# Similar Exposure to a Tobacco-Specific Carcinogen in Smokeless Tobacco Users and Cigarette Smokers

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## Abstract

**Smokeless tobacco has been proposed as a reduced risk substitute for smoking, but no large studies have investigated exposure to the powerful carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in smokeless tobacco users versus smokers. The purpose of this study was to carry out such a comparison. Levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), a biomarker of NNK exposure, and cotinine, a biomarker of nicotine exposure, were quantified in the urine of 420 smokers and 182 smokeless tobacco users who were participants in studies designed to reduce their use of these products. The measurements were taken at baseline, before intervention. Levels of total NNAL per milliliter of urine were significantly higher in smokeless tobacco users than in smokers ($P < 0.0001$). When adjusted for age and gender, levels of total NNAL per milligram of creatinine were also significantly higher in smokeless tobacco users than in smokers ($P < 0.001$). Levels of cotinine per milliliter of urine and per milligram of creatinine were significantly higher in smokeless tobacco users than in smokers ($P < 0.001$). These results show similar exposures to the potent tobacco-specific carcinogen NNK in smokeless tobacco users and smokers. These findings do not support the use of smokeless tobacco as a safe substitute for smoking.** (Cancer Epidemiol Biomarkers Prev 2007;16(8):1567–72)

## Introduction

Smokeless tobacco is ''carcinogenic to humans (group 1)'' according to a working group of the IARC (1). The most prevalent strong carcinogens in smokeless tobacco products are the tobacco-specific nitrosamines (1). Among these, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is the most carcinogenic in laboratory animals, inducing tumors mainly in the lung, but also in the pancreas, nasal mucosa, and liver of rats (2). A mixture of NNK and *N*′-nitrosonornicotine (NNN), when administered to rats by oral swabbing, caused oral cavity tumors (3). NNK and NNN are also rated as ''carcinogenic to humans'' (1). Smokeless tobacco use is generally considered to be less toxic and carcinogenic than cigarette smoking because smokeless tobacco lacks or has considerably lower concentrations of many of the toxicants and carcinogens formed during combustion. Thus, responsible members of the tobacco control community have suggested that switching to ''low nitrosamine'' smokeless tobacco may be an effective harm reduction strategy for smokers who cannot stop using tobacco products (4, 5). Yet there are only scattered data in the literature on exposure to the strong carcinogen NNK in smokeless tobacco users.

Exposure to NNK from tobacco products can be estimated using the urinary biomarker total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), the sum of NNAL and its glucuronides, metabolites of NNK (6). A number of small studies have reported levels of total NNAL in the urine of smokeless tobacco users (7-12), and one compared total NNAL in smokeless tobacco users ($n = 13$) and smokers ($n = 27$; ref. 13), but there have been no reported comparisons of total NNAL in the urine of smokeless tobacco users and smokers in larger studies. In this article, we have compared levels of total NNAL in the urine of subjects who entered studies seeking treatment for tobacco dependence. We include baseline data from three studies involving smokers ($n = 420$) and three studies involving smokeless tobacco users ($n = 182$).

## Materials and Methods

**Subjects.** All studies were approved by the appropriate institutional review boards. Studies 1 to 3 involved smokers recruited for smoking reduction studies. The data reported in the present investigation were obtained at baseline in those studies. In study 1 (14), cigarette smokers, ages 18 to 70 years, and interested in reducing cigarette use but not quitting within the next 30 days, were recruited from the Twin Cities, MN metropolitan area with advertisements. They were screened to determine whether they met specific inclusion criteria. These included: (*a*) smoking 15 to 45 cigarettes per day for the past year, (*b*) in apparently good physical health with no unstable medical condition, (*c*) no contraindications for nicotine replacement use, (*d*) in good mental health, (*e*) not using other tobacco or nicotine products, and (*f*) for females, not pregnant or nursing. Levels of total NNAL and cotinine in first morning urine were determined at a baseline visit. Details of the study design have been described (14). In study 2 (15), cigarette smokers ages 18 to 80 who also had heart disease and were interested in reducing cigarette use but not quitting within the next 30 days were recruited from the Twin Cities, MN metropolitan area with invitation letters and advertisements. Eligibility criteria included (*a*) smoking 15 or more cigarettes per day, (*b*) having at least one of the following diagnoses: coronary artery disease, arrhythmia, congestive heart failure, peripheral vascular disease, or history of a cerebrovascular event, (*c*) no unstable angina within the past 2 weeks, (*d*) no unstable psychiatric or substance use diagnoses, or (*e*) no contraindications to nicotine replacement therapy (including

