

resulting shock and tissue hypoxia have been noted (Ref. 409). Ingestion of lesser amounts can cause gastroenteritis, abdominal pain, and diarrhea that may be bloody. Nausea and vomiting are common with ingested iodine.

The current product labeling recommends that children under 12 be supervised while using the product and warns against use by pregnant or nursing mothers, those with iodine sensitivity, and those with a history of thyroid disorder. Because of the potential toxic side effects, the labeling should include a warning that the product should not be used by children, women of child-bearing years, or anyone suffering from a thyroid disease, disorder, or ailment. Subjects considering long-term use of these ingredients should consult their physician to determine if any conditions exist that might contraindicate use.

ii. *Effectiveness.*

1. *Six-month studies.* Two 6-month studies (Refs. 410 and 411), a 3-week study (Ref. 412), a 6-week study (Ref. 413), and a brief review of the antimicrobial effects of mouthrinses on dental plaque (Ref. 414) were submitted. The 6-month studies (Refs. 410 and 411) were designed similarly, using subjects admitted according to common exclusion criteria. Subjects received a thorough prophylaxis and were then assigned to one of four groups using a test rinse containing hydrogen peroxide and povidone iodine, a rinse containing only one of these ingredients in distilled water, or a distilled water placebo. Because the subject pool was divided into four groups, each group had a relatively limited number of subjects. Ninety total subjects completed one study (Ref. 410) with 23 in the test rinse group, and 96 subjects completed the other study (Ref. 411) with 23 in the test rinse group. Clinical assignments included measurements of plaque using the Turesky modification of the Quigley-Hein Plaque Index and the Papillary Bleeding Scoring, which attempts to quantitatively assess inflammation and bleeding at the interproximal sites.

Several troubling aspects of the protocol jeopardized the value of the studies from the start. The overall sample size was immediately halved by including groups that used only hydrogen peroxide or only povidone iodine. The control rinse was substantially different from the test rinse and did not contain a placebo vehicle. The protocol for both studies included professional subgingival irrigation at 3-week intervals throughout the study. Further, subjects were instructed not to rinse, drink, or eat

anything for 30 minutes following the rinsing procedure.

Results from the two 6-month studies failed to provide convincing clinical data in support of the tested ingredients. For example, while one study showed borderline significant plaque index score differences, the other study did not. Neither study reported the overall gingival index (bleeding index) scores. It appears that there were no significant differences overall for the gingival index in either study. Instead, only scores for sites greater than or equal to three were chosen for analysis. While both studies suggested that significant differences could be determined in this limited and skewed selection of sites, p values for these comparisons were unclear or not reported. Because use of the test solution did not significantly affect plaque buildup in at least one of the studies, it is possible that the positive effect on the gingival condition was due to the subgingival irrigation professionally administered every 3 weeks during the test period. If the test solution altered the subgingival flora but did not significantly change the supragingival flora, the most likely contributing factor would be the professional irrigation.

Further, the two studies were tabulated differently and the results were somewhat difficult to compare. One study compared sites while the other study examined differences between subjects. The number of sites used in these analyses was unclear or unstated. The investigators in one study chose sites over subjects for analysis because of the variation in the number of sites between subjects with a bleeding index greater than 3. Therefore, it is possible that one or only a few subjects had many sites and the remaining subjects had few sites that qualified. Such a distribution could produce results that realistically represent only a few subjects within the group rather than the group itself. As with several other important aspects of these studies, p values and standard errors for specific comparisons were often unclear or unstated.

The studies included a limited number of samples for microbiological examination. The investigators in both studies utilized selective media along with other microbiological assays. Both study reports indicated that opportunistic pathogens (*Candida* and enteric bacteria) did not establish themselves in any of the test groups sampled. The test solution samples tended to show fewer presumed periodontal pathogens compared to control samples. However, the number of periodontal pathogens was generally

quite low or absent depending on the species studied. While the microbiological data hold some interest, the use of professional subgingival irrigations throughout the studies made interpretation of the microbiology data difficult.

The design of these studies made definitive conclusions very difficult, with no consistent or convincingly significant clinical effect on plaque or gingivitis. The toxicology data suggested that the combination is safe, but doubts linger. An appropriately sized study of healthy and thyroid-compromised subjects should be considered using a placebo that more closely resembles the test product. Subjects should not be instructed to refrain from eating, drinking, or rinsing and professional irrigation should not be included, as such procedures might significantly alter the results.

2. *Three and 6-week studies.* Two short-term studies of 3 and 6 weeks (Refs. 412 and 413) showed significant improvement in the clinical parameters reported. However, several ingredients reviewed by the Subcommittee, including some formulations of hydrogen peroxide, have shown positive short-term results only to fall short in long-term studies.

Based on these studies, the Subcommittee finds that there is insufficient evidence to support the safety and effectiveness of the combination of hydrogen peroxide and povidone iodine as an OTC antingivitis/antiplaque agent.

c. *Hydrogen peroxide and sodium bicarbonate.* The Subcommittee concludes that the combination of sodium bicarbonate and hydrogen peroxide at concentrations up to and including 3 percent hydrogen peroxide is safe, but there are insufficient data available to permit final classification of the effectiveness of the combination as an antingivitis/antiplaque agent.

i. *Safety.* Hydrogen peroxide can produce hydroxyl radicals in the presence of iron (Fe+2) or copper (Cu+1) (Refs. 188 and 189) and in vitro studies have shown that sister chromatic exchanges can be produced by hydroxyl radicals. Experimental and clinical data are sparse demonstrating a significant mutagenic effect with the combination of hydrogen peroxide and sodium bicarbonate in oral health care products. Experimental and clinical data, however, do not demonstrate a significant mutagenic potential with the combination of hydrogen peroxide and sodium bicarbonate in oral health care products (Refs. 145, 188, and 189). The rapid decomposition of hydrogen peroxide in the presence of sodium