

Subcommittee concludes that these studies do not support a causal relationship between the use of alcohol-containing mouthrinses and oropharyngeal cancer.

The Subcommittee reviewed unpublished new data that included a specificity analysis (Ref. 37) of the data from the Winn et al. study (Ref. 24). This analysis excluded 75 cases (38 men and 37 women) who did not have oropharyngeal cancer (*i.e.*, epithelial cell cancer of the mouth) based on evaluation of the International Classification of Diseases codes. The excluded cases consisted primarily of tumors of the minor salivary glands and sarcomas and lymphomas that happened to occur within the oral cavity. Excluding these cases left 535 and 256 cases of oropharyngeal cancer in men and women, respectively. Evaluation of smoking and alcoholic beverage use indicated that both of these risk factors were more strongly associated with the included cases than with the total number of cases (included plus excluded). Neither smoking nor alcoholic beverage use were associated with the excluded cases. This analysis indicated that the excluded cases may not have the same etiology as the included cases and, therefore, should not have been included in the original analysis conducted by Winn et al. (Ref. 24) to evaluate risk associated with mouthrinse use.

When odds ratios for mouthrinse use in women were calculated for the included cases, they were decreased relative to the odds ratios for total cases originally reported by Winn et al. (Ref. 24). This was true for a number of subanalyses, including duration of use, frequency of use, age when use began, and alcohol concentration. Higher odds ratios for mouthrinse use among the excluded cases suggested that mouthrinse use was more strongly associated with excluded cases than with included cases. However, there is no biologically plausible explanation for this finding since the excluded cases represent a variety of tumor types whose origins cannot be presently explained by topical exposure to ethanol via mouthrinse use. In addition, the data were inconsistent with a dose-response with respect to duration of use, frequency of use and age when mouthrinse use started, which suggests that this finding may be related to information bias rather than a causal association. The specificity analysis among male cases was less informative than for females and supports neither a causal hypothesis nor information bias as the explanation for the weak association with mouthrinse use (odds

ratio 1.4) originally reported by Winn et al. (Ref. 24). The limited value of the specificity analysis in males is likely related to the fact that: (1) The excluded male cases represented a smaller percentage of the total male cases and (2) the odds ratio for mouthrinse use in males is smaller than it is in females. Both of these factors make it difficult to detect any shifts in odds ratios. The Subcommittee concludes that, overall, the specificity analysis of the Winn et al. study (Ref. 24) indicates that this study does not support a causal association between mouthrinse use and oropharyngeal cancer (Ref. 37).

Preliminary analyses from an unpublished case-control study of laryngeal, esophageal, and oral cancer (Ref. 38) showed that the odds ratio for mouthrinse use in males and females combined (adjusted for cigarette and alcoholic beverage use) was 1.4 (confidence interval 1.0 to 2.0). However, the analyses of frequency, duration, and age when use started showed inconsistencies that question a causal relationship. In addition, when the data were evaluated with respect to alcohol content, the highest odds ratio (unadjusted for smoking and alcoholic beverage use) was found among users of mouthrinses containing no alcohol (*e.g.*, salt water, vinegar, baking soda in water). The Subcommittee concludes that this finding differs from the Winn et al. study (Ref. 24) results showing that odds ratios were elevated only for mouthrinses having the highest alcohol content and is inconsistent with the hypothesis of a causal association between alcohol-containing mouthrinses and oral cancer.

An unpublished review of the literature concerning possible mechanisms of alcoholic beverage consumption and oral cancer risk was submitted to the Subcommittee (Ref. 45). Although alcoholic beverage consumption is a known risk factor for oral cancer and the literature on experimental mechanistic studies (*e.g.*, *in vitro* and animal studies) raises speculations concerning how the biological effects of alcohol may modulate cancer risk, the Subcommittee concludes that the relevance of these studies to mouthrinse use in humans has not been established.

Based on the studies reviewed, the Subcommittee concludes that the available data do not support a causal relationship between the use of alcohol-containing mouthrinses and oral cancer. The vote was unanimous with the Chairman abstaining. The Subcommittee acknowledges that epidemiologic research on oropharyngeal cancer will continue, and

that the conclusion reached by the Subcommittee is based on the data available at the time of its deliberations. However, because some studies did report a relationship between the use of high alcohol-content mouthrinses and pharyngeal cancer, the Subcommittee agrees that further studies should be conducted to determine the relationship between high alcohol-content mouthrinses and oral/pharyngeal cancers. In addition, the Subcommittee recommends that all mouthrinses should be labeled in a readily readable manner with the alcohol concentration in percent, *e.g.*, "Contains \_ % alcohol" on the principal display panel.

#### *H. General Guidelines on Safety and Effectiveness*

##### *1. General Statement*

The Subcommittee arrived at its conclusions and recommendations regarding the safety and effectiveness of all active ingredients after considering all pertinent data and information submitted. The Subcommittee adopted the following general "points to consider." These are not intended to restrict investigators, but are recommendations for studies recognized as desirable approaches to determine the safety and effectiveness of OTC antingivitis/antiplatelet active ingredients. In some cases, other methods may be equally applicable, or newer methods may be preferable. Also, these recommended studies may not produce all information necessary to determine that an ingredient is generally recognized as safe and effective.

##### *2. Guidelines*

An OTC drug included in a monograph is described in § 330.10 as generally recognized among qualified experts as safe and effective for use and as not misbranded. Proof of the safety of an OTC drug ingredient consists of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data. Proof of effectiveness of an OTC drug ingredient consists of controlled clinical investigations as defined in § 314.126(b) (21 CFR 314.126b)) by qualified experts to show that the drug provides clinically significant relief of the type claimed in its labeling. The latter requirement may be waived if it is not reasonably applicable to the drug in question or