EVALUATION OF THE HEALTH ASPECTS OF HYPOPHOSPHITES
AS FOOD INGREDIENTS

1977

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 concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, 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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Life Sciences Research Office
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I. INTRODUCTION

This report concerns the health aspects of using hypophosphites as food ingredients. It 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 1973. 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 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; recent literature searches by the Toxicology Information Response Center, Oakridge, Tennessee; 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, an announcement was made in the Federal Register of June 7, 1977 (42 FR 29105-29107) 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 hypophosphites as food ingredients. The Select Committee received no requests for such a hearing on hypophosphites.

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 the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.130] 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. These sections of the Code also indicate 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 (2) recognizes further that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-228 544/3) 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. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select 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 hypophosphites 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

Four hypophosphites are considered in this report: manganese hypophosphate, Mn(H₂PO₄)₂ which is listed as GRAS for use as a nutrient or dietary supplement [21 CFR 182.5458] (2) and the calcium, potassium and sodium (NaH₂PO₄) salts which are included in a listing of substances presumed to be GRAS but not published (3). Hypophosphate salts are relatively soluble in water; aqueous solutions of the Ca, Mn, Na and K salts are neutral or nearly so (4).

The Food Chemicals Codex provides specifications for food-grade manganese hypophosphate and limits impurities of arsenic, heavy metals (as lead), and lead to not more than 3, 40, and 10 ppm, respectively (5). No food-grade specifications are given in the Codex for the calcium, potassium and sodium salts.

Various hypophosphite salts were once used as constituents of tonics and to treat tuberculosis and anemias. These salts also have been employed as dietary supplements as sources of metals, and calcium hypophosphate has been used to treat a deficiency of calcium (4, 6, 7). With the development of more specific methods for treating tuberculosis and the anemias, the hypophosphites appear to be rarely, if at all, used for these purposes today.
III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee surveyed manufacturers in 1970 by questionnaire concerning the level of addition of GRAS substances to foods and the poundage used (8). These hypophosphites were included in the survey but no food manufacturer indicated that any were being used. In the conduct of this evaluation inquiries directed to the industry revealed no current food uses for the foregoing four hypophosphites (9). In April, 1973 (10) FDA proposed removal of manganese hypophosphite, among other substances, from the GRAS list. Two requests (11,12) were made for retention of manganese hypophosphite on the basis that it was being or might be used in commercial feed and human food products. The proposal to remove all of these substances, including manganese hypophosphite, from the GRAS list was later rescinded by FDA (13).

IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

Hypophosphites given orally or parenterally are rapidly excreted in the urine. In 1902, Panzer (14) fed single 1 g doses (100 mg per kg of body weight) of calcium hypophosphite to a dog. He could detect no tissue concentrations of hypophosphite six hours after administration except in the stomach and intestines; but the urine gave a positive test after 15 minutes and continued positive until the next day. Panzer took 1 g (about 16 mg per kg) of calcium hypophosphite himself and found his urine gave a positive test for hypophosphite after one hour, and continued to be positive for another 24 hours. A woman given 5 g of sodium hypophosphite (0.5 g twice daily for five days, about 16 mg per kg daily) excreted the total dose as hypophosphite in the urine (15).

In rabbits given sodium hypophosphite, either subcutaneously or intravenously, 81 to 84 percent of the dose (500 and 1,000 mg per kg) was excreted as hypophosphite within three days (16).

Two cows (one pregnant) were given intravenously 0.3 moles (about 100 mg per kg) of hypophosphite salts, half calcium and half sodium, and each experiment was repeated three or four times (17). Since at least two-thirds of the doses were excreted as hypophosphite in the urine each time, the authors concluded that hypophosphites were not used as a source of phosphate by the cows. Half of the hypophosphite excreted appeared within two hours, and a diuretic effect was noted during the period of hypophosphite excretion.
Acute toxicity

Studies on the acute toxicity of sodium hypophosphite and sodium phosphite were reported by Engel in 1924 (18). He found hypophosphite to be less toxic than phosphite. The subcutaneous injection of 0.1 g of sodium phosphite killed frogs in a few hours, 0.15 to 0.20 g (about 7.5 g per kg) killed mice, and 0.2 to 0.5 g (about 500 mg per kg) killed guinea pigs. Similar doses of sodium hypophosphite failed to kill frogs and guinea pigs; however, 0.2 g killed mice. Other workers (19) measured the acute toxicity of sodium hypophosphite injected intraperitoneally in male Swiss albino mice. They calculated the LD₅₀ (30 days) to be 1,584 mg per kg.

