THE SCIENCE AND EVIDENCE FOR STABILIZED STANNOUS FLUORIDE

FOREWORD BY
Robert Lee, BDS, MBA
This Scientific Update reviews the evolution of stannous fluoride dentifrice, from the original anti-cavity formulation of the 1950s to today’s stabilized stannous fluoride–sodium hexametaphosphate formulation providing a broad range of therapeutic and cosmetic benefits.

The manual describes:

• key scientific innovations allowing Procter & Gamble to unleash the full potential of this unique fluoride source and formulate it with an advanced anti-calculus and whitening agent, sodium hexametaphosphate

• stannous fluoride’s mechanism of action against plaque, gingivitis, caries, erosion, hypersensitivity, and breath malodor

• sodium hexametaphosphate’s mechanism of action against calculus and extrinsic stain

• laboratory and clinical data demonstrating the significant benefits of the stabilized stannous fluoride–sodium hexametaphosphate formulation for these conditions

We hope this manual assists you in making evidenced-based oral hygiene recommendations for your patients. For additional information on the research studies behind stabilized stannous fluoride–sodium hexametaphosphate dentifrice, visit dentalcare.com.

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Introduction

Stannous fluoride (SnF₂) is unique among fluoride compounds, offering multiple benefits not found with sodium fluoride nor sodium monofluorophosphate. Whilst these latter two compounds provide anti-caries benefits, stannous fluoride when properly formulated can also provide anti-plaque, anti-gingivitis, and anti-sensitivity benefits, as well as advanced protection against dental erosion.

An advanced dentifrice with stabilized stannous fluoride plus the polyphosphate, sodium hexametaphosphate, was introduced to the US market in 2005. This was the first truly multi-benefit dentifrice offering the full array of therapeutic benefits afforded by stannous fluoride, in addition to the tooth whitening and anticalculus benefits that are important to consumers.

This Scientific Update provides the scientific background behind this unique dentifrice, the mechanisms of action responsible for the wide array of benefits it offers, and a review of the laboratory and clinical evidence for each of eight important oral care benefits (Fig. 1).

**Figure 1.** Eight benefits of stabilized stannous fluoride-sodium hexametaphosphate dentifrice
Scientific development and chemistry of stabilized stannous fluoride

The anti-caries benefit of fluoride was confirmed in the mid-1940s. However, an effective anti-caries dentifrice was not brought to market until 1955, when Procter & Gamble was the first to successfully formulate stannous fluoride into a clinically proven dentifrice, with caries reductions of up to 53%. The stannous fluoride in this early dentifrice had limited stability. While fluoride was bioavailable in this formulation to deliver an anti-caries benefit, stannous had limited bioavailability, and thus all of the therapeutic benefits of stannous fluoride were not realised. Subsequently, the stannous fluoride in daily use dentifrices was replaced with more stable fluoride products, mainly sodium monofluorophosphate and sodium fluoride. However, P&G maintained interest in stannous fluoride because of the unique potential of this compound to also provide gingival health and anti-hypersensitivity benefits.

Over the past several decades, a series of inventions by P&G ultimately led the way to the formulation of a stabilized stannous fluoride dentifrice that delivers both the therapeutic potential of stannous fluoride and the cosmetic benefits of whitening and calculus control that are important to consumers.

Firstly, chemical approaches were developed to protect the stannous ion from inactivation by oxidation and hydrolysis which typically occur when stannous fluoride is formulated into a dentifrice. Secondly, groundbreaking research in the 1980s by P&G on anticalculus agents led to the discovery of sodium hexametaphosphate, a powerful whitening and anticalculus ingredient. Thirdly, developing methods to formulate a low-water dentifrice (<3% water vs. 20-70% water in typical dentifrices) allowed stannous fluoride and sodium hexametaphosphate to be combined into one dentifrice formulation that provides stability to both ingredients and allows them to co-exist in the same formulation to deliver their unique benefits (Figs. 2–3).

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is unique, with multiple mechanisms of action that deliver multiple benefits. In addition to the anti-caries benefit of stannous fluoride, the actions of stannous fluoride against oral bacteria impart effectiveness against plaque, gingivitis, and halitosis. Stannous fluoride also promotes the occlusion of open dentinal tubules associated with hypersensitivity and binds to enamel surfaces to protect against acid erosion. Additionally, tooth whitening and calculus control are delivered by the sodium hexametaphosphate.

The following pages address the mechanisms of action and efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice for each of these important oral care benefits.
Anti-plaque activity

The development of supragingival plaque can be divided into several distinct phases: 2,4,5,6

- **Formation of the acquired pellicle.** The pellicle consists mainly of salivary glycoproteins that are adsorbed onto the tooth surface within minutes of exposure of the surface to saliva (e.g., after cleaning). It is acellular, membranous and appears to be unstructured.

- **Attachment of primary plaque-forming bacteria to pellicle-coated tooth surfaces.** Bacterial colonisation begins with Gram-positive cocci and rods which loosely adhere within an hour.

- **Bacterial growth to form micro-colonies on the pellicle.** The bacteria also produce an extracellular matrix that facilitates the attachment and division of bacteria (co-aggregation) and protects the micro-colonies from host defences and antimicrobial agents. Co-adhesion enables other bacteria to adhere to the earlier colonisers. By 8–12 hours, the plaque has become multi-layered.

- **Maturation of the dental plaque (dental biofilm):** it is in this phase of development that the plaque may become pathogenic. At 24–48 hours, only Gram-positive cocci and rods are present and the plaque increases in thickness, however by day five Gram-negative filaments increase in number and begin to coaggregate with the Gram-positive microorganisms and form a more complex structure.

Subgingival plaque develops subsequent to supragingival plaque development. The presence of plaque at the gingival margin results in an inflammatory reaction, which affects the composition of the plaque. The structure of the plaque becomes highly organized with microcolonies interspersed with voids and channels that allow nutrients and other agents to circulate through the plaque (Fig. 4). Different bacterial species also function synergistically or antagonistically within the plaque. Three to twelve weeks after plaque begins to form, Gram-negative cocci and rods, filamentous bacteria and spirochaetes collectively become dominant in the subgingival plaque.

Dental plaque contributes to the development of gingivitis. The onset of gingivitis coincides with an increase in the bacterial load and complexity of plaque as it matures. Stannous fluoride chemotherapeutically acts against the bacteria that cause plaque.

**Mechanism of action of stannous fluoride and anti-bacterial activity**

Scientific evidence indicates that the anti-bacterial activity of stannous fluoride arises mostly from the action of stannous ion. Stannous acts against both Gram-positive and Gram-negative bacteria and inhibits bacterial metabolism. Bacteria exposed to stannous fluoride retain large amounts of tin, and bacterial metabolism could be affected through several different mechanisms. Exposure to stannous fluoride reduces bacterial growth, bacterial adhesion, and the production of acids and other metabolic toxins that contribute to gingivitis. Active levels of tin in plaque persist for up to twelve hours following exposure to stabilized stannous fluoride-sodium hexametaphosphate dentifrice, consistent with the plaque and gingivitis reductions observed for the dentifrice and indicative of a sustained mechanism of action with twice-daily use. 7,8
Early studies of stannous fluoride suggest that stannous affects bacterial adhesion. Plaque bacteria produce extracellular polysaccharides (EPS) which are responsible for the adhesiveness of the plaque. Busscher et al demonstrated that stabilized stannous fluoride-sodium hexametaphosphate dentifrice significantly reduced EPS production in vivo compared to a regular sodium fluoride dentifrice (Fig. 5). This helps to prevent bacterial adhesion and cohesion, thus reducing the thickness and stickiness of plaque.

