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

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Abstract

- **Introduction:** Triclosan is a broad-spectrum antibacterial agent, marketed for use in oral 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 details the results of antibacterial, anti-inflammatory, and short- and long-term plaque and gingivitis studies with a triclosan/copolymer/fluoride dentifrice. Additionally, the Supplement reviews studies on the effect of a triclosan/copolymer/fluoride dentifrice on periodontitis, calculus, caries, whitening and stain removal, oral malodor, and on the microflora.
- **Conclusion:** Clinical studies indicate that the use of a triclosan/copolymer/fluoride dentifrice (Colgate® Total® Toothpaste) may provide oral health benefits beyond those associated with "traditional" toothpaste use, in a manner that is safe and effective. Studies presented in this Supplement demonstrate that Colgate Total Toothpaste provides superior protection against plaque and gingivitis, caries, oral malodor, exhibits superior stain removal, and provides protection against the progression of periodontal disease.

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Introduction

Triclosan

Triclosan is a broad-spectrum antibacterial agent, marketed for use in oral products under the tradename Irgacare MP®, and manufactured by the Ciba-Geigy corporation.[1] The structure for 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.[1,2]

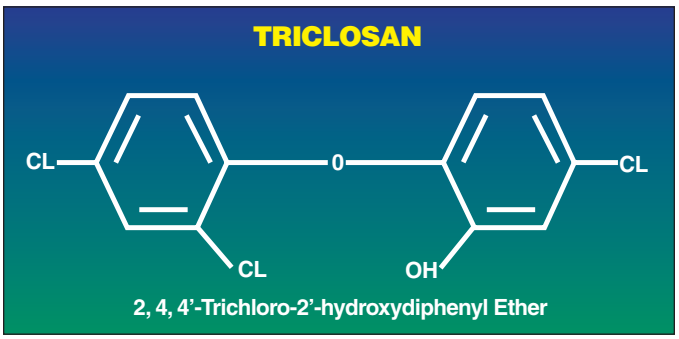


Figure 1. *Chemical structure of triclosan (2, 4, 4'-trichloro-2'-hydroxydiphenyl ether). (This illustration is provided through the courtesy of Dr. Nuran Nabi and Dr. Abdul Gaffar.)*

Triclosan is widely used as an antibacterial agent in such over-the-counter products as deodorant soap bars, liquid soaps and underarm deodorants that are sold in most countries of the world.[3] Antibacterial skin products containing triclosan are utilized in hospitals.[4]

As summarized by Lindhe,[5] triclosan is a useful antibacterial agent to be incorporated into oral products because it has a broad spectrum of activity on oral bacteria, is compatible with the ingredients in oral products, and has a long history of safe use in consumer products. After reviewing all the pharmacological and toxicological information available in 1989, DeSalva, Kong and Lin concluded that triclosan can be considered safe for use in dentifrice and mouthrinse products.[6] Since publication of that review, a number of additional studies and reviews have been authored attesting to the safety of triclosan.[7-10]

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, Mukerjee, Schmid, and Gaffar in 1989 reported the results from *in vitro* and *in vivo* studies using triclosan and the PVM/MA copolymer.[11] 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 presents a graphic representation of these results.

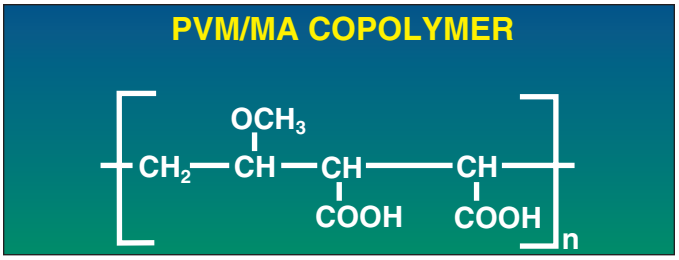
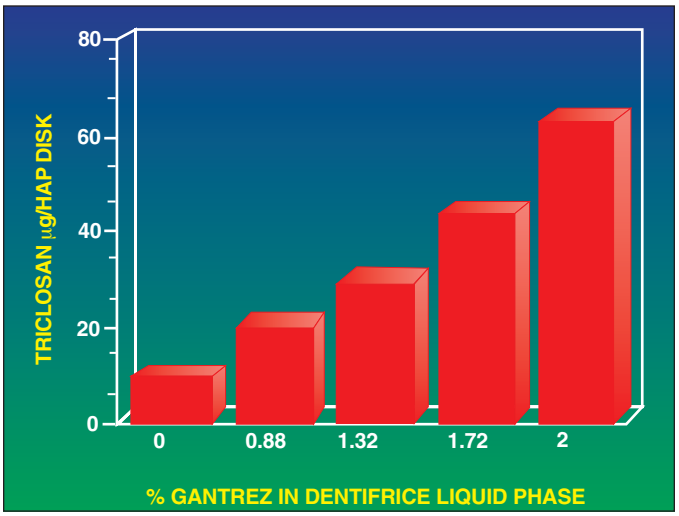


Figure 2. *Chemical structure of polyvinylmethyl ether/maleic acid (PVM/MA) copolymer. (This illustration is provided through the courtesy of Dr. Abdul Gaffar.)*



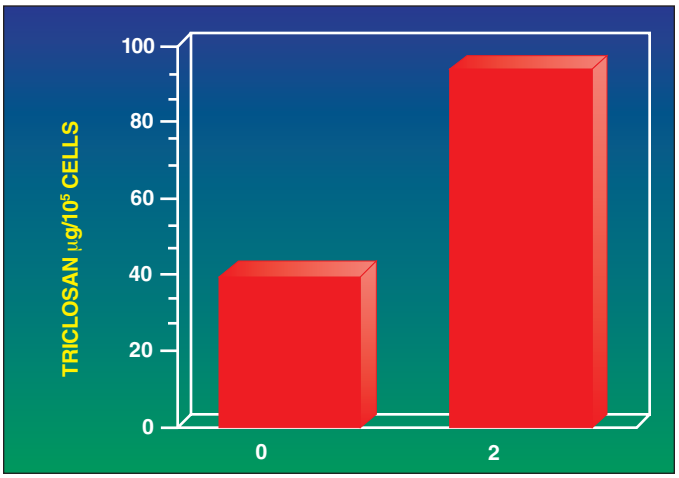


Figure 3. *Graphic representation of the beneficial effect of triclosan retention on enamel and buccal epithelial cells from triclosan and the PVM/MA copolymer. (Reprinted from Nabi, Mukerjee, Schmid and Gaffar,* Am J Dent *1989,[11] with permission.)*

Gaffar, Esposito, and Afflitto in 1990 reported that the PVM/MA copolymer, in the presence of triclosan, inhibited crystal growth in both *in vitro* and *in vivo* studies.[12] 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 products.[13]

