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Hypophosphite: A Review

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ABSTRACT

Efforts to find a suitable sparing agent for nitrite in cured meat products have brought sodium hypophosphite (SHP) to the attention of the scientific community. Hypophosphites were introduced in the mid 1800s as a cure for tuberculosis, but recent reports have suggested SHP could possess antibotulinal and antimicrobial properties. Sodium hypophosphite has good potential as an antimicrobial food ingredient and it is Generally Recognized As Safe (GRAS). This review summarizes SHP chemistry, history, toxicology, regulatory status, applications, and antimicrobial properties.

The hypophosphites were introduced into medicine by Churchill (*11*) in the 1850s as a remedy for pulmonary tuberculosis. He conceived the theory that tuberculosis was caused by insufficient oxygen in the tissues and sought an agent that would increase oxidation in these tissues. He proposed the use of hypophosphites on the assumption that phosphorus exists in an organism in a lower oxidation state than phosphate. This form of phosphorus acted as an initiatory agent in attracting and utilizing the inspired oxygen (*1*).

On the basis of Churchill's theory, hypophosphites were used extensively in pharmaceutical preparations, elixirs, and tonics. Subsequent investigations began to disprove his theory, as many unfavorable reports soon appeared in medical journals (*23*). In the same year that Churchill proposed his theory, two reports (*13,51*) concluded that hypophosphites were worthless for the treatment of tuberculosis. Similarly, Quain (*37*) reported the hypophosphites had no favorable effect on his patients suffering from tuberculosis. Quain also noted that he found none of the other physiological effects claimed by Churchill in any of his patients. Use of hypophosphites in tonics decreased as evidence mounted against the hypophosphites as a remedy and the causes of tuberculosis became clear.

Efforts to find a suitable sparing agent for nitrite in cured meat products again brought hypophosphites to the attention of the scientific community 130 years later. A nitrite-sparing agent would continue to provide protection against botulism but allow lower nitrite levels with decreased potential for nitrosamine formation. Reports by Pierson et al. (*34,35*), Seward et al. (*40*), Leifer (*22*), and Wood et al. (*57*) have shown sodium hypophosphite (SHP) to possess some antibotulinal properties. Recent findings by Rhodehamel (*38*) and Rhodehamel and Pierson (*39*) have shown SHP to have antimicrobial properties against selected foodborne pathogenic and spoilage bacteria. The purpose of this paper is to review the chemistry, toxicity, regulatory status, and the recent developments relating to SHP use as an antimicrobial food preservative.

THE HYPOPHOSPHITES

Physical and chemical properties

Sodium hypophosphite $Na(H_2PO_2)$ is one of the alkali metal salts of hypophosphorous acid (H_3PO_2). Lithium hypophosphite $Li(H_2PO_2)$ and potassium hypophosphite $K(H_2PO_2)$ are the other known alkali metal hypophosphites.

The alkaline earth metal hypophosphites include magnesium hypophosphite $Mg(H_2PO_2)$, calcium hypophosphite $[Ca(H_2PO_2)_2]$, strontium hypophosphite (SrH_2PO_2), barium hypophosphite $Ba(H_2PO_2)$, and manganese hypophosphite $[Mn(H_2PO_2)_2]$ (*53*).

Table 1 shows some physical and chemical properties of sodium hypophosphite.

Hypophosphorous acid is a strong monobasic acid that has only one hydrogen that can be substituted by a metal ion. The acid has a pK equal to 1.1. This pK value is much lower than any of the major organic preservatives in use today. At a pH of 1.1, 50% of the acid is undissociated and in almost all food products, hypophosphorous acid exists almost exclusively in the dissociated form.

