EVALUATION OF THE HEALTH ASPECTS OF SODIUM THIOSULFATE AS A FOOD INGREDIENT

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Prepared for

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

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
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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) or prior sanctioned food substances being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 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 to the public 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.

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| CONTENTS |
|----------|----------|
| I.       | Introduction  | 1 |
| II.      | Background information | 2 |
| III.     | Consumer exposure data | 3 |
| IV.      | Biological studies | 3 |
| V.       | Opinion | 7 |
| VI.      | References cited | 8 |
| VII.     | Scientists contributing to this report | 12 |
I. INTRODUCTION

This report evaluates the health aspects of using sodium thiosulfate 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 March 24, 1975 (40 FR 13016 and 13017) 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 sodium thiosulfate as a food ingredient. The Select Committee received no requests for such a hearing on sodium thiosulfate.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in 21 CFR 121.1, revised April 1, 1974 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 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 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

*The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 sodium thiosulfate 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

Sodium thiosulfate, \( \text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O} \), is a synthetic, crystalline, efflorescent, water-soluble compound with antioxidant properties. It slowly decomposes in acid solution to sulfur and sulfite (1). Food grade sodium thiosulfate should assay not less than 99 percent \( \text{Na}_2\text{S}_2\text{O}_3 \) after drying. It may contain not more than 3 ppm of arsenic; not more than 20 ppm of heavy metals (as Pb); not more than 10 ppm of lead, and not more than 30 ppm of selenium (2).

Sodium thiosulfate is Generally Recognized as Safe (GRAS) as a stabilizer of potassium iodide in iodized salt at a maximum level of 0.1 percent of the salt, as a sequestrant in foods, and as a constituent of paper packaging materials that may migrate to food (3). The Select Committee has no information to indicate that it is now used in foods other than as a sequestrant in alcoholic beverages. Sodium thiosulfate has numerous non-food uses including intravenous injection with sodium nitrite in the treatment of cyanide poisoning, as a bleaching agent for paper pulp, as a photographic fixative, and as a mordant in the textile industry (4, 5).

According to the survey report of a subcommittee of the National Research Council, sodium thiosulfate was first reported to be used in foods in the United States in 1930. The total quantity used in 1970 was about one-third of that used in 1960. It is used at a level of \(<0.0001\) percent in alcoholic beverages (6).
III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee has reported no estimates of consumption of sodium thiosulfate by children and has estimated intakes for adults to be about 3 µg per day based on the weighted mean of the usual percentage used in alcoholic beverages, and other factors (6). This amounts to about 0.05 µg per kilogram of body weight for a 60 kg man. Similar intake estimates can be derived from the annual poundage data also indicated in the NRC subcommittee report (6). In 1970 some 1,230 pounds (559 kg) of sodium thiosulfate representing, according to the NRC subcommittee, about 60 percent of actual usage, were utilized by the food industry. Recalculating this amount to 100 percent and assuming a population of about 210 million, the per capita consumption of sodium thiosulfate is estimated to be 12 µg per day.

IV. BIOLOGICAL STUDIES

Absorption and metabolism

Sodium thiosulfate is a normal constituent of human body fluids and is excreted in the urine of man and higher animals (7). Quantitative studies have demonstrated the consistent presence of 2 to 17 mg of thiosulfate sulfur in 24-hour urine specimens of healthy young adults. Variations in excretion of thiosulfate are related to the extent of protein metabolism, activity of the intestinal flora, and the sulfur-amino acid content of the diet. The sulfur-containing amino acids of dietary protein are the source of the endogenous thiosulfate pool (8). In the rat, 33 percent of the radioactive sulfur of D, L-[35S] cystine, administered subcutaneously (0.8 mg of radioactive cystine and 200 mg of nonradioactive thiosulfate per rat), was excreted in the urine as thiosulfate (9). Rat liver and kidney extracts catalyzed the oxidation of sulfide to thiosulfate (10) and/or the conversion of sulfite and β-mercaptopyruvate to thiosulfate (11).

