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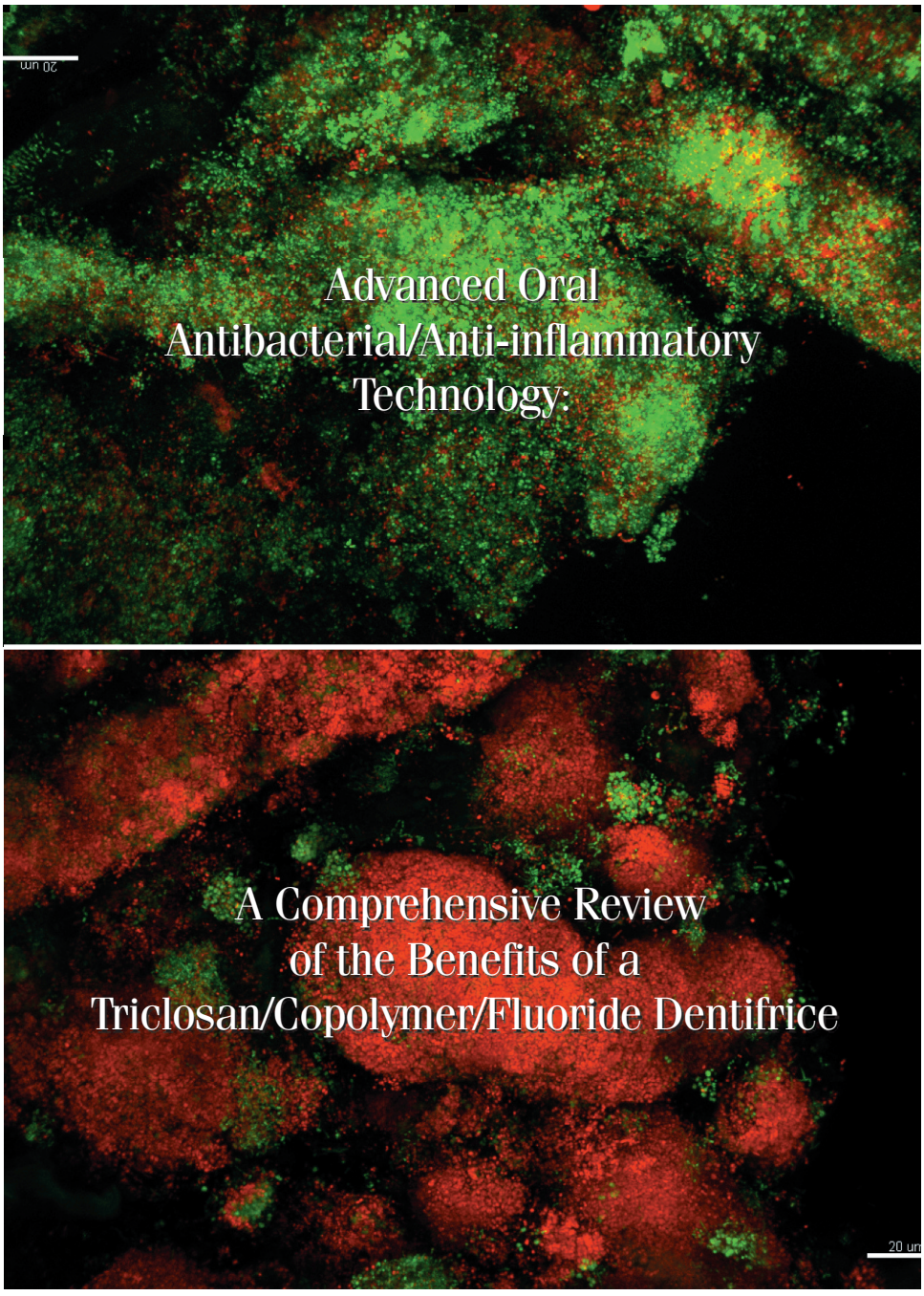

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ON THE COVER
3D confocal laser scanning microscopic image of plaque biofilm showing live (green) and dead (red) bacteria 12 hours after brushing with Colgate Total Toothpaste.

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Advanced Oral Antibacterial/ Anti-Inflammatory Technology:

A Comprehensive Review of the Benefits of a Triclosan/Copolymer/ Fluoride Dentifrice

Advanced Oral Antibacterial/Anti-inflammatory Technology: A Comprehensive Review of the Clinical Benefits of a Triclosan/Copolymer/Fluoride Dentifrice

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Abstract

Triclosan is a broad-spectrum antibacterial agent, marketed for use in oral care products; it is effective against both Gram-positive and Gram-negative bacteria. PVM/MA is the non-proprietary designation for a polyvinylmethyl ether maleic acid copolymer. It has been demonstrated that there is a greater uptake of triclosan to enamel and buccal epithelial cells from the use of a fluoride dentifrice containing triclosan and the PVM/MA copolymer than from a dentifrice containing triclosan alone. This Supplement to *The Journal of Clinical Dentistry* reviews the published literature, which reports the laboratory and clinical studies that have been conducted on a triclosan/copolymer/fluoride dentifrice in a variety of oral health conditions.

The laboratory and clinical studies reviewed within this Supplement clearly indicate that the use of a triclosan/copolymer/fluoride dentifrice (Colgate® Total® Toothpaste, Colgate-Palmolive Company, New York, NY, USA) provides oral health benefits beyond those associated with a "traditional" dentifrice, in a manner that is safe and effective. These demonstrate that Colgate Total Toothpaste provides superior protection against plaque and gingivitis, calculus, caries, oral malodor, and peri-implant mucositis. Colgate Total Toothpaste also provides superior whitening and stain removal benefits. It also provides protection against the progression of periodontal disease. In addition, a specific variant of Colgate Total Toothpaste provides dentin hypersensitivity benefits. Colgate Total Toothpaste has been proven to provide superior oral health benefits to a dentifrice containing stannous fluoride, sodium hexametaphosphate and zinc lactate. Finally, these studies provide the necessary scientific support so that dental professionals can recommend Colgate Total Toothpaste to their patients for use as part of their overall oral hygiene regimen.

(J Clin Dent 2014;25(Suppl):S1-30)

Introduction

Triclosan

Triclosan is a broad-spectrum antibacterial agent, marketed for use in oral care products under the tradename Irgacare MP® and manufactured by BASF.[1] The structure of triclosan is shown in Figure 1; the non-proprietary or chemical name is 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

The primary site of triclosan's antimicrobial action is the bacterial cytoplasmic membrane. Triclosan prevents essential amino acid uptake at *bacteriostatic* concentrations. At *bactericidal* concentrations, triclosan causes cytoplasmic disorganization of the bacterial cytoplasmic membrane, and leakage of cellular contents. Triclosan is effective against both gram-positive and gram-negative bacteria.[2,3]

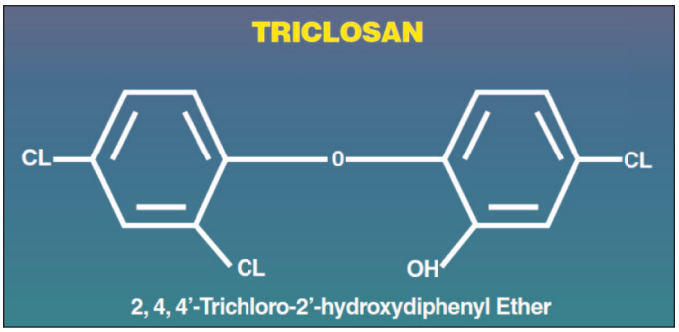


Figure 1. *Chemical structure of triclosan (2, 4, 4'-trichloro-2'-hydroxydiphenyl ether). (This illustration is provided through the courtesy of Drs. Nuran Nabi and Abdul Gaffar.)*

As summarized by Lindhe,[4] triclosan is a useful antibacterial agent to be incorporated into oral care products because it has a broad spectrum of activity on oral bacteria and is compatible with the ingredients in oral care products.

Rodricks, *et al.*[5] undertook a critical review of the available experimental data and developed margins of safety for the use of triclosan in consumer products. The authors determined that "exposure to triclosan in consumer products is not expected to cause adverse health effects in children or adults who use these products as intended." In addition, a number of other studies and reviews have been authored attesting to the safety of triclosan.[6-11]

The European Commission has reviewed the safety and efficacy of the use of triclosan in consumer products on numerous occasions within the past 10 years. In 2009, an opinion on triclosan was issued by the Scientific Committee on Consumer Products (SCCP), which concluded that its use at a maximum concentration of 0.3% in toothpastes is consid-

ered safe.[12] This opinion was updated in 2011 by the Scientific Committee on Consumer Safety (SCCS), which is the successor committee to the SCCP.[13] In this updated opinion, an additional use of triclosan in mouthwashes at a concentration limit of 0.15 or 0.2% is considered safe for the consumer from a toxicological perspective. Additionally, the SCCS issued an opinion on triclosan and antimicrobial resistance in which the SCCS stated that it can only recommend the prudent use of triclosan, for example in applications where a health benefit can be demonstrated.[14] Furthermore, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) of the Australian Government Department of Health and Ageing published a Priority Existing Chemical Assessment Report on Triclosan. The report concluded that: "On the basis of available data, there is also no evidence that the use of triclosan is leading to an increase in triclosan-resistant bacterial populations or that there is any increased risk to humans regarding antibiotic resistance."[15] Finally, several publications have examined the fate of triclosan in the environment. Fuchsman, *et al.* evaluated the terrestrial ecological risks related to triclosan in land-applied biosolids.[16] They concluded that according to the available data, adverse effects on plants, invertebrates, birds, and mammals are unlikely. Lyndall, *et al.* evaluated the triclosan-related risks to the aquatic environment for aquatic and sediment-dwelling organisms and for aquatic-feeding wildlife. They concluded that under most scenarios, adverse effects due to triclosan are unlikely.[17]

Triclosan with a PVM/MA Copolymer

PVM/MA is the non-proprietary designation for a polyvinylmethyl ether/maleic acid copolymer. One manufacturer markets the copolymer under the tradename Gantrez®. The chemical structure of this copolymer is presented in Figure 2. Nabi, *et al.* reported in 1989 the results from *in vitro* and *in vivo* studies using triclosan and the PVM/MA copolymer.[18] These studies demonstrated that there was a greater uptake of triclosan to enamel and buccal epithelial cells from the use of a fluoride dentifrice containing triclosan and the PVM/MA copolymer than from a dentifrice containing triclosan alone (Figure 3).

Gaffar, *et al.* reported in 1990 that the PVM/MA copolymer, in the presence of triclosan, inhibited crystal growth in both *in vitro* and *in vivo* studies.[19] In 1990, Nabi and Gaffar were granted United States Patent Number 4,894,220 on the technology associated with triclosan and PVM/MA copolymer in oral care products.[20]

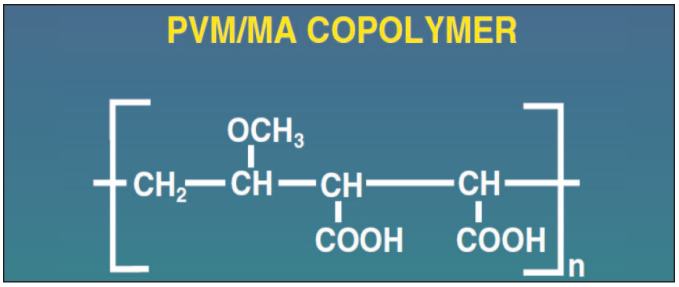


Figure 2. *Chemical structure of polyvinylmethyl ether/maleic acid (PVM/MA) copolymer. (This illustration is provided through the courtesy of Dr. Abdul Gaffar.)*

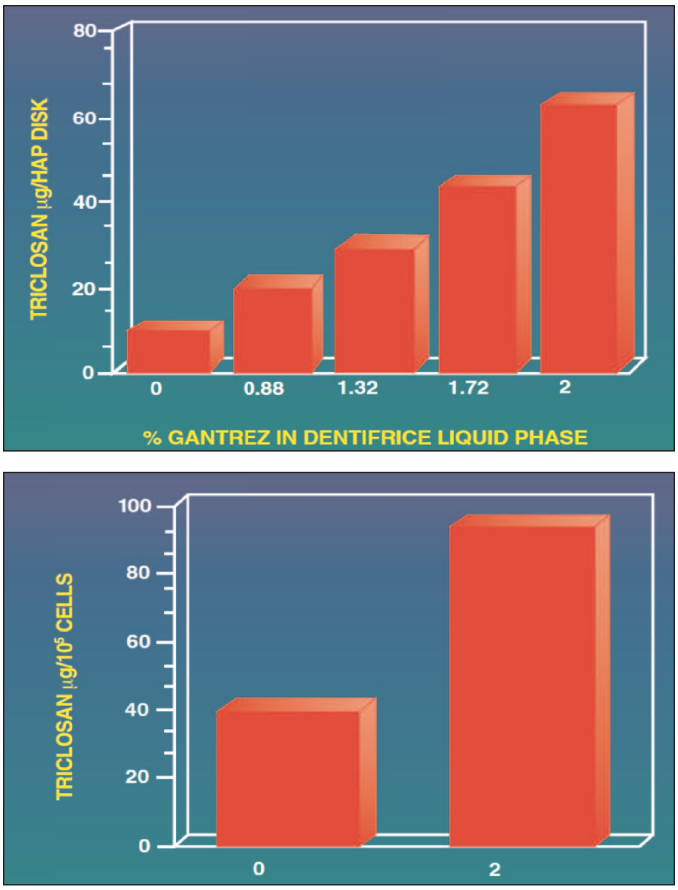


Figure 3. *Graphic representation of the beneficial effect of triclosan retention on enamel and buccal epithelial cells from triclosan and the PVM/MA copolymer. (Reprinted from Nabi, et al.,* Am J Dent *1989[18] with permission.)*

Triclosan's Effect on Oral Microflora

The American Dental Association program guidelines for the acceptance of chemotherapeutic products for the control of gingivitis require microbiological monitoring. Companies must provide evidence that the oral flora has not been adversely affected.[21,22] Four of the long-term plaque and gingivitis clinical efficacy studies discussed in this Supplement included microbiological monitoring of the oral microflora.[23-26] A summary of the microbiological findings from these studies is provided in Table I.

Zambon, *et al.* in 1990[27] reported the results from a microbiologic evaluation of the plaque samples obtained during the course of the Garcia-Godoy, *et al.* plaque and gingivitis clinical efficacy study.[23] These investigators reported that "the use of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer (in a 0.243% sodium fluoride/silica base), over an extended period of time (26 weeks), does not result in shifts in the microflora of supragingival plaque favoring the growth of either opportunistic or pathogenic bacterial species."

Bonta, *et al.* in 1992[28] reported the microbiological monitoring results from a continuation of the Garcia-Godoy, *et al.*[23] study for an additional six months (total of one year's use of the 0.3% triclosan and 2.0% copolymer fluoride dentifrice). These investigators reported that "there were no deleterious effects upon the oral microflora, either in terms of the

Table I
Microbiology
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% Copolymer in a Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects	Duration	Development of Organisms		
					Pathogenic	Opportunistic	Resistant
9	Fine, *et al*., 1998	United States	66	6 months	NO	NO	NO
27	Zambon, *et al*., 1990	Dominican Republic	81	7 months	NO	NO	NO
28	Bonta, *et al*., 1992	Dominican Republic	74	12 months	NO	NO	NO
29	Walker, *et al*., 1994	United States	144	6 months	NO	NO	NO
30	Zambon, *et al*., 1995	United States	144	6 months	NO	NO	NO
31	Cullinan, *et al*., 2013	Australia	40	120 months	NO	NO	NO

emergence of opportunistic or resistant organisms, associated with the long-term use (one year) of a (fluoride) dentifrice containing 0.3% triclosan and 2.0% copolymer, as compared to a placebo dentifrice."

Walker, *et al.* in 1993[29] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy study conducted by Mankodi, *et al*.[24] These investigators reported that "the extended use of a 0.3% triclosan and 2.0% copolymer (fluoride) dentifrice does not disrupt the normal microflora associated with supragingival plaque, favor the growth or colonization of periodontal or opportunistic pathogens, or promote the acquisition of microbial resistance."

Zambon, *et al.* in 1995[30] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy study conducted by Bolden, *et al*.[25] These investigators reported that the study "confirms the microbiological safety of triclosan-containing (fluoride) dentifrices, and suggests that continued use can be associated with beneficial alterations in the bacterial composition of supragingival dental plaque."

Fine, *et al.* in 1998[9] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy study conducted by Denepitiya, *et al*.[26] These investigators concluded that "the data derived from this study therefore confirms the microbiological safety of a 0.3% triclosan/2.0% copolymer/fluoride dentifrice for use in an unsupervised oral hygiene program."

In addition to the studies reported later in this Supplement, Cullinan, *et al.*[31] reported on the collection of dental plaque samples from individuals who were participating in a five-year randomized controlled clinical trial of a 0.3% triclosan/2.0% copolymer/fluoride dentifrice. Samples were collected from both the triclosan/copolymer dentifrice group and from the placebo group. Minimum Inhibitory Concentration (MIC) of triclosan was determined for selected bacterial isolates from both groups. The results showed that at a concentration of 0.3% triclosan, no growth occurred in the bacteria from either group under microaerophilic or anaerobic conditions. The MICs of triclosan for all isolates ranged from 125 to 1000 g/mL in both groups. Long-term usage of a 0.3% triclosan/2.0% copolymer/fluoride dentifrice did not lead to an increase in the MIC of triclosan in oral bacterial isolates.

Furthermore, Haraszthy, *et al*.[32] evaluated the long-term bacterial susceptibility to triclosan on human supragingival plaque samples collected from adults over a period of 20 years. In brief, there were 12 separate evaluations over 20 years, with data from 155 assessments. Supragingival dental plaque was collected from the entire dentition from adults who had not received dental treatment or antimicrobial therapy in the previous 30 days. Aliquots of the subjects' pooled plaque suspensions were distributed onto agar media containing 0, 7.5, and 25 μg/mL triclosan. In the absence of triclosan, large numbers of colony forming units were cultivatable from all supragingival plaque samples. In the presence of triclosan, the number of supragingival plaque bacteria cultivatable from the same samples was significantly reduced ($p < 0.001$). The 20-year average microbial inhibitions of 99.4% and 99.98% were observed on media with 7.5 μg/mL and 25 μg/mL triclosan-containing media, respectively. For each triclosan concentration, regression analyses compared antimicrobial activity over the 20-year evaluation. There was no change in antimicrobial susceptibility ($p = 0.159$ and 0.299 for the 7.5 and 25 μg/mL triclosan, respectively) over time discernible by regression analyses.

