Systemic Absorption and Effects of Nicotine From Smokeless Tobacco

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SYSTEMIC ABSORPTION AND EFFECTS OF NICOTINE FROM SMOKELESS TOBACCO

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Abstract—Nicotine is absorbed in substantial quantities from smokeless tobacco and could contribute to the adverse consequences of smokeless tobacco use. Chronic systemic exposure to nicotine could contribute to accelerated coronary artery disease, acute cardiac ischemic events, and hypertension. Systemic absorption of sodium and mutagenic chemicals from smokeless tobacco could aggravate hypertension or cardiac failure, or contribute to cancer, respectively. Information concerning the potential hazards of nicotine and other systemically absorbed toxins may be incorporated into educational programs to discourage the use of smokeless tobacco.

Key words: Nicotine, smokeless tobacco, tobacco, snuff, cardiovascular, cancer.

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In addition to causing oral pathology, there is concern that smokeless tobacco use produces systemic effects that might adversely affect health. Of particular concern is exposure to nicotine, which is present in substantial amounts in smokeless tobacco. Dr. Henningfield has reviewed the evidence that nicotine exposure results in addiction, which is central to maintaining smokeless tobacco use in many users (Henningfield *et al.*, 1997). I will discuss other possible adverse effects of smokeless tobacco related to nicotine as well as other substances absorbed systemically from smokeless tobacco.

The basic and clinical pharmacology of nicotine has been extensively reviewed elsewhere (Benowitz, 1988, 1996). In brief, the main actions of nicotine involve activation of the sympathetic nervous system, resulting in heart rate acceleration (from 10 to 20 beats/min) and increased blood pressure (from 5 to 10 mm Hg). Nicotine increases circulating levels of catecholamines and free fatty acids, with effects on lipid metabolism that could contribute to higher levels of total cholesterol and lower levels of high-density lipoproteins that are found in cigarette smokers (Craig *et al.*, 1989; Hellerstein *et al.*, 1994). Cigarette smoking promotes coagulation, which is a major mechanism in acute cardiac events. Some animal data suggest that nicotine contributes to platelet activation, but studies of smokeless tobacco users with nicotine levels comparable with those of cigarette smokers showed no evidence of platelet activation in vivo (Folts and Bonebrake, 1982; Wennmalm *et al.*, 1991).

Nicotine has been suspected to contribute to some of the adverse consequences of cigarette smoking (Table 1), although causation has not been proven. Of greatest concern with respect to nicotine and smokeless tobacco use is the acceleration of coronary and peripheral vascular disease. Nicotine could promote atherosclerotic vascular disease by actions on lipid metabolism and/or hemodynamic effects (Benowitz, 1991).

ABSORPTION OF NICOTINE FROM SMOKELESS TOBACCO

Smokeless tobacco contains considerable nicotine, much more than is contained in cigarette tobacco (Table 2). The dose of nicotine available from (*i.e.*, contained in) a typical daily use of snuff is 157 mg (*per* 15 g) and from chewing tobacco 1176 mg (*per* 70 g) (Benowitz *et al.*, 1990). The time course of blood nicotine concentration after typical doses of smokeless tobacco is shown in Fig. 1. Average systemic doses of nicotine in this study of 10 users were 3.6 mg from moist snuff (2.5 g held in the mouth for 30 min), 4.5 mg from chewing tobacco (7.9 g chewed over 30 min), and 1.0 mg nicotine from an average cigarette (Benowitz *et al.*,

1988). There is considerable variation among individuals in the amount of nicotine absorbed from smokeless tobacco, even when they all place the same-sized dose in their mouths.

When snuff or chewing tobacco is used throughout the day, blood nicotine concentrations are similar to those seen with cigarette smoking (Fig. 2). These data are from a cross-over study of eight individuals who used tobacco *ad libitum*, averaging, for oral snuff, 15.6 ± 5.9 g/day, for chewing tobacco, 72.9 ± 21.6 g/day, and for smoking cigarettes, 36.4 ± 10/day (Benowitz *et al.*, 1989).

