

b. *Dicalcium phosphate dihydrate.*

Dicalcium phosphate dihydrate is one of several phosphate preparations that have been used as buffers, fillers, and abrasives in OTC dentifrices and as inactive ingredients in numerous drug products. The Subcommittee concludes that dicalcium phosphate dihydrate is safe when used as a buffer, filler, or abrasive in a dentifrice, but not generally recognized as effective for OTC use as an antigingivitis agent.

i. *Safety.* The safety of dicalcium phosphate dihydrate has been established on the basis of animal experiments and consumer use as a primary component of oral care products. It is included in the list of inactive ingredients in OTC anticaries formulations (45 FR 20666 at 20670), and is also approved by FDA as an optional food additive ingredient in the manufacture of flour (21 CFR 137.105 and 137.185). Dicalcium phosphate dihydrate has a reported oral LD<sub>50</sub> value of greater than 10 g/kg for rats, and a dermal LD<sub>50</sub> value of greater than 7 g/kg for rabbits. It is nonirritating or slightly irritating on rabbit skin and in eye irritation tests, respectively. Rodent oral limit tests, dermal irritation tests, and human irritation tests using various dentifrice formulations containing 5 percent to 88 percent dicalcium phosphate dihydrate were submitted (Ref. 129). These studies were carried out using toothpaste containing from 5 percent to 88 percent dicalcium phosphate dihydrate. The LD<sub>50</sub> in rats is greater than 16 g/kg for a toothpaste containing 60:40 weight to volume (w/v) suspension of dicalcium phosphate dihydrate. Oral tissue irritation or sensitization potential of toothpaste containing dicalcium phosphate dihydrate was also evaluated in a series of studies (Ref. 129). The tests were carried out by having the subject brush 7 days, 5 times a day to provide an exaggerated test for oral tissue irritation. In no instances were any of the dentifrices containing dicalcium phosphate dihydrate either irritating or sensitizing under conditions of the test.

No reports were available regarding the toxicity of ingested dicalcium phosphate dihydrate in humans. It is estimated that the average adult might consume 2 to 3 g of phosphorous per day and, with an extreme diet containing maximum quantities of additives and naturally occurring phosphorous, could consume 6 to 7 g per day. Ingestion of an entire medium-size tube of toothpaste would increase the phosphorous consumption by several g, an amount unlikely to be significantly toxic. The saline cathartic effect of large doses of phosphate-

containing materials would tend to limit their absorption to nontoxic levels. The Subcommittee concludes that, in general, dicalcium phosphate dihydrate can be regarded as safe.

ii. *Effectiveness.* Studies of the short-term use of dicalcium phosphate dihydrate-containing dentifrices in man have shown reduction of supragingival plaque to be greater than toothbrushing with water (Ref. 129). These studies do not implicate dicalcium phosphate dihydrate as an active ingredient but rather might be explained by the abrasive effect of dicalcium phosphate dihydrate in assisting plaque removal by toothbrushing. Gingivitis reduction is also seen in such experiments, but this could also be related to the abrasive effects of dicalcium phosphate dihydrate and removing plaque. The Subcommittee believes there is no evidence for chemical interference with plaque formation or plaque removal and no evidence of dicalcium phosphate dihydrate as an antigingivitis agent. The Subcommittee concludes that, based on the available data, it would be inappropriate to claim that the plaque reduction associated with the use of this abrasive qualifies it as an antigingivitis/antiplaque agent.

c. *Hydrogen peroxide.* The Subcommittee concludes that hydrogen peroxide is safe at concentrations of up to 3 percent, but there are insufficient data available to permit final classification of its effectiveness at 1.5 to 3 percent concentrations for long-term OTC use as an antigingivitis/antiplaque agent.

Hydrogen peroxide was isolated by Thenard in 1818 and has been of commercial interest since the mid-nineteenth century. Hydrogen peroxide has been a component of OTC drugs such as topical antiinfectants, canker sore treatments, and earwax softeners. A 3-percent solution of hydrogen peroxide has been widely used as a topical antiseptic agent for suppurative (producing pus) wounds, inflammation of the skin and mucous membranes, by dentists for irrigation during root-canal therapy, and as a mouthrinse for acute necrotizing ulcerative gingivitis. Decomposition of hydrogen peroxide releases large volumes of oxygen, approximately ten times the volume of the solution. A 30-percent solution has been used for bleaching nonvital pulpless teeth.

The Advisory Review Panel on OTC Oral Cavity Drug Products classified hydrogen peroxide as a Category I ingredient for short-term use in oral wound cleansing and debriding in concentrations from 1.5 to 3 percent in aqueous solution (47 FR 22760 at 22906,

May 25, 1982). Ten percent carbamide peroxide in anhydrous glycerin, which releases 3 percent hydrogen peroxide, is also classified in Category I. Hydrogen peroxide is listed in the USP (Ref. 130).

i. *Safety.* The Subcommittee evaluated the toxicity and mutagenicity of hydrogen peroxide. The toxicity data suggested that 1.5 to 3 percent hydrogen peroxide in aqueous solution has a low toxicity. When ingested in large doses, hydrogen peroxide produces esophagitis and gastritis (Ref. 131). Few primary systemic toxic effects are expected at low concentrations because hydrogen peroxide decomposes in the oral cavity (Ref. 132) and bowel before absorption can occur.

The acute toxicity of hydrogen peroxide depends on the concentration tested, with more concentrated solutions being relatively more toxic than dilute solutions. In rats, concentrations of 0.25 percent to 0.5 percent hydrogen peroxide added to drinking water decreased growth and increased mortality within 6 weeks (Ref. 133). Decreased body weight was seen in Osborne-Mendel rats given 0.45 percent hydrogen peroxide in drinking water for 5 months, but this decreased body weight was regained within 2 weeks after replacing the hydrogen peroxide-containing drinking water with tap water (Ref. 134). The decreased body weight was possibly attributed to decreased liquid intake when hydrogen peroxide was provided in the drinking water. In case studies, fatal poisoning (Refs. 135 and 136) has been reported for ingestion of hydrogen peroxide at concentrations exceeding 3 percent or excessive ingestion of 3 percent hydrogen peroxide. Generally, ingestion of household peroxide (3 to 9 percent) causes no significant toxic effects (Refs. 137, 138, and 139).

The LD<sub>50</sub> of hydrogen peroxide has been established by Ito *et al.* (Ref. 140) as 1,567 mg/kg body weight in rats dosed with a 5-percent solution. The low acute toxicity of hydrogen peroxide is confirmed by unpublished data indicating an LD<sub>50</sub> of 5,000 mg/kg body weight for 6 percent hydrogen peroxide in rats (Ref. 141).

Teratogenic activity has not been demonstrated for hydrogen peroxide (Ref. 142). Hydrogen peroxide can be absorbed through the oral mucosa (Ref. 143) and epidermis (Ref. 144), but the exposure of the oral cavity to hydrogen peroxide is generally limited since it undergoes rapid decomposition. After 1 minute of brushing, less than 20 percent of the hydrogen peroxide introduced into the oral cavity can be recovered (Ref. 145).