

Stannous Fluoride Dentifrice with Sodium Hexametaphosphate: Review of Laboratory, Clinical and Practice-Based Data

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Introduction

Patients today represent one of the most heterogeneous groups in history in terms of age, health status, oral hygiene habits, and other factors. While certain oral health conditions are more prevalent among specific patient groups, such as periodontal disease among diabetic patients,¹ many oral health conditions affect the broad population. According to U.S. surveys, virtually all adult patients have had dental caries, more than half experience gingivitis, and roughly one in three suffers from dental sensitivity.²⁻⁴ Fortunately, home care products are available to help prevent and treat many common oral health conditions in conjunction with routine professional care.

Dentifrice is one important example. Many years ago, the benefits of dentifrice were limited to cleaning and the prevention of tooth decay. It was common for professionals to tell patients to “use any dentifrice with fluoride and the ADA Seal.” However, formulators today can design dentifrices to provide numerous other benefits, both for health and cosmetic purposes. In 2005, a stannous fluoride sodium hexametaphosphate (SFSH) formula* was introduced offering protection against a broad range of health and cosmetic conditions commonly experienced by patients.⁵ The present report reviews the laboratory,

Abstract

Dentifrice was originally used to promote oral hygiene by cleaning teeth. However, with advances in product formulation, it has become a valuable vehicle for the delivery of agents offering health and cosmetic benefits. Stannous fluoride, introduced in 1955 in dentifrice, is one of the longest established of such agents. The well-known anti-caries efficacy of stannous fluoride is based on its impact on the tooth surfaces and on its antibacterial activity. More recently, the demand for tooth whitening products has increased, and sodium hexametaphosphate has been shown to be helpful in whitening surface stains and in controlling calculus. A dentifrice formulation that combines the benefits of stannous fluoride with those of sodium hexametaphosphate is now available. A review of the evidence shows that in addition to effective anti-caries action, this formulation is effective in fighting plaque, gingivitis, and gingival bleeding while inhibiting calculus and extrinsic stain. A practice-based evaluation including data from over 1,200 dental professionals and 1,000 patients demonstrates the product's benefits and excellent acceptability. Collectively, the research shows this stannous fluoride/sodium hexametaphosphate dentifrice provides multiple benefits to meet the oral health and cosmetic needs of patients.

Key Words: stannous fluoride, dentifrice, gingivitis, caries, sensitivity, calculus

clinical and practice-based assessments evaluating the efficacy of this dentifrice formulation.

Stabilized Stannous Fluoride/ Sodium Hexametaphosphate Formulation

The SFSH formula combines the therapeutic benefits of 0.454% stabilized stannous fluoride with the calculus and stain-control characteristics of sodium hexametaphos-

phate in a low-water formulation dentifrice. Stannous fluoride, which unlike sodium fluoride can be used in combination with calcium-based abrasives, has been incorporated in dentifrices since the 1950s to provide protection against caries, pathogenic bacteria, gingivitis, hypersensitivity, and the development of plaque. There is considerable evidence for its efficacy as a therapeutic agent with a wide spectrum of beneficial properties.⁶⁻¹² However, its clinical usage was limited because of as-

*Crest Pro-Health, Procter & Gamble, Cincinnati, OH, USA.

tringent taste, and in some patients, its use resulted in extrinsic staining of the teeth. Stannous fluoride was also somewhat unstable in aqueous solution. The latter problem was resolved with the introduction of stabilized stannous fluoride in the 1990s, which rendered more available stannous fluoride and resulted in a renewed interest in the wide range of benefits offered by stannous fluoride in dentifrices.⁶

Sodium hexametaphosphate was first introduced in a dentifrice in 2000.¹³ It is a chemical whitening agent in the same class as pyrophosphate, which has long been used to inhibit calculus, but the molecule is about 10 times longer than that of pyrophosphate. Sodium hexametaphosphate therefore provides better coverage and retention on the tooth surface, thus increasing its ability to inhibit both calculus and stain formation on the enamel surface.¹⁴ Stability of the dentifrice can be an issue with the inclusion of polyphosphates if ingredients are not properly balanced. Like other polyphosphates, sodium hexametaphosphate does not usually show good long-term stability in aqueous dentifrices. However the novel single-phase SFSH formula, which uses a low-water system in

a silica-based formulation, significantly reduces the hydrolysis of sodium hexametaphosphate and helps to maintain effective levels of whitening activity.⁵