Hypophosphorous acid is made commercially by treating white phosphorus with a boiling slurry of calcium hydroxide (*12*). In the laboratory, barium hydroxide is more commonly used (*31*). The resulting mixture is filtered to remove calcium phosphite, and the calcium hypophosphite is obtained by evaporation and crystallization. Either the sodium salt or the free acid can be obtained by treatment with sulphuric acid or sodium sulfate. An alternative laboratory preparation is to pass phosphine gas into an agitated aqueous suspension of iodine until the color of the iodine is discharged. Distillation under reduced pres-

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TABLE 1. *Physical and chemical properties of sodium hypophosphite.*[a]

Molecular weight[b]:	106
Physical state:	Crystalline solid
Color:	White
Odor:	None
Taste:	Saline
Melting point:	Decomposes violently with evolution of phosphine
Solubility:	Freely soluble in water, glycerol, alcohol; insoluble in ether
pH:	Aqueous solution neutral

[a](26)
[b]Includes one water of hydration.

sure removes hydrogen iodide and water, leaving pure hypophosphorous acid as the residue (*31*).

Nutritional aspects and toxicity

At the end of the nineteenth and beginning of the twentieth centuries, there was widespread use of hypophosphites in dietary supplements and medicinal tonics. This continued in spite of the mounting evidence that began to appear against hypophosphites. Numerous investigators (*1,9,23,24,32,33*) reported that when hypophosphites were given orally or intraperitoneally to humans or animals, nearly the entire amount was excreted in the urine within 24 h. The scientific community concluded since hypophosphites pass through the body rapidly while undergoing little change, there was no evidence that hypophosphite exerted any physiological effect (*23*). As scientific knowledge of the causes and treatment of tuberculosis improved, use of hypophosphite tonics decreased.

As the evidence mounted against hypophosphite use in medicinal tonics, there were still questions of their worth as dietary supplements. Berg (*8*) reported since hypophosphites were excreted rapidly and unchanged, they were useless as a means of adminstration of phosphorus. Results from feeding studies in pigs (*16*), rats (*46*), and cows (*55*) supported Berg's assumption. When animals were fed phosphorous deficient basal diets supplemented with various phosphorous compounds, those animals receiving either calcium or sodium hypophosphite behaved as if they had received no phosphorus at all.

In contrast, Sten'Kin (*45*) studied the effect of phosphorus supplements fed to calves. All phosphorus-containing supplements used (including calcium hypophosphite) increased food utilization and weight gain. However, he noted the monobasic and dibasic sodium phosphates showed a greater effect than calcium hypophosphite.

Thus, with the exception of Sten'Kin's report, the therapeutic value of hypophosphites has proven to be insignificant, since the bioavailability of phosphorus in hypophosphite is very low. Even if the bioavailability of phosphorus in the hypophosphites is low, they have been thought of as a convenient means of administering cations (such as calcium in calcium hypophosphite) in the salt (*2*).

Massol (*24*) postulated earlier that calcium hypophosphite taken orally is not altered in the stomach but combines in the intestines with phosphates from foods. Insoluble tricalic phosphate is formed and eliminated in the feces. Sodium hypophosphite remained in solution and is eliminated in the urine. Thus, calcium hypophosphite does not provide any available calcium to the patient. Massol provided no experimental evidence in support of his theory. In contrast to Massol's speculation, Meyer and Greenberg (*27*) evaluated calcium hypophosphite as a calcium source. They concluded the calcium of calcium hypophosphite was well utilized.

The health aspects of hypophosphites as food ingredients were evaluated in 1977 by the Federation of American Societies for Experimental Biology (*15*). They concluded hypophosphites have low acute toxicity. An LD_{50} (30 d) for mice injected intraperitoneally with sodium hypophosphite is 1.6 g/kg body weight. Calcium and sodium hypophosphite when taken either orally or parenterally are rapidly excreted as hypophosphites in the urine. Finally, although the bioavailability of phosphorus in hypophosphites is low, no adverse effects were found when man and animal were fed hypophosphites. Similarily, Hooker Chemical Corporation's Data Sheet (*3*) on sodium hypophosphite indicates there are no adverse skin, eye, or respiratory reactions known.