Antibacterial Studies

The antibacterial activity of triclosan has been well documented. In 1990, Gaffar, *et al.* reported on the *in vitro* antibacterial activity of triclosan on oral cavity bacteria.[33] Figure 4 presents the MIC for triclosan on the various oral bacteria studied. In 1992, Gaffar, *et al.* presented a schematic diagram (Figure 5) illustrating how triclosan and the PVM/MA copolymer interrelate with enamel and oral soft tissues.[34] In 1989, Afflitto, *et al.* reported a greater retention of triclosan in both plaque and saliva from the use of a dentifrice containing triclosan and the PVM/MA copolymer than from a dentifrice containing triclosan alone.[35] Retention in plaque was again reported in 1994 by Gaffar, *et al*., whose data support the conclusion that the level of triclosan retained in

Microorganism		Minimum Inhibitory Concentration µg/ml
Laboratry Isolates	NCTC #	
S. mitor	7864	0.78
S. mitor	10712	1.14
A. viscosus	10951	0.78
A. odontolyticus	9935	0.78
B. intermedius	9336	0.38
F. nucleatum	10562	1.14
C. ochracea	11654	<0.38
P. asacchrolyticus	—	<0.58
Fresh Isolates	CODE	
A. actinomycetemcomitans	1426	<0.29
A. actinomycetemcomitans	1483	<0.29
A. odontolyyicus	1041	0.78
A. odontolyyicus	1431	0.78
A. viscosus	1218	0.78
Capnocytophaga spp	287	0.78
Capnocytophaga spp	290	2.34
Capnocytophaga spp	310	0.78
F. nucleatum	1446	0.78
P. anaerobius	580	0.58
P. anaerobius	1198	2.34
P. micros	1422	3.12
P. acnes	1305	2.34
S. milleri	1339	2.34
S. milleri	1391	2.34
S, mitor	1384	2.34
S. mitor	1387	2.34
V. parvula	1167	6.25
V. parvula	1459	2.30

Figure 4. In vitro *antibacterial activity of 0.3% triclosan/copolymer dentifrice. (Adapted from Gaffar, et al.,* Am J Dent, *1990[33] with permission.)*

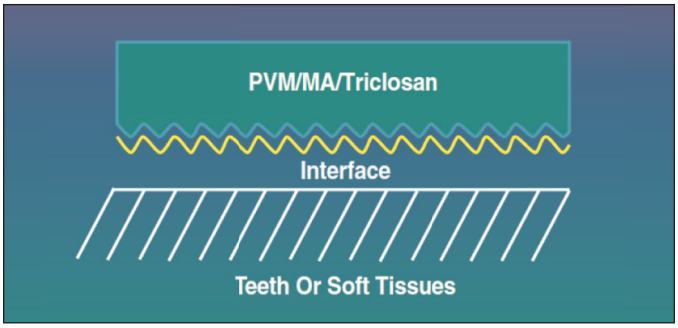


Figure 5. *Diagrammatic representation of the interrelationship between triclosan and the copolymer and the oral tissues. (Reprinted from Gaffar, et al.,* Clinical and Biological Aspects of Dentifrices*, Oxford University Press, 1992[34] with permission.)*

plaque 14 hours after brushing significantly exceeds the MIC for plaque bacteria (which ranges from 0.2 to 3 g/mL).[36]

The 1994 report by Gaffar, *et al.* also discusses an *in vitro* investigation into the long-term effects of a dentifrice containing triclosan and the PVM/MA copolymer at inhibiting bacterial growth. These results are illustrated in Figure 6. They also provided the results of a crossover clinical study (Figure 7), in which plaque samples were obtained from participants both prior to, and at two, six, and 12 hours after brushing with each dentifrice. Plaque samples were obtained from four sites in each subject (the lingual surfaces of the mandibular second molars and the buccal surfaces of the maxillary canines), stained to make the viable and non-viable plaque differentially visible, and subsequently assessed for plaque viability.[36]

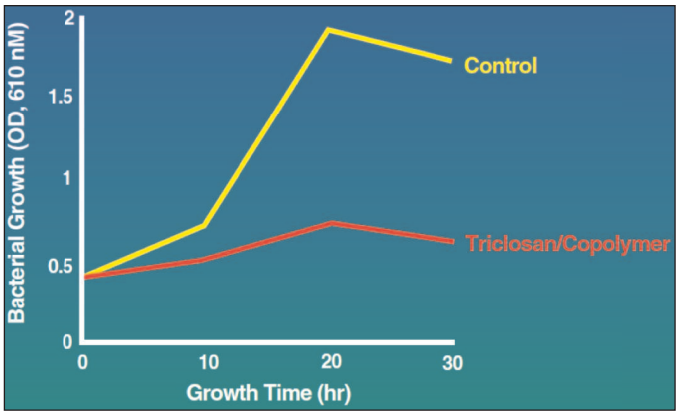


Figure 6. *Bacterial growth on treated hydroxyapatite disks. (Adapted from Gaffar, et al.,* Int Dent J *1994.[36])*

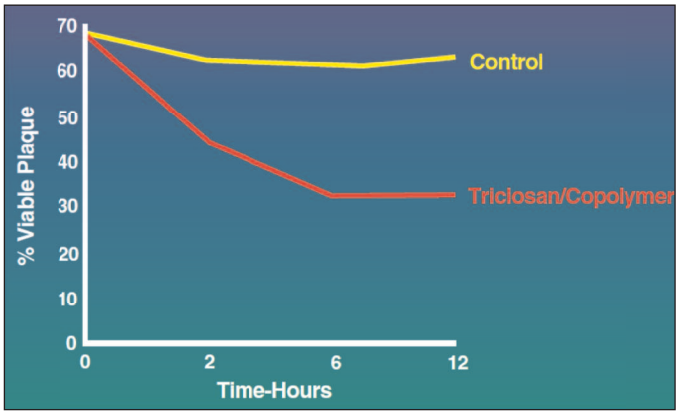


Figure 7. *Plaque viability after brushing. (Adapted from Gaffar, et al.,* Int Dent J *1994.[36])*

Ledder, *et al.* evaluated the antimicrobial activity and specificity of different active ingredients used in marketed dentifrices, including triclosan, stannous fluoride, zinc lactate, and a combination of stannous fluoride and zinc lactate.[37] The ingredients were delivered to tissue culture plate-based hydroxyapatite disc models (HDMs) once daily and to modified drip-flow biofilm reactors (MDFRs) four times daily for six days. Results indicated that triclosan was the most effective ingredient against HDM plaques, significantly reducing total viable counts ($p < 0.05$), while the stannous fluoride, zinc lactate, and combinations of stannous fluoride/zinc lactate were ineffective. Triclosan exhibited specificity for streptococci ($p < 0.01$) and Gram-negative anaerobes ($p < 0.01$) following single dosing, and also on repeated dosing in MDFRs. It was concluded in this study that triclosan was the most potent antibacterial, after single and multiple dosage regimens.

Amornchat, *et al.*[38] have evaluated the plaque viability and triclosan retention in dental plaque for twelve hours after brushing with Colgate Total toothpaste. Results indicated that there was only 38% plaque viability of oral bacteria following a single brushing. The mean concentration of triclosan twelve hours after a single brushing was 5.2 /mL, which is in agreement with previously published results.

In three separate studies by Yang and Sreenivasan,[39] it was reported that a 0.3% triclosan/2.0% PVM/MA copolymer/fluoride dentifrice demonstrated significant dose-dependent

antimicrobial effects compared with a control formulation on anaerobic and facultative oral bacteria. Samples of oral flora from 16 subjects were treated for two minutes with either a triclosan/copolymer/fluoride dentifrice or a fluoride control dentifrice, and were plated on appropriate agar for multiplexed antimicrobial effects on functional groups of oral bacteria associated with specific conditions. Results indicated that the triclosan/copolymer/fluoride dentifrice resulted in a 65% significant decrease of bacteria ($p < 0.05$) compared to the control dentifrice. Gram-positive and gram-negative bacteria were significantly ($p < 0.05$) reduced by 51% and 68%, and microorganisms implicated in caries and malodor by 66–90% and 51–53%, respectively.

In a 24-hour, cross-over, single blind, 11-subject clinical study, Xu, *et al.*,[40] reported that a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/fluoride showed superior plaque control, particularly for periodontal pathogens, relative to a control fluoride dentifrice. After a one-week washout period, dental plaque was collected from each subject who received an oral prophylaxis and then brushed with a test dentifrice. Twenty-four hour post-brushing plaque was again collected. Using the Modified Gingival Margin Plaque Index (MGMPI), results showed that plaque covered 17.88% of the gingival margin of subjects who used the 0.3% triclosan/2.0% PVM/MA copolymer/fluoride dentifrice compared with 30.42% of the gingival margin of subjects using the control fluoride dentifrice ($p < 0.05$). Results from real-time PCR indicated that after brushing with the 0.3% triclosan/2.0% copolymer/fluoride dentifrice, 61% of the subjects showed reductions in gram-negative periodontal pathogens, including *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythenis*, and *P. gingivalis*, versus 40% of subjects who brushed with the control fluoride dentifrice ($p < 0.05$).

Fine, *et al.*[41] compared the antimicrobial effects on microorganisms in subjects who brushed with the 0.3% triclosan/2.0% PVM/MA copolymer/fluoride dentifrice and a control fluoride dentifrice in a cross-over study. Fifteen subjects brushed twice daily for one week with one of the two test products. Plaque samples, saliva, and tongue scrapings were collected six and 12 hours after the final brushing. Compared to the control dentifrice group, the triclosan and 2.0% PVM/MA copolymer/fluoride dentifrice group showed significant reductions ($p < 0.05$) in oral anaerobic bacteria (88% to 96%), Fusobacteria (77% to 92%), and Veillonella (84% to 89%) at six and 12 hours after brushing, and a significant decrease in H_2S-producing bacteria six and 12 hours after brushing ($p < 0.05$).

Fine, *et al.*[42] compared the antibacterial efficacy of three commercial dentifrices after 14 days of brushings. Baseline samples from four sites, plaque, saliva, tongue, and buccal mucosa were collected and evaluated for six microbial types, anaerobes, Streptococci, Actinomyces, hydrogen-sulphide (H_2S)-producing bacteria, Fusobacteria, and Veillonella. On day 14, 12 hours after brushing, samples were collected for microbiological evaluations. For all four oral sites and six organisms evaluated in each site, the triclosan/copolymer/fluoride dentifrice demonstrated significant reductions (49–83%) as compared with the other two dentifrices ($p < 0.01$). The stannous fluoride/sodium hexametaphosphate/ zinc lactate dentifrice showed significant reductions of 14–43% for 14 of 24 outcomes as compared with the sodium fluoride dentifrice group ($p < 0.01$), with no differences in 10 outcomes. The dentifrice containing triclosan/copolymer/fluoride consistently demonstrated significant reductions for a range of microorganisms in diverse oral sites in comparison to the other two dentifrice formulations, as seen 12 hours after brushing.

Du-Thumm, *et al.* have used 3D Confocal Laser Scanning

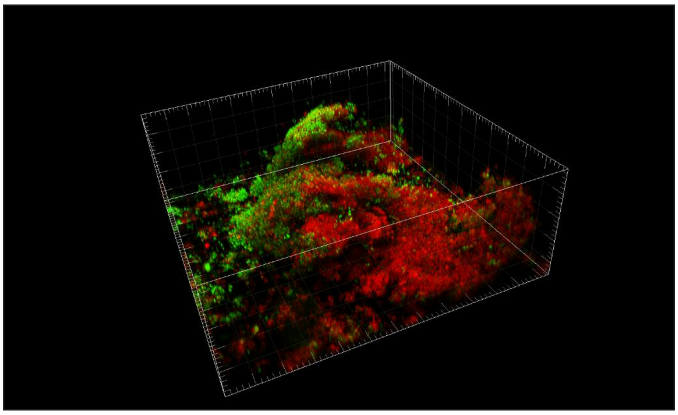


Figure 8. *Representative 3D images of plaque biofilm 12-hrs after treatment with Colgate Total. (Provided courtesy of Dr. Laurence Du-Thumm.)*

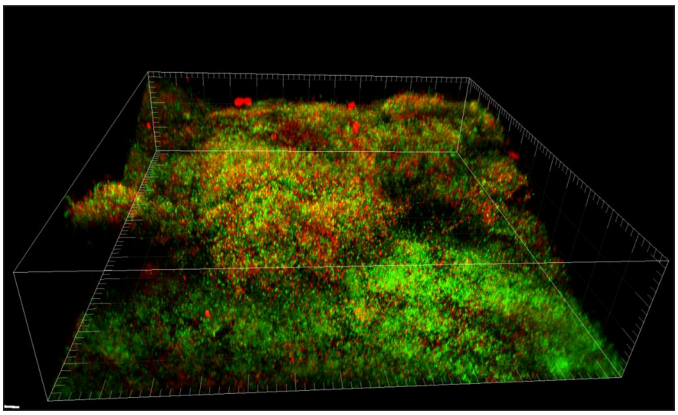


Figure 9. *Representative 3D images of plaque biofilm 12-hrs after treatment with Crest Pro-Health. (Provided courtesy of Dr. Laurence Du-Thumm.)*

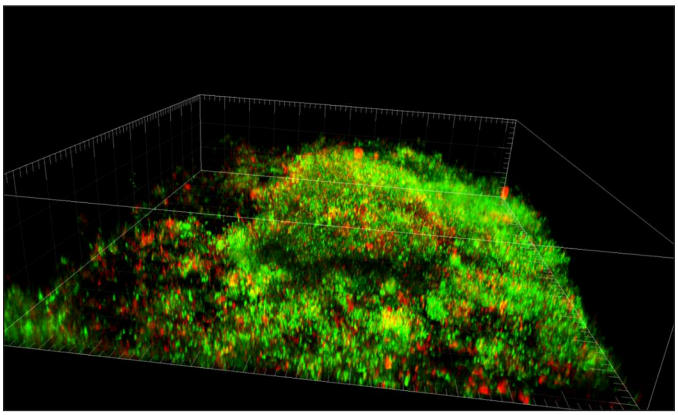


Figure 10. *Representative 3D images of plaque biofilm 12-hrs after treatment with Colgate Cavity Protection. (Provided courtesy of Dr. Laurence Du-Thumm.)*

Microscopy (CLSM) to assess the antimicrobial effects of three toothpastes (Colgate Total, Colgate Cavity Protection, and Crest® Pro-Health) on dental plaque viability 12 hours after brushing. Undisturbed plaque biofilm was formed *in situ* over a 48-hour period using hydroxyapatite discs mounted in an intraoral plastic retainer before treatment with each toothpaste in a cross-over study design. A LIVE/DEAD® BacLight™ bacterial viability kit from Invitrogen was used to fluorescently label bacteria in the biofilm formed on the discs. They were imaged using CLSM and subsequently analyzed using the Imaris 7.4 image analysis software for 3D rendering generation and calculation of the biovolumes for each green (live) and red (dead) channel. The analysis was performed at baseline (before treatment) and 12 hours after brushing. Colgate Total clearly demonstrated the highest level of antimicrobial activity with a clear loss of bacterial viability throughout the deepest layers of the biofilm (Figure 8). Crest Pro-Health (Figure 9) provided some degree of antimicrobial activity as shown with the presence of damaged bacterial cells as compared to Colgate Cavity Protection (Figure 10). Calculation of the green channel biovolumes showed that the mean plaque viability for Colgate Total was 17.72% and was statistically significantly different from the two other treatments ($p < 0.05$). Mean plaque viability was 51.43% for Crest Pro-Health and 72.18% for Colgate Cavity Protection toothpaste. CLSM imaging used with 3-D plaque viability imaging analysis provides a powerful tool to demonstrate the superior bacterial killing power of Colgate Total.[43]

Overall Conclusion from the Antibacterial Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the antibacterial studies discussed in this section clearly demonstrates that the use of a fluoride dentifrice containing triclosan and the PVM/MA copolymer will substantially impact on the level of viable plaque present in the mouth over the 12-hour post-brushing period.

Anti-Inflammatory Activity of Triclosan

Inflammation is the process by which tissues and organs manage damage and infection. It is well known that excessive or prolonged inflammation can lead to tissue destruction. Evidence has suggested that prolonged infection and inflammation at a local site, such as the periodontium, can have systemic implications,[44] influencing cardiovascular disease, diabetes, and respiratory ailments (Figure 11). With respect to inflammation in the oral cavity, the prevention and treatment of gingivitis and periodontitis are beneficial for a healthy mouth and these, in turn, may be important for a healthy body. As described previously, Colgate Total Toothpaste has been shown to be effective in treating gingivitis. The clinical studies presented, combined with extensive laboratory studies, suggest that the antigingivitis effect of Colgate Total Toothpaste results from the combined antimicrobial and anti-inflammatory properties of triclosan.[45]

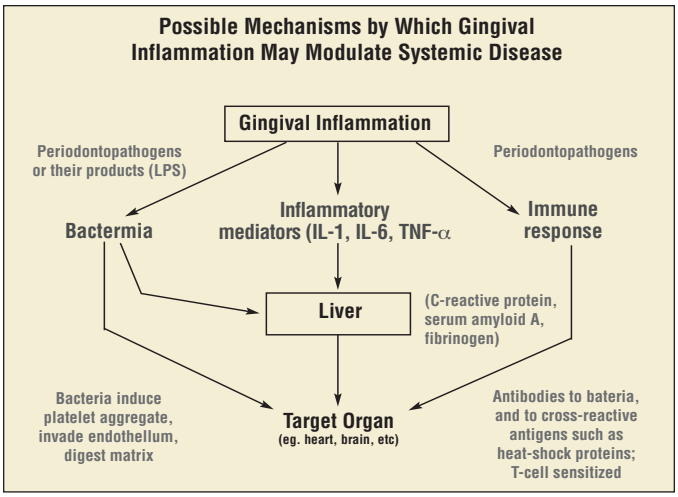


Figure 11. *This illustration shows the local bacterial products that can influence the release of cytokines which could moderate inflammation at a distant site. It also identifies two possible sites for intolerance*

Modeer and colleagues have conducted a number of laboratory studies to elucidate the anti-inflammatory action of triclosan.[46-50] Cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), as well as other local factors play multiple roles in the stimulation of the host inflammatory response. Specifically, both cytokines can induce prostaglandin E_2 (PGE_2) production during the process of inflammation. PGE_2 is the most potent stimulator of bone resorption and exhibits a broad range of inflammatory effects. In one study, Modeer, *et al.* reported that as IL-1β was increased from 50 pg/mL to 200 pg/mL, the presence of triclosan at 1 g/mL prevented a significant increase in PGE_2.[46] In another study, triclosan was shown to inhibit TNF-α-induced PGE_2 production.[47] Additional evidence indicates that triclosan can inhibit the major histocompatability complex in macrophages, as well as inhibiting the production and secretion of proteases by human bone and fibroblastic cells when stimulated by IL-1β or TNF-α.[48,51] Finally, Mustafa, *et al.*, attempting to further dissect the anti-inflammatory mechanism of action of triclosan, demonstrated that ^{14}C-labeled triclosan is absorbed by fibroblastic cells and translocates to the nucleus.[52] Together, these results suggest that the anti-inflammatory effects of triclosan may contribute to the local clinical benefits delivered by Colgate Total Toothpaste, and in turn, may also impart an effect on systemic inflammation.

Barros, *et al.* sought to determine whether triclosan could more broadly suppress multiple inflammatory gene pathways responsible for the pathogenesis of gingivitis and periodontitis using a human *ex vivo* system. Ten milliliter whole blood aliquots were incubated for two hours with 0.3 mg/mL *Escherichia coli* lipopolysaccharide (LPS) with or without 0.5 mg/ml triclosan. Affymetrix microarray gene expression profiles from isolated leucocytes and pathway-specific quantitative polymerase chain reaction arrays were used to investigate changes in expression of target cytokines and cell signaling molecules. *Ex vivo* human whole blood assays indicated that triclosan signifi-

cantly down-regulated the LPS-stimulated expression of toll-like receptor signaling molecules and other multiple inflammatory molecules, including IL-1 and IL-6 and the dampening of signals that activates the T-helper type 1 acquired immune response via suppression of CD70 with concomitant up-regulation of growth factors related to bone morphogenetic protein (BMP)2 and BMP6 synthesis (Figure 12). They concluded that triclosan demonstrated anti-inflammatory effects in an *ex vivo* model that include: 1) suppression of microbial-pathogen recognition pathway molecules; 2) the suppressed synthesis of acute mediators of inflammation including IL-1; 3) the dampening of the TH1 acquired immune response activation by CD70 suppression; 4) attenuating the transition of innate immune response from acute to chronic via inhibition of IL-6; and 5) the up-regulation of the specific growth factors BMP2 and BMP6 which pathways are involved with wound healing.[53]

Wallet, *et al.* evaluated the effects and mechanism of action of triclosan on the response of oral epithelial cells to stimulation with the inflammatory microbial product lipopolysaccharide (LPS), a ligand for toll-like receptor 4 [TLR4] were evaluated. They demonstrated that triclosan is a potent inhibitor of oral epithelial cell LPS-induced pro-inflammatory responses by inducing miRNA regulation of the TLR-signaling pathway. Triclosan was not a pan-suppresser of oral epithelial cell responses as βD2 and βD3 were up-regulated by triclosan following LPS-stimulation. Again, these data demonstrate both a novel antimicrobial mechanism by which triclosan improves plaque control, and an additional anti-inflammatory property that could have beneficial effects in periodontal disease resolution.[54]

Barnes, *et al.* performed a comprehensive analysis of biochemical profiles of gingival crevicular fluid (GCF) samples from healthy, gingivitis, and periodontitis sites collected from periodontitis patients. Progression of periodontal disease was found to be associated with many metabolic changes. A significant finding of the study was that the purine degradation pathway was accelerated by periodontal disease. This suggests that this pathway and its associated reactive oxygen species production might be a significant source of inflammation.[55]

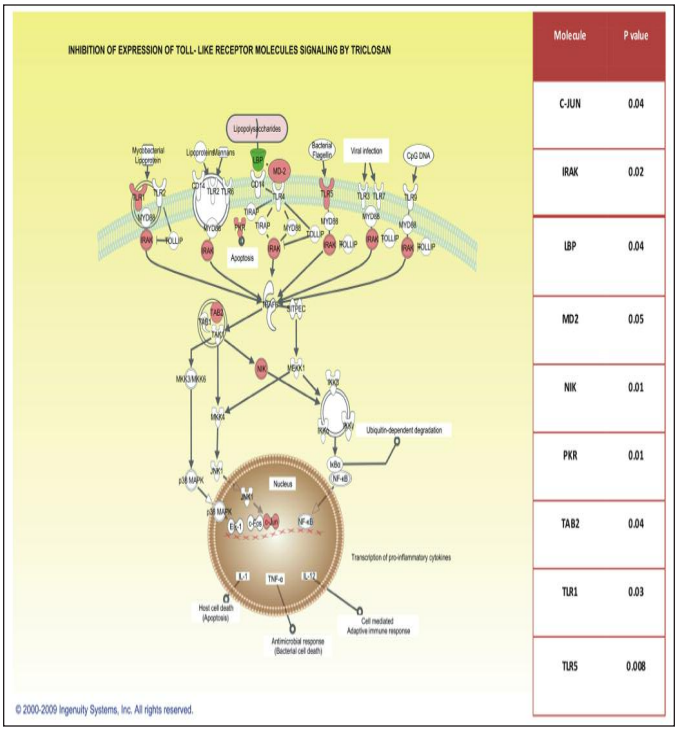


Figure 12. *Inhibition of expression of toll-like receptor molecules signaling by triclosan. (Reprinted from Barros SP, et al.,* J Clin Periodontol *2010,[53] with permission.)*

In a follow-up study, Barnes *et al.* selected the top 10 most significantly changed biochemical markers from the previous study and evaluated how they responded to either a Colgate Total Toothpaste or to a control toothpaste in a six-week clinical study.[56] As in the previous study, samples were taken from healthy, gingivitis, and periodontitis sites collected from periodontitis patients. The results indicate that Colgate Total Toothpaste significantly decreased the levels of four of the markers (inosine, lysine, putrescine, and xanthine) at the gingivitis sites as early as after one-week's use of the toothpaste. The control toothpaste had no effect. This result provides biochemical confirmation for the therapeutic effects of Colgate Total Toothpaste on gingivitis. The biomarkers were significantly altered by Colgate Total Toothpaste before any clinical changes were noted. This suggests that these markers may have predictive value for assessment of disease state.