The resulting dentifrice has improved esthetic qualities over the original stannous fluoride formulation and delivers a broad range of therapeutic and cosmetic benefits (Figure 1). The remainder of this paper provides a summary review of research on stannous fluoride, sodium hexametaphosphate and, especially, the unique SFSH formulation.

Antibacterial and Anti-Inflammatory Action

Most of the oral health benefits of stannous fluoride result from its antibacterial efficacy, particularly against bacteria associated with dental caries, periodontal disease, and oral malodor. Laboratory and clinical studies have shown that stannous fluoride, unlike other fluorides, inhibits bacterial growth by a variety of mechanisms, including interference with metabolic pathways, thus reducing bacterial acid formation, and inhibition of bacterial cohesion and adhesion.¹⁵⁻¹⁷ The Plaque Glycolysis and Regrowth Model (PGRM) is an

in situ method that allows evaluation of a formulation's biological activity based on its effects on plaque metabolism. Using a PGRM, White et al found a statistically significant reduction in acidogenicity associated with the use of stannous fluoride dentifrice versus a standard sodium fluoride control dentifrice.^{18,19} Using the same methodology, Liang et al found that a stannous fluoride dentifrice, as compared to a control placebo, greatly reduced the amount of plaque acid and also inhibited plaque regrowth.²⁰

Comparable results have been obtained in studies of the antibacterial action of this SFSH formula. Ramji et al carried out a series of in vitro and in vivo studies of this new formulation.²¹ In a Live/Dead assay²¹ they found that the new SFSH dentifrice had killed over 90% of the salivary bacteria 16 hours after a single exposure, thus showing strong and lasting antibacterial activity (Figure 2).

In a second study, using PGRM, the SFSH dentifrice produced statistically significant reductions in plaque acid production and plaque regrowth at 15 and 45 minutes after brushing versus a standard sodium fluoride control dentifrice.²¹ Other research demonstrated the presence of soluble tin, which serves as a marker for the active stannous fluoride, at levels above the minimum concentration required for the inhibition of salivary bacterial activity.²¹

Another related value of stannous fluoride is its effect on inflammatory markers, independent of its action on bacteria. In vivo, antibacterial activity also helps reduce inflammation since the inflammatory response should diminish with reduced levels of pathogenic bacteria. A study was conducted with 16 healthy subjects to measure inhibition of several host and bacterial pro-inflammatory enzymes by stannous fluoride.²² Following a one-week period of using a standard sodium fluoride paste and manual brush, a baseline supragingival plaque sample was collected

