

THE SCIENCE AND EVIDENCE FOR
**STABILIZED STANNOUS
FLUORIDE DENTIFRICE**

FOREWORD

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 formulations providing a broad range of therapeutic and cosmetic benefits.

The manual describes:

- key scientific innovations allowing Procter & Gamble to deliver the full potential of this unique fluoride source and formulate it with anti-calculus and whitening agents
- stannous fluoride's mechanism of action against plaque, gingivitis, caries, erosion, hypersensitivity, and breath malodor
- the mechanism of action of anti-calculus and anti-stain ingredients
- laboratory and clinical data demonstrating the significant benefits of stabilized stannous fluoride dentifrice formulations

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 dentifrice, visit dentalcare.com.



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WHY DENTIFRICE IS IMPORTANT

The oral environment is an ecosystem comprised of diverse microorganisms. Plaque biofilms provide a protective matrix in which these bacteria reside. Factors such as oral hygiene, nutrition, and host response impact the toxicity of plaque biofilms and the extent to which they have harmful consequences on hard and soft tissues. Mechanical hygiene is commonly used to remove plaque biofilms, but it is well-recognized that most patients have sub-optimal oral hygiene, largely due to not following proper brushing technique and/or insufficient brushing time (Beals et al. 2000). Poor plaque removal can lead to various oral diseases (e.g., caries, gingivitis) and conditions (e.g., tooth stain, calculus).

This is where the right dentifrice choice plays a critical role in protecting patients' oral health and the appearance of their smile. Dentifrice is a convenient, cost-effective delivery system to provide fluoride, anti-bacterial agents and other ingredients that provide benefits beyond brushing alone. Dental professionals are in a unique position to educate patients on the best dentifrice option to address their specific oral health needs.

STANNOUS FLUORIDE: MORE BENEFITS THAN OTHER FLUORIDES

There is a misconception that “all fluorides are the same”. That’s simply not true. Stannous fluoride is unique among fluoride compounds, offering multiple benefits not found with sodium fluoride or sodium monofluorophosphate. While all three compounds provide anti-caries benefits, stabilized stannous fluoride has demonstrated broader and significantly greater protection than other fluorides against plaque (Sharma et al. 2013; Garcia-Godoy et al. 2015), gingivitis (Archila et al. 2004; Mallatt et al. 2007), erosion (Hooper et al. 2007; West et al. 2017), sensitivity (Schiff et al. 2005; He et al. 2011) and halitosis (Farrell et al. 2007). (See Table 1)



Table 1. Stannous fluoride offers broader and greater protection relative to other fluorides.

Fluoride Type	Sodium Fluoride	Sodium Monofluorophosphate	Stannous Fluoride
			
Plaque			X
Gingivitis			X
Erosion			X
Sensitivity			X
Halitosis			X

So why isn't stannous fluoride used in every dentifrice? Stannous fluoride has some inherent challenges to formulate, requiring skill and expertise to ensure it is delivered in a bioavailable, esthetically pleasing dentifrice (White 2013). These challenges can be overcome by including extrinsic whitening agents and ingredients to stabilize the stannous fluoride (e.g., chelants), but it's not a simple process. The following section describes decades of innovations by Procter & Gamble resulting in the largest portfolio of stabilized stannous fluoride dentifrices available to improve patients' oral health and provide a brushing experience that delights them.

(See Figure 1)

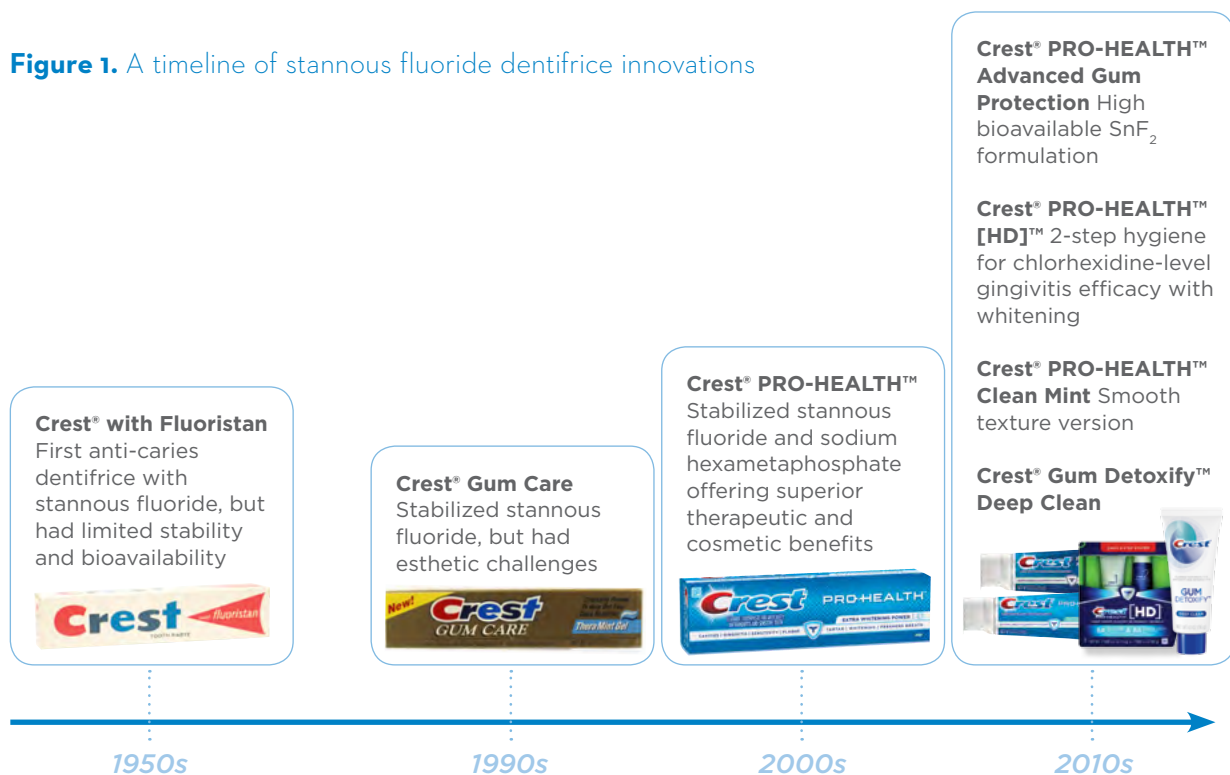
1950s

The anti-caries benefit of fluoride was confirmed in the mid-1940s (Dean et al. 1942). However, an effective anti-caries dentifrice was not brought to market until 1955, when Procter & Gamble and collaborators at Indiana University became the first to successfully formulate stannous fluoride into a clinically proven dentifrice, with caries reductions of up to 53% (Muhler et al. 1954). The stannous fluoride in this early dentifrice had limited stability. While the product delivered an anti-caries benefit, the full therapeutic benefits of stannous fluoride were not realized. Subsequently, the stannous fluoride in daily use dentifrice 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.

1990s

By the early 1990s, stannous fluoride systems had been stabilized and reformulated with a new abrasive system in the formulation. During this era, there was also more focus from the dental professional community on plaque and gingivitis control. After researching a number of formulations, a new stabilized stannous dentifrice (Crest® Gum Care) was launched in the mid-1990s focused on periodontal health (White 1995). The reception was mixed. The new dentifrice was highly effective at plaque and gingivitis control as well as caries prevention. Trade-offs persisted, however, such as a lack of anti-tartar effect and some extrinsic staining. The challenge was how to provide therapeutic benefits, while concurrently providing cosmetic benefits of tooth whitening and tartar control.

Figure 1. A timeline of stannous fluoride dentifrice innovations



2000s

A series of inventions by P&G ultimately led to the formulation of a stabilized stannous fluoride dentifrice with an advanced anti-calculus and whitening agent, sodium hexametaphosphate (Baig & He 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. The formulation was marketed across the globe as Crest® PRO-HEALTH™ or Oral-B® Pro-Expert, depending on the region.

The first key invention leading to this breakthrough included developing chemical approaches to protect the stannous ion from inactivation by oxidation and hydrolysis which typically occur when stannous fluoride is formulated into a dentifrice. Second, groundbreaking research on tartar control agents led to the discovery of sodium hexametaphosphate, a powerful whitening and anti-calculus ingredient. Third, 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.

2010s

The current decade has seen three more innovations in the Procter & Gamble stabilized stannous fluoride dentifrice portfolio to further enhance efficacy and provide esthetic alternatives to meet different patient preferences:

- A high bioavailable version of Crest® PRO-HEALTH™ (Crest® PRO-HEALTH™ Advanced Gum Protection) was launched containing stannous chloride as a reservoir for stannous to allow even greater stannous bioavailability for enhanced gingivitis efficacy (Gerlach & Amini 2012, He et al. 2012a, He et al. 2012b).
- A novel 2-step system was launched as Crest® PRO-HEALTH™ [HD]™. Patients brush with stabilized stannous fluoride dentifrice for 1 minute (step 1) followed by a 1-minute brushing with hydrogen peroxide whitening gel (step 2). Separating oral hygiene into two consecutive steps optimizes gingival health benefits to a level comparable to chlorhexidine but also provides significant extrinsic whitening (Gerlach et al. 2015, Sagel et al. 2016).
- A “smooth texture” stabilized stannous fluoride dentifrice version was introduced with zinc citrate as the anti-calculus agent to appeal to patients who don’t like the characteristic “gritty texture” of formulas with sodium hexametaphosphate (Milleman et al. 2017). This formula also includes distinct flavors and foaming to create a novel brushing experience.

Each stabilized stannous fluoride dentifrice provides multiple mechanisms of action and delivers 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 (Baig & He 2005). Stannous fluoride also promotes the occlusion of open dentinal tubules associated with hypersensitivity and binds to the enamel surfaces to protect against acid erosion (Zsiska et al. 2011, Faller & Eversole 2014). Additionally, tooth whitening and calculus control are delivered by sodium hexametaphosphate or other ingredients, depending on the specific formulation (Schiff et al. 2005, Terezhalmay et al. 2007, Farrell et al. 2016, Friesen et al. 2017).

The following pages address the mechanisms of action and efficacy of the stabilized stannous fluoride dentifrice formulas for each important oral care benefit.

1 IA																										18 VIIIA									
1 H Hydrogen 1.008																		2 He Helium 4.003																	
3 Li Lithium 6.941		4 Be Beryllium 9.012																																	
Periodic Table of the Elements																																			
11 Na Sodium 22.990		12 Mg Magnesium 24.305																		13 B Boron 10.811		14 C Carbon 12.011		15 N Nitrogen 14.007		16 O Oxygen 15.999		17 F Fluorine 18.998		18 Ne Neon 20.180					
19 K Potassium 39.098		20 Ca Calcium 40.078		21 Sc Scandium 44.956		22 Ti Titanium 47.88		23 V Vanadium 50.942		24 Cr Chromium 51.996		25 Mn Manganese 54.938		26 Fe Iron 55.933		27 Co Cobalt 58.933		28 Ni Nickel 58.693		29 Cu Copper 63.546		30 Zn Zinc 65.39		31 Ga Gallium 69.732		32 Ge Germanium 72.61		33 As Arsenic 74.922		34 Se Selenium 79.972		35 Br Bromine 79.904		36 Kr Krypton 84.89	
37 Rb Rubidium 84.463		38 Sr Strontium 87.62		39 Y Yttrium 88.906		40 Zr Zirconium 91.224		41 Nb Niobium 92.906		42 Mo Molybdenum 95.95		43 Tc Technetium 98.907		44 Ru Ruthenium 101.07		45 Rh Rhodium 102.906		46 Pd Palladium 106.42		47 Ag Silver 107.865		48 Cd Cadmium 112.411		49 In Indium 114.818		50 Sn Tin 118.710		51 Sb Antimony 121.760		52 Te Tellurium 127.6		53 I Iodine 126.904		54 Xe Xenon 131.29	
55 Cs Cesium 132.905		56 Ba Barium 137.327		57-71		72 Hf Hafnium 178.49		73 Ta Tantalum 180.948		74 W Tungsten 183.85		75 Re Rhenium 186.207		76 Os Osmium 190.23		77 Ir Iridium 192.22		78 Pt Platinum 195.08		79 Au Gold 196.967		80 Hg Mercury 200.59		81 Tl Thallium 204.383		82 Pb Lead 207.2		83 Bi Bismuth 208.980		84 Po Polonium [209]		85 At Astatine 208.98		86 Rn Radon 222.018	
87 Fr Francium 223.020		88 Ra Radium 226.025		89-103		104 Rf Rutherfordium [261]		105 Db Dubnium [262]		106 Sg Seaborgium [266]		107 Bh Bohrium [264]		108 Hs Hassium [269]		109 Mt Meitnerium [268]		110 Ds Darmstadtium [269]		111 Rg Roentgenium [272]		112 Cn Copernicium [277]		113 Uut Ununtrium [284]		114 Fl Flerovium [289]		115 Uup Ununpentium [292]		116 Lv Livermorium [293]		117 Uus Ununseptium [294]		118 Uuo Ununoctium [294]	
Lanthanide				57 La Lanthanum 138.906		58 Ce Cerium 140.115		59 Pr Praseodymium 140.908		60 Nd Neodymium 144.24		61 Pm Promethium 144.913		62 Sm Samarium 150.36		63 Eu Europium 151.965		64 Gd Gadolinium 157.25		65 Tb Terbium 158.925		66 Dy Dysprosium 162.50		67 Ho Holmium 164.930		68 Er Erbium 167.26		69 Tm Thulium 168.934		70 Yb Ytterbium 173.04		71 Lu Lutetium 174.967			
Actinide				89 Ac Actinium 227.028		90 Th Thorium 232.038		91 Pa Protactinium 231.036		92 U Uranium 238.029		93 Np Neptunium 237.048		94 Pu Plutonium 244.064		95 Am Americium 243.061		96 Cm Curium 247.070		97 Bk Berkelium 247.070		98 Cf Californium 251.080		99 Es Einsteinium [254]		100 Fm Fermium 257.095		101 Md Mendelevium 258.1		102 No Nobelium 259.101		103 Lr Lawrencium [262]			

ANTI-PLAQUE ACTIVITY

It is widely acknowledged that mechanical hygiene is the most common method to remove plaque, however mechanical plaque removal is not enough (Bellamy et al. 2014). Stannous fluoride chemotherapeutically inhibits plaque regrowth and metabolism to improve plaque control.

The development of supragingival plaque can be divided into several distinct phases (Marsh 2006, Liljemark & Bloomquist 1996, Hojo et al. 2009, Lovegrove 2004):

- **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 colonization 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 extra-cellular matrix that facilitates the attachment and division of bacteria (co-aggregation) and protects the micro-colonies from host defenses and antimicrobial agents. Co-adhesion enables other bacteria to adhere to the earlier colonizers. 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 organised with micro-colonies interspersed with voids and channels that allow nutrients and other agents to circulate through the plaque (*Figure 2*). 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.

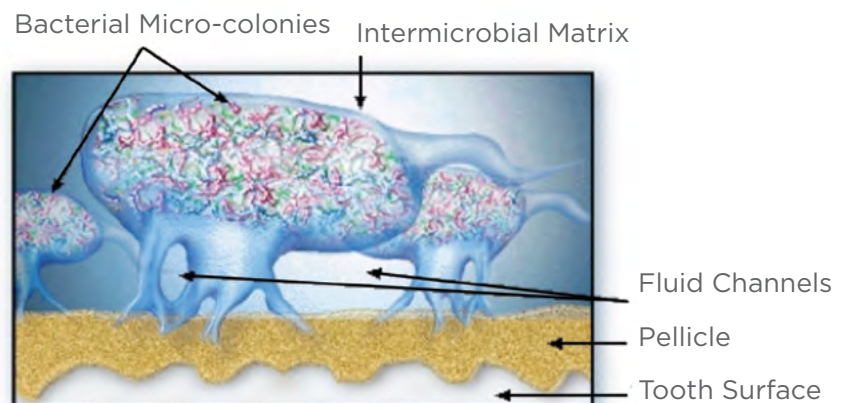


Figure 2. The structure of dental plaque

Image courtesy of dentalcare.com

Mechanism of action of stannous fluoride and anti-bacterial activity

Scientific evidence indicates the anti-bacterial activity of stannous fluoride 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 dentifrice, consistent with the plaque and gingivitis reductions observed for the dentifrice and indicative of a sustained mechanism of action with twice-daily use (Ramji et al. 2005, Otten et al. 2012).

Early studies of stannous fluoride suggest that it affects bacterial adhesion. Plaque bacteria produce extracellular polysaccharides (EPS) which are responsible for the adhesiveness of the plaque. Busscher et al. (2008) demonstrated that stabilized stannous fluoride dentifrice significantly reduced EPS production in vivo compared to a regular sodium fluoride dentifrice. 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 (Ellingsen et al. 1980). 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 (Ramji et al. 2005). 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.

Most recently, research has shown that stannous fluoride makes plaque less toxic, or less virulent, by neutralizing lipopolysaccharides (LPS), or bacterial endotoxins (Haught et al. 2016a, Haught et al. 2016b, Huggins et al. 2016, Klukowska et al. 2017). LPS are responsible for activating toll-like receptors, which trigger the host response and inflammatory cascade associated with periodontal disease. By blocking the reactivity of LPS with tissue receptors that trigger inflammation, stannous fluoride decreases the pathogenicity of plaque.



Stannous fluoride inhibits plaque by:

- Killing bacteria
- Inhibiting plaque metabolism/acid production/regrowth
- Reducing bacterial adhesion and cohesion
- Reducing plaque virulence
- Sustained activity (retained up to 12 hours)

Research Summaries ●●●●●●●●●●

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for plaque control.

A 24-Hour Dental Plaque Prevention Study with a Stannous Fluoride Dentifrice

Full text available in the Research Database at www.dentalcare.com

Reference: White DJ, Kozak KM, Gibb RD, Dunavent JM, Klukowska M, Sagel PA.
J Contemp Dent Pract. 2006; 7(3):1-11

CONCLUSION

Crest® PRO-HEALTH™ produced a statistically significant reduction in dental plaque coverage 24 hours following last use.

OBJECTIVE

To determine whether the antiplaque efficacy of Crest® PRO-HEALTH™, a dentifrice containing anti-bacterial stannous fluoride (and sodium hexametaphosphate for cosmetic benefits), extended to 24 hours post use.

MATERIALS AND METHODS

- The study design comprised 3 phases:
 1. An initial 1-week treatment period with a regimen that included toothbrushing with standard sodium fluoride dentifrice (Cavity Protection Regular) in conventional b.i.d. brushing;
 2. A second 1-week treatment period regimen where a modified hygiene regimen was applied using - Cavity Protection Regular. A non-brushing period of 24 hours was included.
 3. A third 1-week treatment period which was identical to the second treatment period except subjects used Crest® PRO-HEALTH™ instead of Crest® Cavity Protection Regular.
- A digital plaque image analysis (DPIA) technique was used to quantify in situ plaque formation. Plaque formation was assessed in morning measurements following either standard evening hygiene (treatment period 1) or 24 hours since brushing (treatment periods 2 and 3). Post-brushing plaque measurements were also taken in each treatment regimen.
- Study subjects were adults with sufficient plaque levels in pilot pre-screening to warrant participation.



Imaging System

RESULTS

- Sixteen subjects completed all three treatment regimens with no side effects or oral complaints.
- Treatment period 1:
Morning plaque coverage was 13.3%.
- Treatment period 2:
Plaque coverage significantly increased when pre-bedtime brushing was discontinued, with 24-hour growth covering 18.4% of the dentition.
- Treatment period 3:
Intervention of the antimicrobial stannous fluoride dentifrice provided significant inhibition of plaque regrowth over 24 hours (15.2% coverage, a 17.4% reduction vs. sodium fluoride dentifrice control).
- These results support the strong retention and lasting antimicrobial efficacy of Crest® PRO-HEALTH™ dentifrice.

Morning Pre-Brushing Treatment Comparisons

Dentifrice Treatment	Number of Subjects	Plaque % Coverage Mean (SD)	Treatment Comparison <i>P</i> -value* vs. Sodium Fluoride 24 Hour Protocol
Period 1 - Standard Protocol			
Sodium Fluoride	16	13.3 (4.27)	<0.0001
Period 2 - 24 Hour Protocol			
Sodium Fluoride	16	18.4 (5.97)	
Period 3 - 24 Hour Protocol			
Stannous Fluoride	16	15.2 (6.87)	0.0002

* Two-sided *P*-values from a paired-difference t-test.

Plaque Control Evaluation of a Stabilized Stannous Fluoride Dentifrice Compared to a Triclosan Dentifrice in a Six-Week Trial

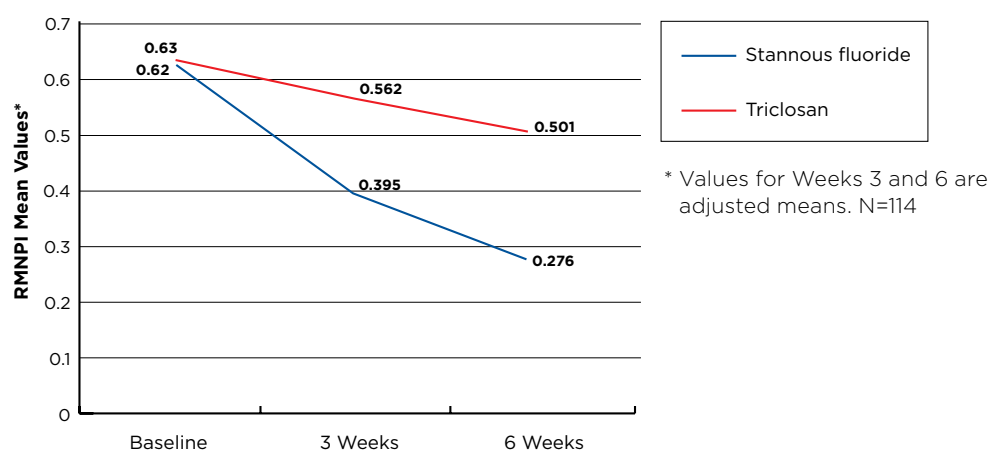
Reference: Sharma N, He T, Barker ML, Biesbrock AR. *J Clin Dent* 2013;24:31-36

KEY CLINICAL RESULTS

Both the stannous fluoride dentifrice and the triclosan dentifrice produced a statistically significant reduction from baseline in mean plaque values for whole mouth, gingival margin, and interproximal plaque at Weeks 3 and 6 ($P < 0.02$ for all comparisons).

The stannous fluoride dentifrice showed a statistically significantly ($P < 0.0001$) lower adjusted mean plaque level compared to the triclosan group for all three tooth areas at both Weeks 3 and 6. Whole mouth plaque scores for the stannous fluoride dentifrice were 29.7% lower at Week 3 and 44.9% lower at Week 6 than the triclosan dentifrice (Figure 1).

Figure 1. Whole mouth plaque levels at Baseline, Week 3 and Week 6 per group.



OBJECTIVE

To compare a stabilized 0.454% stannous fluoride dentifrice to a 0.3% triclosan/sodium fluoride dentifrice for anti-plaque efficacy.

METHODS

- This was a 6-week, randomized, double-blind, two-treatment, parallel-group clinical trial.
- Generally healthy adults with baseline plaque levels ≥ 0.5 as assessed by Rustogi, et al. Modified Navy Plaque Index (RMNPI) were randomized to one of the following treatments:
 - 0.454% stannous fluoride dentifrice (Crest® PRO-HEALTH™ Advanced Deep Clean, Procter & Gamble)
 - or
 - 0.3% triclosan/0.24% sodium fluoride dentifrice (Colgate Total, Colgate-Palmolive)

Subjects brushed their teeth with a soft manual toothbrush (Oral-B® Indicator™, Procter & Gamble) using their assigned treatment dentifrice according to the manufacturer's instructions.