Most recently, Barnes, *et al.*[57] investigated the effect of triclosan on the expression of Matrix Metalloproteinase-13 (*MMP-13*) in hormone-stimulated osteoblasts. *MMP-13* is an important enzyme for the modulation of gingival recession. Elevated levels of *MMP-13* are associated with periodontal ligament destruction and gingival attachment loss, which are clinical signs of periodontal disease. The results of this study have identified a mechanism of action of triclosan that accounts for triclosan's ability to inhibit *MMP-13* expression in osteoblastic cells that is induced by either parathyroid hormone or prostaglandin E_2.

Plaque and Gingivitis Efficacy

Short-Term Studies

Table II summarizes five independent and double-blind short-term clinical studies which were conducted to determine the effect of a fluoride dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer on supragingival plaque and gingivitis.[58-62] The first three clinical studies utilized adult male and female subjects and began with an oral prophylaxis, after which the subjects brushed their teeth in their normal manner with a soft-textured toothbrush using either a placebo dentifrice or a triclosan/copolymer/fluoride dentifrice. In the fourth study, no initial prophylaxis was performed, and no placebo or negative control dentifrice was included. In all four studies, tooth brushing was performed twice daily for one minute each time. In the fifth study, no initial prophylaxis was performed, a negative control dentifrice was included, and the subjects were instructed to brush normally.

Clerehugh, *et al.* reported that the one-week use of a 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.76% sodium monofluorophosphate/insoluble sodium metaphosphate base) significantly reduced ($p < 0.01$) supragingival plaque accumulation by 16% as compared to the similar

Table II
Plaque and Gingivitis Efficacy
Triclosan/Copolymer Dentifrice Short-Term Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Plaque Efficacy Versus Placebo** Q-H Index	Plaque Efficacy Versus Placebo** P S Index	Gingivitis Efficacy Versus Placebo** L-S Index	Gingivitis Efficacy Versus Placebo** G S Index
58	Clerehugh, *et al*., 1989	England	30	1 week	Parallel with a Prophy at Start	-16.0%	not reported	not reported	not reported
59	Singh, *et al*., 1989	USA	86	6 weeks	Parallel with a Prophy at Start	-20.0%	-65.7%	not reported	not reported
60	Palomo, *et al*., 1989	Guatemala	97	14 weeks	Parallel with a Prophy at Start	-38.8%	-68.9%	-50.7%	not reported
61	Lim, *et al*., 1991***	France	65	6 weeks	Parallel without Prophy at Start	-14.5% -14.5%	-32.8% -36.4%	-23.9% -26.8%	-72.7% -73.2%
62	Muller, *et al*., 2006	Kuwait	32	10 weeks	Parallel without Prophy at Start	(1) The odds ratio (OR) of bleeding on probing was 30% less in the triclosan/copolymer group (2) Causal relationship between supragingival plaque and gingival bleeding was attenuated in the triclosan/copolymer group but not in the negative control group.			

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo (or negative control) dentifrice group who completed the entire study.

** Plaque and gingivitis efficacy results pertain to data obtained at the final clinical examination. All percentages relating to plaque and gingivitis efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice and were statistically significant at the 0.01 level of significance. Q-H Index refers to the Quigley-Hein (Turesky, *et al.* Modification) Plaque Index; L-S Index refers to the Löe-Silness (Talbot, Mandel, and Chilton Modification) Gingival Index; P S Index refers to the Plaque Severity Index of Palomo and co-workers; G S Index refers to the Gingivitis Severity Index of Palomo and co-workers.

*** The upper and lower numbers represent the percentage changes from baseline associated with 1100 ppm F and 1500 ppm F dentifrices, respectively. This study did not employ a placebo treatment. The sample size for this study refers to the two triclosan/copolymer dentifrice groups.

use of a placebo dentifrice.[58]

Singh, *et al.* reported that the six-week use of a 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.243% sodium fluoride/silica base) significantly reduced ($p < 0.01$) supragingival plaque accumulation by 20% as compared to the similar use of a placebo dentifrice.[59]

Palomo, *et al.* reported that after fourteen weeks' use of a 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.76% sodium monofluorophosphate/alumina base), supragingival plaque and gingivitis were significantly reduced ($p < 0.01$) by 39% and 51%, respectively, as compared to the similar use of a placebo dentifrice.[60]

Lim, *et al.* reported that after six weeks' use of dentifrices containing 0.3% triclosan and 2.0% PVM/MA copolymer in either a 0.243% or 0.331% sodium fluoride/silica base, significant reductions ($p < 0.05$) from baseline (no initial prophylaxis) were noted for both supragingival plaque (14% for both levels of fluoride) and gingivitis (24% for 0.243% NaF, 27% for 0.331% NaF).[61]

Muller, *et al.* using multivariate multilevel models, reported that after brushing with a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride/silica dentifrice, subject random error was significantly reduced ($p < 0.05$) from 0.6 to below 0.2. The odds ratio (OR) or bleeding on probing (BOP) was about 30% less ($p < 0.05$) in the triclosan/copolymer/fluoride dentifrice group than in the placebo dentifrice group.[62]

In addition, a series of independent and double-blind short-term clinical studies were conducted to determine the effect of a fluoride dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer on supragingival plaque using MGMPI.[63-66] This index measures plaque along the gingival margin vs. the length of the gingival margin and is calculated as:

MGMPI = (X (gingival margin plaque in mm) / Y (length of tooth gingival margin in mm))*100

Twenty (20) clinical studies were conducted (Table III) comparing Colgate Total Toothpaste and a regular fluoride toothpaste (either Colgate Cavity Protection Fluoride Toothpaste or Colgate Winterfresh Gel). All clinical studies were of a cross-over design and most started with an oral prophylaxis. Subjects entered a seven-day washout period and only brushed with a regular fluoride dentifrice. After seven days, subjects reported to the clinical facility where they brushed for one minute with a regular fluoride dentifrice, rinsed with water, brushed with one of the test products, rinsed with a disclosing solution and water, and then had plaque scored using the criteria of the MGMPI. Subjects refrained from oral hygiene for the next 24 hours, reported back to the clinical site, and had plaque scored using the criteria of the MGMPI. Results from all 20 clinical studies showed that the subjects who brushed with the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/fluoride had statistically significantly lower MGMPI scores ($p < 0.01$) when comparing baseline and 24-hour

Table III
Plaque Efficacy using MGMPI*
Triclosan/Copolymer Dentifrice Short-Term Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer)

Reference No.	Investigators	Location	Number of Subjects	Triclosan/Copolymer Baseline MGMPI	Triclosan/Copolymer 24-Hour MGMPI	Negative Control Baseline MGMPI	Negative Control 24-Hour MGMPI
63	Xu, Barnes, 2003	United States	18	24.77	31.68	18.21	43.51
			15	26.63	40.60	23.89	58.95
			13	26.13	39.45	24.06	47.00
64	Xu, Barnes, 2005	United States	17	23.77	31.68	18.21	43.51
			15	26.63	40.60	23.89	58.95
			13	26.13	39.45	24.06	47.00
			15	21.09	34.78	15.97	42.93
			17	24.40	34.85	19.47	42.26
			17	25.85	34.81	21.47	48.46
			17	27.46	37.41	27.66	43.44
			13	26.13	39.45	24.06	47.00
			12	18.66	28.21	18.81	37.92
			14	27.54	43.11	24.82	60.48
			18	29.84	39.18	25.40	60.82
65	Barnes, *et al.*, 2008	United States	17	20.79	29.56	12.77	31.48
			16	21.89	29.79	19.51	34.20
					Change from Baseline		Change from Baseline
66	Moazezz, *et al.*, 2010	England**	15	---	11.51	---	34.90
			15	---	10.53	---	32.83
			15	---	10.41	---	33.42
			15	---	13.23	---	38.67

* MGMPI (Modified Gingival Margin Plaque Index) measures the percentage of the gingival margin in direct contact with dental plaque at baseline and after 24 hours.
** These four studies report the difference between baseline and 24-hour MGMPI scores.

scores than did the subjects who used the regular fluoride dentifrice.

Long-Term Studies Using a Common Protocol

Table IV presents the plaque and gingivitis efficacy results from seventeen independent and double-blind, long-term (six months or greater) clinical studies, conducted in different geographic areas of the world by different clinicians, all of which compared a 0.3% triclosan/2.0% PVM/MA copolymer/fluoride dentifrice to a placebo dentifrice.[24-27,67-79] These plaque and gingivitis clinical efficacy studies were conducted in accordance with ADA Guidelines in place at the time,[21,22] as well as the 1994 revisions to those guidelines prepared at the request of the American Dental Association by the Task Force on Design and Analysis in Dental and Oral Research, as appropriate.[80] A summary of the current guidelines is provided in Figure 13.

Clinical Design and Protocol. Thirteen of the studies listed in Table IV were initiated with a complete oral prophylaxis in order to evaluate the effect of a triclosan/PVM/MA copolymer/fluoride dentifrice on supragingival plaque accumulation and gingivitis.[23-26,67-69,72-74,76-78] Four clinical studies listed in Table IV were not initiated with an oral prophylaxis in order to evaluate the effect of a triclosan and PVM/MA copolymer fluoride dentifrice on existing supragingival plaque and gingivitis.[70,71,75,79]

The seventeen independent and double-blind long-term

Acceptance Program Guidelines - Chemotherapeutic Products for Control of Supragingivial Plaque and Gingivitis

In brief, the American Dental Association Guidelines require the following:

- At least two independent, well-designed 6-month clinical studies utilizing a placebo control
- The study population should represent typical product users and at least one study shall be conducted on a US population
- The average proportionate reduction in gingivitis across the studies must be no less than 20% and be statistically significant
- Plaque reductions must be statistically significant
- Data supporting safety should include examinations of oral soft tissues and teeth
- Evidence must be provided from at least one study that the oral flora has not been adversely affected through the development of opportunistic and pathogenic organisms

Source: American Dental Association (2008)[22]

Figure 13. *American Dental Association Guidelines for the acceptance of chemotherapeutic agents for the control of supragingival plaque and gingivitis.*

Table IV
Plaque and Gingivitis Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer in a Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Plaque Efficacy Versus Placebo** Q-H Index	Plaque Efficacy Versus Placebo** P S Index	Gingivitis Efficacy Versus Placebo** L-S Index	Gingivitis Efficacy Versus Placebo** G S Index
23	Garcia-Godoy, *et al*., 1990	Dominican Republic	108	7 months	Parallel with a Prophy at Start	-58.9%	-97.7%	-30.1%	-87.5%
24	Mankodi, *et al*., 1992	United States	294	6 months	Parallel with a Prophy at Start	-11.9%	-19.3%	-19.7%	-73.6%
25	Bolden, *et al*., 1992	United States	306	6 months	Parallel with a Prophy at Start	-17.0%	-18.6%	-29.0%	-47.6%
26	Denepitiya, *et al*., 1992	United States	145	6 months	Parallel with a Prophy at Start	-18.4%	-29.2%	-31.5%	-57.1%
67	Cubells, *et al*., 1991	Spain	108	6 months	Parallel with a Prophy at Start	-24.9%	-50.8%	-19.7%	-57.5%
68	Deasy, *et al*., 1991	United States	121	6 months	Parallel with a Prophy at Start	-32.3%	-73.6%	-25.6%	-57.1%
69	Palomo, *et al*., 1994	Guatemala	98	6 months	Parallel with a Prophy at Start	-12.7%	-23.1%	-24.1%	-38.4%
70	Triratana, *et al*., 1993	Thailand	120	6 months	Parallel without Prophy at Start	-32.9%	-46.0%	-18.8%	-38.3%
71	Lindhe, *et al*., 1993	Sweden	110	6 months	Parallel without Prophy at Start	-31.2%	not reported	-26.6%	Significantly Less Bleeding Sites***
72	Hu, *et al*., 1997	China	153	6 months	Parallel with a Prophy at Start	-16.1%	not reported	-24.3%	not reported
73	Allen, *et al*., 2002	United States	110	6 months	Parallel with a Prophy at Start	-29.9%	-59.2%	-21.4%	-69.2%
74	Mankodi, *et al*., 2002	Scotland	109	6 months	Parallel with a Prophy at Start	-18.7%	-60.5%	-22.2%	-85.1%
75	Triritana, *et al*., 2002	Thailand	124	6 months	Parallel without Prophy at Start	-34.9%	-52.1%	-25.7%	-40.3%
76	Mateu, *et al*., 2008	Spain	94	6 months	Parallel with a Prophy at Start	-23.4%	-27.1%	-21.3%	-64.5%
77	Kraivaphan, *et al*., 2006	Thailand	120	9 months	Parallel with a Prophy at Start	not reported	not reported	-38.45%	not reported
78	Schiff, *et al*., 2006	United States	77****	6 months	Parallel with a Prophy at start	-15.0%	-18.5%	not reported	not reported
79	Mankodi, *et al*., 2011	United States	115	6 months	Parallel without a Prophy at Start	-18.8%	-50%	-19.6%	-60%

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.
** Plaque and gingivitis efficacy results pertain to data obtained at the final clinical examination. All percentages relating to plaque and gingivitis efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice and were statistically significant at the 0.01 level of significance. Q-H Index refers to the Quigley-Hein (Turesky, *et al*. Modification) Plaque Index; L-S Index refers to the Löe-Silness (Talbot, Mandel, and Chilton Modification) Gingival Index; P S Index refers to the Plaque Severity Index of Palomo and co-workers; G S Index refers to the Gingivitis Severity Index of Palomo and co-workers.
*** At the conclusion of the study the triclosan/copolymer dentifrice group had significantly less bleeding sites (and significantly more gingivitis-free sites) than the placebo.
**** Subjects in the triclosan/copolymer dentifrice group and the placebo group flossed their teeth after the one-minute tooth brushing.

(minimum of six months in duration) supragingival plaque and gingivitis efficacy studies had a common clinical design. All utilized adult male and female subjects who met the inclusion and exclusion criteria of the protocol, including specified levels of supragingival plaque and gingivitis at baseline. These subjects were then stratified into balanced groups

according to baseline plaque and gingivitis scores.

One group of subjects was assigned to the use of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base, and another group of subjects was assigned to the use of a placebo dentifrice (0.243% sodium fluoride in a silica base). All subjects were instructed to brush their teeth with their assigned dentifrice and a soft-textured toothbrush twice daily for one minute each time. Subjects were reevaluated for plaque and gingivitis at an intermediate time (usually three months) and at the conclusion of the study.

Plaque Scoring Methodology. The clinical scoring procedure used to assess supragingival plaque formation was a modification of the Quigley-Hein (Turesky Modification) Plaque Scoring Index.[81,82] The modified Quigley-Hein Plaque Scoring Index requires the use of a disclosing solution, and scores supragingival plaque formation on a numerical scale illustrated in the box below.

Plaque Scoring Methodology

0 = No plaque present.
1 = Separate flecks of plaque at the cervical margin.
2 = A thin, continuous band of plaque (up to 1 mm) at the cervical margin.
3 = A band of plaque wider than 1 mm but covering less than one-third of the surface.
4 = Plaques covering at least one-third but less than two-thirds of the surface.
5 = Plaque covering more than two-thirds of the surface.

Source: Quigley & Hein (1962),[81] Turesky, Gilmore, Glickman (1970).[82]

Each tooth was scored in six areas: 1) mesio-facial; 2) midfacial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) distolingual. The maximum score per tooth is 30. All teeth are included, except third molars and those teeth with prosthetic crowns or cervical restorations. A Plaque Index score for each subject is calculated by adding all the individual plaque scores (six per tooth), and dividing this sum by the total number of measurements (number of teeth scored multiplied by six).

A Plaque Severity Index was also calculated for all subjects, as described and reported by Palomo, *et al.* in 1989.[60] This index allows for a comparison of the tooth surface sites from each dentifrice group that received the most severe Quigley-Hein Plaque Index scores; that is, a Quigley-Hein Plaque Index score of 3, 4, or 5. The mean Plaque Severity Index was calculated for each subject by dividing the total number of tooth surface sites scored either 3, 4, or 5 by the total number of tooth surface sites scored in the mouth for plaque formation (number of teeth scored multiplied by six). A diagrammatic representation of the difference between the standard Quigley-Hein Plaque Index and the Plaque Severity Index is presented in Figure 14.

Gingivitis Scoring Methodology. The clinical scoring procedure used to assess gingivitis is the Löe-Silness Gingival Scoring Index[83] as modified by Talbott, *et al.*[84] The modified Löe-Silness Gingival Scoring Index scores gingivitis on a numerical scale according to the criteria numerated in the box below.

Gingivitis Scoring Methodology

0 = Absence of inflammation.
1 = Mild inflammaton: Slight change in color and texture. There is no bleeding on probing.
2 = Moderate inflammation.: Moderate glazing, redness, edema and hypertrophy. There is bleeding upon probing.
3 = Severe inflammation: Marked redness and hypertrophy, a tendancy to spontaneous bleeding and ulceration.

Source: Löe & Silness (1963)[83] Talbott, Mandel, & Chilton (1977).[84]

Each tooth is scored in six areas: 1) mesio-facial, 2) midfacial, 3) disto-facial, 4) mesio-lingual, 5) mid-lingual, 6) distolingual. The maximum score per tooth is 18. All teeth are included except third molars and those teeth with prosthetic crowns or cervical restorations. A modified Löe-Silness Gingival Index for each subject is calculated by adding all individual scores (six per tooth) and dividing this sum by the number of measurements (number of teeth scored multiplied by six).

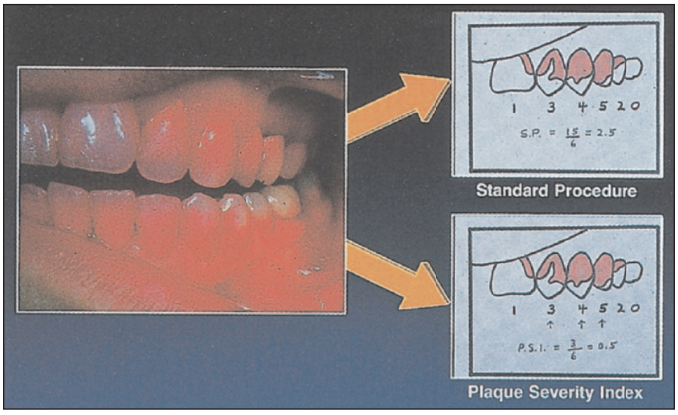


Figure 14. *Diagrammatic illustration of the difference in plaque assessment between the standard Quigley-Hein Plaque Index and the Plaque Severity Index. Photo illustrates one measurement per tooth, (This illustration was provided through the courtesy of Dr. Anthony R. Volpe.)*

A Gingivitis Severity Index was also calculated for all subjects, as described by Palomo, *et al.* in 1989.[60] This index allows for a comparison of the gingival sites from each dentifrice group that received the most severe Löe-Silness Gingival Index scores; that is, a Löe-Silness Gingival Index score of 2 or 3, by the total number of sites scored in the entire mouth for gingivitis (number of teeth scored multiplied by six). The Gingivitis Severity Index represents Löe-Silness scores which

are characterized by bleeding upon probing, as shown in Figure 15.

