Evaluation of Carcinogen Exposure in People Who Used "Reduced Exposure" Tobacco Products

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Background: **Although tobacco products with reportedly reduced carcinogen content are being marketed, carcinogen uptake in people who use these products has not been assessed systematically.** ***Methods:*** **Between June 2001 and November 2002, 54 users of smokeless tobacco and 51 cigarette smokers were randomly assigned to one of two groups. One used test products (Swedish snus for users of smokeless tobacco or OMNI cigarettes for smokers), while the other quit and used medicinal nicotine (the nicotine patch). All participants were assessed for urinary levels of total NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide], metabolites of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Smokers were also assessed for levels of 1-hydroxypyrene (1-HOP), a biomarker of polycyclic aromatic hydrocarbon uptake. Assessments were made weekly during 2 weeks of baseline normal tobacco use and 4 weeks of treatment. Statistical tests were two-sided.** ***Results:*** **Primary data analyses were conducted on 41 users of smokeless tobacco and 38 cigarette smokers who met the inclusion criteria. Total NNAL levels were statistically significantly lower in users of smokeless tobacco after they switched to snus or to nicotine patch ($P<.001$ for both groups) than they were before the switch, although the overall mean total NNAL level among subjects who used the nicotine patch was statistically significantly lower than that among those who used snus (mean = 1.2 and 2.0 pmol of NNAL/mg of creatinine, respectively; mean difference = 0.9 pmol of NNAL/mg of creatinine, 95% confidence interval [CI] = 0.2 to 1.5; $P = .008$). Compared with baseline levels, total NNAL levels ($P = .003$), but not 1-HOP levels, were statistically significantly reduced in cigarette smokers who switched to the OMNI cigarette, although both total NNAL levels and 1-HOP levels were statistically significantly reduced in smokers who switched to the nicotine patch ($P<.001$ for both). The overall mean total NNAL levels among smokers who used the nicotine patch was statistically significantly lower than that among smokers who used the OMNI cigarette (mean = 1.2 and 1.9 pmol of NNAL/mg of creatinine, respectively; mean difference = 0.6 pmol of NNAL/mg of creatinine, 95% CI = 0.1 to 1.1; $P = .022$).** ***Conclusion:*** **Switching to reduced-exposure tobacco products or medicinal nicotine can decrease levels of tobacco-associated carcinogens, with greater reductions being observed with medicinal nicotine. Medicinal nicotine is a safer alternative than modified tobacco products. [J Natl Cancer Inst 2004;96:844–52]**

In the United States, although the majority of smokers want to quit, it is estimated that only 4% of smokers quit smoking successfully for at least 1 year *(1)* and that less than 10% are interested in taking action to quit *(2)*. Therefore, the many tobacco users who are unable or not ready to quit continue to expose themselves to toxins in tobacco and in tobacco smoke. Consequently, methods aimed at reducing tobacco-related harms are being considered to help reduce tobacco-related morbidity and mortality without completely eliminating tobacco use *(3)*.

Several methods have been suggested to reduce exposure to tobacco toxins, including modifying tobacco products or heating rather than burning tobacco to produce toxin levels that are lower than those in conventional products. This study focuses on two tobacco products, Swedish moist snuff (snus) and the OMNI cigarette, that are purported by the makers of the products and, in the case of snus, also by researchers *(4)*, to contain lower levels of specific carcinogens than conventional products marketed in the United States.

Tobacco-specific nitrosamines are the most abundant and potent carcinogens in smokeless tobacco products and are among the most prevalent in cigarette smoke *(5–7)*. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN) are well-established rodent carcinogens *(6)*. Rats exposed to NNK develop tumors of the lung, nasal cavity, pancreas, and liver, whereas rats exposed to NNN develop mainly esophageal and nasal tumors. Rats swabbed orally with a mixture of NNK and NNN develop oral cavity tumors *(5)*.

Tobacco-specific nitrosamines are formed from tobacco alkaloids during the curing, fermentation, and aging of the tobacco leaves. Some tobacco companies are using methods to reduce the formation of these carcinogens. For example, Swedish Match, a maker of snus, uses a special process to kill microorganisms in tobacco, which results in the formation of lower levels of tobacco-specific nitrosamines than produced by the curing methods used for many products marketed in the United States. In addition, snus does not undergo fermentation, the absence of which also leads to reduced nitrosamine levels in the tobacco product *(4)*. It is estimated that the level of total tobacco-specific nitrosamines in snus is approximately 8.8 μg/g of tobacco [cited in *(8)*]. Total tobacco-specific nitrosamine levels in the most widely used U.S. brands of moist snuff range from 11.0 to 17.2 μg/g of tobacco *(9)*. For one tobacco-specific nitrosamine, NNK, our laboratory has found a 65% lower level in snus than in the leading brand of smokeless tobacco sold in the United States (unpublished data).