One important mechanism that has been proposed for stannous fluoride’s anti-bacterial action is the oxidation by stannous of thiol groups in the enzymes involved in bacterial glycolysis. In vivo plaque glycolysis and regrowth models have shown that stabilized stannous fluoride dentifrice exerts strong inhibitory actions on plaque acid production and regrowth relative to a regular sodium fluoride dentifrice. A minimum metabolic inhibitory concentration was determined for stannous by measuring the reduction in acid production by bacteria in human saliva samples; 99% inhibition of metabolic activity occurred as low as 20 ppm stannous.

Plaque vitality is reduced following use of stabilized stannous fluoride-sodium hexametaphosphate dentifrice in vivo. After two weeks of regular use, Busscher et al found that the proportion of viable plaque bacteria was 32% lower twenty-four hours following the last toothbrushing for subjects using the stabilized stannous fluoride dentifrice vs. a standard sodium fluoride dentifrice (p<0.05) (Fig. 6a). Fluorescent dyes can be used to demonstrate plaque viability. In Figure 6b, reduced plaque vitality following exposure to stabilized stannous fluoride dentifrice in vitro can be observed – the viable bacteria with intact cytoplasms are green, while the other areas indicate nonviable bacterial cells.

Anti-plaque efficacy of stabilized stannous fluoride dentifrice
Clinical studies confirm the antiplaque benefit of this dentifrice. White et al (2006) conducted a digital plaque imaging study (n=16) with a phased intervention protocol measuring 24-hour plaque levels following use by each subject of: Phase 1) twice-daily toothbrushing with a standard sodium fluoride dentifrice; Phase 2) toothbrushing with the same dentifrice using a modified hygiene regimen including a period of no oral hygiene for twenty-four hours; and Phase 3) toothbrushing with the stabilized stannous fluoride-sodium hexametaphosphate dentifrice again with no oral hygiene for twenty-four hours following its use.
Overnight plaque formation was measured using digital plaque imaging (Figs. 7a-c) in the morning following either standard hygiene (Phase 1) or twenty-four hours post-hygiene (Phases 2 and 3). Morning plaque coverage results were as follows: Phase 1: 13.3%; Phase 2: 18.4% coverage; Phase 3: 15.2% coverage, representing 17% less plaque for stannous fluoride-sodium hexametaphosphate dentifrice than with the same protocol using sodium fluoride dentifrice (Phase 2). This clinical study design demonstrated a 24 hour sustained effect for the stabilized stannous fluoride dentifrice.

Two six-month, randomized, double-blind, parallel-group studies conducted by Mankodi et al (2005)\textsuperscript{13}, and Mallatt \textit{et al} (2007)\textsuperscript{14}, demonstrated statistically significantly greater anti-plaque efficacy for the stabilized stannous fluoride-sodium hexametaphosphate dentifrice versus a negative control at 6 months.

In two studies of six weeks\textsuperscript{15} and three weeks\textsuperscript{16} duration, statistically greater plaque reductions were found for stabilized stannous fluoride compared to a positive control antimicrobial dentifrice (0.3% triclosan/copolymer). In the 6-week study, which assessed plaque using the Rustogi Modified Navy Plaque Index, the stannous fluoride-dentifrice showed a 44.9% lower whole mouth plaque score versus the positive control at Week 6 (Fig. 8). Plaque scores were 17% lower for the stannous fluoride dentifrice versus the positive control in the 3-week study, which used Digital Plaque Image Analysis to measure plaque (Fig. 9).

**Conclusion**

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is highly effective as an anti-plaque agent with twice-daily use.

**Clinical Significance**

- These results in combination demonstrate statistically significant plaque reductions with use of stabilized stannous fluoride-sodium hexametaphosphate dentifrice
- The comparative studies demonstrate stabilized stannous fluoride-sodium hexametaphosphate dentifrice provides statistically significantly greater plaque reductions compared to 0.3% triclosan/copolymer dentifrice at three and six weeks
Anti-gingivitis activity

The onset of gingivitis follows the accumulation of dental plaque and can be evident as early as 48 hours after dental plaque begins to form (Fig. 10). Gingivitis can be prevented by maintaining low levels of plaque, and it can also be reversed.

Plaque produces an inflammatory reaction in the gingival tissues that results in increased blood flow and dilation of blood vessels. This is accompanied by an increase in all types of inflammatory cells, leading to swelling and reddening of the tissues after 48–96 hours. Continued exposure to plaque bacteria and their byproducts, such as metabolic toxins and proteolytic enzymes, promotes further inflammation and swelling, as well as engorgement and stasis of blood flow giving the tissues a bluish or purplish hue after fourteen to twenty-one days. At this point it is defined as an established gingivitis and it is not associated with irreversible damage. It may remain stable or progress to periodontitis with loss of attachment and destruction of the alveolar bone.

There are three ways in which gingivitis reductions can be achieved:
- Mechanical removal of plaque
- Anti-bacterial control of plaque
- Suppression of the host (human) inflammatory response

Mechanism of action of stannous fluoride

The reductions in gingivitis observed with stabilized stannous fluoride-sodium hexametaphosphate dentifrice are due to the broad-spectrum anti-bacterial activity of stannous fluoride. Stannous fluoride inhibits bacterial metabolism, and thus reduces bacterial growth, bacterial adhesion and the production of toxins that potentiate gingival inflammation.

The stannous ion has high substantivity in the oral cavity, imparting a long-lasting anti-bacterial effect. Otten et al recently demonstrated that twelve hours after brushing with stabilized stannous fluoride-sodium hexametaphosphate dentifrice, plaque samples retained enough residual anti-bacterial activity to inhibit fresh, unexposed plaque samples. Given that dental plaque is associated with gingivitis, reducing and inhibiting plaque results in reductions in gingivitis. Retention of the stannous ion in plaque that remains after oral hygiene is important since the plaque that is missed during brushing is often in hard to reach areas where removal matters most to prevent the build-up of plaque and the onset of gingivitis.

Efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice

Several reports confirm the anti-gingivitis benefit of stabilized stannous fluoride dentifrice. One 6-month, randomized, double-blind, parallel-group gingivitis study by Mankodi et al (2005) compared stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test) with sodium monofluorophosphate dentifrice (negative control). An 11.5% reduction at three months and a 21.7% reduction at six months (Fig. 11) was found for the test dentifrice vs. the control dentifrice for the Modified Gingival Index (MGI). The reduction in the gingival bleeding index (GBI) was 57% at six months for the test dentifrice vs. control (P <0.0001) (Fig. 12). The anti-gingivitis benefits for the stannous fluoride dentifrice were confirmed in a second six-month, randomized, parallel group clinical trial versus a negative control conducted by Mallatt et al (2007).
A third randomized six-month study, by Archila et al (2004), compared stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test) with an antimicrobial dentifrice containing 0.3% triclosan/2% copolymer (positive control). Both the test and positive control dentifrices demonstrated significant reductions in measures of gingivitis versus baseline. The six-month Löe-Silness gingival index (GI) score was 25.8% lower for the stannous fluoride-sodium hexametaphosphate dentifrice vs. the positive control, and the adjusted mean number of gingival bleeding sites was 27.4% lower (P <0.001). An overview of the results from these three studies can be found in Table 1.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Length</th>
<th># Subjects</th>
<th>Test and Control Group Dentifrices</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mankodi et al²¹</td>
<td>6 months</td>
<td>130</td>
<td>Test: Stabilized stannous fluoride</td>
<td>Modified Gingival Index (MGI)</td>
<td>Test dentifrice: 11.5% and 21.7% reductions in MGI at 3 and 6 months respectively vs. control 47.7% and 57% reductions in GBI at 3 and 6 months respectively vs. control (P ≤0.0001 for all measures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control: Sodium monofluorophosphate</td>
<td>Gingival Bleeding Index (GBI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallatt et al²⁴</td>
<td>6 months</td>
<td>128</td>
<td>Test: Stabilized stannous fluoride</td>
<td>Modified Gingival Index (MGI)</td>
<td>Test dentifrice: 6.8% and 16.9% reductions in MGI at 3 and 6 months respectively vs. control 33.8% and 40.8% reductions in GBI at 3 and 6 months respectively vs. control (P &lt;0.001 for all measures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control: Sodium monofluorophosphate</td>
<td>Gingival Bleeding Index (GBI)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Archila et al²¹</td>
<td>6 months</td>
<td>186</td>
<td>Test: Stabilized stannous fluoride 0.3% triclosan/2% copolymer</td>
<td>Löe and Silness Gingival Index</td>
<td>Test dentifrice: 25.8% reduction in GI at 6 months vs. positive control 27.4% reduction in bleeding sites at 6 months vs. positive control (P ≤0.001 for all measures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control: 0.3% triclosan/2% copolymer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Anti-gingivitis efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice**

**Conclusion**
Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is highly effective as an anti-gingivitis agent.

**Clinical Significance**
- These results in combination demonstrate statistically significant gingivitis and bleeding site reductions with use of stabilized stannous fluoride-sodium hexametaphosphate dentifrice
- The comparative results demonstrate a statistically significant improvement with stabilized stannous fluoride-sodium hexametaphosphate dentifrice compared to 0.3% triclosan/copolymer dentifrice in gingivitis and bleeding site reductions at three and six months
- These results indicate the significant reductions in gingivitis that can be anticipated with twice-daily use of 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice as part of an oral hygiene regimen
Anti-caries benefit

Dental caries is endemic globally. The prevalence of dental caries in the general population is significant throughout the world and particularly affects people in regions where consumption of refined sugar is high. Table 2 shows caries prevalence for the 6-19-year-old age group in a number of countries.

Cariogenic bacteria in supragingival dental plaque, predominantly Mutans streptococci and Lactobacilli, metabolise fermentable carbohydrates to produce acids that cause demineralization of the dental hard tissues. Without adequate remineralization the caries balance is disturbed, resulting in net mineral loss that will eventually lead to cavitation. Fluoride is the most frequently-used chemotherapeutic agent to combat dental caries.

Mechanisms of action of fluorides

Twice-daily use of fluoride dentifrices is well-established as being effective in reducing caries and reversing early carious lesions. Interventions that increase the amount of fluoride available to alter the plaque/tooth surface interaction are the most successful for caries prevention:

- When the fluoride ion is present at the tooth surface and in plaque following use of a fluoride dentifrice, it is available to promote remineralization and to help prevent demineralization during acid attacks
- When incorporated into the tooth mineral structure, it results in a more resistant, less soluble mineral than the original carbonated hydroxyapatite (Fig. 13)

Higher concentrations of fluoride generally offer greater protection:
- 2,800 ppm sodium fluoride dentifrice has demonstrated 20.4% greater caries reduction compared to a regular 1,100 ppm sodium fluoride dentifrice
- 2,500 ppm sodium monofluorophosphate dentifrice has demonstrated a 16–20% greater reduction in caries (DMFS) compared to 1,000 ppm

Table 2. Prevalence of dental caries

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of Caries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>89%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>84%</td>
</tr>
<tr>
<td>India</td>
<td>83%</td>
</tr>
<tr>
<td>South Korea</td>
<td>83%</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>76%</td>
</tr>
<tr>
<td>China</td>
<td>55%</td>
</tr>
<tr>
<td>Hong Kong (SAR)</td>
<td>38%</td>
</tr>
<tr>
<td>Japan</td>
<td>16%</td>
</tr>
<tr>
<td>Brazil</td>
<td>89%</td>
</tr>
<tr>
<td>France</td>
<td>81%</td>
</tr>
<tr>
<td>USA</td>
<td>78%</td>
</tr>
<tr>
<td>South Africa</td>
<td>60%</td>
</tr>
<tr>
<td>Australia</td>
<td>55%</td>
</tr>
<tr>
<td>Germany</td>
<td>54%</td>
</tr>
<tr>
<td>UK</td>
<td>54%</td>
</tr>
</tbody>
</table>

Demineralization by acid in plaque

Remineralization

Figure 13. Mechanism of action in fluoride
Mechanisms of action of stannous fluoride
The caries demineralization-remineralization balance described above is valid for all fluoride compounds which allow dissociation of the fluoride ion in the oral cavity. Stabilized stannous fluoride may offer additional anti-caries benefits through its antiglycolytic actions. Stannous fluoride significantly inhibits bacterial glycolysis, the pathway by which bacteria produce cariogenic acids.

Laboratory studies
A set of in vitro studies conducted by Pfarrer et al (2005) confirmed the anti-caries potential of stabilized stannous fluoride-sodium hexametaphosphate dentifrice. Single-treatment fluoride uptake was determined using demineralized enamel chips. After taking microscopic standardized sample biopsies (Fig. 14), the base level of enamel fluoride content was determined using fluoride ion-selective electrode analysis. The chips were then exposed to a centrifuged stannous fluoride dentifrice-whole saliva slurry for thirty minutes. Repeat biopsy samples were then taken to determine the post-exposure fluoride content.

A standard United States Pharmacopeia (USP) reference 1,100 ppm stannous fluoride dentifrice and a 250 ppm stannous fluoride dentifrice (negative control) resulted in mean fluoride uptakes of 7.44 μg F/cm² (SD 0.98) and 5.48 μg F/cm² (SD 0.25) respectively. The 1,100 ppm stabilized stannous fluoride-sodium hexametaphosphate dentifrice resulted in a mean fluoride uptake of 8.09 μg F/cm² (SD 0.25). The standard USP reference dentifrice and the stabilized stannous fluoride-sodium hexametaphosphate dentifrice were not significantly different, and were statistically significantly superior to the 250 ppm fluoride dentifrice (P <0.05).