- Overnight plaque accumulation was evaluated by an experienced examiner using the RMNPI at baseline, Week 3 and Week 6. Groups were compared using analysis of covariance separately for Weeks 3 and 6, and by repeated measures for Weeks 3 and 6 combined.

A Clinical Trial to Assess Plaque Prevention with Use of a Daily Two-Step Dentifrice and Gel System

Reference: García-Godoy C, Duque N, Rothrock JA. *J Dent Res* 2016; 95 (Spec Iss A): Abstract 1708.

KEY CLINICAL FINDING

The two-step dentifrice and gel system group had significantly ($P \leq 0.011$) less overnight (pre-brush) percent plaque area than the control group at Week 1 (52.9%) and Week 2 (45%). See Figures 1 & 2. Step 1 is a 0.454% stannous fluoride dentifrice and Step 2 is a 3% hydrogen peroxide whitening gel.

Figure 1. Mean Overnight (Pre-Brush) Percent Plaque Area

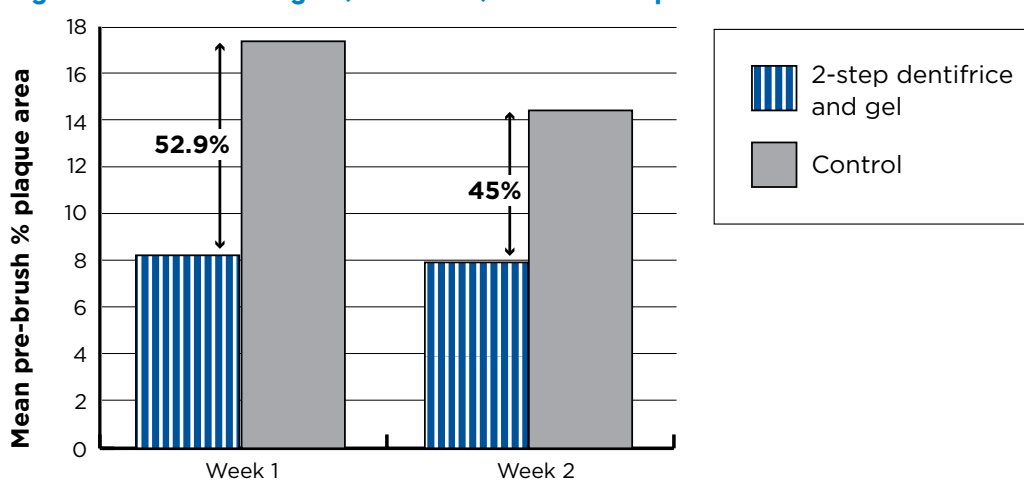
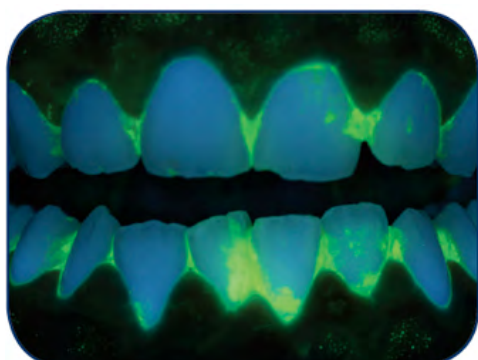
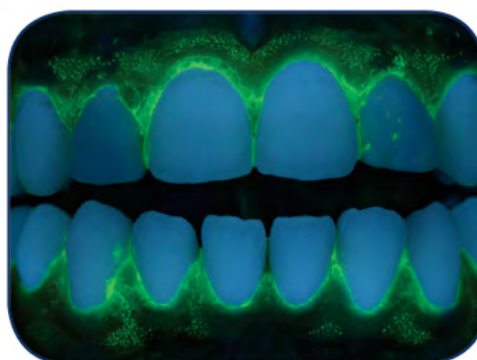


Figure 2. Representative response of overnight plaque coverage at Week 1



Standard oral hygiene control
19.4%



2-step dentifrice and gel system
6.8%



OBJECTIVE

To assess plaque area following a dental prophylaxis and twice daily use of a 2-step dentifrice and gel system versus a standard oral hygiene control.

METHODS

- This was a randomized, controlled, examiner-blind, 2-treatment parallel group plaque prevention study among healthy adult volunteers with plaque.
- Following a whole-mouth dental prophylaxis, subjects were randomized to one of two groups:
 - Standard oral hygiene control group: 0.76% sodium monofluorophosphate dentifrice (Colgate® Cavity Protection, Colgate-Palmolive) and a soft, regular manual toothbrush (Oral-B® Indicator™, Procter & Gamble)
 - 2-step dentifrice and gel system (Crest® PRO-HEALTH™ [HD]™, Procter & Gamble): Step 1, 0.454% stannous fluoride dentifrice; Step 2, 3% hydrogen peroxide whitening gel. The system was used with a soft, regular manual toothbrush (Oral-B® Indicator™).
- Overnight percent plaque area was assessed after 1 and 2 weeks of treatment by digital image analysis of fluorescein-disclosed plaque.

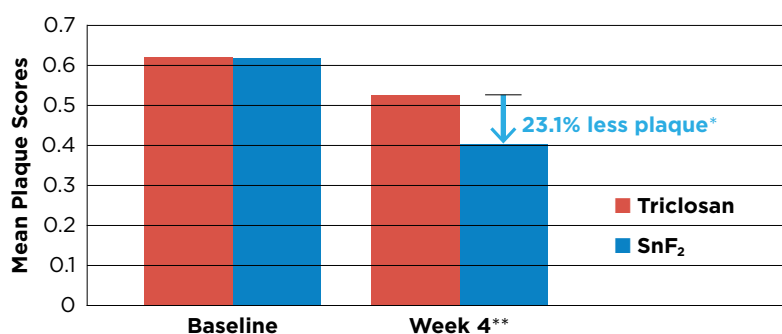
Comparative Anti-plaque Effect of Stabilized Stannous Fluoride and Triclosan Dentifrices

Reference: Friesen L, Goyal CR, Qaqish J, et al. *J Dent Res* 2017; 96 (Spec Iss A): Abstract 0214.

KEY CLINICAL FINDINGS

- After 4 weeks of use, the stabilized stannous fluoride (SnF₂) dentifrice group had 23.1% lower whole mouth plaque scores and 43.5% lower interproximal plaque scores than the triclosan positive control dentifrice group ($P < 0.0001$). See Figures 1 and 2.
- Both the triclosan and SnF₂ dentifrice groups demonstrated statistically significant ($P < 0.0001$) reductions in plaque levels at Week 4 versus Baseline.
- Both treatments were well tolerated.

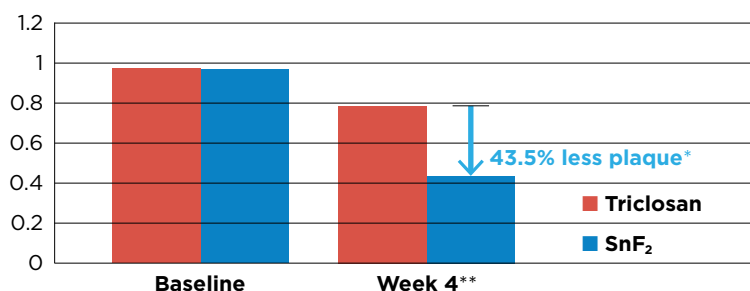
Figure 1. Whole mouth plaque scores at Baseline and Week 4.



N=118. *Statistically significant difference between groups, $P < 0.0001$.

**Week 4 values are adjusted means.

Figure 2. Interproximal plaque scores at Baseline and Week 4.



OBJECTIVE

To compare the effect of a SnF₂ dentifrice versus triclosan dentifrice on reduction of plaque over a 4-week period.

STUDY DESIGN

- This was a randomized, parallel, double-blind, 4-week clinical trial including subjects with evidence of plaque.
- Subjects were randomized to one of two treatment groups:
 - Experimental 0.454% stabilized SnF₂ dentifrice (Crest® PRO-HEALTH™ Clean Mint [Smooth Formula], Procter & Gamble) or
 - Triclosan positive control dentifrice with 0.24% sodium fluoride (Colgate® Total®, Colgate-Palmolive). Both groups used a soft, regular manual toothbrush (American Dental Association) and brushed with their respective product according to manufacturer's instructions at-home.
- Plaque was evaluated using the Rustogi Modification of the Navy Plaque Index (RMNPI) at Baseline and after 4 weeks of product use.
- Statistical analyses utilized analysis of covariance with baseline value as covariate.

CLINICAL COMMENT

Chemotherapeutic antimicrobial dentifrices play an important role in the control of plaque-induced oral diseases, such as gingivitis. Both SnF₂ and triclosan dentifrices have been shown to provide significant inhibition of plaque.^{1,2} This study showed the new smooth formula SnF₂ dentifrice provided significantly greater plaque control than the triclosan dentifrice. These findings are consistent with other studies in the literature showing superior plaque protection for SnF₂ versus triclosan dentifrice.^{3,4}

¹White DJ, et al. *J Contemp Dent Pract.* 2006;July (7)3:001-011.

²Rover JA, et al. *Am J Dent.* 2014 Jun;27(3):167-70.

³He T, et al. *Am J Dent.* 2013;26: 303-306.

⁴Sharma NC et al. *J Clin Dent.* 2013;24:31-36.



Clinical Significance

- These results demonstrate stabilized stannous fluoride dentifrice is an effective anti-plaque agent.
- The comparative studies demonstrate stabilized stannous fluoride dentifrice provides greater plaque reductions compared to 0.3% triclosan/copolymer dentifrice at three and six weeks.

ANTI-GINGIVITIS ACTIVITY

Gingivitis is a common oral disease, reported to affect 4 of 5 adults across the globe (Beaglehole 2009). 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 (*Figure 3*). Gingivitis can be prevented by maintaining low levels of plaque, and it can also be reversed (Tonetti et al. 2015).

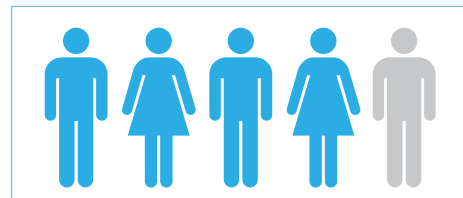
Plaque produces an inflammatory reaction in the gingival tissues that results in increased blood flow and dilation of blood vessels. This is accompanied by an increase in all types of inflammatory cells, leading to swelling and reddening of the tissues after 48–96 hours. Continued exposure to plaque 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. Without intervention, it may remain stable or progress to periodontitis with loss of attachment and destruction of the alveolar bone.



Figure 3. Gingivitis with redness and swelling

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



Gingivitis affects 4 of 5 adults globally

Mechanism of action of stannous fluoride

The reductions in gingivitis observed with stabilized stannous fluoride dentifrice are due to the broad-spectrum anti-bacterial activity of stannous fluoride (Ramji et al. 2005). Stannous fluoride inhibits bacterial metabolism, and thus reduces bacterial growth, bacterial adhesion and the production of toxins that potentiate gingival inflammation (Ramji et al. 2005, White 1995). Stannous fluoride also reduces the virulence of plaque by blocking the reactivity of LPS with tissue receptors that trigger inflammation (Haught et al. 2016a).

The stannous ion has high substantivity in the oral cavity, imparting a long-lasting anti-bacterial effect (Scott et al. 2009). Stannous levels in plaque remain above levels that are sufficient to inhibit metabolic activity up to twelve hours after exposure (Ramji et al. 2005). Otten et al. (2012) demonstrated that twelve hours after brushing with stabilized stannous fluoride 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 contributes to 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.



Stannous fluoride reduces gingival bleeding and inflammation by:

- Killing bacteria
- Inhibiting plaque metabolism/acid production/regrowth
- Reducing bacterial adhesion and cohesion
- Reducing plaque virulence
- Sustained activity (retained up to 12 hours)

Gingivitis Research Summaries ●●●●●●●●●●

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for the reduction of gingivitis.

Anti-Gingivitis Efficacy of a Stabilized 0.454% Stannous Fluoride Dentifrice: A Controlled 6-Month Clinical Trial

Reference: Mankodi S, Bartizek RD, Winston JL, et al. *J Clin Periodontol*. 2005;32(1):75-80.

CONCLUSION

Over a 6-month period a 0.454% stabilized stannous fluoride (Crest® PRO-HEALTH™) dentifrice showed a statistically significant and clinically relevant effect on the control and prevention of gingivitis compared to a negative control dentifrice (Colgate® Cavity Protection).

OBJECTIVE

To investigate the long-term anti-gingivitis efficacy of a 0.454% stabilized stannous fluoride dentifrice (with sodium hexametaphosphate for cosmetic benefits) compared to a negative control dentifrice.

MATERIALS AND METHODS

- 0.454% stabilized stannous fluoride experimental dentifrice (Crest® PRO-HEALTH™) was compared to a negative control dentifrice (Colgate® Cavity Protection).
- Study subjects were 143 generally healthy adults with a minimum of 18 natural teeth, a baseline Modified Gingival Index score of 1.75-2.3, and a Turesky Plaque Index score of ≥ 1.5 .
- Subjects were randomly assigned to either the experimental stannous fluoride dentifrice or the negative control dentifrice to use over 6 months and were instructed to brush twice daily for 1 minute with a manual soft toothbrush.
- At baseline, oral soft tissue was examined. Subjects were scored for gingivitis (Modified Gingival Index), plaque (Turesky Plaque Index), and gingival bleeding (Gingival Bleeding Index), and received a dental prophylaxis.
- At months 3 and 6 plaque, gingivitis, gingival bleeding, and safety were reassessed.

RESULTS

- 130 subjects completed the 6-month study.

- At 6 months, scores for the experimental group compared to the negative control group were significantly reduced for gingivitis (Modified Gingival Index) (21.7%; $P<0.001$), for bleeding (Gingival Bleeding Index) (57.1%; $P<0.001$), and for plaque (Plaque Index) (6.9%; $P=0.01$).
- No adverse oral soft-hard-tissue effects or extrinsic tooth staining were observed.

6-Month Results

Treatment	N	Baseline Mean $\pm$ SD	Adjusted Mean ^a $\pm$ SE	% Reduction ^b
Modified Gingival Index				
Control	66	2.04 $\pm$ 0.10	2.01 $\pm$ 0.03	
Experimental	64	2.03 $\pm$ 0.10	1.57 $\pm$ 0.03	21.7%
Gingival Bleeding Index				
Control	66	8.68 $\pm$ 3.40	8.88 $\pm$ 0.39	
Experimental	64	9.39 $\pm$ 3.22	3.81 $\pm$ 0.40	57.1%
Plaque Index				
Control	66	2.91 $\pm$ 0.35	2.30 $\pm$ 0.05	
Experimental	64	2.73 $\pm$ 0.41	2.14 $\pm$ 0.05	6.9%

^a Adjusted means and standard errors from analysis of covariance with baseline score as covariate.

^b Percent reduction = 100% $\times$ (control-experimental mean)/control mean.

Assessment of the Effects of a 0.454% Stannous Fluoride Dentifrice on Gingivitis in a 2-Month Positive-Controlled Clinical Trial

Reference: He T, Barker ML, Goyal CR, Biesbrock AR. *Am J Dent.* 2012;25:136-140

KEY CLINICAL RESULTS

- Baseline values were balanced across the treatment groups ($P>0.36$) with overall baseline means of 2.09 for gingivitis, 15.8 for gingival bleeding and 15.6 for number of bleeding sites. Relative to baseline, both the stannous fluoride dentifrice group and the positive control group demonstrated a statistically significant ($P<0.0001$) reduction in gingivitis, gingival bleeding, and number of bleeding sites at Month 2.
- Between-treatment group comparisons for change from baseline showed the improvement from baseline for the stannous fluoride group was 45% greater for gingivitis, 60% greater for gingival bleeding and 62% greater for number of bleeding sites versus that of the positive control group ($P<0.0001$). See Figures 1–3.
- At Month 2, the stannous fluoride dentifrice group demonstrated statistically significantly lower adjusted mean scores versus the positive control group for all 3 measures ($P<0.0001$).

Figure 1 - Analysis of Covariance Summary for gingivitis (MGI). Improvement from baseline at Month 2.

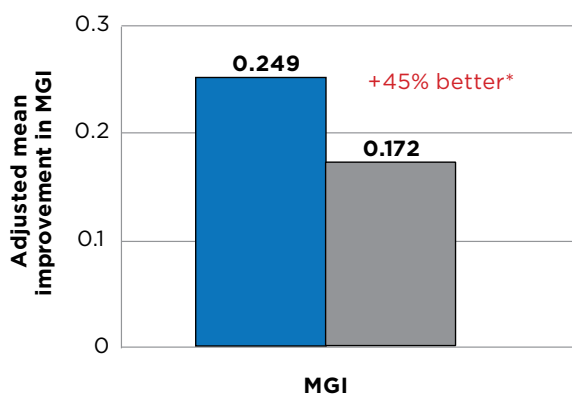


Figure 2 - Analysis of Covariance Summary for gingival bleeding (GBI). Improvement from baseline at Month 2.

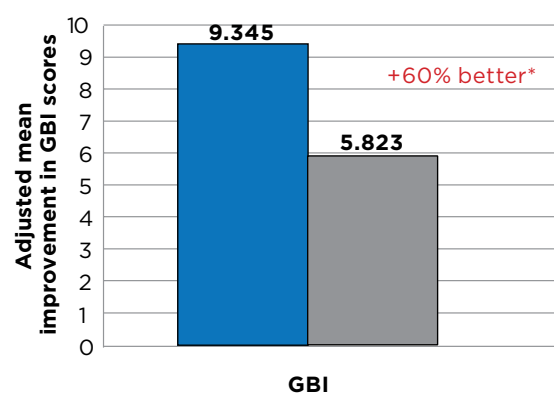
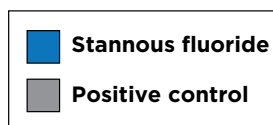
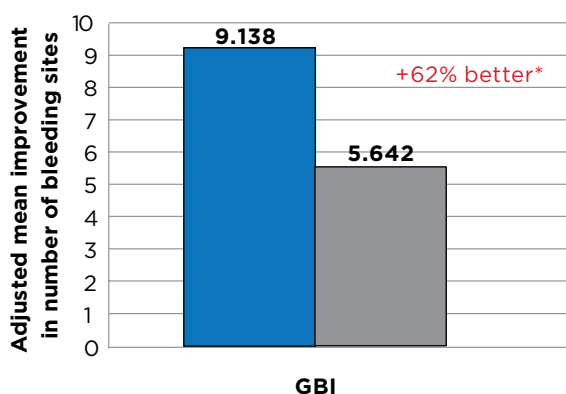


Figure 3 - Analysis of Covariance Summary for number of bleeding sites. Improvement from baseline at Month 2.



* Statistically significant difference between groups, favoring the stannous fluoride group ($P<0.0001$)

OBJECTIVE

To assess the effects of a 0.454% stannous fluoride dentifrice on the treatment of gingivitis as compared to a positive control dentifrice in a 2-month clinical trial.

STUDY DESIGN

- This was a randomized, positive-controlled, double-blind, parallel-group, singlecenter study with two treatment groups composed of healthy adult volunteers.
- 200 qualified subjects were enrolled; each treatment group contained 100 subjects. 99 subjects in the stannous fluoride group and 97 in the positive control group completed the study.
- During the treatment phase, subjects performed their treatment routine unsupervised using their assigned dentifrice (Crest® PRO-HEALTH™ Clinical Gum Protection with 0.454% stannous fluoride, Procter & Gamble, or Colgate® Total with 0.3% triclosan and 0.32% sodium fluoride, Colgate-Palmolive) per manufacturers' instructions (twice daily for stannous fluoride dentifrice; three times daily for the control) for 2 months. Both groups used an ADA soft reference manual toothbrush.
- Efficacy measurements were obtained at Baseline and 2-months posttreatment. Anti-gingivitis efficacy was determined using mean Modified Gingival Index (MGI) and Gingival Bleeding Index (GBI).
- Oral soft tissue and hard tissue assessments were conducted at each examination interval.

A Randomized 2-Month Clinical Trial Evaluating the Anti-Gingivitis Efficacy of a Stabilized Stannous Fluoride Dentifrice versus a Triclosan Dentifrice

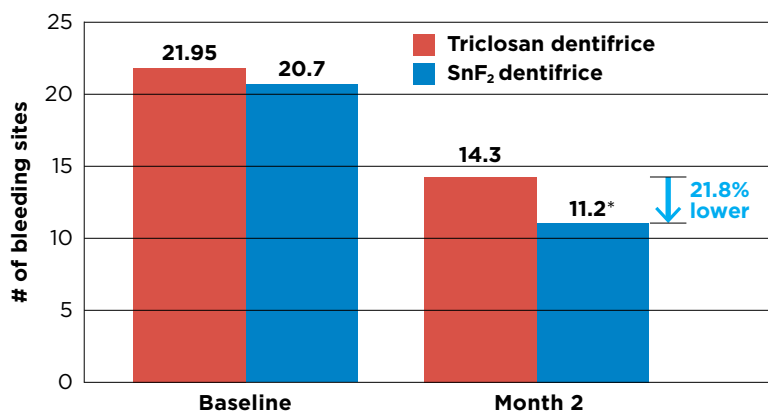
Reference: CR Goyal¹, JG Qaqish¹, T He², R Eusebio².

¹All Sum Research, Mississauga, Ontario, Canada. ²Procter & Gamble, Mason, OH USA

KEY CLINICAL FINDINGS

- After 2 months of use, the stabilized stannous fluoride (SnF₂) test dentifrice group had 21.8% fewer bleeding sites versus the triclosan positive control dentifrice group ($P < 0.001$).
- Both groups showed statistically significant reductions in bleeding sites from Baseline ($P < 0.0001$).

Figure 1. Number of bleeding sites per group



* Significant difference between groups at Month 2, $P < 0.001$. Groups were not significantly different at Baseline ($P > 0.05$).

OBJECTIVE

To compare the anti-gingivitis efficacy of a stabilized SnF₂ dentifrice versus a positive control triclosan dentifrice over a 2-month period.

METHODS

- This was a randomized, positive-controlled, double-blind, parallel-group clinical trial involving generally healthy adults with mild to moderate gingivitis.
- Qualifying subjects were randomized to one of two treatment groups:
 - 0.454% stabilized SnF₂ dentifrice (Crest® PRO-HEALTH™ Clean Mint [Smooth Formula], Procter & Gamble)
 - Positive control dentifrice with 0.3% triclosan and 0.243% sodium fluoride (Colgate® Total®, Colgate-Palmolive)
- Dentifrice was distributed over-labeled or over-tubed for blinding purposes, with a soft manual flat-trim toothbrush (Oral-B® Indicator™, Procter & Gamble). Subjects were instructed to brush with their respective dentifrice according to each manufacturer's instructions.

- The following efficacy and safety evaluations were conducted at Baseline and Month 2: Gingival Bleeding Index; Modified Gingival Index; and Oral Soft Tissue.
- Treatment groups were compared using analysis of covariance with Baseline value as covariate. All statistical tests were two-sided with a 5% level of significance.

CLINICAL COMMENT

Gingival bleeding is an important early sign of gingivitis, the initial stage of periodontal disease. Reducing gingival bleeding is the ultimate goal of treating gingivitis, since research indicates the absence of gingival bleeding is a reliable indicator for sustained periodontal health.* This clinical trial showed subjects using the SnF₂ dentifrice had significantly fewer (21.8%) bleeding sites than those using a positive control triclosan dentifrice after 2 months of use. Based on these findings, dental professionals should consider recommending the SnF₂ dentifrice to patients with gingivitis to reduce bleeding and improve periodontal health.