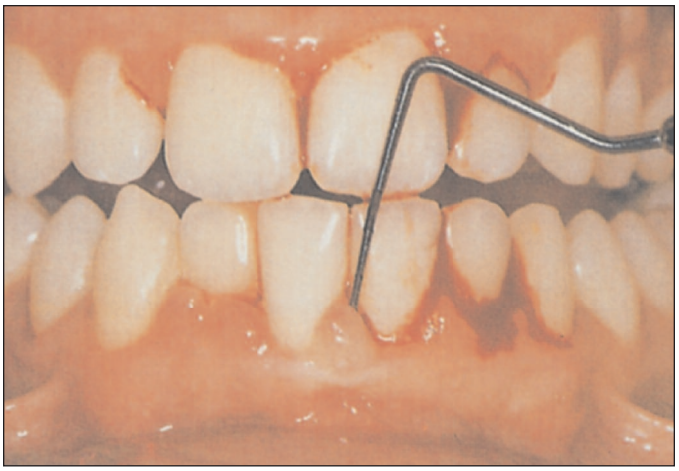


Figure 15. *Photograph illustrating the gingival bleeding associated with the Gingivitis Severity Index. (Reprinted from* Color Atlas of Dental Medicine*, KH Rateitschak, Ed., Thieme Medical Publishers, New York, p. 43, 1989, with permission.)*

The distinction between the calculation of the overall Gingival Index score and the overall Gingival Severity Index score is completely analogous to that for the plaque scores, as was illustrated in Figure 14.

Plaque Efficacy – Quigley-Hein Plaque Index Results. As indicated in Table IV, sixteen of the long-term clinical studies provided statistically significant differences ($p < 0.05$) in supragingival plaque accumulation in favor of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base as compared to a placebo dentifrice (0.243% sodium fluoride in a silica base). One study did not report these results. The Quigley-Hein Plaque Index efficacy results from the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice ranged from 12% to 59%, with an average efficacy score of 25%.

Plaque Efficacy – Plaque Severity Index Results. Table IV also presents Plaque Severity Index scores for the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice that were reported in fourteen of the seventeen studies. The Plaque Severity Index efficacy results ranged from 19% to 98%, with an average efficacy score of 44%.

Gingivitis Efficacy – Löe-Silness Gingival Index Results. As indicated in Table IV, sixteen long-term clinical studies provided statistically significant differences ($p < 0.05$) in gingivitis in favor of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base as compared to a placebo dentifrice (0.243% sodium fluoride in a silica base). One study did not report this result. The Löe-Silness Gingival Index efficacy results from the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice ranged from 19% to 32%, with an average efficacy score of 25%.

Gingivitis Efficacy – Gingivitis Severity Index Results. Table IV also presents gingivitis efficacy results for the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice with the Gingivitis Severity Index. This index was reported in thirteen of the studies. As indicated in Table IV, the Gingivitis Severity Index efficacy results from the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice ranged from 38% to 88%, with an average efficacy score of 60%.

Overall Conclusion from Seventeen Long-Term Plaque and Gingivitis Clinical Efficacy Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the seventeen independent, double-blind long-term plaque and gingivitis clinical efficacy studies shown in Table IV, which were conducted in accordance with the 1986, 1994, and 2008 American Dental Association Guidelines, is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.05$) and clinically beneficial effect on both supragingival plaque and gingivitis as compared to the similar use of a placebo dentifrice.

Additional Long-Term Studies

Table V presents the plaque and gingivitis efficacy results from three additional independent long-term (six months or greater) clinical studies which compared a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice to a placebo dentifrice.[85-87] What principally differentiates the three studies in Table V from those in Table IV is the choice of index employed, as indicated by the footnotes.

Periodontitis Clinical Studies

In addition to the antigingivitis effects of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice, a number of studies have been conducted to demonstrate the effects of this dentifrice on periodontitis.

One short-term study conducted by Furuichi, *et al,*[88] lasted two weeks and was designed to evaluate the effects of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice on healing following scaling and root planing. Subjects that used the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice, followed by the application of a 0.3% triclosan/2.0% PVM/MA copolymer/fluoride gel via stint, had reductions of bleeding on probing and gingival index scores that were greater than those for the control gel/dentifrice. The results of this study indicate that triclosan, when applied both supragingivally and subgingivally, reduced gingival inflammation following routine scaling and root planing.

Six long-term studies periodontitis studies, ranging from 24 to 36 months, have also been conducted as shown in Table VI.[89-94] Five of these studies[89,91-94] evaluated the effects of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice on the progression of periodontal disease following scaling and root planing. Two of these studies were also conducted in specialized populations, specifically adolescents[91] and smokers.[92] The results from all five studies indicated that the use of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice, following scaling and root planing, resulted in a decrease in bleeding on probing, attachment level gain, and an overall reduction in periodontal disease.

Table V
Plaque and Gingivitis Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer in a 0.243% Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Plaque Efficacy Versus Placebo** S-L Index	Gingivitis Efficacy Versus Placebo** Bleeding Index
85	Svatun, *et al*., 1993	Norway	94	7 months	Parallel with a Prophy at Start	-19.0%	-25.5%
86	Kanchanakamol, *et al*., 1995	Thailand	124	6 months	Parallel with a Prophy at Start	-7.2%***	-25.0%***
87	Renvert and Birkhed, 1995	Sweden	60	6 months	Parallel without Prophy at Start	-25.0%	-18.2%

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.
** Plaque and gingivitis efficacy results pertain to data obtained at the final clinical examination. All percentages relating to plaque and gingivitis efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice. S-L Index refers to the Silness-Löe Plaque Index; Bleeding Index refers to the Ainamo and Bay Bleeding Index.
*** Plaque and gingivitis efficacy results pertain to data obtained at the 3-month clinical examination. Reductions at six months were not statistically significant. Percentages relating to plaque and gingivitis efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice. Plaque efficacy was determined by the Quigley-Hein Plaque Index (Turesky, *et al*. Modification); gingivitis efficacy was determined by the Löe-Silness Gingival Index (Talbot, Mandel, and Chilton Modification).

The sixth study, Rosling, *et al.*[90] evaluated the effects of a 0.3% triclosan and 2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice on the subgingival microbiota in a periodontitis-susceptible population. Forty subjects who had previously received non-surgical periodontal therapy and had exhibited, during subsequent maintenance appointments, areas of recurrent periodontal disease, were recruited. The subjects were given either a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice or a placebo dentifrice without triclosan/copolymer. The subjects used the assigned dentifrice to perform meticulous supragingival plaque removal. At 36 months, subgingival plaque samples revealed that the subjects who used the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice had both a quantitative and qualitative reduction in subgingival microbiota, and recurrent periodontitis was almost completely eliminated.

Overall Conclusion from Six Periodontitis Efficacy Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the six independent, double-blind periodontitis clinical efficacy studies shown in Table VI is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.05$) and clinically beneficial effect on reducing attachment loss, reducing bleeding on probing, and reducing the recurrence of periodontal disease, as compared to the similar use of a placebo dentifrice.

Calculus Efficacy

Table VII presents the calculus efficacy results from five independent and double-blind long-term (three months or greater)[95-99] and two 2-month clinical studies,[100,101] which compared a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base to a placebo dentifrice. These calculus clinical efficacy studies were conducted in accordance with the Volpe-Manhold clinical design and calculus scoring methodology.[102-106] The Volpe-Manhold calculus scoring methodology measures supragingival calculus formation in three planes (mesio-facial, mid-facial, and disto-facial) with a periodontal probe graduated in millimeters, on the lingual surfaces of the six mandibular anterior teeth. The Volpe-Manhold calculus scoring methodology is described in the following box and illustrated in Figure 16.

As indicated in Table VII, all seven clinical studies provided statistically significant differences ($p < 0.05$) in supragingival calculus formation in favor of the triclosan/PVM/MA copolymer/fluoride dentifrice in a silica base, as compared to a placebo dentifrice containing 0.243% sodium fluoride in a silica base. The Volpe-Manhold Calculus Index efficacy results from the use of the 0.3% triclosan/2.0% PVM/MS copolymer/0.243% sodium fluoride dentifrice ranged from 23% to 55%, with an average efficacy score of 35%.

Overall Conclusion from Seven Calculus Clinical Efficacy Studies with Triclosan/PVM/MA/Copolymer Fluoride Dentifrice

The overall conclusion from the seven independent, double-blind calculus clinical efficacy studies shown in Table VII, which employed the Volpe-Manhold study design and calculus scoring methodology, is that the use of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.05$) and clinically beneficial effect on supragingival calculus as compared to the similar use of a placebo dentifrice.

Tooth Whitening and Stain Removal Efficacy

Tooth whitening and stain removal have become of critical importance to patients. The three components of an

Table VI
Periodontitis Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% Copolymer in a 0.243% Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design
89	Rosling, *et al*., 1997	Sweden	60	36 months	Evaluate the effects of a triclosan/copolymer dentifrice in the progression of periodontal disease
90	Rosling, *et al*., 1997	Sweden	40	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the effect of subgingival microbiota in periodontitis-susceptible patients
91	Ellwood, *et al*., 1998	UK	480	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents
92	Furuichi, *et al*., 1999	Sweden	60	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on healing after non-surgical periodontal therapy of recurrent periodontitis
93	Cullinan, *et al*., 2003	Australia	504	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the progression of periodontal disease in adults
94	Kerdvongbundit and Wikesjo, 2003	Thailand	60	24 months	Evaluate the effects of a triclosan/copolymer dentifrice on healing after non-surgical periodontal therapy in smokers

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.

Table VII
Calculus Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% Copolymer in a 0.243% Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Calculus Efficacy Versus Placebo** Volpe-Manhold Total Scores
95	Schiff, *et al*., 1990	United States	147	3 months	Parallel with a Prophy at Start	-23.1%
96	Lobene, *et al*., 1991	United States	79 70	3 months 6 months	Parallel with a Prophy at Start	-26.3% -36.2%
97	Volpe, *et al*., 1992	United States	92	3 months	Parallel with a Prophy at Start	-35.5%
98	Bánóczy, *et al*., 1995	Hungary	73	3 months	Parallel with a Prophy at Start	-54.7%
99	Schiff, *et al*., 2008	United States	77	3 months	Parallel with a Prophy at Start	- 34.8%
100	Allen, *et al*., 2002	United States	100	2 months	Parallel with a Prophy at Start	-24.8%
101	Sowinski, *et al*., 2002	United States	63	2 months	Parallel with a Prophy at Start	-34.13%

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.
** Calculus efficacy results pertain to data obtained at the final clinical examination. All percentages relating to calculus efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice and were statistically significant at the $p \leq 0.05$ level of significance.

effective dentifrice-based cleaning system are: 1) a surface-active agent that helps loosen and remove material that has adhered to the tooth surface; 2) a thickening agent that holds the abrasive component together while in the tube and in the mouth; and 3) the abrasive component. Nine clinical studies (Table VIII) have been reported in seven publications using a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice supplemented with the addition of high cleaning silica.[74,107-112] Seven of these studies[107,108,110-112] were conducted over a six-week period, while the remaining two studies[74,109] were up to six months in duration. A total of 975 subjects participated in these studies. All studies were of a parallel design, and no

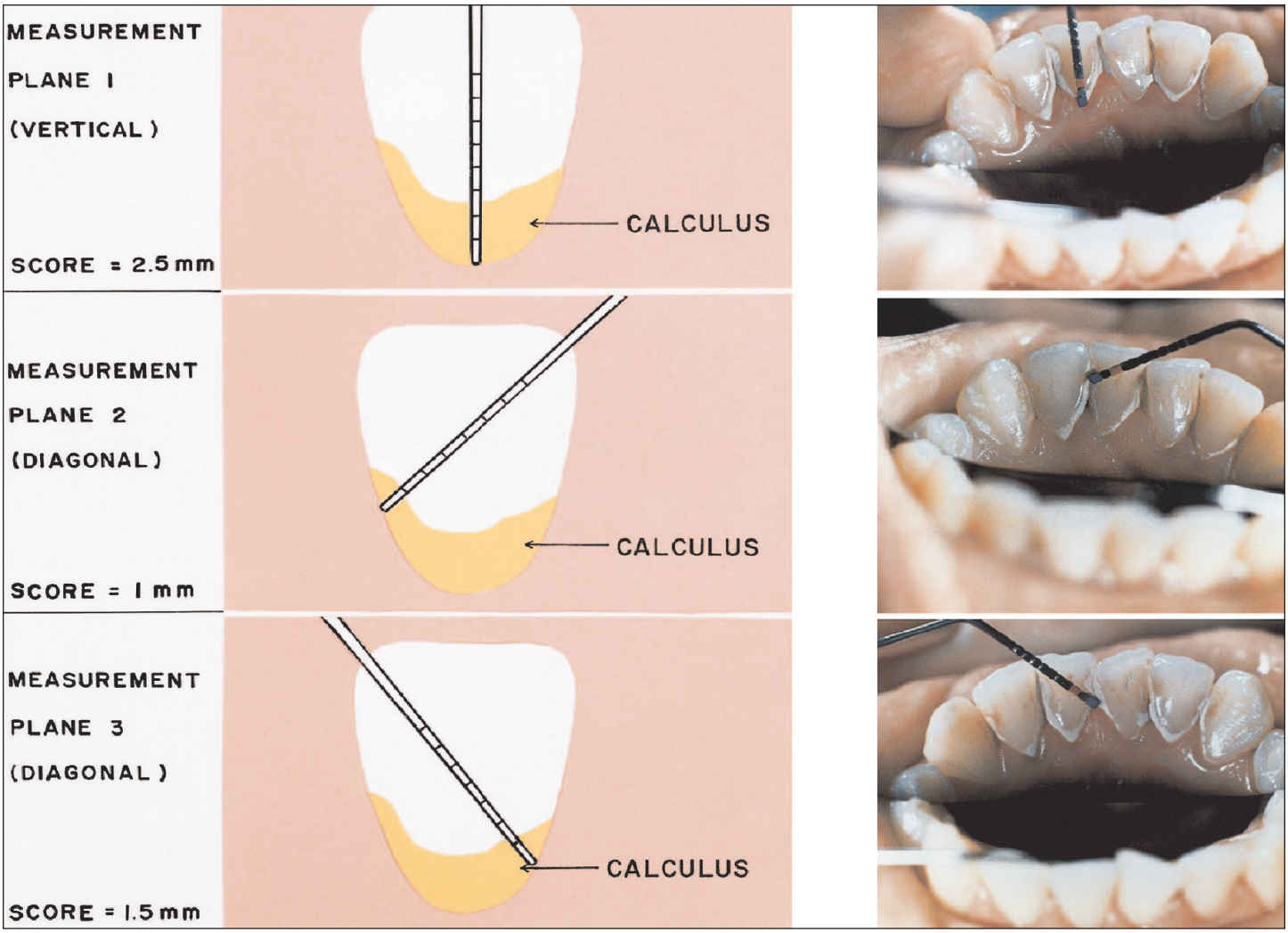


Figure 16. *Schematic and corresponding photographic illustration of the Volpe-Manhold calculus assessment procedure. Measurement plane 1 (vertical) is for gingival measurements. Measurement plane 2 (diagonal) is for distal measurements. Measurement plane 3 (diagonal) is for mesial measurements. The procedure can be used for scoring both anterior and posterior teeth. (Reprinted from* J Clin Dent *(Suppl. B), p. B7, 1991. Photographs copyrighted by the American Academy of Periodontology.)*

Volpe-Manhold Calculus Clinical Study Design

The design for the studies in Table VII were characterized as follows:

- Subjects with a history of supragingival calculus formation were identified.
- The subjects then received an oral prophylaxis, and participated in a three-month pre-test study wherein they used a placebo dentifrice in order to determine their rate of calculus formation under controlled conditions.
- After three-months' use of the placebo dentifrice, subjects were evaluated for supragingival calculus formation using the Volpe-Manhold calculus scoring methodology. These calculus scores were then utilized as baseline scores for stratification purposes.
- One group of subjects was assigned to the use of a 0.3% triclosan and 2.0% PVM/MA copolymor dentifrice in a 0.243% sodium fluoride/silica base, and a second group of subjects was assigned to the use of a placebo dentifrice (0.243% sodium fluoride in a silica base).
- All subjects were instructed to brush their teeth with their assigned dentifrice and a soft-textured toothbrush twice daily for one minute each time.
- After three- and six-months' use of the assigned dentifrices, the subjects were again evaluated for supragingival calculus formation using the Volpe-Manhold calculus scoring methodology.

Volpe, et al. (1965),[102] *Manhold,* et al. (1965),[103] *Volpe,* et al. (1967),[104] *Volpe,* et al. (1969)[105]

prophy was performed at the start for most of the studies.

The assessment of tooth whitening/stain removal was performed for all studies using the Lobene Stain Index.[113] This index is based on scoring two parameters of tooth whitening/stain removal: stain intensity and stain area. The box below provides a summary of scoring methodology.

The scores are recorded on an exam form (Figure 17) for the facial aspect of teeth #s 6–11, and the facial and lingual

Index	Stain Intensity	Index	Stain Area
0	No stain	0	No stain detected
1	Light stain-yellow/tan	1	Stain up to on-third of the region
2	Moderate stain-medium brown	2	Stain up to two-thirds of the region
3	Heavy stain-dark brown/black	3	Stain over more than two-thirds of the region

aspects of teeth #s 22–27. An average tooth stain area score and intensity score are calculated from these data. In two studies a stain composite score was calculated which combines the stain intensity and stain areas scores.

All of the studies reported that at the end of the study period, subjects who used the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a high cleaning silica base exhibited statistically significantly lower levels of extrinsic stain area and stain intensity as compared to the placebo or the negative control. The stain intensity level reductions for those studies ranged from 40.2% to 55.6% and the stain area reductions ranged from 43.9% to 52.0%. For those studies in which the stain composite score was determined, the reductions ranged from 39.8% to 61.8%. The results of these studies confirm that the addition of high cleaning silica to Colgate Total Toothpaste is effective in removing extrinsic tooth stain.

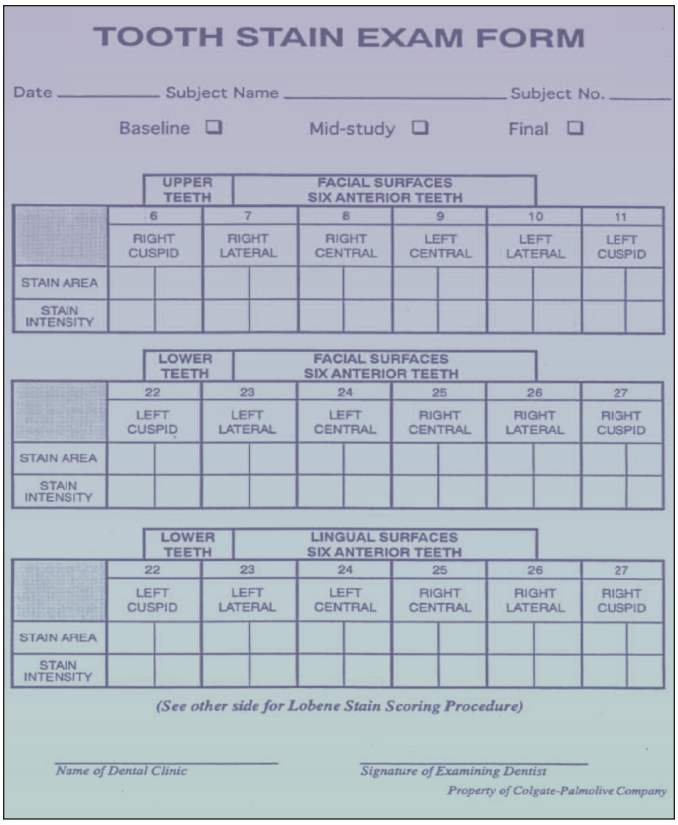
Overall Conclusion Concerning from Nine Whitening and Stain Removal Clinical Efficacy Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the nine independent and double-blind whitening and stain removal efficacy studies shown in Table VIII, which employed the Lobene Stain Area, Stain Intensity, as well as the Stain Composite Indices, is that the use of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.05$) and clinically beneficial effect on whitening and stain removal as compared to the similar use of a placebo dentifrice.

