

## Health Implications of Smokeless Tobacco Use

This article is adapted from the statement issued at the National Institutes of Health Consensus Development Conference on Smokeless Tobacco, January 13–15, 1986.

A list of the panel members who participated in the conference is in the accompanying box.

Cochairmen of the conference planning committee were William J. Blot, PhD, Chief of the Biostatistical Branch and the Analytical Studies Section, Division of Cancer Etiology, and Gayle Boyd, PhD, Research Psychologist, Office of the Director, Division of Cancer Prevention and Control, both of the National Cancer Institute.

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**S**MOKELESS TOBACCO includes both chewing tobacco and snuff. These products contain tobacco leaf and a variety of sweeteners, flavorings, and scents. In chewing tobacco, the leaf may be shredded (looseleaf), pressed into bricks or cakes (plugs), or dried and twisted into rope-like strands (twists). A portion is either chewed or held in place in the cheek or between the lower lip and the gum. The two categories of snuff, dry and moist, are made from powdered or finely cut tobacco leaves. In some countries, including, historically, the United Kingdom, dry snuff is sniffed through the nose, but in the United States both dry and moist snuff are used in the mouth or “dipped.” A small amount (pinch) is usually held in place between the lip or cheek and the gum.

Although smokeless tobacco was widely used in the United States in the past, during this century its use has declined sharply. There is now evidence

that this trend has reversed and that smokeless tobacco is regaining popularity. Market data show increases in manufacturing and sales, especially in the category of moist snuff, and total annual sales of smokeless tobacco are now close to \$1 billion. Reports from schools in different regions of the country indicate that smokeless tobacco—principally moist snuff—is being used by very young people, especially adolescent males.

Serious questions have been raised regarding the health and behavioral effects of smokeless tobacco use. Most notably, it has been linked to oral cancer. If smokeless tobacco use does produce adverse health effects, then its extensive use could have long-term public health consequences. It is important at this time that the available information be assessed, both to provide the scientific community with a synthesis of current knowledge and a framework for further research and to

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provide the public with the information it needs to make informed decisions regarding use of smokeless tobacco.

To this end, the National Cancer Institute, the National Institute of Dental Research, and the National Institutes of Health (NIH) Office of Medical Applications of Research convened a consensus development conference on Health Implications of Smokeless Tobacco Use on January 13-15, 1986. After a day and a half of presentations by experts in relevant fields, a consensus panel that included representatives of epidemiology, cancer, dentistry, psychology, pediatrics, psychopharmacology, education, and the public considered the evidence and agreed on answers to the following questions:

- What are the current trends in the use of smokeless tobacco in the United States?
- Does the use of smokeless tobacco increase the risk of oral or other cancers?
- Does the use of smokeless tobacco increase the risk of periodontal disease or other oral and health problems?
- What are the behavioral consequences of smokeless tobacco use?
- What issues regarding the health consequences of smokeless tobacco use require further research?

### **Current Use Trends**

The panel estimates that at least 10 million Americans have used smokeless tobacco within the past year, with 3 million of these users being less than 21 years old. Recent data indicate that significant proportions of teenage boys are current users, and the number of users in this age group is steadily increasing.

Detailed national data on trends in the use of smokeless tobacco are not currently available. There are indications, however, of recent significant changes. One such indication is the amount of smokeless tobacco manufactured in the United States. Production declined steadily from 1930 until the late 1960s. Subsequently, there has been a resurgence of production, with a steady increase in total smokeless tobacco output of about one-third in the last 15 years; but in just the last 5 years, the production of moist snuff alone, the form often used by youth, has increased by one-third (1-3).

The frequency of use of smokeless tobacco has only recently become a subject for national investigation. Initial results from a 1985 study based on a national sample of nearly 8,000 persons revealed

that 16 percent of males between 12 and 17 years of age had used some form of smokeless tobacco within the past year, and of these, about one-third used it one or more times per week (4). Males over 21 years of age used somewhat less, with use decreasing for older groups. These figures mask wide variations among subgroups. Black and Hispanic males used smokeless tobacco less than whites. Patterns of use appear to be similar in most of the country, although the lowest use is in the Northeast. Less than 2 percent of females used smokeless tobacco.