* Lang NP. et al. *J Clin Periodontol*. 1990 Nov;17(10):714-21.

A Randomized Clinical Trial to Assess Gingivitis, Plaque, and Tooth Color after Use of a Daily Two-Step Dentifrice and Gel System versus Chlorhexidine Rinse

Reference: Gerlach RW, Sagel PA, Barker ML, et al. *J Dent Res* 2015; 94 (Spec Iss A): Abstract 0293.

KEY CLINICAL FINDINGS

Overall

- Use of a daily 2-step dentifrice and gel system resulted in plaque and gingivitis reductions comparable to chlorhexidine (with regular brushing) plus provided tooth whitening benefits. Step 1 is a 0.454% stannous fluoride dentifrice and Step 2 is a whitening gel.

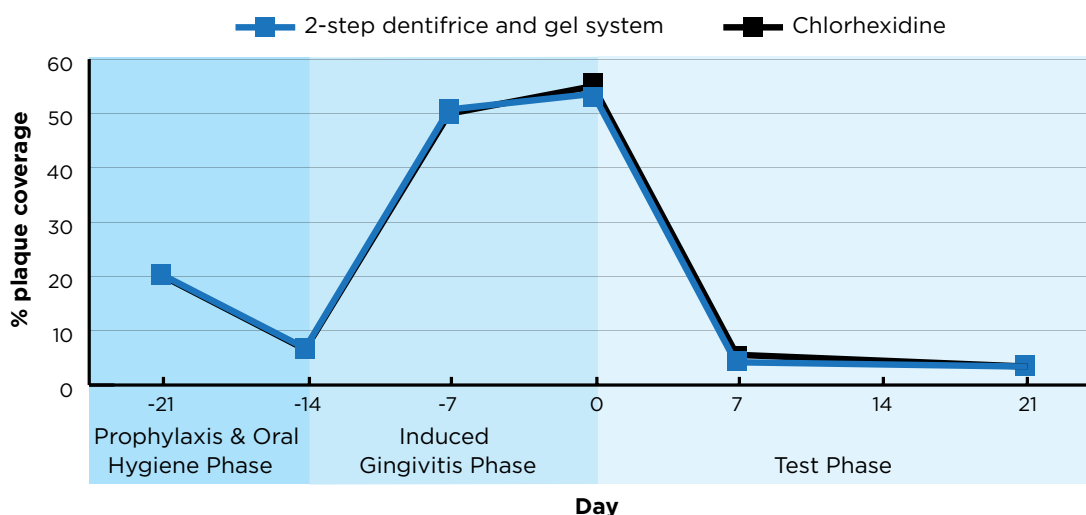
Plaque and Gingivitis

- The daily 2-step dentifrice and gel system group and the chlorhexidine group had statistically significant ($P<0.01$) improvements in plaque area and gingivitis color measurements at both Day 7 and Day 21 from Day 0. See Figures 1 and 2.
- There were no statistically significant differences between the 2-step dentifrice and gel system group and the chlorhexidine group in plaque and gingivitis reduction at Day 7 and Day 21.

Tooth Color

- The 2-step dentifrice and gel system group demonstrated statistically significantly ($P<0.03$) greater improvement in tooth color lightness (L^*) values compared to the chlorhexidine group at Day 7 and 21. See Figure 3.

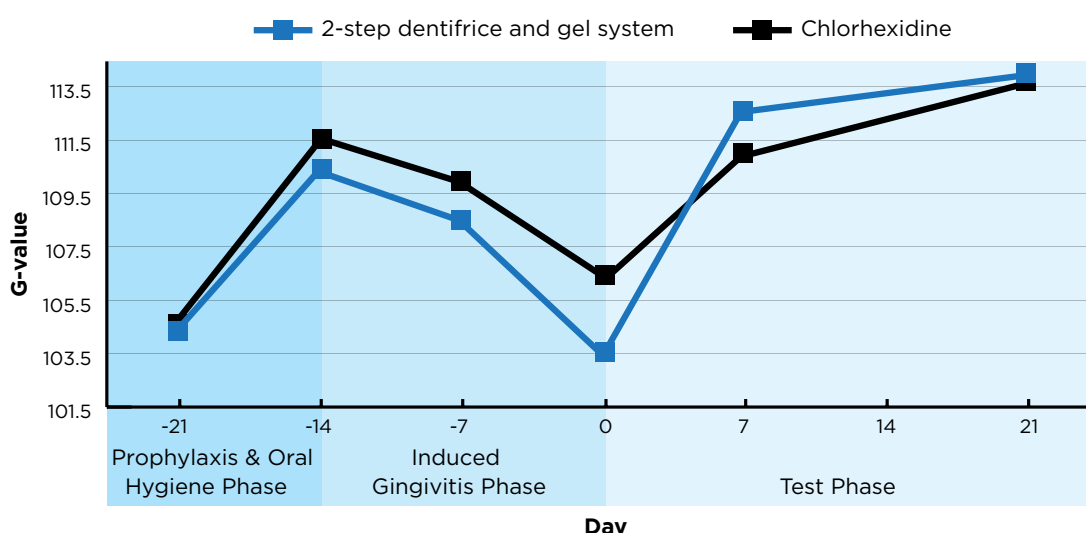
Figure 1. Percent Plaque Coverage



* Day 7 and Day 21 are Means adjusted for Day 0. For both groups, Day 7 and Day 21 scores were statistically significantly different ($P<0.0001$) from Day 0.

Figure 2. Gingivitis

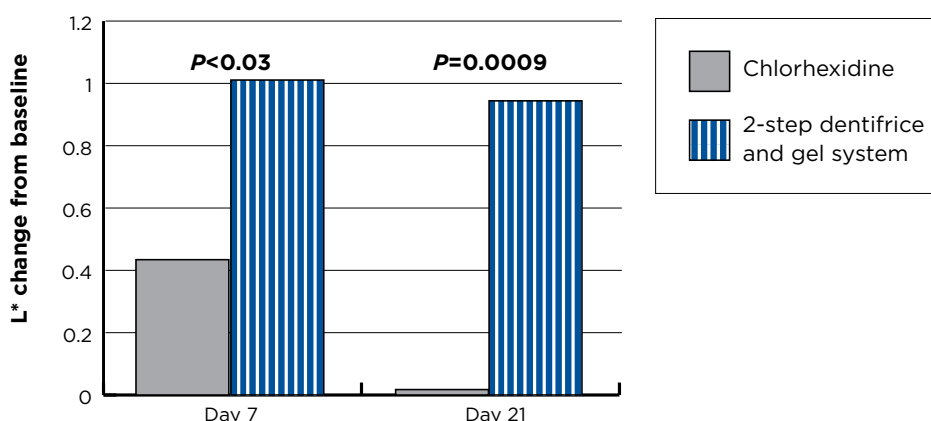
(Digital Gingival Imaging, a higher G-value indicates less gingivitis)



* Day 7 and Day 21 are Means adjusted for Day 0 For both groups, Day 7 and Day 21 scores were statistically significantly different ($P < 0.007$) from Day 0.

Figure 3. Tooth color lightness (L^*) change from baseline

(Combined Arches, Analysis of Covariance)

**OBJECTIVE**

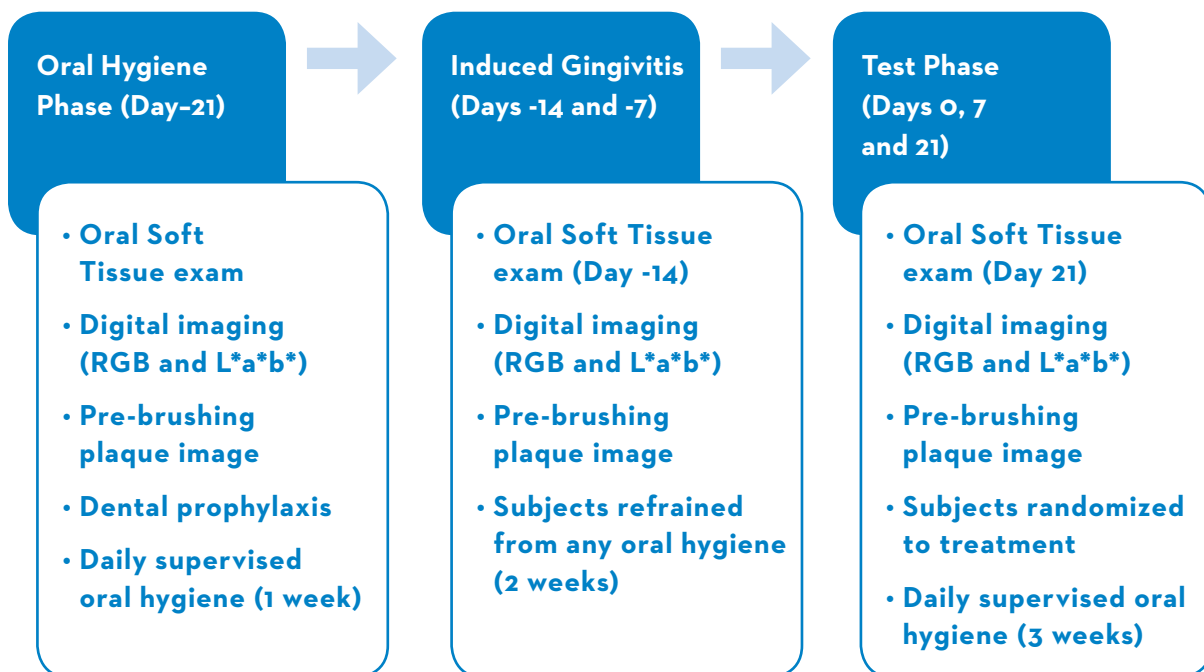
To assess the effect of a daily 2-step dentifrice and gel system versus chlorhexidine (with regular brushing) using imaging of plaque, gingivitis and tooth color in an induced gingivitis model.

METHODS

- This was a single-blind, supervised-use, randomized, parallel-group, positive-controlled clinical trial.
- During the Oral Hygiene Phase, up to 40 healthy volunteers received a dental prophylaxis and used regular oral hygiene products under supervision for one week. During the Induced Gingivitis Phase, subjects refrained from oral hygiene for two weeks. After gingivitis induction, subjects were randomized into 2 treatment groups for the test phase: 2-step dentifrice and gel system or chlorhexidine mouth rinse plus regular brushing. Gingivitis (RGB*), plaque (area %) and tooth color ($L^*a^*b^*$) were measured by digital image analysis after one and three weeks of product use. See Figure 4.

- During the test phase, subjects were randomly assigned to one of the following treatment groups based on average gingival redness (G) score and pre-brush percent plaque coverage:
 1. Daily 2-Step System (Crest® PRO-HEALTH™ [HD]™, Procter & Gamble): Step 1, 0.454% stannous fluoride dentifrice; Step 2, 3% hydrogen peroxide whitening gel and a soft, regular manual toothbrush (Oral-B® Indicator™).
 2. 0.12% chlorhexidine gluconate oral rinse (Oral-B®), 0.76% sodium monofluorophosphate dentifrice (Colgate® Cavity Protection toothpaste) and a soft, regular manual toothbrush (Oral-B® Indicator™).
- Subjects were instructed on product use. Study personnel supervised product use twice daily at least 5 and up to 7 days a week until the end of the study.

Figure 4. Study Design



* Standard Test Method for Objective Measurement of Gingival Color Using Digital Still Cameras. ASTM E2545 - 07(2012). <http://www.astm.org/Standards/E2545.htm>



Clinical Significance

- These results demonstrate significant gingivitis and bleeding site reductions with use of stabilized stannous fluoride dentifrice.
- The comparative results demonstrate a significant improvement with stabilized stannous fluoride dentifrice compared to 0.3% triclosan/copolymer dentifrice in gingivitis and bleeding site reductions.
- These results indicate the significant reductions in gingivitis that can be anticipated with twice-daily use of 0.454% stabilized stannous fluoride- dentifrice as part of an oral hygiene regimen.

ANTI-CARIES BENEFIT

Dental caries is endemic globally (Beaglehole et al. 2009). 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. *Figure 4* shows caries prevalence for the 6–19 year-old age group in a number of countries (Beaglehole 2009).

Cariogenic bacteria in supragingival dental plaque, predominantly *Mutans streptococci* and *Lactobacilli*, metabolize 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

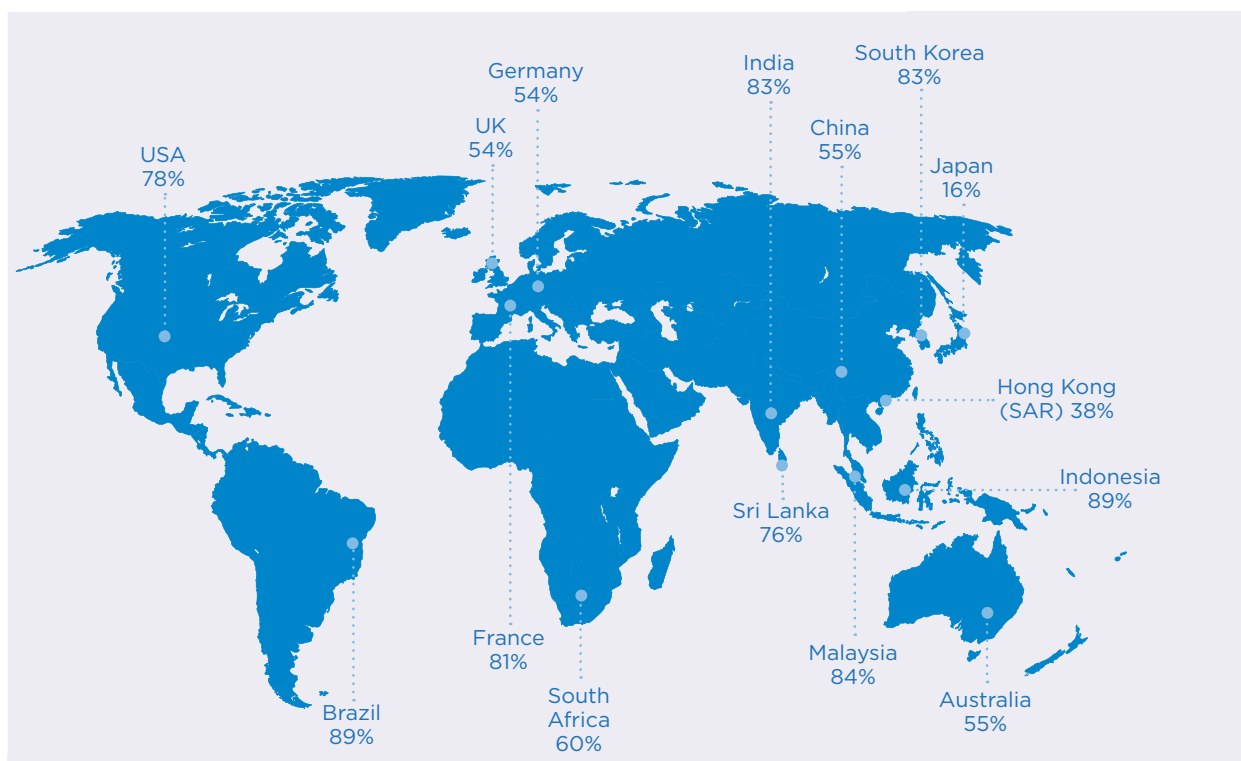
Twice daily use of fluoride dentifrices is well-established as being effective in reducing caries and reversing early carious lesions (Marinho et al. 2003). Interventions that increase the amount of fluoride available to alter the plaque/tooth surface interaction are the most successful for caries prevention:

- 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 (*Figure 5*)

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 (Biesbrock et al. 2001)
- 2,500 ppm sodium monofluorophosphate dentifrice has demonstrated a 16–20% greater reduction in caries (DMFS) compared to 1,000 ppm (Stephen et al. 1988)

Figure 4. Prevalence of dental caries



Remineralization

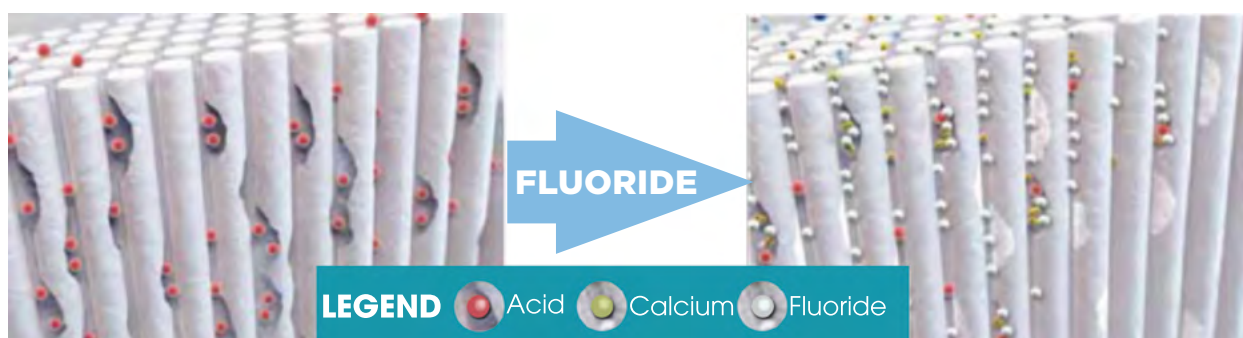
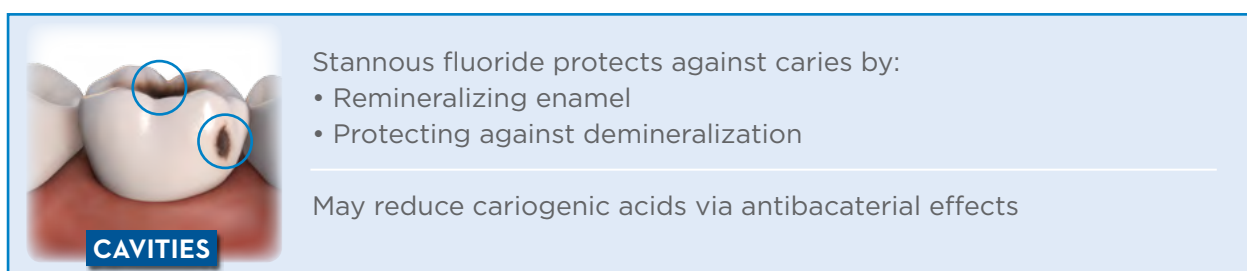


Figure 5. Mechanism of action in fluoride

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 the anti-bacterial actions of stannous which reduce the production of plaque acids (Kasturi et al. 1995).



Caries Research Summaries

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for caries protection.

A Stabilized Stannous Fluoride Dentifrice: In Vitro Studies of Anticaries Potential

Full text available in the Research Database at www.dentalcare.com

Reference: Pfarrer AM, McQueen CM, Lawless MA, Rapozo-Hilo M, Featherstone JDB. *Compend Contin Educ Dent*. 2005;26(Suppl1):41-46.

CONCLUSION

In vitro studies demonstrated the anticaries potential of the stabilized stannous fluoride dentifrice.

OBJECTIVE

To examine the anticaries potential of a stabilized stannous fluoride dentifrice with sodium hexametaphosphate (for cosmetic benefits).

MATERIALS AND METHODS

In vitro anti-caries profile methods were:

- Fluoride uptake into demineralized enamel: single-treatment, mechanism-of-action study.
- Remineralization/inhibition of demineralization: multiple-treatment study under lesion progression pH-cycling conditions. Dentifrices compared in the respective profile methods were:
 - **Fluoride uptake**
 - Stabilized stannous fluoride with sodium hexametaphosphate (1,100 ppm fluoride as stannous fluoride, sodium hexametaphosphate, and silica)
 - United States Pharmacopeia (USP) Reference Standard (1,100 ppm fluoride as stannous fluoride and silica)
 - Dose-response control USP Reference Standard (diluted to 250 ppm fluoride as stannous fluoride and silica)
 - Placebo negative control (<1ppm fluoride and silica)
 - **Remineralization/inhibition of demineralization**
 - Stabilized stannous fluoride with sodium hexametaphosphate
 - Sodium fluoride with sodium hexametaphosphate (1,100 ppm fluoride as sodium fluoride, sodium hexametaphosphate, and silica)
 - Stannous fluoride USP Reference Standard (1,100 ppm fluoride as stannous fluoride and silica)
 - Sodium fluoride USP Reference Standard (1,100 ppm fluoride as sodium fluoride and silica)
 - Dose-response sodium fluoride control
 - Placebo negative control (<1ppm fluoride)

- **Fluoride uptake**

Human enamel samples from extracted teeth – 3 mm diameter cores – were decalcified for 24 hours to produce early caries lesions 20-30 µm deep. Samples were taken from the cores by the microdrill biopsy technique. Samples were measured for fluoride levels pre-dentifrice treatment. Groups of specimens were treated with dentifrice/saliva slurries. Samples were taken to determine post-treatment fluoride levels. The difference between pre and post levels determined fluoride uptake.

- **Remineralization/inhibition of demineralization**

Caries-free human molar or premolar crowns were each treated to produce a 3 x 2 mm window on one surface as the entry point for demineralization. 24-hour test cycles – 6 hours demineralization, 1 minute dentifrice treatment, 16 hours remineralization, 1 minute treatment – were repeated for 14 days. Cycles were designed to model normal demineralization and remineralization. The resulting lesions were measured for progression into the enamel, and mineral loss from each lesion calculated.

RESULTS

- **Fluoride uptake**

There was no statistically significant difference between the stannous fluoride with sodium hexametaphosphate toothpaste and the stannous fluoride USP Reference Standard toothpaste.

- **Remineralization/inhibition of demineralization**

The stannous fluoride with sodium hexametaphosphate toothpaste was at least as good as the clinically proven stannous fluoride and sodium fluoride USP Reference Standard toothpastes.

Product	Mean Fluoride Uptake* µgF/cm ² (SD)	Mean mineral loss: ΔZ [†] µm x Vol % min (SD)
Stannous fluoride with SHMP	8.09 (0.25) ^a	36 (260) ^a
Sodium fluoride with SHMP	-	85 (257) ^a
Stannous fluoride USP Reference Standard	7.44 (0.98) ^a	281 (139) ^a
Sodium fluoride USP Reference Standard	-	298 (401) ^a
Dose-response control	5.48 (0.25) ^b	738 (642) ^b
Placebo	2.76 (0.84) ^c	2,567 (870) ^c
* Mean (n = 4) values with different letter designations are significantly different (P<.05) by the least significant difference test. † Mean (n = 10) values with different letter designations are significantly different (P<.05) by the least significant difference test. SD = standard deviation; SHMP=sodium hexametaphosphate; USP=United States Pharmacopeia.		

The Relative Anticaries Effectiveness of Three Fluoride-Containing Dentifrices in Puerto Rico

Full text available in the Research Database at www.dentalcare.com

Reference: Stookey GK, Mau MS, Isaacs RL, Gonzalez-Gierbolini C, Bartizek RD, Biesbrock AR. *Caries Res.* 2004;38:542-550.

CONCLUSION

In a 2-year clinical trial, subjects in both the high-dose sodium fluoride dentifrice (2,800 ppm F) group and the 0.454% stabilized stannous fluoride dentifrice (SnF_2 , 1,100 ppm F) group showed significantly fewer caries increments than subjects in the sodium fluoride positive control dentifrice group (1,100 ppm F). The low-NaF group (550 ppm F) and the positive control group did not differ.

OBJECTIVE

To compare the anticaries effectiveness of a low-dose (500 ppm F) and high-dose (2,800 ppm F) sodium fluoride dentifrice (low-NaF and high Na-F) and an experimental dentifrice (SnF_2 ; 1,100 ppm F) with a sodium fluoride positive control dentifrice (1,100 ppm F) over 2 years. (Note: This was an early prototype of the eventual marketed stannous fluoride/sodium hexametaphosphate product.)