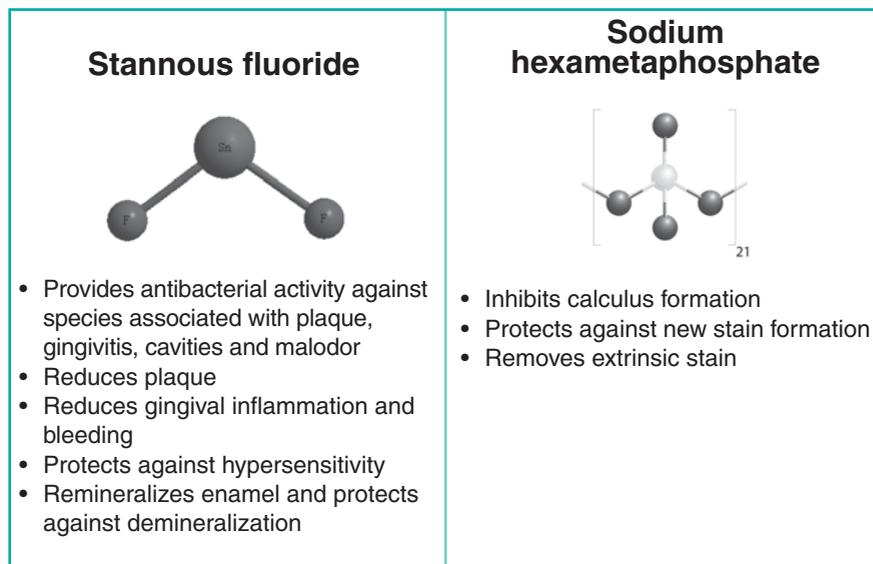


Figure 1. Benefits of stannous fluoride and sodium hexametaphosphate

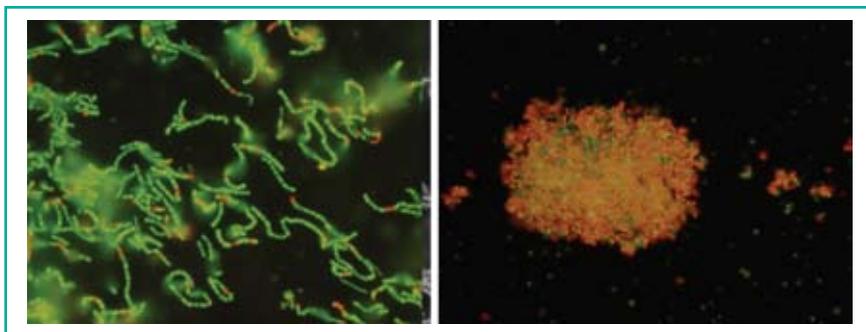


Figure 2. Bactericidal activity assessment 16 hours after exposure. Left; water control. Right; stannous fluoride/sodium hexametaphosphate dentifrice. Green-stained cells are live microbial cells; red-stained cells are dead cells (from Ramji et al²¹).

from subjects. Subjects then rinsed with a slurry of stannous fluoride/sodium hexametaphosphate dentifrice; plaque samples were taken immediately post-rinsing and 12 hours later. An analysis of the samples showed that stannous fluoride inhibited several pro-inflammatory enzymes, including mammalian matrix metalloproteinase subtypes and bacte-

rial gingipain. These enzymes can break down proteins (e.g., collagen) and are involved in processes such as pocket formation. At the 12-hour analysis, enough stannous fluoride was retained to inhibit about 40% of most enzymes measured.

These studies demonstrate the sustained antibacterial and anti-inflammatory effects of this SFSH

dentifrice, supporting its antiplaque and antigingivitis efficacy.

Antiplaque and Antigingivitis Efficacy

Many studies have investigated the effects of stannous fluoride on gingivitis and plaque. These evaluations have involved a wide range of trial durations, subject populations and modes of application (Table 1).²³⁻³⁴ The majority of these trials report significant reductions in plaque and gingivitis, supporting the agent's ability to improve gingival health when used twice daily.

In addition, long-term research has been conducted to evaluate stannous fluoride among special populations.³⁵ A 2-year study investigated the periodontitis prevention efficacy of a dual-phase stabilized 0.454% SFSH dentifrice compared to a positive control (sodium fluoride/triclosan dentifrice) in a population of

Table 1. Long-term clinical trials examining the effect of stabilized stannous fluoride on reduction of plaque, gingivitis and gingival bleeding.