Long-Lasting Antibacterial Activity Studies

The antibacterial activity of triclosan has been well documented. In 1990, Gaffar, Nabi, and co-workers reported on the *in vitro* antibacterial activity of triclosan on oral cavity bacteria.[14]

Figure 4 presents the minimum inhibitory concentrations (MIC) for triclosan on the various oral bacteria studied. In 1992, Gaffar, Volpe, and Lindhe presented a schematic diagram (Figure 5) illustrating how triclosan and the PVM/MA copolymer interrelate with enamel and oral soft tissues.[15] In 1989, Afflitto, Fakhry-Smith, and Gaffar 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.[16] Retention in plaque was again reported in 1994 by Gaffar, Afflitto, Nabi, Herles, Kruger, and Olsen, whose data support the conclusion that the level of triclosan retained in plaque

Microorganism		Minimum Inhibitory Concentration µg/ml
Laboratory 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. odontolyticus	1041	0.78
A. odontolyticus	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. mitior	1384	2.34
S. mitior	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, Nabi and co-workers,* Am J Dent, *1990.[14])*

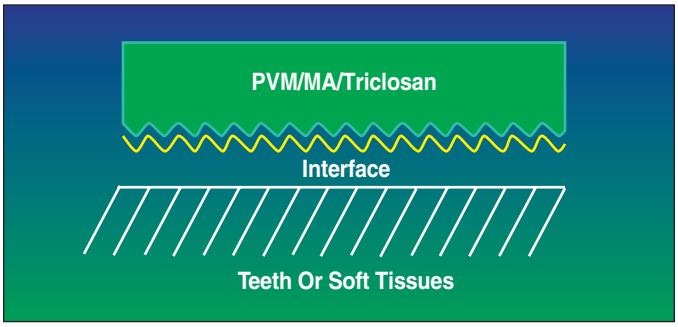


Figure 5. *Diagrammatic representation of the interrelationship between triclosan and the copolymer and the oral tissues. (Reprinted from Gaffar, Volpe and Lindhe,* Clinical and Biological Aspects of Dentifrices, *Oxford University Press, 1992,[15] with permission.)*

14 hours after brushing significantly exceeds the MIC for plaque bacteria (which ranges from 0.2 to 3 µg/ml).[17]

This 1994 report by Gaffar and co-workers[17] 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. Gaffar and co-workers[17] also provide 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 differentially visible the viable and non-viable plaque, and subsequently assessed for plaque viability.[17]

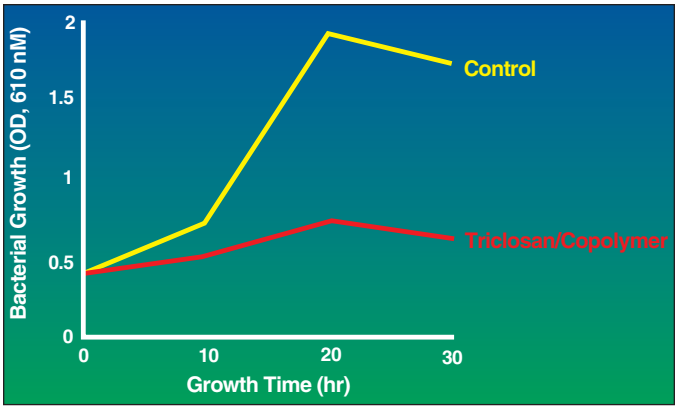


Figure 6. *Bacterial growth on treated hydroxyapatite disks. (Adapted from Gaffar, Afflitto, Nabi, Herles, Kruger and Olsen,* Int Dent J *1994,[17] with permission.)*

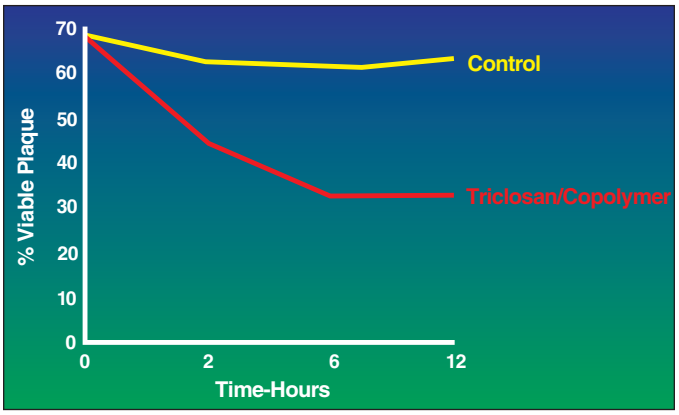


Figure 7. *Plaque viability after brushing. (Adapted from Gaffar, Afflitto, Nabi, Herles, Kruger and Olsen,* Int Dent J *1994,[17] with permission.)*

Overall Conclusion from the Long-Lasting Antibacterial Activity Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

The overall conclusion from the two long-lasting antibacterial action studies, as depicted in Figures 6 and 7, 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. Recent evidence has suggested that prolonged infection and inflammation at a local site, such as the periodontium, can have systemic implications,[19] influencing cardiovascular disease, diabetes, and respiratory ailments (Figure 8). 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 we will describe in the next section, Colgate® Total® Toothpaste (Colgate-Palmolive Company, New York, NY, USA) 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.[20]

Modeer and colleagues have conducted a number of laboratory studies to elucidate the anti-inflammatory action of triclosan.[21-25] 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 µg/ml prevented a significant increase in PGE_2.[21] In another study, triclosan was shown to inhibit TNF-α–induced PGE_2 production.[22] Recent 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.[23,26] Finally, Mustafa and colleagues, attempting to further dissect triclosan's anti-inflammatory mechanism of action, demonstrated that ^{14}C–labeled triclosan is absorbed by fibroblastic cells and translocates to the nucleus.[27] Together, these results suggest that the

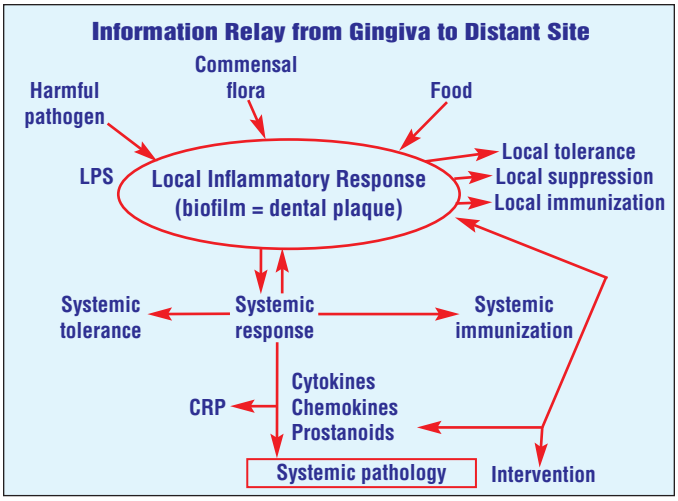


Figure 8. *This illustration shows the local bacterial products that can influence the release of cytokines, which could moderate inflammation at a distant site. It also identifies two possible sites for intervention.*

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.