A pH cycling test utilized a standard 24-hour demineralization-remineralization cycling model, which involved an initial six hour demineralization phase, then a one minute dentifrice treatment followed by an overnight 16 hour remineralization phase. The next morning another one minute treatment was applied before the next round of demineralization. This process was repeated for fourteen days. At the conclusion of the cycling steps, specimens were sectioned longitudinally through the lesions, and microhardness measurements were taken the entire depth of the lesion to calculate the relative mineral loss from each lesion. The test dentifrice was not statistically different from the USP reference stannous fluoride dentifrice or the USP reference sodium fluoride dentifrice for mean mineral loss.

Clinical efficacy of stabilized stannous fluoride dentifrice for caries prevention
A randomized, controlled, double-blind clinical trial was conducted by Stookey et al (2004) involving 955 subjects aged 9–12 years (mean age 10.5 – 10.6 for each dentifrice group). The attrition rate of subjects was 28.5% during the two-year study, with statistically similar numbers dropping out from each group. All subjects were stratified by age, gender and baseline DMFS and randomized into four groups: 1,100 ppm dual-phase, early prototype of stabilized stannous fluoride-sodium hexametaphosphate dentifrice, n=160 at two years; 500 ppm NaF, n=168 at two years; 1,100 ppm NaF (reference control), n=174 at two years; or 2,800 ppm NaF, n=180 at two years. For two years, the children brushed for one minute twice-daily with the dentifrice under supervision at school and ad libitum outside of normal school hours. Visual and tactile examinations to detect carious enamel and cavitated lesions were performed by two calibrated examiners at baseline, twelve months and twenty-four months using the naked eye, artificial light and fibre-optic illumination, together with an air syringe and dental explorer. Bitewing radiographs were also taken. With the exception of proximal lesions, all other lesions were only noted as carious if they were accompanied by a change in tactile sensation (visible white spots with no tactile change were not noted as carious lesions).
At two years, the 1,100 ppm stabilized stannous fluoride-sodium hexametaphosphate dentifrice group and the 2,800 ppm sodium fluoride dentifrice group had statistically similar adjusted mean DMFS scores. Subjects in the 2,800 ppm sodium fluoride dentifrice group showed 13-23% significantly fewer caries increments than subjects in the 1,100 ppm sodium fluoride dentifrice group. Subjects in the stannous fluoride dentifrice group had 17%-25% fewer caries increments than those in the 1,100 ppm sodium fluoride dentifrice group (Fig. 15). The 500 ppm sodium fluoride group and the reference control group did not differ.

**Conclusion**

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is effective as an anti-caries agent, and an early dual-phase prototype provided a similar level of protection compared to a prescription strength dentifrice in a two-year clinical trial.

**Clinical Significance**

- Stabilized stannous fluoride-sodium hexametaphosphate dentifrice provides effective caries management as part of a multi-benefit dentifrice.
Anti-erosion

Dental erosion is prevalent in children and adults globally, with some researchers finding it present in approximately half of adolescents. Estimated prevalence in some locations can be found in Table 3.

<table>
<thead>
<tr>
<th>Country and Author</th>
<th>Population Group</th>
<th>Prevalence of Erosion</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (Nayak et al)</td>
<td>5-year-olds</td>
<td>29%</td>
</tr>
<tr>
<td>Malaysia (Manaf et al)</td>
<td>19-24-year-olds</td>
<td>68%</td>
</tr>
<tr>
<td>Beijing, China (Hou et al)</td>
<td>12-year-olds</td>
<td>61%</td>
</tr>
<tr>
<td>Southern China (Wang et al)</td>
<td>12-13-year-olds</td>
<td>27%</td>
</tr>
<tr>
<td>Australia (Kazoullis et al)</td>
<td>5-14-year-olds</td>
<td>78%*</td>
</tr>
<tr>
<td>Australia (Kazoullis et al)</td>
<td>5-14-year-olds</td>
<td>25%**</td>
</tr>
<tr>
<td>Brazil (Corrêa et al)</td>
<td>2-20-year-olds</td>
<td>25%</td>
</tr>
<tr>
<td>Greece (Mantonanaki et al)</td>
<td>Pre-school children</td>
<td>78%</td>
</tr>
<tr>
<td>USA (Deery et al)</td>
<td>Adolescents</td>
<td>41%</td>
</tr>
<tr>
<td>Germany (Wiegand et al)</td>
<td>2-7-year-olds</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Primary dentition  **Permanent dentition

Table 3. Estimated prevalence of dental erosion

Dental erosion occurs primarily due to the excessive presence of non-bacterial extrinsic acids (especially dietary acids such as acidic drinks), as well as intrinsic gastric acid associated with gastroesophageal reflux disease (GERD) and bulimia. Dental erosion involves the demineralization and softening of the tooth surface, which once softened, is highly susceptible to abrasion and attrition (Fig. 16). A diagnosis of erosion can be made based on the pattern of surface loss of enamel and/or dentine (Figs. 17a,b).

Exposure to acid  Demineralization

Figure 16. Demineralization associated with dental erosion

Figure 17a. Generalised erosion

Figure 17b. Severe palatal erosion and loss of tooth structure.

Courtesy of Prof. Ian Meyers
Unlike dental caries where demineralization is initially mainly subsurface and is also reversible in its early stages, dental erosion involves repeated demineralisation of the surface with subsequent surface loss and this process is irreversible (Figs. 18a, b).

Reversible
Enamel crystals are weakened, but remain structurally intact. The early caries process is reversible

Irreversible
Enamel crystals are damaged structurally from the surface down into the tooth. The erosive process is irreversible

**Figure 18a. Dental caries process**

**Figure 18b. Dental erosion process**

**Mechanism of action for anti-erosion effect of stabilized stannous fluoride**

The deposition of stannous fluoride at the tooth surface helps protect it against dental erosion:

- Deposition of stannous fluorophosphate or stannous oxide layers onto enamel surfaces has been reported after stannous fluoride treatment
- Stannous fluoride forms a protective layer on the surface that is highly resistant to acids

A recent *in vitro* study compared the ability of various fluoride toothpastes to form a protective barrier layer. The toothpastes evaluated included 1,100 ppm stannous fluoride, 1,100 ppm sodium fluoride, 1,000 ppm sodium monofluorophosphate and 1,400 ppm amine fluoride. The study involved exposing etched samples to toothpaste–saliva slurries, rinsing them, and then exposing them to 2% alizarin Red-S. Dye deposition was assessed using a 5-point scale, with 0 being no dye deposition and 4 being complete dye coverage. A low score indicates a barrier layer is present, preventing the deposition of dye. The stannous fluoride toothpaste had the lowest score, 0.25. At the other extreme, amine fluoride resulted in a score of 3.7 (Fig. 19). This *in vitro* test confirmed the ability of stannous to form a protective barrier layer, and demonstrated that stannous fluoride is a preferred fluoride for delivering an enamel protection benefit via a barrier mechanism to erosive acids.