Regulatory status of sodium hypophosphite

Prior to August 1982, manganese hypophosphite was listed as Generally Recognized As Safe (GRAS) for use as nutrient or dietary supplement in Title 21 of the Code of Federal Regulations (CFR) 182.5458. The Food and Drug Administration (FDA) in 1961 issued an opinion letter saying that calcium, potassium, and sodium hypophosphite were GRAS (*5*).

Manufacturers were surveyed in 1970 by a National Research Council subcommittee concerning the use, level of addition, and estimated annual poundage of GRAS substances. The hypophosphites were included in the survey, but no food manufacturer indicated that they were currently in use (*15*). For this reason, FDA in April 1973 proposed removal of manganese hypophosphite, among other substances, from the GRAS list.

Two letters were received by the Hearing Clerk of the FDA requesting retention of manganese hypophosphite GRAS status on the basis that it was or might be used in commercial feed and human food products. Subsequently, the proposal to remove manganese hypophosphite was rescinded by the FDA in July of the same year (*15*).

The FDA on October 10, 1978, again proposed revoking the GRAS status of manganese, calcium, sodium, and potassium hypophosphites, on the grounds there was no evidence of direct use in foods. The FDA said it would reconsider its position if information was submitted indicating direct use in foods, levels of addition, intended technical effects, and foodgrade specifications (*4*).

In response to the FDA's proposal to revoke GRAS status of sodium hypophosphite, Beecham Products provided information on the level of use, annual poundage

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used, and estimated intake of sodium hypophosphite based on the recommended dosage of cod-liver oil. Beecham Products revealed that sodium hypophosphite has been used in this product since early in the century and serves as an emulsifier or stabilizer. On August 31, 1982, the FDA affirmed the GRAS status of sodium hypophosphite (CFR 184.1764), and as proposed by the agency, revoked the GRAS status of manganese hypophosphite (CFR 182.5458) (*5*).

The third edition of the Food Chemicals Codex (*30*) lists specification for sodium hypophosphite and sets limits on impurities for arsenic, fluoride, heavy metals, and insoluble substances at not more than 3 μg/ml, 10 μg/ml, 100 μg/ml, and 1,000 μg/ml, respectively.

Applications of hypophosphites

Hypophosphites find application as reducing agents in electroless plating of nickel onto steel and plastics (*12,50,54*), especially for plating odd shaped objects and railroad tank cars. Sodium hypophosphite is oxidized to phosphite and supplies the two electrons that reduce the nickel ion (Ni^{+2}) to nickel metal (Ni^{+0}).

Hypophosphites have been used as antioxidants and stabilizers in pharmaceutical preparations (*7,25*), cod-liver oil (*28*), and shark-liver oil (*29*). Beecham Products, as previously mentioned, in responding to the FDA's proposal to remove sodium hypophosphite from the GRAS list, gave evidence that sodium hypophosphite serves as a stabilizer in cod-liver oil.

Shahidi et al. (*43*) studied the antioxidant effects of individual pickle ingredients in cooked meat stored in plastic bags at 4°C for 35 d. Lipid oxidation was measured using the 2-thiobarbituric acid (TBA) procedure. They found SHP at the 3,000 μg/ml level caused a slight decrease in TBA numbers compared to the control with no additives. When SHP (3,000 μg/g) was added to meat containing sodium chloride (2%), sucrose (1.5%), sodium ascorbate (550 μg/g), sodium tripolyphosphate (STPP - 3,000 μg/g), and dinitrosyl-ferrohemochrome (12 μg/g), the TBA numbers were not significantly altered. Reduction of SHP and STPP levels from 3,000 to 1,500 μg/g caused a marginal increase in TBA numbers after 35 d.

In U.S. patent 1,911,009, Woidich (*56*) described a process for controlling and accelerating meat pickling by the addition of hypophosphorous or phosphoric acids, or the salts of these acids to pickling salt mixtures. Calvert and Atkinson (*10*) reported a process where the hypophosphites are employed as plastic flow inducing agents in the preparation of a hydratable vegetable protein food product.

