

the plaster models. Subjects were instructed to place a measured quantity of dentifrice into the indentations in the tooth shield twice daily prior to its insertion in the mouth, and brush the remaining teeth. Plaque and gingivitis were assessed after 21 days. Various concentrations of zinc citrate in toothpaste or other ingredients alone or in combination with zinc citrate were used as well as placebos, which were not as effective as active ingredients. Because these studies were not randomized clinical trials, they cannot be considered as evidence of the effectiveness of zinc citrate.

The first 6-month study by Hefti and Marks (Ref. 374) was conducted to evaluate the relative effectiveness of a hydrogen peroxide/baking soda/fluoride/zinc citrate dentifrice with a commercially available fluoride dentifrice and a commercially available fluoride antitartar dentifrice. This was essentially a supragingival calculus study where subjects were selected based on having a score of at least 6.0 on the Volpe-Manhold Calculus Index at the time of screening. Clinical exams during the trial period were done at 45, 90, and 180 days. The Modified Gingival Index by Lobene et al. (Ref. 112) was used for gingival assessment. Only simple means for the 6 months assessment were given for the 3 groups of 60 to 63 subjects. A simple p value was given, indicating the multiingredient product and the other antitartar toothpaste group had statistically lower scores than the fluoride-only commercially available toothpaste. Three means were given for 45 and 90 days, plus one p value, showing similar results. No information was provided about subject characteristics, inclusion or exclusion criteria other than Volpe-Manhold Calculus Index scores, examiners, compliance, indicators of measurement error or uncertainty, or blinding. The conclusions concerning zinc citrate effectiveness were based on a multiagent product compared to other agents/ingredients.

The second 6-month clinical study (Ref. 375) included 295 subjects selected from a population of 330 adults of which 311 fulfilled strict dental and medical health requirements. No further details on health requirements were given. No information was provided about the study population, e.g., age, sex, education, and socioeconomic status. Inclusion criteria included a gingival index score greater than 0.5 but less than 2.5 on a scale of 0 to 3. One-third of the qualifying subjects were selected for plaque collection, which was performed prior to disclosing for

the plaque assessment. There was no information on how these subjects were selected.

The products used were described as supplied by the sponsor in identical two-chamber, 5.2 oz pump dispensers, each with one of three three-letter codes. The report (Ref. 375) describes the three as "negative control dentifrice," "experimental dentifrice," and "experimental dentifrice." An accompanying summary identified the products only as "dual-phase dentifrices containing stannous salts and/or zinc citrate." One of the three-letter codes was identified only as "the zinc citrate-containing dentifrice." Thus, there was no information about the composition and concentration of ingredients or details about differences in color, odor, and taste in the products tested. The Subcommittee does not believe this study adhered to strict criteria for a double-blind study because the following appeared in the report: "Except for some complaints about the taste and staining associated with experimental dentifrice 'ABC,' the products were favorably received." These complaints were associated with only one of the three tested products. This suggests that one product differed from the others in taste and staining and, therefore, the study was not a double-blind study.

Examiners were described only as "experimental examiners, who participated in a calibration exercise prior to initiating the investigation, performed the same assessments at each examination." The report did not discuss the number of examiners and their background, whether calibration was successful, or testing for intra-examiner and inter-examiner reliability.

Mean gingival index scores plus standard error were given for each of the three groups at baseline, 3 months, and 6 months (279 of 295 subjects completed 6 months). All scores were reduced from baseline at 3 and 6 months. The dentifrice containing zinc citrate was statistically significantly different ($p < 0.03$) from the "control" group. Mean scores at 3 months were 0.87 ± 0.02 for the control dentifrice, 0.83 ± 0.2 for the test dentifrice without zinc citrate, and 0.81 ± 0.02 for the test dentifrice containing zinc citrate. At 6 months the scores were 0.92 ± 0.2 for the control dentifrice, 0.86 ± 0.2 ($p < 0.04$) for the test dentifrice without zinc citrate, and 0.85 ± 0.02 ($p < 0.04$) for the test dentifrice containing zinc citrate. The study does not provide evidence that a clinically significant improvement in gingival index scoring was due to zinc citrate.

The 3-year trial (Ref. 376), of which results from the first 2 years were submitted, was a caries study. The main objectives of the trial were to establish the reduction of caries increments caused by increasing the level of sodium monofluorophosphate and to investigate whether the inclusion of 0.5 percent zinc citrate affected caries increments. Three thousand children with a mean age of 12.5 years and all within a 1-year age range were recruited. Two clinicians assessed all subjects, who were then randomly assigned to one of six toothpaste groups. One-half of the subjects used a toothpaste containing zinc citrate. Plaque (using Greene and Vermillion's Simplified Oral Health Index (OHI-S)) and gingivitis (Loe and Silness Gingival Index) were assessed each year. Six teeth were assessed: One molar, premolar, and incisor in each arch, at four surfaces on each tooth.

Differences between cumulative mean scores for groups using toothpastes with and without zinc citrate were calculated. One examiner showed nonstatistically significant differences for years 1 and 2 and a second examiner showed statistically significant differences. When pooled together, the small differences were statistically significant. There was no other information about examiner calibration or testing for intra and interexaminer reliability. Clinically significant effects due to zinc citrate could not be determined from this study.

The Subcommittee's criteria for data submitted from randomized clinical trials include presenting information on all of the major study components, e.g., the protocol (study population, agents, outcomes, rationale for statistical analysis), methods of randomization, concealment of allocation to study group, and method of blinding. Results should be presented with appropriate indicators of measurement error or uncertainty, avoiding dependence solely on statistical hypothesis testing, such as the use of p values, which fail to convey important quantitative information. Based on these criteria, the Subcommittee concludes that the data submitted were insufficient to permit final classification of the effectiveness of zinc citrate as an OTC antigingivitis/antiplaque agent.

2. Category III Combinations of Active Ingredients

Data to demonstrate safety and effectiveness as an antigingivitis/antiplaque agent will be required in accordance with the general guidelines on safety and effectiveness in section II.H of this document.