bone and stomach, 0.50; heart, 0.22; and muscle, 0.11 (5). The mean concentration in urine has been reported to be 0.011 mg per kg and in blood, 0.12 mg per kg (5).

Tin has been reported to be nutritionally essential for the growth of rats (6). There is no direct evidence concerning its essentiality as a nutrient for man.
Because of its reducing and antioxidant properties, stannous chloride is used for color retention, and is added to such processed foods as asparagus (7), wax beans (8), and sauerkraut (9). This use is permitted as a chemical preservative (10) with a tolerance of 15 ppm calculated as tin. In 1968, FDA allowed the use of stannous chloride in concentrations not to exceed 20 ppm (calculated as tin) for color retention in asparagus packed in glass with lids lined with an inert material (11).

The Food Chemicals Codex (12) specifies that food grade stannous chloride should contain not less than 98.0 percent and not more than 102.2 percent of SnCl₂·2H₂O and limits such impurities as arsenic, iron, and other heavy metals.

In the food industry stannous chloride is used in amounts ranging from 0.002 to 0.0008 percent (equivalent to about 0.001 to 0.0004 percent or 10 to 4 ppm of tin) in the following categories of foods arranged in decreasing order of content: processed vegetables, non-alcoholic beverages, and processed fruits (13).

The total use of stannous chloride in U.S. foods increased about sevenfold between 1960 and 1970 (13). However, there is no information available to the Select Committee to indicate whether the added tin content of the foregoing food categories changed significantly during that period.

In 1953 the United Kingdom Food Standards Committee reduced the permissible limit of tin in canned foods from 286 ppm to 250 ppm. The original figure had been set in 1908 (14).

In 1971, the Joint FAO/WHO Expert Committee on Food Additives confirmed its previous evaluation that no acceptable daily intake figure for elemental tin and stannous chloride could be assigned, concluding that "there was no need to depart from the limits set by good manufacturing practice." However, the report continued, "further assessment will be needed when the results of work in progress become available" (15). There have been no subsequent reports on tin from that committee.

III. CONSUMER EXPOSURE DATA

A comprehensive survey by a National Research Council subcommittee has provided information on the possible daily human intake of stannous chloride in the total diet, as shown in Table I for individuals in various age groups (13). The Select Committee has converted these figures to possible intakes per kg of body weight.
Table I

Possible Daily Intake of Stannous Chloride

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total intake, mg</th>
<th>Intake, mg per kilogram of body weight*</th>
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<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Maximum</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>0.095</td>
<td>0.231</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>1.176</td>
<td>3.100</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>2.249</td>
<td>4.865</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>3.899</td>
<td>8.193</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (16) and the following estimated weights of infants by age groups: 0-5 months, 5 kg; 6-11 months, 8 kg; and 12-23 months, 11 kg (17).

The range of daily intake of stannous chloride for the 2-65+ age group indicated in Table I, amounts to about 1.9 to 4.1 mg of tin.

These daily intake figures should be considered in respect to the total amount of stannous chloride reported to be added to processed food. The NRC subcommittee survey (13) has estimated the amount of stannous chloride used in foods in 1970 by the companies responding to be approximately 40,581 pounds (18,446 kg) and has also estimated that this amount represented about 60 to 70 percent of the total quantity used by the entire food industry. Assuming 60 percent recalculated to 100 percent and a U.S. population of 210 million, this would supply enough stannous chloride to provide, on the average, 0.40 mg per person per day, a figure that is less than most of the figures indicated in Table I. For this reason the Select Committee considers the figures
in Table I as moderate overestimates of the amount of added stannous chloride present in the diets of the four age groups. The NRC subcommittee has also recognized the likelihood that their intake estimates are overstated.*

IV. BIOLOGICAL STUDIES

The oral LD$_{50}$ of stannous chloride for mice has been reported as 215 mg per kg (18), and 250 mg per kg (19). After oral intubation of 1000 mg per kg practically all animals exhibited premortal signs within 8 hours and were killed to prevent any postmortem influence on the pathological and histological findings (18). Autopsy revealed necrosis of the liver and spleen and thrombi in the hepatic portal veins.

The lethal dose of stannous chloride administered intramuscularly for 6 days was reported to be 40 to 60 mg per kg per day, or a total of 240 to 360 mg per kg, in the mouse, guinea pig, and rabbit. Death was accompanied by convulsions, dyspnea, and paralysis. Oral administration of about 200 mg per kg caused severe and occasionally fatal intestinal disorders in dogs (20).