MATERIALS AND METHODS

- The four dentifrices compared were as follows: an experimental dentifrice (0.454% SnF_2 and sodium hexametaphosphate for cosmetic benefits), low-NaF, high-NaF, positive control.
- Study subjects were 955 schoolchildren (-9-12 years) from an urban area in Puerto Rico.
- Subjects were randomly assigned to the four treatments and were supplied with their dentifrice and toothbrushes, which were replaced every 3 months. Their 1-minute toothbrushing was supervised twice a day by teachers in the classroom; brushing was *ad libitum* outside school hours.
- Caries were assessed by visual-tactile examinations (with aid of fiber-optic illumination and artificial light, mouth mirror, compressed air, dental explorer) as DMFS (decayed, missing, and filled surfaces) by two examiners and supplemented with a radiographic examination at baseline and after 12 and 24 months.
- Both examiners examined all subjects. Examiners were tested for the sensitivity and specificity of their examinations and repeatability of their results prior to the study.

RESULTS

- 799 subjects completed the year 1 assessment; 683 subjects were re-examined at year 2.
- Considering evaluable subjects (i.e., those who attended at least 60% of the supervised brushing sessions over the 2-year study period):
 - Both examiners showed that caries increments were lower in the high-NaF group than the control group.
 - Both examiners showed statistically significantly less caries in the SnF_2 group than the positive control group.
 - Neither examiner showed statistically significant differences in caries increments between low-NaF and positive control groups.

Two-year caries increment results for evaluable subjects (attended 60% of supervised visits)

Dentifrice	n	mean ^a	Adjusted mean DMFS		
			SEM	% reduction ^b	p value
Examiner A					
500 ppm F	161	6.05	0.355	2.7	0.631
1,100 ppm F	168	6.21	0.347	-	-
2,800 ppm F	176	5.38	0.339	13.4	0.043
Experimental	159	5.16	0.369	17.0	0.019 ^c
Examiner B					
500 ppm F	161	4.30	0.308	12.2	0.916
1,100 ppm F	168	4.89	0.300	-	-
2,800 ppm F	176	3.76	0.294	23.2	0.004
Experimental	150	3.64	0.319	25.5	0.002 ^d
a Adjusted means from analysis of covariance.					
b Percent reduction = 100% (1,100 ppm mean minus treatment mean) divided by 1,100 ppm mean.					
c Two-sided p-value is 0.038.					
d Two-sided p-value is 0.005.					

In Situ Evaluation Of Sodium Hexametaphosphate-Containing Dentifrices

Reference: Wefel JS, Stanford CM, Ament DK, Hogan MM, Harless JD, Pfarrer AM, Ramsey LL, Leusch MS, Biesbrock AR. *Caries Res.* 2002;36(2):122-8.

CONCLUSION

Based on this research, sodium hexametaphosphate does not interfere with the normal fluoride activity of the toothpastes tested. Relative to the positive and negative controls, the experimental dentifrice with stannous fluoride was numerically better at inhibiting demineralization of sound root surfaces.

OBJECTIVE

An investigator-blinded, in situ clinical study was conducted to evaluate the effects of two experimental dentifrice formulations containing sodium hexametaphosphate, an anticalculus/whitening agent, on demineralization/remineralization.

MATERIALS AND METHODS

Experimental dentifrices were:

- Stannous fluoride (SnF_2) with sodium hexametaphosphate (Note: This was an early prototype of the eventual marketed stannous fluoride/sodium hexametaphosphate product.)
- Sodium fluoride (NaF) and sodium hexametaphosphate

Both experimental dentifrices were packaged in a dual-phase tube

Three controls were used to evaluate the experimental dentifrice formulations' ability to alter demineralization-remineralization:

- SnF_2 -positive control
- NaF -positive control
- No fluoride placebo-negative control

The single-section crown model, developed at the University of Iowa, was used to evaluate the fluoride efficacy of the treatments.

The crown slot held:

- 1) a sound root section;
- 2) a root surface lesion section; and
- 3) enamel surface lesion section.

Thirty subjects were randomized to one of 10 treatment sequences involving 5 dentifrice treatments. Each dentifrice was used twice per day for 1 month over the 5-month period. At the end of each leg, the gold crown was removed and replaced by a new crown with three new substrates.

RESULTS

Results suggested a clinical level of anticaries activity for the experimental SnF₂ and NaF dentifrice formulations that was as good as either of the positive controls, when evaluated using polarized light microscopy.

Root Sections: Analysis of Variance

Treatment	N	Root lesion mean difference	SE	Ranking*
Placebo	27	-114.18	11.22	A
SnF ₂ positive control	27	-80.91	11.23	B
NaF positive control	27	-69.88	11.24	B
NaF-SHMP experimental	28	-61.10	10.97	B
SnF ₂ -SHMP experimental	28	-57.60	10.97	B

Treatment	N	Sound root mean depth, µm	SE	Ranking*
Placebo	26	260.82	22.48	A
NaF positive control	27	202.51	22.00	B
NaF-SHMP experimental	28	161.77	21.47	BC
SnF ₂ positive control	27	153.06	21.96	BC
SnF ₂ -SHMP experimental	28	118.91	21.47	C

* Based on pairwise comparisons ($P < 0.05$)
See publication for additional results.



Clinical Significance

- Stabilized stannous fluoride dentifrice provides effective caries management as part of a multi-benefit dentifrice.
- Research shows an early dual-phase prototype of the stannous fluoride formula with sodium hexametaphosphate provided a similar level of protection compared to a prescription strength (2,800 ppm F) dentifrice in a two-year clinical trial.

ANTI-EROSION

Dental erosion is prevalent in children and adults globally, with some researchers finding it present in approximately half of adolescents (Al-Dlaigan et al. 2001; McGuire et al. 2009). Estimated prevalence in some locations can be found in *Figure 6*.

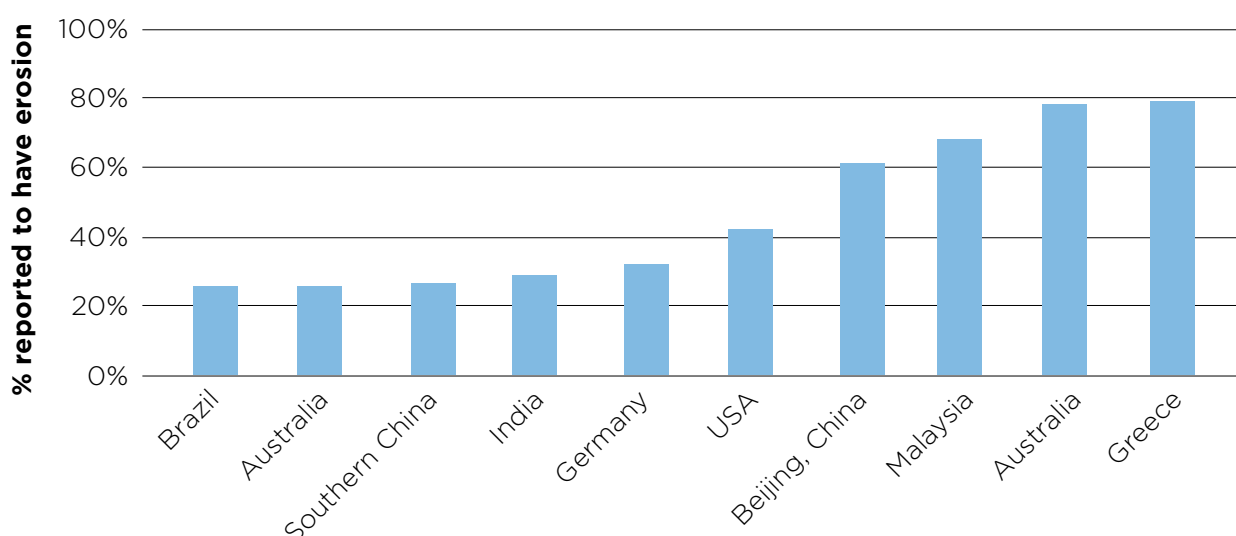


Figure 6. Estimated prevalence of dental erosion among youth

(Nayak et al. 2010; Hou et al. 2009; Wiegand et al. 2006; Deery et al. 2000; Kazoullis et al. 2007; Wang et al. 2010; Manaf et al. 2012; Mantonanaki et al. 2013; Nahás et al. 2011)

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 (Moazzez et al. 2004; Bouqot & Seime 1997). Dental erosion involves the demineralization and softening of the tooth surface, which once softened, is highly susceptible to abrasion and attrition (*Figure 7*). A diagnosis of erosion can be made based on the pattern of surface loss of enamel and/or dentin (*Figures 8a,b*)

Exposure to acid



Demineralization



● Acid

Figure 7. Demineralization associated with dental erosion



Figure 8a. Generalized erosion
Courtesy of Prof. Ian Meyers



Figure 8b. 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 demineralization of the surface with subsequent surface loss and this process is irreversible (*Figures 9a, b*).

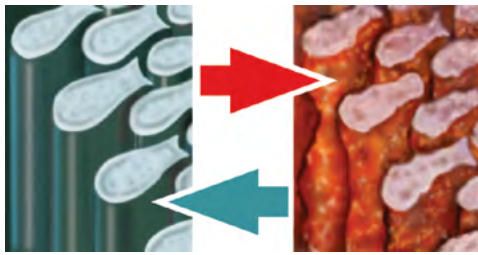


Figure 9a. Dental caries process

Reversible

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

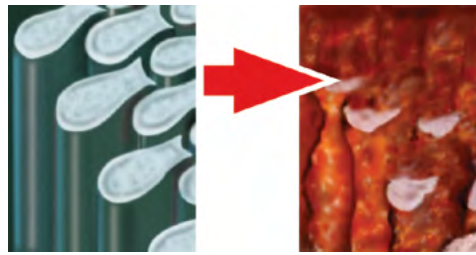


Figure 9b. Dental erosion process

Irreversible

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

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

The deposition of stannous ions at the tooth surface helps protect it against dental erosion (Faller & Eversole 2014):

- Deposition of stannous fluorophosphate or stannous oxide layers onto enamel surfaces has been reported after stannous fluoride treatment
- Deposition occurs primarily as a result of the attachment of the stannous ion to free phosphate sites on the surface of enamel
- Stannous 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 (Faller & Eversole 2014). 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 (*Figure 10*). 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.

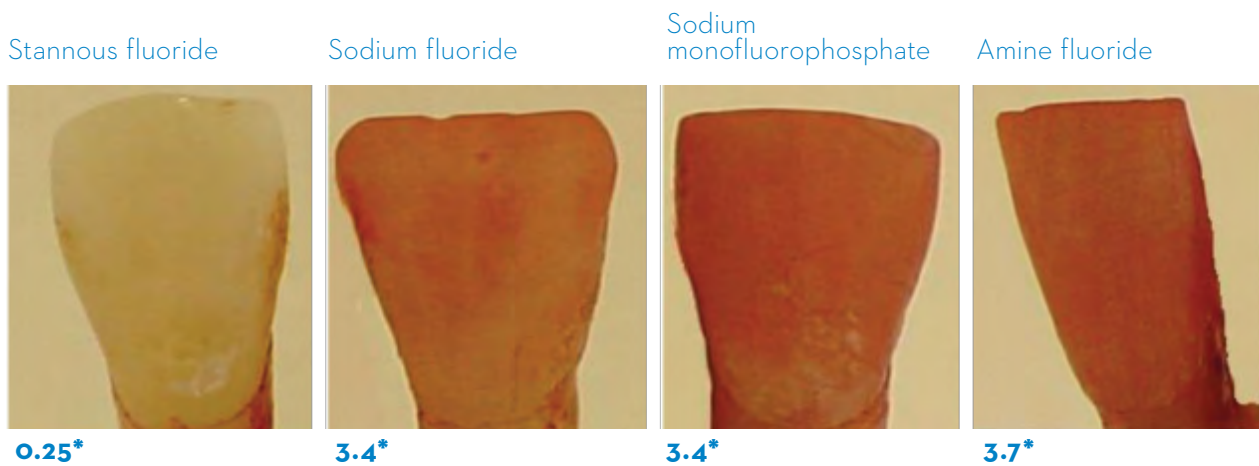


Figure 10. Degree of dye deposition on enamel samples following exposure to toothpaste slurry followed by dye

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

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 (Figure 11; Faller 2012). 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.

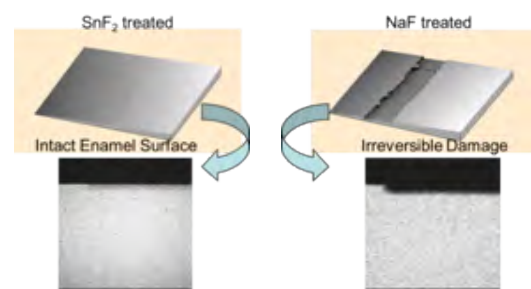
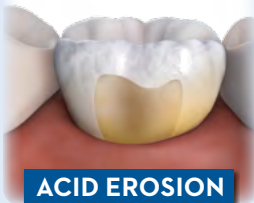


Figure 11. Stannous fluoride vs. sodium fluoride in in vitro treated enamel slabs



Stannous fluoride protects against erosion by:

- Forming a protective layer on the surface that is highly resistant to acids
- Strengthening enamel through remineralization

ACID EROSION

Erosion Research Summaries

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for protection against acid erosion.

In addition, an independent consensus statement by the European Federation of Conservative Dentistry found “oral hygiene products, such as toothpastes or mouth rinses, containing stannous fluoride or stannous chloride have the potential to slow the progression of erosive tooth wear.” The authors found data are limited for other products. (Carvalho et al. 2015)

The Protective Effects of Toothpaste Against Erosion By Orange Juice: Studies in Situ and in Vitro

Reference: Hooper SM, Newcombe RG, Faller R, Eversole S, Addy M, West NX. *J Dent.* 2007 Jun;35(6):476-81. Epub 2007 Feb 27

CONCLUSION

The results of this study provide further support for tooth brushing before meals. Results further suggest the stannous fluoride dentifrice could be used to provide significant erosion protection in susceptible patients versus that provided by conventional fluoride products.

OBJECTIVE

Consumption of soft drinks, fruit juices and sport drinks has increased dramatically in the UK, the US, and elsewhere. Previous studies have demonstrated the erosive nature of these acidic soft drinks. The objective of this study was to determine the protective effects of experimental stannous fluoride-based toothpaste, containing sodium hexametaphosphate, against an erosive challenge (orange juice) on tooth enamel.

MATERIALS AND METHODS

- This research included a 15-day challenge in vitro study and a 15-day in situ single blind, 3-way, crossover clinical trial.
- The following formulations were tested:
 - 1) experimental stannous fluoride dentifrice with sodium hexametaphosphate for cosmetic benefits (P&G);
 - 2) a benchmark sodium fluoride dentifrice (Crest® Cavity Protection, P&G);and
 - 3) negative control, water.
- Flat, polished human enamel samples with a surface profile of $\pm 0.1\mu\text{m}$, were exposed to the three regimens.
- The orange juice used as erosion challenge had a pH 3.8.
- 15 volunteers wore an intra-oral appliance with 2 specimens of enamel embedded in the mid-palatal region from 9:00 to 17:00 (removed for 1 hour at lunchtime). Whilst appliances were in place, no food or drink other than water and the designated orange juice were consumed. Volunteers were asked to rinse with a toothpaste slurry or water at 9:00 and 13:00 followed by consumption of 250 ml orange juice 1 and 3 h later.
- Subjects were treated with one study formulation for 5 days followed by two non-treatment days.
- A profilometer was used to measure depths of the resulting eroded areas at days 5, 10 and 15.

RESULTS

There was significantly more erosive damage on the specimens exposed to the benchmark toothpaste (NaF) and negative control (water) compared to the test stannous fluoride toothpaste in both the in situ (Figure 1) and in vitro (Figure 2) studies.

Figure 1. In Situ Loss of Material*

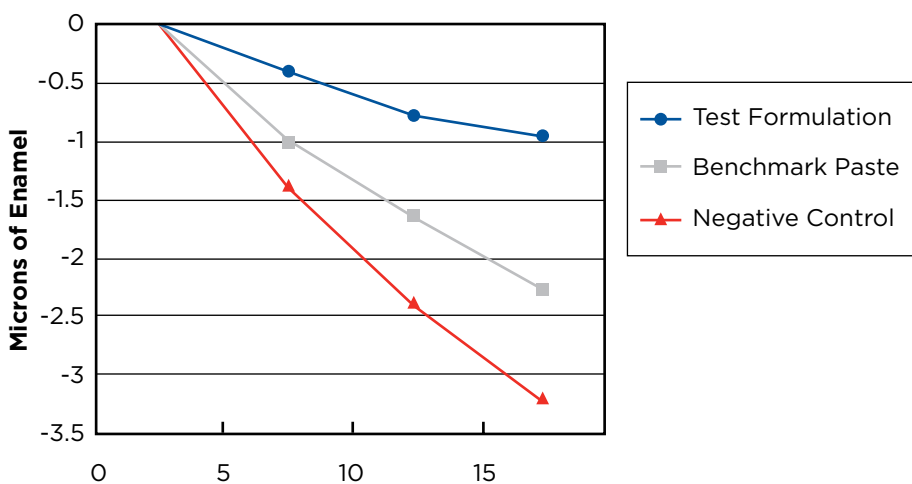
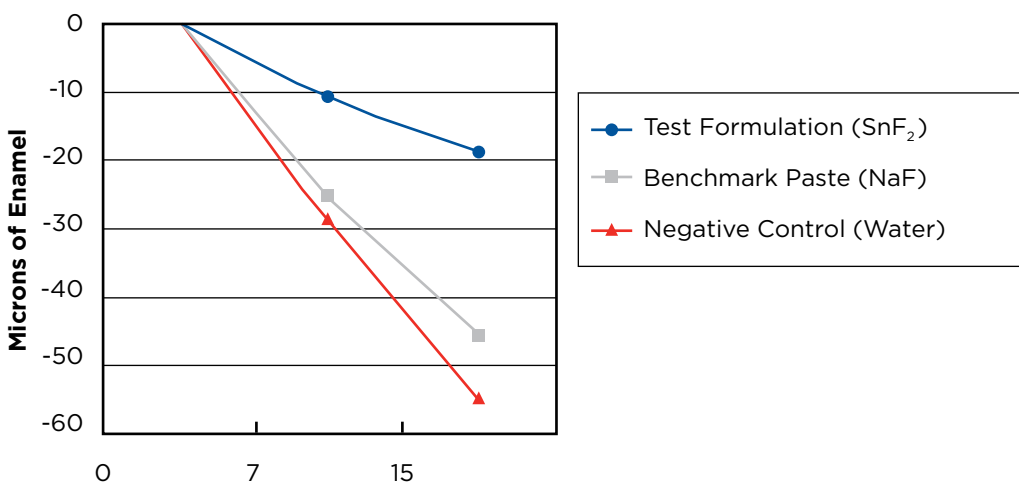


Figure 2. In Vitro Loss of Material*



* mean value based on duplicate determinations of two enamel specimens

Enamel Protection vs. Abrasivity - A Study of Relevance

Reference: Faller RV, Eversole SL, Tzeghai G. *J Dent Res*. 2009;88 (Spec Iss A): Abstract 3368.

CONCLUSION

- These results indicate
 - 1) the primary driver for enamel protection benefits is more likely the particular F salt, rather than RDA of the formulation.
 - and
 - 2) this model is reproducible.
- Under the conditions of these studies, SnF_2 provided superior protection against acid mediated enamel tooth surface loss.

OBJECTIVE

Dentifrices with $\text{RDA} < 250$ are considered safe for daily use. Some researchers believe products with low RDA may be less aggressive on erosively softened enamel. Others believe that once softened, erosively challenged enamel will be removed by any friction, even by the tongue. This research was conducted to determine the primary driver of enamel protection benefits: is abrasivity or fluoride (F) salt the more important factor?

MATERIALS AND METHODS

- Cores of extracted, human enamel were cleaned, ground and polished to provide a virgin enamel surface, soaked in human saliva (pellicle formation), and treated in a 1:3 (product:saliva) slurry of toothpaste representing a range of actives/RDA values [SnF_2 (RDA-150), NaF#1(RDA-100), NaF#2(RDA-50)].
- Specimens were subjected to dynamic pH cycling conditions including exposure to multiple 1% citric acid challenges over a 5-day period.
- Treatment slurries and saliva baths were constantly stirred to ensure a steady flow, representing repetitive challenges to the enamel by a combination of common dietary acid and abrasive elements.
- The study was run in duplicate to test model reproducibility. Results were averaged.

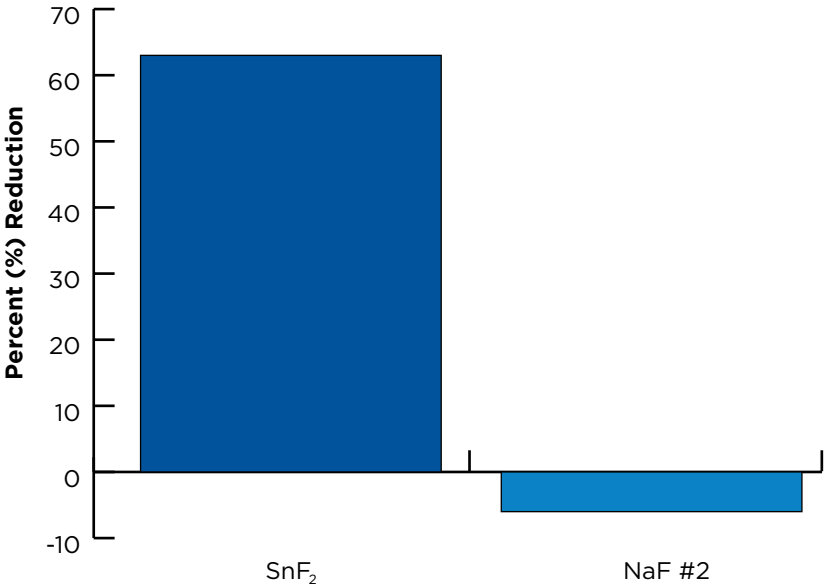
RESULTS

- The product with RDA-150 provided significant ($P=0.05$, ANOVA) protection against damage ($8.0\mu\text{m}$ of surface loss), with lower RDA products (RDA-50 or 100) showing no significant differences between them in their ability to protect enamel against damage (27.3 and $25.4\mu\text{m}$ of surface loss, respectively). See Table and Figure.
- It is important to note the active F species in the RDA-150 formulation was SnF_2 . SnF_2 provides significant protection against erosive acid damage by forming a protective barrier layer on the enamel surface, protecting against external challenges.
- The model is reproducible.

Table. Results

Product Tested	RDA	Depth of Total Mineral Loss (µm)	Depth of Total Mineral Loss (µm)	Depth of Total Mineral Loss (µm)
		STUDY 1	STUDY 2	AVERAGE
SnF ₂	150	8.0	8.0	8.0
NaF #1	100	28.0	22.8	25.4
NaF #2	50	27.1	27.5	27.3

Figure. Average % Reduction in Total Mineral Loss*



* (vs. NaF product)

A Randomized Clinical Trial to Measure the Erosion Protection Benefits of a Stannous Fluoride Dentifrice versus a Triclosan/Copolymer Dentifrice

Reference: N. West, T. He, Hellin N, et al. *J Dent Res* 2017;96 (Spec Iss A): Abstract 0610

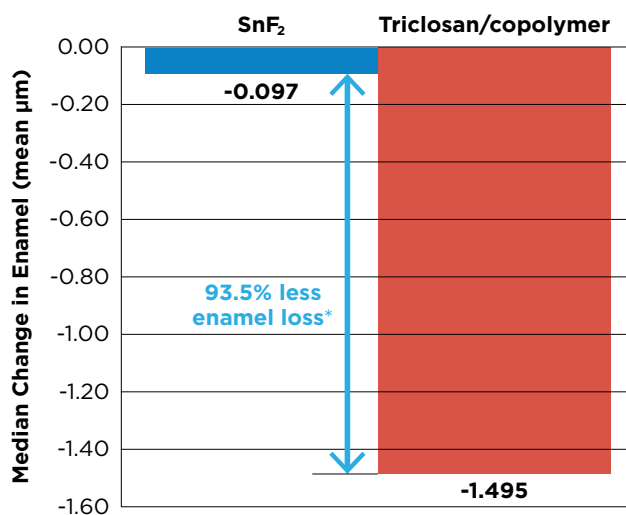
KEY CLINICAL FINDINGS

Crest® PRO-HEALTH™ Advanced dentifrice (SnF₂) demonstrated significantly greater protection against dental erosion relative to the Colgate Total (triclosan/copolymer) dentifrice in a 10-day in situ clinical study.