Short-Term Plaque and Gingivitis Clinical Efficacy Studies With a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Table I summarizes a series of independent and double-blind short-term clinical studies[15-18] which were conducted to determine the effect of a fluoride dentifrice containing 0.3% triclosan and 2.0% of the PVM/MA copolymer on supragingival plaque and gingivitis. The first three of these 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 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice. In the fourth study, no initial prophylaxis was performed, and no placebo dentifrice was included. In all four studies, tooth brushing was performed twice daily for one minute each time.

Clerehugh and co-workers 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 use of a placebo dentifrice.[28]

Singh and co-workers 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.[29]

Palomo and co-workers 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.[30]

Lim, Petrone, Volpe, DeVizio, and co-workers 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 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).[31]

Common-Protocol Long-Term Plaque and Gingivitis Clinical Efficacy Studies With a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Table II presents the plaque and gingivitis efficacy results from thirteen 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 and 2.0% PVM/MA copolymer fluoride dentifrice to a placebo dentifrice. These plaque and gingivitis clinical efficacy studies were conducted in accordance with the American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Dental Plaque and Gingivitis,[32] 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.[33] A summary of these guidelines is provided in Figure 9.

Table I
Plaque and Gingivitis Efficacy
Triclosan/Copolymer Fluoride 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**		Gingivitis Efficacy Versus Placebo**	
						Q-H Index	P S Index	L-S Index	G S Index
28	Clerehugh and Co-Workers, 1989	England	30	1 week	Parallel with a Prophy at Start	–16%	not reported	not reported	not reported
29	Singh and Co-Workers, 1989	United States	86	6 weeks	Parallel with a Prophy at Start	–20.0%	–65.7%	not reported	not reported
30	Palomo and Co-Workers, 1989	Guatemala	97	14 weeks	Parallel with a Prophy at Start	–38.8%	–68.9%	–50.7%***	not reported
31	Lim, Petrone and Co-Workers, 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%***

† The dentifrices tested in the studies reported by Singh and Lim contained sodium fluoride in a silica base. The dentifrices tested in the study reported by Clerehugh contained 0.76% sodium monofluorophosphate in an insoluble sodium metaphosphate base. The dentifrices tested in the study reported by Palomo contained 0.76% sodium monofluorophosphate in an alumina base.

*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.

***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.

Table II
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**		Gingivitis Efficacy Versus Placebo**	
						Q-H Index	P S Index	L-S Index	G S Index
34	Garcia-Godoy and Co-Workers, 1990	Dominican Republic	108	7 months	Parallel with a Prophy at Start	–58.9%*	–97.7%	–30.1%	–87.5%
35	Cubells and Co-Workers, 1991	Spain	108	6 months	Parallel with a Prophy at Start	–24.9%*	–50.8%	–19.7%	–57.5%
36	Deasy and Co-Workers, 1991	United States	121	6 months	Parallel with a Prophy at Start	–32.3%*	–73.6%	–25.6%	–57.1%
37	Mankodi and Co-Workers, 1992	United States	294	6 months	Parallel with a Prophy at Start	–11.9%	–19.3%	–19.7%	–73.6%
38	Denepitiya and Co-Workers, 1992	United States	145	6 months	Parallel with a Prophy at Start	–18.4%	–29.2%	–31.5%	–57.1%
39	Bolden and Co-Workers, 1992	United States	306	6 months	Parallel with a Prophy at Start	–17.0%	–18.6%	–29.0%	–47.6%
40	Palomo and Co-Workers, 1994	Guatemala	98	6 months	Parallel with a Prophy at Start	–12.7%	–23.1%	–24.1%	–38.4%
41	Triratana and Co-Workers, 1993	Thailand	120	6 months	Parallel without Prophy at Start	–32.9%	–46.0%	–18.8%	–38.3%
42	Lindhe and Co-Workers, 1993	Sweden	110	6 months	Parallel without Prophy at Start	–31.2%	not reported	–26.6%	Significantly Less Bleeding Sites***
43	Deyu and Co-Workers, 1997	China	153	6 months	Parallel with a Prophy at Start	–16.1%	not reported	–24.3%	not reported
44	Allen and Co-Workers, 2002	United States	110	6 months	Parallel with a Prophy at Start	–29.9%	–59.2%	–21.4%	–69.2%
45	Mankodi and Co-Workers, 2002	Scotland	109	6 months	Parallel with a Prophy at Start	–18.7%	–60.5%	–22.2%	–85.1%
46	Triritana and Co-Workers, 2002	Thailand	124	6 months	Parallel without Prophy at Start	–34.9%	–52.1%	–25.7%	–40.3%

*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.

Common Clinical Design and Protocol

All thirteen clinical studies presented in Table II[34-46] were designed and conducted in accordance with the American Dental Association guidelines. (Three additional studies utilizing a similar protocol but different indices are summarized in Table III). Ten of the studies listed[34-40,43-45] were initiated with a complete oral prophylaxis in order to evaluate the effect of a triclosan and PVM/MA copolymer fluoride dentifrice on supragingival plaque accumulation and gingivitis. Three clinical studies listed in Table II (Triratana and co-workers 1993, Lindhe, Rosling, Socransky and Volpe 1993, and Triratana and co-workers 2002) 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.

The thirteen independent and double-blind long-term (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 and 2.0% PVM/MA copolymer dentifrice (in a 0.243% sodium fluoride/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 tooth-

American Dental Association Guidelines for the Acceptance of Chemotherapeutic Agents for the Control of Supragingival Dental Plaque and Gingivitis

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

- Two independent studies should be conducted.
- The study populations should represent typical product users.
- The test product should be used in a normal regimen and compared to a placebo.
- The study design should be either parallel or crossover.
- Each study should be at least six months in duration.
- The plaque and gingivitis scoring procedure should be conducted at baseline, after six months, and at an intermediate period of time.
- Microbiological profile should demonstrate that pathogenic or opportunistic microorganisms do not develop over the course of the study.

1994 Revision

To demonstrate efficacy, the following criteria must be achieved in two studies:

1) Statistically significant plaque reductions.
2) The *average* reduction in gingivitis across the studies must be no less than 20% and statistically significant.