<table>
<thead>
<tr>
<th>Stannous fluoride</th>
<th>Sodium fluoride</th>
<th>Sodium monofluorophosphate</th>
<th>Amine fluoride</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25*</td>
<td>3.4*</td>
<td>3.4*</td>
<td>3.7*</td>
</tr>
</tbody>
</table>

* Average deposition of stain (based on the 5-point scale)

**Figure 19. Degree of dye deposition on enamel samples following exposure to toothpaste slurry followed by dye**
Other *in vitro* tests have also demonstrated the superior protective effect of stannous fluoride-treated enamel slabs in comparison to sodium fluoride-treated enamel slabs during an erosive challenge (Fig. 20). Exposure to dietary acid in an erosion cycling model resulted in surface demineralization and surface loss for the slabs treated with sodium fluoride toothpaste slurry while minimal demineralization or surface loss occurred with the slabs treated with stannous fluoride toothpaste slurry.

**Efficacy of stannous fluoride against dental erosion**

The efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice in protecting against erosion is clinically proven, as well as being supported by *in vitro* studies.

Hooper *et al* (2007)\(^42\) conducted a fifteen-day single-blind, crossover *in situ* study as well as a fifteen-day *in vitro* study to compare the protective effects of 1,100 ppm stabilized stannous fluoride-sodium hexametaphosphate dentifrice, a 1,100 ppm sodium fluoride dentifrice (benchmark) and a mineral water with a pH of 7.8 (negative control). For the *in situ* study, subjects (n=15) wore intraoral appliances with two flat, polished human enamel samples, with a surface roughness profile of +/- 0.1 μm, between 9 am and 5 pm except for an hour at lunchtime. While wearing the appliance, subjects only drank water and the acid challenge orange juice (pH 3.8) and did not eat. They rinsed under supervision for one minute with toothpaste slurry (3 g toothpaste/10 ml water) or water (10 ml) each morning and then drank 250 ml of orange juice (25 ml/min for 10 min) one hour and three hours later. This procedure was repeated in the afternoon. Two washout days were included between the three test periods of fifteen days each for the two dentifrice formulations and the negative control. The *in situ* test demonstrated the superior protection against erosion offered by the stabilized stannous fluoride-sodium hexametaphosphate dentifrice relative to a conventional fluoride dentifrice (Fig. 21). For the *in vitro* study a similar cycling protocol was performed with enamel samples to simulate 15 days of product use and acid challenge. The same order of protective effects was observed for the test agents in the *in vitro* cycling study as in the *in situ* study, validating this *in vitro* model.

Faller *et al* (2011)\(^43\) conducted *in vitro* studies to compare the relative ability of three different types of fluoride to protect human enamel when exposed to dietary acid attack. The study compared 1,100 ppm stabilized stannous fluoride-sodium hexametaphosphate dentifrice, a 1,100 ppm sodium fluoride dentifrice and a 1,000 ppm sodium monofluorophosphate dentifrice. Sound, human pellicle-coated enamel samples were exposed to an erosion cycling regimen mimicking the intraoral environment. The enamel samples were treated with the respective dentifrice-whole saliva slurry for two minutes, rinsed in distilled de-ionised water, placed in saliva for one hour, exposed to an erosive acid challenge for ten minutes, rinsed again and placed in saliva for approximately one hour.
This sequence was performed 4-times-daily for five days. Separate citric and phosphoric acid erosive cycling tests were conducted. The results demonstrated significantly greater enamel protection with the stabilized stannous fluoride-sodium hexametaphosphate dentifrice relative to the 1,100 NaF and 1,000 SMFP dentifrices against both types of erosive challenge (Table 4).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Citric Acid Challenge*</th>
<th>Phosphoric Acid Challenge*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,100 ppm stabilized SnF2 - SHMP</td>
<td>10.3 (2.39) a</td>
<td>2.0 (0.44) a</td>
</tr>
<tr>
<td>1,100 ppm NaF</td>
<td>24.5 (0.87) b</td>
<td>12.8 (2.07) b</td>
</tr>
<tr>
<td>1,000 SMFP</td>
<td>28.0 (1.35) b</td>
<td>14.9 (1.63) b</td>
</tr>
</tbody>
</table>

*values with the same letters in each column are not significantly different at the 5% significance level

Table 4. Mean enamel surface loss ± SEM (μm)

West et al conducted a 15-day *in situ* study comparing the anti-erosion benefits of a stannous fluoride-sodium hexametaphosphate dentifrice (1450ppm F; 1100 ppm F as SnF₂ and 350 ppm F as NaF) and a 1450 ppm F as NaF dentifrice with 0.3% triclosan/copolymer. The study protocol was similar to that previously described for the Hooper study, where subjects wore an intraoral device fitted with enamel samples, swished with the treatment toothpaste slurry twice daily and then underwent 4 erosive challenges (orange juice) per treatment day. Results showed the stannous fluoride dentifrice demonstrated 68% lower enamel loss than the NaF/triclosan dentifrice at Day 15 (Fig. 22).

**Conclusion**

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is effective in preventing dental erosion and offers superior protection for enamel compared to other types of fluoride dentifrices.

**Clinical Significance**

- The prevalence of dental erosion is increasing due to changes in the modern diet, which includes more acidic beverages
- Dental erosion is irreversible and therefore must be prevented
- The protective coating deposited on the tooth surface with the use of stabilized stannous fluoride-sodium hexametaphosphate dentifrice offers exceptional protection against erosion, making this dentifrice a suitable option for the prevention of erosion
- Relative to other fluorides, stannous fluoride is unique in providing protection against enamel erosion
Anti-hypersensitivity

Dentine hypersensitivity occurs when dentinal tubules are exposed and open to the oral environment. Exposed root surfaces following gingival recession and loss of cementum, as well as erosive risk factors, are considered significant predisposing factors. Abrasion, as well as temporary loss of the smear layer during periodontal procedures, is also associated with dentine hypersensitivity. According to Brannström’s hydrodynamic theory, fluid movement within these open dentinal tubules in response to stimuli (hot/cold/sweet/sour foods or drinks, cold air or touch) results in pain. (Fig. 23) In addition, dentine hypersensitivity can result in inadequate oral hygiene as the sensitive areas are avoided during brushing. Home use of desensitizing dentifrices is typically recommended as the first line of defence for the management of this condition.

Mechanism of action of stabilized stannous fluoride dentifrice

Early treatments using solutions and later gels demonstrated the desensitizing effect of stannous fluoride. The dentinal tubules are occluded by precipitated stannous salts, inhibiting fluid movement within the tubules and thereby preventing nerve stimulation and pain (Figs. 24, 25).

