

studies that tested the currently marketed toothpaste containing 750 µg/g of sanguinaria extract, only one 6-month, double-blind study (Ref. 271) demonstrated a significant decrease in plaque at 3 months. Results from this study also showed that gingival index scores in the active group were significantly lower than the placebo group at 28 weeks. The other two studies were short-term studies of 1 and 4 weeks (Refs. 272 and 273) in which no differences were detected between the active and placebo groups. A 10-week study (Ref. 274) showed that the toothpaste formulation containing 300 µg/g of sanguinaria extract reduced plaque and gingival bleeding, but the zinc chloride in the formulation diminished the plaque-reducing effect. It was not clearly documented whether zinc chloride affects the effectiveness of the currently marketed toothpaste. Based on the short-term clinical studies, the effectiveness of the toothpaste containing 750 µg/g sanguinaria extract in plaque and gingivitis reduction cannot be determined. The effect of zinc chloride on the effectiveness of the toothpaste also needs further study.

Five studies used a toothpaste formula containing 750 µg/g sanguinaria extract and 0.8 percent sodium monofluorophosphate (Refs. 263, 264, 273, 275, and 276). Equivocal results were noted in two 6-month studies (Refs. 263 and 276) and in a 1-week study (Ref. 264). One toothbrushing study (Ref. 273) compared the effect of eight toothpaste formulations on plaque and gingivitis in school children. Because the study design concerning the control product and subject selection was inadequate, this study did not support effectiveness. One-way analysis of variance (ANOVA) showed that the differences between groups were not statistically significant. In addition, no significant differences in plaque or gingivitis reduction were noted between groups using a fluoride toothpaste containing zinc chloride plus sanguinaria extract and a dentifrice containing zinc chloride without sanguinaria extract.

A 1-week, exaggerated use effectiveness study (Ref. 275) tested three regimens of the toothpaste and oral rinse on plaque reduction. The study design and protocol employed did not allow accurate testing of the effectiveness of the toothpaste. Based on all of the data submitted, none of the studies provided evidence of effectiveness.

The Subcommittee evaluated 26 additional controlled clinical studies (Ref. 277). Seven of the 26 studies (Refs. 265 and 278 through 283) provided

equivocal results. The remaining 19 studies (ranging from 1 to 8 weeks), conducted for various reasons, evaluated proper dosage, clinical study designs, optimal plaque and gingival indices to be employed, product safety, effectiveness of the regimen (toothpaste and oral rinse combination use), and the role of zinc chloride in plaque reduction.

Among the 19 studies, 9 tested the effectiveness of an oral rinse with a final pH of 4.5. Some short-term clinical trials, employing the 7-day exaggerated use study design, demonstrated statistically significant differences between an earlier rinse product (pH 3.2) and the placebo control in plaque reduction only. However, the only two long-term, 6-month studies testing the effectiveness of this earlier rinse product (pH 3.2) did not demonstrate any effectiveness in plaque or gingivitis reduction when compared to a placebo. The 7-day exaggerated use study design was validated as a screening test for formulation development (Ref. 284). In addition, studies investigating the role of zinc chloride in the effectiveness of the oral rinse provided confusing and controversial results. Two 1-week studies (Refs. 285 and 286) demonstrated that no significant difference in plaque reduction was observed between a sanguinaria extract and zinc chloride rinse and a rinse without sanguinaria extract. The effect of zinc chloride alone was only mildly less than that obtained with the combination of sanguinaria extract and zinc chloride. However, a 2-week, experimental gingivitis, crossover study (Ref. 287) demonstrated that the oral rinse with sanguinaria extract and zinc chloride performed significantly better than the placebo in plaque reduction. The effect on gingivitis was equivocal.

One study trial (Ref. 288) evaluated the effect of the oral rinse on viable microorganisms after a single 60-second rinse. The rinse exhibited a selective effect on anaerobic organisms without adversely affecting aerobes or alpha-hemolytic streptococci. No long-term studies were available.

While some data exist on the short-term effectiveness of the sanguinaria extract oral rinse or dentifrice, the Subcommittee evaluated selected studies that supported the effectiveness of the oral rinse used in combination with one of the sanguinaria toothpaste products. Five short-term (1 to 9 weeks) studies (Refs. 265 and 289 through 292) demonstrated reductions in plaque or gingivitis. Four 6-month studies also produced significant differences for the active regimen compared to placebo (Refs. 293 through 296). However, these

nine studies varied substantially in design and formulation of the test dentifrice and oral rinse combinations. In studies prior to 1984, low dose toothpaste (300 µg/mL sanguinaria extract) and pH 3.2 oral rinse were used, whereas studies conducted since 1988 have included the 750 µg/g sanguinaria extract toothpaste and a pH 4.5 oral rinse. Even if effectiveness were demonstrated for the combined regimen, the contribution of sanguinaria extract alone is not clear.

The in vitro efficacy of the individual active components was also investigated. In vitro MICs of sanguinaria chloride and sanguinaria extract were tested against 176 clinical isolates and 43 reference strains of oral bacteria (Ref. 297). MIC's for sanguinaria chloride ranged from 16 to 32 µg/mL for all but 7 reference isolates. MICs for sanguinaria extract ranged from 16 to 24 µg/mL for all strains except *Wolinella succinogenes* and one strain of *Wolinella curva*. For fresh isolates, MIC's for sanguinaria chloride and sanguinaria extract ranged from 16 to 32 µg/mL. Laboratory tests were also conducted on sanguinaria and fluoride-containing toothpaste to evaluate the bioequivalence of the product to positive controls. Tests included bioavailability, rat caries fluoride stability (Ref. 298), remineralization/demineralization, and in vivo bovine enamel fluoride uptake (Ref. 299). These tests are consistent with the required biological testing procedures for fluoride dentifrices (October 6, 1995, 60 FR 52474 at 52510). Results obtained from these studies indicated that the sanguinaria/fluoride toothpaste formula was biologically equivalent to the clinically-tested control in promoting remineralization, promoting fluoride uptake into artificial enamel lesions, reducing the effects of acid challenge on enamel, and reducing caries in the rat caries model. Sanguinaria extract and zinc chloride were also shown not to interfere with fluoride bioavailability uptake profiles with decalcified enamel qualitatively comparable to profiles obtained from sound enamel.

The Subcommittee concludes that, although mild staining and oral irritation may occur, sanguinaria extract at 0.03 to 0.075 percent concentration is safe. However, given the wide variations in study designs, test product concentrations and formulations, placebo controls, and statistical analyses, conclusions cannot be drawn regarding the effectiveness of sanguinaria extract as an OTC antigingivitis/antiplaque agent.

e. *Sodium bicarbonate*. The Subcommittee concludes that sodium