

chloride for 21 days on the everted hamster cheek pouch. Abrasion was also carried out. No significant differences were found between the control and study animals.

Contact sensitization potential was assessed using a 25-percent concentration of cetylpyridinium chloride in petrolatum for sensitization and a 10-percent concentration for challenge. No evidence of sensitization was observed in any of the 24 participants (Ref. 65).

Pharmacokinetic studies assessing absorption, distribution, and elimination of cetylpyridinium chloride were done in rats and dogs (Ref. 65). In the rat study, approximately 85 percent of a single dose of radiolabeled cetylpyridinium chloride was detected in the feces and about 10 percent in the urine. The dog study was inconclusive, since only 56.5 percent of the radiolabeled cetylpyridinium chloride administered was recovered from the urine, feces, case rinses, organs, and carcass.

The safety data were systematically collected from several clinical trials (Refs. 68, 69, and 70). Adverse events did not differ between placebo and control except for tongue and tooth discoloration associated with cetylpyridinium chloride. In contrast, Lobene et al. (Ref. 71) found that approximately a quarter of the subjects using cetylpyridinium chloride reported a slight, transient irritation of the gingiva. In one short-term study (Ref. 72), more subjects in the cetylpyridinium chloride group were found to have aphthous ulcers than the placebo group. Gingival irritation and aphthous ulcers were not reported in other randomized controlled clinical trials of cetylpyridinium chloride-containing mouthrinses. Further studies of the mucosal irritancy potential of cetylpyridinium chloride, especially in those with hyposalivation, are warranted.

Studies (Refs. 65 and 73) showed that there are no significant changes in the balance of the human oral flora or in the overgrowth of potential pathogens such as *Candida*. It appears that cetylpyridinium chloride has activity in the range of 0.12 to 8 micrograms per milliliter ( $\mu\text{g/mL}$ ) in vitro against *S. aureus*, *S. sanguis*, *E. corrodens*, *Neisseria*, *Veillonella parvula*, *P. gingivalis*, *F. nucleatum*, and *Candida albicans*.

Data on teratogenic and mutagenic effects are available from in vitro and in vivo animal studies (Ref. 65). However, long-term cumulative effects on metabolism and teratogenic effects are not available from controlled human

studies. The FDA spontaneous adverse reaction reports and adverse events reports submitted suggest that clinical experience following long-term OTC use of the ingredient has not revealed overt toxic manifestations. Although the summarized FDA spontaneous adverse drug reaction report (Ref. 65) indicates that three deaths and six comas occurred after ingestion of cetylpyridinium chloride-containing mouthrinses, it is unclear to what extent the mouthrinses or other circumstances may have contributed to these severe adverse events. The Subcommittee notes that tooth and tongue staining, as well as oral irritation, may occur with the use of products containing cetylpyridinium chloride.

In summary, the safety of cetylpyridinium chloride has been extensively evaluated in a variety of controlled, clinical and nonclinical studies. Based on this information, in addition to adverse event data collected during more than 55 years of U.S. marketing of mouthrinses containing cetylpyridinium chloride, the Subcommittee concludes that cetylpyridinium chloride is safe when used at concentrations of 0.045 percent to 0.1 percent in mouthrinse formulations.

ii. *Effectiveness*. The Subcommittee concludes that cetylpyridinium chloride is effective as an OTC antigingivitis/antiplaque ingredient within the dosage limits proposed above.

The Subcommittee evaluated six placebo-controlled, blinded, clinical efficacy trials (Ref. 65). In five of the six studies, a 15- to 27-percent reduction in supragingival plaque was obtained with cetylpyridinium chloride in concentrations ranging from 0.05 to 0.1 percent. The reduction seems to persist for 6 months. Four 6-month trials and several shorter trials were also submitted (Refs. 70 and 73). All of the studies demonstrated a significant reduction of supragingival dental plaque with the use of 0.045 to 0.1 percent cetylpyridinium chloride mouthrinse. This is a reproducible finding in both short-term and 6-month studies based on the data submitted and in the published literature (Ref. 74).

The results of two 6-month studies (Refs. 68 and 69), a 2-month study (Ref. 75), and a 4-month study (Ref. 76) showed reductions in gingivitis (based upon gingival index) ranging from 15.7 to 41 percent. Although trends were noted, no clear-cut dose response in the antigingivitis effect was documented in any one study in that range.

Data from four other 6-month studies (Ref. 70) (three of which were carried out by different research groups) did not

demonstrate a statistically significant reduction in gingivitis. In the Ciancio study (Ref. 77), there was no statistically significant reduction in gingivitis, although there was a reduction in plaque. Similarly, in the Lobene study (Ref. 78), no differences in gingival index were seen at 4, 20, or 26 weeks, although there was a statistically significant reduction in gingival index at 8 weeks. In two studies (012-035 and 012-037) by Ackerman and DeGenero (Ref. 79), a mouthrinse containing cetylpyridinium chloride showed no effect on gingivitis at 6 months. In a 6-week study by Moran (Ref. 80), cetylpyridinium chloride in a mouthrinse had no effect on plaque or gingivitis. Although most of the formulations reduced plaque, the gingivitis results in these studies are not consistent.

The Subcommittee believes that differences in the results of studies on the effectiveness of cetylpyridinium chloride mouthrinse are likely explained by the use of different formulations (Refs. 65, 70, and 81). Based on the data presented, the biological effectiveness and chemical availability of cetylpyridinium chloride in a mouthrinse appear to be greatly affected by the particular formulation. Cetylpyridinium chloride in mouthrinse formulations all at approximately 0.045 percent nominal concentrations were shown to vary markedly between 4 and 77 percent. Thus, it is clear that inactivation of cetylpyridinium chloride is likely based upon formulation. It is recommended that the bioavailability of cetylpyridinium chloride in each formulation be determined to reduce the possibility that the active ingredient is removed due to chemical reaction, complexing, micelle (a colloid particle formed by an aggregation of small molecules) formation, or other sources of deactivation. Assessment of mouthrinses containing cetylpyridinium chloride in formulations similar to those tested in the positive studies (Refs. 68, 69, 76, and 77) show that 72 to 76 percent of the cetylpyridinium chloride is available (Ref. 82). Therefore, it is reasonable to assume that formulations containing 72 to 76 percent available cetylpyridinium chloride are active in reducing gingivitis and plaque.

At the request of the Subcommittee, the manufacturer conducted additional analyses demonstrating the effectiveness of cetylpyridinium chloride on a site and subject basis, relative to other oral healthcare practices, and on the basis of odds-ratio calculations. Specifically, using a minimum 33 percent reduction in bleeding criterion, results of 4 long-term studies were pooled to estimate an