Figure 23. Fluid movement in open dentinal tubules

Figure 24. Dentinal tubule occlusion: Note the effective occlusion of dentinal tubules with stabilized stannous fluoride dentifrice (SEM x2000)

Figure 25. Pre- and post-brushing SEMs: pre- and post-treatment with open and occluded dentinal tubules

Figure 26. Relative dentinal tubule occlusion for stabilized stannous fluoride-sodium hexametaphosphate dentifrice versus two other anti-hypersensitivity dentifrices after treatment, mechanical agitation, and one minute acid exposure.
In addition to the onset of smear layer formation, the durability of the tubule occlusions also impacts the effectiveness of the anti-hypersensitivity agent. Stabilized stannous fluoride-sodium hexametaphosphate dentifrice forms a smear layer that is resistant to both daily mechanical and acid challenges. Figure 26 compares a stabilized stannous fluoride-sodium hexametaphosphate dentifrice to two other anti-hypersensitivity toothpastes which also act by a tubule occlusion mechanism. The smear layer of the stabilized stannous fluoride-sodium hexametaphosphate dentifrice is more resistant to a dietary acid challenge than that of either of the other products.49

**Efficacy of stabilized stannous fluoride dentifrice**

Stabilized stannous fluoride dentifrice offers rapid onset and long-lasting reductions in sensitivity when used twice daily as a dentifrice by occluding the dentinal tubules. It has been proven in numerous clinical studies to be highly effective for the treatment of dentine hypersensitivity.

Schiff et al (2005)50 conducted a randomized, controlled, parallel-group, double-blind clinical trial comparing stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test; n=38, mean age 31.7) with a sodium fluoride dentifrice (negative control; n=39, mean age 31.1). Subjects were instructed to brush twice daily with the designated dentifrice for eight weeks. At four and eight weeks, significant reductions in thermal (cold air) and tactile sensitivity were observed for the stabilized stannous fluoride-sodium hexametaphosphate dentifrice relative to the control (P <0.0001). At week eight, subjects using the stabilized stannous fluoride dentifrice had 44% less cold air sensitivity and two-times greater tolerance to tactile sensitivity (Figs. 27a, b).

![Figure 27a. Thermal (air) sensitivity](image)
**Significant reduction in thermal sensitivity**

![Figure 27b. Tactile sensitivity (Yeaple probe)](image)
**Significant increase in tolerance of tactile stimulation**

Schiff et al (2006)51 conducted a second randomized, controlled, parallel-group, double-blind clinical trial comparing stabilized stannous fluoride-sodium hexametaphosphate dentifrice (n=45, mean age 32.3) to a negative control sodium fluoride dentifrice (n=45, mean age 32.2), again finding significant reductions in thermal (air) and tactile sensitivity at four and eight weeks (P <0.0001) versus the negative control dentifrice. At week eight, the adjusted mean Schiff thermal sensitivity score was 44% lower for the stabilized stannous fluoride-sodium hexametaphosphate dentifrice group, and tolerance to tactile sensitivity was 1.7 times greater.

He et al (2011)52 investigated the rapid onset of sensitivity relief for a stabilized stannous fluoride-sodium hexametaphosphate dentifrice. A randomized, controlled, parallel-group, examiner-blinded clinical trial was conducted. Subjects with reproducible sensitivity to thermal and tactile stimuli in at least two teeth were randomly assigned to a stabilized stannous fluoride dentifrice (test; n=56, mean age 44) or to a 0.76% sodium monofluorophosphate dentifrice (negative control; n=55, mean age 44). Cold air sensitivity was assessed immediately after product use, and at three days and two weeks. Tactile sensitivity was also assessed at three days and two weeks. Highly significant reductions were observed for all measurements for the stabilized stannous fluoride dentifrice versus control (P <0.0001) (Figs. 28a, b).
He et al (2011) also investigated the rapid onset of sensitivity relief for a stabilized stannous fluoride dentifrice versus a marketed positive control. A randomized, controlled, parallel-group, examiner-blind clinical trial compared the 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test; n=40, mean age 42.4) to an 8% arginine, calcium carbonate, 1450 ppm sodium monofluorophosphate dentifrice (positive control; n=40, mean age 44.9). Sensitivity was assessed by the Thermal Schiff Air Index and a subject self-assessed Thermal Air Visual Analog Scale (VAS). Subjects had at least two sensitive teeth (canines or premolars, in different quadrants) showing reproducible sensitivity to thermal stimuli. Compared to the positive control dentifrice, use of 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice resulted in a statistically significant reduction in sensitivity after first use (7.4%) and week two (20%) based on the Thermal Schiff Air Index (p≤0.005) and after first use (7.2%), day three (15.8%) and week two (28.2%) (P<0.0001) based on VAS (Figs. 29a, b).

**Conclusion**

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is effective for the management of dentine hypersensitivity, and provides for significant immediate and sustained reductions in dentine hypersensitivity.

**Clinical Significance**

- Given the high incidence of dentine hypersensitivity, the effectiveness of this dentifrice provides clinicians with an efficacious desensitizing dentifrice to recommend to patients
- The stabilized stannous fluoride-sodium hexametaphosphate dentifrice offers anti-hypersensitivity benefits that sensitivity dentifrices offer, and additionally offers multiple other important benefits concurrently with treating hypersensitivity
- Stabilized stannous fluoride dentifrice provides both rapid and sustained sensitivity relief
- In addition to rapid onset, the stabilized stannous fluoride dentifrice smear layer is resistant to acid challenges which occur through the modern diet
**Anti-calculus benefit**

Dental calculus forms through the mineralisation of dental plaque, resulting in a variety of different crystalline forms.\(^4\) Firstly, new crystals form, that are composed of calcium and phosphate, which then grow and harden into calculus (Figs. 30-31). The mineral content for supragingival and subgingival calculus is on average 37% and 58% by volume, respectively.\(^5\) Supragingival calculus also contains bacterial debris and toxins as well as viable aerobic and anaerobic bacteria.\(^6,7,8\) This is of clinical significance as it can be a reservoir of pathogenic bacterial species.\(^8\) Dental calculus is common in adults, and less common in children.\(^9\)

**Figure 30. Formation of dental calculus**

Further, dental calculus can only be removed by professional treatment, thus a greater quantity of calculus results in more chair time being required for calculus removal.\(^6\)

Given these facts, several anti-calculus agents have been introduced and studied since the mid-1980s,\(^6,1-66\) including pyrophosphate. The first tartar control toothpaste was introduced in 1985, as Crest Tartar Control. More recently, sodium hexametaphosphate formulations have been found to be highly effective.\(^6,67,68\)

**Figure 31. Supragingival calculus**
Mechanism of action of stabilized stannous fluoride-sodium hexametaphosphate dentifrice

Pyrophosphate helps to reduce dental calculus through a mineral chelating effect that inhibits plaque mineralization. It has a natural binding affinity for calcium ions. The anticalcus effect is due to adsorption and binding of the pyrophosphate to the tooth surface and to forming crystals of calcium phosphate in plaque, helping to inhibit the growth and maturation of calculus.\(^{69,70,71}\)