At Day 10, the SnF₂ dentifrice demonstrated 93.5% lower enamel loss than the triclosan/copolymer dentifrice with median loss of 0.097 µm and 1.495 µm, respectively, which was statistically significant ($P < 0.0001$). See Figure.

Both products were well tolerated.

Figure. Treatment comparison at Day 10: Median Change in Enamel (µm)



* Treatment difference at Day 10 was statistically significant. $P < 0.0001$
N=34.

OBJECTIVE

To compare the enamel protection efficacy (loss of tooth enamel due to erosion as measured by surfometry) of a marketed stannous fluoride dentifrice and a marketed triclosan/copolymer sodium fluoride dentifrice in a 10-day in situ erosion model.

STUDY DESIGN

- A single center, double-blind, randomized, 2-treatment, and 4-period crossover clinical study was conducted involving healthy adults.
- Subjects presented for 4 study periods and were randomized to treatment sequences, receiving one of the two marketed dentifrice products each period:
 1. Crest® PRO-HEALTH™ Advanced — 0.454% Stannous fluoride (1100 ppm fluoride), The Procter & Gamble Company, Cincinnati, OH.
 2. Colgate® Total® Clean Mint — 0.24% Sodium fluoride with 0.3% Triclosan/ copolymer, Colgate-Palmolive Co., New York, NY.
- Each study period was comprised of 10 treatment days. On each treatment day, subjects brushed their teeth at home in their usual manner, using a non-treatment toothpaste (Crest® Decay Protection, 1450 ppm F as sodium fluoride, Procter & Gamble) and a manual toothbrush (Oral-B® 35, Procter & Gamble) supplied at the screening visit.
- Subjects then attended the clinical trials unit where they collected their upper palatal intra-oral appliance fitted with two enamel samples and placed it in their mouth. Subjects wore the appliance for approximately 6 hours total over the course of each study day. While wearing the appliance, subjects swished twice a day with their assigned treatment toothpaste slurry at the clinical site for 60 seconds.
- The erosive challenge occurred with the appliance in the mouth. The subjects were required to sip 25mL of orange juice over a timed minute, swishing it around their mouth, then spitting out. This was repeated 10 times so that a total of 250mL of orange juice was exposed to the enamel samples over a 10 minute period. The erosive challenge occurred a total of four times on each treatment day.
- On Day 10, the enamel samples were measured for tissue loss using a calibrated contact surface profilometer. Measurements were taken at baseline, prior to the start of the study, and at the end of treatment Day 10. Fresh enamel samples were placed in the intra-oral appliance at the beginning of each study period.

A Randomized Clinical Trial to Measure the Erosion Protection Benefits of a Stabilized Stannous Fluoride Dentifrice versus a Control Dentifrice

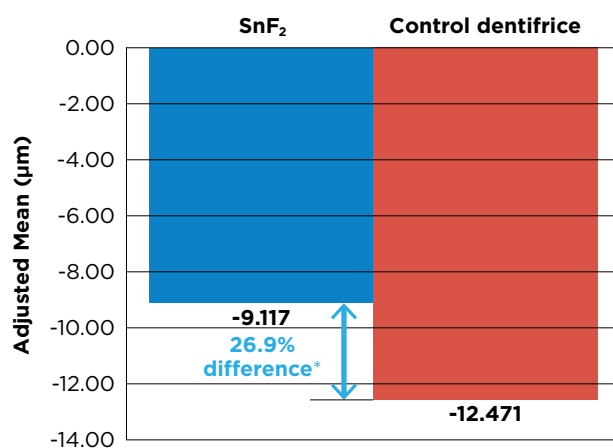
Reference: XY Zhao¹, T He², Y He², C Cheng², HJ Chen².

¹Fourth Military Medical University, Xi'an, PR China; ²Procter & Gamble.

KEY CLINICAL RESULTS

The experimental stabilized stannous fluoride (SnF₂) dentifrice provided 26.9% greater erosion protection relative to the control dentifrice at Day 10 ($P<0.03$).

Figure 1. Enamel loss at Day 10



* Treatment difference at Day 10 was statistically significant. ($P=0.0227$).
N=12 subjects; 18 observations per product.

OBJECTIVE

To compare the enamel protection efficacy of a stabilized stannous fluoride dentifrice and a marketed control dentifrice in a 10-day in situ erosion model.

STUDY DESIGN

- A single center, double-blind, randomized, 2-treatment, and 3-period crossover clinical study was conducted involving healthy adults.
- Subjects presented for 3 study periods and were randomized to treatment sequences, receiving one of the two marketed dentifrice products each period:
 - 1) Experimental 0.454% stabilized SnF₂ dentifrice (Crest® PRO-HEALTH™ Clean Mint [Smooth Formula], Procter & Gamble)
 - 2) Sodium fluoride dentifrice with potassium nitrate marketed for protection from the effects of acid erosion (Sensodyne® Pronamel®, GlaxoSmithKline)

- Each study period was comprised of 10 treatment days. On each treatment day, subjects brushed their teeth at home in their usual manner, using a non-treatment toothpaste and a regular, soft manual toothbrush supplied at the screening visit.
- Subjects then attended the clinical trials unit where they collected their lower palatal intra-oral appliance fitted with 8 enamel samples and placed it in their mouth. Subjects wore the appliance for approximately 6 hours total over the course of each study day. While wearing the appliance, subjects brushed their lingual teeth for 30 seconds, and swished with their assigned treatment toothpaste slurry for 90 seconds twice a day under the supervision of clinic staff.
- The erosive challenge occurred with the appliance in the mouth. The subjects were required to sip 25mL of orange juice over a timed minute, swishing it around their mouth, then spitting out. This was repeated 10 times so that a total of 250mL of orange juice was exposed to the enamel samples over a 10 minute period. The erosive challenge occurred a total of four times on each treatment day.
- On Day 10, the enamel samples were measured for tissue loss using a calibrated contact surface profilometer. Measurements were taken at baseline, prior to the start of the study, and at the end of treatment Day 10. Fresh enamel samples were placed in the intra-oral appliance at the beginning of each treatment period.
- Statistical analyses utilized a general linear mixed model with period and treatment as fixed effects and subject as a random effect.

CLINICAL COMMENT

Stabilized SnF₂ dentifrice has been shown to provide significantly greater protection from acid erosion compared to other types of fluoride dentifrice.* In this trial, a novel stabilized stannous fluoride dentifrice showed a significant anti-erosion benefit over a sodium fluoride/potassium nitrate dentifrice which is marketed for protecting enamel against acid erosion. Dental professionals should consider recommending this SnF₂ dentifrice for its high level of protection against acid erosion as well as its benefits for reduction of gingivitis and plaque.

*Lussi A. *Int Dent J* 2014; 64 (Suppl 1): 2-3.



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 through the use of stabilized stannous fluoride dentifrice offers exceptional protection against erosion, making this dentifrice a suitable option for the prevention of erosion.
- Relative to other fluorides, stannous fluoride provides greater protection against enamel erosion.

ANTI-HYPERSENSITIVITY

Dentin 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 (Von Troil et al. 2002), is also associated with dentin hypersensitivity. According to Brännström'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. (Figure 12; Brännström & Aström 1971) In addition, dentin 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 defense for the management of this condition.

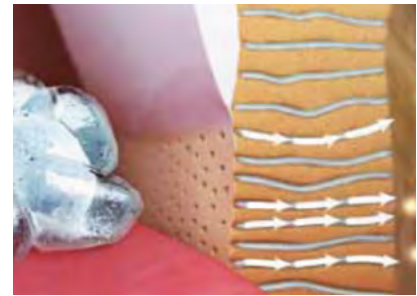


Figure 12. Fluid movement in open dentinal tubules

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 (Figures 13, 14; Miller et al. 1994; Thrash et al. 1995).

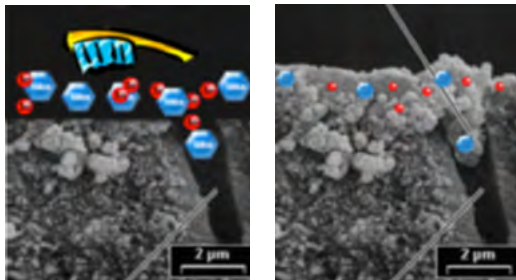
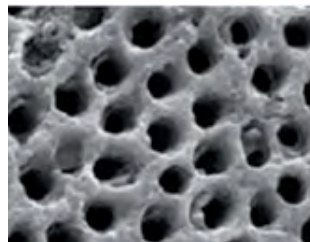


Figure 13. Dentinal tubule occlusion: Note the effective occlusion of dentinal tubules with stabilized stannous fluoride dentifrice (SEM x2000)

Pre-treatment



Post-brushing with stabilized stannous fluoride dentifrice

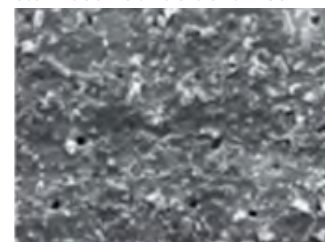
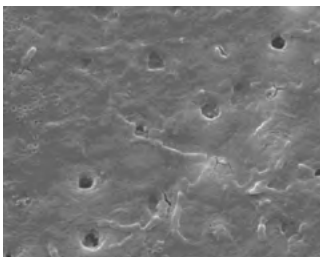
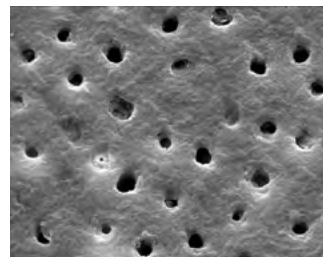


Figure 14. Pre- and post-brushing SEMs: pre-and post-treatment with open and occluded dentinal tubules
Courtesy of Cosmetics & Toiletries

Stabilized Stannous Fluoride



Arginine-Calcium Carbonate



Strontium Acetate

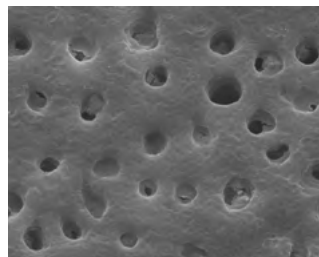


Figure 15. Relative dentinal tubule occlusion for stabilized stannous fluoride dentifrice versus two other anti-hypersensitivity dentifrices after treatment, mechanical agitation, and one minute acid exposure.

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 dentifrice forms a smear layer that is resistant to both daily mechanical and acid challenges. *Figure 15* compares a stabilized stannous fluoride dentifrice to two other anti-hypersensitivity toothpastes which also act by a tubule occlusion mechanism. The smear layer of the stabilized stannous fluoride dentifrice is more resistant to a dietary acid challenge than that of either of the other products (Zsiska et al. 2011).



Stannous fluoride protects against dentinal hypersensitivity by:

- Blocking exposed dentinal tubules with a smear layer to reduce fluid flow within the tubule
- Creating a smear layer that is resistant to mechanical and acid challenges

Hypersensitivity Research Summaries ●●●●●●●●●●

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for the reduction of hypersensitivity.

Efficacy and Safety of a Novel Stabilized Stannous Fluoride and Dentifrice for Dentinal Hypersensitivity

Reference: Schiff T, He T, Sagel L, et al. *J Contemp Dent Pract.* 2006;7(2):1-8.

CONCLUSION

Crest® PRO-HEALTH™ provided statistically significant reductions in dentinal hypersensitivity at 4 and 8 weeks compared to the sodium fluoride control dentifrice.

OBJECTIVE

To compare the efficacy of Crest® PRO-HEALTH™ vs a negative control dentifrice in the reduction of dentinal hypersensitivity over an 8-week period.

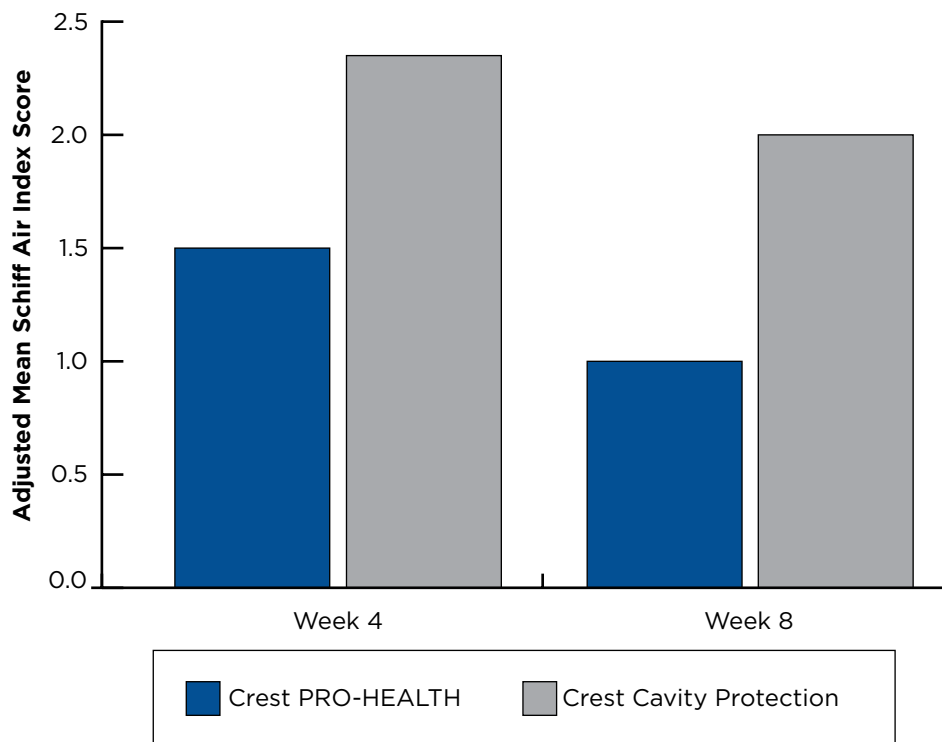
MATERIALS AND METHODS

- Crest® PRO-HEALTH™ (a novel 0.454% stabilized stannous fluoride dentifrice with sodium hexametaphosphate for cosmetic benefits) was compared to a negative control dentifrice containing 0.243% sodium fluoride (Crest® Cavity Protection).
- Study subjects were 90 generally healthy adults with moderate dentinal hypersensitivity: minimum of 2 bicuspid or cuspid teeth with sensitivity criteria of Yeaple Probe Index score = 10 g and Schiff Air Sensitivity Scale score of >1.
- Tooth sensitivity was measured by tactile examination using the Yeaple probe (only teeth responding positively to 10 g and rechallenge at 10 g were evaluated) and cold air using the Schiff Air Index (teeth responding to air stimulus were evaluated).
- Oral soft tissue examinations were performed.
- Subjects were randomized to either the stabilized stannous fluoride dentifrice or the control dentifrice.
- Subjects brushed twice daily with their assigned dentifrice using a manual soft toothbrush for 8 weeks.
- Subjects were assessed again for sensitivity and safety at weeks 4 and 8.

RESULTS

- Data were analyzed for all 90 subjects (45 in each treatment group).
- Schiff Air Index scores were statistically significantly lower for the stabilized stannous fluoride group than the sodium fluoride control group at both weeks 4 and 8 ($P < 0.0001$).
- Compared to the sodium fluoride control group, the stannous fluoride group showed a 33% lower Schiff Air Index score (adjusted mean) than the sodium fluoride control group at week 4 and a 44% lower score at week 8.
- Yeaple Probe Index scores were statistically significantly higher for the stabilized stannous fluoride group than the sodium fluoride control group at both weeks 4 and 8 ($P < 0.0001$).

- Compared to the sodium fluoride control group, the stabilized stannous fluoride group had a mean Yeaple Probe Index score 14 units higher (representing a mean desensitizing improvement of 114% greater) than that of the sodium fluoride control group at week 4, and 11 units higher (representing a mean desensitizing improvement of 71% greater) at week 8.
- No adverse events were reported or observed.



Lower Schiff Air Index scores indicate less tooth sensitivity.

Desensitizing Effect of a Stabilized Stannous Fluoride Dentifrice

Full text available in the Research Database at www.dentalcare.com

Reference: Schiff T, Saletta L, Baker RA, et al. *Compend Contin Educ Dent*. 2005;26(9 suppl 1):35-40.

CONCLUSION

Crest® PRO-HEALTH™ showed a clinically and statistically significant decrease in hypersensitivity compared to a negative control dentifrice.

OBJECTIVE

To evaluate the desensitizing properties of Crest® PRO-HEALTH™ compared to a negative control dentifrice.

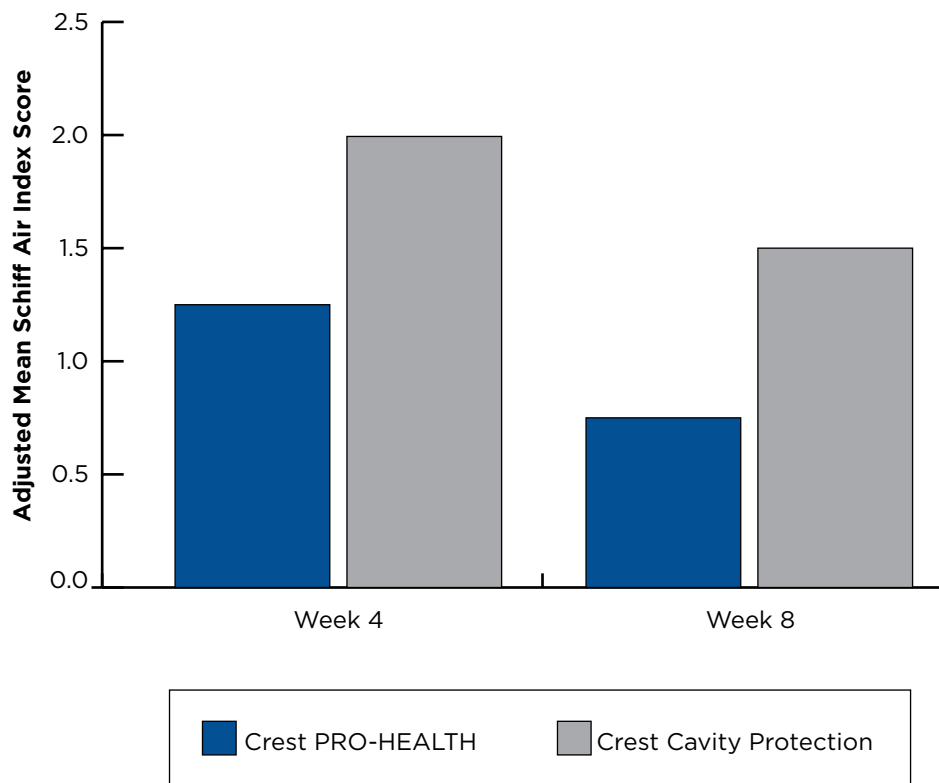
MATERIALS AND METHODS

- Crest® PRO-HEALTH™ (0.454% stabilized stannous fluoride dentifrice with sodium hexametaphosphate for cosmetic benefits) was compared to a marketed negative control dentifrice containing 0.243% sodium fluoride (Crest® Cavity Protection).
- Study subjects were adults with a minimum of 2 bicuspid/cuspid teeth with sensitivity criteria of Yeaple Probe Index = 10 g and Schiff Air Sensitivity Scale score of >1.
- Tooth sensitivity was measured by tactile examination using the Yeaple probe and thermal examination using the Schiff Air Index.
- Oral soft tissue examinations were conducted and adverse events recorded.
- Subjects were randomized to either the stabilized stannous fluoride dentifrice or the control dentifrice.
- Subjects brushed twice daily with their assigned dentifrice using a manual soft toothbrush for 8 weeks.
- Subjects were examined again for tooth sensitivity and safety at weeks 4 and 8.

RESULTS

- Data were analyzed for 77 subjects who had complete data.
- Yeaple Probe Index scores were statistically significantly higher for the stabilized stannous fluoride group than the sodium fluoride control group at both weeks 4 and 8 ($P < 0.0001$). Higher Yeaple Probe Index scores indicate less tooth sensitivity.
- Compared to the sodium fluoride control group, the stabilized stannous fluoride group had a mean Yeaple Probe Index score 1.6 times that of the sodium fluoride group at week 4 and 2 times at week 8.
- Schiff Air Index scores were statistically significantly lower for the stabilized stannous fluoride group than the sodium fluoride control group at both weeks 4 and 8 ($P < 0.0001$). Lower Schiff Air Index scores indicate less tooth sensitivity.

- Compared to the sodium fluoride control group, the stabilized stannous fluoride group showed a 36% lower Schiff Air Index score (adjusted mean) than the sodium fluoride group at week 4 and a 44% lower score at week 8.
- No adverse events were reported or observed.



Lower Schiff Air Index scores indicate less tooth sensitivity.

A Clinical Trial Evaluating Immediate Sensitivity Relief of a 0.454% Stannous Fluoride Dentifrice

Reference: T He, ML Barker, Qaqish J, et al. *J Clin Dent* 2011; 22: 46-50.

KEY CLINICAL RESULTS

- The stannous fluoride (SnF_2) dentifrice provided superior sensitivity protection relative to the negative control immediately after the first use based on the Thermal Schiff Index (13.8%, $P<0.0001$) and the Thermal Air Visual Analog Scale (14.6%, $P<0.0001$). See Figures 1 & 2.
- The SnF_2 dentifrice also provided superior ($P<0.0001$) relief relative to the negative control at Day 3 and at Week 2 based on the Thermal Schiff Air Index (31.8% and 61.3%, respectively), the Thermal Air Visual Analog Scale (34.8% and 66.6%, respectively) and the Tactile Yeaple Probe (186% and 239%, respectively). See Figures 1 & 2 and Table 1.
- The test products were well tolerated.

