

TABLE 2.—CATEGORIZATION OF SINGLE ACTIVE INGREDIENTS—Continued

| Active Ingredients                 | Safety | Efficacy |
|------------------------------------|--------|----------|
| Cetylpyridinium chloride           | I      | I        |
| Dicalcium phosphate dihydrate      | I      | III      |
| Hydrogen peroxide                  | I      | III      |
| Sanguinaria extract                | I      | III      |
| Sodium bicarbonate                 | I      | III      |
| Sodium lauryl sulfate              | I      | III      |
| Stannous fluoride (for gingivitis) | I      | I        |
| Zinc citrate                       | I      | III      |

TABLE 3.—CATEGORIZATION OF COMBINATIONS OF ACTIVE INGREDIENTS

| Active Ingredient Combination   | Safety | Efficacy |
|---|--------|----------|
| Alkyl dimethyl amine oxide and alkyl dimethyl glycine                       | III    | III      |
| Eucalyptol, menthol, methyl salicylate, and thymol                          | I      | I        |
| Hydrogen peroxide and povidone iodine                                       | III    | III      |
| Hydrogen peroxide and sodium bicarbonate                                    | I      | III      |
| Hydrogen peroxide, sodium citrate, sodium lauryl sulfate, and zinc chloride | I      | III      |
| Peppermint oil and sage oil   | I      | III      |
| Polydimethylsiloxane and poloxamer  | I      | III      |
| Stannous pyrophosphate and zinc citrate                                     | I      | III      |

#### A. Category I Conditions

The Subcommittee recommends Category I labeling for all Category I single antingivitis/antiplatelet active ingredients and combinations of active ingredients (see section II.D of this document).

#### 1. Category I Single Active Ingredients

Cetylpyridinium chloride (rinse)  
Stannous fluoride (dentifrice)

#### a. Cetylpyridinium chloride (rinse).

The Subcommittee concludes that cetylpyridinium chloride at concentrations of 0.045 to 0.1 percent with at least 72 to 77 percent chemically available cetylpyridinium chloride is safe and effective for use in mouthrinse formulations as an OTC antingivitis/antiplatelet agent. Cetylpyridinium-containing mouthrinses have been used in the United States since 1940. Cetylpyridinium chloride 0.025 percent to 0.1 percent has been marketed nationally in several products. Products containing cetylpyridinium chloride have also been marketed internationally. The more than 55-year U.S. marketing history is significant with respect to the ingredient's safety.

Cetylpyridinium chloride is a quaternary nitrogenous compound 1-hexa-decyl pyridinium chloride with antimicrobial activity against many microorganisms, including viruses. Its chemical and physical properties are well described in the USP (Ref. 58). It is classified as a cationic surface-active agent and contains a cetyl radical substituted for hydrogen atom on position 1. In hydrochloric acid it forms a chloride salt. The cetyl radical renders the molecule lipophilic, contributing to the lipophilic/hydrophilic balance which is necessary for the antimicrobial activity of such quaternary nitrogenous compounds. The antimicrobial activity is dependent upon the positioning of the charged molecule with bacterial cells that carry a net negative charge. This positioning allows the hydrophilic portion of the cetylpyridinium chloride to interact with the cell membrane, resulting in leakage of cellular components, disruption of cellular metabolism, inhibition of cell growth, and cell death (Refs. 59 through 62). Because the positively charged hydrophilic region is critical to antimicrobial activity, any formulation that diminishes the activity of this cationic group or that competes with this group may inactivate the product. Therefore, it is essential to establish that the cetylpyridinium chloride in products is sufficiently biologically active to justify an antingivitis claim.

i. *Safety.* The Subcommittee believes there are sufficient safety data to permit final classification of the safety of cetylpyridinium chloride as an OTC antimicrobial agent for topical use in the oral cavity when used within the proposed dosage limits set forth below. The Subcommittee bases its conclusions on the safety of cetylpyridinium chloride mouthrinses used in animal and pharmacokinetic studies, assessment of adverse events in randomized, placebo-controlled clinical

trials, and postmarket spontaneous adverse event data reported to the manufacturer and FDA.

The LD<sub>50</sub> of cetylpyridinium chloride is 250 milligrams per kilogram (mg/kg) given subcutaneously, 6 mg/kg intraperitoneally, 30 mg/kg intravenously, and 200 mg/kg given orally as a pure compound (Ref. 63). The data (Ref. 64) show that the oral LD<sub>50</sub> values in the rat from a mouthrinse containing 0.05 percent cetylpyridinium chloride were 34 mg/kg to 48 mg/kg of the mouthrinse alone. This lower LD<sub>50</sub> with the rinse formulation as compared to cetylpyridinium chloride in solution is likely due to the other components of the mouthrinse, such as the alcohol.

Subchronic toxicity studies of cetylpyridinium chloride administered orally at dose levels ranging from 5 to 500 mg/kg showed morbidity and death at 125, 250, and 500 mg/kg. At lower doses, the only significant finding in rats and dogs was gastric irritation at doses of 50 mg/kg per day and higher (Ref. 65). These studies are similar to studies conducted prior to 1950.

Two chronic exposure safety studies of 6 months and 1 year were reported (Ref. 65). Doses administered daily by oral gavage ranged from 5 to 75 mg/kg. Significant decreases in body weight and weight gain were noted in 40- and 75-mg/kg animals of both sexes. At necropsy, GI irritation was manifested as thickening of the stomach mucosa observed at the 40- and 75-mg/kg level, and in some animals administered 15 mg/kg.

Local irritation studies (Ref. 65) included eye irritation tests and dermal exposure. Evidence of eye irritation was observed at high concentrations but no dermal lesions were observed. Local irritation using cetylpyridinium chloride mouthrinse formulations was assessed in the canine oral mucosa irritation model (Ref. 65). A cotton plug saturated with cetylpyridinium chloride mouthrinse was applied to the gingival mucosa three to five times a day for 4 days. Mouthrinse formulations containing up to 0.45 percent cetylpyridinium chloride did not induce irritation after 20 applications. Lin et al. (Ref. 66) evaluated inhalation toxicity in rats and found clinical signs of toxicity, including respiratory difficulty, eye irritation, and nasal discharge at concentrations of approximately 0.1 mg cetylpyridinium chloride/liter and above. However, these nonlethal effects were reversible.

A study of the effects of alcohol and cetylpyridinium chloride on the buccal mucosa of hamsters was reported (Ref. 67). Animals received daily applications of 0.05 percent cetylpyridinium