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**Table 1. Demographic data for the subjects in this study**

| Smokers | No. of subjects | Gender (% male) | Race (% white) | Mean age (95% CI) | Mean weight, lbs (95% CI) | Mean cigarettes/d (95% CI) |
|---|---|---|---|---|---|---|
| Study 1 | 114 | 48 | 97 | 45.4 (43.5-47.4) | 177 (170-185) | 26.0 (24.7-27.3) |
| Study 2 | 120 | 91 | 94 | 58.8 (57.2-60.4) | 195 (189-202) | 27.4 (25.2-29.7) |
| Study 3 | 186 | 52 | 62 | 45.9 (40.0-47.9) | 183 (175-191) | 24.7 (23.0-26.5) |
| Pooled (studies 1-3) | 420 | 62 | 80 | 49.5 (48.2-50.7) | 185 (181-189) | 25.8 (24.8-26.9) |
| **Smokeless tobacco users** | **No. of subjects** | **Gender (% male)** | **Race (% white)** | **Mean age (95% CI)** | **Mean weight, lbs (95% CI)** | **Mean tins per wk (95% CI)** |
| Study 4 | 80 | 100 | 100 | 32.6 (30.9-34.2) | 215 (206-223) | 4.1 (3.8-4.5) |
| Study 5 | 60 | 100 | 98 | 32.8 (31.2-34.3) | 219 (209-229) | 4.2 (3.6-4.7) |
| Study 6 | 42 | 100 | 97 | 33.6 (31.5-35.8) | 224 (213-234) | 4.3 (3.8-4.9) |
| Pooled (studies 4-6) | 182 | 100 | 99 | 32.9 (31.9-33.9) | 218 (213-224) | 4.2 (3.9-4.4) |

pregnancy or intention to become pregnant). Participants were randomized to a smoking reduction intervention that used a combination of behavioral and pharmacologic treatment to encourage at least 50% reduction in cigarette consumption or usual care, and followed for 18 months. Total NNAL and cotinine in urine were measured once at baseline. In study 3, smokers interested in reducing their smoking via scheduled smoking by use of a printed manual or a handheld computer were recruited from television and print advertisements in the Washington, DC-northern Virginia metropolitan area. They were selected if they met the following criteria: (*a*) self-report of smoking 15 or more cigarettes per day for 1 or more years, (*b*) an unsuccessful quit attempt in the past year, (*c*) no specific plan to quit in the next 30 days and willing to attempt smoking reduction as a short-term goal, (*d*) used other tobacco products three or fewer times in the past week, (*e*) no current use of nicotine replacement therapy, (*f*) no use of Zyban in the past 2 weeks, (*g*) not pregnant, and (*h*) no treatment for alcohol or drug abuse in the past year. Total NNAL was measured in urine samples taken at baseline. Cotinine was measured in saliva; urine cotinine data were not available from this study.

Studies 4 to 6 involved smokeless tobacco users who were seeking treatment for smokeless tobacco reduction. Baseline data from these studies were used. The studies examined the effects of tobacco-free snuff use (an herbal snuff-like product; study 4; ref. 16), brand switching (study 5; ref. 17), or use of a nicotine lozenge (study 6) compared with a control group on reduction of smokeless tobacco use. Subjects for studies 4 to 6 were recruited from the Twin Cities, MN metropolitan area through newspaper and television advertisements. Subjects were screened over the telephone to determine interest and eligibility. During this screening, subjects were informed that the study compared different interventions for smokeless tobacco use reduction. Interested participants were asked to attend a meeting for orientation and screening and to obtain informed consent. Potential subjects were eligible for enrollment if they were: (*a*) between the ages of 18 and 70 years, (*b*) interested in reducing smokeless tobacco use but not quitting (i.e., having an established quit date within the next 90 days), (*c*) using smokeless tobacco daily (≥6 dips/d) for the past 6 months, (*d*) in good physical health (i.e., absence of an unstable medical condition or use of a medication that might affect tobacco use or be affected by tobacco use reduction), and (*e*) in good mental health (i.e., not taking psychotropic medications or manifesting a psychiatric comorbidity within the past 6 months). If subjects met these criteria, they were scheduled for baseline clinic visits during which tobacco use histories and first morning urine samples were obtained.

