

Several studies challenge the carcinogenesis of hydrogen peroxide. Cell culture experiments rich in catalase show a marked decrease in the mutagenic effects of hydrogen peroxide (Refs. 185 and 186). Further, variations exist between species in their ability to control the destructive effects by the release of catalase and reduced glutathione (Ref. 187). The mutagenic potential of hydrogen peroxide as measured by production of hydroxyl radicals in the presence of Fe<sup>2+</sup> has also been shown to be concentration dependent in a Chinese hamster cell line (Ref. 188). Additional mechanistic studies (Refs. 189 and 190) also suggested that the gel and paste phases of a toothpaste reduce the formation of free radicals. A generous supply of catalase in the oral cavity and studies demonstrating that hydrogen peroxide is rapidly degraded in the oral cavity indicate that hydrogen peroxide is unlikely to have a mutagenic potential at concentrations up to 3 percent (Ref. 191).

The ECETOC 1992 Joint Assessment of the toxic effects of hydrogen peroxide (Refs. 153 and 154) had the following conclusions: (1) Hydrogen peroxide concentrations of less than 1 percent do not appear to have gastrointestinal (GI) tumor-promoting potential; (2) chronic ingestion of 0.1 to 0.15 percent hydrogen peroxide causes an inflammatory response in gastroduodenal tissue of mice; (3) the mutagenicity of hydrogen peroxide in bacteria is a function of the genotype of the strain; (4) hydrogen peroxide has genotoxic potential only through the direct exposure of hydroxyl radicals on target DNA; (5) catalase reduces or abolishes the mutagenic response to hydrogen peroxide; (6) in vivo, many factors may contribute to the reduction of bioavailable hydrogen peroxide for systemic genotoxic action; (7) the possibility of genotoxic effect on cells that directly contact hydrogen peroxide at the site of application cannot be ruled out; and (8) no data are available to fully evaluate chronic toxicity and resulting carcinogenic potential of hydrogen peroxide.

The rate of decomposition of hydrogen peroxide in the oral cavity was determined in adults, children, and xerostomics. Hydrogen peroxide decomposition was so rapid that it was difficult to establish a rate of decomposition. In all cases, less than 27 percent of the hydrogen peroxide introduced into the oral cavity was present after 1 minute of brushing with dentifrices containing up to 3 percent hydrogen peroxide (Ref. 145). Most residual hydrogen peroxide would be

expectorated with the dentifrice after brushing, leaving very little for ingestion. Based on clinical studies and adverse event reporting, the lack of irritation to soft tissues of the oral mucosa following use of hydrogen peroxide-containing dentifrices provides further evidence of the safety of long-term use of hydrogen peroxide-containing dental products.

Hydrogen peroxide presents safety concerns at concentrations above 3 percent because of the lack of controlled studies conducted with concentrations between 3 percent and 30 percent hydrogen peroxide. Available evidence indicates that acute toxic effects encountered with high concentrations of hydrogen peroxide (i.e., 30 percent) are rapidly repaired, leaving no deleterious effects. The discussion above mentions only some of the many published articles detailing the mutagenic potential of this ingredient. Despite some safety concerns, the gathering of appropriate clinical data outweighs the currently documented risks, which are inconclusive. While the experimental data suggest a mutagenic effect of hydrogen peroxide, the Subcommittee's review of current data indicates that, at concentrations of up to 3 percent in oral care products, the risk appears to be especially minimal and hydrogen peroxide is safe for its intended use.

ii. *Effectiveness.* Because of the preponderance of anaerobic and microaerophilic microorganisms associated with most forms of periodontal disease, the testing of oxygenating agents to inhibit or kill these microorganisms is understandable. The primary killing mechanism for hydrogen peroxide is through the release of oxygen. Unfortunately, the action is short-lived and inhibited by organic matter.

Hydrogen peroxide added to a mouthrinse has been shown to increase the release of hypothiocyanate into saliva. Hypothiocyanate has been reported to be a bacteriostatic agent against some microbial species (Refs. 192 and 193) through the activation of the lactoperoxidase system (Ref. 194). The addition of hydrogen peroxide to human whole saliva resulted in increased amounts of hypothiocyanate and this effect was concentration dependent (Ref. 195). This study also showed that the concentration of hydrogen peroxide was critical to obtain optimum bacteriocidal effect. Incubation time for inhibitory effects required several minutes, which may be a significant stumbling block in utilizing exogenous hydrogen peroxide through this mechanism of action. Another study of the lactoperoxidase/

hypothiocyanate antimicrobial mechanism found that rinsing with a solution containing hydrogen peroxide can readily produce hypothiocyanate, although the amount was dependent on the volume and pH of the rinse and the concentration and pH of the hydrogen peroxide (Ref. 196).

In a 2-week, crossover study, Wennstrom and Lindhe (Ref. 197) found that a hydrogen peroxide-containing mouthrinse effectively prevented the colonization of several morphological groups of microorganisms, e.g., fusiforms, filaments, motile and curved rods, and spirochetes. These groups have been repeatedly associated with several forms of periodontal diseases. Plaque and gingivitis scores were also markedly reduced. The concentration of hydrogen peroxide released was not determined. In another short-term study, a 1.5-percent hydrogen peroxide rinse significantly reduced both plaque and gingivitis scores over the 7-day test period (Ref. 198). In a study using a rat model in which test animals on a high cariogenic diet were inoculated with plaqueforming microbial species, a 10-percent urea (carbamide) peroxide gel and 1 percent hydrogen peroxide solution significantly reduced the accumulation of plaque (Ref. 199). A 3-week study using 10 percent urea (carbamide) peroxide gel compared with a placebo showed a significant decrease in gingivitis but no comparable reduction in plaque scores (Ref. 200). The authors suggested that the oxygenating effects of the test solution produced an environment unsuitable for the microbial species responsible for the development of gingivitis. Similar results were found in another 3-week study using 10 percent urea peroxide gel (Ref. 201).

In contrast, a 3-week study comparing 1 percent hydrogen peroxide, 0.12 percent chlorhexidine, and a placebo rinse found little effect of the hydrogen peroxide on gingivitis scores and no demonstrable effects on plaque scores (Ref. 202). A 2-week study using a 1.5-percent hydrogen peroxide rinse compared to a placebo showed no benefit from the hydrogen peroxide either as a rinse or when delivered by an irrigation system (Ref. 203).

Testing of an 11-percent urea (carbamide) peroxide gel in a 3-month study (Ref. 204) and a 6-month study (Ref. 205) showed that plaque scores were significantly reduced when compared to conventional oral hygiene toothpaste controls. However, no effect on gingivitis could be determined in either study. In an 18-month study comparing a 1.5-percent hydrogen peroxide rinse with a fluoridated rinse