Caries Efficacy

Caries clinical studies were conducted in order to determine whether the addition of 0.3% triclosan and 2.0% PVM/MA copolymer would impact the anticaries efficacy of fluoride-containing dentifrices. Results of an *in situ* study reported by Mellberg, *et al.* indicated that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base was highly effective in preventing demineralization and enhancing remineralization, as compared to a non-fluoride placebo dentifrice and to a positive control sodium fluoride/silica dentifrice.[114]

Results of a clinical study reported by Kertesz, *et al.* concerning the accumulation of fluoride in dental plaque, suggested that the addition of 0.3% triclosan and 2.0% PVM/MA copolymer to dentifrices containing either 0.243% or 0.331% NaF (1100 ppm and 1500 ppm F, respectively) resulted in increased levels of ionizable plaque fluoride, which did not differ significantly from each other after eight weeks' use.[115]


TOOTH STAIN EXAM FORM

Date _____ Subject Name _____ Subject No. _____

Baseline ☐ Mid-study ☐ Final ☐

	UPPER TEETH — FACIAL SURFACES SIX ANTERIOR TEETH					
	6	7	8	9	10	11
	RIGHT CUSPID	RIGHT LATERAL	RIGHT CENTRAL	LEFT CENTRAL	LEFT LATERAL	LEFT CUSPID
STAIN AREA						
STAIN INTENSITY						

	LOWER TEETH — FACIAL SURFACES SIX ANTERIOR TEETH					
	22	23	24	25	26	27
	LEFT CUSPID	LEFT LATERAL	LEFT CENTRAL	RIGHT CENTRAL	RIGHT LATERAL	RIGHT CUSPID
STAIN AREA						
STAIN INTENSITY						

	LOWER TEETH — LINGUAL SURFACES SIX ANTERIOR TEETH					
	22	23	24	25	26	27
	LEFT CUSPID	LEFT LATERAL	LEFT CENTRAL	RIGHT CENTRAL	RIGHT LATERAL	RIGHT CUSPID
STAIN AREA						
STAIN INTENSITY						

(See other side for Lobene Stain Scoring Procedure)

Name of Dental Clinic *Signature of Examining Dentist*

Property of Colgate-Palmolive Company

Figure 17. *Scoring sheet used for the recording of the Lobene Stain Index.*

The caries efficacy results from three independent, double-blind, long-term (30 months or longer) clinical studies[116-118] and one double-blind study of 24 months duration,[119] which compared a 0.3% triclosan/2.0% PVM/MA copolymer/sodium fluoride dentifrice in a silica base to a comparable, clinically proven, positive control dentifrice containing sodium fluoride in a silica base, are shown in Table IX. All of these studies were conducted in accordance with the American Dental Association 1988 Guidelines for the comparison of the clinical anticaries efficacy of fluoride dentifrices.[120] The recommended design characteristics for such studies are presented in Figure 18, and the criteria which must be satisfied in order for the results of a clinical caries study to support a conclusion in favor of the clinical anticaries efficacy of a fluoride dentifrice[121] are presented in Figure 19.

The study reported by Hawley, *et al.* was conducted in England over 24 months and involved 3,462 school children who completed the entire duration of the study.[116] This clinical study compared the anticaries efficacy of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base to a clinically proven, positive control dentifrice containing 0.243% sodium fluoride in a silica base. A comparison of the 30-month DFS (decayed and filled surfaces) and DFT (decayed and filled teeth) caries increments indicated that the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base provided increments of 4.57 for DFS and 2.76 for DFT, while the corresponding caries increments for the posi-

Table VIII
Whitening Efficacy
Triclosan/Copolymer Dentifrice Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer in a 0.243% Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Whitening Efficacy Versus Placebo** Stain Intensity	Stain Area	Composite
74	Mankodi, *et al*., 2002	Scotland	109	6 months	Parallel Without a Prophy at Start	-45.3%	-46.3%***	
107	Sielski, *et al*., 2002	United States	97	6 weeks	Parallel Without a Prophy at Start	-49.3%	-43.9%	
108	Ayad, *et al*., 2002	Canada	93	6 weeks	Parallel Without a Prophy at Start	-49.0%	-50.4%	
109	Singh, *et al*., 2002	United States	86	6 months	Parallel Without a Prophy at Start	-45.6%	-44.3%	
110	Nathoo, *et al*., 2002	United States	123	6 weeks	Parallel Without a Prophy at Start	-49.3%	-50.0%	
111	Nathoo, *et al*., 2008	United States	114	6 weeks	Parallel With a Prophy at Start	-55.6%	-52.0%	
111	Nathoo, *et al*., 2008	United States	119	6 weeks	Parallel Without a Prophy at Start	-40.2%	-48.0%	
112	Nathoo, *et al*., 2011	United States	78	3 weeks 6 weeks	Parallel Without a Prophy at Start	-- --	-- --	39.8%*** 58.8%***
112	Nathoo, *et al*., 2011	United States	77	3 weeks 6 weeks	Parallel Without a Prophy at Start	-- --	-- --	40.7%*** 61.8%***

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.
** Whitening efficacy results pertain to data obtained at the final clinical examination. All percentages relating to whitening efficacy of the triclosan/copolymer dentifrice were calculated relative to the placebo dentifrice. Stain Intensity refers to the Lobene Stain Intensity Index; Stain Area Index refers to the Lobene Stain Area Index, Composite refers to the Lobene Composite Stain Index.
*** Whitening efficacy results pertain to data obtained at the final clinical examination. All percentages relating to whitening efficacy of the triclosan/copolymer dentifrice were calculated relative to the positive control dentifrice.
**** Two separate formulas of Colgate Total were evaluated against a placebo. There were no statistical differences between the two Colgate Total formulas.

tive control dentifrice containing 0.243% sodium fluoride in a silica base were 4.62 for DFS and 2.81 for DFT.

The clinical caries study reported by Feller, *et al.* was conducted in the United States and involved 1,542 male and female adult subjects who completed the 36 months of the study.[117] This clinical study compared the anticaries efficacy of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base to a clinically proven, positive control dentifrice containing 0.243% sodium fluoride in a silica base. A comparison of the 36 month DFS and DFT caries increments indicated that the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base provided increments of 2.07 for DFS and 0.63 for DFT, while the corresponding caries increments for the positive control dentifrice containing 0.243% sodium fluoride in a silica base were 2.16 for DFS and 0.68 for DFT.

American Dental Association Guidelines for Caries Clinical Trials of Fluoride Dentifrices: Study Design Criteria

The American Dental Association Guidelines require the following clinical study design criteria:

- Two independent studies should be conducted.
- The study populations should represent typical product users.
- Each study should be at least two years in duration.
- Each study should have a baseline examination, an intermediate examination, and a final examination.

Source: American Dental Association 1988 Guidelines[120]

Figure 18. *Study design criteria for the American Dental Association guidelines for caries clinical trials of fluoride dentifrices.*

The clinical caries study reported by Mann, *et al.* was conducted in Israel and involved 1,296 male and female adult subjects who completed the 36 months of the study.[118] This clinical study compared the anticaries efficacy of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.331% sodium fluoride in a silica base to a clinically proven, positive control dentifrice containing 0.331% sodium fluoride in a silica base. A comparison of the 36-month DFS and DFT caries increments indicated that the use of the 0.3% triclosan/2.0% PVM/MA copolymer/0.331% sodium fluoride dentifrice in a silica base provided increments of 5.21 for DFS and 1.30 for DFT, while the corresponding caries increments for the positive control dentifrice containing 0.331% sodium fluoride in a silica base were 5.23 for DFS and 1.39 for DFT.

Table IX
Caries Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% Copolymer in a Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Caries Efficacy: Positive Control Dentifrice** DFS	Positive Control Dentifrice** DFT	Triclosan/Copolymer Dentifrice DFS	Triclosan/Copolymer Dentifrice DFT
116	Hawley, *et al*., 1995	England	3,462	30 months	Parallel	4.62	2.81	4.57	2.76
117	Feller, *et al*., 1996	United States	1,542	36 months	Parallel	2.16	0.68	2.07	0.63
118	Mann, *et al*., 1996	Israel	1,296	36 months	Parallel	5.23	1.39	5.21	1.30
119	Mann, *et al*., 2001	Israel	3,392	24 months	Parallel	-16.6% caries treatment vs. positive control			
122	Vered, *et al*., 2009	Israel	1,357	36 months	Parallel	0.038***	0.23****	0.07***	0.06****

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the 24-, 30-, or 36-month exam.
** Statistical analysis of the 30- and 36-month DFS and DFT caries increments indicated that the triclosan/copolymer fluoride dentifrice provided a level of anti-caries efficacy which was "at least as good as" that provided by the positive control, clinically proven sodium fluoride/silica dentifrice.
*** Adjusted mean root caries increment ($p < 0.05$).
**** Mean dental crown failure increment ($p < 0.05$).

Mann, *et al.* also conducted a 24-month study in Israel where the anticaries efficacy of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base was compared to a Crest Cavity Fighting Toothpaste with Fluorostat (Procter & Gamble Company, Cincinnati, OH, USA), which contains 0.243% sodium fluoride in a silica base.[119] A total of 3,392 subjects completed the study. At both the one-year and two-year intervals, the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base demonstrated a 12.2% and 16.6% reduction in caries increment scores, respectively, versus the positive control dentifrice. It is noted that both the DFS and DFT increments were numerically lower for the triclosan/copolymer/sodium fluoride dentifrices as compared to the positive control dentifrices in the first three studies. For each study, a 90% confidence interval for the ratio of mean caries increments (0.3% triclosan/2.0% PVM/MA copolymer/sodium fluoride dentifrice over the positive control) was statistically constructed in accordance with the American Dental Association 1988 Guidelines.[120] For each study, the resultant confidence intervals for both DFS and DFT consisted entirely of values that did not exceed 110%. Thus, all four clinical caries studies support the conclusion that the anticaries efficacy provided by a 0.3% triclosan/2.0% PVM/MA copolymer/sodium fluoride dentifrice in a silica base is "at least as good as" that provided by the positive control sodium fluoride/silica dentifrice.[121]

Also in Table IX, Vered, *et al.* report the results from a 36-month study in Israel, which compared the root caries efficacy and the survival of dental crowns after brushing with a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base to brushing with a dentifrice without triclosan and the copolymer (0.243% sodium fluoride in a silica base).[122] A total of 1,357 subjects completed the study. Within-treatment and between-treatment Katz Root Caries Index[123] baseline and three-year scores were compared to determine root caries efficacy. The adjusted mean root caries increment was 0.07 for the group using the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base and 0.38 for the group using the dentifrice containing sodium fluoride in a silica base, indicating an almost six-fold significantly higher incidence of root caries for the group using the dentifrice containing sodium fluoride in a silica base ($p < 0.05$). Dental crowns were dichotomized for success and failure at the end of the study. The mean dental

American Dental Association Guidelines for Caries Clinical Trials of Fluoride Dentifrices: Criteria for Support of a Conclusion of Clinical Anticaries Efficacy

The American Dental Association Guidelines specify the following requirements:

- The test dentifrice must be evaluated against a clinically proven positive control fluoride dentifrice.
- The results must support the conclusion that the test dentifrice is equivalent to, "at least as good as," or superior to the active control dentifrice, as described below.
  - Criterion for equivalence: A 90% confidence interval is constructed for the ratio of mean caries increments (test over control); this entire interval must consist of values which lie between 90% and 110%.
  - Criterion for "at least as good as:" A 90% confidence interval is constructed for the ratio of mean caries increments (test over control); this entire interval must consist of values which are no greater than 110%.
  - Criteria for superiority: (1) The observed improvement for the test dentifrice over the active control dentifrice must be at least 10%. (2) The mean caries increment associated with the test dentifrice must be significantly lower than that associated with the active control dentifrice (one-sided test, 0.05 level of significance).

Source: American Dental Association 1988 Guidelines,[120] Proskin, Kingman, Naleway and Wozniak (1995)[121]

Figure 19. *American Dental Association guidelines for caries clinical trials of fluoride dentifrices to support a conclusion of clinical anticaries efficacy.*

crown failure increment was 0.06 for the group using the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base and 0.23 for the group using the dentifrice containing sodium fluoride in a silica base, indicating an almost four-fold significantly higher incidence of dental crown failure for the group using the dentifrice containing sodium fluoride in a silica base ($p < 0.05$).

Overall Conclusion from Five Long-Term Caries Clinical Efficacy Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the five independent, double-blind, long-term caries clinical studies shown in Table IX, all of which were conducted and analyzed in accordance with the American Dental Association 1988 Guidelines for the comparison of fluoride dentifrices, is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% or a 0.331% sodium fluoride/silica base provides a level of anticaries efficacy which has been shown to be statistically "at least as good as" that provided by the corresponding sodium fluoride/silica dentifrice without the triclosan and copolymer.

Oral Malodor Efficacy

Oral malodor studies were conducted in order to assess the effectiveness of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice for controlling breath odor 12 hours after brushing. Six studies were conducted and a summary of these studies is presented in Table X.[124-129] Five studies[124,126-129] were conducted using a nine-point hedonic scale as the principal assessment method. Four of these studies[124,127-129] compared the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice to a placebo dentifrice, while the fifth[126] compared the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a silica base to the 0.3% triclosan and 2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice in a high-cleaning silica base. A description of the nine-point hedonic scale is provided in the box below.

1 = Most Pleasant	6 = Slightly Unpleasant
2 = Very Pleasant	7 = Moderately Unpleasant
3 = Moderately Pleasant	8 = Very Un pleasant
4 = Slightly Pleasant	9 = Most Unpleasant
5 = Neither Pleasant nor Unpleasant	

According to the American Dental Association-approved study protocol, the following clinical endpoints are required to determine the effectiveness of the study:

1. A statistically significant reduction in mean breath odor scores from baseline to twelve hours for subjects is required for the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group;
2. The mean twelve-hour breath odor score for subjects in the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group must be within the range of values corresponding to pleasant breath odor (*i.e.*, lower than 5); and
3. A statistically significant difference in mean breath odor scores between subjects in the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group and subjects in the placebo group must be present after 12 hours.

The five studies demonstrated a range of 12-hour breath odor scores for the test products from 3.42 to 4.91, which are within the range of values corresponding to pleasant breath odor (lower than 5). In contrast, the placebo dentifrices provided a range of 12-hour breath odor scores from 6.05 to 7.03.

In the study reported by Hu, *et al.*, plaque samples were collected at baseline and at the 12-hour evaluations to determine the ability of the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base to reduce bacteria-causing oral malodor. Plaque samples were collected from the teeth on the left side of each subject's mouth at baseline and on the right side of the mouth after 12 hours. Microbial colony forming units per milliliter (CFU/mL) scores were obtained. These scores were transformed using a logarithmic conversion (base 10) to normalize the data. Mean values were transformed using an antilog conversion (base 10) in order to provide findings in terms of geometric means. Results showed that when the group using the dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base was compared to the group using the placebo dentifrice, the triclosan/copolymer/fluoride dentifrice group exhibited a statistically significant 49.5% ($p < 0.05$) reduction in 12-hour microbial CFU scores.[129]

The study by Niles, *et al.* utilized chromatography to measure the levels of volatile sulfur compounds (VSCs) in mouth air. A total of 19 subjects participated in this double-blind, two-treatment, two-period cross-over study. Subjects brushed with either a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice or a placebo dentifrice, and then had VSCs measured using a 565 Tracor gas chromatograph equipped with a flame photometric detector. At seven hours following brushing, subjects using the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice had 5.62 ng/mL VSCs versus 7.10 ng/mL VSCs when subjects used the placebo dentifrice. Overnight scores for subjects using the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice were 9.63 ng/mL VSCs versus 12.64 ng/mL VSCs for subjects using the placebo dentifrice.[125] This study demonstrated that the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice was effective in reducing the levels of VSCs produced in mouth air, and provided objective support to the breath odor scores reported in the other studies.

An additional monadic study has been conducted by Sreenivasan, *et al.*[130] who examined the effect of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice and a toothbrush with a tongue cleaner on oral malodor (organoleptic and mouth air sulfur levels) and oral bacteria.

Table X
Malodor Efficacy
Triclosan/Copolymer Dentifrice Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer in a Sodium Fluoride/Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Assessment Method	Summary of Results**
124	Sharma, *et al.*, 1999	Canada	63	12 hours	Nine-point hedonic scale	The mean 12-hour breath odor score for the Colgate Total Toothpaste group was 4.77, which was within the range of values corresponding to pleasant breath odor; the mean 12-hour breath odor score for the placebo group was 6.05, which is above the value corresponding to unpleasant breath odor.
125	Niles, *et al.*, 1999	United States	19	Overnight	Chromatography	The mean overnight breath score was 9.63 ng/ml for Colgate Total Toothpaste and the 12.64 ng/ml for placebo dentifrice.
126	Sharma, *et al.*, 2002	Canada	83	12 hours	Nine-point hedonic scale	The mean 12-hour breath scores for Colgate Total Plus Whitening Toothpaste and Colgate Total Toothpaste groups were 4.89 and 4.67, respectively, which are within the range of values corresponding to pleasant breath odor.
127	Hu, *et al.*, 2005	China	81	12 hours day and night	Nine-point hedonic scale	The mean 12-hour breath odor score for the Colgate Total Advanced Fresh Toothpaste group was 3.42, which was within the range of values corresponding to pleasant breath odor; the mean 12-hour breath odor score for the placebo group was 7.03, which is above the value corresponding to unpleasant breath odor.
128	Sharma, *et al.*, 2007	Canada	76	12 hours	Nine-point hedonic scale	The mean 12 hour breath score for the Colgate Total Toothpaste group was 4.65, which was within the range of values corresponding to pleasant breath odor; the mean 12 hour breath odor score for the placebo group was 6.11, which is above the value corresponding to unpleasant breath odor.
129	Hu, *et al.*, 2008***	China	76	12 hours	Nine-point hedonic scale	The mean 12 hour breath score for the Colgate Total Toothpaste group was 4.91, which was within the range of values corresponding to pleasant breath odor; the mean 12 hour breath odor score for the placebo group was 6.86, which is above the value corresponding to unpleasant breath odor. Colgate Total Toothpaste exhibited a 49.1% reduction in 12 hour microbial CFU scores.

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.
** Malodor efficacy results pertain to data obtained at the final clinical examination. Mean breath scores were calculated using the scores provided by a panel of four expert judges, with 1 = most pleasant, 9 = most unpleasant
*** Plaque samples from all subjects were processed in the laboratory and microbial colony forming units per milliliter (CFU/ml) scores were obtained.

Subjects were examined at baseline and after 28 days of twice-daily brushing. At each time point, examinations occurred 12 hours after the last brushing. After 28 days, all subjects had statistically significantly reduced organoleptic scores and mouth air sulfur levels compared to baseline. Furthermore, there was a statistically significant reduction in *Enterococcus Faecalis,* Neisseria sp., *Peptostreptococcus micros, Prevotella melaninogenica, Porphyromonas gingivalis, Solobacterium moorei,* and Streptococci sp.

It is also important to note that laboratory studies by Sreenivasan, *et al.* provide additional data in support of the malodor controlling effects of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice.[131,132] In the first study, a double-blind cross-over design, subjects used either a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice or a placebo fluoride dentifrice that did not contain triclosan/copolymer. Following seven days of product use, subject saliva was collected and bacterial counts (total and VSC-producing) were determined. Results from this study demonstrated that the use of a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice decreased both the overall and VSC-producing bacteria versus the placebo dentifrice. In the second study, a 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice demonstrated significant antimicrobial effects against 13 strains of oral bacteria, some of which have been implicated in bad breath, versus two non-antimicrobial fluoride dentifrices. When taken together with the previous clinical data, it is clear that the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice is effective at controlling oral malodor.

Overall Conclusion from Six Malodor Efficacy Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the six independent and double-blind malodor clinical efficacy studies shown in Table X is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.05$) and clinically beneficial effect on oral malodor, as compared to the similar use of a placebo dentifrice. Supporting studies confirm that the use of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base reduces the overall number of bacteria and the number of VSC-producing bacteria.

