

antiflatulents, and as an additive to certain foods without any report of harmful effects indicates that this combination is safe in the dosages and formulations in current use. The estimated daily intake varies from 0.2 g or less for sprays, gels, dentifrices, rinses, or dental floss to a high of 0.4 g per breath mint or candy (Ref. 451).

ii. *Effectiveness.*

1. *Mechanisms of action.* This combination acts by reducing the surface energy of the tooth (Ref. 452). Glantz (Ref. 453) showed a rapid increase in plaque formation with increasing surface energy in an in vitro assay. By reducing the surface energy with various surfactants, the rate of dental plaque build up can be theoretically reduced, particularly in the initial stages of dental plaque formation.

2. *Results from human clinical trials.* In general, most of the human studies have shown a marginal reduction in plaque formation in the test groups, using assorted formulations, as compared to the placebo or control group. In those studies that monitored gingivitis, no detectable difference in gingivitis was observed between the test and control groups.

TABLE 18.—TYPICAL PLAQUE SCORES FROM REPRESENTATIVE STUDIES MEASURING CHANGES FROM A BASELINE WITH OR WITHOUT AN INITIAL PROPHYLAXIS (REF. 454)

Study	Groups(n)	Baseline	End	Mean Difference
Study 1986–01	Test(10)	1.83	2.04	0.21
(OTC vol. 210259)	Control(10)	1.78	2.10	0.31
Study 1986–02	Test(13)	0	1.62	T vs C <sup>1</sup>
(OTC vol. 210259)	Control(13)	0	1.78	0.16
Study WHOIT–1990	Test(32)	0	2.06–2.16	T vs C
(OTC vol. 210259)	Control(32)	0	2.30	0.14–0.24
Study WHD–001	Test(30)	2.75	2.73	0.02
(OTC vol. 210259)	Control(30)	2.62	2.69	0.06
Study 47–01	Test(30)	0	1.87	T vs C
(OTC vol. 210260)	Control(30)	0	2.11	0.24
(Gingival Index score)	Test(30)	0	1.47	T vs C
	Control(30)	0	1.56	0.09

<sup>1</sup>T vs C means Test versus Control.

The protocols differed significantly from one another, as did the formulations of the test products. Nevertheless, it was clear that the differential effect on plaque scores between test and controls, while statistically significant, was not clinically relevant. Nor was it likely that the reduction in plaque scores is responsible for any potential cosmetic benefits that might be claimed. Therefore, it is misleading to claim that this combination has a plaque inhibitory effect. Such a claim might suggest a beneficial therapeutic or at least a cosmetic effect. While the plaque claim may be technically correct, the marginal nature of the effect is unlikely to have any clinically significant benefit, either therapeutic or cosmetic.

g. *Stannous pyrophosphate and zinc citrate.* The Subcommittee concludes that this combination of ingredients is safe, but there is insufficient evidence of its effectiveness as an OTC antigingivitis/antiplaque agent. Stannous pyrophosphate has the chemical formula  $\text{Sn}_2\text{P}_2\text{O}_7$  and is a free

flowing, odorless white to offwhite powder (Ref. 455). The commercial form of stannous pyrophosphate is anhydrous stannous pyrophosphate. This ingredient has been used in a dentifrice based on prior demonstrated antibacterial effects, which have been ascribed to the soluble stannous ion.

Because of reported antiplaque and anticalculus effectiveness, zinc citrate was combined in a dentifrice with stannous pyrophosphate (see discussion of zinc citrate chemistry in section III.C of this document).

i. *Safety.* Based on animal studies and human use, the two ingredients used in the combination do not appear to present a risk in terms of acute toxicity, chronic toxicity, reproduction toxicity, genotoxicity, carcinogenicity, phototoxic sensitization, or oral irritation. Oral ecology studies were done to ensure that long-term use of antimicrobial agents does not result in a significant change in the balance of the normal flora. In a 21-day experimental gingivitis study by Watson, Jones, and Richie (Ref. 456) and

a 6-month clinical trial by Jones et al. (Ref. 457), following use of a dentifrice containing stannous pyrophosphate (1 percent) and zinc citrate (0.5 percent), there were no significant changes in plaque flora, no increase in opportunistic organisms in saliva, and no development of resistance.

ii. *Effectiveness.* Data on the clinical effectiveness of a fluoride toothpaste containing stannous pyrophosphate (1 percent) and zinc citrate (0.5 percent) included four studies: (1) An 18-hour plaque growth inhibition test, (2) a 21-day experimental gingivitis trial, (3) a 12-week motivational brushing trial, and (4) a 6-month normal use clinical trial.

The plaque growth inhibition studies used an 18-hour protocol described by Harrap (Ref. 458) to test the effect of the combination dentifrice on plaque growth in vivo. Lloyd (Ref. 459) reported that the formulation reduced plaque significantly compared to a placebo toothpaste, showing the antimicrobial activity of the two