Source: American Dental Association Guidelines,[32] *Imrey* et al.[33]

Figure 9. *American Dental Association guidelines for the acceptance of chemotherapeutic agents for the control of supragingival dental plaque and gingivitis (incorporating the 1994 revision).*

brush 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.[47,48] 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 = Plaque 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),[47] *Turesky,* et al. *(1970)*[48]

Each tooth is scored in six areas: 1) mesio-facial, 2) mid-facial, 3) disto-facial, 4) mesio-lingual, 5) mid-lingual, 6) disto-lingual. The maximum score per tooth therefore 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 and co-workers in 1989.[30] 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 sur-

Table III
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** S-L Index	Gingivitis Efficacy Versus Placebo** Bleeding Index
51	Svatun and Co-Workers, 1993	Norway	94	7 months	Parallel with a Prophy at Start	–19.0%***	–25.5%***
52	Kanchanakamol and Co-Workers, 1995	Thailand	124	6 months	Parallel with a Prophy at Start	–7.2%***	–25.0%***
53	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).

face 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 10.

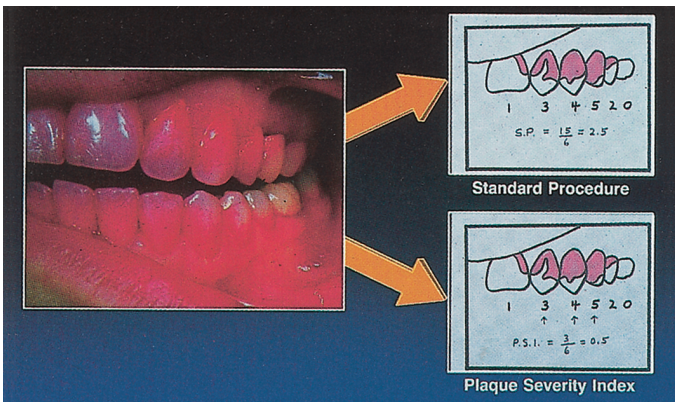


Figure 10. *Diagrammatic illustration of the difference in plaque assessment between the standard Quigley-Hein Plaque Index and the Plaque Severity Index. Photo illustrates one measurement per tooth. (This illustration was provided through the courtesy of Dr. Anthony R. Volpe.)*

Gingivitis Scoring Methodology

The clinical scoring procedure used to assess gingivitis is the Löe-Silness Gingival Scoring Index[49] as modified by Talbott, Mandel, and Chilton.[50] The modified Löe-Silness Gingival Scoring Index scores gingivitis on a numerical scale according to the criteria enumerated in the box below.

Gingivitis Scoring Methodology

0 = Absence of inflammation.
1 = Mild inflammation: 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 tendency to spontaneous bleeding and ulceration.

Source: Löe & Silness (1963),[49] Talbott, Mandel & Chilton (1977).[50]

Each tooth is scored in six areas: 1) mesio-facial, 2) mid-facial, 3) disto-facial, 4) mesio-lingual, 5) mid-lingual, 6) disto-lingual. The maximum score per tooth, therefore, 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 the individual scores (six per tooth) and dividing this sum by the number of measurements (number of teeth scored multiplied by six).

A Gingivitis Severity Index was also calculated for all subjects, as described by Palomo and co-workers in 1989.[30] 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 11.

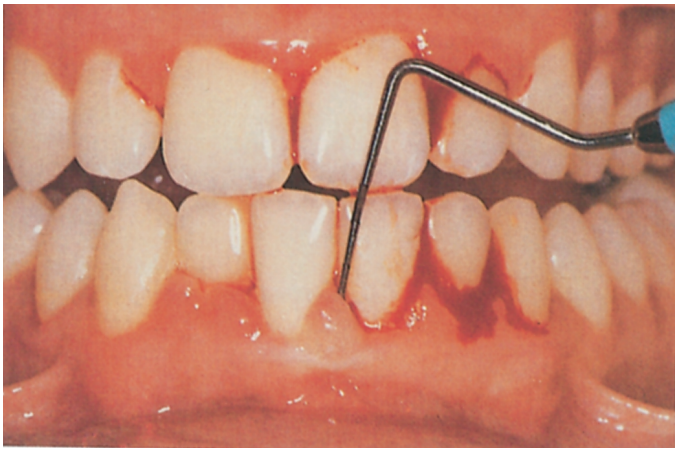


Figure 11. *Photograph illustrating the gingival bleeding associated with the Gingivitis Severity Index. (Reprinted from* Color Atlas of Dental Medicine, *KH Rateitschak, Ed., Thieme Medical Publishers, New York, p. 43, 1989, with permission.)*

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 10.

Plaque Efficacy Results from Long-Term Clinical Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Quigley-Hein Plaque Index Results. As indicated in Table II, all thirteen long-term clinical studies provided statistically significant differences ($p < 0.01$) in supragingival plaque accumulation in favor of the 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.243% sodium fluoride/silica base) as compared to a placebo dentifrice (0.243% sodium fluoride in a silica base). The Quigley-Hein Plaque Index efficacy results from the use of the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice ranged from 12% to 59%, with an average efficacy score of 26%.

Plaque Severity Index Results. Table II also presents Plaque Severity Index scores for the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice that were reported in eleven of the thirteen studies. The Plaque Severity Index efficacy results ranged from 19% to 98%, with an average efficacy score of 48%.

Gingivitis Efficacy Results from the Long-Term Clinical Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Löe-Silness Gingival Index Results. As is indicated in Table II, all thirteen long-term clinical studies provided statistically significant differences ($p < 0.01$) in gingivitis in favor of the 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.243% sodium fluoride/silica base) as compared to a placebo dentifrice (0.243% sodium fluoride in a silica base). The Löe-Silness Gingivitis Index efficacy results from the use of the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice ranged from 19% to 32%, with an average efficacy score of 25%.

Gingivitis Severity Index Results. Table II also presents gingivitis efficacy results for the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice with the Gingivitis Severity Index. This index was reported in eleven of the studies. As indicated in Table II, the Gingivitis Severity Index efficacy results from the use of the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice ranged from 38% to 88%, with an average efficacy score of 59%.

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

The overall conclusion from the thirteen independent and double-blind long-term plaque and gingivitis clinical efficacy studies shown in Table II, which were conducted in accordance with the 1986 and 1994 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 ($p < 0.01$) and clinically beneficial effect on both supragingival plaque and gingivitis, as compared to the similar use of a placebo dentifrice.

Additional Long-Term Plaque and Gingivitis Clinical Efficacy Studies With a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Table III 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 and 2.0% PVM/MA copolymer fluoride dentifrice to a placebo dentifrice.[51-53] As with the studies presented in Table II, these plaque and gingivitis clinical efficacy studies were conducted in accordance with the American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Dental Plaque and Gingivitis,[32] 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.[33] What principally differentiates the three studies in Table III from those in Table II is the choice of index employed, as indicated by the footnotes below each Table.

Short and Long-Term Periodontitis Clinical Efficacy Studies With a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

In addition to the anti-gingivitis effects of the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice, a number of studies have been conducted to demonstrate the effects of the dentifrice on periodontitis. These studies are summarized in Table IV. A total of seven clinical studies have been conducted,[54-60] and all but one[56] were 24 months or greater in duration.

