

in conjunction with toothbrushing in subjects undergoing orthodontic treatment, a clear benefit was found for the hydrogen peroxide rinse group (Ref. 206). The rinse appeared to prevent the accumulation of plaque and the subsequent development of gingivitis. However, once plaque formed, the experimental rinse did not reduce the established plaque and gingivitis. In contrast, a 24-week study comparing a 1.5-percent hydrogen peroxide rinse with water rinses did not find a significant reduction in either plaque scores or in papillary bleeding scores (Ref. 207). A 2-year study comparing a 1.5-percent hydrogen peroxide rinse with a 0.1-percent chlorhexidine rinse, but without a placebo control, found a reduction in sulcus bleeding but not plaque scores for the hydrogen peroxide group (Ref. 208).

The Subcommittee concludes that there is a lack of well-controlled studies of sufficient length to draw firm conclusions regarding the effectiveness of hydrogen peroxide. The clinical data suggest that hydrogen peroxide may positively effect plaque and gingivitis scores, but the data are contradictory, lacking well-controlled clinical studies of adequate length. Further studies are needed to determine the value of this ingredient as an antiplaque agent. Optimizing the concentration, required exposure time, and best delivery vehicle would be major steps forward. The potential positive effect as an active ingredient is suggested by the current data. However, long-term efficacy is unknown.

d. *Sanguinaria extract*. The Subcommittee concludes that sanguinaria extract at 0.03 to 0.075 percent concentration is safe, but there are insufficient data available to permit final classification of its effectiveness in an oral rinse or dentifrice dosage form as an OTC antigingivitis/antiplaque active ingredient.

Sanguinaria extract is prepared by warm acidulated alcoholic extraction of the rhizome of *Sanguinaria canadensis* (more commonly known as blood root or puccoon), followed by precipitation with a metal salt. Six principal benzophenanthridine alkaloids are present in the extract with sanguinarine (50 percent) and chelerythrine (25 percent) being the major ones. Sanguinaria extract is a bright orange, free-flowing, amorphous powder that is hygroscopic and electrostatic. It is soluble at 25° C in methanol to 1 percent weight per weight (w/w), in chloroform to 0.75 percent w/w, in water or water buffered with one percent citric acid to 2 percent w/w. Sanguinaria extract exhibits a pH

dependent lipophilicity and partitions to a significant extent into the lipid phase of a lipid/water mixture above pH 6.5. Sanguinaria extract has been described in several pharmacopeia (Refs. 209 and 210) and textbooks (Ref. 211). Uses include relief of spongy and red gums and in OTC cough syrups as an expectorant. Sanguinaria extract was introduced into homeopathic practice in 1837.

i. *Safety*. Safety studies addressing acute toxicity, irritation potential, sensitization potential, reproductive toxicity, birth defect potential, chronic organ toxicity, and carcinogenic potential were conducted in animals using sanguinaria extract and sanguinarine chloride.

The acute toxicity of sanguinaria extract was determined by oral gavage to Sprague-Dawley rats with doses from 500 to 3,000 mg/kg. In one study (Ref. 212), the oral LD<sub>50</sub> of sanguinaria extract was 1,440 mg/kg. This suggests that sanguinaria extract is probably poorly absorbed orally. The lethal dose of sanguinaria extract in two *Cynomolgus* monkeys was above 50 mg/kg. The acute dermal LD<sub>50</sub> in a limited study using 10 adult New Zealand rabbits was greater than 200 mg/kg body weight. Acute inhalation toxicity of sanguinaria extract (2.2 mg/liter) in 10 rats resulted in mortality in 3 of 5 males and no females. Gross pathology examination revealed no lesions or abnormalities. The LD<sub>50</sub> from two studies of sanguinarine chloride determined by oral gavage in rats was 1,525 and 1,663 mg/kg. The intravenous LD<sub>50</sub> in rats was 28.7 mg/kg, and the intraperitoneal LD<sub>50</sub> in mice was 17.7 mg/kg.

Studies concerning the multidose subchronic toxicity of sanguinaria extract (Refs. 213, 214, and 215) and sanguinarine chloride (Refs. 216, 217, and 218) were conducted in rats and monkeys at doses ranging from 5 to 405 mg/kg for 2 to 13 weeks. In a 4-week oral gavage study in monkeys (Ref. 215), 100 mg/kg of sanguinaria extract was determined to be the appropriate high-dose for a subsequent 13-week toxicity study in monkeys. A 13-week gavage study in monkeys (Ref. 216) with 0 to 60 mg/kg showed no treatment-related toxicity except minor GI irritation of limited duration. The study suggested a NOAEL of 30 mg/kg per day once tolerance is achieved. A 13-week oral gavage study in rats (50 to 400 mg/kg per day) (Ref. 214) showed evidence of dose-related toxicity, principally involving GI irritation and body weight loss at all dosage levels. Mortality was observed at doses of 100 mg/kg per day and above, with a NOAEL of less than 50 mg/kg per day. Administration in the

diet appears to protect against GI irritation. A 4-week dietary toxicity study in rats (5 to 405 mg/kg per day) (Ref. 213) showed a group mean body weight loss at 405 mg/kg. Based on these studies, evidence of minor treatment-related toxicity associated with sanguinaria extract and sanguinarine chloride is limited to GI irritation.

Pharmacokinetic studies assessing metabolism, disposition, distribution, and elimination of sanguinaria extract and sanguinarine chloride were conducted in rats and mice (Refs. 219, 220, and 221). The metabolism of sanguinaria extract was tested in vitro in rat and rabbit liver homogenates and in vivo in 10 human subjects for at least 6 months (Ref. 219). Results indicated that no benz[c]acridine (50 parts per billion (ppb) detection limit) was formed in the rat or rabbit liver homogenates. Neither benz[c]acridine (1 ppb detection limit) nor sanguinarine chloride (25 ppb detection limit) was found in the urine of the human subjects.

Studies evaluating the biological disposition of radiolabeled sanguinarine chloride in rats (Ref. 220) and mice (Ref. 221) suggested low absorption, with excretion of over 50 percent (mice) and 88 percent (rats) of the total dose in feces. Less than 1.0 percent (rats) and 0.9 percent (mice) was excreted in the urine.

Analysis of rat tissues collected 96 hours following oral administration of 5 mg/kg indicated a total recovery of approximately 6.1 percent of the administered radioactivity. Excretion via urine, feces, and expired air accounted for 95.1 percent of the administered dose in the 96-hour post-administration period. Blood levels in the rat achieved less than 1.5 percent of the net dose administered orally, peaking around 8 hours and declining to near 1 hour levels by 96 hours.

Expired air accounted for an average of 18.3 percent (mice) and 6.0 percent (rats) of the dose administered. The nature of the blood radioactive residues and excreted <sup>14</sup>C-carbon was not determined. An overall mean recovery in mice of 97.89 percent of the <sup>14</sup>C-carbon during the 96 hours following oral administration of sanguinarine chloride labeled at one and/or both methylene-dioxy groups suggests that a substantial portion of the radiolabeled test product may be transformed into nonlabeled benzophenanthridine metabolites. These results suggested that sanguinarine chloride is satisfactorily recovered after oral or intravenous administration.

A cardiovascular study in dogs treated intravenously with sanguinarine