Dentin Hypersensitivity Efficacy

It has been estimated that dentin hypersensitivity affects up to 57% of the adult population.[133] Dentin hypersensitivity occurs when dentin tubule openings become exposed and fluid movement occurs as a result of tactile, chemical, evaporative, or osmotic stimuli. One method to relieve dentin hypersensitivity uses occlusion technology to plug or seal the tubules to prevent fluid movement within the dentin tubules. Published laboratory studies reported moderate reductions in dentin permeability from the treatment of dentin with solutions or dentifrices containing PVA/MA copolymers.[134-137] Recently, a new formulation of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice was developed which added clinically proven dentin hypersensitivity relief to its multi-benefit package. This variant combines the triclosan and PVM/MA copolymer with a specially designed silica to occlude dentin tubules. This combination of ingredients does not appear in all Colgate Total Toothpaste variants and is not available in all countries. The silica provides high purity particles of optimal surface area to maximize attraction to dentin surfaces along with specific diameters that enable occlusion and penetration of dentin tubules. Currently, the results from four studies have been reported with the new formulation (Table XI).

Zaidel, *et al.* evaluated the laboratory dentin occlusion efficacy and effects on dentin permeability of the triclosan/copolymer/fluoride/specially designed silica dentifrice when compared to a dentifrice containing stannous fluoride/sodium hexametaphosphate/zinc lactate, a placebo dentifrice, and a negative control dentifrice.[138] Results indicated that dentin specimens treated with the triclosan/copolymer/fluoride/specially designed silica dentifrice, when visualized with CLSM, were occluded significantly more than the placebo dentifrice and the negative control dentifrice; that the level of occlusion remaining after a challenge with cola was highest for dentin treated with the triclosan/copolymer/fluoride/specially designed silica dentifrice in CLSM xz views; and that the triclosan/copolymer/fluoride/specially designed silica dentifrice produced dentin surface deposits and tubule plugs containing silicon in addition to calcium and phosphorus. CLSM visualization revealed a significantly higher amount of occluded tubules for dentin treated with the triclosan/copolymer/fluoride/specially designed silica dentifrice compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice, the placebo dentifrice, and the negative control dentifrice. Etched dentin treated with the triclosan/copolymer/fluoride/specially designed silica dentifrice was significantly less permeable compared to etched dentin treated with the negative control dentifrice; the occlusion provided by the triclosan/copolymer/fluoride/specially designed silica dentifrice provided significantly greater reduction in permeability after extended pulpal pressure and acid challenge compared to dentin treated with the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice. All comparisons were statistically significant at the 0.05% level.

An eight-week clinical study reported by Chaknis, *et al.* compared dentin hypersensitivity efficacy of the new triclosan/copolymer/fluoride/specially designed silica dentifrice to a 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice and a negative control dentifrice using tactile stimulation (Yeaple Probe) and the Schiff Cold Air Sensitivity Scale. Subjects brushed their teeth twice daily for one minute for eight weeks.[139] Dentin hypersensitivity assessments were done at baseline and after four and eight weeks of brushing. Results showed that the triclosan/copolymer/fluoride/specially designed silica dentifrice provided statistically significant greater relief of dentin hypersensitivity compared to a dentifrice containing 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate and the negative control dentifrice in both tactile and air blast sensitivity ($p < 0.05$).

Overall Conclusion Concerning the Effect of a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice on Dentin Hypersensitivity

The overall conclusion from the two studies shown in Table XI is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer and 0.243% sodium fluoride with a specially designed silica base provides a statistically significantly ($p < 0.05$) greater beneficial effect on dentin hypersensitivity when compared to a placebo dentifrice and compared to a positive control dentifrice (Crest Pro-Health Toothpaste).

Table XI
Dentin Hypersensitivity Efficacy
Triclosan/Copolymer Dentifrice Clinical Studies
(0.3% Triclosan/2.0% PVM/MA Copolymer in an 0.243% Sodium Fluoride/Specially Designed Silica Base)

Reference No.	Investigators	Location	Number of Subjects*	Duration	Clinical Design	Efficacy	
138	Zaidel, *et al.*, 2011	United States	—	—	Acid etched human dentin	Significant dental occlusion*** evaluated with CLSM and SEM**	
139	Chaknis, *et al.*, 2011	United States	118	8 weeks	Parallel Without a Prophy at Start	61.1%[1] 34.0%[3]	37.9%[2] 27.2%[4]

* Refers to the number of subjects in dentifrice groups who completed the entire study.
** CLSM = Confocal laser scanning microscopy; SEM = Scanning electron microscopy. All reductions at the 0.05% level.
*** Versus dentifrice containing 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate and negative control dentifrice.
[1]tactile hypersensitivity percent reduction of triclosan/copolymer/specially designed silica dentifrice relative to negative control dentifrice ($p < 0.05$)
[2]tactile hypersensitivity percent reduction of triclosan/copolymer/specially designed silica dentifrice relative to 0.454% stannous fluoride/sodium
[3]cold air blast hypersensitivity percent reduction of triclosan/copolymer/specially designed silica dentifrice relative to negative control dentifrice ($p < 0.05$)
[4]cold air blast hypersensitivity percent reduction of triclosan/copolymer/specially designed silica dentifrice relative to 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice ($p < 0.05$).

Effects on Peri-Implant Mucositis

Peri-implant mucositis is generally considered to be a reversible inflammatory lesion affecting the soft tissues around an implant, and is estimated to affect about 80% of patients restored with implants. Lesions of peri-implant mucositis are associated with biofilms present on the implant surface. The microbiota of the submarginal biofilm in sites with peri-implant mucositis appear to be similar to those at gingivitis/periodontitis sites. As the number of patients with dental implants increases and with the prospect of dental implant therapy assuming a greater role in dental practice, clinical investigations have focused on the prevention and management of diseases of successfully osseointegrated dental implants. Oral biofilm accumulation on dental implants can cause peri-implant inflammation as it does in the periodontium around teeth. Thus, proper oral hygiene is important to control oral biofilms; nonetheless, most people demonstrate less than perfect plaque control. In addition, to address the concern articulated at the 6th European Workshop on Periodontology as to the need to determine whether antimicrobials used in periodontal therapy are also effective in the treatment of peri-implant diseases and to what extent initial improvements are sustained over the long term, two six-month clinical studies have been reported which compared the effects of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base on peri-implant mucositis (Table XII).

In a randomized controlled clinical trial, Ramberg, *et al.* observed that subjects with peri-implant mucositis who used a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride during a six-month period, as an adjunct to mechanical tooth brushing, exhibited significantly fewer clinical signs of inflammation than subjects who used a regular fluoride dentifrice ($p < 0.05$). The BOP scores were reduced from 53.8% to 29.1% in the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group, while there was an increase in scores in the placebo dentifrice group. The individual mean pocket probing depth, as well as the frequency of sites with 5 mm and > 6 mm deep pockets, were reduced significantly more in the 0.3% triclosan/2.0% PVM/MA copolymer/fluoride dentifrice group than in the placebo dentifrice group ($p < 0.05$).[140]

Sreenivasan, *et al.* conducted a six-month, double-blind, two-treatment, parallel group study examining the effects of a 0.3% triclosan/2.0% copolymer/0.243% sodium fluoride dentifrice on clinical and microbiological parameters of both dental implants and natural teeth in the same patients. Results showed that subjects in the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group had significantly lower levels of dental plaque, gingivitis, and BOP after three and six months of product use at both the implant and the contralateral tooth when compared with the fluoride dentifrice ($p < 0.05$). There were significantly fewer Gram-negative anaerobes in the in the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice group ($p < 0.05$), including > 90% reductions in *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Eubacterium saburreum*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella melaninogenica*, *Solobacterium moorei*, and *Tannerella forsythia*. Based on these results, twice-daily use of a triclosan/copolymer dentifrice may enhance dental implant maintenance by reducing dental plaque and gingival inflammation.[141]

Overall Conclusion from Two Long-Term Peri-Implant Mucositis Clinical Studies with a Triclosan/PVM/MA Copolymer/Fluoride Dentifrice

The overall conclusion from the two independent, double-blind, long-term (six months) clinical studies shown in Table XII is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides statistically significantly ($p < 0.05$) greater beneficial effect on peri-implant mucositis (inflammation around dental implants) when compared to a placebo dentifrice, thereby increasing the life of oral implants.

Direct Comparisons Clinical Studies

A series of studies[42,43,138,139,142-148] was conducted to compare the efficacy of a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a silica base (marketed globally as Colgate Total Toothpaste) to a denti-

Table XII
Peri-Implant Mucositis Efficacy
Triclosan/Copolymer Dentifrice Long-Term Clinical Studies
(0.3% Triclosan/2.0% Copolymer in a 0.243% Sodium Fluoride/Silica Base)

Reference No.	Investigator	Location	Number of Subjects*	Duration	Clinical Design	Efficacy vs. Placebo ($p < 0.05$)
140	Ramberg, *et al.*, 2009	Italy	59	6 Months	Parallel without Prophy at Start	Statistically significantly less peri-implant mucositis in triclosan/PVM/MA copolymer dentifrice group.
141	Sreenivasan, *et al.*, 2011	Israel	120	6 Months	Parallel without Prophy at Start	Statistically significantly lower plaque, gingivitis and bleeding site scores and fewer Gram negative anaerobes in triclosan/ PVM/MA copolymer dentifrice group.

*Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the entire study.

Table XIII
Direct Comparisons
Colgate Total Toothpaste
(0.3% Triclosan and 2.0% PVM/MA Copolymer/0.243% Sodium Fluoride/Silica
vs.
Crest Pro-Health Toothpaste
(0.454% Stannous Fluoride, Sodium Hexametaphosphate, Zinc Lactate)

Reference No.	Parameter	Investigator	Location	Number of Subjects*	Duration	Clinical Design	Efficacy****
42	Antimicrobial	Fine, *et al*., 2012	United States	35	14 days	Microbial Viability	Significantly greater reductions for Colgate Total
138	Hypersensitivity	Zaidel, *et al*., 2011	United States	--	---	Laboratory	Significant greater efficacy for Colgate Total
139	Hypersensitivity	Chaknis, *et al*., 2011	United States	118	8 Weeks	Tactile and Air Blast	Significant greater efficacy for Colgate Total
142	Antimicrobial	Haraszthy, *et al*., 2010	United States	28	12 Days	MIC***	Significantly greater efficacy for Colgate Total
143	Antimicrobial	Haraszthy, *et al*., 2010	United States	18	7 Days	MIC***	Significant greater efficacy for Colgate Total
144	Antimicrobial	Ledder and McBain, 2012	England	N/A	N/A	Microbial Viability	Significant greater reduction for Colgate Total
145	Plaque (MGMPI)	Barnes, *et al*., 2010	United States	25**	24 hours	Parallel with Prophy at Start	Significant greater efficacy for Colgate Total
146	Plaque/Gingivitis	Singh, *et al*., 2010	United States	105	6 Weeks	Parallel without Prophy at Start	Significant greater efficacy for Colgate Total
147	Plaque/Gingivitis	Ayad, *et al*., 2010	Canada	122	6 Weeks	Parallel without Prophy at Start	Significant greater efficacy for Colgate Total
148	Plaque/Gingivitis	Elias-Boneta, *et al*., 2010	Puerto Rico	109	6 Months	Parallel without Prophy at Start	Significant greater efficacy for Colgate Total

* Refers to the number of subjects in both the Colgate Total Toothpaste and Crest Pro-Health dentifrice groups who completed the entire study.
** The same 25 subjects were used in three separate 24 hour clinical studies with a one-week wash-out period,
*** Minimum Inhibitory Concentration (MIC) of each dentifrice was determined for resident oral bacteria including those associated with dental caries, periodontitis and malodor. Evaluations were performed on individual laboratory strains and from oral bacteria from plaque samples and rinse samples from subjects.
**** Statistically significant at the $p < 0.05$ level of confidence.

frice containing 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate (marketed as Crest Pro-Health Toothpaste) for antimicrobial activity, plaque/gingivitis efficacy, and dentin hypersensitivity efficacy (Table XIII).

Fine, *et al.* compared the antimicrobial effects of a triclosan/PVM/MA copolymer/fluoride dentifrice to a stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice and to a sodium fluoride dentifrice on six types of microorganisms collected from four distinct oral habitats. The triclosan/PVM/MA copolymer/fluoride dentifrice demonstrated a sustained and statistically significantly greater reduction in each of the six microbial groups evaluated across all four oral habitats (24 outcomes), as measured 12 hours after the final dentifrice application as compared to the other dentifrices. In contrast, the differences between the other two test products were less marked with no observed differences in almost half of the 24 microbial outcomes. This research supports that the triclosan/PVM/MA copolymer/fluoride dentifrice provides an antimicrobial effect across a broad range of bacteria and is compatible with its published clinical efficacy.[42]

As previously discussed, Du-Thumm, *et al.* used 3D CLSM to assess the antimicrobial effects of three toothpastes (Colgate Total, Colgate Cavity Protection, and Crest Pro-Health) on dental plaque viability. CLSM analyses were performed at baseline (before treatment) and 12 hours after brushing. Colgate Total clearly demonstrated the highest level of antimicrobial activity with a clear loss of bacterial viability throughout the deepest layers of the biofilm. Mean plaque viability for Colgate Total was 17.72% and was statistically significantly different from the two other treatments ($p < 0.05$). Mean plaque viability was 51.43% for Crest Pro-Health and 72.18% for Colgate Cavity Protection Toothpaste.[43]

In a study by Haraszthy, *et al.*, the antimicrobial activity of two dentifrices was examined. MIC results indicated that the triclosan/PVM/MA copolymer/fluoride dentifrice demonstrated a four-fold greater broad spectrum laboratory antimicrobial activity when compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice ($p < 0.05$).[142] It showed significantly greater inhibition of a variety of oral bacteria, including species causing dental caries, periodontitis and oral

halitosis. In addition, the triclosan/copolymer/fluoride dentifrice demonstrated substantially greater broad-spectrum inhibition of bacteria from oral rinse and dental plaque samples when compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice.

In a second study, Haraszthy, *et al.* again reported on the effects of the triclosan/PVM/MA copolymer/fluoride dentifrice and the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice on oral microorganisms.[143] Oral rinse samples and supragingival plaque from adults were taken to determine antimicrobial effects on the entire microbial diversity of these samples, including biofilm-derived microorganisms. MIC results showed that the triclosan/PVM/MA copolymer/fluoride dentifrice demonstrated lower MICs as compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice ($p < 0.05$) and inhibited the entire group of Gram-positive and Gram-negative bacteria. In addition, results showed that the triclosan/PVM/MA copolymer/fluoride dentifrice demonstrated substantially greater broad spectrum inhibition of bacteria from oral rinse and dental plaque samples when compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice.

The antiplaque effects of a triclosan/PVM/MA copolymer/fluoride dentifrice were compared to those of a stannous fluoride/sodium hexametaphosphate /zinc lactate dentifrice using three *in vitro* systems which represent major compositional variants of dental plaque commonly found in the mouth. The three systems were the hydroxyapatite disc model, the modified drip flow biofilm reactor, and the Multiple Sorbarod Device. Both dentifrices were comparably effective at reducing viability and plaque accumulation in mature supragingival plaques. However, the triclosan/PVM/MA copolymer/fluoride dentifrice produced statistically significantly greater reductions in total streptococci and anaerobes in nascent plaques and greater reductions in Gram-negative anaerobes and streptococci in subgingival plaques, as compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice.[144]

As reported by Barnes, *et al.*, three separate short-term studies were performed.[145] These studies compared the triclosan/PVM/MA copolymer/fluoride dentifrice to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice on the formation of plaque over 24 hours using the MGMPI, which measures plaque along the gingival margin versus the length of the gingival margin. In all three clinical studies, the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice provided statistically significantly greater antiplaque activity when compared to the 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice ($p < 0.05$).

Two six-week clinical studies, one reported by Singh, *et al*[146] and the other by Ayad, *et al.*,[147] were conducted to compare the established plaque and gingivitis efficacy of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice to the 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice. Subjects in both studies received a gingivitis and plaque examination using the Löe-Silness Gingival Index (Talbott, Mandel, Chilton Modification) and Quigley-Hein Plaque Index (Turesky Modification). They brushed their teeth for one minute twice a day, in the mornings and evenings, with their assigned dentifrice and a soft-bristled toothbrush. After six weeks they received a second plaque and gingivitis examination. The results indicated that subjects using the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice exhibited statistically significantly greater reductions in plaque and gingival and plaque indices scores, (18.7% and 22.0%) and (15.8% and 19.2%), respectively, after six weeks of product use, compared to the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice ($p < 0.05$).

Elias-Boneta, *et al.* conducted a long term, six-month clinical study to compare the antigingivitis and antiplaque efficacy of the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice compared to the 0.454% stannous fluoride/sodium hexametaphosphate/zinc citrate dentifrice.[148] Subjects received a gingivitis and plaque examination using the Modified Löe-Silness Gingival Index and the Modified Quigley-Hein Plaque Index, were instructed to brush their teeth twice daily for one minute in the morning and evening, and were re-examined for gingivitis and plaque after six weeks, three months, and six months of product use. Results from the clinical study indicated that after six months' use of the products, subjects using the 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride dentifrice exhibited statistically significantly 17.1% and 25.8% (both $p < 0.05$) greater reductions in gingivitis and plaque index scores, respectively, when compared to the subjects using the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice.

As previously reported, a study by Zaidel, *et al.* reported that the triclosan/copolymer/fluoride dentifrice exhibited a significantly higher amount of dentin treated occluded tubules and that the occlusion provided significantly better reduction in permeability after extended pulpal pressure and acid challenge compared to dentin treated with the stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice.[138]

Overall Conclusion When Comparing the Plaque, Gingivitis, Antimicrobial, and Dentin Hypersensitivity Effects of Two Commercially Marketed Multi-Benefit Dentifrices.

The overall conclusion from a series of direct comparison clinical studies shown in Table XIII is that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base (Colgate Total Toothpaste) provides statistically significantly ($p < 0.05$) greater beneficial effects with regard to plaque, gingivitis, antimicrobial activity, and dentin hypersensitivity as compared to a dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate (Crest Pro-Health Toothpaste).

All comparisons were statistically significant at the 0.05% level. Also, an eight-week clinical study reported by Chaknis *et al.* reported that a dentifrice containing 0.3% triclosan/2.0% PVM/MA copolymer/0.243% sodium fluoride in a specially designed silica provided statistically significant greater relief of dentin hypersensitivity compared to a dentifrice containing 0.454% stannous fluoride/sodium hexametaphosphate/zinc lactate in both tactile and air blast sensitivity ($p < 0.05$).[139]

Summary

Clinical and laboratory studies clearly indicate that the use of Colgate Total Toothpaste provides oral health benefits beyond those associated with "traditional" toothpaste use, in a manner that is safe and effective.[149] Furthermore, the Cochrane Oral Health Group has recently published a review of 30 clinical trials that included 14,835 participants and examined the effect of Colgate Total Toothpaste as compared to an ordinary fluoride toothpaste on various endpoints[150] and concluded that there was "moderate-quality evidence" supporting the fact that Colgate Total toothpaste reduced plaque and gingivitis, including gingival inflammation and gingival bleeding, as compared to a fluoride toothpaste. Furthermore, they concluded that there was "high quality evidence" that Colgate Total Toothpaste led to a reduction in coronal caries, but weaker evidence for a reduction in root caries and calculus.

The studies summarized in this Supplement (Table XIV) support these findings and demonstrate that Colgate Total Toothpaste provides protection against plaque and gingivitis, calculus, caries, oral malodor, and peri-implant mucositis. Colgate Total Toothpaste also provides superior whitening and stain removal benefits. It also provides protection against the progression of periodontal disease and has been proven to provide superior oral health benefits compared to a dentifrice containing stannous fluoride, sodium hexametaphosphate, and zinc lactate. In addition, a specific variant provides dentin hypersensitivity benefits. Dental healthcare professionals can confidently recommend Colgate Total Toothpaste to their patients for use as part of their oral hygiene regimen.