Some local studies have reported use by 30 to 40 percent of males in high school, with some investigations reporting use by more than 10 percent of grammar school students (5). In a sample of colleges, about 20 percent of the males reported use of smokeless tobacco (6).

In the one local longitudinal study, covering 1976 to 1982, tobacco chewing doubled and snuff dipping tripled, with peak use among boys 12 to 14 years old (7). It is of interest that in some schools, the percentage of males reporting regular use of smokeless tobacco was higher than the percentage reporting regular use of cigarettes.

### **Risk of Oral and Other Cancers**

Observations of human beings provide convincing evidence for an increased risk of oral cancer as the result of use of smokeless tobacco. Data on humans are insufficient to determine whether cancers at sites other than the mouth and throat are related to smokeless tobacco use.

**Human data.** With respect to human data, a North Carolina study of women provides the most compelling evidence of a role for snuff dipping in the causation of oral cancer (8). In this study, among nonsmokers the risk of oral cancer was 4.2 times greater for those who used snuff than for those who did not. For those who were users over several decades, the risk was much higher. These data are particularly striking in that (a) the cancer risks were greatest in those locations of the mouth where the snuff was placed; (b) the risk increased with increasing duration of snuff use; (c) factors such as diet, dental hygiene, alcohol intake, and cigarette smoking were found not to be responsible for the association between snuff and oral cancers; and (d) the risks were so large that it would be difficult to postulate alternative explanations for the association between oral cancer and snuff other than a causal one.

These findings are supported by other epidemiologic studies, primarily of the case-control type, and by clinical case series. However, most of these studies did not specify the type of smokeless tobacco product, such as snuff or chewing tobacco. Thus, it seems prudent to recognize the carcinogenic potential of all smokeless tobacco products while acknowledging that the effect of snuff has been more fully documented.

Although this relationship has been most clearly demonstrated for elderly rural women residing in the southeastern United States, there is reason to believe that snuff would also be carcinogenic in women and men in all geographic locations. In fact, men using smokeless tobacco experienced a 3.9-fold increased risk for oral cancer in a study based on the Third National Cancer Survey (9). Young people who start the use of snuff in grade school and continue its use through adult life are likely to experience comparable risks.

Our conclusion with respect to oral cancer is supported by multiple studies showing a relationship between oral cancer and chewing of betel quid containing tobacco in India and Southeast Asia (10). Furthermore, the conclusion is consistent with the judgment of a recent working group of the International Agency for Research on Cancer, which reported that the evidence associating snuff with oral cancer is "sufficient" to indicate a causal relationship (11).

**Carcinogens in smokeless tobacco.** Chemical analysis of various types of smokeless tobacco has revealed the presence of polonium-210, a radioactive alpha-emitter and known radiation carcinogen, and representatives of two classes of powerful chemical carcinogens, the polycyclic aromatic hydrocarbons and the nitrosamines.

Of the 19 nitrosamines identified in smokeless tobacco, the carcinogenic nitrosamines presenting the highest concentrations are NNN and NNK, both of which are related chemically to nicotine (12). Snuff contains 1.6 to 135 milligrams per kilogram (mg/kg) of NNN and 0.1 to 14 mg/kg of NNK. Looseleaf and plug tobacco contain 0.2 to 8.2 mg/kg of NNN and 0 to 1.0 mg/kg of NNK. For comparison, U.S. foods and beverages may not contain more than 0.01 mg/kg of nitrosamines.

Both NNN and NNK readily produce cancer in rats and hamsters in organs such as the nose, trachea, esophagus, and liver (13). Benign tumors (papillomas) of the mouth are induced when NNN and NNK are applied directly to the mouth of rats.

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**Carcinogenesis tests in animals.** Repeated experimental studies in animals have failed to provide adequate evidence that chewing tobacco, snuff, or extracts derived from them induce cancer.