The one short-term study conducted was by Furuichi and co-workers.[56] This study lasted two weeks and was designed to evaluate the effects of a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice on healing following scaling and root planing. Subjects that used the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice, followed by application of a 0.3% triclosan and 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 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.

The other six studies were long-term in nature, ranging from 24 months to 36 months. Five of these studies[54,57-60] evaluated the effects of a 0.3% triclosan and 2.0% PVM/MA copolymer

Table IV
Periodontitis 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
54	Rosling and Co-Workers, 1997	Sweden	60	36 months	Evaluate the effects of a triclosan/copolymer dentifrice in the progression of periodontal disease
55	Rosling and Co-Workers, 1997	Sweden	40	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the effect of subgingival microbiota in periodontitis-susceptible patients
56	Furuichi and Co-Workers, 1997	Sweden	16	2 weeks	Evaluate the short-term effects of a triclosan/copolymer dentifrice on healing after subgingival scaling
57	Ellwood and Co-Workers, 1998	UK	480	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents
58	Furuichi and Co-Workers, 1999	Sweden	60	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on healing after non-surgical periodontal therapy of recurrent periodontitis
59	Cullinan and Co-Workers, 1997	Australia	504	36 months	Evaluate the effects of a triclosan/copolymer dentifrice on the progression of periodontal disease in adults
60	Kerdvongbundit and Co-Workers, 2003	Thailand	60	24 months	Evaluate the effects of a triclosan/copolymer dentifrice on healing after non-surgical periodontal therapy in smokers

fluoride dentifrice on the progression of periodontal disease following scaling and root planing. Two studies, by Ellwood and co-workers and Kerdvongbundit and co-workers, were conducted in specialized populations, specifically adolescents[57] and smokers.[60] The results from all five studies indicated that the use of a 0.3% triclosan and 2.0% PVM/MA copolymer 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.

Finally, a study by Rosling and co-workers evaluated the effects of a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice on the subgingival microbiota in a periodontitis-susceptible population.[55] 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 and 2.0% PVM/MA copolymer 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 and 2.0% PVM/MA copolymer fluoride dentifrice had both a quantitative and qualitative reduction in subgingival microbiota, and recurrent periodontitis was almost completely eliminated.

Overall Conclusion from the Seven Periodontitis Efficacy Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

The overall conclusion from the seven independent and double-blind periodontitis clinical efficacy studies shown in Table IV, 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 ($p < 0.01$) 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.

Effect of a Triclosan and PVM/MA Copolymer Fluoride Dentifrice on Oral Microflora

A further requirement of the 1986 American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Dental Plaque and Gingivitis pertains to microbiological monitoring.[32] Four of the long-term plaque and gingivitis clinical efficacy studies listed in Table II included microbiological monitoring of the oral microflora.[34,37-39] A summary of these studies is provided in Table V.

Zambon and co-workers in 1990[61] 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.[34] These investigators reported that "the use of a dentifrice containing 0.3% triclosan and 2.0% 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 and co-workers in 1992[62] reported the microbiological monitoring results from a continuation of the Garcia-Godoy, *et al.*[34] 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 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 and co-workers in 1993[63] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy study conducted by Mankodi and co-workers.[37] 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 and co-workers in 1995[64] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy

Table V
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
61	Zambon and Co-Workers, 1990	Dominican Republic	81	7 months	NO	NO	NO
62	Bonta and Co-Workers, 1992	Dominican Republic	74	12 months	NO	NO	NO
63	Walker and Co-Workers, 1993	United States	144	6 months	NO	NO	NO
64	Zambon and Co-Workers, 1995	United States	144	6 months	NO	NO	NO
65	Fine and Co-Workers, 1996	United States	66	6 months	NO	NO	NO

study conducted by Bolden and co-workers.[39] 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 and co-workers in 1996[65] reported the microbiological monitoring results from the plaque and gingivitis clinical efficacy study conducted by Denepitiya and co-workers.[38] These investigators reported 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."

Overall Conclusion Concerning the Effect of a Triclosan and PVM/MA Copolymer Dentifrice on the Oral Microflora

The overall conclusion from the microbiological monitoring associated with five independent and double-blind long-term plaque and gingivitis clinical studies is that the long-term use (up to one year) of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base does not cause the development of either pathogenic, opportunistic, or resistant oral microorganisms.

Long-Term Calculus Clinical Efficacy Studies With a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Table VI presents the calculus efficacy results from four independent and double-blind long-term (three months or greater)[66-69] and two 2-month clinical studies[70,71] which compared a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice to a placebo dentifrice. These calculus clinical efficacy studies were conducted in accordance with the Volpe-Manhold clinical design and calculus scoring methodology.[72-76] 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 12.

Volpe-Manhold Calculus Clinical Study Design

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

- Subjects with a history of supragingival calculus formation were identified.
- These 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 copolymer 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),*[72] *Manhold* et al. *(1965),*[73] *Volpe* et al. *(1967),*[74] *Volpe* et al. *(1969)*[75]

Table VI
Calculus 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	Calculus Efficacy Versus Placebo** Volpe-Manhold Total Scores
66	Schiff and Co-Workers, 1990	United States	147	3 months	Parallel with a Prophy at Start	–23.1%
67	Lobene and Co-Workers, 1991	United States	79 70	3 months 6 months	Parallel with a Prophy at Start	–26.3% –36.2%
68	Volpe and Co-Workers, 1992	United States	92	3 months	Parallel with a Prophy at Start	–35.5%
69	Bánóczy and Co-Workers, 1995	Hungary	73	3 months	Parallel with a Prophy at Start	–54.7%
70	Allen and Co-Workers, 2002	United States	100	2 months	Parallel with a Prophy at Start	–24.8%
71	Sowinski and Co-Workers, 2002	United States	63	2 months	Parallel without 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/polymer dentifrice were calculated relative to the placebo dentifrice and were statistically significant at the 0.01 level of significance.
***Calculus efficacy results pertain to data obtained at the final clinical examination. All percentages relating to calculus efficacy of the triclosan/polymer dentifrice were calculated relative to the placebo dentifrice and were statistically significant at the 0.05 level of significance.