Sodium hexametaphosphate (Fig. 32) is a longer-chain form of pyrophosphate, with more binding sites. It has a greater affinity for hydroxyapatite surfaces, and binds strongly to the tooth surface and the surface of developing calculus in plaque.\(^{69,72,73}\)

![Hexametaphosphate molecule](image)

Figure 32. Hexametaphosphate molecule

Efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice in inhibiting dental calculus

Schiff et al (2005)\(^{74}\) conducted a randomized, double-blind, parallel-group 6-month clinical trial to compare the anti-calculus effect of a stabilized stannous fluoride-hexametaphosphate dentifrice to a positive control. Subjects were graded for their baseline calculus score, received a prophylaxis and then were randomly assigned to brush twice daily with the 0.454% stabilized stannous fluoride-sodium hexametaphosphate test dentifrice (n=40, mean age 27.6) or the 0.3% triclosan/2% copolymer positive control dentifrice (n=40, mean age 27.4). Criteria for inclusion included a known history of forming at least 1.5 mm of supragingival calculus during a two-month pre-trial period, good oral and general health, and no known sensitivity to tartar-control dentifrices. Subjects were assessed at three and six months, using the Volpe-Manhold Index (V-MI) to measure calculus on the lingual surfaces of the lower six anterior teeth.

At both three and six months, use of test dentifrice resulted in significantly less calculus formation compared to the positive control dentifrice (P<0.0001) with an adjusted mean calculus score that was 56% lower at six months (P <0.0001). Sub-group analyzes further revealed the superior ability of the test dentifrice to inhibit calculus formation in high-calculus-forming subjects (47% lower at months three and six; P<0.01) medium calculus-forming subjects (57% lower at months three and six; P<0.01) and low-calculus-forming subjects (59% and 66% lower at months three and six, respectively; P<0.01). Both dentifrices were found to be safe with no adverse effects during the clinical trial (Table 5).
Baseline Mean (mm) | Covariance (adj. mean) (SE)* (mm) | P Value**
---|---|---
Month 3
Triclosan/copolymer | 15.88 | 11.74 (0.60) | <.0001
Stannous fluoride/SHMP | 16.6 | 5.41 (0.60) |
Month 6
Triclosan/copolymer | 15.88 | 15.79 (0.80) | <.0001
Stannous fluoride/SHMP | 16.6 | 6.92 (0.80) |

* Means adjusted for baseline value; SE is Standard Error  
** All comparisons are 2-sided comparisons at the 0.05 significance level

Table 5. Volpe-Manhold Index Scores: Stabilized stannous fluoride-hexametaphosphate dentifrice inhibits calculus formation versus positive control.

Milleman et al (2011) conducted a three-month, parallel-group, double-blind, randomized and controlled clinical trial to compare the anti-calculus efficacy of 0.454% stannous fluoride test dentifrice with sodium hexametaphosphate with that of 0.3% triclosan/2% copolymer positive control dentifrice. Following a dental prophylaxis and two-month run-in phase, subjects showing the ability to form calculus were randomized to use either the test dentifrice or positive control twice daily for one minute with a standard manual toothbrush over three months. Safety and calculus assessments (V-MI) were done at baseline, week six and month three. Seventy-five of the seventy-seven subjects completed the trial. At both post-treatment visits, use of the test dentifrice resulted in significantly less calculus formation compared to the positive control dentifrice (P <0.01). At week six and month three, the test dentifrice group demonstrated 30.3% and 26.5% lower median levels, respectively, of calculus build-up versus the positive control. Both dentifrices were well tolerated.

Conclusion
Stabilized stannous fluoride-sodium hexametaphosphate dentifrice effectively and safely reduces dental calculus formation. Clinically, this novel dentifrice has proven to be superior to a positive control dentifrice in the inhibition of calculus.

Clinical Significance
- Calculus has a rough surface which has greater potential for more plaque build-up than smooth, clean surfaces; therefore, reducing calculus helps to reduce plaque build-up
- The ability to prevent and control calculus formation with twice-daily use of stabilized stannous fluoride-sodium hexametaphosphate toothpastes helps patients be able to brush more efficiently without accumulations of dental calculus interfering with brushing
- Less dental calculus also means that patients will have easier, more efficient dental cleanings
Anti-stain and whitening

Extrinsic staining on the tooth surface can result from the diet, smoking, and poor oral hygiene. Extrinsic stain can be removed by mechanical means and by chemical means. The use of abrasives in toothpaste helps to remove stain mechanically during toothbrushing, while chemical cleaning agents in the toothpaste can help to displace surface stains from the tooth pellicle (Fig 34). In addition, some chemical compounds have a high enough affinity for the tooth surface and pellicle to actually help prevent new stain from adhering. Polyphosphate molecules, such as sodium hexametaphosphate, that are used for calculus control have also been shown to both prevent stain and whiten teeth.

Figure 34. Binding of pyrophosphates to calcium hydroxyapatite at the tooth surface

Mechanism of Action of stabilized stannous fluoride-sodium hexametaphosphate dentifrice

The stain prevention and whitening effects of stabilized stannous fluoride-sodium hexametaphosphate dentifrice are provided by an advanced, high cleaning silica system and sodium hexametaphosphate (polyphosphate) in the formulation. The high cleaning silica gently removes stain mechanically during brushing, while the sodium hexametaphosphate works chemically.

The sodium hexametaphosphate provides for excellent stain removal and prevention:

- Sodium hexametaphosphate has a strong affinity for and attraction to the tooth surface and the pellicle film at the tooth surface to which surface stain is attached.
  - The sodium hexametaphosphate molecule is negatively charged while the calcium ions in the pellicle and enamel are positively charged. Since opposites attract, the polyphosphate is strongly attracted to these calcium sites.
- The sodium hexametaphosphate adsorbs to the pellicle, disrupting it.
  - As a result of disruption of the pellicle, the stain that was attached to and trapped in it becomes displaced, released and lifted away from the tooth surface.
- Thirdly, the retention of sodium hexametaphosphate at the tooth surface and in the tooth pellicle prevents new stain from binding and accumulating at the tooth surface. (Fig. 35)

Figure 35. Stain prevention and displacement
Efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice

Terézhalmy et al (2007) conducted two independent two-week trials in subjects with pre-existing extrinsic stain (n=29 and n=30, respectively). Subjects in each study were randomly assigned in equal numbers to twice-daily use of either stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test) or 0.3% triclosan/2% copolymer whitening dentifrice (positive control with Seal of the American Dental Association (ADA) for whitening). Stain was measured at baseline and at the end of the two-week trial using the modified Lobene Stain Index for examination of the facial surfaces of the incisors. Stain reductions were 61.8% and 61.9% in Study 1, and 96.6% and 94.4% in Study 2, for the test and positive control dentifrices, respectively. Both dentifrices statistically significantly reduced stain versus baseline in the two studies. There were no statistically significant differences between groups in either study.