### Analyses

*Biomarker Analyses.* For studies 1 and 2, total NNAL was determined by adding amounts of NNAL and NNAL-Gluc, analyzed separately (18). In studies 3 to 6, total NNAL was determined directly essentially as described (19, 20). Both methods give the same values for total NNAL (19). Total cotinine (cotinine plus its glucuronide) and creatinine were quantified as described (21).

*Statistical Analyses.* In exploratory analyses, total NNAL and cotinine were summarized using geometric means because of the skewness of their distributions. The corresponding confidence intervals (95% CI) were constructed on the natural logarithmic scale and then back-transformed to the original scale. The box-and-whisker plots were displayed for total NNAL in each individual study side by side, and for the pooled samples of smokers and smokeless tobacco users for total NNAL and cotinine. For comparison of smokers and smokeless tobacco users, we used two sample *t* tests and multiple linear regressions to adjust for demographic characteristics. Both analyses were based on the logarithmic scale to satisfy normality and constant variance assumptions. The estimated regression coefficients and confidence intervals for

**Table 2. Total NNAL and cotinine in the urine of smokers (*n* = 420) and smokeless tobacco users (*n* = 182)**

| | Geometric mean (95% CI) | | | |
|---|---|---|---|---|
| | Total NNAL | | Cotinine | |
| | pmol/mL | pmol/mg creatinine | nmol/mL | nmol/mg creatinine |
| Smokers | | | | |
| Study 1 | 2.12 (1.88-2.38) | 2.01 (1.79-2.25) | 25.0 (22.2-28.1) | 23.7 (21.3-26.4) |
| Study 2 | 2.06 (1.81-2.34) | 2.24 (2.01-2.49) | 19.0 (16.4-22.1) | 20.8 (18.5-23.3) |
| Study 3 | 2.31 (2.05-2.61) | 2.62 (2.39-2.87) | — | — |
| Pooled (studies 1-3) | 2.18 (2.03-2.35) | 2.33 (2.19-2.47) | 21.7 (19.7-23.9) | 22.2 (20.5-24.0) |
| Smokeless tobacco users | | | | |
| Study 4 | 3.52 (3.05-4.07) | 2.35 (2.05-2.70) | 50.6 (44.1-58.1) | 33.8 (29.4-38.8) |
| Study 5 | 3.81 (3.09-4.69) | 2.50 (2.04-3.07) | 38.8 (31.6-47.7) | 25.5 (21.2-30.6) |
| Study 6 | 4.30 (3.42-5.42) | 2.98 (2.31-3.84) | 32.9 (26.3-41.2) | 22.5 (17.8-28.4) |
| Pooled (studies 4-6) | 3.79 (3.40-4.21) | 2.54 (2.28-2.82) | 42.1 (37.9-46.8) | 28.1 (25.4-31.2) |

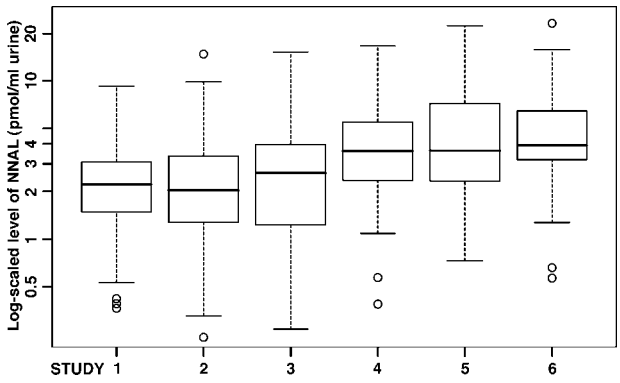


**Figure 1.** Log-scaled levels of total NNAL (pmol/mL) in the urine of subjects in studies 1 to 3 (smokers) and studies 4 to 6 (smokeless tobacco users). *Boxes,* 25th and 75th percentile values (interquartile range). *Bars,* maximum observation below the upper fence (1.5 times the interquartile range above the 75th percentile), and the minimum observation above the lower fence (1.5 times the interquartile range below the 25th percentile). *Circles,* outliers. *Lines,* median.

the log-transformed variables were exponentiated such that the results could be interpreted on their original scale as a percentage difference in the median of the outcome. All statistical tests were two-sided.