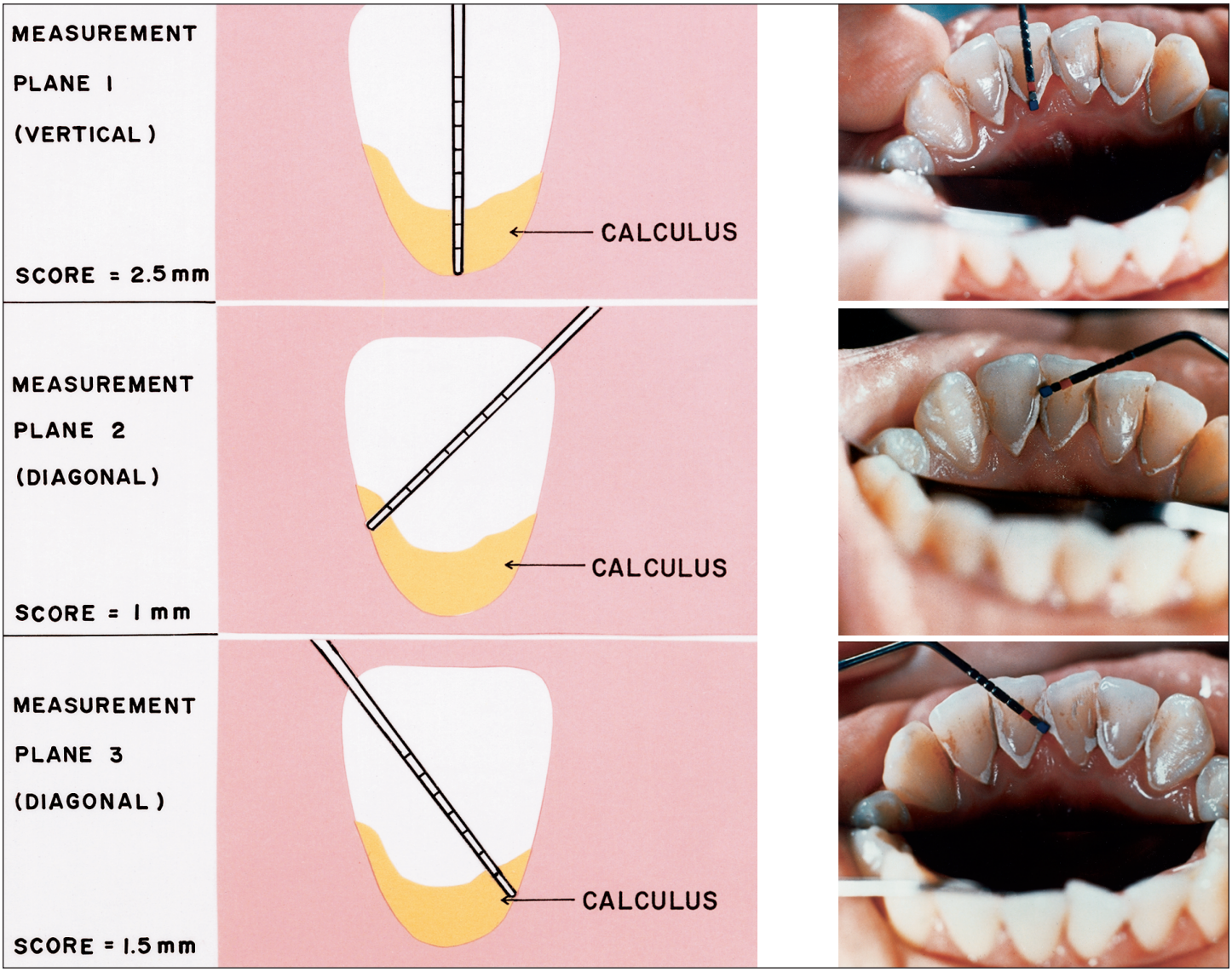


Figure 12. *Schematic and corresponding photographic illustration of the Volpe-Manhold calculus assessment procedure. Measurement plane 1 (vertical) is for gingival measurements. Measurement plane 2 (diagonal) is for distal measurements. Measurement plane 3 (diagonal) is for mesial measurements. The 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.)*

Calculus Efficacy Results from the Long-Term Clinical Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

As indicated in Table VI, all six clinical studies provided statistically significant differences ($p < 0.01$) in supragingival calculus in favor of the 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice (in a 0.243% sodium fluoride/silica base), as compared to a placebo dentifrice (0.243% sodium fluoride in a silica base). The Volpe-Manhold Calculus Index efficacy results from the use of the 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice ranged from 23% to 55%, with an average efficacy score of 40%. The results of these studies, conducted according to an American Dental Association-approved protocol, support the conclusion that a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice is effective for controlling the accumulation of supragingival calculus, and provides a greater level of calculus-inhibiting benefit than a negative control dentifrice.

Overall Conclusion from the Six Long-Term Calculus Clinical Efficacy Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

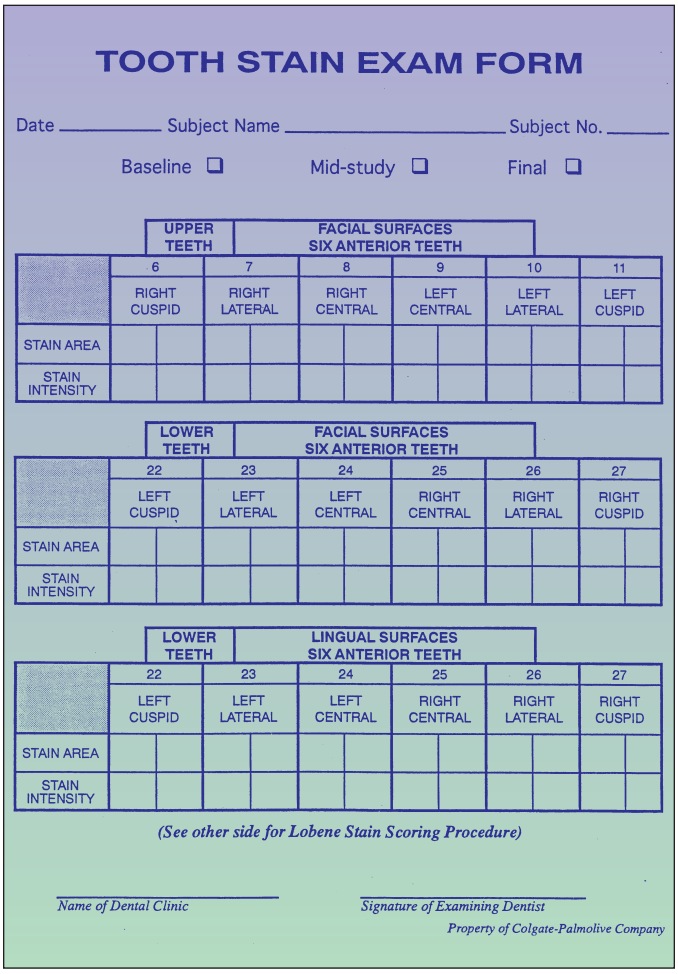
The overall conclusion from the six independent and double-blind long-term calculus clinical efficacy studies shown in Table VI, which employed the Volpe-Manhold study design and calculus scoring methodology, is that the use of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base provides a statistically significant ($p < 0.01$) and clinically beneficial effect on supragingival calculus, as compared to the similar use of a placebo dentifrice.