Orally administered thiosulfate that is absorbed from the gastrointestinal tract is excreted in the urine unchanged or after oxidation to sulfate. After oral administration of sodium thiosulfate (about 800 mg per kg of body weight), 23 percent was excreted as sulfate in the urine of rats (12). From 5 to 70 percent of an oral dose of sodium thiosulfate is considered to be absorbed from the gastrointestinal tract of man and the remainder to be excreted in the feces (13). When a human subject received a 10 g oral dose of sodium thiosulfate (about 170 mg per kg), 80 percent appeared in the urine as sulfate within 48 hours, and about 5.5 percent was excreted unchanged. In the same series of experiments, after intravenous doses of
1 g of sodium thiosulfate, about 35 percent of the thiosulfate was excreted unchanged in the urine (14).

Three female dogs, trained for urine collection studies, received intravenous injections of doses of sodium thiosulfate that produced arterial plasma concentrations of 18 to 55 mg per 100 ml, without producing toxic effects (15). Because glomerular filtration of sodium thiosulfate occurs without appreciable tubular resorption, "thiosulfate clearance" can be used as a measure of the glomerular filtration rate, especially in acidotic conditions.

Animal studies

The intraperitoneal LD$_{50}$ of sodium thiosulfate for male mice has been reported to be 7.5 ± 0.75 g per kg (16).

Eight male rats were injected intramuscularly with 50 mg of sodium thiosulfate per day for 1 to 3 months. The dose, estimated to be about 125 mg per kg per day, produced histologic evidence of atrophy of the glomeruli with diminished number of cells, dilatation of the proximal tubules and the glomerular capillaries, and eosinophilic infiltration of the capillaries in the loops of Henle of the kidneys. A decreased permeability of the capillary walls of the vasculature of the liver and an increased number of Kupffer stellate cells in the liver sinusoids were noted (17).

The antineoplastic properties of sodium thiosulfate were studied in a strain of albino mice that develops spontaneous sarcomas and pulmonary adenomas. The addition of 0.4 percent of ground, crystalline sodium thiosulfate to their diet, one week prior to challenging these mice with a single 0.9 mg subcutaneous injection of methylcholanthrene or ethylurethane (0.15 mg parenterally or 0.15 percent in the diet), halved the number of tumors as compared with control mice. No untoward effects of feeding a dose of sodium thiosulfate (estimated to be about 600 mg per kg per day) for four months were observed; the food intakes and body weights were similar to those in the control animals. A similar anticarcinogenic effect was noted when mice were fed 0.4 percent thiosulfate and 0.015 percent $p$-dimethylaminoazobenzene in their diet (18). A delay in the appearance of methylcholanthrene-induced tumors was produced in white rats injected subcutaneously every three to six days for four months with 0.01 to 0.02 g of sodium thiosulfate (about 80 to 160 mg per kg of body weight) (19, 20).

In another study, 3 g of sodium thiosulfate pentahydrate per kg of body weight was administered intravenously over a 20-minute period to five mongrel dogs. Metabolic acidosis, hypoxemia, hypernatremia, electrocardiographic changes (T-wave flattening and inversion) and arterial and venous pressure increases were noted. Four of the dogs survived the
experimental period and two were alive 24 hours thereafter. These investigators concluded that the metabolic and hemodynamic effects were due to the sodium loading. In other experiments in this study, dogs tolerated a dose of 1.5 g of sodium thiosulfate pentahydrate per kg of body weight administered intravenously over a 30 minute period (21).

Various biochemical effects have been reported following the administration of sodium thiosulfate. These include: an increase in the glutathione level in blood following the parenteral administration of 2.5 to 5 g of sodium thiosulfate per kg of body weight to pigeons (22), an inhibition of the activity of streptomycin in vitro (23), an increase of 30 to 40 percent in the activity of histaminase and cholinesterase in humans receiving therapeutic injections (2 g) of sodium thiosulfate (24), an antianaphylactic effect in guinea pigs administered 50 mg of sodium thiosulfate intraperitoneally at least 20 minutes prior to challenge with horse serum (25), and an anticoagulant effect on human blood in vitro and in vivo after therapeutic injection (100 ml of a 6.5 percent solution) of sodium thiosulfate (26).