Reference	No. of Subjects	% SnF ₂	Mode of Delivery	Treatment Frequency	Length of Trial	Plaque Reduction	% Reduction Gingivitis : Bleeding
Archila et al ³¹	186 adults	0.45	Dentifrice	Twice daily	6 months	ND	25.8%** : 27.4%**
Archila et al ³²	38 adults resistant to NaF treatment	0.45	Dentifrice	Twice daily	12 weeks	ND	54%** : 55%**
Boyd et al ²⁸	23 adolescent orthodontic	0.4	Brush-on gel	Twice daily	18 months	50% **	55%** : 50%**
Beiswanger et al ⁹	140 adults	0.45	Dentifrice	Twice daily	6 months	3% ns	19%* : 31% ns
Ciancio et al ²⁷	28 adults	0.1	Mouth rinse	Twice daily	3 weeks	28% **	ND
Chitke et al ²⁶	26 handicapped children	0.2	Spray	Twice daily	3 weeks	48% *	52%* : ND
Mallatt et al ³⁰	128 adults	0.45	Dentifrice	Twice daily	6 months	8%**	17%** : 41%**
Mankodi et al ²³	104 adults	0.45	Dentifrice	Twice daily	6 months	20%**	21%** : ND
Mankodi et al ²⁴	130 adults	0.45	Dentifrice	Twice daily	6 months	7% **	22%** : 57%**
Perlich et al ²⁹	154 adults	0.45	Dentifrice	Twice daily	6 months	3% ns	21%* : 33%*
Tinanoff et al ²⁵	31 adults, partial denture	0.4	Brush-on	Twice daily	6 months	55% * ¹	48%* : 69%*
Williams et al ¹⁰	112 adults	0.45	Dentifrice	Twice daily	6 months	23% **	22%** : ND

All reductions are versus control except for Archila³² and Chitke²⁶ which were relative to baseline values.

¹Significant difference for abutment teeth.

* p ≤ 0.05 ** p ≤ 0.01 ND-no data ns-non significant

over 330 subjects with medication-induced xerostomia. The study also evaluated the product's ability to remineralize root caries lesions. Results showed that twice daily use of stannous fluoride/sodium hexametaphosphate dentifrice demonstrated comparable benefits to the positive control, which was a sodium fluoride/triclosan dentifrice, in reducing periodontal pocket depth, attachment loss and bleeding on probing as well as remineralizing root caries.³⁵

Recent studies have evaluated the antigingivitis efficacy of SFSH dentifrice.^{24,30-32} One such six-month trial found statistically significant reductions of 22% in gingivitis, 57% less bleeding and 7% less plaque relative to a negative control.²⁴ In a second 6-month trial with 128 subjects, Mallatt et al found a 17% reduction in gingivitis ($p \leq 0.001$), a 41% reduction in gingival bleeding ($p \leq 0.001$) and an 8% reduction in plaque ($p \leq 0.001$) with the SFSH dentifrice versus a negative control dentifrice.³⁰ The SFSH dentifrice also demonstrated significant reductions in gingivitis (26%) and gingival bleeding (27%) relative to a triclosan/copolymer control.³¹ In a follow-up to this study, Archila et al chose subjects who had used the triclosan/copolymer dentifrice twice a day but who had proved unresponsive to it, and still had high bleeding scores at the end of the six-month study period.³² After three months' use of the stannous fluoride/sodium hexametaphosphate dentifrice both gingivitis and bleeding had decreased significantly, by 54% and 55% respectively. These results showed that, even for those who have persistent problems with gingival disease, the SFSH dentifrice can offer significant health benefits when compared to other dentifrices.

In a three-phase study involving use of digital plaque imaging analysis (Figure 3), White et al investigated the longer-term efficacy of the SFSH formula in the control of plaque.³⁶ In Phase 1, subjects brushed twice daily using a standard

sodium fluoride dentifrice; in Phase 2, brushing frequency was reduced to once a day using the same dentifrice; in Phase 3, the daily brushing regimen was continued using the antimicrobial stannous fluoride/sodium hexametaphosphate dentifrice. Morning plaque coverage was 13% during Phase 1, increased to 18% in Phase 2, but decreased significantly in Phase 3, showing a 17% reduction as compared with the sodium fluoride dentifrice control. This supports the sustained antibacterial effects reported by Ramji et al.²¹

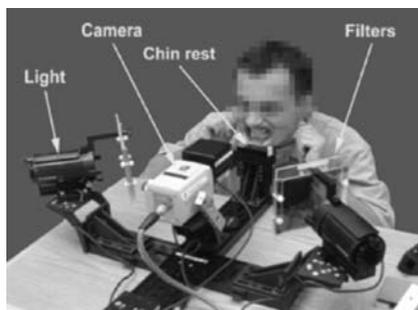


Figure 3. Plaque imaging system

Results of multiple independent clinical trials using the SFSH dentifrice mirror those investigating earlier stannous fluoride dentifrices; the recent formulation also shows benefits in the control of gingival disease where it is significantly more efficacious than sodium fluoride based dentifrices.