Other food related patents include, French patent 2,073,233 (*19*) which describes a vitamin E and calcium preparation for treating disorders of metabolism and growth. In French patent 2,119,882 (*36*), a calcium hypophosphite, ascorbate, and protein mixture is used as an appetite stimulant for treatment of retarded growth in children and anorexia. French patent 2,265,677 (*59*) describes use of calcium hypophosphite as a direct supplement to "living creatures" having deficiency of calcium and phosphorus. U.S.S.R. patent 376,388 (*20*) describes the preparation of synthetic fat substitutes from hypophosphites. Japan Kokai No. 71,508 (*58*) lists a procedure for the purification of palm oil by treatment with hypophosphites.

Hypophosphite as an antimicrobial inhibitor

Recently, a new potential application for SHP as an antimicrobial preservative in foods has been investigated. Prior to 1981, there were few reports describing the antimicrobial properties of SHP. Van Dolah and Christenson (*52*) investigated the effect of various compounds on the activity of streptomycin on *Escherichia coli, Staphylococcus aureus,* and *Bacillus subtilis*. They found when streptomycin was reduced by SHP or other reducing agents the bacteriostatic effectiveness against *B. subtilis* was decreased. Sjostrom (*44*) found the addition of 0.001-0.005% SHP to skim milk at curdling impeded *Enterobacter aerogenes* fermentation in cheese for the first few critical days, but then a late fermentation started.

Seward et al. (*40*) studied the effects of potassium sorbate and other antibotulinal agents on germination and outgrowth of *Clostridium botulinum* type E spores. They reported that SHP, at the concentrations tested, did not inhibit germination and outgrowth of *C. botulinum* type E spores. However, 0.5% and 1.0% (wt/v) SHP led to aberrant cell development, defective cell division, and cell lysis. Similar morphological changes occurred with 1.0% and 2.0% (wt/v) potassium sorbate at pH 7.0 to 7.2, suggesting a similar mechanism of action with SHP. This is interesting since it suggests that when SHP is used as a sparing agent for nitrite the combined antimicrobial properties are effective, but the mechanism of action may be different for the two compounds.

There exists two reports in the literature of utilization of SHP by bacteria. Foster and Winans (*17*) reported they had isolated a pure culture of *Bacillus* sp. from Cape Canaveral soil samples capable of utilizing SHP as the sole source of phosphorous. They suggested that hypophosphite was oxidized to phosphate anaerobically and incorporated into cell components, probably via intermediates of the Embden-Meyerhoff pathway. In a similar report, Foster et al. (*18*) inoculated the *Bacillus* isolate in a phosphorus-free basal medium containing 175 μg/ml SHP. They reported the optimum concentration of hypophosphite was approximately 60 to 65 μg/ml. Higher concentrations resulted in reduced bacterial growth, suggesting that higher concentration of hypophosphite may be toxic to the organism.

Hypophosphite as an antibotulinal inhibitor

In recent years concern over the possible health hazards of nitrite and its reaction products has led to efforts to eliminate or reduce nitrite levels in cured meats. Subsequently, research to find suitable substitutes for nitrite and/or nitrite-free meat curing systems was undertaken (*22,34,35,40,41,42,43,57*). Initial research concentrated on finding compounds which could replace nitrite's antibotu-

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linal activity. Sodium hypophosphite was thought to have potential as an alternative to nitrite after it appeared to have a favorable toxicological evaluation, suitable concentrations necessary for *C. botulinum* inhibition, and the fact that like nitrite it was a reducing agent and a GRAS compound.

Currently, there are four U.S. patents for use of SHP to inhibit growth and toxin production by *C. botulinum*. In U.S. patent 4,282,260, Jadlocki and Thompson (*21*) described a process in which *C. botulinum* growth and toxin production are inhibited, and nitrosamine formation is reduced by adding 1,000-3,000 μg/g SHP and 40 μg/g sodium nitrite during smoked meat processing. Similarly, Thompson and Jadlocki (*47,48,49*) hold U.S. patents 4,277,507, 4,346,117, and 4,348,419 for smoked fish, bacon, corned beef, poultry, and comminuted meat products. In all applications the meat, poultry, or fish products have SHP as partial replacement for sodium nitrite to inhibit *C. botulinum*.