## Results

Demographic data are summarized in Table 1. The 420 smokers were 62% male, 80% were white, and had a mean age of 49.5 years (95% CI, 48.2-50.7). They smoked a mean of 25.8 cigarettes per day (95% CI, 24.8-26.9). The 182 smokeless tobacco users were all male, 99% were white, and had a mean age of 32.9 years (95% CI, 31.9-33.8). Gender, age, weight, and race were significantly different among smokers and smokeless tobacco users ($P < 0.0001$). The smokeless tobacco users consumed an average of 4.2 tins per week (95% CI, 3.9-4.4).

Ten percent of the smokers used regular cigarettes (>14.5 mg tar), 39% smoked light cigarettes (>6.5-14.5 mg tar), 30% smoked ultra-light cigarettes (≤6.5 mg tar) and brand data were not available for the rest. The smokeless tobacco users used Copenhagen (31.5%), Skoal (12.7%), Kodiak (47.0%), and other brands (8.8%).

Total NNAL and cotinine per milliliter of urine and per milligram of creatinine for the subjects in each study, and the pooled data, are summarized in Table 2. Urinary cotinine was not available for the subjects in study 3. Total NNAL per milliliter of urine in each study is also summarized in Fig. 1. Total NNAL levels per milliliter of urine were higher in each group of smokeless tobacco users than in each group of smokers. The combined data are illustrated in Fig. 2. Total NNAL per milliliter of urine from smokeless tobacco users was significantly higher than in smokers ($P < 0.0001$, $t$ test, and Wilcoxon Mann-Whitney test).

Stratified data for total NNAL per milliliter of urine are presented in Table 3. Because all smokeless tobacco users were male, their data were compared with male smokers only. Because the smokeless tobacco users were younger than the smokers, the data were compared in smokeless tobacco users and smokers under the age of 45 and because most of the smokeless tobacco users were white, the data were compared in white smokeless tobacco users and smokers only. Further comparisons were made between younger male smokers and younger smokeless tobacco users, and younger white male smokers and younger white smokeless tobacco users. In all cases, total NNAL per milliliter of urine was significantly greater in the smokeless tobacco users ($P < 0.0001$). Based on multiple regression, adjusting for age and gender, smokeless tobacco users had a 73% (95% CI, 45-105%; $P < 0.0001$) higher median level of total NNAL per milliliter of urine than did smokers (3.76 versus 2.18 pmol/mL for males of median age 45).

The levels of total NNAL expressed per milligram of creatinine in smokers and smokeless tobacco users are illustrated in Fig. 3 and summarized by strata in Table 3. There were no significant differences between the median levels in the whole groups or in any of the strata ($t$ test and Wilcoxon Mann-Whitney test). However, as shown in Table 3, creatinine levels were significantly higher in smokeless tobacco users, in both the entire group and in each stratum. When multiple linear regression was used to adjust for age and gender, smokeless tobacco users had a significant 32% (95% CI, 13-53%; $P < 0.001$) higher level of total NNAL per milligram of creatinine than did smokers (2.83 versus 2.15 pmol/mg creatinine for males of median age 45).

Although we did not have 24 h urine samples, the excretion of total NNAL in smokers versus smokeless tobacco users can be estimated from data in the literature on creatinine levels in males of different weights (22). Applying this to the younger male smokers (average weight, 183 ± 53.5 lbs), the geometric mean 24 h excretion of total NNAL would be 3.5 nmol (1,600 mg creatinine/24 h × 2.2 pmol total NNAL/mg creatinine) whereas that for the younger male smokeless tobacco users (average weight, 218 ± 37.4 lbs) would be 4.3 nmol (1,800 mg creatinine/24 h × 2.39 pmol total NNAL/mg creatinine).

