

overall odds ratio for improvement relative to a placebo. After 3 months of product use, the odds ratio was 3.12 with a 95 percent confidence interval of 2.85 to 3.40. After 6 months, the odds ratio was 3.10 with a 95 percent confidence interval of 2.75 to 3.45. Based on the totality of the data, the Subcommittee concludes that cetylpyridinium chloride mouthrinse is safe and effective as an OTC antigingivitis/antiplaque agent.

b. *Stannous fluoride (dentifrice)*. The Subcommittee concludes that stannous fluoride in a compatible dentifrice base at a concentration of 0.454 percent is safe and effective for OTC use as an antigingivitis active ingredient.

i. *Safety*. Stannous fluoride has been used as an OTC caries-preventive agent in toothpastes in the United States since 1954. Since 1981, it has been largely replaced by sodium fluoride or sodium monofluorophosphate. However, during this 27-year period, it is estimated that at least 70 billion doses of stannous fluoride were sold in the United States. Thus, a long market history exists to support its safety.

The toxicity of ingesting fluoride from toothpaste has been reviewed extensively (Ref. 83). Concern has been expressed over the need to supervise the use of fluoridated toothpaste by young children because of the potential risk of developing fluorosis (Ref. 84). Acute toxicity of stannous fluoride in the rat (LD₅₀) appears to range from 31 to 300 mg/kg. Thus, it appears to have an acute toxicity comparable to that of sodium fluoride (Refs. 85 and 86). Toxicity studies show that a dentifrice formulation containing stannous fluoride plus stannous chloride was comparable to other nationally marketed fluoride-containing dentifrices.

Several subchronic toxicity tests of stannous fluoride dentifrice formulations have been carried out (Ref. 85). In a study conducted over 3 months, rats received either 3.3 grams (g) dentifrice/kg/daily (= 13.2 mg of stannous fluoride/kg/daily) or 8.4 g dentifrice/kg/daily (= 33.6 mg of stannous fluoride/kg/daily) by gavage. Any observed effects were not attributed to stannous fluoride. Two additional 91-day studies were conducted in rats. Dentifrice slurries in distilled water were administered by gavage. All dentifrice groups revealed microscopic alterations in the stomach lining, such as eosinophilic gastritis, squamous epithelial hyperplasia, and squamous vacuolization. No other abnormalities were observed. No tumorigenic effects have been reported from studies conducted in male or female rats or mice. Studies conducted in human

volunteers who received 50 mg a day of the stannous ion as stannous chloride revealed that about 3 percent of the dose is absorbed.

Based on results from a 13-week oral toxicity study in rats on stannous chloride conducted through the National Toxicology Program (NTP), a safety factor of 5,000 exists for potential exposure to stannous salts from use of a dentifrice containing 0.454 percent stannous fluoride. The safety factor is defined as the ratio between no observed adverse effect level (NOAEL) in the NTP study and the anticipated exposure to stannous salts from twice daily use of stannous fluoride toothpaste.

The Subcommittee's analyses of clinical studies, including detailed examination of soft tissue and microbiological assays, revealed no adverse shifts among the oral microbiological populations studied, no overgrowth of opportunistic pathogens, and no development of oral microbial resistance to stannous fluoride. Significant reductions in *S. mutans* were observed among subjects exhibiting higher levels of this organism. Based on these data, the Subcommittee concludes that a 0.454 percent stannous fluoride dentifrice is safe for long-term use.

Stannous ion in stannous fluoride dentifrices has been associated with staining of tooth surfaces, which in some instances may be severe (Refs. 87 and 88). In studies CC-191, CC-238, and CC-247 (Ref. 89), 2.1 percent of subjects discontinued the trial due to self-perceived tooth staining. Oral desquamation was reported by five subjects using a stannous fluoride dentifrice. This adverse effect does not appear to be an extensive problem because persons with hyposalivation have used stannous fluoride gels without adverse effects.

Because staining is a common phenomenon with the use of stannous fluoride, the Subcommittee evaluated data concerning the extent of consumer sensitivity to dental staining and the ease with which these stains can be removed. Studies demonstrated that dental staining with 0.454 percent stannous fluoride was noticed by a minority of consumers and that staining can be removed from enamel surfaces and dental restorations during conventional prophylactic procedures. However, the Subcommittee recommends that product labeling include a restriction on use by children and a statement concerning the likelihood of tooth staining.

ii. *Effectiveness*. Stannous fluoride has been incorporated into numerous

dentifrice formulations that contain a variety of abrasive substances, including hydrated silica gels, calcium pyrophosphate, and a variety of excipient agents (see the **Federal Register** of March 28, 1980, 45 FR 20666 at 20684 to 20688).

The careful formulation of stannous fluoride dentifrices to prevent rapid oxidation and hydrolysis, and thereby inactivation, of stannous ions is critical for clinical effectiveness of these dentifrices. Oxidation can be prevented in several ways. In one approach, water is excluded from the formulation. Another approach involves use of chelating agents such as pyrophosphate, citrate, gluconate, gantrez (a copolymer of maleic acid and methyl ether) or phytate, which form soluble stannous complexes. In addition, incorporation of another stannous compound, such as stannous pyrophosphate or stannous chloride, provides a steady-state situation in which the concentration of bioavailable stannous fluoride is relatively stable. It is essential to note that the inclusion of stannous fluoride alone in a dentifrice without stabilization is not sufficient to obtain optimum clinical effectiveness. Clearly, products containing stannous fluoride may have a defined shelf life.

Stannous fluoride has a long and well-established history as a caries-preventive agent (Ref. 90). Stannous fluoride at a 0.4-percent concentration results in a concentration of 970 parts per million (ppm) fluoride (Ref. 86). Effects of stannous fluoride on plaque formation and gingivitis have given mixed results which, in part, reflect the duration of the studies, the concentration used, and the type of subjects studied.

The Subcommittee evaluated the results of three primary trials and three supportive trials (Refs. 85 and 89) of a stabilized 0.454-percent stannous fluoride dentifrice for antiplaque and antigingivitis claims. Two of the primary 6-month trials (CC-191 and CC-238) carried out in Indiana had results that are consistent with each other (Ref. 89). The final assessments were consistent with the interim 3-month assessments. The third study (CC-247), conducted in Northfield, lasted for 7 months and had results that appeared to differ in some measures from those in Indiana (Ref. 89). The Indiana studies had reductions of 18.8 percent and 20.5 percent in gingival index, 30.5 percent and 33.4 percent in bleeding index, and a nonsignificant reduction of 2.6 percent and 3.1 percent compared with placebo in plaque. In contrast, the Northfield study (one evaluator) reported a 10.7-percent