

ingredients reduced plaque formation by 43 percent in 15 subjects who used these ingredients for 7 days. Gingivitis apparently was not assessed. The report lacked essential information.

In a combined animal and human study (Ref. 397) and a separate human study (Ref. 398), a toothpaste containing 1 percent of the combination of alkyl dimethyl amine oxide and alkyl dimethyl glycine applied topically three times weekly had no effect in preventing caries.

In a more recent single-blind, randomized, crossover study in 20 subjects (Ref. 399), the effects of four ingredients, including the combination of alkyl dimethyl amine oxide and alkyl dimethyl glycine, were compared with saline in preventing plaque regrowth. Subjects rinsed twice daily for 1 minute and suspended normal oral hygiene measures. Plaque was scored using a plaque index and plaque area assessment. The combination of alkyl dimethyl amine oxide and alkyl dimethyl glycine was significantly less effective than the other three agents tested, but was more effective than saline. Gingivitis was not assessed.

Based on the data submitted, the Subcommittee concludes that there is insufficient evidence to support the safety and effectiveness of the combination of alkyl dimethyl amine oxide and alkyl dimethyl glycine as an OTC antigingivitis/antiplaque agent.

b. *Hydrogen peroxide and povidone iodine.* The Subcommittee has determined that there is insufficient evidence to support the safety and effectiveness of the combination of hydrogen peroxide and povidone iodine as an OTC antigingivitis/antiplaque agent.

i. *Safety.*

The Subcommittee concludes that hydrogen peroxide is safe at concentrations of up to 3 percent. Because the final concentration of hydrogen peroxide in this combination is 1.5 percent when the separately packaged solutions are mixed, the Subcommittee considers this portion of the combination to be safe. The povidone iodine component of the combination (5 percent final concentration), however, raises several safety concerns, including acute and chronic toxicity.

1. *Acute toxicity study.* An acute toxicity study (Ref. 400) was performed on rats to determine the LD₅₀ iodine concentration. Ten animals were dosed with 5 g/kg with no fatalities occurring. The data established that povidone iodine is not considered toxic when the LD₅₀ is greater than 5 g/kg. The only noted toxic effect at this level was

hydronephrosis (distention with urine) of the kidneys of two male rats.

2. *Oral mucosal toxicity study.* Oral mucosal toxicity was also examined in rats (Ref. 401). A solution containing 1.5 percent hydrogen peroxide and 5 percent povidone iodine was applied three times daily for 7 days to the oral mucosa of 12 albino rats. Two other groups of 12 rats were exposed to the components individually. While there were animals in each group that did not gain weight normally, the differences between the groups were not significant. In the group that received the combination of ingredients, 5 of the 12 animals showed signs of acute iodine toxicity, including lethargy, diarrhea, and abnormalities in the GI tract. These signs suggest possible acute toxicity in humans due to iodine overdose. These abnormalities were not noted in the two groups exposed to hydrogen peroxide or povidone iodine solutions individually. No negative control group was included.

3. *Acute dermal toxicity study.* In an acute dermal toxicity study, a 10-percent povidone iodine solution mixed with 3 percent hydrogen peroxide at 2 g/kg of body weight was applied to 10 albino rats (Ref. 402). Skin reactions were recorded as slight, but 8 of 10 animals showed lethargy, nasal discharges, diarrhea, and other signs of GI disturbances. All 10 animals survived, showing only mild dermal irritation. The investigators defined the test mixture as nontoxic because the LD₅₀ was greater than 2 g/kg of body weight.

4. *Eye irritation study.* An eye irritation study was conducted on six albino rats by placing a standard mixture of 10 percent povidone iodine and 3 percent hydrogen peroxide (Ref. 403) into the conjunctival sac and scoring by the Draize technique at 1, 2, and 3 days after dosing. The test mixture was determined to be an irritant, causing iritis and moderate conjunctival irritation in five of six animals.

5. *Chronic toxicity study.* Chronic toxicity is also of concern because of the activity of iodine on the thyroid. A 6-month prospective study in 50 subjects to assess thyroid function and iodine levels following prolonged exposure to the mouthrinse showed that iodine levels were significantly elevated in test subjects with increased protein bound iodine in blood and in urine samples (Ref. 404). In general, thyroid function tests remained within normal limits. These tests included serum thyroxine (T4), free T4, triiodothyronine (T3), and free T4 index measurements. A small but significant rise in the serum thyroid stimulating hormone (TSH) was

consistently noted. The investigators suggested that this small increase in serum TSH should be considered a normal physiological adaptive response to increased iodine intake and had no adverse effects on the subjects. While the study was a good first step in establishing the safety of chronic use of the test solution, there were several concerns. The total number of healthy subjects was relatively small and may not reveal possible side effects in a larger population. While the investigators considered increased TSH without concomitant serious side effects as a sign that subjects were able to tolerate increased iodine, an alternative interpretation is that the increased TSH was an early indication of a thyroid system that is not functioning properly. A larger and perhaps longer study is needed.

6. *Chronic use test in compromised thyroids.* Although a second much smaller study examined the effects of chronic use of a mouthrinse containing hydrogen peroxide and povidone iodine in subjects with compromised thyroids, the number of subjects was completely inadequate to establish possible side effects.

7. *Mutagenicity tests.* Tests to determine the mutagenicity of povidone iodine were carried out using the Salmonella/microsome mutagenesis assay, a micronucleus test in rats, and a rat hepatocyte DNA repair assay (Refs. 405, 406, and 407). While the tests indicated cell toxicity, they did not indicate a mutagenic effect. A cytotoxicity study examining the cytotoxic effects on Chinese hamster ovary cells was also reported (Ref. 408). The study concluded that the combination rinse is cytotoxic at concentrations of 2,500 µg/mL. The report indicated that when a metabolic activation mixture with the appropriate buffer and cofactors was added to the assay, the test rinse was no longer considered cytotoxic. The report did not elaborate on the possible ramifications of these results.

In order to evaluate the acute toxicity studies submitted, the Subcommittee examined iodine toxicity in general. Acute toxicity of iodine tincture (2 percent iodine and 2.4 percent sodium iodine in a 50 percent ethanol solution) has been recorded at levels relevant to the concentration of povidone iodine (5 percent) in this combination. Fatal events have occurred when as little as 30 mL of tincture of iodine have been ingested (Ref. 409). Acute toxic effects produce local actions in the GI tract. Iodine is corrosive, but is also readily inactivated by foodstuffs. When large concentrations of iodine are ingested,