The levels of cotinine per milliliter of urine and per milligram of creatinine were significantly higher in smokeless tobacco users than in smokers (Fig. 4A and B; Table 4; $P < 0.001$, $t$ test and Wilcoxon Mann-Whitney test), and in each stratum except when expressed per milligram of creatinine in younger smokers versus younger smokeless tobacco users. The estimated geometric mean daily levels of cotinine in the urine of younger male smokers would be 33 μmol, whereas those in younger male smokeless tobacco users would be 49 μmol.

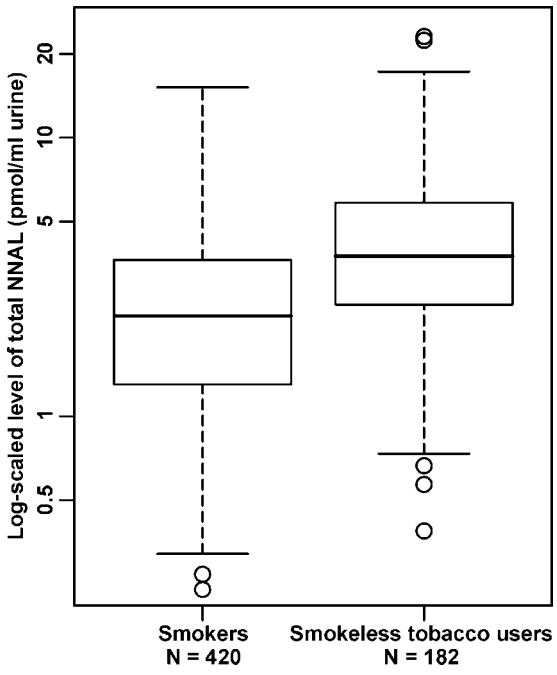


**Figure 2.** Log-scaled level of total NNAL (pmol/mL) in the urine of smokers (studies 1-3) and smokeless tobacco users (studies 4-6).

**Table 3. Levels of total NNAL and creatinine in smokers and smokeless tobacco users stratified by gender, age, and race**

| Group | *N* | Age, y (mean ± SD) | Total NNAL (pmol/mL urine) Geometric mean (95% CI) | *P* | Total NNAL (pmol/mg creatinine) Geometric mean (95% CI) | *P* | Creatinine* (mg/mL urine) Geometric mean (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|
| Smokers | 420 | 49.5 ± 12.9 | 2.18 (2.03-2.35) † | <0.0001 | 2.33 (2.19-2.47) ‡ | 0.17 | 0.94 (0.88-1.00) | <0.0001 |
| Smokeless tobacco users | 182 | 32.9 ± 6.76 | 3.79 (3.40-4.21)§ | | 2.54 (2.28-2.82)‖ | | 1.49 (1.39-1.61) | |
| Male smokers | 260 | 51.0 ± 13.2 | 2.17 (1.97-2.38) | <0.0001 | 2.27 (2.11-2.45) | 0.10 | 0.95 (0.87-1.04) | <0.0001 |
| Male smokeless tobacco users | 182 | 32.9 ± 6.76 | 3.79 (3.40-4.21) | | 2.54 (2.28-2.82) | | 1.49 (1.39-1.61) | |
| Younger smokers¶ | 148 | 35.9 ± 8.02 | 2.31 (2.03-2.64) | <0.0001 | 2.12 (1.91-2.36) | 0.12 | 1.08 (0.97-1.20) | <0.0001 |
| Younger smokeless tobacco users¶ | 171 | 31.9 ± 5.42 | 3.67 (3.29-4.10) | | 2.39 (2.15-2.65) | | 1.54 (1.42-1.66) | |
| White smokers | 331 | 50.2 ± 13.2 | 2.08 (1.91-2.26) | <0.0001 | 2.39 (2.23-2.56) | 0.29 | 0.87 (0.81-0.93) | <0.0001 |
| White smokeless tobacco users | 174 | 33.0 ± 6.82 | 3.81 (3.41-4.24) | | 2.56 (2.30-2.86) | | 1.48 (1.38-1.60) | |
| Younger male smokers | 79 | 35.6 ± 8.24 | 2.43 (2.02-2.92) | <0.0001 | 2.20 (1.90-2.54) | 0.37 | 1.10 (0.94-1.28) | 0.0001 |
| Younger male smokeless tobacco users | 171 | 31.9 ± 5.42 | 3.67 (3.29-4.10) | | 2.39 (2.15-2.65) | | 1.54 (1.42-1.66) | |
| Younger white male smokers | 60 | 35.0 ± 8.32 | 2.25 (1.79-2.83) | <0.0001 | 2.19 (1.82-2.62) | 0.32 | 1.02 (0.84-1.23) | 0.0002 |
| Younger white male smokeless tobacco users | 165 | 32.0 ± 5.45 | 3.70 (3.31-4.13) | | 2.43 (2.18-2.70) | | 1.52 (1.41-1.65) | |