Dentinal Hypersensitivity

Reports indicate that dentinal hypersensitivity affects more than

40 million people in the U.S. annually,³⁷ or up to 30% of adults at some time during their lifetime.³⁸ Hypersensitivity is characterized by a short, sharp pain arising from exposed dentin in response to a stimulus that cannot be ascribed to any other form of dental defect or pathology,³⁹ it arises from exposure of the dentinal tubuli to the stimulus. Unlike potassium nitrate, which alleviates sensitivity by acting on the nerve synapse, stannous fluoride reacts with enamel or dentin surfaces to produce solid complexes or insoluble precipitates that wholly or partially occlude the tubuli, as has been shown by means of scanning electron microscopy (Figure 4).⁴⁰

This action is thought to produce the clinical efficacy of stannous fluoride in the prevention and control of dentinal hypersensitivity.⁴¹⁻⁴⁴ Schiff and his collaborators carried out two studies to assess the efficacy of the SFSH formula in reducing hypersensitivity on a sample population of 77.^{45,46} The first used an eight-week randomized trial to compare the effects on dentinal sensitivity of twice-daily brushing with the stannous fluoride/sodium hexametaphosphate dentifrice and with a sodium fluoride-based, negative control dentifrice.⁴⁵ Outcomes were assessed at 4 and 8 weeks with tests of tactile sensitivity (Yeaple Probe Index) and thermal sensitivity (Schiff Air Index). On all assessments, the SFSH dentifrice produced a significant decrease in sensitivity ($p \leq 0.0001$) as compared

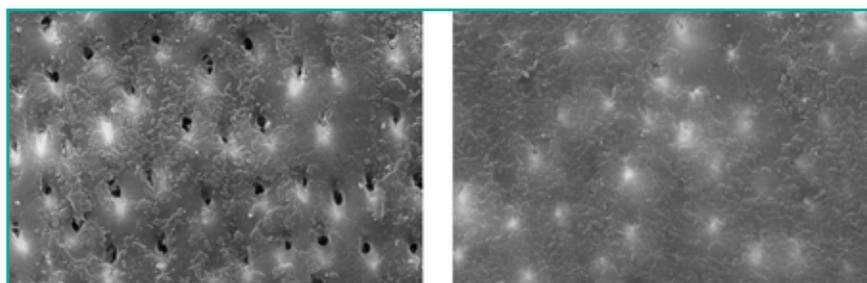


Figure 4. Left: Scanning electron microscopy images showing open tubuli after treatment with a sodium fluoride toothpaste (left) and closed tubuli after treatment with a SFSH dentifrice (right). From Baig and He.⁵

to the control dentifrice. In the second study, which used essentially the same procedures, results were similar, with the stannous fluoride/sodium hexametaphosphate group (n=45) producing significant reduction in sensitivity compared to the control (n=45) (Figure 5).⁴⁶ At 8 weeks, the SFSH showed improvements of 71% and 44% versus the negative control for tactile and thermal measurements, respectively.

These studies support that the SFSH dentifrice shares the anti-sensitivity characteristics of previous stannous fluoride formulations.