Using plasma cotinine as an indicator of daily intake of nicotine from smokeless tobacco, one can compare different populations of tobacco users. Several studies have shown that cotinine levels in smokeless tobacco users are similar to those in cigarette smokers, although, among professional baseball players, blood cotinine levels were found to be lower, particularly among users of chewing tobacco, compared with smokers (Gritz *et al.*, 1981; Holm *et al.*, 1991; Wennmalm *et al.*, 1991; Siegel *et al.*, 1992). The lower level of cotinine in baseball players probably reflects intermittent use, often just in conjunction with playing baseball.

TABLE 1

POTENTIAL ADVERSE EFFECTS OF NICOTINE

Nicotine Intoxication	Delayed Wound Healing
Accelerated Atherosclerosis	Reproduction Toxicity (low birth weight, prematurity, spontaneous abortion)
Acute Myocardial Infarction	Fetal Neurotoxicity
Sudden Death	Peptic Ulcer Disease
Stroke	Esophageal Reflux
Hypertension	

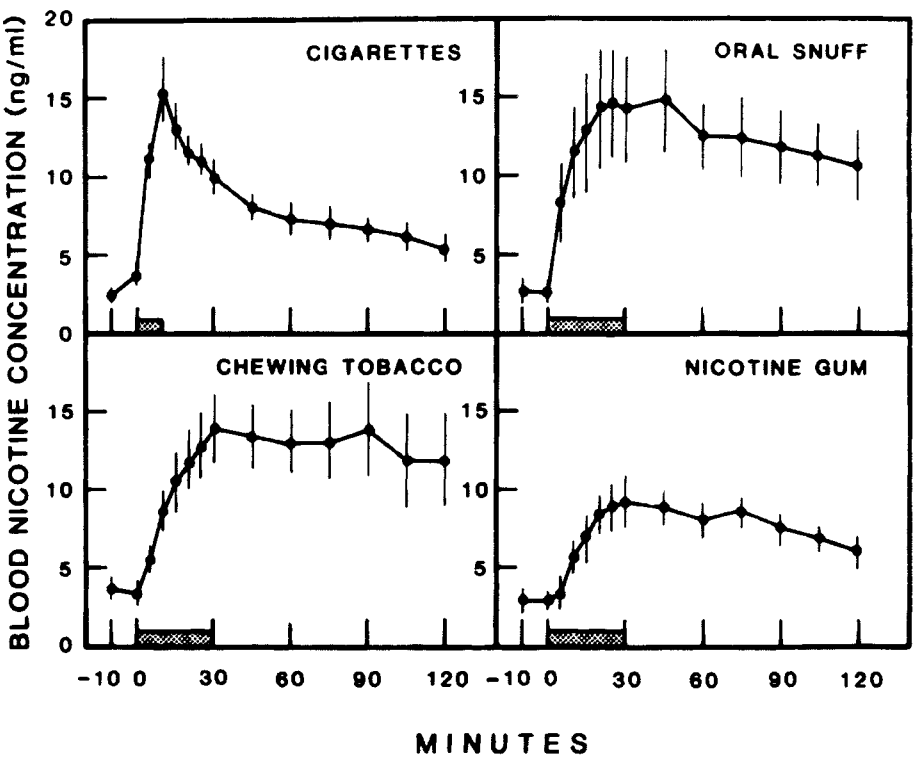

Fig. 1—Blood nicotine concentrations with cigarette smoking and the use of smokeless tobacco in single doses (reprinted with permission from Benowitz et al., *1988).*

CARDIOVASCULAR EFFECTS OF SMOKELESS TOBACCO

The use of single doses of snuff or chewing tobacco increases heart rate and blood pressure to a degree similar to that observed after the smoking of a cigarette (Fig. 3) (Benowitz *et al.*, 1988). During regular cigarette smoking, heart rate increases with the first few cigarettes of the day and then remains elevated throughout the day and overnight, with an average of 7 beats/min above that observed in a non-smoking condition (Benowitz *et al.*, 1984). Similar increases are seen with the daily use of snuff and chewing tobacco (Fig. 4) (Benowitz *et al.*, 1989). Likewise, urine cate-cholamine excretions are similar in individuals using moist snuff, chewing tobacco, and smoking cigarettes (Benowitz *et al.*, 1989). Thus, insofar as the hemodynamic effects of nicotine contribute to adverse health consequences of cigarette smoking, nicotine derived from smokeless tobacco would be expected to produce similar hazards.