* Data was missing for one subject.
† Arithmetic mean: 2.84 ± 2.17.
‡ Arithmetic mean: 2.82 ± 1.99.
§ Arithmetic mean: 4.86 ± 3.76.
‖ Arithmetic mean: 3.29 ± 2.63.
¶ <45 yrs old.

There was a significant correlation between total NNAL and cotinine in smokeless tobacco users [Pearson correlation coefficient 0.58 (95% CI, 0.47-0.67; $P < 0.001$); Spearman correlation coefficient 0.64 (95% CI, 0.55-0.72; $P < 0.0001$)] and in smokers [Pearson 0.57 (95% CI, 0.47-0.65; $P < 0.001$), Spearman 0.54 (95% CI, 0.44-0.62; $P < 0.0001$)].

## Discussion

The results of this study show that levels of urinary total NNAL are significantly higher in smokeless tobacco users who used conventional and popular U.S. brands of smokeless tobacco than in cigarette smokers. Differences in the route of administration of NNK in smokeless tobacco users (oral) and smokers (inhalation) could affect the levels of NNAL in urine. Pharmacokinetic data on NNK and NNAL in smokers and smokeless tobacco users are limited. One study showed that the distribution half-lives of NNAL and its glucuronides were significantly less in smokeless tobacco users than in smokers whereas the terminal half lives were the same (13). Nevertheless, the results of the present study indicate that exposure to NNK is at least comparable in smokeless tobacco users and smokers.

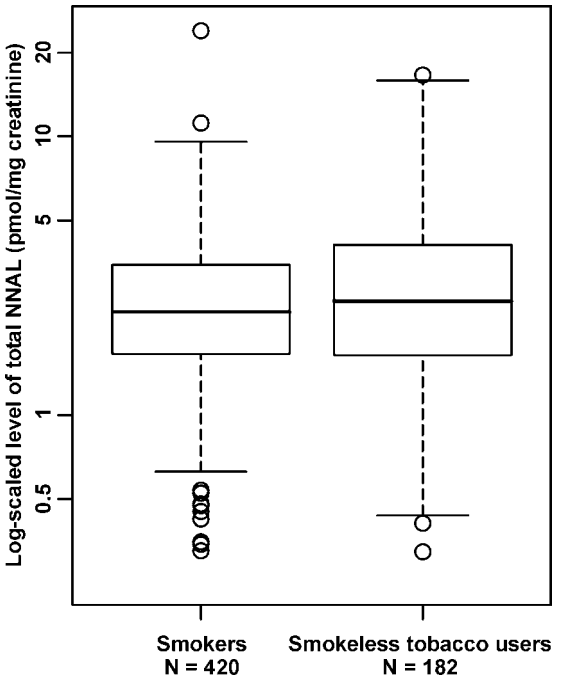


**Figure 3.** Log-scaled levels of total NNAL (pmol/mg creatinine) in the urine of smokers (studies 1-3) and smokeless tobacco users (studies 4-6).

