

426), the subjects in this large-scale, long-term study had diagnosed early periodontitis. Keyes et al. (Refs. 432 and 433), in uncontrolled and poorly documented reports, indicated reductions in signs and symptoms associated with periodontal diseases when using a regimen consisting of a thick mix of sodium bicarbonate slightly moistened with a few drops of water and 3 percent hydrogen peroxide.

Because of a lack of properly designed studies showing conclusively that the combination of hydrogen peroxide and sodium bicarbonate is effective, this combination of ingredients does not appear to present any added benefit to oral hygiene products. Further, most reports indicated that the two ingredients were no better at controlling plaque and gingivitis than products currently on the market which do not contain these ingredients. Moreover, many of the published references exploring the effects of these ingredients tested small numbers of subjects, did not employ controls, and/or used subjects with inappropriate disease entities, such as mild to moderate periodontitis. Many of the published references instituted a variety of professional cleanings, irrigations, instructional oral hygiene sessions, and additional possibly active ingredients during the test periods, thus further clouding the already contradictory results. Several studies did not disclose the concentrations of either ingredient, making it difficult to make conclusions.

d. *Hydrogen peroxide*, sodium citrate, sodium lauryl sulfate, and zinc chloride. The Subcommittee concludes that the combination of these ingredients is safe, but there is insufficient evidence to permit final classification of its effectiveness as an OTC antigingivitis/antiplaque agent. The Subcommittee is aware of three formulations of a combination of hydrogen peroxide, sodium citrate, sodium lauryl sulfate, and zinc chloride. All of the active ingredients have potentially useful properties when included in a mouth rinse.

*Hydrogen peroxide (0.595 to 1.5 percent)*. Hydrogen peroxide is used for its antibacterial and foaming properties (see section III.C of this document).

*Sodium citrate (0.024 to 0.12 percent)*. Sodium citrate is used as an astringent and to enhance the antibacterial activity of zinc chloride.

*Sodium lauryl sulfate (0.06 to 0.15 percent)*. Sodium lauryl sulfate is used for its emulsifying and antiplaque formation properties (see section III.C of this document).

*Zinc chloride (0.016 to 0.08 percent)*. Zinc chloride is used for its antibacterial

properties and its ability to reduce plaque accumulation and acid production by plaque bacteria. Zinc has also been shown to be effective in inhibiting calculus formation by interfering with the conversion of amorphous calcium phosphate to more crystalline calcium phosphate compounds and their growth (Ref. 434). The antibacterial effect of zinc salts may be enhanced in the presence of sodium lauryl sulfate.

i. *Safety*. Because the above ingredients are used in combination, the safety and efficacy of these ingredients must be examined under conditions of combined use.

*Toxicity in animals*. Acute oral toxicity tests in rats (Ref. 435) indicated that one of the three formulations (it is not clear from the protocol which one), is relatively nontoxic. The purpose of the study was to assess the toxicity of the combination of ingredients administered orally as a single dose to Sprague-Dawley rats, followed by a 14-day observation period. The combination was administered by oral gavage to five male and five female rats at a dose of 40 g/kg of body weight. Over the following 14 days all animals survived in apparent good health, although they exhibited hunched postures and loose stools for the first 2 days. No abnormal findings were observed at necropsy. This dose is considerably higher than the likely intake by subjects using these ingredients in a rinse.

In another study on the effect of topical application of this formulation to hamster cheek pouches, 76 hamsters were divided into 3 groups of 22 animals each, with equal numbers of males and females, and a fourth group of 10 animals. The test group received daily topical applications of the test formulation to their cheek pouches for a 30-day period. The negative control group received comparable applications of water. The positive control group received 5 percent sodium lauryl sulfate. An additional group of 10 animals received a fixed combination of essential oils and water. At the end of the 30-day period, the cheek pouches were examined clinically and histologically. The results indicated no evidence of mucosal irritation in the form of epithelial damage, inflammation, hyperplasia, atrophy, or hyperkeratosis when compared to the water control (Ref. 436).

Another hamster study of 30-days duration compared topical applications of the test formulation to abraded and non-abraded hamster cheek pouches with application of 0.12 percent chlorhexidine gluconate, 1, 2, and 3

percent hydrogen peroxide, 5 percent sodium lauryl sulfate, and tap water. The animals on the test formulation gained weight normally and did not demonstrate any evidence of mucosal irritation in the form of inflammation, epithelial ulceration, hyperplasia (abnormal multiplication of cells in a tissue), atrophy, or hyperkeratosis (enlargement of the keratin layer due to increase in cell size), as compared to the water control. The test formulation did not interfere with the healing of abraded pouches (Ref. 436).

ii. *Effectiveness*.

1. *Mechanism of action*. It is not clear how this complex mixture behaves under conditions of normal use. One formulation contains 0.6 percent hydrogen peroxide and is dispensed in a single bottle. In the other two formulations, the rinses are dispensed in two bottles, one of which contains hydrogen peroxide. The directions state that the contents of the two bottles should be mixed just prior to rinsing. According to the data, these latter two formulations have 2.5 to 3 times the concentration of the active ingredients found in the first formulation and are combined with 1.5 percent hydrogen peroxide versus 0.6 percent hydrogen peroxide used in the first formulation. One of the latter two rinses also has 5 times as much zinc chloride as the first rinse. The proportions of the ingredients vary among the three formulations, but are generally found in relatively low concentrations. The concentration ranges for the active ingredients are as follows: Hydrogen peroxide, 0.595 to 1.5 percent; sodium citrate, 0.024 to 0.12 percent; sodium lauryl sulfate, 0.06 to 0.15 percent; and zinc chloride, 0.016 to 0.08 percent (Ref. 437).

2. *In vitro studies*. Study 1 evaluated the effect of the combination formulation on acid production by *S. mutans* and included three experimental groups: (1) *S. mutans* in an enriched growth medium (control), (2) *S. mutans* in an enriched growth medium exposed for various durations to the combination formulation with a 1:4 dilution, (3) *S. mutans* in an enriched growth medium exposed for various durations to the combination formulation with a 1:8 dilution. After a 5-minute exposure, the cells were centrifuged, washed, resuspended in combination formulation-free medium, and incubated. The viability of the bacterial cells was not affected by the exposure to the formulation, and the formulation did not kill the bacteria during a 5-minute exposure. However, acid production by *S. mutans* was inhibited for 8 hours as a result of the