The use of smokeless tobacco as well as smoking cigarettes results in a transient increase in blood pressure (Benowitz *et al.*, 1988). Cigarette smoking is not associated with an increased risk of hypertension in general, although complications of hypertension are more common in smokers. Nicotine could aggravate underlying hypertension by increasing cardiac output and constricting blood vessels. Cases have been reported in which hypertension has been acutely worsened by the use of smokeless tobacco (McPhaul *et al.*, 1984; Wells and Rustick, 1986; Adelman, 1987), and one survey of college students indicates that smokeless tobacco users have a higher prevalence of increased blood pressure (Schroeder and Chen, 1985). A large cross-sectional survey of Swedish construction industry workers examined between 1971 and 1974 found a significantly increased risk of hypertension (diastolic blood pressure > 90 mm Hg) in snuff users 46 to 55 years old (odds ratio 1.8, 95% CI 1.5-2.1) compared with that in age-matched non-users (odds ratio

TABLE 2

NICOTINE CONTENT
OF CIGARETTES AND SMOKELESS TOBACCO

	Concentration of Nicotine (mg/g)	Typical Single Dose (g Tobacco)	Nicotine in Single Dose (mg)	Nicotine in Dose Typically Consumed in 1 Day
Cigarettes (15)[a]	15.7 (13.3-26.9)[b]	0.54	8.4	168 mg *per* 20 cigarettes
Moist snuff (8)[a]	10.5 (6.1-16.6)[b]	1.4	14.5	157 mg *per* 15 g
Chewing tobacco (2)[a]	16.8 (8.1-24.5)[b]	7.9	133.0	1176 mg *per* 70 g

[a] Number of brands tested.
[b] Range.

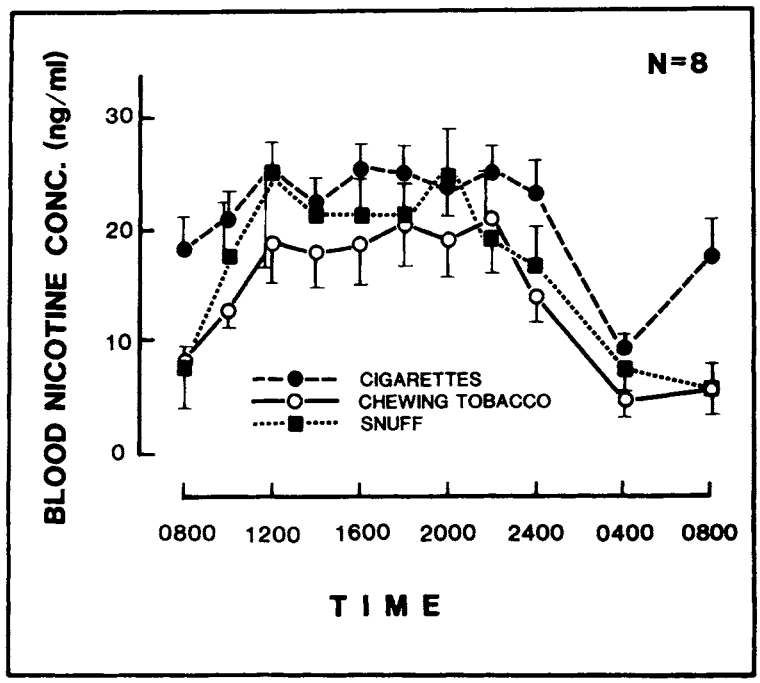

Fig. 2—Blood nicotine concentrations with daily cigarette smoking and use of smokeless tobacco (reprinted with permission from Benowitz et al., *1989).*

1.0), and cigarette smokers (odds ratio 0.8, 95% CI 0.7-0.9) (Bolinder *et al.*, 1992). Of note, the risk of hypertension was seen primarily in middle-aged and older workers and less or none at all in younger snuff users.

On the other hand, Eliasson *et al.* (1991) found no difference in blood pressure among young snuff users compared with smokers or non-tobacco-users, and Siegel *et al.* (1992) found no relationship between smokeless tobacco use or serum cotinine level and blood pressure in a large cohort of American professional baseball players. Thus, reports on the effects of smoke-less tobacco use on blood pressure are conflicting, and future studies will need to be done to clarify this relationship and specifically to look at the interaction among smokeless tobacco use, age, and blood pressure.