Figure 1. Thermal Schiff Air Index Adjusted Mean Scores

(Lower score indicates less sensitivity)

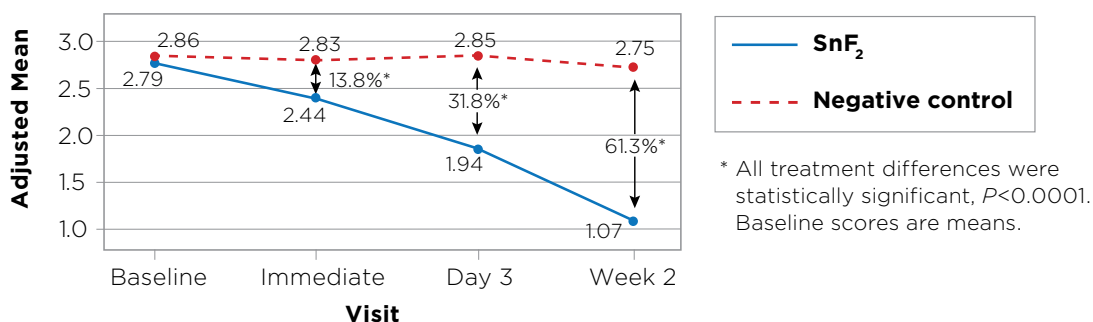


Figure 2. Thermal Air Visual Analog Scale Adjusted Mean Scores

(Lower score indicates less sensitivity)

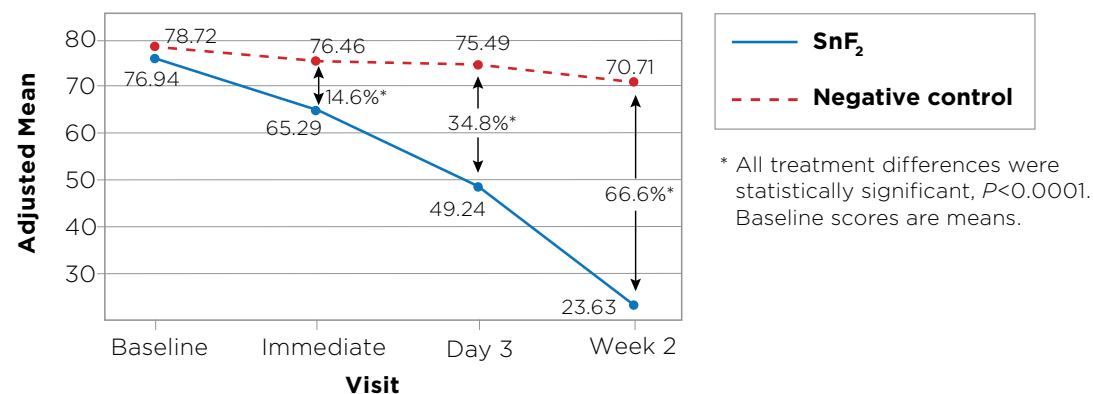


Table 1. Tactile Yeaple Probe Mean Scores

(Higher score indicates less sensitivity)

	Baseline	Day 3	Week 2
SnF₂ dentifrice	10.00	29.64	42.86
Negative control	10.00	10.36	12.64

OBJECTIVE

To evaluate the efficacy of a SnF₂ dentifrice in the reduction of dentinal hypersensitivity after immediate use, 3 days and 2 weeks of use as compared to a negative control dentifrice.

STUDY DESIGN

- This was a controlled, randomized, examiner-blind, two-treatment, parallel group clinical trial.
- One hundred eleven healthy adult subjects with moderate dentinal hypersensitivity were enrolled and randomized to one of two treatment groups.
- At the Baseline visit, subjects received an oral soft tissue (OST) exam to evaluate the overall health of the mouth and then were reassessed for tooth sensitivity. Subjects with at least two sensitive teeth demonstrating reproducible sensitivity to both thermal and tactile stimuli and who met all eligibility criteria were enrolled in the study. For those subjects who had greater than two teeth meeting the eligibility criteria, only two were selected for enrollment in the study.
- Subjects were then randomized to treatment (either Crest® PRO-HEALTH™ Sensitive Shield with 0.454% stannous fluoride, The Procter & Gamble Company or Colgate Cavity Protection dentifrice with 0.76% Sodium monofluorophosphate, Colgate-Palmolive). Products and treatment kits were identical in appearance to preserve blinding.
- Subjects were instructed, according to manufacturer's usage instructions, to brush with their assigned dentifrice thoroughly twice a day (morning and evening). Subjects in the stannous fluoride dentifrice group brushed the sensitive teeth first.
- Subjects performed their first product use on site under the supervision of site staff. Immediately (within 5 minutes) following the first treatment, both the examiner and subjects re-assessed thermal sensitivity for each enrolled tooth using the Schiff Air Index (assessed by examiner) and Thermal Air Visual Analog Scale (assessed by subjects).
- Safety and efficacy measurements, using Schiff Air Index, Thermal Air Visual Analog Scale and Tactile Yeaple Probe, were re-assessed at the Day 3 and Week 2 study visits.

A Randomized Clinical Trial Evaluating a 2-step Stannous Fluoride Dentifrice and Whitening Gel System Versus a Potassium Nitrate Dentifrice for Sensitivity Relief

Reference: Gerlach RW, Underwood J, Miner M. Data on file, 2016.

KEY CLINICAL RESULTS

- A 2-step stannous fluoride dentifrice and whitening gel system (Crest® PROHEALTH™ [HD]™, CPH-HD) provided superior tactile and thermal sensitivity relief ($P<0.05$) versus a positive control potassium nitrate dentifrice (Sensodyne® Extra Whitening). Both groups provided a significant benefit relative to baseline for both measures ($P<0.0001$). See Figures 1 & 2.
- Seventy-two percent (72%) of teeth tested in the CPH-HD group experienced an improvement in thermal sensitivity compared to 53% in the positive control group. Fifty-five percent of teeth tested using the CPH-HD product experienced relief from tactile sensitivity compared to 37% for the positive control.

Figure 1. Mean thermal sensitivity scores at Baseline and Week 2. N=69

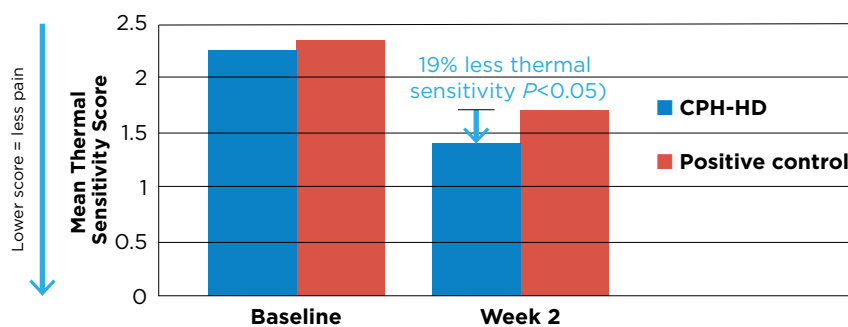
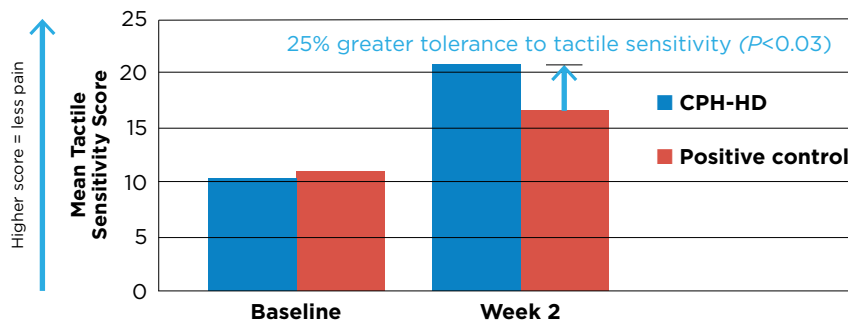


Figure 2. Mean tactile sensitivity scores at Baseline and Week 2. N=69



OBJECTIVE

To evaluate changes in dentinal hypersensitivity in response to using a two-step stannous fluoride dentifrice and whitening gel system relative to a positive control potassium nitrate sensitivity toothpaste.

- This was a randomized, controlled, double-blinded study to assess changes in dentinal hypersensitivity over a 2 week period.
- 71 healthy adult volunteers with current dentinal hypersensitivity were enrolled and randomized to one of the groups for twice a day oral hygiene:
 - Crest® PRO-HEALTH™ [HD]™: Step 1 is a 0.454% stannous fluoride dentifrice; Step 2 is a 3% is a hydrogen peroxide whitening gel (Procter & Gamble)
 - Positive Control: Sensodyne Extra Whitening with sodium fluoride and 5% potassium nitrate (GlaxoSmithKline)
- Both groups used a soft, manual toothbrush (Oral-B® Indicator®, Procter & Gamble)
- Assessment of dentinal hypersensitivity was made at baseline (before any treatment) and after 2 weeks of using the randomly assigned treatment using the Schiff Air Index1 (thermal) and Yeaple Probe2 (tactile).
- Safety was assessed from clinical examination.

CLINICAL COMMENT

Dentinal hypersensitivity is defined as a brief, sharp pain from the exposure of dentin to thermal, tactile, osmotic, chemical, or evaporative stimuli, which cannot be attributed to any other form of dental defect or disease. Patients commonly manage dentinal hypersensitivity by using a dentifrice containing a desensitizing agent, such as potassium nitrate or stannous fluoride. Potassium nitrate is reported to reduce sensitivity by interfering with the transmission of pain signals. Stannous fluoride has been shown to occlude open dentin tubules, reducing fluid flow in response to stimuli and thereby reducing pain.

Stabilized stannous fluoride dentifrice has been shown to provide superior relief from thermal and tactile dentinal hypersensitivity versus negative and positive controls.³ Consistent with published literature, the 2-step stannous fluoride dentifrice and whitening gel system provided superior sensitivity relief compared to a marketed potassium nitrate whitening dentifrice.* This 2-step system has also been shown to provide gingivitis reductions comparable to chlorhexidine* with significant whitening benefits.^{4,5} Thus, dental professionals can recommend this system to patients with dentinal hypersensitivity with confidence they will not only experience relief from sensitivity, but also improvements in gingival health and tooth whitening.

* via Step 1 stannous fluoride dentifrice

1 Schiff T, et al. *J Clin Dent* 1994;5 Spec No: 87-92.

2 Schiff T, et al. *J Contemp Dent Pract* 2006;May;(7)2:001-008.

3 Walters P. Dentinal Hypersensitivity: A Review. Updated Dec 2014; dentalcare.com CE Course #200.

4 Gerlach RW, et al. *J Dent Res* 2015;94 (Spec Iss A): Abstract 293.

5 Garcia-Godoy, C et al. *J Dent Res* 2016; 96 (Spec Iss A): Abstract 92.



Clinical Significance

- Given the high incidence of dentin hypersensitivity, the effectiveness of stabilized stannous fluoride dentifrice provides clinicians with an efficacious desensitizing dentifrice to recommend to patients.
- Stabilized stannous fluoride dentifrice offers anti-hypersensitivity benefits and provides multiple other important benefits concurrently with treating hypersensitivity.
- Stabilized stannous fluoride dentifrice provides both rapid and sustained sensitivity relief with continued use.
- In addition to rapid onset, the stabilized stannous fluoride dentifrice smear layer is resistant to acid challenges which occur through the modern diet.

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 (Tonzetich 1977). 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.

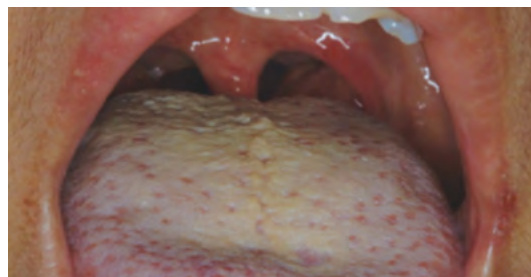


Figure 16. Coating on tongue and heavy bacterial load

Tongue cleaning has also been recommended to help combat oral malodor since odor-producing bacteria commonly reside on the tongue (*Figure 16*; Outhouse et al. 2006; Tonzetich & Ng 1976, Van der Sleen et al. 2010).

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 (*Figure 17*).

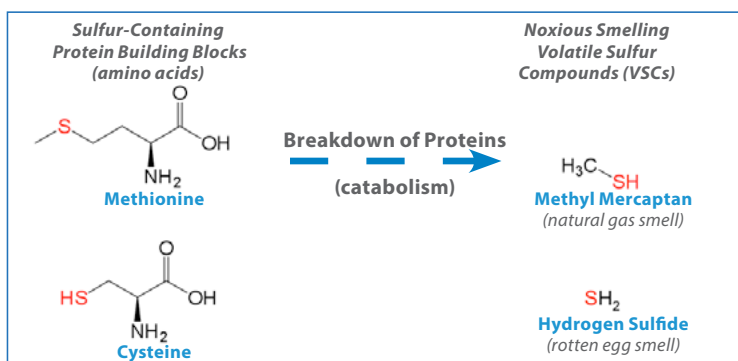


Figure 17. Source of Oral Malodor: GNA bacteria use protein as an energy source and produce volatile sulfur-containing by-products



Stannous fluoride reduces halitosis by:

- Anti-bacterial effects against gram-negative anaerobes that produce foul-smelling VSCs

MALODOR

Halitosis Research Summaries

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for reduction of breath malodor.

Effects of 0.454% SnF₂ Dentifrice on Daytime and Overnight Malodor

Reference: Farrell S, Gerlach RW, Barker ML, et al. *J Dent Res.* 2008;87(spec issue B): abstract 3161.

CONCLUSION

The use of the 0.454% stabilized stannous fluoride dentifrice resulted in significant reduction in short-term and long-term daytime and overnight malodor relative to a control dentifrice.

OBJECTIVE

A clinical study was conducted to evaluate daytime and overnight oral malodor reduction benefit of a 0.454% stabilized stannous fluoride therapeutic dentifrice with short-term and long-term use.

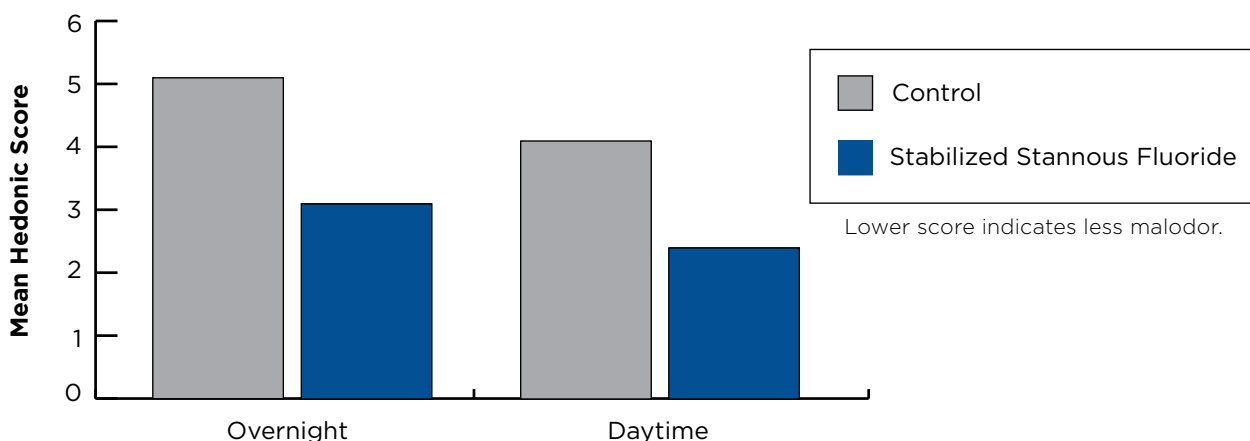
MATERIALS AND METHODS

- The study was a randomized, double-blinded, 2-treatment, 3-period crossover clinical trial.
- After completing an acclimation period, 45 subjects with existing oral malodor were randomly assigned to a crossover treatment sequence consisting of Crest® PRO-HEALTH™ dentifrice (0.454% stabilized stannous fluoride dentifrice) and Crest® Cavity Protection dentifrice (control).
- For each treatment period, subjects brushed with the assigned product twice a day for 7 days. Oral malodor was assessed on a 9-point hedonic scale at baseline, day 2-overnight, day 2-daytime (4 hours post morning brushing), day 8-overnight, day 8-daytime (4 hours post morning brushing). Treatment periods were separated by washout periods during which subjects brushed with the control dentifrice.

RESULTS

- Subjects had a mean age of 39 years, 58% of the subjects were female and the mean baseline hedonic score was 7.4.
- Relative to the control, use of the stabilized stannous fluoride dentifrice resulted in significant ($P<0.002$) improvement of the overnight and daytime malodor both short-term at day 2 and long-term at day 8.
- The mean overnight hedonic scores were 3.2 and 5.1 at day 8 after 1 week of brushing for the stabilized stannous fluoride and the control dentifrices, respectively. The mean daytime hedonic scores were 2.4 and 4.1 at day 8 for the stabilized stannous fluoride and the control dentifrices, respectively.

Mean Hedonic Scores at Day 8



Oral Malodor Reduction With 3-Week Use of 0.454% SnF₂ Dentifrice

Reference: Nachnani S, La S, Lee S, et al. *J Dent Res*. 2008;87(spec issue B):abstract 2864.

CONCLUSION

Three-week use of the 0.454% stabilized stannous fluoride dentifrice resulted in sustained significant improvement in oral malodor relative to a control dentifrice.

OBJECTIVE

This clinical study evaluated the effects of the 3-week use of a 0.454% stabilized stannous fluoride therapeutic dentifrice on oral malodor.

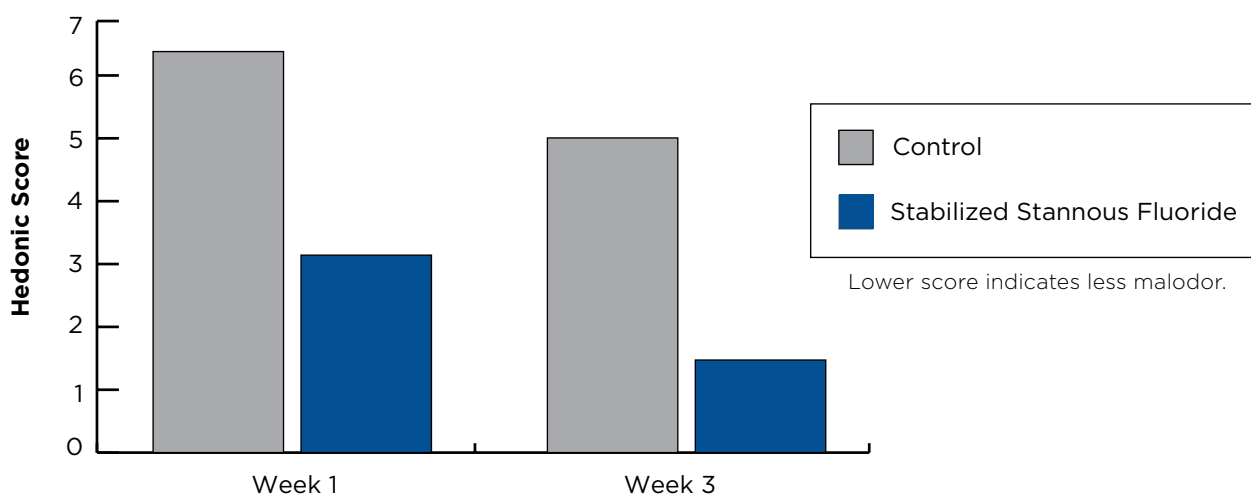
MATERIALS AND METHODS

- The study was a randomized, double-blinded, 2-treatment, parallel design clinical trial.
- After completing an acclimation period, 71 subjects with existing oral malodor were randomized to 1 of the 2 treatments: 0.454% stabilized stannous fluoride dentifrice (Crest® PRO-HEALTH™) or Crest® Cavity Protection dentifrice (control). Subjects brushed with the assigned product twice a day for 3 weeks.
- Oral malodor was assessed on a 9-point hedonic scale at baseline, week 1, and week 3.

RESULTS

- The mean age of study participants was 37.8 years, and 59% were female. The baseline mean hedonic score was 8.19.
- At week 1, the mean hedonic scores (SE) were 3.40 (0.18) and 6.62 (0.18) for the stabilized stannous fluoride dentifrice and the control dentifrice, respectively.
- At week 3, the mean hedonic scores (SE) were 1.55 (0.18) and 5.28 (0.18) for the stabilized stannous fluoride dentifrice and the control dentifrice, respectively.
- Relative to the control, the use of the stabilized stannous fluoride dentifrice resulted in significantly ($P < 0.0001$) greater reduction in oral malodor at both visits. Both treatments were well tolerated.

Mean Hedonic Scores





Clinical Significance

- Reducing oral malodor is a desirable patient benefit.
- Stabilized stannous fluoride dentifrice can provide the patient with short-term benefits, and long-lasting results, with twice daily usage.
- Multi-benefit stabilized stannous fluoride dentifrice offers the ability to control halitosis, along with many other important benefits.

ANTI-CALCULUS BENEFIT

Dental calculus forms through the mineralization of dental plaque, resulting in a variety of different crystalline forms (Sidaway 1978). First, new crystals form, that are composed of calcium and phosphate, which then grow and harden into calculus (*Figures 18-19*). The mineral content for supragingival and subgingival calculus is on average 37% and 58% by volume, respectively (Friskopp & Isacson 1984). Supragingival calculus also contains bacterial debris and toxins as well as viable aerobic and anaerobic bacteria (Tan et al. 2004a; Tan et al. 2004b; White et al. 1997). This is of clinical significance as it can be a reservoir of pathogenic bacterial species (Tan et al. 2004b). Dental calculus is common in adults, and less common in children (Anerud et al. 1991).

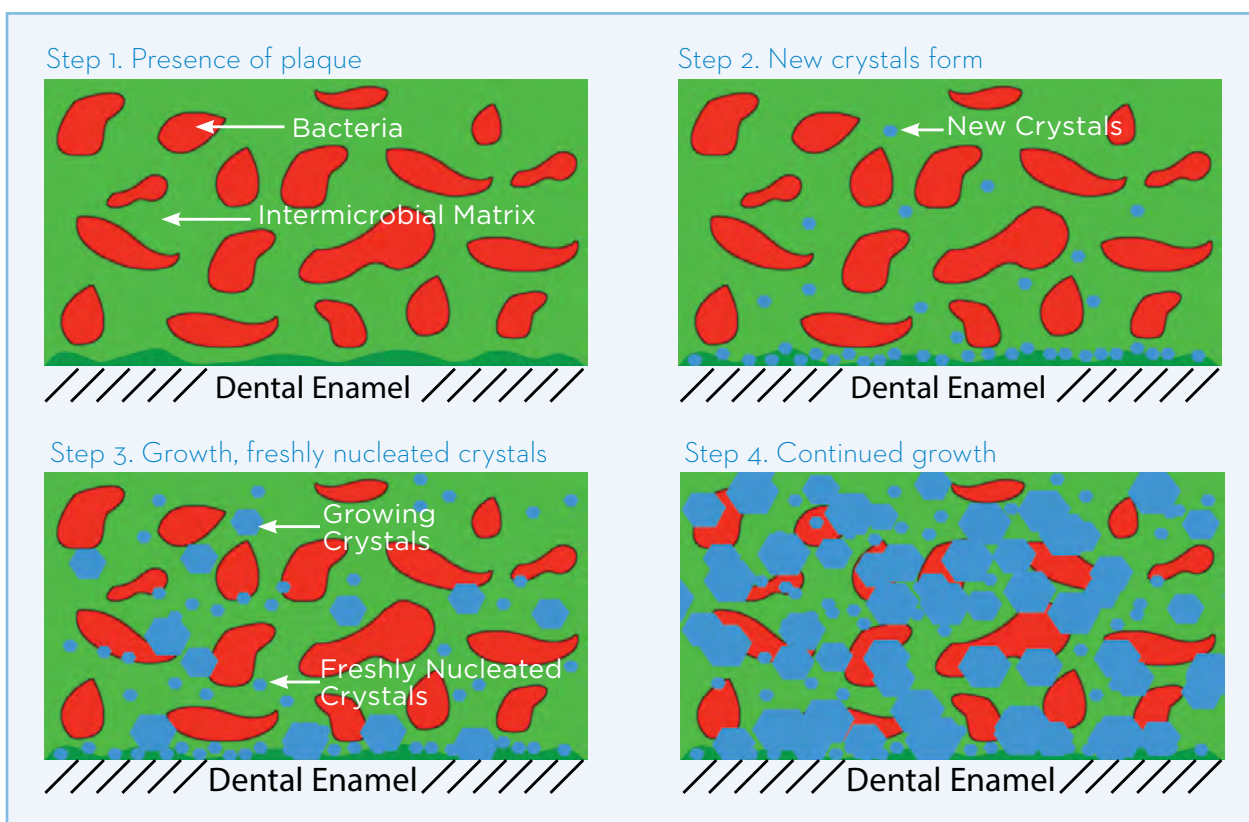


Figure 18. Formation of dental calculus

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 (Bellini 1974).