Our results raise serious questions about the strategy of using smokeless tobacco as a substitute for cigarette smoking. Proponents of this strategy have focused on "low-nitrosamine" smokeless tobacco products such as Swedish snus (4). We have previously shown that switching from typical American smokeless tobacco products such as those used here, to Swedish snus, does in fact lower levels of urinary total NNAL by ~56%, from 3.2 to 1.4 pmol/mg of creatinine (9). The latter amount is also significantly lower than the amount of urinary total NNAL in smokers (2.8 pmol/mg creatinine), but is significantly higher than the amount in people who switched to nicotine replacement therapy (9). Swedish snus, although lower in nitrosamines than popular American brands, is however *not* a low-nitrosamine product, and its users still have substantial amounts of NNAL in their urine. Encouraging people to switch from cigarette smoking to smokeless tobacco also may have the unintended consequence of increasing sales of American brands of smokeless tobacco such as those used by the subjects in this study. NNK exposure in smokeless tobacco users as shown in this study presents an unacceptable risk and should not be encouraged.

Administration of NNK in the drinking water to rats resulted in lung and pancreatic cancer (23). Would smokeless tobacco users be at similar risk? This question is difficult to examine because few epidemiologic studies have sufficient numbers of smokeless tobacco users who were not also smokers at some time in their lives. The large prospective American Cancer Society Cancer Prevention Studies 1 and 2 did however address this question (24). Whereas study 1 found no increased risk of lung cancer in smokeless tobacco users, study 2 did show a significantly increased 2-fold mortality hazard ratio for lung cancer in smokeless tobacco users compared with controls who did not use any type of tobacco product (24). A prospective study of smokeless tobacco use in Norway showed an increased risk of pancreatic cancer compared with non–tobacco users, which is also consistent with the carcinogenic effects of NNK

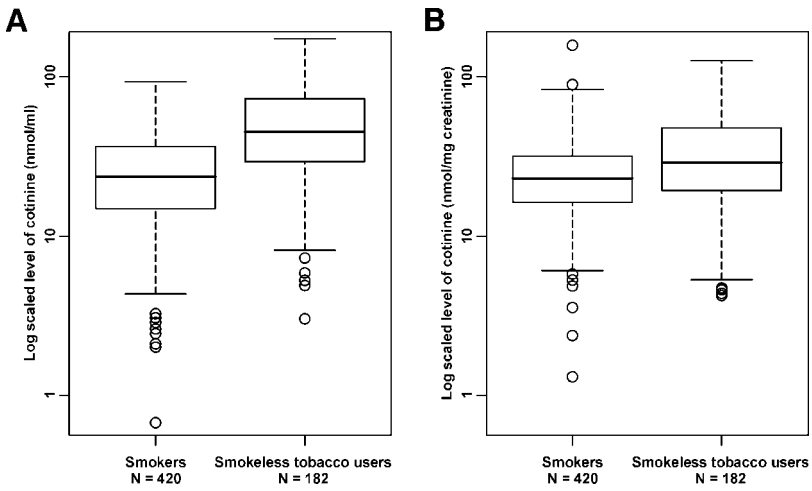


**Figure 4.** Log-scaled levels of cotinine [nmol/mL (**A**) and nmol/mg creatinine (**B**)] in the urine of smokers and smokeless tobacco users.

in the rat (25). Smokeless tobacco is also a recognized cause of oral cavity cancer (although this was not observed in Cancer Prevention Studies 1 and 2; refs. 1, 26). A mixture of NNK and NNN caused oral tumors in rats (3). Levels of NNN in smokeless tobacco are consistently higher than those of NNK (27, 28). Although NNN levels in urine were not measured here, previous studies have shown the presence of NNN in the saliva and urine of smokeless tobacco users (29, 30).

There is no doubt that the risk for lung cancer is greater in smokers than in smokeless tobacco users (1, 30). This is not inconsistent with the data presented here. Cigarette smoke contains, in addition to NNK, multiple carcinogenic combustion products which are not present, or present in only low amounts, in smokeless tobacco (31). These include several types of carcinogens such as polycyclic aromatic hydrocarbons, aldehydes, ethylene oxide, and benzene which are implicated as causes of lung cancer, along with toxicants such as acrolein, weakly acidic tumor promoters, and cocarcinogens, as well as free radicals which can enhance carcinogenicity (32, 33). Furthermore, NNK is directly deposited in the lungs of smokers, which is likely to increase its carcinogenic effect in that organ. But the data presented here show that smokeless tobacco use is far from safe.