Short-term studies

Two studies deal with the effect of feeding hypophosphites to rats. Takahashi (20) placed 60 g male white rats on a phosphorus deficient basal diet containing 0.055 percent phosphate as P₂O₅ (about 20 mg P per kg body weight) from meat sources. Calcium level in the basal diet is estimated to have been about 3.2 mg per g diet (500 mg per kg body weight). He added various concentrations of hypophosphorous acid to the basal diet and found no growth over a period of four months at concentrations up to 0.5 percent (about 800 mg per kg); at 1.5 to 2 percent levels (2400 to 3200 mg per kg) the animals died within a few days. Presumably hypophosphorous acid is not oxidized and used as a source of phosphate to any appreciable extent under these experimental conditions. However, Meyer and Greenberg (21) in evaluating calcium hypophosphite as a calcium source found that rats showed good growth on diets containing 0.43 to 4.3 percent calcium hypophosphite (about 430 to 4300 mg per kg body weight). Groups of 7 to 8 young Sprague-Dawley rats were fed for 25 days a basal ration containing 0.33 percent phosphorus (330 mg per kg) and 0.03 percent calcium (30 mg per kg) supplemented with 0.43, 2.1 or 4.3 percent calcium hypophosphite; 0.43 percent each of calcium and sodium hypophosphites; 0.43, 3.0 or 4.3 percent calcium hypophosphite, each with added nucleic acid to equalize phosphorus and calcium levels without the addition of a phosphate salt; 0.43 percent dibasic calcium phosphate; 10.8 percent calcium gluconate or 2.5 percent calcium carbonate as alternate calcium sources. Growth was not depressed by calcium hypophosphite, and assimilation of calcium was about the same whether supplied by hypophosphite, gluconate, phosphate or carbonate. Because the phosphorus level in the basal diet was sufficient to prevent phosphorus deficiency, no conclusion was reached concerning utilization of phosphorus in hypophosphites.

No direct information on the biological effects of manganous hypophosphite was available to the Select Committee. However, manganese is an essential nutrient and considerable information has been reported on the biological effects of manganous ion. This information has been reviewed by the Select
Committee in an evaluation of other manganous salts as food ingredients (22). It was concluded that the available information indicates a wide margin exists between present intake levels of manganous ion and levels that have been reported to produce harmful effects. This information can be extended to manganous ion in manganous hypophosphite. No reports were available on long-term animal toxicity, carcinogenicity, teratogenicity, or mutagenicity of hypophosphites.

V. OPINION

The hypophosphites do not appear to be currently used as ingredients in foods as indicated by a survey of the food industry conducted by a National Research Council subcommittee in 1970 and more recent information obtained from industry by the Select Committee. They had limited medical use many years ago in tonics and as therapeutic agents but appear to be no longer used for these purposes.

The acute toxicity of hypophosphites is relatively low; injected intraperitoneally in mice, the LD$_{50}$ (30 days) for the sodium salt was 1.6 g per kg body weight. Calcium and sodium hypophosphites given orally or parenterally to experimental animals and man are rapidly excreted as hypophosphite in the urine. It is the opinion of the Select Committee that potassium hypophosphate is comparable to the sodium salt in excretion and toxicity.

Although animal feeding experiments indicate that the phosphorus in hypophosphites is not biologically available, no adverse effects were reported in young rats fed diets containing calcium hypophosphite (up to 4.3 g per kg). Growth and calcium assimilation were as good as observed on diets containing salts recognized as good sources of calcium.

Although no reports were available on the biological effects of manganese hypophosphite, an evaluation of the health aspects of other manganous salts by the Select Committee has found no evidence that would indicate a hazard from manganous hypophosphite if used as a nutrient or dietary supplement.

In view of the foregoing the Select Committee concludes that:

There is no evidence in the available information on manganous, calcium, potassium or sodium hypophosphite that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used in the manner now practiced and at the levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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Report submitted by:

October 28, 1977

Date

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