Effect of a Triclosan and PVM/MA Copolymer Fluoride Dentifrice on Tooth Whitening and Stain Removal

Tooth whitening and stain removal have become of critical importance to patients. The three components of an 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 which holds the abrasive component together while in the tube and in the mouth; and 3) the abrasive component. Five clinical studies (Table VII) have been conducted using a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice supplemented with the addition of high cleaning silica (Colgate® Total® Plus Whitening Toothpaste, Colgate-Palmolive Company, New York, NY, USA) relative to Colgate Total Toothpaste. Three studies[77,78,80] were conducted over a 6-week period, while the remaining two studies[79,81] were conducted up to six months. A total of 508 subjects participated in these studies. All studies were of a parallel design, and no prophy was performed at the start of the studies.

Assessment of tooth whitening/stain removal was performed utilizing the Lobene Stain Index.[77] 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 13) for the facial aspect of teeth #s 6–11, and the facial

Index	Stain Intensity	Index	Stain Area
0	No stain	0	No stain detected
1	Light stain-yellow/tan	1	Stain up to one-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


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 13. *Scoring sheet used in this study for the recording of the Lobene Stain Index.*

Table VII
Whitening 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	Whitening Effect Versus Placebo**	
						Stain Intensity	Stain Area
77	Sielski and Co-Workers, 2002	United States	97	6 weeks	Parallel Without a Prophy at Start	–49.3%	–43.9%
78	Ayad and Co-Workers, 2002	Canata	93	6 weeks	Parallel Without a Prophy at Start	–49.0%	–50.4%
79	Singh and Co-Workers, 2002	United States	86	6 months	Parallel Without a Prophy at Start	–45.6%	–44.3%
80	Nathoo and Co-Workers, 2002	United States	123	6 weeks	Parallel Without a Prophy at Start	–49.3%	–50.0%
81	Mankodi and Co-Workers, 2002	Scotland	109	6 months	Parallel Without a Prophy at Start	–45.3%	–46.3%***

*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.

***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. Stain Intensity refers to the Lobene Stain Intensity Index; Stain Area Index refers to the Lobene Stain Area Index.

and lingual aspects of teeth #s 22–27. An average tooth stain area score and intensity score are calculated from this data.

All of the studies reported that at the end of the study period, subjects who used Colgate Total Plus Whitening Toothpaste exhibited statistically significant lower levels of extrinsic stain area and stain intensity. The stain intensity levels ranged from 45% to 49% lower, and the stain area ranged from 44% to 50% lower versus Colgate Total Toothpaste. The results of these studies confirm that the addition of a high cleaning silica to Colgate Total Toothpaste is effective in removing extrinsic tooth stain.

Overall Conclusion Concerning the Effect of a Triclosan and PVM/MA Copolymer Dentifrice on Whitening and Stain Removal

The overall conclusion from the five independent and double-blind whitening and stain removal efficacy studies shown in Table VII, which employed the Lobene Stain Area and Stain Intensity 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 ($p < 0.01$) and clinically beneficial whitening and stain removal effect, as compared to the similar use of a placebo dentifrice.

Long-Term Caries Clinical Studies of a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

Caries clinical studies were conducted in order to determine whether the addition of 0.3% triclosan and 2.0% PVM/MA copolymer would impact on the anti-caries efficacy of fluoride-containing dentifrices. Results of an earlier *in situ* study reported by Mellberg and co-workers[82] had indicated that a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% NaF/silica base was highly effective in preventing demineralization and enhancing remineralization, as compared to a non-fluoride placebo dentifrice and to a positive control NaF/silica dentifrice.

Results of a clinical study reported by Kertesz and co-workers concerning the accumulation of fluoride in dental plaque, had 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.[83]

The caries efficacy results from three independent, double-blind, long-term (30 months or longer) clinical studies[84-86] and one double-blind study of 24 months duration,[87] which compared a 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice in a sodium fluoride/silica base to a comparable, clinically proven, sodium fluoride/silica positive control dentifrice, are shown in Table VIII. All of these studies were conducted in accordance with the American Dental Association 1988 Guidelines for the comparison of the clinical anti-caries efficacy of fluoride dentifrices.[88] The recommended design characteristics for such studies are presented in Figure 14, 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 anti-caries efficacy of a fluoride dentifrice[89] are presented in Figure 15.

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[88]

Figure 14. *Study design criteria for the American Dental Association guidelines for caries clinical trials of fluoride dentifrices.*

Table VIII
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
84	Hawley and Co-Workers, 1995	England	3,462	30 months	Parallel	4.62	2.81	4.57	2.76
85	Feller and Co-Workers, 1996	United States	1,542	36 months	Parallel	2.16	0.68	2.07	0.63
86	Mann and Co-Workers, 1996	Israel	1,296	36 months	Parallel	5.23	1.39	5.21	1.30
87	Mann and Co-Workers, 2001	Israel	3,392	24 months	Parallel	–16.6% caries treatment vs. positive control			

* Refers to the number of subjects in both the triclosan/copolymer dentifrice group and the placebo dentifrice group who completed the 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 anticaries efficacy which was "at least as good as" that provided by the positive control, clinically proven sodium fluoride/silica dentifrice.

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,[88] Proskin, Kingman, Naleway and Wozniak (1995)[89]

Figure 15. *American Dental Association guidelines for caries clinical trials of fluoride dentifrices to support a conclusion of clinical anticaries efficacy.*

The study reported by Hawley and co-workers in 1995 was conducted in England over a 30-month period of time, and involved 3,462 school children who completed the entire duration of the study.[84] This clinical study compared the anti-caries efficacy of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base to a clinically proven, positive control 0.243% sodium fluoride/silica dentifrice. 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 and 2.0% PVM/MA copolymer dentifrice in a 0.243% sodium fluoride/silica base provided increments of 4.57 for DFS and 2.76 for DFT, while the corresponding caries increments for the positive control 0.243% sodium fluoride/silica dentifrice were 4.62 for DFS and 2.81 for DFT.

The clinical caries study reported by Feller and co-workers in 1996 was conducted in the United States over a 36-month period of time and involved 1,542 male and female adult subjects who completed the 36 months of the study.[85] This clinical study compared the anti-caries efficacy of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.243% sodium fluoride/silica base to a clinically proven, positive control 0.243% sodium fluoride/silica dentifrice. A comparison of the 36-month DFS and DFT caries increments indicated that the use of the 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice in a 0.243% sodium fluoride/silica base provided increments of 2.07 for DFS and 0.63 for DFT, while the corresponding caries increments for the positive control 0.243% sodium fluoride/silica dentifrice were 2.16 for DFS and 0.68 for DFT.