In a study of smokeless tobacco use in individuals consuming a diet of constant sodium content, it was discovered that urinary excretion of sodium increased during snuff or chewing tobacco treatments (Benowitz *et al.*, 1989). Sodium is present in smokeless tobacco as part of an alkaline buffer to facilitate buccal absorption of nicotine. An average of 26 and 41 mEq of sodium was absorbed during daily use of oral snuff and chewing tobacco, respectively (Fig. 5). This level of sodium consumption could contribute to hypertension in salt-sensitive individuals and could aggravate congestive heart failure or other edematous states in individuals with such medical conditions.

Studies of blood levels of nicotine and cotinine in smokeless tobacco users compared with cigarette smokers indicate that there is considerable gastrointestinal absorption of nicotine from smokeless tobacco (Benowitz *et al.*, 1989). This observation indicates that saliva containing various constituents of smokeless tobacco is swallowed, which raises the question of potential systemic absorption of other tobacco toxins. There is evidence that smokeless tobacco users are systemically exposed to potentially carcinogenic compounds. This conclusion is based on the observation that urine mutagenicity, as tested by the Ames salmonella test, a widely used test of potential carcinogenic activity, was significantly increased during the use of chewing tobacco as well as the smoking of cigarettes (Fig. 5) (Benowitz *et al.*, 1989). There was no increase in mutagenic activity of the urine with the use of oral snuff. The finding of mutagenic urine with the use of chewing tobacco suggests that there could be a risk of tobacco-related cancers other than those of the oral cavity in the users of chewing tobacco. While such cancers have not been documented to date, surveillance is clearly indicated.

EVIDENCE OF CARDIOVASCULAR DISEASE IN SMOKELESS TOBACCO USERS

The data on the absorption and cardiovascular effects of nicotine during smokeless tobacco use raise the possibility

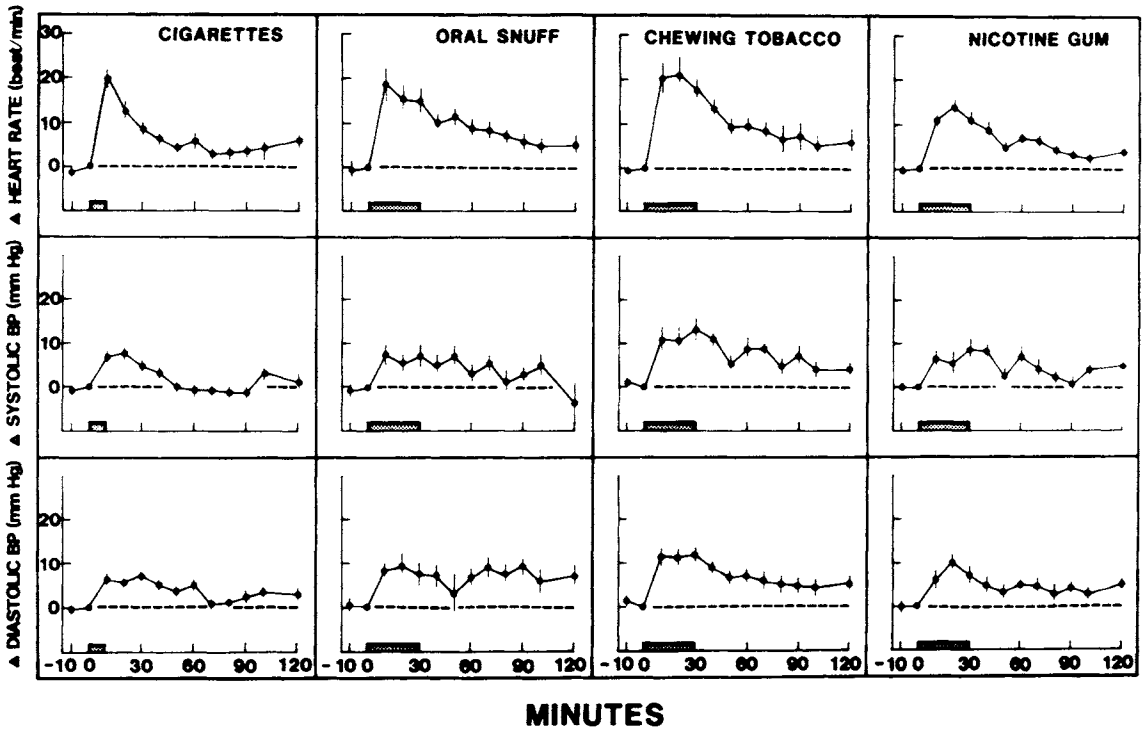

Fig. 3—Acute cardiovascular effects of cigarette smoking and the use of single doses of smokeless tobacco (reprinted with permission from Benowitz et al., *1988).*