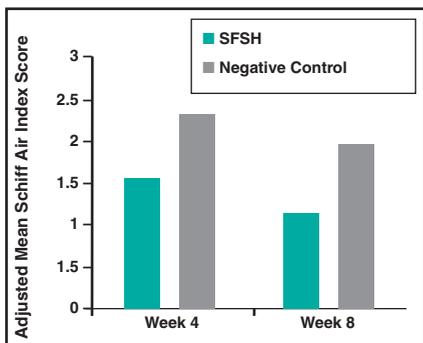


Figure 5. Thermal sensitivity scores for the SFSH dentifrice and negative control (lower scores indicate less sensitivity)⁴⁶

Anticaries Effects

The anticaries effects of stannous fluoride have been recognized for over 50 years, and in the 1960s, the stannous fluoride-containing dentifrice, Crest® with Fluoristan™, received a Seal of Acceptance by the ADA's Council on Dental Therapeutics. Fluoride, in various forms, is well recognized for its ability to foster remineralization of partially demineralized tooth enamel using the calcium and phosphate present in saliva. In addition to these remineralization effects, stannous fluoride has been shown to react with enamel to form a tin fluorophosphate complex that coats and protects the surface of the enamel.^{48,49} The antibacterial activity of stannous fluoride, which was discussed

above, provides further protection by suppression of bacteria, particularly *Streptococcus mutans*, which is one of the primary pathogens associated with dental caries.^{50,51} The anticaries benefits of stannous fluoride are therefore due to both physical chemistry and its bacteriological effects.

Before the introduction of this SFSH dentifrice, a large number of clinical trials had been carried out that demonstrated the efficacy of stannous fluoride in the control of dental caries.⁵² More recently, Stookey et al carried out a large-scale clinical trial with 955 subjects comparing the anticaries efficacy of a dual-phase early prototype SFSH dentifrice with a positive control standard sodium fluoride dentifrice, and also a high-dose (2800 ppm F) and a low-dose (500 ppm F) sodium fluoride formulation.⁵³ Visual-tactile examination was supplemented with a radiographic examination at baseline, after 12 months, and at the end of the trial at 24 months. Both examiners found that there was significantly less caries in the SFSH (17% and 25%) and high-dose (2800 ppm) sodium fluoride groups (13% and 23%) than in the positive control group treated with 1100 ppm fluoride. In an in situ study of mineralization-demineralization, Wefel et al reported that a dual-phase stannous fluoride/sodium hexametaphosphate dentifrice produced anticaries activity that was as good as that of positive controls and concluded that the addition of sodium hexametaphosphate does not interfere with the normal activity of stannous fluoride.⁵⁴

A series of in vitro studies evaluating the anticaries potential of the SFSH formulation have been reported in one publication by Pfarrer and colleagues.⁵⁵ In a study of fluoride uptake into demineralized enamel, it exhibited uptake comparable to a clinically proven stannous fluoride and silica dentifrice.⁵⁵ In a second lesion progression pH-cycling experiment, the stannous fluoride/so-

dium hexametaphosphate dentifrice provided almost complete protection against lesion initiation and progression; it was comparable to conventional clinically proven dentifrices.⁵⁵

These studies indicate that this SFSH dentifrice is as effective as clinically proven fluoride dentifrices both in its mode of action and in its clinical effects.

Anticalculus Effects

Dental calculus results from the mineralization of bacterial plaque formed on the surfaces of teeth. Agents that inhibit crystal growth, particularly condensed phosphates, have been found to be very useful in the prevention of calculus development. In this class of phosphates, sodium hexametaphosphate has been shown to be particularly effective. In vitro studies by White et al have shown significant reductions in hydroxyapatite crystal growth and mineralization of plaque in the presence of sodium hexametaphosphate either in aqueous solution or in a dentifrice.⁵⁶ The effects were significantly greater than for a conventional anti-tartar dentifrice containing pyrophosphate. This finding has been supported by four 6-month clinical trials in which sodium hexametaphosphate produced significant reductions in calculus formation – when combined with sodium fluoride or stannous fluoride – as compared to a regular sodium fluoride dentifrice or a triclosan/copolymer dentifrice.⁵⁷⁻⁶⁰ A total of 866 subjects participated in the four 6-month clinical trials. Efficacy was assessed using a standard clinical method (Volpe-Manhold Index) that measures supragingival calculus coverage on the lingual surfaces of the 6 anterior teeth. In the 2 studies evaluating SFSH formulations, calculus reductions of 55% and 56% were seen versus the respective controls at 6 months.^{59,60}