Given these facts, several anti-calculus agents have been introduced and studied since the mid-1980s (Svatun et al. 1993; Gaengler et al. 1993; White & Cox 2001; Schaeken et al. 1993; Triratana et al. 1995; Claydon et al. 1996).

Pyrophosphate was used in the first tartar control toothpaste in 1985, and more recently a longer chain phosphate, sodium hexametaphosphate, has been incorporated into stannous fluoride formulations (Winston et al. 2007; Liu et al. 2002). Zinc is used in Crest® PRO-HEALTH™ [HD]™ and the Crest® PRO-HEALTH™ smooth variant to inhibit calculus.



Figure 19. Supragingival calculus

Mechanism of action

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 anticalculus 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 (White & Gerlach 2000; Rykke & Rolla 1990; Rolla et al. 1988). Sodium hexametaphosphate (Figure 20) 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. (Figure 21 White & Gerlach 2000; Baig et al. 2002, Busscher et al. 2002)

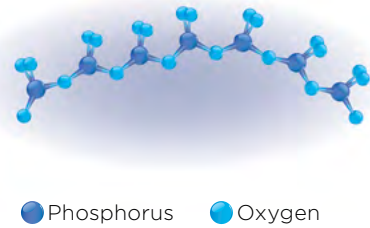


Figure 20. Hexametaphosphate molecule

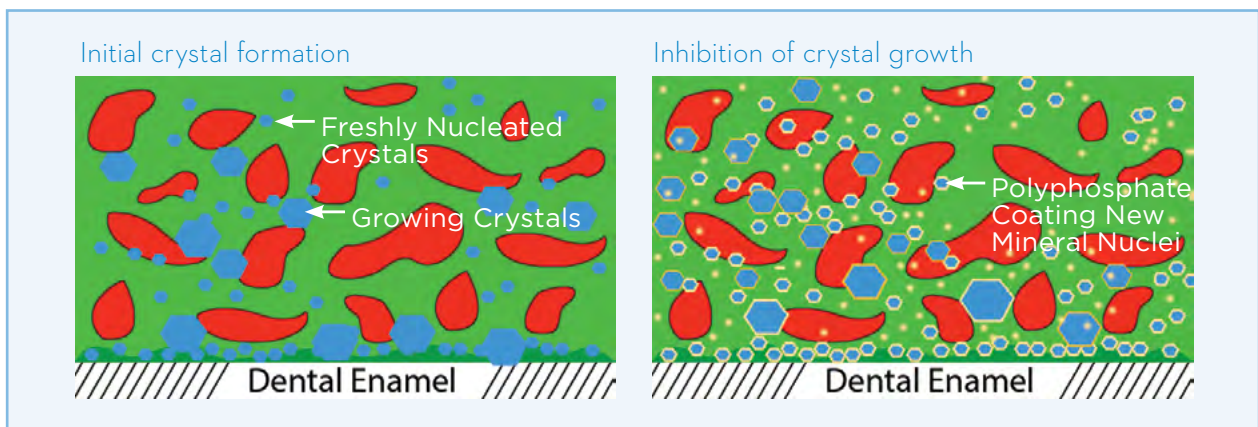


Figure 21. Mechanism of action of sodium hexametaphosphate

In the 2-step and smooth texture formulas, the positively charged zinc ion (Zn^{2+}) inhibits crystal growth by substituting for calcium in the crystal lattice of calcium phosphate (Figure 22). This interferes with the crystal formation and slows crystal growth (Segreto et al. 1991). Stannous fluoride also inhibits plaque formation, which is the structure on which calcium and phosphate precipitate.

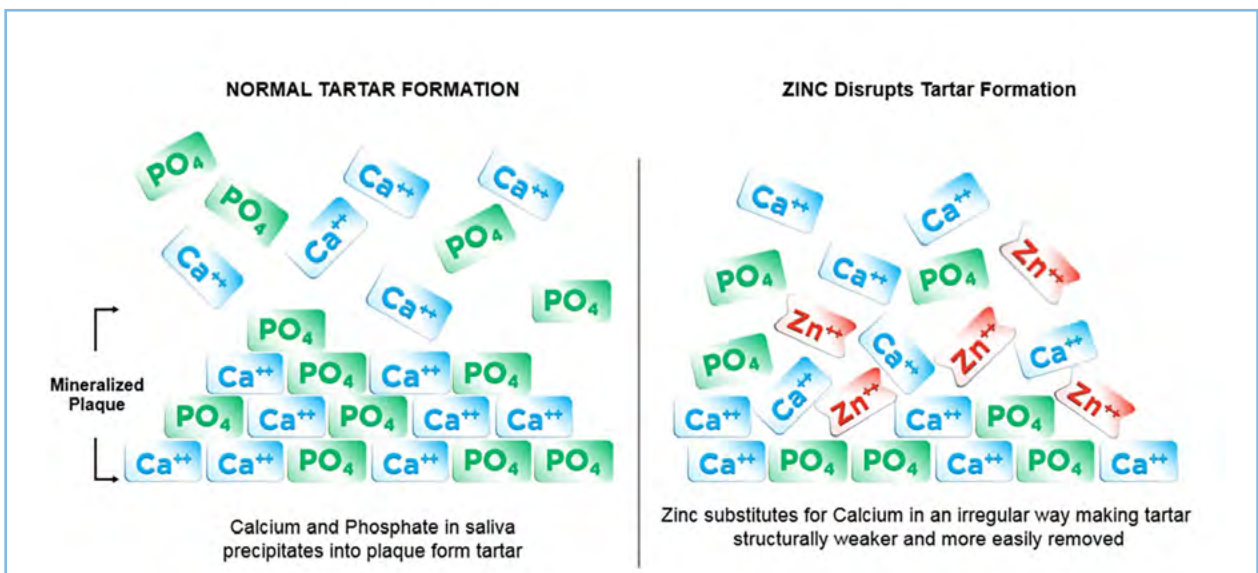
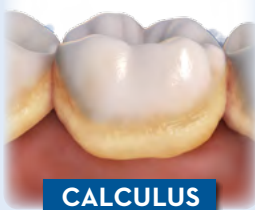


Figure 22. Mechanism of action of zinc



Sodium hexametaphosphate and zinc inhibit calculus by:

- interfering with crystal formation
- slowing crystal growth

Calculus Research Summaries ●●●●●●●●●●

The following study summaries represent a sample of research demonstrating the benefits of stabilized stannous fluoride dentifrice for calculus inhibition.

Anticalculus Efficacy and Safety of a Stabilized Stannous Fluoride Dentifrice with Hexametaphosphate

Full text available in the Research Database at www.dentalcare.com

Reference: Schiff T, Saletta L, Baker RA, et al. Compend Contin Educ Dent. 2005; 26(9 suppl 1):29-34.

CONCLUSION

Over a 6-month period a stabilized stannous fluoride dentifrice with sodium hexametaphosphate showed superior anticalculus efficacy compared with a marketed tartar control triclosan/copolymer control.

OBJECTIVE

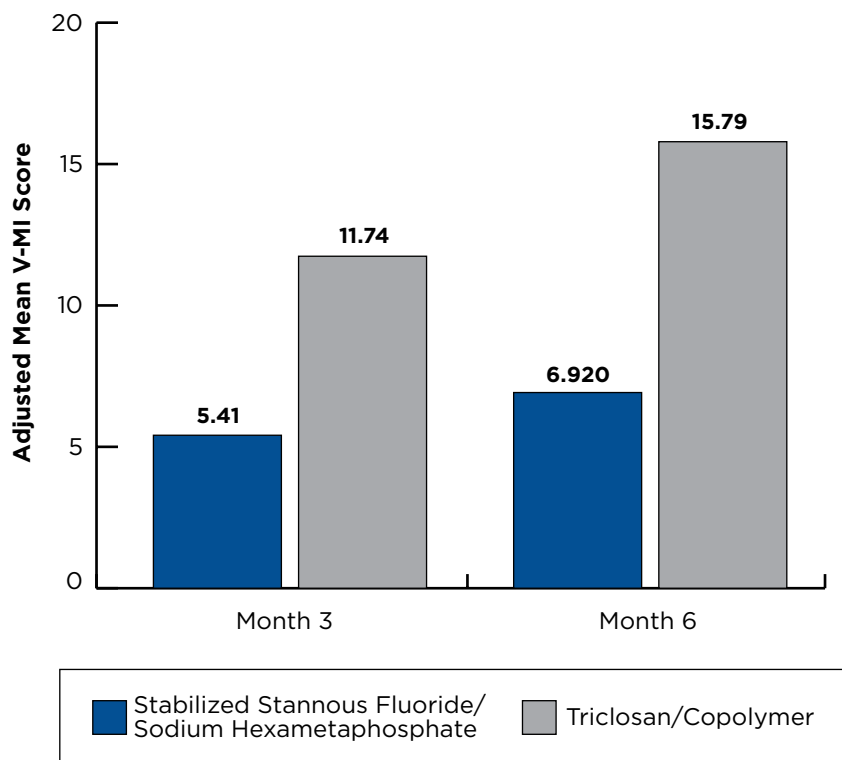
To assess the anticalculus efficacy of a 0.454% stabilized stannous fluoride dentifrice with sodium hexametaphosphate vs a positive control dentifrice.

MATERIALS AND METHODS

- A 0.454% stabilized stannous fluoride dentifrice with sodium hexametaphosphate was compared to a marketed tartar control (0.30% triclosan/0.243% sodium fluoride/2% Gantrez copolymer) dentifrice.
- Study subjects were 81 adult participants with the ability to form at least 1.5 mm of calculus on anterior mandibular teeth (lingual surfaces) in an 8-week pretest phase following dental prophylaxis.
- The Volpe-Manhold Index was used to measure calculus on the lingual surfaces of the lower 6 anterior teeth.
- Oral soft and hard tissue examinations were also conducted.
- The Lobene Index was used to measure stain on the facial surfaces of 12 anterior teeth.
- Subjects were randomized to either the stabilized stannous fluoride/sodium hexametaphosphate dentifrice or the control dentifrice.
- Subjects used their assigned dentifrice twice a day for 6 months.
- Subjects were examined again for calculus, stain, and soft tissue safety at months 3 and 6.

RESULTS

- Data were analyzed for 80 subjects who had complete data.
- Volpe-Manhold Index scores were statistically significantly lower for the stabilized stannous fluoride/sodium hexametaphosphate group than the triclosan/sodium fluoride copolymer group at both months 3 and 6 ($P<0.0001$).
- Compared to the triclosan/sodium fluoride copolymer group, the stabilized stannous fluoride/sodium hexametaphosphate group showed a 54% reduction (adjusted means) in calculus accumulation at month 3 and a 56% reduction at month 6.
- Neither group of subjects showed any appreciable extrinsic stain accumulation.
- No adverse events were reported.



Lower V-MI scores indicate less calculus.

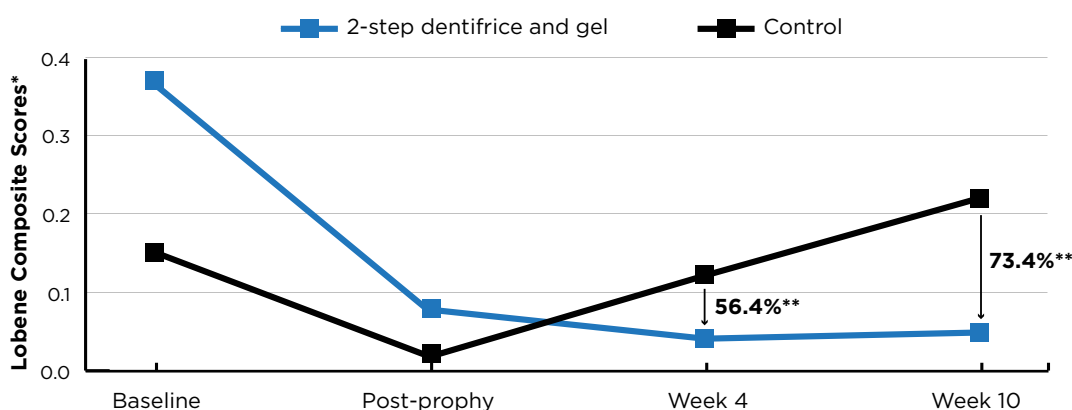
A Randomized Clinical Trial to Evaluate a Daily Two-Step Dentifrice and Gel System in the Prevention of Stain, Plaque and Calculus following a Dental Prophylaxis

Reference: Gerlach R, Farrell S, Anastasia MK, Amini P. *J Dent Res* 2016; 95 (Spec Iss A): Abstract 0093.

KEY CLINICAL FINDINGS

- A 2-step dentifrice and whitening gel system helped maintain the cleaning results of a dental prophylaxis versus a regular anti-cavity dentifrice used as a negative control through 2.5 months. Step 1 is a 0.454% stannous fluoride dentifrice and Step 2 is a 3% hydrogen peroxide whitening gel.
- After 10 weeks of twice daily use, the 2-step dentifrice and gel system exhibited statistically lower ($P<0.001$) percent accumulations versus the control group in tooth stain (73.4%), plaque (30.5%), and calculus (58.6%). See Figures 1-3.
- Both products were well-tolerated.

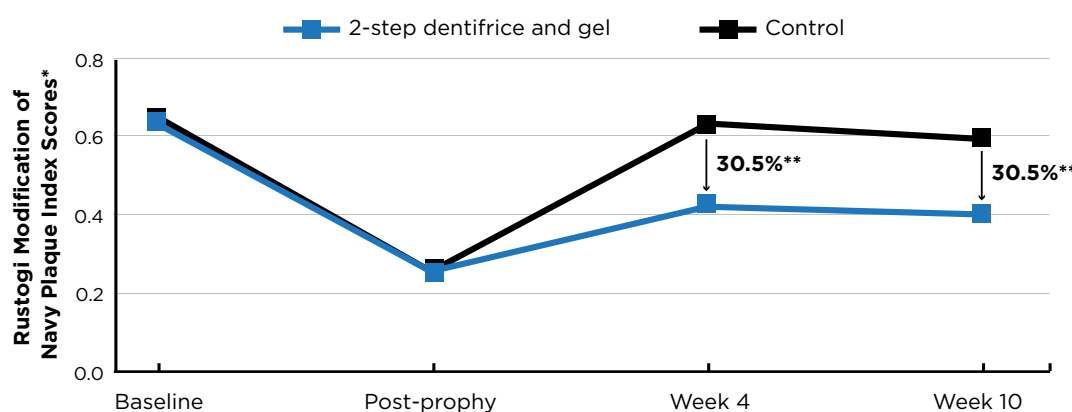
Figure 1. Tooth Stain Scores



* Baseline and post-prophy scores are means; Week 4 and Week 10 scores are adjusted means.

** $P<0.0005$

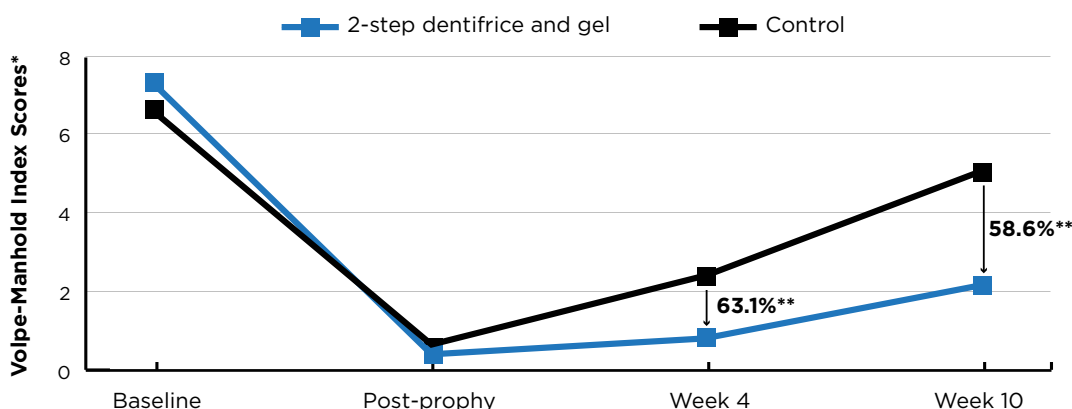
Figure 2. Plaque Scores



* Baseline and post-prophy scores are means; Week 4 and Week 10 scores are adjusted means.

** $P<0.0001$

Figure 3. Calculus Scores



* Baseline and post-prophy scores are means; Week 4 and Week 10 scores are adjusted means.

** $P < 0.01$

OBJECTIVE

To assess the effectiveness of a daily 2-step dentifrice and gel system to prevent the formation of stain, calculus and plaque after a dental prophylaxis.

METHODS

- This was a randomized, controlled, examiner-blind, 2-treatment parallel group study. Forty-eight healthy adult volunteers with evidence of plaque and either stain or calculus completed the trial.
- Following a whole-mouth dental prophylaxis, subjects were randomized to one of two groups:
 - Negative control - 0.76% sodium monofluorophosphate dentifrice (Colgate® Cavity Protection, Colgate-Palmolive)
 - Daily 2-step dentifrice and gel system (Crest® PRO-HEALTH™ [HD]™) - Step 1, 0.454% stannous fluoride dentifrice; Step 2, 3% hydrogen peroxide whitening gel

Both groups brushed twice daily with a soft manual toothbrush (Oral-B® Indicator™, Procter & Gamble).

- Stain (Lobene Index¹), calculus (Volpe-Manhold Index²) and plaque (Rustogi Modification of the Navy Plaque Index³) were measured clinically prior to receiving a dental prophylaxis, immediately after a dental prophylaxis, and after 4 and 10 weeks of product use.

¹ Lobene RR. Effect of dentifrices on tooth stain with controlled brushing. *J Am Dent Assoc.* 1968;77:849-855.

² Volpe AR, Manhold JH, Hazen SP. In vivo calculus assessment. I. A method and its examiner reproducibility. *J Periodontol.* 1965;36:32-38.

³ Rustogi KN, Curtis JP, Volpe AR, Kemp JH, McCool JJ, Korn LR. Refinement of the modified Navy Plaque Index to increase efficiency in gumline and interproximal tooth areas. *J Clin Dent.* 1992;3 (Suppl C):C9-12.

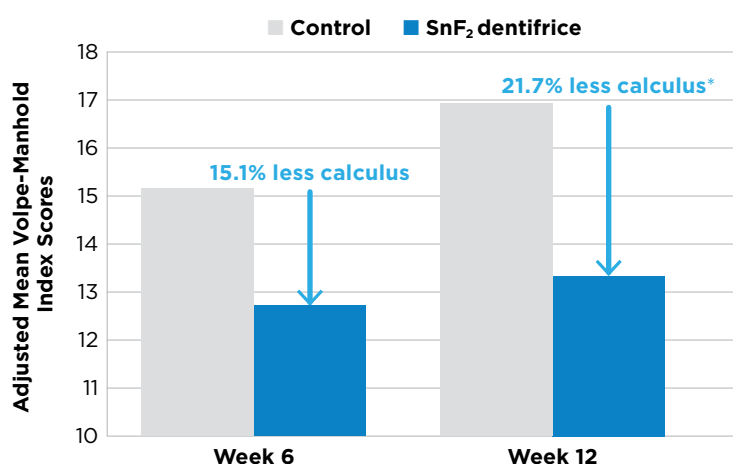
Anti-calculus Efficacy of a Stabilized Stannous Fluoride Dentifrice in a 3-month Clinical Trial

Reference: Milleman JL, He T, Anastasia MK. *J Dent Res* 2017; 96 (Spec Iss A): Abstract 2816.

KEY CLINICAL FINDINGS

- Subjects using the stabilized stannous fluoride (SnF_2) dentifrice demonstrated 15.1% less calculus at Week 6 ($P=0.05$) and 21.7% less calculus at Month 3 ($P<0.01$) compared to subjects in the control group.
- Both test products were well tolerated.

Figure. Calculus scores (VMI) per group.



N=78. *Significant difference between groups ($P<0.05$) using analysis of covariance.

OBJECTIVE

To assess the calculus prevention benefit of an experimental stabilized SnF_2 dentifrice relative to a negative control dentifrice.

STUDY DESIGN

- This was a 3-month, parallel-group, double-blind, randomized and controlled clinical trial.
- Subjects received a dental prophylaxis and then entered a 2-month run-in phase. At the end of 2 months, subjects received a Volpe-Manhold Index (V-MI) calculus examination.
- Qualified subjects who formed a minimum of 9 mm of calculus on the lingual surfaces of the six mandibular anterior teeth received another prophylaxis and were randomly assigned to one of the two treatments:
 - Experimental 0.454% stabilized SnF_2 dentifrice (Crest® PRO-HEALTH™ Clean Mint [Smooth Formula], Procter & Gamble) with zinc to control calculus; or
 - Negative control dentifrice (Colgate® Cavity Protection, Colgate-Palmolive).
- Subjects brushed with their assigned product twice daily using a standard manual toothbrush, one minute per brushing, during the 3-month trial.

- Safety and calculus measurements were taken via Oral Soft Tissue and Volpe-Manhold Index examinations at Baseline, Week 6 and Month 3.
- Treatment groups were compared using analysis of covariance. All statistical tests were two-sided with a 5% level of significance.

CLINICAL COMMENT

Calculus build-up can lead to less efficient oral hygiene and tooth discoloration, as well as extending the time required for a dental prophylaxis. This research demonstrated a directional anti-calculus benefit for the SnF₂ dentifrice relative to the control dentifrice in as early as 6 weeks. The relative benefit for the SnF₂ dentifrice was even greater after 12 weeks of use. Dental professionals should consider recommending the SnF₂ dentifrice for patients who form calculus, as it also improves gingival health and strengthens enamel.



Clinical Significance

- Calculus has a rough surface which has greater potential for more plaque build-up than smooth, clean surfaces.
- The ability to prevent and control calculus formation with twice-daily use of anti-calculus stabilized stannous fluoride 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 (St. John & White, 2015). All Crest dentifrice meets the International Standards Organization specifications for Relative Dentin Abrasivity (RDA), which has an upper limit of 250. Dentifrices at or below 250 RDA are considered safe and effective.

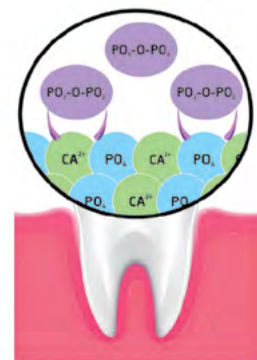
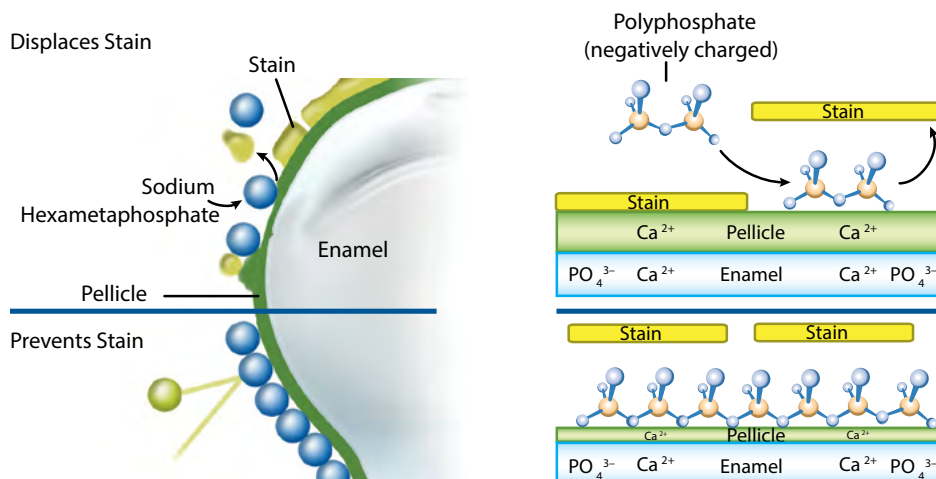


Figure 23. Binding of pyrophosphates to calcium hydroxyapatite at the tooth surface

Chemical cleaning agents in the toothpaste can help to displace surface stains from the tooth pellicle (Figure 23). 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 (Baig et al. 2005). Hydrogen peroxide is another highly effective anti-stain ingredient under appropriate formulation and usage conditions (Gerlach et al. 2015).

