

TABLE 17.—DATA FOR SHIELDED TEETH FROM THE BESSELAAR LABS STUDY (REF. 440)—Continued

| Experimental Groups | Modified Plaque Index Baseline | Mean $\pm$ Std. Error 3-Week |
|---------------------|--------------------------------|------------------------------|
| Group 3 (Control)   | 1.91 $\pm$ 0.07                | 2.24 $\pm$ 0.06              |

The study results indicated that the test rinses had a marginal effect, at best, on plaque reduction, because plaque scores actually increased for all groups on shielded teeth, although less so, for the experimental rinses. None of the tested rinses had any effect to prevent development of gingivitis.

Data collected in individual dental offices by dental practitioners (Ref. 437) had no protocols and lacked the basic requirements for controlled, randomized clinical trials. Therefore, these data were of questionable value.

The Subcommittee concludes that this combination of ingredients is safe, but there are insufficient data to support its effectiveness as an OTC antigingivitis/antiplaque agent.

e. *Peppermint oil and sage oil.* The Subcommittee concludes that peppermint oil and sage oil are safe, but there are insufficient data to classify the effectiveness of the combination as an OTC antigingivitis/antiplaque agent.

Peppermint oil is described as the volatile oil distilled with steam from the fresh overground parts of the flowering plant *Mentha piperita linne*, rectified by distillation and neither partially nor wholly dementholized (Refs. 441 and 442).

Sage oil is derived from the dried leaves of the plant *Salvia officinalis*, which contains the essential oil (Ref. 443). It is described as having carminative and astringent properties and is used as a flavoring agent. It is used with other volatile agents in preparations for respiratory-tract disorders, and in mouthwashes and gargles for disorders of the mouth and throat. It is also used in homeopathic medicine.

Both peppermint oil and sage oil were reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products, which classified them as inactive ingredients (47 FR 22760 at 22764).

i. *Safety.* Peppermint oil has been used as a food flavoring for many years (21 CFR 182.20). Safety studies on peppermint oil continue to the present. For example, Spindler and Madsen (Ref. 444) conducted a toxicity study in rats giving peppermint oil orally to groups of rats at dosage levels of 0, 10, 40, and 100 mg/kg body weight. Some encephalopathy and nephropathy were seen at the highest dose. The authors determined a NOAEL of 40 mg/kg body weight per day.

Immunotoxicity testing of commonly used food flavoring ingredients including peppermint oil was reported (Ref. 445). Humoral and cell-mediated immune responses in mice were evaluated. Only at very high dose levels did peppermint oil increase mortality rate and reduce survival time in the host resistance assay, but it did not significantly alter humoral immunity.

Toothpaste and mouth rinse products containing both peppermint oil and sage oil were tested on the skin of rabbits with either no or slight-to-moderate irritant effects reported. Oral toxicity in rats showed no gross post mortem change. No untoward irritation or sensation relative to the oral mucosa was reported (Ref. 446).

ii. *Effectiveness.* The Subcommittee concludes that there are insufficient data from controlled studies to permit final classification of the effectiveness of peppermint oil and sage oil as OTC active ingredients for the reduction of plaque and gingivitis.

A single-blind study (Ref. 447) showed significantly less bleeding and less plaque in 25 dental students following 1 month use of the test toothpaste and oral rinse compared to 25 students using the placebo. However, all the relatively young dental students (age 25.5  $\pm$  2.1 years) began with relatively low initial scores.

Although several efficacy studies of a toothpaste and an oral rinse containing peppermint oil and sage oil have been conducted (Ref. 448), these studies lack various aspects of double-blind, well-controlled research.

f. *Polydimethylsiloxane and poloxamer.* The Subcommittee concludes that these ingredients are safe, but there are insufficient data available to permit final classification of the effectiveness of the combination of polydimethylsiloxane and poloxamer as an OTC antigingivitis/antiplaque agent. The active ingredient is polydimethylsiloxane (dimethicone, simethicone), a fully methylated linear siloxane polymer used for its antifoaming properties in a number of marketed ingestible products such as antacids and certain foods (21 CFR 176.200). In order to insure the emulsification of the active ingredient, poloxamer, a polymer of polyoxyethylene, is used as a nonionic surfactant.

Polydimethylsiloxane combines readily with a number of other ingredients and has been packaged into different formulations (including sprays, mouthrinses, and dentifrices) and incorporated into oral hygiene devices (such as floss and interdental stimulators) and chewing gum. The ratio of the poloxamer to the polydimethylsiloxane varies from 100:1 in rinses to 1:1 in chewing gums. Concentrations range from 0.4 to 4 percent for liquid and gel emulsions, including toothpastes, and .01 to 0.2 g per use for interdental cleansing devices coated with solid emulsion, as well as chewing gum and mints.

#### i. *Safety.*

1. *Toxicity in animals.* Toxicity data in animals (Ref. 449) and humans (Ref. 450) indicate that polydimethylsiloxane has minimal toxicity. The biological safety of polydimethylsiloxane has been tested by subdermal, intramuscular, and subcutaneous administration at greatly exaggerated dose levels in rats for periods of up to 26 weeks and further followups of up to 2 years. Monitoring included hematological and urinary chemistry, clinical parameters, and gross and microscopic anatomy. No effect was noted on the survival, body weights, clinical chemistry, hematology, urine chemistry, organ weights, or gross and microscopic anatomical features of the test animals that could be related to the tested product (Ref. 449). Acute toxicity testing of the poloxamer indicated minimal or no side effects from exaggerated doses via ingestion and intraocular administration of the tested products (Ref. 449).

The combination of poloxamer and dimethicone, packaged as a gel, was tested for acute oral toxicity in rats and in a 20-day hamster cheek pouch application study. At a dose level of 10 g/kg of body weight no deaths were observed in the rat study. If this combination were toxic, at this dose level it would have been expected to kill one half or more of the animals. Additionally, no abnormal changes were observed in the cheek pouches after topical applications of 0.1 mL of the combination three times daily for 4 weeks.

2. *Toxicity in humans.* No human toxicity data were submitted because poloxamer and dimethicone are categorized as safe (Ref. 450). The long-term use of the ingredients in antacids,