

potentiating effect in the production of squamous cell carcinoma in animal cheek pouches treated with 7,12-dimethylbenz(a)-anthracene (DMBA). Decreased latency and larger tumors were observed as compared to controls.

Other animal studies (Refs. 29, 30, 32, and 33) have demonstrated similar effects. These studies were older and implied a model that is not comparable to what happens in humans. Moreover, some carcinogens are extremely species-specific, and limited information is available on direct experiments performed on the human mucosa.

If the synergistic effect of alcohol in causing an increased risk of oral cancer is attributed to a topical effect, as noted in the animal studies, then daily use of oral rinses containing a high concentration of alcohol may have a tissue altering effect. Whether this may be as significant as alcoholism in the epidemiology of oral cancer warrants continued investigation.

One of the few mechanistic evidences for a local alcohol effect has been demonstrated by permeability studies. In the presence of nicotine, alcohol had a greater relative effect on penetration of carcinogens in and across the floor of the oral mucosa (floor of the mouth, oral mucosa) (Ref. 34). Also, pharmaceutical studies have demonstrated that the oral mucosa can have a reservoir effect, so that compounds are rapidly taken up and held in the oral epithelium, extending the duration of their effect (Ref. 35). This mechanism has recently been utilized in a formulation using alcohol to increase permeability, thereby obtaining systemic delivery of proprietary drugs after only a mucosa exposure.

It is clear that further research is needed to investigate the role of alcohol as an enhancer of the penetration of carcinogens through the oral mucosa. In addition, the threshold of alcohol concentration necessary to achieve this phenomena needs to be investigated.

## 2. The Subcommittee's Conclusions and Recommendations Regarding Alcohol Content in Mouthrinses

On June 6, 1996, the Subcommittee, along with other scientific experts (e.g., epidemiologists and statisticians) held a workshop (Ref. 36) to further consider whether alcohol-containing mouthrinses contributed to oral cancers. Although some studies have implicated high alcohol-content mouthrinses as a possible cause of oral/pharyngeal cancer, the relationship between high alcohol-content mouthrinses and oral/pharyngeal cancer is not clear. The findings of various studies are contradictory and do not show a

consistent dose-response relationship. A major difficulty in deciding cause and effect in these studies is the possibility of confounding by known risk factors, such as high alcoholic beverage consumption and tobacco use.

The Subcommittee reviewed new data consisting of a specificity analysis (Ref. 37) using data from the Winn *et al.* study (Ref. 24) and a preliminary analysis from an unpublished study of laryngeal, esophageal, and oral cancer (Ref. 38). In addition, the Subcommittee reviewed seven case-control studies, published between 1979 and 1991 (Refs. 12, 13, and 23 through 27), of the association between mouthrinse use and oral cancer. These studies are described below.

Weaver *et al.* (Ref. 23) reported the use of alcohol-containing mouthrinses among 11 subjects with oropharyngeal cancer who indicated that they did not smoke or drink alcoholic beverages. These cases became part of a case-control study regarding an association between alcohol-containing mouthrinses and oropharyngeal cancer. Although the study was unevaluable, it generated the hypothesis that led to subsequent studies.

A 1983 case-control study by Wynder *et al.* (Ref. 12) evaluated the relationship between mouthrinses and oropharyngeal cancer. No positive findings were reported for men. In women, the relative risk, unadjusted for smoking and alcoholic beverage consumption, was statistically significant for daily use of mouthrinses. However, there was no consistent relationship for duration or frequency of use. Further, a refined analysis using a multiple logistic model indicated no association between mouthrinse use and oropharyngeal cancer. The investigators concluded that, due to the absence of a dose-response relationship and the possibility of confounding by tobacco and alcoholic beverage use, it was not possible to attribute an association between daily mouthrinse use and oral cancer in women.

A 1983 case-control study by Blot *et al.* (Ref. 13) included female subjects from a previous study of snuff use. A relative risk of 1.94 was reported for women who used a mouthrinse but did not use tobacco products. However, this was not statistically significant (confidence interval = 0.8 to 4.7), and there were no consistent dose-response relationships for years of use, frequency of use, time retained in the mouth, or concentration (i.e., diluted vs. full strength). Because dose-response relationships are important in considering whether there is an association between mouthrinse use and

oral cancer, the Subcommittee concludes that this study does not support a causal association between alcohol-containing mouthrinses and oropharyngeal cancer.

The Subcommittee reviewed three additional case-control studies published between 1985 and 1989 (Refs. 25, 26, and 27). One study by Kabat *et al.* (Ref. 26) is of particular interest because, although mouthrinses were not associated with increased oral cancer risk in terms of frequency or duration of use, cases were significantly more likely than controls to state that mouthrinses were used to disguise breath odors caused by alcoholic beverages or tobacco. In contrast, similar proportions of cases and controls reported using a mouthrinse to conceal food odors or for mouth infections or dental problems. The Subcommittee concludes that these findings indicate that mouthrinse use may be serving as a surrogate for underreported drinking and/or smoking.

A 1991 study by Winn *et al.* (Ref. 24) was the largest case-control study among the seven published studies evaluating mouthrinses (866 cases and 1,249 controls). Odds-ratios for oropharyngeal cancer risk after adjusting for tobacco and alcoholic beverage use were 1.4 (confidence interval 1.0 to 1.8) in men and 1.6 (confidence interval 1.1 to 2.3) in women. Dose-response relationships, such as duration of use, frequency of use, and age when use started, were questionable, with no trend analysis of these relationships reported. This study also showed a decreased odds-ratio for dental X-rays. There is no biologically plausible reason to expect X-rays to be protective against oral cancer, and the negative association is likely a reflection of less frequent visits for dental care by cases versus controls. However, the negative association could not be eliminated by adjustment for factors that are relevant to quality of dental care (e.g., education).

Thus, this study was capable of producing a statistically significant noncausal association that could not be eliminated by adjustment of the data. Further, regarding the odds ratio for mouthrinse use, confounding due to underreported use of tobacco and alcoholic beverages, both strong risk factors for oropharyngeal cancer, could result in an artificially elevated odds ratio. Such a false association can be produced even though the extent of underreporting is the same in both the case and control groups (Ref. 39). Information in the published literature indicates that especially drinking and sometimes smoking are underreported (Refs. 40 through 44). The