**Implications for human health.** The risk of oral cancer in the United States is small for persons who do not smoke, drink alcoholic beverages, or use smokeless tobacco. The data considered at the Consensus Development Conference, however, raise the concern that regular users of snuff, especially those beginning use as children, may develop oral cancer later in life. The panel believes that the public should be warned that the use of smokeless tobacco, particularly snuff, increases the risk of oral cancer.

### **Risk of Other Oral Health Problems**

Evidence supports an association of smokeless tobacco use with gingival recession and oral leukoplakia, but there is insufficient evidence of an association with periodontitis or tooth decay. Other potential physical health hazards are essentially unexplored.

**Gingival recession, gingivitis.** Both case reports and studies of larger samples show an association of smokeless tobacco use with localized gingival recession (receding gums), especially where the tobacco is habitually placed (14,15). One study has reported a significant association of smokeless tobacco use with generalized gingivitis (16). Data currently are insufficient to support an association of smokeless tobacco use with generalized or advanced periodontal disease.

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**Tooth decay.** There are disparate data on whether smokeless tobacco use increases or decreases tooth decay. The absence of reliable data that take into account the diversity of smokeless tobacco products and the amount and bioavailability of contained sugars and fluoride may contribute to the lack of agreement among the few reports on this topic.

**Leukoplakia.** Several reports associate snuff use and, in at least one report, chewing tobacco use with the presence of white patches of the oral mucosa clinically known as leukoplakia (17). Indeed, leukoplakia is a frequent concomitant of smokeless tobacco use. Although multiple studies describe the transformation of leukoplakia to malignancy within the range of 1 to 18 percent of patients over observation periods ranging from several months to 11 years, there are few data on whether snuff-associated leukoplakia per se undergoes similar frequencies of malignant transformation (18). The studies done to date probably have not been conducted for sufficient time or with sufficient numbers of long-term users to define the incidence of malignant transformation. Studies from India and Southeast Asia, involving different tobacco products and use patterns, suggest that the long-term risk for malignant change of smokeless tobacco-associated leukoplakia may be significant (19).

**Other health risks.** Blood levels of nicotine achieved by cigarette smoking, which are similar to those achieved by smokeless tobacco use (20), cause elevations of blood pressure, heart rate, certain blood lipids, and catecholamines. However, no direct epidemiologic data are available on cardiovascular morbidity and mortality in association with smokeless tobacco use.

The complex array of constituents in smokeless tobacco presents a variety of potential health risks for the user as well as for the offspring of pregnant female users. In addition to nicotine, heavy metals such as lead and cadmium have been found in smokeless tobacco at levels that represent potential risks to the fetus and young child.

## **Behavioral Consequences**

**The effects of nicotine.** Tobacco produces psychological effects variously described as relaxing, arousing, and euphoriant. Over the past two decades, laboratory and clinical studies have indicated that these effects are mediated by nicotine and blocked by mecamylamine, a drug that competes for nicotine receptors in the brain. Tobacco use leads to a state of dependence in most regular users (21). This state is characterized by tolerance, physical dependence, and willingness to expend considerable efforts to maintain blood levels within a range of values bounded on the high side by toxic effects and on the low side by the onset of withdrawal symptoms. Blood levels achieved by smokeless tobacco use are similar to those of cigarette smoking. Nicotine self-administration patterns are very similar to those of other central nervous system stimulant drugs in both laboratory animal and human studies.

The abuse liability of a substance—the degree of its ability to gain control over the user—is correlated with the delay between administration and brain levels sufficient to engender a psychological effect. Because nicotine from smokeless tobacco is presumed to reach the brain more slowly than that from cigarette smoke, it might be hypothesized that smokeless tobacco would have lower abuse liability. However, in studies of teenagers who attempted to stop using smokeless tobacco, only a small percentage were able to do so, suggesting that tobacco by the oral route has substantial addicting properties. The continued use of smokeless tobacco even by those who experience serious adverse health consequences attests to its addicting powers.