Pierson et al. (*34*) studied the effect of SHP alone and in combination with sodium nitrite on the inhibition of *C. botulinum* growth and toxin production in bacon. They found SHP to be an effective antibotulinal agent in temperature-abused bacon packs inoculated with *C. botulinum* type A and B spores. They reported that in nitrite-free bacon, the presence of 0.1% and 0.3% (wt/wt) SHP increased the time to first swell formation and decreased the number of toxic swells. All variables containing 40 μg/g nitrite and 0.05% to 0.3% (wt/wt) SHP delayed time to swell and toxin formation when compared to bacon containing only 40 μg/g nitrite.

Since bacon inoculated with *C. botulinum* will often become toxic before gas formation in the package, Pierson et al. (*34*) also sampled one group of packages for toxicity of nonswells during temperature abuse at 27°C. There were no toxic nonswells observed over the testing period in the variable where no nitrite and high concentrations of SHP were used, as well as the variables designed to test SHP as a sparing agent (40 μg/g nitrite and 0.1% or 0.3% SHP).

Prior to initiating the bacon studies, the authors examined whether there were any undesirable changes in cured pork containing hypophosphite. No differences in pH between variables both before and after heating were observed. Additionally, SHP did not alter the color or odor reactions of either the unheated or heated samples. Results from this study indicated that SHP could function as a sparing agent for nitrite and be used as an antimicrobial food preservative.

Leifer (*22*) studied the effects of SHP and sodium nitrite on the inhibition of growth and toxin production of *C. botulinum* in a model meat system. His results supported those of Pierson et al. (*34*) in that he found SHP alone or in combination with 50 μg/g sodium nitrite to be an effective antibotulinal agent. As the sodium chloride concentration increased, SHP inhibition was enhanced. Similarly, at any one sodium chloride level, an increase in the SHP concentration reduced the rate of toxic swell formation.

Leifer (*22*) reported evidence that the hypophosphite anion is the responsible inhibitory agent, and the cations had no effect on SHP inhibition of *C. botulinum*. Addition of Fe^{+2}, Mn^{+2}, Zn^{+2}, and Mg^{+2} appeared to have no appreciable effect on SHP inhibition. The lack of a significant effect by Fe^{+2} supports Seward and his coworkers' (*40*) supposition that inhibition by SHP is through a different mechanism than that of nitrite.

Additionally, Leifer (*22*) found SHP was very stable to heat processing and subsequent storage at 27°C. This finding is consistent with an earlier report by El-Ahraf et al. (*14*) who found aqueous solutions of hypophosphites stored at room temperature to have a shelf-life of more than one year. This is important in that, unlike sodium nitrite, SHP's antibotulinal protection does not dissipate during the heat processing and shelf-life of a product.

Pierson et al. (*35*) determined the effectiveness of several potential inhibitors which could be used for delaying *C. botulinum* toxin formation in temperature-abused hot and cold processed smoked chub and sable. They concluded SHP exhibited some antibotulinal activity in smoked fish, but the overall effects were minimal. This suggests SHP may not be as an effective antibotulinal inhibitor in all foods and thus have limited use in some food systems.

Recent developments with hypophosphites

Another approach to the development of nitrite-free meat curing systems has been to utilize a multi-component curing system (*41,42,43,57*). The objective of these studies was to produce meat products that resemble ones with which consumers were already familiar. Each component or combination of components would be responsible for duplicating one of nitrite's multifunctional properties. Wood et al. (*57*) evaluated a number of nitrite-free model meat systems using compounds with reported antibotulinal properties and compared them to the antibotulinal effect of nitrite. Meat slurries with various cure combinations were inoculated with spores of *C. botulinum* types A and B, heat processed, and subsequently incubated at either 10°C and/or 27°C. They found the treatment containing 3,000 μg/g SHP most closely resembled the 150 μg/g nitrite control in its ability to prevent spore outgrowth and toxin production. SHP treatments delayed toxin production 14 d when samples were incubated at 27°C, while some samples remained toxin-free throughout the 30 d storage period. All other treatments, monoethyl fumerate, ethylene diamine tetracetic acid (EDTA), potassium sorbate, and tertiary butyl hydroquinone (TBHQ), were less inhibitory than SHP. They concluded their nitrite-free meat curing mixtures with SHP possessed a similar microbial stability to their nitrite-cured counterparts.

