Additional Evidence Implicating Moist Snuff as a Potent Carcinogen

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A decade has passed since the U.S. Surgeon General (1) and the International Agency for Research on Cancer (2) concluded that smokeless tobacco products are a cause of cancer in humans. The association between smokeless tobacco use and cancer is strongest for cancers of the oral cavity and pharynx (3,4), although there may be some role of smokeless tobacco in other cancers (1).

In this issue of the Journal, Hoffmann et al. (5) present data on brand-specific levels of carcinogenic N-nitrosamines in moist snuff. This study suggests that the best-selling brands of moist snuff in the United States deliver not only the highest levels of bioavailable nicotine, but also the highest concentrations of tobacco-specific N-nitrosamines. Hoffmann et al. estimated that persons who use 10 g of these brands of moist snuff daily may be exposed to levels of carcinogenic N-nitrosamines that are 1.5-2.8 times higher than the levels inhaled by persons who smoke 20 cigarettes per day.

In response to the evidence for carcinogenicity of smokeless tobacco products, the marketing practices of the smokeless tobacco industry, and the explosive growth in the popularity of these products, in 1986 the U.S. Congress passed the Comprehensive Smokeless Tobacco Health Education Act (Public Law 99-252) (6). This legislation mandated the inclusion of warning labels on packages of snuff and chewing tobacco, banned television and radio advertisements for smokeless tobacco products, and required manufacturers of smokeless tobacco to provide lists of additives and the nicotine content of their products to the U.S. Department of Health and Human Services. (The Office on Smoking and Health is the repository for this information.)

Unfortunately, the list of additives that has been provided by these manufacturers is largely useless to researchers and the general public for two reasons: 1) The list is an amalgamation of more than 500 additives in the many brands produced by the 10 major manufacturers of smokeless tobacco products in the United States, making it impossible to discern the contents of any specific brand of snuff or chewing tobacco; and 2) no information is provided on the quantity or concentration of these additives, precluding any assessment of the health risks associated with any single constituent. The sheer number of chemicals added to smokeless tobacco products presents logistical difficulties in determining the toxicity, teratogenicity, or carcinogenicity of these additives.

In moist snuff and other tobacco products, it is the psychoactive alkaloid nicotine that accounts for the addictive properties of tobacco (7). The important indirect toxicologic role of nicotine is to sustain repeated and long-term use. Published studies (8,9), testimony before the U.S. House of Representatives Subcommittee on Health and the Environment (10), and smokeless tobacco industry documents (11) provide strong evidence that the level of bioavailable nicotine in moist snuff can be controlled by altering the pH level in solution. An alkaline pH environment at the interface of moist snuff and oral mucosa greatly enhances the conversion of nicotine to its unionized form, which facilitates its passage through oral epithelium, into the bloodstream, and to its central nervous system receptors (12-14). Therefore, changes in the pH of moist snuff can directly affect its pharmacologic and psychoactive effects. Control of pH can be accomplished in moist snuff by the use of alkaline additives, such as sodium carbonate (15). The bioavailability of nicotine can thereby be controlled, and moist

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snuff brands that collectively offer a wide range of doses of nicotine and rates of delivery can be—and have been—produced. Furthermore, these products have facilitated a marketing strategy to attract new users to brands that deliver low levels of nicotine (and thus lessen the probability of an adverse reaction to nicotine in novice users) and then to "graduate" them to brands delivering progressively higher nicotine levels as their addiction to nicotine develops (11).

Systemic absorption and blood levels of nicotine are substantial and are generally comparable in smokeless tobacco users and cigarette smokers (16). Clinically, this phenomenon manifests itself in the form of severe nicotine dependency and rather low success rates in smokeless tobacco cessation trials (17-20). The likelihood of exhibiting a symptom of nicotine addiction increases in direct relation to the number of times per day or days per month these products are used (21). A recent study (22) suggested that young people who use moist snuff brands that deliver higher levels of bioavailable nicotine are more likely to exhibit symptoms of nicotine addiction than those who use brands that deliver low- or medium-nicotine doses. This pattern persisted even after statistically controlling for frequency and intensity of snuff use. Despite the weight of the evidence that moist snuff and other forms of oral tobacco can lead to nicotine addiction (7), manufacturers of these products continue to deny that nicotine has addictive properties (10).

In view of the possible greater potential for addiction associated with brands of moist snuff that deliver higher levels of bioavailable nicotine (22) and the evidence from the study by Hoffmann et al. (5) that those brands may also carry the highest carcinogenic potential, there is great cause for concern: The most carcinogenic brands of moist snuff are also likely the most addictive.

Sales of moist snuff in the United States have increased from 17.2 million pounds in 1972 to 53.2 million pounds in 1994 (23). Most of this growth has been among adolescent and young adult males. The prevalence of snuff use among men aged 18-24 years increased from 0.7% in 1970 to 6.2% in 1991, a nearly ninefold increase (24). In 1994, approximately 20% of male students in the 10th and 12th grades of high school reported using snuff or chewing tobacco in the preceding 30 days (25).