Addicted users of nicotine become tolerant to the drug; that is, despite experiencing initial unpleasant side effects such as tremulousness, dizziness, and nausea, such users increase their dosage until it levels off at one that fulfills their need. Such users seek nicotine continually. Some users of smokeless tobacco use it even while sleeping.

The physical dependence associated with nicotine induces withdrawal symptoms when addicted users

abruptly discontinue its use. Thereafter, ex-users often experience craving for nicotine and many become users again.

**Other behavioral effects.** Tobacco withdrawal produces increased irritability and decrements in several basic cognitive functions. These disruptive effects begin within hours of the last nicotine dose. Such cycles of intake and abstinence are typical of use patterns by youth in school and adults in many employment situations. Thus, the associated cognitive impairments could have adverse effects on academic and job performance.

Behaviors can become interchangeable based on their function to the individual. For example, current opinion is that some smokers are switching to smokeless tobacco because the latter is considered a safe alternative for maintaining their nicotine dependence. Other opinions are that young people using smokeless tobacco often switch to cigarettes. Use of smokeless tobacco in children is sometimes associated with the use of hard liquor, beer, wine, cigarettes, and marijuana.

Behavioral pharmacology and learning studies show that the determinants of the initiation, maintenance, and reduction of substance use result from the interaction between biochemical and behavioral processes. For smokeless tobacco, nonbiochemical factors that are correlated and readily manipulable include advertisements about smokeless tobacco, influence from peers, parental acceptance of smokeless tobacco use, and a perception that smokeless tobacco may be less harmful than smoking tobacco.

## Further Research

There is a pressing need for well-designed studies of

1. Prevalence of smokeless tobacco use based on continuing national probability sample data, including type of product, age, sex, region, and concomitant cigarette smoking. In addition, longitudinal studies should be conducted.

2. Users and nonusers of smokeless tobacco products, to characterize better the prevalence and incidence of periodontal diseases, caries, leukoplakia, and cancer. These studies should identify, as far as possible, the nature and contents of products used, patterns and durations of use, concomitant use of other substances such as alcohol and smoking tobacco, and occurrence of viral infections. Where appropriate, they should

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use tissue biopsy as well as critical clinical and laboratory measurements.

3. Cancers of sites other than the mouth carried out in geographic areas with high rates of smokeless tobacco use.

4. Potential role of smokeless tobacco in cardiovascular disease and adverse outcomes of pregnancy.

5. Potential of users of smokeless tobacco to produce nitrosamines in vivo.

6. Research on the relationship between amounts of smokeless tobacco used and plasma levels of lead, cadmium, and other potential toxins.

7. Strategies for the development and evaluation of prevention programs, including school-based programs, taking into consideration regional, ethnic, age, socioeconomic, and other variables.

8. Development and evaluation of early intervention and treatment programs to reduce smokeless tobacco dependence, including a range of approaches based on pharmacological and behavioral treatments.

Specific populations that deserve special consideration include elementary school, junior and senior high school, and college age young people; persons with specific risk or disease conditions, including malignancies, cardiovascular disease, women at risk for pregnancy; and workplace- and industry-specific populations where elevated smokeless tobacco use is common.

## Conclusions

Use of smokeless tobacco has a long history in the United States, but trends in recent years, in particular the increasing use of snuff by children and young adults, have led to concerns about possible health consequences. National data suggest that at least 10 million persons have used

smokeless tobacco of one kind or another in the past year. Patterns of use by age, sex, and type of product vary across the country, but prevalence of use overall is relatively comparable.

The human evidence that use of snuff causes cancer of the mouth is strong. Risk is particularly high for parts of the mouth where the snuff is usually placed. Data are currently insufficient to come to any conclusions regarding the relationship of smokeless tobacco use to cancers at other sites. Repeated experimental studies in animals have failed to provide adequate evidence that chewing tobacco, snuff, or extracts derived from them induce cancer. However, nitrosamines chemically related to nicotine occur at high levels in snuff and, generally, at lower levels in chewing tobacco. These compounds are highly carcinogenic in animals. The concentrations of nitrosamines in smokeless tobacco are far higher than the levels of these compounds allowed in any U.S. food or beverage.