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Table XIV

Overall Summary and Conclusions

Short-Term and Long-Term Clinical Studies with a Fluoride Dentifrice Containing 0.3% Triclosan and 2.0% PVM/MA Copolymer

Clinical Study Parameter(s)	Duration of Studies	Number of Studies	Total Subjects in Studies	Conclusions
Microbiology	6–120 months	6	549	Use of a fluoride dentifrice containing triclosan and a copolymer does not cause the development of either pathogenic, opportunistic or resistant microorganisms.
Plaque and Gingivitis	24 hours–9 months	45	3,207	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in supragingival plaque and gingivitis.
Periodontitis	24 months 36 months	6	1,204	Use of a fluoride dentifrice containing triclosan and a copolymer promotes healing following non-surgical periodontal therapy, controls periodontal causing bacteria and reduces the progress and recurrence of periodontitis.
Calculus	2–6 months	7	701	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in supragingival calculus.
Tooth Whitening/ Stain Removal	2 weeks–6 months	9	858	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in extrinsic tooth stain.
Caries	24–36 months	5	11,049	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in dental caries.
Malodor	12 hours	6	398	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in oral malodor.
Dentin Hypersensitivity	8 weeks	2	118	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in dentin hypersensitivity.
Peri-Implant Mucositis	6 months	2	179	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in peri-implant mucositis and a greater dental implant success rate.
Direct Comparison	24 hours–6 Months	10	525	Use of a sodium fluoride dentifrice containing triclosan and a copolymer (Colgate Total Toothpaste) provides greater plaque, gingivitis, dentin sensitivity and antimicrobial efficacy when compared to a stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice (Crest Pro-Health Toothpaste).

References

1. BASF – Safety Data Sheet (Irgacare MP®), 2009
2. Ciba-Geigy Corporation Technical bulletin (Irgasan DP 300—Broad Spectrum Antibacterial, 1988.
3. Regos J, Hitz HR. Investigations on the mode of action of triclosan, a broad spectrum antibacterial agent. *Zbl Bakt Hyg* 1974;226:390–401.
4. Lindhe J. Triclosan/copolymer/fluoride dentifrices: A new technology for the prevention of plaque, calculus, gingivitis and caries. *Am J Dent* 1990;3:S3–54.
5. Rodricks JV, Swenberg JA, Borzelleca JF, Maronpot RR, Shipp AM. Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. *Criti Rev Toxicol*, 2010;40(5):422-84.
6. DeSalva SJ, Kong BM, Lin Y-J. Triclosan: A safety profile. *Am J Dent* 1989;2:185–96.
7. Bagley DM, Lin Y-J. Clinical evidence for the lack of triclosan accumulation from daily use in dentifrices. *Am J Dent* 2000;13:148–52.
8. Barbolt TA. Chemistry and safety of triclosan, and its use as an antimicrobial coating on coated VICRYL plus antibacterial suture (coated polyglactin 910 suture with triclosan). A two-year clinical study. *Surg Infect* 2002;3:S45–53.
9. Fine DH, Furgang D, Bonta Y, DeVizio W, Volpe AR, Reynolds H, Zambon JJ, Dunford RG. Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and concurrent oral microflora monitoring. *Am J Dent* 1998;11:259–70.
10. Cullinan MP, Hamlet SM, Westerman B, Palmer JE, Faddy MJ, Seymour GJ. Acquisition and loss of Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and Prevotella intermedia over a 5-year period: Effect of a triclosan/copolymer dentifrice. *J Clin Periodontol* 2003;30:532–41.
11. Cullinan MP, Palmer JE, Carle AD, West MJ, Seymour GJ. Long term use of triclosan toothpaste and thyroid function. *Sci Total Environ* 2012;416:75-79.
12. SCCP (Scientific Committee on Consumer Products), Opinion on triclosan, 21 January 2009.
13. SCCS (Scientific Committee on Consumer Safety), Opinion on triclosan, ADDENDUM to the SCCP Opinion on Triclosan (SCCP/1192/08) from January 2009, 22 March 2011.
14. SCCS (Scientific Committee on Consumer Safety), Opinion on triclosan (antimicrobial resistance), 22 June 2010.
15. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). (2009) Priority Existing Chemical Assessment Report No. 30.Triclosan. *http://www.nicnas.gov.au/Publications/CAR/PEC/PEC30.asp*
16. Fuchsman P, Lyndall J, Bock M, Lauren D, Barber T, Leigh K, Perruchon E, Capdevielle M. Terrestrial Ecological Risk Evaluation for Triclosan in Land-Applied Biosolids. *Integr Environ Assess Manag* 2010;6:405–18.
17. Lyndall J, Fuchsman, Bock M, Barber T, Lauren D, Leigh K, Perruchon E, Capdevielle M. Probabilistic Risk Evaluation for Triclosan in Surface Water, Sediments, and Aquatic Biota Tissue. *Integr Environ Assess Manag* 2010;6:419–40.
18. Nabi N, Mukerjee C, Schmid R, Gaffar A. *In vitro* and *in vivo* studies on triclosan/PVM/MA copolymer/NaF combination as an anti-plaque agent. *Am J Dent* 1989;2:197–206.
19. Gaffar A, Esposito A, Afflitto J. *In vitro* and *in vivo* anticalculus effects of a triclosan/copolymer system. *Am J Dent* 1990;3(Spec Iss):S37–42.
20. Nabi N, Gaffar A. Antibacterial antiplaque oral composition. United States Patent No. 4,894,220; Issued January 16, 1990.
21. *Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Dental Plaque and Gingivitis*. American Dental Association Council on Dental Therapeutics. *J Am Dent Assoc* 1986;112:529–32.
22. *Acceptance Program Guidelines: Chemotherapeutic Products for Control of Gingivitis*. American Dental Association Council on Scientific Affairs, July 2008.
23. Garcia-Godoy F, Garcia-Godoy F, DeVizio W, Volpe AR, Ferlauto RJ, Miller JM. Effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A 7-month clinical study. *Am J Dent* 1990;3(Spec Iss):S15–26.
24. Mankodi S, Walker C, Conforti N, DeVizio W, McCool JJ, Volpe AR. Clinical effect of a triclosan-containing dentifrice on plaque and gingivitis: A six-month study. *Clin Prev Dent* 1992;14:4–10.
25. Bolden TE, Zambon JJ, Sowinski J, Ayad F, McCool J, Volpe AR, DeVizio W. The clinical effect of a dentifrice containing triclosan and a copolymer in a sodium fluoride/silica base on plaque formation and gingivitis: A six-month clinical study. *J Clin Dent* 1992;4:125–31.
26. Denepitiya JL, Fine D, Singh S, DeVizio W, Volpe AR, Person P. Effect upon plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: A 6-month clinical study. *Am J Dent* 1992;5:307–11.
27. Zambon JJ, Reynolds HS, Dunford RG, Bonta CY. Effect of a triclosan/ copolymer/fluoride dentifrice on the oral microflora. *Am J Dent* 1990;3(Spec Iss):S27–34.
28. Bonta Y, Reynolds HS, Dunford RG, Zambon JJ. Long term effect of a triclosan/copolymer dentifrice on oral microflora. *J Dent Res* 1992;71:557.
29. Walker C, Borden LC, Zambon JJ, Bonta CY, DeVizio W, Volpe AR. The effects of a 0.3% triclosan-containing dentifrice on the microbial composition of supragingival plaque. *J Clin Periodontol* 1994;21:334–41.
30. Zambon JJ, Reynolds HS, Dunford RG, DeVizio W, Volpe AR, Berta R, Tempro JP, Bonta Y. Microbial alterations in supragingival dental plaque in response to a triclosan-containing dentifrice. *Oral Microbiol Immunol* 1995;10:247–55.
31. Cullinan MP, Bird PS, Heng N, West MJ, Seymour GJ. No evidence of triclosan-resistant bacteria following long-term use of triclosan-containing toothpaste. *J Periodont Res* 2013; doi:10.1111/jre.12098.
32. Haraszthy V, Sreenivasan P, Zambon J. Twenty year survey of bacterial susceptibility to triclosan. *J Dent Res* 2012; 91(Spec Iss A):542.
33. Gaffar A, Nabi N, Kashaba B, Williams M, Herles S, Olsen S, Afflitto J. Antiplaque effects of dentifrices containing triclosan/copolymer/NaF system versus triclosan dentifrices without the copolymer. *Am J Dent* 1990;3(Spec Iss):S7–14.
34. Gaffar A, Volpe AR, Lindhe J. Recent advances in plaque/gingivitis control. In: Emberg G, Rölla G, eds., *Clinical and Biological Aspects of Dentifrices*, Oxford University Press, pp. 229–47, 1992.
35. Afflitto J, Fakhry-Smith S, Gaffar A. Salivary and plaque triclosan levels after brushing with a 0.3% triclosan/copolymer/NaF dentifrice. *Am J Dent* 1989;2:207–10.
36. Gaffar A, Afflitto J, Nabi N, Herles S, Kruger I, Olsen S. Recent advances in plaque, gingivitis, tartar and caries prevention technology. *Int Dent J* 1994;44:63–70.
37. Ledder RG, Sreenivasan PK, DeVizio W, McBain AJ. Evaluation of the specificity and effectiveness of selected oral hygiene actives in salivary biofilm microcosms. *J Med Microbiol* 2010;59:1462–8.
38. Amornchat C, Kraivaphan P, Triratana T. Investigation of a triclosan/copolymer dentifrice on plaque viability and triclosan retention in dental plaque in a Thai population. *Mahidol Dent J* 2004;24:103–111.
39. Yang Y, Sreenivasan PK. An *ex-vivo* multiplexed antibacterial test on oral microflora. *Oral Microbiol Immunol* 2005;20:180–85.
40. Xu T, Deshmukh M, Barnes VM, Trivedi HM, Du-Thumm L, Richter R, Cummins D. Analysis of the antibacterial activity and plaque control benefit of Colgate Total dentifrice via clinical evaluation and real-time polymerase chain reaction. *J Clin Dent* 2005;16:117–22.
41. Fine DH, Furgang D, Markowitz K, Sreenivasan PK, Klimpel K, DeVizio W. The antimicrobial effect of a triclosan/copolymer dentifrice on oral microorganisms in vivo. *J Am Dent Assoc* 2006;137:1406–13.
42. Fine DH, Sreenivasan PK, McKiernan M, Tischio-Bereski D, Furgang D. Whole mouth antimicrobial effects after oral hygiene: comparison of three dentifrice formulations. *J Clin Periodontol* 2012;39:1056–64.
43. Du-Thumm L, Vandeven M, Miller S, Cummins D. 3-D Confocal plaque viability study 12 hours after toothpaste brushing. *J Dent Res* 2013;92(Spec Iss A):3402.
44. Scannapieco FA. Periodontal inflammation: From gingivitis to systemic disease? *Compend Cont Educ Dent* 2004;25(Suppl 1):16–25.
45. Xu T, Deshmukh M, Barnes VM, Trivedi HM, Cummins D.

Effectiveness of triclosan/copolymer dentifrice on microbiological and inflammatory parameters. *Compend Cont Educ Dent* 2004;25:46–53.
46. Modeer T, Bengtsson A, Rolla F. Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 *in vitro*. *J Clin Periodontol* 1996;23:927–33.
47. Mustafa M, Wondimu B, Ibrahim M, Modeer T. Effect of triclosan on interleukin-1 production in human gingival fibroblasts challenged with tumor necrosis factor. *Eur J Oral Sci* 1998;106:637–43.
48. Mustafa M, Bakhiet M, Wondimu B, Modeer T. Effect of triclosan on interferon-production and major histocompatibility complex class II expression in human gingival fibroblasts. *J Clin Periodontol* 2000;27:733–7.
49. Skold-Larsson K, Yucel-Lindberg T, Twetman S, Modeer T. Effect of triclosan-containing dental gel on the levels of prostaglandin I2 and interleukin-1 in gingival crevicular fluid from adolescents with fixed orthodontic appliances. *Acta Odontol Scand* 2003;61:193–6.
50. Mustafa M, Wondimu B, Yucel Lindberg T, Kats A-Hallstrom T, Jonsson AS, Modeer T. Triclosan reduces microsomal prostaglandin E sythase-1 expression in human gingival fibroblasts. *J Clin Periodontol* 2005;32:6–11.
51. Panagakos FS, Kumar E. Triclosan inhibition of cytokine-stimulated MMP production by osteoblast-like cells. *J Dent Res* 2003;82:2248.
52. Mustafa M, Wondimu B, Hultenby K, Yucel-Lindberg T, Modeer T. Uptake, distribution and release of 14C-triclosan in human gingival fibroblasts. *J Pharm Sci* 2003;92(8):1648–53.
53. Barros SP, Wirojchanasak S, Barrow DA, Panagakos FS, DeVizio W, Offenbacher S. Triclosan inhibition of acute and chronic inflammatory gene pathways. *J Clin Periodontol* 2010;37:412–8.
54. Wallet MA, Calderon NL, Alonso TR, Choe CS, Catalfamo DL, Lalane CJ, Neiva KG, Panagakos F, Wallet SM. Triclosan alters antimicrobial and inflammatory responses of epithelial cells. *Oral Dis* 2013;19:296–302.
55. Barnes VM, Teles R, Trivedi HM, De Vizio W, Xu T, Mitchell MW, Milburn MV, Guo L. Acceleration of purine degradation by periodontal diseases. *J Dent Res* 2009;88:851–5.
56. Barnes VM, Teles R, Trivedi HM, Devizio W, Xu T, Lee DP, Mitchell MW, Wulff JE, Milburn MV, Guo L. Assessement of the effects of dentifrice on periodontal disease biomarkers in gingival crevicular fluid. *J Periodontol* 2010;81:1273–9.
57. Barnes VM, Xu T, Shimizu E, Nakatani T, Jefcoat S, Vasilov A, Qin L, Partridge NC. Triclosan blocks *Mmp 13* expression in hormone-stimulated osteoblasts. *J Periodontol* DOI: 10.1902/jop.2013.120154.
58. Clerehugh V, Worthington H, Clarkson J, Davies TGH. The effectiveness of two test dentifrices on dental plaque formation: A 1-week clinical study. *Am J Dent* 1989;2:221–4.
59. Singh SM, Rustogi KN, Volpe AR, Petrone M, Kirkup R, Collins M. Effect of a dentifrice containing triclosan and a copolymer on plaque formation: A 6-week clinical study. *Am J Dent* 1989;2:225–30.
60. Palomo F, Wantland L, Sanchez A, DeVizio W, Carter W, Baines E. The effect of a dentifrice containing triclosan and a copolymer on plaque formation and gingivitis: A 14-week clinical study. *Am J Dent* 1989;2:231–7.
61. Lim C, Petrone ME, Volpe AR, DeVizio W, Lim C, Hescot P, Flament-Lamotte D, Simon A, Joseph L. Comparative efficacy of a dentifrice containing 0.3% triclosan and 1100 ppm sodium fluoride and a dentifrice containing 0.3% triclosan and 1500 ppm sodium fluoride in the control of plaque and gingivitis. Unpublished clinical study data on file, Colgate-Palmolive Technology Center, 1991.
62. Muller HP, Barrieshi-Nusair, Kononen E, Yang M. Effect of triclosan/copolymer-containing toothpaste on the association between plaque and gingival bleeding: a randomized controlled clinical trial. *J Clin Periodontol* 2006;33:811–8.
63. Xu T, Barnes VM. The development of a new dental probe and a new plaque index. *J Clin Dent* 2003;14:93–7.
64. Xu T, Barnes VM. Comparison of two clinical methods for evaluating the anti-plaque efficacy of a dentifrice. *J Clin Dent* 2005;16:97–102.
65. Barnes VM, Richter R, Vandeven M, Xu T, DeVizio W. Clinical investigation of the antiplaque efficacy of a new variant of a commercially-available triclosan/copolymer/fluoride dentifrice. *J Clin Dent* 2008;19:81-4.
66. Moazzez R, Booth V, Barnes VM, Richter R, Xu T, DeVizio W. The use of the modified gingival margin plaque index (MGMPI) method to investigate the inhibitory effect of various toothpastes on dental plaque formation. *J Clin Dent* 2010;21:1–3.
67. Cubells AB, Dalmau LB, Petrone ME, Chaknis P, Volpe AR. The effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A six-month clinical study. *J Clin Dent* 1991;2:63–9.
68. Deasy MJ, Singh SM, Rustogi KN, Petrone DM, Battista G, Petrone ME, Volpe AR. Effect of a dentifrice containing triclosan and a copolymer on plaque formation and gingivitis. *Clin Prev Dent* 1991;13:12–9.
69. Palomo F, Wantland L, Sanchez A, Volpe AR, McCool JJ, DeVizio W. The effect of three commercially available dentifrices containing triclosan on supragingival plaque formation and gingivitis: A six-month clinical study. *Int Dent J* 1994;44(Suppl 1):75–81.
70. Triratana T, Tuongratanaphan S, Kraivaphan P, Rustogi KN, Volpe AR. The effect on established plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: A six-month clinical study. *J Dent Assoc Thailand* 1993;43:19–28.
71. Lindhe J, Rosling B, Socransky SS, Volpe AR. The effect of a triclosan-containing dentifrice on established plaque and gingivitis. *J Clin Periodontol* 1993;20:327–34.
72. Hu D, Zhang J, Wan H, Zhang YP, Volpe A, Petrone ME. Efficacy of a triclosan/copolymer dentifrice in the control of plaque and gingivitis: A six month study in China. *West China J Stomatol* 1997;15(4):333–5.
73. Allen DR, Battista GW, Petrone DM, Petrone ME, Chaknis P, DeVizio W, Volpe AR. The clinical efficacy of Colgate total plus whitening toothpaste containing a special grade of silica and Colgate total fresh stripe toothpaste in the control of plaque and gingivitis. A six-month clinical study. *J Clin Dent* 2002;13(Spec Iss):59–64.
74. Mankodi S, Lopez M, Smith I, Petrone D, Petrone ME, Chaknis P, DeVizio W, Volpe AR, Proskin HM. Comparison of two dentifrices with respect to efficacy for the control of plaque gingivitis, and with respect to extrinsic tooth staining. A six-month clinical study on adults. *J Clin Dent* 2002;13:228–33.
75. Triratana T, Rustogi KN, Volpe AR, DeVizio W, Petrone M, Giniger M. Clinical effect of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. A six-month clinical study. *JADA* 2002;133:219–25.
76. Mateu FA, Elias Boneta A, Stewart B, DeVizio W, Proskin H. A clinical investigation of the efficacy of two dentifrices for controlling established supragingival plaque and gingivitis. *J Clin Dent* 2008;19:85–94.
77. Kraivaphan P, Amornchat C, Triratana T, Leethochawalit U. Clinical efficacy of a triclosan containing dentifrice on gingivitis during pregnancy and post-partum. *Southeast Asian J Trop Med Public Health* 2006;37(4):820–5.
78. Schiff T, Proskin HM, Zhang YP, Petrone M, DeVizio W. A clinical investigation of the efficacy of three different treatment regimens for the control of plaque and gingivitis. *J Clin Dent* 2006;17:138–44.
79. Mankodi S, Chaknis P, Panagakos FS, DeVizio W, Proskin HM. Comparative investigation of a dentifrice containing triclosan/copolymer/sodium fluoride and specially-designed silica and a dentifrice containing 0.243% sodium fluoride in a silica base for the control of established supra-gingival plaque and gingivitis: a 6-month clinical study. *Am J Dent* 2011;24 Sp Is A:21A–7.
80. Imrey PB, Chilton NW, Pihlstrom BL, Proskin HM, Kingman A, Listgarten MA, Zimmerman SO, Ciancio SG, Cohen ME, D'Agostino RB, Fischman SL, Fleiss JL, Gunsolly JC, Kent RL, Killoy WJ, Laster LL, Marks RG, Varma O. Recommended revisions to American Dental Association guidelines for acceptance of chemotherapeutic products for gingivitis control. *J Periodontol Res* 1994;29:299–304.
81. Quigley GA, Hein JW. Comparative cleansing efficacy of manual and power brushing. *J Am Dent Assoc* 1962;65:26–9.
82. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of victamine C. *J Periodontol* 1970;41:41–3.
83. Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odont Scand* 1963;21:533–51.
84. Talbott K, Mandel ID, Chilton NW. Reduction of baseline gingivitis scores with repeated prophylaxes. *J Prev Dent* 1977;4:28–9.
85. Svatun B, Saxton CA, Huntington E, Cummins D. The effects of three silica dentifrices containing triclosan on supragingival plaque