Whitening Effects

There is an increasing demand for tooth whitening products and also for oral care products that sustain whitening effects. Peroxide is a successful bleaching agent when delivered via whitening strips or in tray-based systems, but it is not particularly effective in dentifrices because of the brief contact time with the tooth surface.⁶¹ Pyrophosphates, on the other hand, help maintain whitening and control staining because they have a strong affinity for the minerals in teeth. Sodium hexametaphosphate has been shown to have important effects on the chemical mechanisms of chromogen adsorption and desorption.⁶²⁻⁶³ It appears that the polymer chains interact with pellicle films to lift stain material out of the pellicle and to prevent the adsorption of new chromogens. Gerlach et al reported a 29% reduction in composite stain relative to a negative control following 6 weeks' use of a sodium fluoride dentifrice containing 7% sodium hexametaphosphate.⁶⁴ Clinical studies providing evidence for the efficacy of sodium hexametaphosphate in the control of extrinsic staining have been reviewed by Baig et al.⁶⁵

A number of recent clinical trials have assessed the extrinsic stain removal efficacy of the SFSH dentifrice. In their 6-month study of anticalculus effects, Schiff et al⁵⁹ also assessed extrinsic stain, using the Lobene Stain Index on the facial surfaces of the 12 anterior teeth; at neither 3 nor 6 months did subjects in the SFSH group show signs of developing any such stain. Four recent clinical trials, which were summarized in 2 publications, have used similar methodologies to compare the extrinsic stain removal efficacy of the SFSH dentifrice with that of a positive control whitening dentifrice.^{66,67} All 4 were randomized, double-blind studies in which efficacy was measured using a modified Lobene Stain Index. Two studies assessed whitening at

baseline and 2 weeks;⁶⁷ the other 2 studies measured stain at baseline, 3 and 6 weeks.⁶⁶ In all cases, there was highly significant stain removal in the experimental groups and also in the positive control groups. There were no significant differences in the effects of the SFSH and positive control dentifrices.

In reviewing these data, it appears that combining sodium hexametaphosphate with stannous fluoride in the SFSH formulation removes and inhibits extrinsic stain formation and that the SFSH dentifrice is as effective as positive control whitening dentifrices.

Practice-Based Evaluation

The efficacy and safety of dentifrice with stannous fluoride or a combination of stannous fluoride and sodium hexametaphosphate is supported by an extensive body of evidence. However, its success ultimately depends on its acceptability to users as part of their personal home oral hygiene routine. In order to assess the acceptability of the SFSH dentifrice, a practice-based assessment was undertaken involving dental professionals and their patients.⁶⁸ Dentists and hygienists across the USA participated in the study, and samples of the SFSH formulation were offered to participating professionals to provide a supply to a small group of their patients for 3-4 months use, until their next visit. Patients' oral health was assessed at the beginning and end of the trial by the dental professional using a questionnaire (not clinical indices). Conditions assessed included gingivitis, gingival bleeding, inflammation, calculus, extrinsic staining, and sensitivity. Professionals submitted a survey report, and patients completed a questionnaire at the end of the study.

In total, 1267 completed surveys were returned by dentists and dental hygienists. Approximately 75% of the evaluations were based on

3-4 months' use and the remainder of subjects had used the product for up to 6 months. Responses analyzed were those in which dentists or hygienists provided both pre-trial and post-trial oral health assessments and gave answers to questions. Sixty-eight percent of all these responses reported improvement in their patients' oral health, including improvements in gingival bleeding and inflammation and reduction in calculus formation. Reductions in sensitivity were reported by 61% of professionals and in staining by 57%. Eighty percent reported they would recommend the SFSH dentifrice; this rose to 91% among those professionals who observed improvements.