In one long-term feeding study involving 108 mice receiving 5 ppm of stannous chloride in the drinking water from weaning to natural death, tin accumulated in the spleen, but no toxic effects were observed and the median life span was not affected (21).

In rats, 5 ppm of tin as stannous chloride in the drinking water over the lifespan of the animals did not affect the growth rates significantly or the serum cholesterol levels (22). The longevity of the females appeared to be reduced, but because of the experimental difficulties in studying longevity, this effect was not attributed to the small amount of stannous chloride ingested.

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (13). 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 of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
A series of experiments on mice showed no differences in weight gain in animals fed 1000 or 5000 ppm of tin as sodium chlorostannate in the drinking water or 5000 ppm of tin as stannous oleate in the diet over a period of a year (14).

De Groot et al. (23) have reported that anemia in rats resulting from feeding of tin salts and a low dietary level of iron, may be due to inhibition of hematopoiesis, possibly by impairing intestinal absorption of iron. The no-effect level of tin salts in diets containing liberal amounts of iron was found to be 0.1 percent, equivalent to about 22 mg of tin per kg per day.

Daily intravenous injections of 28 mg of tin as "Stanoxyl" for a week into each of two men in a metabolic study led to no unusual physiological effects (24). From 52 to 75 percent of the dose of tin was excreted in the urine.

A case was reported in 1963 of an infant with a complete agenesis of the right hand, born of a mother who had taken 3 taenifuge pills a day for 5 days during her early pregnancy (25). Each pill contained 60 mg of metallic tin and 60 mg of tin oxide. Also, a dose of 250 mg of pyridoxine was taken each day for 3 days during the same period. The authors speculated whether the pyridoxine might have complexed with the tin to form a teratogenic substance. No confirming report has been found.

Gastrointestinal disorders among 38 women were ascribed by public health officials to a fruit punch that contained 2000 ppm of tin (26). The high tin content presumably resulted from improper storage in a 5-gallon milk can. The onset of illness was abrupt, beginning with a bloated feeling, followed by overwhelming nausea, stomach cramps, vomiting, and diarrhea. No fatalities occurred.

The few reported observations concerning the possible carcinogenicity of stannous chloride and elemental tin have been negative. Mice fed a diet containing 0.28 µg tin per g of food in the form of stannous chloride stabilized with ascorbic acid, showed no significant differences in the incidence of tumors as compared with the controls (27). Rats given 5 ppm tin as stannous chloride in their drinking water over their lifespan showed no carcinogenic signs (22). A lower incidence of malignant lymphoma, hepatoma, and pulmonary adenoma was noted in mice receiving 1000 or 5000 ppm tin as sodium chlorostannate in the drinking water or 5000 ppm tin as stannous oleate in the diet for a year as compared with control mice (14). The subcutaneous implantation of tin foil failed to induce tumors in rats, in contrast to sarcomata produced by some other metals (28).
However, one experiment suggests caution; three malignant tumors were observed in 30 rats which were fed a diet containing 2 percent sodium chlorostannate and survived for a year or more (29). No neoplasms were observed in 27 rats which survived a year on the diet containing initially 1 percent, then 0.5 percent stannous 2-ethylhexoate. The authors regarded the three tumors as probably without significance in the light of the small number of animals involved and the complexity of studying the possible carcinogenic effect of ingested substances.

When injected into the yolk sacs of 4- and 8-day-old chick embryos, stannous chloride showed no teratogenic effect (30). This was in contrast to the injurious effects caused by salts of nine other elements included in this comprehensive study of 53 elements. Oral intubation of up to 50 mg stannous chloride per kg of body weight for 10 consecutive days (day 6 through day 15 of gestation) in pregnant mice and rats and for 5 consecutive days (day 6 through day 10 of gestation) in pregnant hamsters, showed no observable effect on nidation, maternal survival, fetal survival, and tissue abnormalities of the fetus (31).

Stannous fluoride is used widely in preventive dentistry to control dental caries (32). There are no reports of toxic effects after this local application.

V. OPINION

Feeding tests of stannous chloride on several species of animals, including observations on carcinogenicity and teratogenicity, at dosage levels significantly above those present in the daily diet, did not reveal evidence that this compound is harmful. Human experience gained after the accidental ingestion of large amounts of tin containing materials or experimental intravenous injection of such materials reinforces this conclusion.

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

There is no evidence in the available information on stannous chloride that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


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