that smokeless tobacco use could cause or aggravate coronary heart disease. Two studies on the epidemiology of smokeless tobacco use have been performed in Sweden, a country in which oral snuff is used by a high percentage of the male population, often for many years or lifelong. The Huhtasaari study was a case-control study of first myocardial infarction in 585 individuals in Sweden, with a similar number of population-derived controls (Huhtasaari *et al.*, 1992). This study found no increase in the risk for myocardial infarction with oral snuff use (odds ratio 0.89, 95% CI 0.62-1.29) compared with no tobacco use. In the same study, cigarette smoking increased the risk of myocardial infarction, with an odds ratio of 1.87 (95% CI 1.40-2.48) compared with no tobacco use.

The second study by Bolinder and co-workers was an observational cohort study of 135,036 Swedish construction industry workers (Bolinder *et al.*, 1994). These individuals were studied initially in 1971-1974 and were followed through 1985. At entry, 4.7% (6297) were snuff users. This study found that the age-adjusted risk for death from cardiovascular disease in snuff users was 1.4 (95% CI 1.2-1.6), as compared with the relative risk of 1.9 (95% CI 1.7-2.2) for smokers of 15 or more cigarettes *per* day. Of note, this study did not adjust for cholesterol or alcohol use. Thus, available epidemiologic data are conflicting, but there is adequate concern, based on biological plausibility and two positive epidemiological studies, to pursue further research on the risk of smokeless tobacco as a cause of cardiovascular disease. In the absence of definitive data, it is prudent to warn individuals who have hypertension or who are at risk for coronary heart disease about the potential adverse cardiovascular effects of smokeless tobacco use.

CONCLUSION

The following can be concluded about nicotine and the health hazards of smokeless tobacco use:

(1) Systemic absorption and levels of nicotine are similar in users of smokeless tobacco and smokers of cigarettes.

(2) Nicotine absorbed from smokeless tobacco produces a level and temporal pattern of sympathetic neural arousal and hemodynamic effects similar to those produced by the smoking of cigarettes.

(3) Health hazards caused by cigarette smoking and suspected to be related to chronic nicotine exposure are expected to be a hazard of habitual smokeless tobacco use. There are conflicting epidemiological data on snuff use and the occurrence of cardiovascular disease. The nature and magnitude of the cardiovascular hazards remain to be elucidated.

(4) Sodium absorption from smokeless tobacco is substantial and could contribute to blood pressure elevation and/or aggravation of cardiac failure and other sodium-retaining conditions.

(5) Increased mutagenic activity in the urine with the use of chewing tobacco indicates systemic exposure to potentially carcinogenic chemicals and the possible risk of cancers other than those of the oral cavity.