and calculus formation and on gingivitis. *Int Dent J* 1993;43(Suppl 1):441–52.
86. Kanchanakamol U, Umpriwan R, Jotikasthira N, Srisilapanan P, Tuongratanaphan S, Sholitkul W, Chat-Uthai T. Reduction of plaque formation and gingivitis by a dentifrice containing triclosan and copolymer. *J Periodontol* 1995;66:109–12.
87. Renvert S, Birkhed D. Comparison between 3 triclosan dentifrices on plaque, gingivitis and salivary microflora. *J Clin Periodontol* 1995;22:63–70.
88. Furuichi Y, Ramberg P, Krok L, Lindhe J. Short-term effects of triclosan on healing following subgingival scaling. A two-week clinical study. *J Clin Periodontol* 1997;24:777–82.
89. Rosling B, Wannfors B, Volpe AR, Furuichi Y, Ramberg P, Lindhe J. The use of triclosan/copolymer dentifrice may retard the progression of periodontitis. *J Clin Periodontol* 1997;24:873–80.
90. Rosling B, Dahlen G, Volpe A, Furuichi Y, Ramberg P, Lindhe J. Effect of triclosan on the subgingival microbiota of periodontitis-susceptible subjects. *J Clin Periodontol* 1997;24:881–7.
91. Ellwood RP, Worthington HV, Blinkhorn ASB, Volpe AR, Davies RM. Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. *J Clin Periodontol* 1998;26:363–7.
92. Furuichi Y, Rosling B, Volpe AR, Lindhe J. The effect of a triclosan/copolymer dentifrice on healing after non-surgical treatment of recurrent periodontitis. *J Clin Periodontol* 1999;26:63–6.
93. Cullinan MP, Westerman B, Hanlet SM, Palmer JE, Faddy MJ, Seymour GJ. The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. *J Clin Periodontol* 2003;30:414–9.
94. Kerdvongbundit V, Wikesjo UME. Effect of triclosan on healing following non-surgical periodontal therapy in smokers. A two-year clinical study. *J Clin Periodontol* 2003;30:1024–30.
95. Schiff T, Cohen S, Volpe AR, Petrone ME. Effects of two fluoride dentifrices containing triclosan and a copolymer on calculus formation. *Am J Dent* 1990;3(Spec Iss):S43–5.
96. Lobene RR, Battista GW, Petrone DM, Volpe AR, Petrone ME. Clinical efficacy of an anticalculus fluoride dentifrice containing triclosan and a copolymer: A 6-month study. *Am J Dent* 1991;4:83–5.
97. Volpe AR, Schiff TJ, Cohen S, Petrone ME, Petrone D. Clinical comparison of the anticalculus efficacy of two triclosan-containing dentifrices. *J Clin Dent* 1992;3:93–5.
98. Bánóczy J, Sari K, Schiff T, Petrone M, Davies R, Volpe AR. Anticalculus efficacy of three dentifrices. *Am J Dent* 1995;8:205–8.
99. Schiff T, Delgado E, DeVizio W, Proskin HM. A clinical investigation of the efficacy of two dentifrices for the reduction of supragingival calculus formation. *J Clin Dent* 2008;19:102–5.
100. Allen D, Battista GW, Petrone DM, Petrone ME, DeVizio W, Volpe AR. A clinical study to compare the anticalculus effect of three dentifrice formulations. *J Clin Dent* 2002;13(Spec Iss):69–72.
101. Sowinski JA, Battista GW, Petrone DM, Petrone ME, DeVizio W, Volpe AR. A clinical study to assess the anticalculus efficacy of a new dentifrice containing a special grade of silica (Colgate Total Plus Whitening Toothpaste). A clinical trial on adults. *J Clin Dent* 2002;13(Spec Iss):65–8.
102. Volpe AR, Manhold JH, Hazen SP. *In vivo* calculus assessment: Part I. A method and its examiner reproducibility. *J Periodontol* 1965;36:292–8.
103. Manhold JH, Volpe AR, Hazen SP, Parker L, Adams SH. *In vivo* calculus assessment: Part II. A comparison of scoring techniques. *J Periodontol* 1965;36:299–304.
104. Volpe AR, Kupczak LJ, King WJ. *In vivo* calculus assessment: Part III. Scoring techniques, rate of calculus formation, partial mouth examinations vs. full mouth examinations, and intra-examiner reproducibility. *Periodontics* 1967;5:184–93.
105. Volpe AR, Kupczak LJ, King WJ, Goldman HM, Schulman SM. *In vivo* calculus assessment: Part IV. Parameters of human clinical studies. *J Periodontol* 1969;40:76–86.
106. Barnett ML, Charles CH, Gilman RM, Bartels LL. Correlation between Volpe-Manhold calculus index scores and actual calculus area. *Clin Prev Dent* 1989;11:3–5.
107. Sielski C, Berta RL, Petrone ME, Chaknis P, DeVizio W, Volpe AR, Proskin HM. A study to assess the tooth whitening efficacy of a new dentifrice formulation variant containing a special grade of silica. A six-week study on adults. *J Clin Dent* 2002;13(Spec Iss):77–81.
108. Ayad F, Khalaf A, Chaknis P, Petrone ME, DeVizio W, Volpe AR, Proskin HM. Clinical efficacy of a new tooth whitening dentifrice. *J Clin Dent* 2002;13(Spec Iss):82–5.
109. Singh S, Mankodi S, Chaknis P, Petrone ME, DeVizio W, Volpe AR, Proskin HM. The clinical efficacy of a new tooth whitening dentifrice formulation. A six-month study in adults. *J Clin Dent* 2002;13(Spec Iss):86–90.
110. Nathoo S, Petrone ME, DeVizio W, Chaknis P, Volpe AR. A six-week study to compare the stain removal efficacy of three dentifrices. *J Clin Dent* 2002;13(Spec Iss):91–4.
111. Nathoo S, Singh S, Petrone DM Wachs GN, Chaknis P, DeVizio W, Proskin HM. Clinical studies to assess the extrinsic stain prevention and stain removal efficacy of a variant of a commercially available dentifrice containing a new dual silica system. *J Clin Dent* 2008;19:95-101.
112. Nathoo S, Mateo LR, Delgado E, Zhang YP, DeVizio W. Extrinsic stain removal efficacy of a new dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, 0.243% NaF and specially-designed silica for sensitivity relief and whitening benefits as compared to a toothpaste containing 0.3% triclosan, 2.0% PVM/MA copolymer, 0.243% NaF and to a negative control dentifrice containing 0.243% NaF: a six-week study. *Am J Dent* 2011;24(Spec No A):28A-31.
113. Lobene RR. Effects of dentifrices on tooth stains with controlled brushing. *J Am Dent Assoc* 1968;77:849-55.
114. Mellberg JR, Blake-Haskins J, Petrou ID, Grote NE. Remineralization and demineralization *in situ* from a triclosan/co-polymer/fluoride dentifrice. *J Dent Res* 1991;70:1441–3.
115. Kertesz P, Bánóczy J, Volpe AR, Gaffar A, Petrone M, Nemes J. The influence of NaF/triclosan/copolymer toothpastes on human dental plaque. *J Dent Res* 1995;74:941.
116. Hawley GM, Hamilton FA, Worthington HV, Davies RM, Holloway PT, Davies TGH, Blinkhorn AS. A 30-month study investigating the effect of adding triclosan/copolymer to a fluoride dentifrice. *Caries Res* 1995;29:163–7.
117. Feller R, Kiger R, Triol CW, Sintes JL, Garcia L, Petrone ME, Volpe AR, Proskin HM. Comparison of the clinical anti-caries efficacy of an 1100 NaF silica-based dentifrice containing triclosan and a copolymer to an 1100 NaF silica-based dentifrice without those additional agents: A study on adults in California. *J Clin Dent* 1996;7:85–9.
118. Mann J, Karniel C, Triol CW, Sintes JL, Garcia L, Petrone ME, Volpe AR, Proskin HM. Comparison of the clinical anti-caries efficacy of a 1500 NaF silica-based dentifrice containing triclosan and a copolymer to a 1500 NaF silica-based dentifrice without those additional agents: A study on adults in Israel. *J Clin Dent* 1996;7:90–5.
119. Mann J, Vered Y, Babalof I, Sintes J, Petrone ME, Volpe AR, Stewart B, DeVizio W, McCool JJ, Proskin HM. The comparative anticaries efficacy of a dentifrice containing 0.3% triclosan and 2.0% copolymer in a 0.243% sodium fluoride/silica base and a dentifrice containing 0.243% sodium fluoride/silica base. A two-year coronal caries clinical trial on adults in Israel. *J Clin Dent* 2001;12:71–6.
120. Report of workshop aimed at defining guidelines for caries clinical trials: superiority and equivalence claims for anti-caries dentifrices. *J Am Dent Assoc* 1988;117:663–5.
121. Proskin HM, Kingman A, Naleway C, Wozniak WT. Comparative attributes for the description of the relative efficacy of therapeutic agents: General concepts and definitions, and application to the American Dental Association guidelines for the comparison of the clinical anti-caries efficacy of fluoride dentifrices. *J Clin Dent* 1995;6:176–84.
122. Vered Y, Zini A, Mann J, DeVizio W, Stewart B, Zhang YP, Garcia L. Comparison of a dentifrice containing 0.243% sodium fluoride, 0.3% triclosan, and 2.0% copolymer in a silica base, and a dentifrice containing 0.243% sodium fluoride in a silica base: a three-year clinical trial of root caries and dental crowns among adults. *J Clin Dent* 2009;20:62–5.
123. Katz RV. The RCI revisited after 15 years: used, reinvented, modified, debated, and natural logged. *J Public Health Dent* 1996;56:28–34.
124. Sharma NC, Galustians JH, Qaquish J, Galustians A, Rustogi KN,

Petrone ME, Chaknis P, Garcia L, Volpe AR, Proskin HM. The clinical effectiveness of a dentifrice containing triclosan and a copolymer for controlling breath odor measured organoleptically twelve hours after tooth brushing. *J Clin Dent* 1999;10:131–4.
125. Niles HP, Vaquez J, Rustogi KN, Williams M, Gaffar A, Proskin HM. The clinical effectiveness of dentifrice containing triclosan and a copolymer for providing long-term control of breath odor measured chromatographically. *J Clin Dent* 1999;10:135–8.
126. Sharma NC, Galustians HJ, Qaqish J, Galustians A, Petrone ME, Rustogi KN, Zhang YP, Chaknis P, DeVizio W, Volpe AR. The clinical efficacy of Colgate Total plus whitening toothpaste containing a special grade of silica and Colgate Total Toothpaste for controlling breath odor twelve hours after tooth brushing. A single-use clinical study. *J Clin Dent* 2002;13(Spec Iss):73–6.
127. Hu D, Zhang YP, Volpe A, DeVizio W, Giniger M. Clinical effectiveness of a triclosan/copolymer/sodium fluoride dentifrice in controlling oral malodor: A three-week clinical trial. *Oral Dis* 2005;11(Suppl 1):51–3.
128. Sharma NC, Galustians HJ, Qaqish J, Galustians A, Rustogi K, Petrone ME, Chaknis P, Garcia L, Volpe AR, Proskin HM. Clinical effectiveness of a dentifrice containing triclosan and a copolymer for controlling breath odor. *Am J Dent* 2007;20:79–82.
129. Hu D, Zhang YP, DeVizio W, Proskin HM. A clinical investigation of the efficacy of two dentifrices for controlling oral malodor and plaque microflora overnight. *J Clin Dent* 2008;19:106–10.
130. Sreenivasan PK, Haraszthy VI, Zambon JJ, DeVizio W. Efficacy of a triclosan/copolymer dentifrice and a toothbrush with tongue cleaner in the treatment of oral malodor: A monadic clinical trial. *Oral J Stomatol* 2013;3:63–69.
131. Sreenivasan P. The effects of a triclosan/copolymer dentifrice on oral bacteria including those producing hydrogen sulfide. *Eur J Oral Sci* 2003;111:233–7.
132. Sreenivasan PK, Furgang D, Zhang Y, DeVizio W, Fine DH. Antimicrobial effects of a new therapeutic liquid dentifrice formulation on oral bacteria including odorigenic species. *Clin Oral Invest* 2005;9:38–45.
133. Irwin CR, McCusker P. Prevalence of dentine hypersensitivity in a general dental population. *J Ir Dent Assoc* 1997;43:7–9.
134. Mason S, Levan A, Crawford R, Fisher S, Gaffar A. Evaluation of tartar control dentifrices in *in vitro* models of dentin sensitivity. *Clin Prev Dent* 1991;13:6–12.
135. Miller S, Gaffar A, Sullivan R, Heu R, Truong T, Stranick M. Evaluation of a new dentifrice for the treatment of sensitive teeth. *J Clin Dent* 1994;5:(Spec Iss):71–9.
136. Liu X, Barnes V, DeVizio W, Yang H, Malmstrom H, Ren Y. Effects of dentin tubule occlusion by dentifrice containing a PVM/MA bioadhesive copolymer in a silica base. *J Dent* 2011;39:293-301.
137. Wang Q, Kang Y, Barnes V, DeVizio W, Kashi A, Ren Y. Dentin tubule occlusion and erosion protection effects of dentifrice containing bioadhesive PVM/MA copolymers. *Clin Oral Investig* 2013;17:775–83.
138. Zaidel L, Patel R, Mello S, Heu R, Stranick M, Chopra S, Principe M. Anti-hypersensitivity mechanism of action for a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, 0.243% NaF and specially-designed silica. *Am J Dent* 2011;24(Spec Iss A):6A–13.
139. Chaknis P, Panagakos FS, DeVizio W, Sowinski J, Petrone D, Proskin H. Assessment of hypersensitivity reduction of a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, 0.243% NaF and specially-designed silica as compared to a dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate and zinc lactate and to a dentifrice containing 0.243% NaF on dentin hypersensitivity reduction: an 8-week study. *Am J Dent* 2011;24(Spec Iss A):14A–20.
140. Ramberg P, Lindhe J, Botticelli D, Botticelli A. The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. *J Clin Dent* 2009:20:103–7.
141. Sreenivasan PK, Vered Y, Zini A, Mann J, Kolog H, Steinberg D, Zambon JJ, Haraszthy VI, da Silva MP, DeVizio W. A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. *J Clin Periodontol* 2011;38:33–42.
142. Haraszthy VI, Zambon JJ, Screenivasan PK. Evaluation of the antimicrobial activity of dentifrices on human oral bacteria. *J Clin Dent* 2010;21(Spec Iss):96–100.
143. Haraszthy VI, Zambon JJ, Sreenivasan PK. The antimicrobial efficacy of commercial dentifrices. *Gen Dent* 2010;58:50–5.
144. Ledder RG, McBain AJ. An *in vitro* comparison of dentifrice formulations in three distinct oral microbiotas. *Arch Oral Biol* 2012;57:139–47.
145. Barnes VM, Richter R, DeVizio W. Comparison of the short-term antiplaque/antibacterial efficacy of two commercial dentifrices. *J Clin Dent* 2010;21(Spec Iss):101–4.
146. Singh S, Chaknis P, DeVizio W, Petrone M, Panagakos FS, Proskin HM. A clinical investigation of the efficacy of three commercially available dentifrices for controlling established gingivitis and supragingival plaque. *J Clin Dent* 2010;21(Spec Iss):105–10.
147. Ayad F, Stewart B, Zhang YP, Proskin HM. A comparison of the efficacy of a triclosan/ copolymer/sodium fluoride dentifrice, a stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice, and a sodium fluoride dentifrice for the control of established supragingival plaque and gingivitis: a six week clinical study. *J Clin Dent* 2010;21(Spec Iss):111–6.
148. Boneta AE, Aguilar MM, Romeu FL, Stewart B, DeVizio W, Proskin HM. Comparative investigation of the efficacy of triclosan/copolymer/sodium fluoride and stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrice for the control of established supragingival plaque and gingivitis in a six-month clinical study. *J Clin Dent* 2010;21(Spec Iss):117–23.
149. DeVizio W, Davies R. Rationale for the daily use of a dentifrice containing triclosan in the maintenance of oral health. *Compend Cont Educ Dent* 2004;25(Suppl 1):54–7.
150. Riley P, Lamont T. Triclosan/copolymer containing toothpastes for oral health. Cochrane Database Syst Rev. 2013 Dec 5;12:CD010514. doi: 10.1002/14651858.CD010514.pub2.

Supplemental Readings

a. Addy M, Jenkins S, Newcomb R. Toothpastes containing 0.3% and 0.5% triclosan. II. Effects of single brushings on salivary bacteria counts. *Am J Dent* 1989;2:215–9.
b. Barnes VM, Vandeven M, Richter R, Xu T. The modified gingival margin plaque index: a predictable clinical method. J Clin Dent 2008;19:131–3.
c. Blinkhorn A, Bartold PM, Cullinan MP, Madden TE, Marshall RI, Raphael SL, Seymour GJ. Is there a role for triclosan/copolymer toothpaste in the management of periodontal disease? *Br Dent J* 2009;207:117–25.
d. Ciancio S, Panagakos F. Superior management of plaque and gingivitis through the use of a triclosan/copolymer dentifrice. *J Clin Dent* 2010;21(Spec Iss):93–95.
e. Ciancio S. Improving our patients' oral health: the role of a triclosan/copolymer/ fluoride dentifrice. *Compend Contin Educ Dent* 2007;28:178–80.
f. Ciancio SG, Newman MG, Shafer R. Recent advances in periodontal diagnosis and treatment: Exploring new treatment alternatives. *J Am Dent Assoc* 1992;123:34–43.
g. Furuchi RP, Lindhe J, Gaffar A. A model for studying the effects of mouthrinses on *de novo* plaque formation. *J Clin Periodontol* 1992;19:509–20.
h. Garcia-Godoy F. Triclosan/copolymer/NaF dentifrice prophylaxis, reduced etching time and shear bond strength of a resin composite to enamel. *Am J Dent* 1992;5:312–4.
i. Garcia-Godoy F, O'Quinn JA, Donohue M. Effect of a triclosan/copolymer/fluoride dentifrice prophylaxis on the shear bond strength of a composite resin to enamel. *Am J Dent* 1991;4:167–9.
j. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc* 2006;137:1649–57.
k. Jenkins S, Addy M, Newcombe R. Toothpastes containing 0.3% and 0.5% triclosan. I. Effects on 4-day plaque regrowth. *Am J Dent* 1989;2:211–4.
l. Lang NP, Schätzle MA, Löe H. Gingivitis as a risk factor in periodontal disease. *J Clin Periodontal* 2009;36(Suppl 10):3–8.
m. Li Y, Lee S, Hujoel P, Su M, Zhang W, Kim J, Zhang YP, DeVizio W. Prevalence and severity of gingivitis in American Adults. *Am J Dent* 2010;23:9–13.
n. Lin Y-J, Fung KK, Kong BM, DeSalva SJ. Gingival absorption of triclosan following topical mouthrinse application. *Am J Dent* 1994;7:13–6.

o. Marsh PD. Microbiological aspects of the chemical control of plaque and gingivitis. *J Dent Res* 1992;71:1431–8.
p. Marsh PD. Dentifrices containing new agents for the control of plaque and gingivitis: Microbiological aspects. *J Clin Periodontol* 1991;18:462–7.
q. Report on the use of triclosan/copolymer dentifrices in the control of plaque and gingivitis. *Am J Dent* 1989;2(Spec Iss):183–240.
r. Report on recent advances in dentifrice and mouthrinse technology for the prevention of oral diseases. *Am J Dent* 1990;3(Spec Iss):S1–72.
s. Sreenivasan PK, DeVizio W, Prasad KV, Patil S, Chhabra KG, Rajesh G, Javali SB, Kulkarni RD. Regional differences within the dentition for plaque, gingivitis and anaerobic bacteria. *J Clin Dent* 2010;21:13–9.
t. Urquhart E, Addy M. The chemical control of plaque. *Dent Health* 1991;30:8–13.
u. Yiu CKY, Wei SHY. Clinical efficacy of dentifrices in the control of calculus, plaque and gingivitis. *Prev Dent* 1993;24:181–7.
v. Waaler SM, Rölla G, Skjörland KK, Ogaard B. Effects of oral rinsing with triclosan and sodium lauryl sulfate on dental plaque formation: A pilot study. *Scand J Dent Res* 1993;101:192–5.
w. Wade WG, Addy M. Antibacterial activity of some triclosan-containing toothpastes and their ingredients. *J Periodontol* 1992;63:280–2.
x. Wei SHY, Yiu CKY. The role of dentifrices in the control of calculus, plaque and gingivitis. *Asia-Pacific Dent News* (Oct)1990;1–4.
y. Zhang J, Xuan D, Fan W, Zhang X, Dibart S, DeVizio W, Panagakos F, Zhang YP. Severity and prevalence of plaque-induced gingivitis in the Chinese population. Compend Contin Educ Dent. 2010;31:624-9.

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