The brands of moist snuff analyzed by Hoffmann et al. (5) are the preferred brands of more than 80% of adolescent and young adult smokeless tobacco users (22). Their choice of (and addiction to) brands with high levels of carcinogenic nitrosamines and nitrosamino acids are likely to result in future increases in the incidence of oral and pharyngeal cancers.

The study by Hoffmann et al. (5) may help pave the way for providing consumers of tobacco with information that could be of health significance. It would enable consumers to evaluate brands on the basis of the specific product constituents, as they can presently do for food product constituents such as salt and saturated fat (26). However, care must be exercised to avoid the problem that has occurred with assessment of cigarette "tar" and nicotine yields, which may not provide accurate estimates of human dosages (26).

As Hoffmann et al. (5) discussed and Swedish manufacturers of smokeless tobacco (27) demonstrated, it is feasible to produce moist snuff with substantially lower levels of nitrosamines. Although manufacturers of smokeless tobacco deny that their merchandise is carcinogenic (10), this reduction in the levels of carcinogens would be a step toward reducing the risk of cancer from these products. In addition, in our opinion, it is necessary to institute public health interventions that prevent or reduce the use of smokeless tobacco products by young people. These measures include continued health education on the adverse health consequences of using smokeless tobacco, enforcement of laws prohibiting the sale of tobacco to minors in all states and communities, and increases in the real price of smokeless tobacco products. Also, advertising that targets young people and the distribution of utilitarian objects carrying smokeless tobacco brand logos, such as caps, tee shirts, and pocketknives, should be eliminated (28-30). Free sampling of snuff and chewing tobacco, a major marketing strategy for these products (31), should be discontinued (29). Given the potential addictiveness and carcinogenicity of some of the most popular brands of moist snuff, nothing less should be acceptable.

References

The European Organization for Research and Treatment of Cancer (EORTC) and the U.S. National Cancer Institute (NCI) are offering an exchange program to enable cancer researchers to work at NCI or EORTC-related institutions for one to three years.

**General Conditions**

Awardees will receive an annual subsistence allowance of $30,000. Half of this amount will be provided by U.S. sources, the remainder by European sources.

European awardees will receive the U.S. contribution either from the NCI or from their extramural host institution. The European contribution of the exchangeship will be provided either by the scientist's home institution or by a European granting agency.

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**Documentation**

The following documents are required, in English, from all applicants:

- Completed application form.
- Description of the research to be undertaken, not to exceed three typewritten pages.
- Letter of invitation from the prospective host.
- Agreement to release the applicant from the home institution for the duration of the exchangeship.
- Statement concerning the provision of 50 percent of financial support by European sources. Non-EORTC member country candidates must continue at full salary at the home institution for the duration of the exchangeship.
- Three letters of recommendation mailed directly to the NCI Liaison Office by the recommending individuals.

**For More Information Contact:**

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**European Organization for Research and Treatment of Cancer**

**U.S. National Cancer Institute**
NCI Cooperative Breast Cancer Tissue Registry

What is the Registry?
The Registry is a collection of formalin-fixed, paraffin-embedded tissues with associated clinical and follow-up data from breast cancer patients for research studies, particularly those that translate basic research findings to clinical application. Four organizations collaborate to provide a patient base that reflects the local populations of four geographically diverse areas of the United States. Participants include: Fox Chase Cancer Center, Philadelphia, PA; Kaiser Foundation Research Institute, Portland, OR; University of Miami, Miami, FL; and Washington University, St. Louis, MO. A computerized central database is maintained in Silver Spring, MD.

What can the Registry provide?
The Registry can provide tissue sections from large numbers of formalin-fixed, paraffin-embedded primary breast cancer prepared, when possible, to meet the requirements of the research project. It can provide clinical and outcome data, including demographic data, diagnosis, extent of disease, treatment, followup, recurrence, survival, and vital status. It cannot identify patients or provide family history information. Researchers pay for preparation of sections and the costs of shipping. The Registry does not fund studies. Studies on Registry material may be funded by Federal or non-Federal sources. Documentation of the availability of Registry materials, in support of applications for research funding, may be provided for high-priority research.

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How do researchers apply?
Applicants complete brief proposals providing information on the study design and requirements for sample preparation, and clinical and followup data. They must document approval for use of human subjects following the requirements of the NIH Office of Protection From Research Risks. Annual application receipt dates are the fifteenth of May, September and January.

How are requests evaluated?
Requests are evaluated by the Research Evaluation and Decision Panel (REDP), a multidisciplinary, independent panel of experts that reviews applications for scientific merit and recommends priorities to the Registry Coordinating Committee. The Coordinating Committee sets operating policies, and determines the feasibility of providing tissue for studies.

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Additional information and forms may be obtained from:
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