A total of 1078 questionnaires were returned by patients. Of these, 88% reported positive assessments of the SFSH dentifrice (Excellent/Very Good/Good) and two thirds of all patients stated that they intended to continue to use the product; this percentage rose to 77% when patients reported noticeable improvements in their oral health. In terms of rating specific effects, roughly 9 out of 10 patients rated the product positively for "keeping mouth healthy," "cleaning teeth thoroughly," being a "comprehensive toothpaste," "making gums healthier," and "freshening breath" (Figure 6). Eighty-three percent rated it positively for reducing surface stains and 77% for reducing gingival bleeding.⁶⁸

It is important to differentiate practice-based evaluations from randomized, controlled clinical studies. For example, clinical trials typically involve calibrated examiners who use standardized indices to assess the status of a specific disease or condition. Often the examiner and subject are blind to treatment. In this practice-based assessment, practicing professionals and their patients assessed oral conditions using a questionnaire. Calibration was not done across offices, and the product identity was known. This type of evaluation is

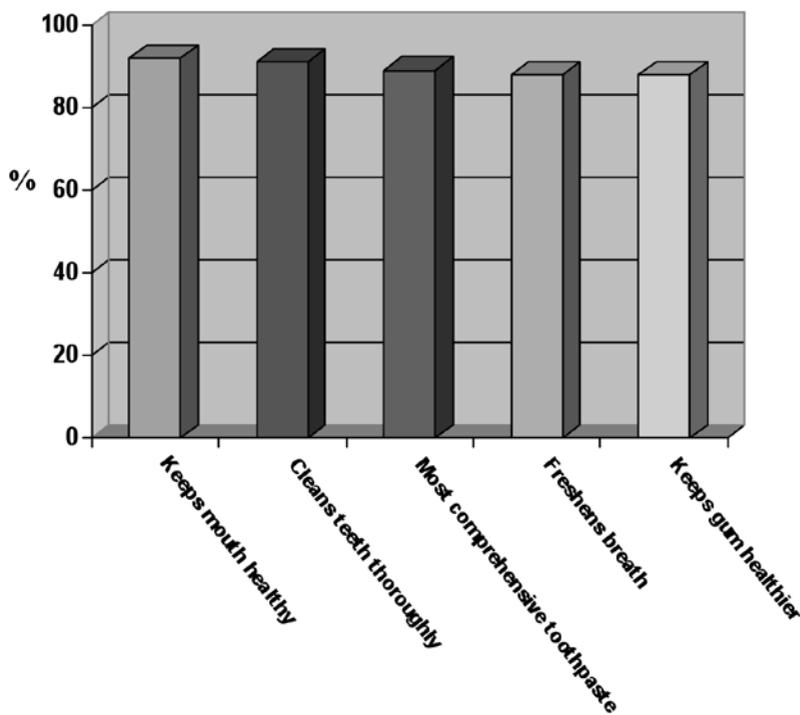


Figure 6. Results from patient surveys; Percent of patients rating SFSH product “Excellent/Very Good/Good”.

similar to the assessments practicing professionals do on a routine basis. They recommend a home care product and then use their experience and clinical judgment to determine the effect it has on the patient’s oral health. This large, practice-based assessment with the SFSH dentifrice complements findings of the controlled clinical trials. The major outcome is that it provides evidence of excellent professional acceptance and an equal level of acceptance among patients, expressed as an intention to continue using the SFSH dentifrice.

Conclusions

Extensive laboratory and clinical research add to the body of research supporting the value of stannous fluoride as a multi-benefit dentifrice ingredient. Stannous fluoride reduces bacterial growth, bacterial activity, and inflammatory markers as well as protects against plaque, gingivitis and gingival bleeding, hypersensitivity, and caries. Research also suggests the effectiveness of sodium hexameta-phosphate in the control of calculus and extrinsic staining. Seventeen

published clinical and laboratory papers demonstrate the efficacy of these dentifrice ingredients when they are combined in a dentifrice formulation, which is therefore able to deliver a wide combination of health and cosmetic benefits.^{21, 24, 30-32, 35, 36, 45- 47, 53-55, 59, 60, 66, 67} Results from a large practice-based assessment involving over 1,200 dental professionals and over 1,000 patients further support the product is widely acceptable and beneficial for improving oral health.⁶⁸

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