Figure 24. Stain prevention and displacement



Mechanism of Action

The stain prevention and whitening effects of many stabilized stannous fluoride formulations in Procter & Gamble's portfolio are provided by an advanced, high cleaning silica system and sodium hexametaphosphate (polyphosphate). 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 (Baig et al. 2005; Terezhalmay et al. 2007):

- 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. (Figure 24)

The 2-step stabilized stannous fluoride formula contains hydrogen peroxide in the second step to provide whitening by disruption of carbon bonds. Stain is composed of materials containing carbon bonds that reflect back only the wavelengths of light that appear colored. Hydrogen peroxide breaks the carbon bonds, so the stain then reflects back more wavelengths of light, making the stain appear white (Goldstein & Garber, 1995).

The smooth texture stabilized stannous fluoride formula uses a combination of silica and zinc citrate for stain prevention. The silica gently removes surface stains while the zinc citrate indirectly protects against stains by preventing calcification of plaque into tartar, thereby reducing the surface area that can attract stains.



Sodium hexametaphosphate whitens by:

- Its affinity for the tooth surface, lifting existing stains and preventing the adsorption of new stain

Hydrogen peroxide whitens by:

- breaking carbon bonds in stained material

Zinc whitens indirectly by:

- Inhibiting calculus

Silica whitens by:

- Gentle physical removal of surface stains

Whitening Research Summaries ●●●●●●●●●●

The following study summaries represent a sample of research demonstrating the anti-stain and extrinsic whitening benefits of stabilized stannous fluoride dentifrice.

Extrinsic Stain Removal Efficacy of a Stannous Fluoride Dentifrice With Sodium Hexametaphosphate

Reference: He T, Baker R, Bartizek RD, et al. *J Clin Dent.* 2007;18(1):7-11.

CONCLUSION

In 2 studies, Crest® PRO-HEALTH™ demonstrated significant extrinsic stain removal vs baseline and comparable stain removal to the positive control dentifrice.

OBJECTIVE

To compare stain removal of a dentifrice containing stabilized stannous fluoride and sodium hexametaphosphate to a positive control dentifrice in 2 independent, double-blind, randomized 6-week trials.

The following dentifrices were tested in each study:

- Crest® PRO-HEALTH™ (0.454% stabilized stannous fluoride + sodium hexametaphosphate).
- Positive control dentifrice (Colgate Total Plus Whitening with sodium fluoride).

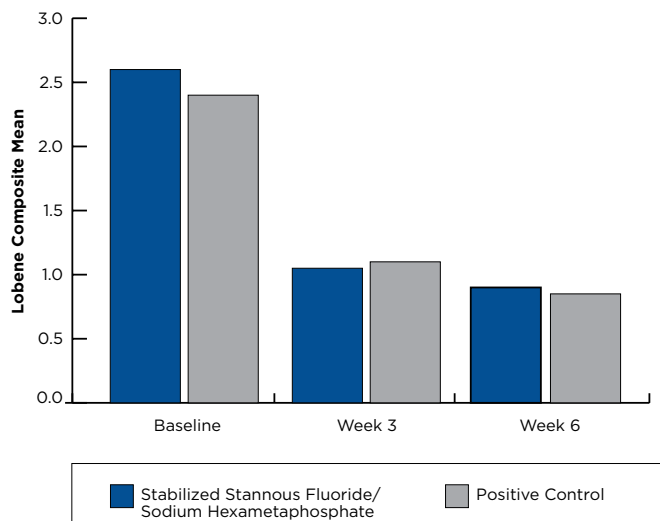
MATERIALS AND METHODS

- Both studies followed the same protocol.
- Study subjects were healthy adults with visible extrinsic tooth stain.
- The modified Lobene Stain Index was used to measure stain on the facial surfaces of the 8 central and lateral incisors at baseline.
- Oral soft and hard tissue examinations were also conducted.
- Subjects were randomized to either the stabilized stannous fluoride + sodium hexametaphosphate toothpaste or positive control toothpaste.
- Subjects used their assigned dentifrice twice a day for 6 weeks.
- Patients were examined again for stain and safety at weeks 3 and 6.

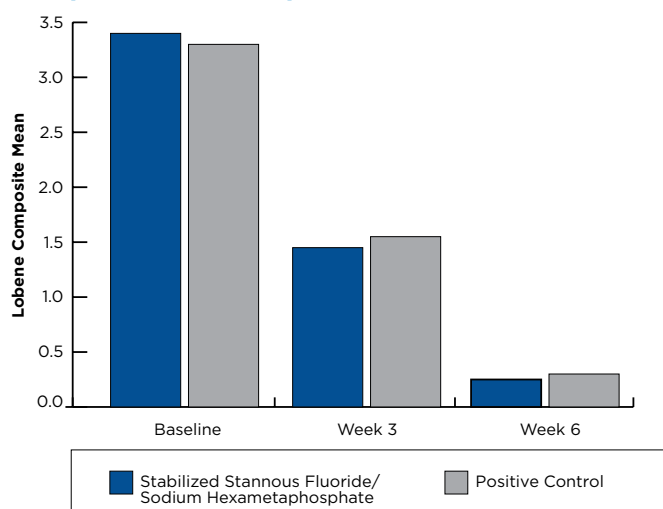
RESULTS

- 52 subjects completed Study 1; 58 subjects completed Study 2.
- Lobene composite stain scores were not statistically significantly different between the 2 dentifrice groups at all 3 time points (baseline, week 3, and week 6) in each study.
- Relative to baseline scores, both dentifrice groups showed statistically significant reductions in Lobene composite stain scores at week 3 ($P < 0.0001$) and week 6 ($P < 0.0001$).

Study 1. Lobene Composite Stain Score, Evaluable Subjects



Study 2. Lobene Composite Stain Score, Evaluable Subjects



Weeks 3 and 6 are adjusted mean values.

A Randomized Clinical Trial to Assess Gingivitis, Plaque, and Tooth Color after Use of a Daily Two-Step Dentifrice and Gel System versus Chlorhexidine Rinse

Reference: Gerlach RW, Sagel PA, Barker ML, et al. *J Dent Res* 2015; 94 (Spec Iss A): Abstract 0293.

KEY CLINICAL FINDINGS

Overall

- Use of a daily 2-step dentifrice and gel system resulted in plaque and gingivitis reductions comparable to chlorhexidine (with regular brushing) plus provided tooth whitening benefits. Step 1 is a 0.454% stannous fluoride dentifrice and Step 2 is a whitening gel.

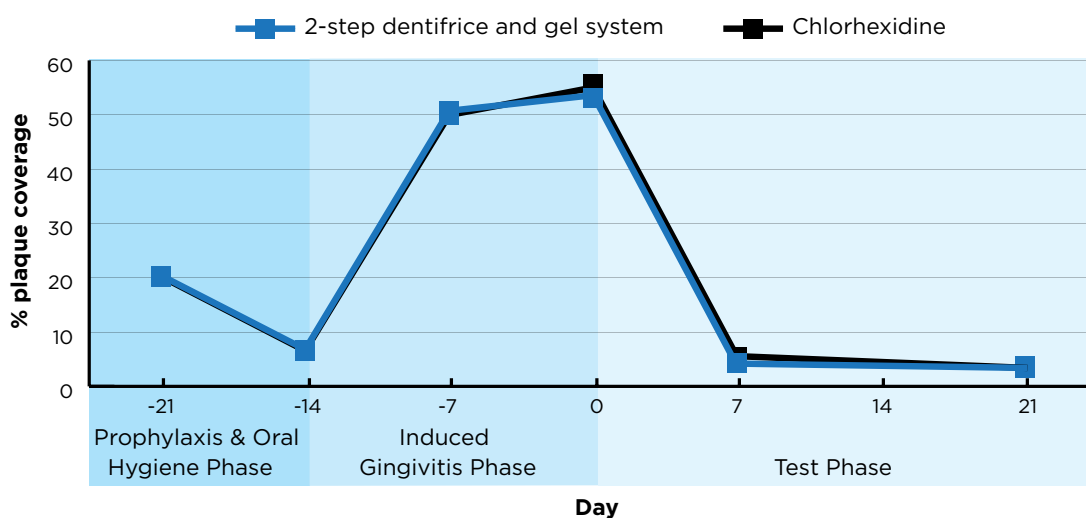
Plaque and Gingivitis

- The daily 2-step dentifrice and gel system group and the chlorhexidine group had statistically significant ($P<0.01$) improvements in plaque area and gingivitis color measurements at both Day 7 and Day 21 from Day 0. See Figures 1 and 2.
- There were no statistically significant differences between the 2-step dentifrice and gel system group and the chlorhexidine group in plaque and gingivitis reduction at Day 7 and Day 21.

Tooth Color

- The 2-step dentifrice and gel system group demonstrated statistically significantly ($P<0.03$) greater improvement in tooth color lightness (L^*) values compared to the chlorhexidine group at Day 7 and 21. See Figure 3.

Figure 1. Percent Plaque Coverage

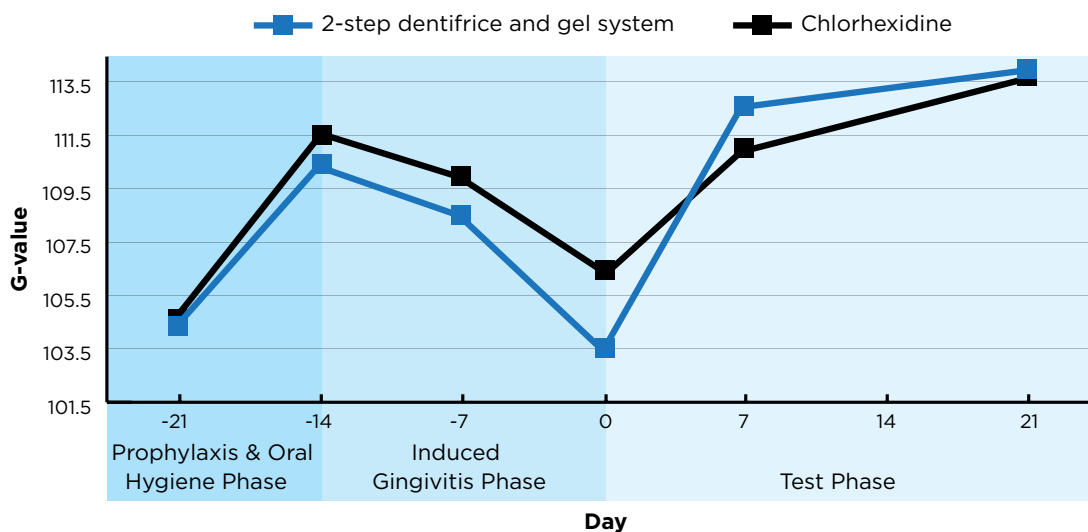


* Day 7 and Day 21 are Means adjusted for Day 0.

For both groups, Day 7 and Day 21 scores were statistically significantly different ($P<0.0001$) from Day 0.

Figure 2. Gingivitis

(Digital Gingival Imaging, a higher G-value indicates less gingivitis)

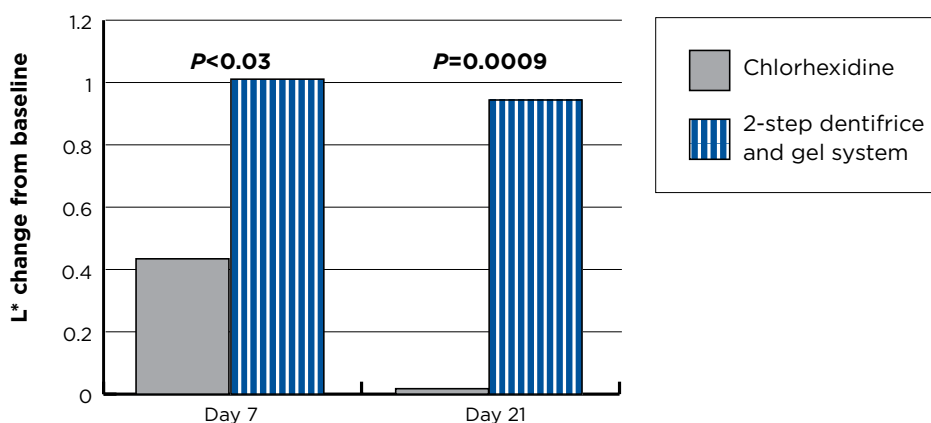


* Day 7 and Day 21 are Means adjusted for Day 0

For both groups, Day 7 and Day 21 scores were statistically significantly different ($P < 0.007$) from Day 0.

Figure 3. Tooth color lightness (L^*) change from baseline

(Combined Arches, Analysis of Covariance)



OBJECTIVE

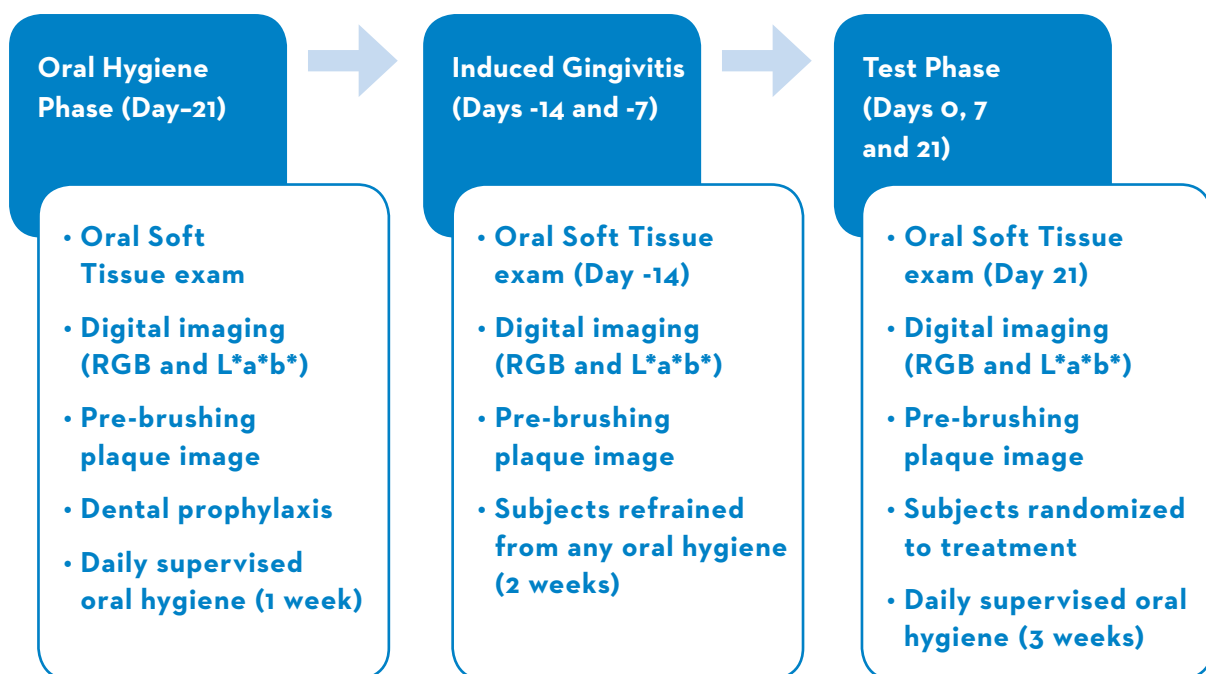
To assess the effect of a daily 2-step dentifrice and gel system versus chlorhexidine (with regular brushing) using imaging of plaque, gingivitis and tooth color in an induced gingivitis model.

METHODS

- This was a single-blind, supervised-use, randomized, parallel-group, positive-controlled clinical trial.
- During the Oral Hygiene Phase, up to 40 healthy volunteers received a dental prophylaxis and used regular oral hygiene products under supervision for one week. During the Induced Gingivitis Phase, subjects refrained from oral hygiene for two weeks. After gingivitis induction, subjects were randomized into 2 treatment groups for the test phase: 2-step dentifrice and gel system or chlorhexidine mouth rinse plus regular brushing. Gingivitis (RGB*), plaque (area %) and tooth color ($L^*a^*b^*$) were measured by digital image analysis after one and three weeks of product use. See Figure 4.

- During the test phase, subjects were randomly assigned to one of the following treatment groups based on average gingival redness (G) score and pre-brush percent plaque coverage:
 1. Daily 2-Step System (Crest® PRO-HEALTH™ [HD]™, Procter & Gamble): Step 1, 0.454% stannous fluoride dentifrice; Step 2, 3% hydrogen peroxide whitening gel and a soft, regular manual toothbrush (Oral-B® Indicator™).
 2. 0.12% chlorhexidine gluconate oral rinse (Oral-B®), 0.76% sodium monofluorophosphate dentifrice (Colgate® Cavity Protection toothpaste) and a soft, regular manual toothbrush (Oral-B® Indicator™).
- Subjects were instructed on product use. Study personnel supervised product use twice daily at least 5 and up to 7 days a week until the end of the study.

Figure 4. Study Design



* Standard Test Method for Objective Measurement of Gingival Color Using Digital Still Cameras. ASTM E2545 - 07(2012). <http://www.astm.org/Standards/E2545.htm>

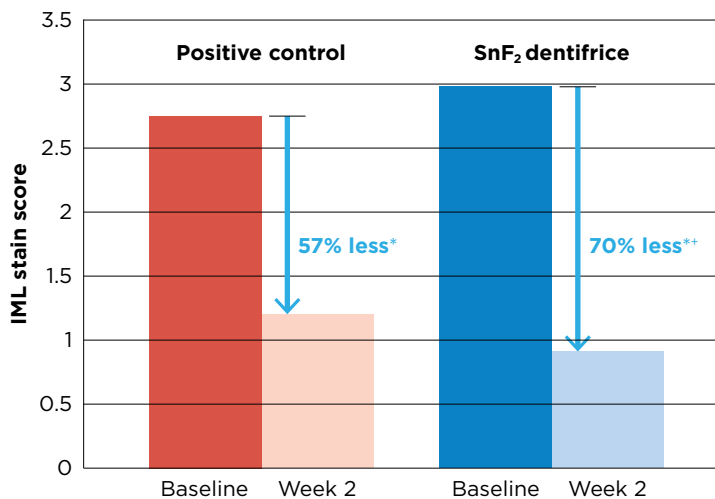
Extrinsic Stain Removal Efficacy of a Stabilized Stannous Fluoride Dentifrice

Reference: L Friesen, T He, R. Eusebio. *J Dent Res* 2017; 96 (Spec Iss A): Abstract 1941.

KEY CLINICAL FINDINGS

- After 2 week of use, the experimental stabilized stannous fluoride (SnF_2) group demonstrated significantly less Interproximal Modified Lobene (IML) stain overall (see Figure) and interproximal surface stain than the positive control dentifrice group ($P<0.0012$).
- Both groups showed statistically significant reductions in IML stain scores at Week 2 ($P<0.0001$) relative to Baseline. The median percent change reductions were 57% for the positive control and 70% for the SnF_2 dentifrice.

Figure. Interproximal Modified Lobene Stain Scores per Group.



N=25 per group.

* Both groups showed a statistically significant reduction versus Baseline, percents based on median percent change.

+ Statistically significant difference between groups at Week 2 ($P<0.0012$).

OBJECTIVE

To assess the extrinsic stain removal benefit delivered by a SnF_2 dentifrice and a positive control dentifrice over a two-week period.

METHODS

- This study utilized a randomized, two-week, double-blind, parallel group design.
- At Baseline, an IML examination[‡] was performed on the facial surfaces of the twelve anterior teeth. The two teeth with the highest IML composite scores were selected as the test teeth.
- Subjects were stratified on stain scores of the test teeth, and gender, and randomized to one of two treatment groups:
 - Experimental 0.454% stabilized stannous fluoride dentifrice (Crest® PRO-HEALTH™ Clean Mint [Smooth Formula], Procter & Gamble); or
 - 0.243% sodium fluoride/0.3% triclosan positive control whitening dentifrice (Colgate® Total® Whitening, Colgate-Palmolive).
- Subjects were instructed to use their respective test product following the manufacturer's instructions at home over the two week study duration.
- Tooth color was reassessed at Week Two.
- Baseline to post-treatment change in stain score was tested using paired t-tests. Analysis of covariance (ANCOVA) with treatment as a factor and Baseline Lobene score as the covariate was used to assess treatment differences post-treatment. All comparisons were two-sided using a 5% level of significance.

CLINICAL COMMENT

Stabilized SnF₂ dentifrice has been shown to provide significant oral health benefits, including protection against caries, plaque, gingivitis and sensitivity.[§] SnF₂ formulations have also been developed to provide esthetic benefits consumers desire, including extrinsic stain removal. This high silica containing toothpaste is uniquely formulated to provide effective cleaning and surface stain removal.

[‡] Friesen L, et al. *Am J Dent* 2016; 29:20-24.

[§] Baig A and He T. *Compend Contin Educ Dent*. 2005;26 (Suppl 1): 4-11.



Clinical Significance

- The stabilized stannous fluoride dentifrice formulations not only prevent stain from forming, but they actually provide whitening by removing surface stains, an esthetic benefit that is important to the patient.
- Now the health benefits of stannous fluoride are fully realized without the esthetic drawback of potentially causing stain in some individuals.

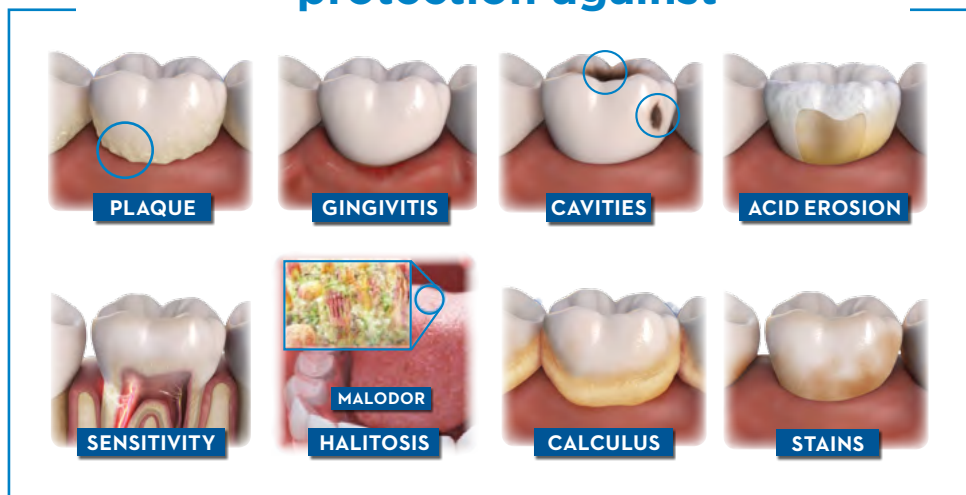
SUMMARY

Stannous fluoride is unique among fluorides because it offers oral health benefits beyond caries protection. Developing a stannous fluoride dentifrice that is stabilized and bioavailable, however, requires innovation and formulation expertise. Scientists at Procter & Gamble are the global leaders in stannous fluoride dentifrice innovation, offering a broad portfolio of stabilized stannous fluoride dentifrice so patients can achieve optimal oral health protection and a brushing experience that delights them. Each formula offers the following benefits:

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



protection against



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