Sodium thiosulfate was found to cause no mutagenic effects when tested by the following procedures and in the doses indicated: host-mediated assay in mice, 50 to 5000 mg per kg orally; observation of aberrations in bone marrow metaphase chromosomes in the rat, 50 to 5000 mg per kg orally; observation of aberrations in anaphase chromosomes of human embryonic lung cells in tissue culture, 8 to 8000 micrograms per ml; dominant lethal assay in rats, 50 to 5000 mg per kg orally (27).

Oral intubation of maximum daily doses of 550 mg sodium thiosulfate per kg of body weight to pregnant mice on day 6 through day 15 of gestation, or 400 mg per kg to pregnant rats on day 6 through day 15 of gestation, or 400 mg per kg to pregnant hamsters on day 6 through day 10 of gestation, had no effect on nidation, maternal or fetal survival, or fetal development (28).

In teratogenicity studies in avian embryos, sodium thiosulfate did not significantly increase mortality at a dose of 220 mg per kg when injected into the air cell at 0 hours, but did significantly increase embryo deaths at a dose of 556 mg per kg. When injected into the air cell after 96 hours of incubation, a significant increase in embryo mortality was observed at doses of 110 mg per kg and above. When injected into the yolk at both 0 hours and after 96 hours of incubation, sodium thiosulfate was toxic only at a dose of 556 mg per kg. A statistically significant increase in the incidence of abnormalities occurred at doses of 110 mg per kg and above after air cell injection. The dose relationship was linear only in treatments at 0 hours and the data yielded an estimate of 77, 503 mg per kg as the level which would produce a 50 percent incidence of abnormal embryos (29).
It is to be noted in connection with the mutagenic and teratogenic studies reported above, that estimated average daily human consumption of sodium thiosulfate added to food is of the order of 0.05 to 0.2 micrograms per kg.

**Human studies**

The toxicity of sodium thiosulfate has been studied in connection with its use as a poison antidote. Two volunteers took 200 and 250 g intravenously over a period of two weeks; no changes were observed in blood morphology or biochemistry in the ensuing four months. Patients receiving a single injection of 50 ml of a 50 percent solution of sodium thiosulfate (about 400 mg per kg body weight) showed no significant changes other than a prolonged blood clotting time. Patients receiving lower dosages did not exhibit any hematologic changes or blood chemical abnormalities (26). However, twelve patients who ingested relatively low doses (about 50 mg per kg per day) of sodium thiosulfate for 1 to 2 weeks developed a moderate degree of cyanosis. It was concluded that the unsaturation of hemoglobin was caused by a decreased affinity of hemoglobin for oxygen and not by deterioration of the red call hemoglobin (30).

Sodium thiosulfate has been used to measure extracellular water in women by the intravenous injection of sodium thiosulfate in a 6.7 percent solution (about 73 mg sodium thiosulfate per kg of body weight) over a period of 8 to 14 minutes. In three studies, 26 patients received this treatment; no comment was made concerning any untoward effects (31).

In another study, forty patients with multiple sclerosis received 50 to 70 intravenous doses, over a period of several weeks. Doses ranged from 10 to 33 mg sodium thiosulfate per kg of body weight. No untoward effects related to the administration of the thiosulfate were reported, but minor to significant improvement was reported in 95 percent of the patients (32). One 45-year-old patient received a total of 22.5 g of sodium thiosulfate (presumably six injections intravenously) for treatment of eczema. Edema of the legs and feet resulted and the medication was discontinued (33).

An examination was made of the effects of daily intravenous doses of 2 g sodium thiosulfate in cancer patients. While various effects on several types of cancer were noted, no toxic effects were considered attributable to the sodium thiosulfate administered (34).
V. OPINION

Thiosulfate is a normal constituent of human body fluids, and is a metabolite of dietary constituents. Experimental animal studies show that sodium thiosulfate is well tolerated. All investigations in which it has been administered to normal and diseased persons, clearly show that very large therapeutic doses cause no adverse effects. The reported use of sodium thiosulfate as a stabilizer of potassium iodide in iodized salt, as a sequestrant in alcoholic beverages, and as a substance that may migrate to foods from packaging materials, results in human exposure far below that needed to produce untoward biological effects.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on sodium thiosulfate 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 the future.
VI. REFERENCES CITED


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