Smokeless tobacco use increases the frequency of localized gum recession and leukoplakia where the snuff is usually placed, but evidence on its relationship to other diseases of the oral cavity is inadequate. The presence of lead in smokeless tobacco may pose a special risk for the developing fetus.

Use of smokeless tobacco releases nicotine into the bloodstream and produces blood levels of nicotine comparable to those produced by smoking tobacco. The primary behavioral consequence of regular use of smokeless tobacco is long-term nicotine dependence and its associated health risks.

Use of smokeless tobacco is one of a number of health-endangering behaviors which frequently coincide, raising the clear potential for long-term and serious consequences.

References.....

1. U.S. Department of Agriculture: Tobacco: outlook and situation report. U.S. Government Printing Office, Washington, DC, 1985.

2. Shelton, A.: Smokeless sales continue to climb. Tobacco Reports 109: 42-44 (1982).

3. U.S. Department of Agriculture: Annual report. Tobacco statistics 1976. Statistical Bull. No. 570, Washington, DC, 1977.

4. Rouse, B. A.: National prevalence of smokeless tobacco use. NIH Consensus Development Conference on Health Implications of Smokeless Tobacco Use, Bethesda, MD, 1986.

5. U.S. Public Health Service: The health consequences of using smokeless tobacco. A report to the Surgeon General. U.S. Government Printing Office, Washington, DC, 1986.

6. Glover, E. D., et al.: Smokeless tobacco trends in the United States. World Smoking and Health. In press.

7. Hunter, S. M., et al.: Longitudinal patterns of cigarette smoking and smokeless use in youth. Am J Public Health 76: 193-195 (1986).

8. Winn, D. M., et al.: Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 304: 745-749 (1981).

9. Williams, R. R., and Horn, J. W.: Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. JNCI 58: 525-547 (1977).

10. Gupta, P. C., Pindborg, J. J., and Mehta, F. S.: Comparison of carcinogenicity of betel quid with and without tobacco. An epidemiologic review. Ecol Dis 1: 213-219 (1982).

11. International Agency for Research on Cancer: Tobacco habits other than smoking; betel-quid and areca-nut chewing and some related nitrosamines. IARC Monogr 37. World Health Organization, Lyon, France, 1985.

12. Hoffmann, D., et al.: Carcinogenic agents in snuff. JNCI 76: 435-438 (1986).

13. Hoffmann, D., and Hecht, S. S.: Nicotine-derived N-nitrosamines and tobacco-related cancer: current status and future directions. Cancer Res 45: 935-944 (1985).

14. Offenbacher, S., and Weathers, D. R.: Effects of smokeless tobacco on the periodontal, mucosal and caries status of adolescent males. J Oral Pathol 14: 169-181 (1985).

15. Poulson, T. C., Lindenmuth, J. E., and Greer, R. O.: A comparison of the use of smokeless tobacco in rural and urban teenagers. CA 34: 248-261 (1984).

16. Moders, T., Lavstedt, S., and Ahlund, C.: Relation between tobacco consumption and oral health in Swedish school children. Acta Odontol Scand 38: 223-227 (1980).

17. Axell T, et al.: International seminar on oral leukoplakia and associated lesions related to tobacco habits. Community Dent Oral Epidemiol 12: 145-154 (1984).

18. Silverman, S., Gorsky, M., and Lozada, F.: Oral leukoplakia and malignant transformation. Cancer 53: 563-568 (1984).

19. Mehta, F. S., Gupta, P. S., and Pindborg, J. J.: Chewing and smoking habits in relation to precursor and oral cancer. J Cancer Res Clin Oncol 99: 35-39 (1981).

20. Gritz, E. B., et al.: Plasma nicotine and cotinine concentration in habitual smokeless tobacco users. Clin Pharmacol Ther 30: 201-209 (1981).

21. Henningfeld, J. E., and Goldberg, S. R.: Stimulus properties of nicotine in animals and human volunteers: A review. In Behavioral pharmacology: the current status, edited by L. E. Seiden. Alan Liss, New York, 1985, pp. 433-449.