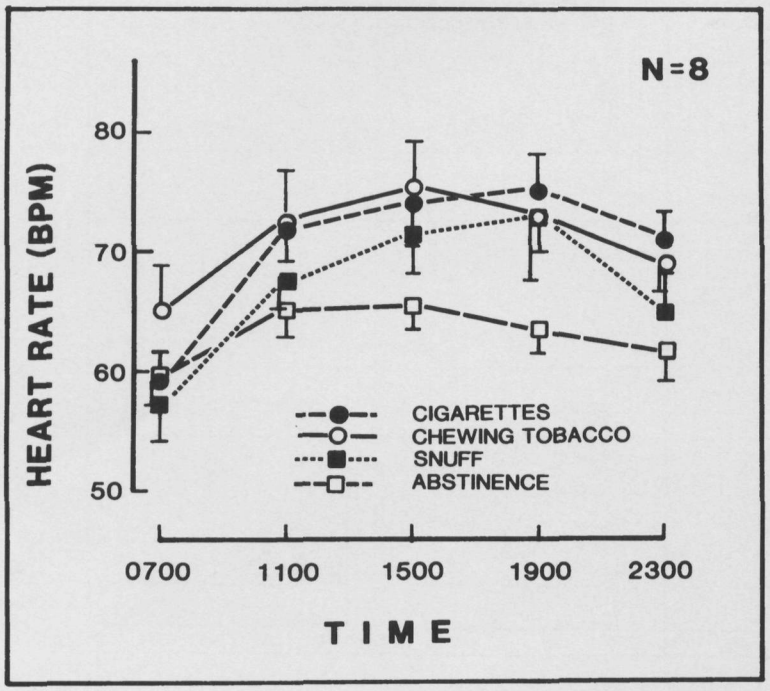

Fig. 4—Heart rate effects with daily cigarette smoking and the use of smokeless tobacco (reprinted with permission from Benowitz et al., *1989).*

(6) Although not reported in this paper, insofar as levels of nicotine are similar, it is expected that cigarette smokers and smokeless tobacco users will have a similar addiction liability. This expectation is supported by the research of others.

(7) Information concerning the potential hazards of nicotine as well as the oral pathology associated with habitual use of smokeless tobacco may be incorporated into educational programs to discourage the use of smokeless tobacco.

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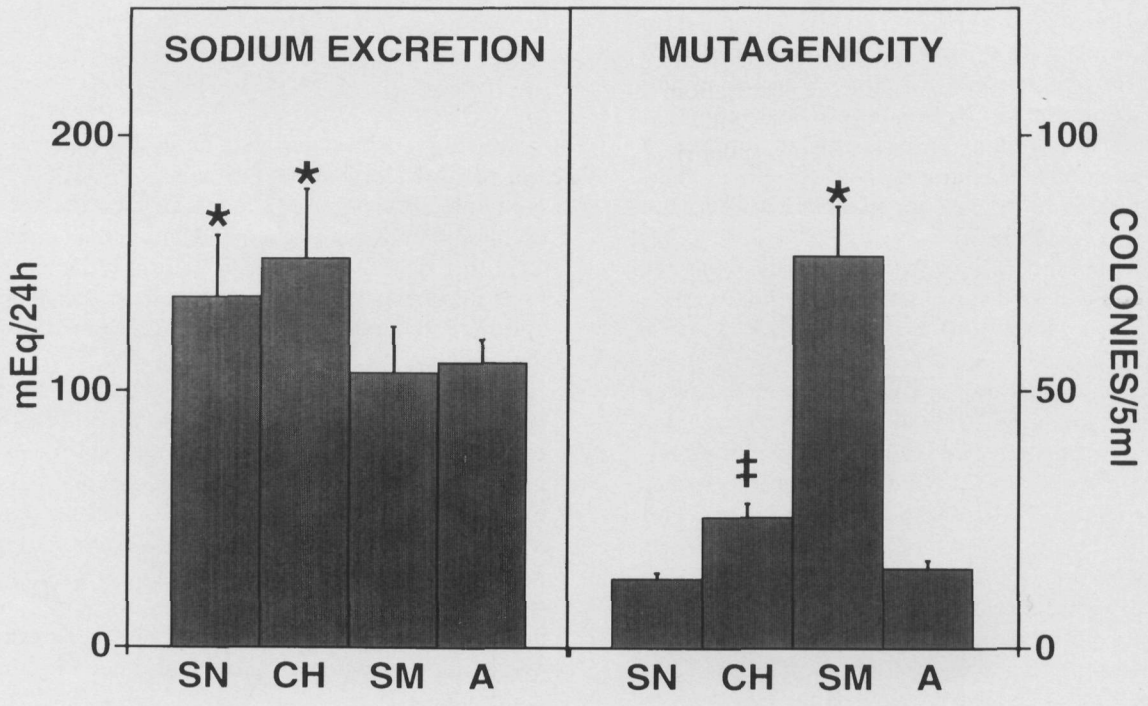

Fig. 5—Urinary sodium and mutagenic activity with daily cigarette smoking and smokeless tobacco use (reprinted with permission from Benowitz et al., *1989). SN = snuff; CH = chewing tobacco; SM = cigarette smoking; A = tobacco abstinence. * = $p < 0.05$, compared with abstinence; ‡ = $p < 0.10$, compared with abstinence.*

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