The levels of cotinine in the urine of smokeless tobacco users in this study were significantly higher than in smokers. The pharmacokinetics of nicotine have been compared in smokeless tobacco users and smokers (34). Although similar, the ratio of cotinine to nicotine area under the curve was significantly greater while using smokeless tobacco compared with smoking, possibly due to first pass clearance of swallowed nicotine (34, 35). Our results are consistent with this and a number of previous studies which have shown comparable uptake of nicotine, as measured by cotinine levels, in smokeless tobacco users and smokers (36-39). These results show that, in a treatment-seeking population, smokeless tobacco users strive to achieve similar nicotine levels as do cigarette smokers in order to satisfy their craving.

A limitation of this study is that our smokers and smokeless tobacco users were seeking to reduce their tobacco use. These dependent individuals may have had higher levels of total NNAL and cotinine in their urine than tobacco users who were not seeking treatment. A more appropriate design would have been a cross-sectional investigation of a representative sample of smokers and smokeless tobacco users.

In summary, the results of this study show similar exposure to the tobacco-specific carcinogen NNK in smokers and smokeless tobacco users and do not support the general concept that most or even all currently available smokeless tobacco should be used as a substitute for cigarette smoking. Advocating for the use of smokeless tobacco as a substitute for smoking may have the unintended consequence of increasing the use and sales of smokeless tobacco products which lead to

**Table 4. Levels of cotinine in smokers and smokeless tobacco users stratified by gender, age, and race**

| | | | Cotinine | | | |
|---|---|---|---|---|---|---|
| | | | (nmol/mL urine) | | (nmol/mg creatinine) | |
| Group | *N* | Age, y (mean ± SD) | Geometric mean (95% CI) | *P* | Geometric mean (95% CI) | *P* |
| Smokers | 232 | 52.3 ± 11.7 | 21.7 (19.7-23.9)* | <0.0001 | 22.2 (20.5-24.0)† | 0.0003 |
| Smokeless tobacco users | 180 | 32.9 ± 6.76 | 42.1 (37.9-46.8)‡ | | 28.1 (25.4-31.2)§ | |
| Male smokers | 162 | 54.6 ± 11.1 | 21.8 (19.3-24.7) | <0.0001 | 20.8 (18.9-22.8) | <0.0001 |
| Male smokeless tobacco users | 180 | 32.9 ± 6.76 | 42.1 (37.9-46.8) | | 28.1 (25.4-31.2) | |
| Younger smokers‖ | 61 | 37.7 ± 6.85 | 28.3 (24.0-33.3) | 0.0003 | 22.7 (19.4-26.4) | 0.08 |
| Younger smokeless tobacco users | 170 | 31.9 ± 5.42 | 41.6 (37.3-46.5) | | 27.1 (24.4-30.1) | |
| White smokers | 214 | 52.4 ± 11.9 | 21.7 (19.6-24.0) | <0.0001 | 22.6 (20.9-24.6) | 0.0001 |
| White smokeless tobacco users | 172 | 33.0 ± 6.82 | 43.6 (39.1-48.5) | | 29.2 (26.4-32.4) | |
| Younger male smokers | 31 | 38.6 ± 6.14 | 30.2 (23.7-38.5) | 0.02 | 20.6 (16.8-25.2) | 0.04 |
| Younger male smokeless tobacco users | 170 | 31.9 ± 5.42 | 41.6 (37.3-46.5) | | 27.1 (24.4-30.1) | |
| Younger white male smokers | 28 | 38.5 ± 6.24 | 30.1 (22.9-39.5) | 0.02 | 21.2 (17.0-26.5) | 0.04 |
| Younger white male smokeless tobacco users | 164 | 32.0 ± 5.45 | 42.8 (38.4-47.9) | | 28.1 (25.4-31.2) | |

*Arithmetic mean: 27.4 ± 17.5.
†Arithmetic mean: 26.3 ± 16.8.
‡Arithmetic mean: 52.1 ± 31.5.
§Arithmetic mean: 34.9 ± 22.3.
‖<45 yrs old.

similar uptake of tobacco-specific carcinogens as cigarettes, particularly in an environment that does not regulate the amount of toxicants in tobacco products. Long-term use of nicotine replacement therapy may be a better option.

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