The clinical caries study reported by Mann and co-workers in 1996 was conducted in Israel over a 36-month period of time and involved 1,296 male and female adult subjects who completed the 36 months of the study.[86] This clinical study compared the anti-caries efficacy of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.331% sodium fluoride/silica base to a clinically proven, positive control 0.331% sodium fluoride/silica dentifrice. A comparison of the 36-month DFS and DFT caries increments indicated that the use of the 0.3% triclosan and 2.0% PVM/MA copolymer dentifrice in a 0.331% sodium fluoride/silica base provided increments of 5.21 for DFS and 1.30 for DFT, while the corresponding caries increments for the positive control 0.331% sodium fluoride/silica dentifrice were 5.23 for DFS and 1.39 for DFT.

Mann and co-workers also conducted a 24-month study in Israel where the anti-caries efficacy of a dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.331% sodium fluoride/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.[87] A total of 3,392 subjects completed the 24-month study. At both the one-year and two-year intervals, the dentifrice containing 0.3% triclosan and 2.0% PVM/MA copolymer in a 0.331% sodium fluoride/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/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 (triclosan/copolymer fluoride dentifrice over a positive control) was statistically constructed in accordance with the American Dental Association 1988 Guidelines.[88] For each study, the resultant confidence intervals for both DFS and DFT consisted entirely of values which did not exceed 110%. Thus, all four clinical caries studies support the conclusion that the anti-caries efficacy provided by a 0.3% triclosan/2.0% PVM/MA copolymer sodium fluoride/silica dentifrice is "at least as good as" that provided by the positive control sodium fluoride/silica dentifrice.[89]

Overall Conclusion From the Four Long-Term Caries Clinical Efficacy Studies with a Triclosan and PVM/MA Copolymer Dentifrice

The overall conclusion from the four independent and double-blind long-term (30- to 36-month) caries clinical studies shown in Table VIII, 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 anti-caries 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.

Effect of a Triclosan and PVM/MA Copolymer Fluoride Dentifrice on Oral Malodor

Oral malodor studies were conducted in order to assess the effectiveness of a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice, Colgate Total Toothpaste, for controlling breath odor 12 hours after brushing. A total of four studies were conducted and a summary of these studies is presented in Table IX. Three of the studies[90,92,93] were conducted using a nine-point Hedonic Scale as the principal assessment method. Two of the studies[90,93] compared Colgate Total Toothpaste to a placebo, while the third[92] compared Colgate Total Toothpaste with Colgate Total Toothpaste Plus Whitening. 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 Unpleasant
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 in the Colgate Total Toothpaste group;
2. The mean twelve-hour breath odor score for subjects in the Colgate Total Toothpaste 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 Colgate Total Toothpaste group and subjects in the placebo group must be present after 12 hours.

These three studies demonstrated a range of 12-hour breath odor scores for Colgate Total Toothpaste and Colgate Total Toothpaste Plus Whitening from 3.42 to 4.89, 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.

A study by Niles and co-workers[91] utilized chromatography to measure the levels of volatile sulfur compound (VSCs) in mouth air. A total of 19 subjects participated in this double-blind, two-treatment, two-period cross-over study. Subjects brushed with a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice, Colgate Total Toothpaste, and then had VSCs measured using a 565 Tracor gas chromatograph equipped with a flame photometric detector. At seven hours following brushing, the subjects who used Colgate Total Toothpaste had a 5.62 ng/ml VSCs versus 7.10 ng/ml VSCs for placebo dentifrice. Overnight scores for subjects who used Colgate Total Toothpaste were 9.63 ng/ml VSCs versus 12.64 ng/ml VSCs for placebo dentifrice. This study demonstrated that Colgate Total Toothpaste 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 three studies.

It is also important to note that laboratory studies by Sreenivasan and co-workers provide additional data in support Colgate Total Toothpaste's malodor effects.[94,95] In the first study, a double-blind crossover design, they used either a 0.3% triclosan and 2.0% PVM/MA copolymer fluoride dentifrice, or a fluoride

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

Reference No.	Investigators	Location	Number of Subjects*	Duration	Assessment Method	Clinical Design
90	Sharma and Co-Workers, 1999	Canada	63	12 hours	Nine-point Hedonic Scale	The mean 12-hour breath odor score or 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
91	Niles and Co-Workers, 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
92	Sharma and Co-Workers, 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.
93	Hu and Co-Workers, 2003	China	81	12 hours	Nine- Point Hedonic scale	The mean 12 hour breath odor score for the Colgage 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

* 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 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.

dentifrice that did not contain triclosan/copolymer. Following seven days of 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 and 2.0% PVM/MA copolymer fluoride dentifrice decreased both the overall and VSC-producing bacteria versus the fluoride-containing dentifrice. In the second study, a liquid variant of Colgate Total Toothpaste demonstrated significant antimicrobial effects against 13 strains of oral bacteria, some of which have been implicated in bad breath, versus 2 placebo dentifrices. When taken together with the previous clinical data, it is clear that Colgate Total Toothpaste is effective at controlling oral malodor.

Overall Conclusion from the Four Malodor Efficacy Studies with a Triclosan and PVM/MA Copolymer Fluoride Dentifrice

The overall conclusion from the four independent and double-blind malodor clinical efficacy studies shown in Table IX, 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 ($p < 0.01$) 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.

Summary

Clinical studies clearly indicate that the use of Colgate Total Toothpaste may provide oral health benefits beyond those associated with "traditional" toothpaste use, in a manner that is safe and effective.[96] Studies summarized in this paper (Table X) have demonstrated that Colgate Total Toothpaste provides protection against plaque and gingivitis, caries, and oral malodor, exhibits stain removal, and provides protection against the progression of periodontal disease. Dental healthcare team members can confidently recommend Colgate Total Toothpaste to their patients for use as part of their normal oral hygiene regimen.

OVERALL SUMMARY AND CONCLUSIONS

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
Plaque and Gingivitis	6 months	13	1,906	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in supragingival plaque and gingivitis.
Periodontitis	2 weeks–36 months	7	1,220	Use of a fluoride dentifrice containing triclosan and a copolymer promotes healing following non-surgical periodontal therapy and reduces the progression and recurrence of periodontitis.
Microbiology	6–12 months	5	509	Use of a fluoride dentifrice containing triclosan and a copolymer does not cause the development of either pathogenic, opportunistic, or resistant microorganisms.
Calculus	2–6 months	6	624	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in supragingival calculus.
Caries	24–36 months	4	9,692	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in dental caries.
Malodor	12 hours	4	246	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in oral malodor.
Tooth Whitening/ Stain Removal	6 weeks–6 months	5	508	Use of a fluoride dentifrice containing triclosan and a copolymer provides a clinically beneficial reduction in extrinsic tooth stain.

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