

There was no significant difference in the mean plaque index between any of the groups. The gingival index declined in all groups, with no differences detected between groups. No differences were observed among any groups at any time.

Based on the analyses of effectiveness on a site and subject basis compared to other oral health care practices and on odds-ratio calculations conducted on the submitted data, the Subcommittee concludes that, although available clinical data do not show reproducible long-term effects in reducing dental plaque mass, stannous fluoride is safe and effective in a dentifrice at an appropriately formulated concentration of 0.454 percent as an OTC antigingivitis agent.

2. Category I Combinations of Active Ingredients (See General Combination Policy in section II.E of this document)

Eucalyptol, menthol, methyl salicylate, and thymol. The Subcommittee concludes that a combination of essential oils consisting of eucalyptol (0.092 percent), menthol (0.042 percent), methyl salicylate (0.060 percent), and thymol (0.064 percent) in a hydroalcoholic vehicle containing 21.6 to 26.9 percent alcohol in a mouthrinse is safe and effective as an OTC antigingivitis/antiplaque agent.

a. *Safety.* Eucalyptol is a volatile oil prepared by steam distillation of the fresh leaves of *Eucalyptus globulus*. Eucalyptol is colorless, or a pale yellow volatile liquid with a characteristic aromatic, somewhat camphoraceous odor, and a spicy and cooling taste. Eucalyptol is also known as cineol, cineolcayeptol, and cajuptol. It is insoluble in water, but it is miscible with alcohol, chloroform, and ether.

The Dental Panel concluded that eucalyptol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used at a concentration of 0.025 to 0.1 percent in the form of a rinse, mouthwash, gargle, or spray (47 FR 22712 at 22826, May 25, 1982). It was reviewed and found safe by the Flavor and Extract Manufacturer's Association of the United States (FEMA) (Ref. 99).

Menthol is a secondary alcohol extract from peppermint oil or made synthetically. Chemically, it is also known as hexahydrothymol and 3-paramenthanol. Menthol may be made synthetically by the hydrogenation (reduction) of thymol. The Dental Panel concluded that menthol is safe as an OTC active ingredient for topical use on the mucous membranes of the mouth and throat at a concentration of 0.04 to

2.0 percent in the form of a rinse (47 FR 22712 at 22813). Menthol was reviewed and found safe by FEMA (Ref. 100).

Methyl salicylate is the methyl ester of salicylic acid. Prior to the discovery of a method for chemical synthesis of methyl salicylate, it was produced by steam distillation from natural sources. The natural-source products are known as gaultheria oils, betula oil, sweet birch oil, teaberry oil, and wintergreen oil. Today, these names are used synonymously with methyl salicylate. Methyl salicylate is prepared synthetically by esterifying salicylic acid with methanol. The Dental Panel concluded that methyl salicylate is safe for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit up to a 0.4-percent concentration in the form of a rinse, mouthwash, gargle, or spray, not more than three to four times daily (47 FR 22712 at 22828). Methyl salicylate was reviewed and found safe by FEMA (Ref. 101).

Thymol, also known as thyme camphor, is 5-methy-2-isopropyl-2-phenol. It may be prepared synthetically or obtained from volatile oils distilled from *Thymus vulgaris* and other related plant sources. Thymol is an alkyl derivative of phenol and has bactericidal and fungicidal properties. It was reviewed and found safe by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (the Dental Panel) (47 FR 22712 at 22829, May 25, 1982) and by FEMA (Ref. 102).

The safety of the combination of the four ingredients has been assessed in numerous long-term clinical studies. These studies showed no clinical pathologic change or adverse reactions (Refs. 103, 104, and 105).

Because OTC drug products are readily available, the determination of the safety of single ingredients and combinations of ingredients also requires consideration of possible abuse. Exaggerated use studies have been done. In one study (Ref. 106), 47 healthy adult subjects screened for sensitivity and allergy histories rinsed with 20 mL of the combination of essential oils for 30 seconds under supervision at 5 hourly intervals each day for 5 days and repeated 18 days later for 1 day. No subject developed any oral mucosal lesions attributable to the test product. A second study (Ref. 107) of 45 adult subjects followed a similar protocol. One subject had erythema (2-centimeter lesion) and epithelial sloughing on day 5 of the irritation phase of the study. In a third exaggerated use study involving 18 xerostomic (dryness of the mouth from salivary gland dysfunction) adults,

2 subjects experienced what was described as "utransient mucosal sloughing" and continued the regimen. The remaining xerostomic subjects did not develop mucosal lesions (Ref. 108). These studies showed that the potential for mucosal irritation is minimal when these ingredients are used according to label directions.

Two studies evaluated possible shifts in oral microbial populations and the emergence of opportunistic organisms or potential pathogens. One study in 83 subjects (Ref. 109) showed analysis of plaque samples from active agent and control groups. There were no significant increase in presumptive oral pathogens, spirochetes, black-pigmented Bacteroides, *S. mutans*, or *C. albicans*. A second 6-month study (Ref. 110) examined plaque at 3 and 6 months. Three microbiological approaches were used: (1) Microscopic enumeration of cocci, motile and nonmotile rods, and spirochetes, (2) recovery on selective and nonselective culture media, and (3) enumeration by colony morphology on a nonselective medium. No clinically significant shifts were found in the composition of the flora.

Mutagenicity studies have been reported (Ref. 111). The fixed combination of essential oils did not show mutagenic potential in the Ames test, the Unscheduled DNA Synthesis test, and the Mouse Micronucleus test.

Much of the evidence of the safety of the combination of these ingredients comes from their extensive history of use (well over 100 years) and the low incidence of consumer complaints reported by the manufacturer. The data included an estimate of one adverse reaction report for every 38,700,000 doses of these ingredients sold, which is described as an extremely low rate. The four ingredients in this combination have had a long and safe marketing history which contributes to the Subcommittee's conclusion that the combination is safe when used according to label directions.

b. *Effectiveness.* The Subcommittee evaluated seven 6-month, randomized, controlled trials of the effectiveness of a fixed combination of eucalyptol (0.092 percent), menthol (0.042 percent), methyl salicylate (0.060 percent), and thymol (0.064 percent) in a hydroalcoholic vehicle containing 21.6 to 26.9-percent ethyl alcohol. One study was a 6-month, randomized, controlled study (Ref. 103) involving 145 students and staff at an East Coast university, aged 18 to 54 years, randomized into three groups using either the above fixed combination, a vehicle control (a 26.9-percent hydroalcoholic vehicle containing all the ingredients in the test