He et al (2007) conducted two independent, double-blind, six-week trials comparing the stain removal efficacy of stabilized stannous fluoride-sodium hexametaphosphate dentifrice (test) with that of 0.3% triclosan/2% copolymer whitening dentifrice (positive control with ADA Seal for whitening). For both studies, healthy subjects with extrinsic stain were recruited and randomized to use one of the two dentifrices twice-daily for six weeks. The modified Lobene Stain Index was used to measure stain on the facial surfaces of each anterior tooth at baseline, week three and week six. In both studies (n=52 and n=58), these dentifrices were found to provide statistically significant stain reductions compared to baseline at weeks three and six (P<0.0001). There were no statistically significant differences between groups (Figs. 36a, b).

Gerlach et al (2007) concluded from their meta-analysis of 14 randomized trials and 2246 spontaneous consumer reports of all types, that use of 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice yielded significant reductions in tooth stain in clinical studies, without increased extrinsic stain accumulation in longer-term randomized controlled trials, or appreciable evidence from spontaneous consumer reports (Fig. 37).

*Statistically significant reduction versus baseline, P<0.001.

Figure 36a. Stain removal in Study 1: Stain removal comparable to whitening dentifrice

*Statistically significant reduction versus baseline, P<0.001.

Figure 36b. Stain removal in Study 2: Whitening benefit confirmed in second study

Figure 37. Stain reductions after 2 weeks use of stabilized stannous fluoride-sodium hexametaphosphate dentifrice from clinical trial

Courtesy of American Journal of Dentistry
Conclusion
Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is highly effective at preventing and removing extrinsic stain and is as effective as a whitening dentifrice with the ADA Seal for whitening.

Clinical Significance
- Now the health benefits of stannous fluoride are fully realised without the esthetic drawback of potentially causing stain in some individuals.
- The stabilized stannous fluoride-sodium hexametaphosphate dentifrice not only prevents stain from forming, but actually provides whitening by removing surface stains, an esthetic benefit that is important to the patient.
Anti-halitosis

Halitosis is primarily the result of anaerobic Gram-negative bacteria breaking down sulfur-containing proteins and producing volatile sulfur compounds (VSCs) – mostly methyl mercaptans and hydrogen sulphides. Oral malodor may also occur due to mouth breathing, oral infections, dietary constituents, as well as extra-oral factors. Meticulous oral hygiene reduces the level of oral bacteria, the production of VSCs, and therefore oral malodor. Tongue cleaning has also been recommended to help combat oral malodor since odor-producing bacteria commonly reside on the tongue (Fig. 38).

Mechanism of action of stabilized stannous fluoride dentifrice

VSCs are the bacterial byproducts of metabolic activity, especially in anaerobic Gram-negative bacteria that proliferate on the tongue. Stannous fluoride exerts its anti-bacterial effect, primarily through metabolic inhibition. Ultimately, this leads to a reduction in the production of VSCs. Stannous ion can also bind directly to the sulfur sites in the sulfur-containing metabolic substrates (e.g. the sulfur-containing amino acids methionine and cysteine) creating competitive antagonism for their metabolism. The net effect of either mechanism of action is to reduce the level of foul-smelling VSCs (Fig. 39).

Figure 38. Coating on tongue and heavy bacterial load

Sulfur-Containing Protein Building Blocks (amino acids)

<table>
<thead>
<tr>
<th>Sulfur-Containing Protein Building Blocks (amino acids)</th>
<th>Noxious Smelling Volatile Sulfur Compounds (VSCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>Methyl Mercaptan (natural gas smell)</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Hydrogen Sulfide (rotten egg smell)</td>
</tr>
</tbody>
</table>

Figure 39. Source of Oral Malodor: GNA bacteria use protein as an energy source and produce volatile sulfur-containing byproducts

Efficacy of stabilized stannous fluoride dentifrice

Stabilized stannous fluoride is effective in reducing and controlling oral malodor. Farrell et al (2007) conducted two independent controlled, double-blind, cross-over design studies to compare the effects of stabilized stannous fluoride-sodium hexametaphosphate dentifrice with a sodium fluoride control dentifrice on overnight breath malodor after only one day of product use. In the first study (n=26), a halimeter was used to measure VSCs at baseline in the morning before brushing and twenty-four hours later after the assigned product had been used for a morning and evening brushing (i.e. one day of product use). The halimeter measures VSCs in parts per billion, primarily hydrogen sulfide and additionally methyl mercaptans (Fig. 40). In the second study (n=49), a hedonic scale was used to measure breath odor. The hedonic scale is a subjective assessment performed by breath judges who rate the quality of breath odor (‘9’ being the most unpleasant and ‘1’ the most pleasant). In both studies, the stabilized stannous fluoride-sodium hexametaphosphate dentifrice provided a statistically significant greater improvements relative to the control after one day of product use.
Nachnani et al (2008) demonstrated the long-term effectiveness of 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice in reducing halitosis with three weeks of twice daily use. The study was a randomized, double-blind, parallel-group, two-treatment clinical trial with seventy-one subjects randomized to either the stabilized stannous fluoride-sodium hexametaphosphate dentifrice or 1,100 ppm sodium fluoride dentifrice (negative control). The level of halitosis was measured, using a hedonic score (1 to 9) at baseline, week one and week three before morning brushing. Significantly greater reductions in halitosis were observed with the stabilized stannous fluoride-sodium hexametaphosphate than with the control dentifrice at both time points (P <0.0001) (Table 6).

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean</th>
<th>Week 1 Mean (SE)</th>
<th>Week 3 Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SnF}_2 \cdot \text{SHMP dentifrice}$</td>
<td>8.19</td>
<td>3.4* (0.18)</td>
<td>1.55* (0.18)</td>
</tr>
<tr>
<td>NaF dentifrice</td>
<td>8.19</td>
<td>6.62 (0.18)</td>
<td>5.28 (0.18)</td>
</tr>
</tbody>
</table>

*Significantly greater reduction versus NaF dentifrice (p<0.0001).

**Table 6. Breath odor (hedonic) scores at baseline, week one and week three**

**Conclusion**
These studies prove the efficacy of 0.454% stabilized stannous fluoride-sodium hexametaphosphate dentifrice in reducing halitosis with short-term overnight use as well as longer-term use over a period of several weeks.

**Clinical Relevance**
- Reducing oral malodor is a desirable patient benefit
- A stabilized stannous fluoride dentifrice can provide the patient with short-term benefits, and long-lasting results, with twice daily usage
- This multi-benefit stabilized stannous fluoride dentifrice offers the ability to control halitosis, along with many other important benefits
Summary

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice is unique among fluoride dentifrices, offering eight therapeutic and cosmetic benefits.

In summary, this breakthrough dentifrice offers:

• Effective reductions in gingivitis, plaque and halitosis due to anti-bacterial mechanisms of action
• Effective anti-caries protection
• Effective management of dentine hypersensitivity through tubule occlusion
• Superior anti-erosion capabilities compared to other fluorides
• Effective anti-calculus activity
• Effective whitening (stain prevention) and stain removal

Stabilized stannous fluoride-sodium hexametaphosphate dentifrice: proven efficacy for eight oral care benefits
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