Rhodehamel (*38*) studied the potential of SHP to inhibit growth of *C. botulinum* and other gram-positive bacteria in laboratory media. He found SHP was effective in inhibiting the growth of *Clostridium perfringens* and *C. botulinum* strains 62A, 52A, and Lamanna B but generally ineffective against *S. aureus* and *Bacillus cereus*. The combined effects of decreasing pH and increased NaCl

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concentrations greatly enhanced SHP inhibition of *C. perfringens* and all three *C. botulinum* strains. These factors had little effect on SHP inhibition of *S. aureus* or *B. cereus*. The apparent contradictory results from this study and the previously mentioned data of Foster et al. (*18*) can be explained by the different growth conditions used in the two studies. Rhodehamel (*38*) tested *B. cereus* growth aerobically under nearly optimal conditions in a medium that was not phosphorus-limiting. This may explain why the higher concentrations of hypophosphites used in that study were not inhibitory. The ability of SHP to inhibit some gram-positive bacteria at a neutral pH is important, since the activity of most antimicrobial preservatives decreases as the pH increases. The author felt the results of his study indicate SHP has potential use in low acid foods as an antimicrobial food preservative.

Rhodehamel and Pierson (*39*) studied the potential of SHP to inhibit the growth of selected gram-negative foodborne pathogenic and spoilage bacteria in laboratory media. Sodium hypophosphite was most effective in inhibiting growth of several gram-negative facultatively anaerobic bacteria tested, particularly *Salmonella typhimurium* and *Vibrio parahaemolyticus*, but generally ineffective against *Pseudomonas fluorescens* and the *Campylobacter* strains tested. However, SHP alone never completely inhibited (prevented) growth of any of the bacteria tested but usually slowed the rate of growth. Sodium hypophosphite does not appear to be a potent antimicrobial compound. All inhibition studies were performed with optimal or nearly optimal growth conditions, so they can be considered an arduous test of SHP's effectiveness. The authors concluded, although the inhibition studies were performed with laboratory media, SHP may have potential use as antimicrobial food additive.

Conclusions

In summary, hypophosphite does not appear to have adverse toxicological effects, and the sodium, calcium, and potassium salts are considered GRAS. Hypophosphite use in foods may not be limited to one function. Hypophosphites have been used in foods as antioxidants (*7,25,28,29*), stabilizers (*7,25*), meat pickling accelerator (*56*), and vegetable protein flow inducer (*10*). There needs to be additional studies, however, on the stability and potential interactions of this substance with food components. Several studies have shown SHP to be an effective antibotulinal inhibitor (*22,34,35,57*) in food systems. Reports by Rhodehamel (*38*) and Rhodehamel and Pierson (*39*) indicate SHP restricts growth of some foodborne pathogenic and spoilage bacteria. The ability of SHP to inhibit certain bacteria near neutral pH values is important, since the effectiveness of many antimicrobials decreases if the pH is raised. Of the major preservatives used today, only the parabens have antimicrobial activity over a wide pH range. They are most active against yeast and molds but least active against gram-negative bacteria (*6*). Thus, as an antimicrobial food preservative, SHP has possible uses in cured meat systems and low acid foods, since none of the current major preservatives exhibit the same properties as SHP. Current consumer trends toward fresh-refrigerated foods may provide additional opportunities for SHP use. The antimicrobial properties of hypophosphite as well as its other functions in foods suggest that this compound has potential as a multifunctional food ingredient.

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6	2	565	99.6
7	1	566	99.8
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