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Similar curing processes have been used with cigarettes to reduce nitrosamine levels *(3)*. Tobacco has also been treated with palladium, providing a catalytic process to reduce the concentration of certain carcinogens. The OMNI cigarette, manufactured by Vector Tobacco, is such a cigarette. According to information provided by the manufacturer (http://www.omnicig.com), the mainstream smoke of the OMNI cigarette has 53% less NNK than do conventional cigarettes (based on the Federal Trade Commission [FTC] method to analyze smoke constituents) and 20% less pyrene than does a leading competitive brand. Although pyrene is noncarcinogenic, it is a representative polycyclic aromatic hydrocarbon (PAH). PAHs, formed from the incomplete combustion of tobacco during smoking, are potent carcinogens in animal models and are probably carcinogenic in humans *(10–17)*. NNK and PAH are considered causative agents for lung cancer in people who smoke cigarettes *(13)*.

How reduced-exposure tobacco products will affect efforts to reduce the harms associated with tobacco smoking is unclear. Indeed, several unresolved issues related to the use of reduced-exposure tobacco products need to be addressed. First, because tobacco products marketed as "reduced exposure" may be construed as safer, tobacco users may be deterred from trying to quit entirely, or ex–tobacco users may be encouraged to relapse. Second, only a few independent scientists have examined the validity of the claims of reduced exposure or disease risk associated with reduced-exposure tobacco products, and few studies have measured the actual exposure of toxins in humans *(18,19)*. Third, because no comparisons have been made across alternative nicotine-containing products, the public is unaware of the relative extent of exposure to tobacco toxins across the various products, including medicinal nicotine. The purpose of the present study was to determine the effect of use of modified reduced-exposure tobacco products on exposure to carcinogens and to compare these toxin exposures to those in people who used medicinal nicotine products (the nicotine patch) as an aid to quitting smoking.

METHODS

Subjects

Men who used brands of smokeless tobacco marketed in the United States and men who smoked conventional cigarettes were recruited between June 2001 and November 2002 from the local Minneapolis–St. Paul metropolitan area via posted flyers, advertisements in the local and university newspapers, and advertisements on the radio for a study that was "comparing new tobacco products and nicotine replacement products." Only men were recruited because very few women use smokeless tobacco, and we wanted comparable groups of individuals who smoked and who used smokeless tobacco. Potential participants attended an informational meeting that described the study in detail. To be eligible to participate in the study, subjects had to be between the ages of 21 and 65 years, had to be in good physical and mental health as confirmed by a medical history, had to have smoked at least 15 cigarettes per day or used at least one tin of moist snuff per week for a minimum of 1 year, could not currently be using other types of tobacco products on a regular basis, and could not currently be using any methods for quitting tobacco or for cutting down on tobacco use. All participants provided written informed consent.

Procedure

The study design is shown in Fig. 1. During the first 2 weeks of the study, participants were asked to continue to use their usual brand of tobacco. Outcome measures were assessed during two clinic visits that took place during the first 2 weeks of the study (i.e., their *ad libitum* baseline tobacco use). At the end of these 2 weeks, participants were randomly assigned in an unblinded manner to one of two treatment conditions until each group consisted of approximately 25 subjects. The randomization code was determined by a study biostatistician using a block randomization method, and researchers assigned participants to the appropriate treatment condition. Participants who used smokeless tobacco were randomly assigned to one of two groups. Group 1 quit smokeless tobacco by using the 21-mg transdermal nicotine patch (Nicoderm CQ, donated by GlaxoSmithKline), whereas group 2 switched from their usual brand of smokeless tobacco to the unflavored 1-g-portion pouches of snus (General Snus). Two participants used mint-flavored 1-g-portion pouches of snus. Snus was chosen because it is a widely used tobacco product in Sweden, and Swedish Match, the manufacturer, is now marketing snus in the United States. The U.S. brands of smokeless tobacco with low nitrosamine levels are not widely used, possibly because they deliver relatively low levels of nicotine *(20)*. Cigarette smokers were randomly assigned to one of two groups. Group 1 quit smoking by using the 21-mg nicotine patch, whereas group 2 switched from their usual brand of cigarettes to OMNI Light cigarettes. For all participants, the duration of treatment was 4 weeks. Participants were required to

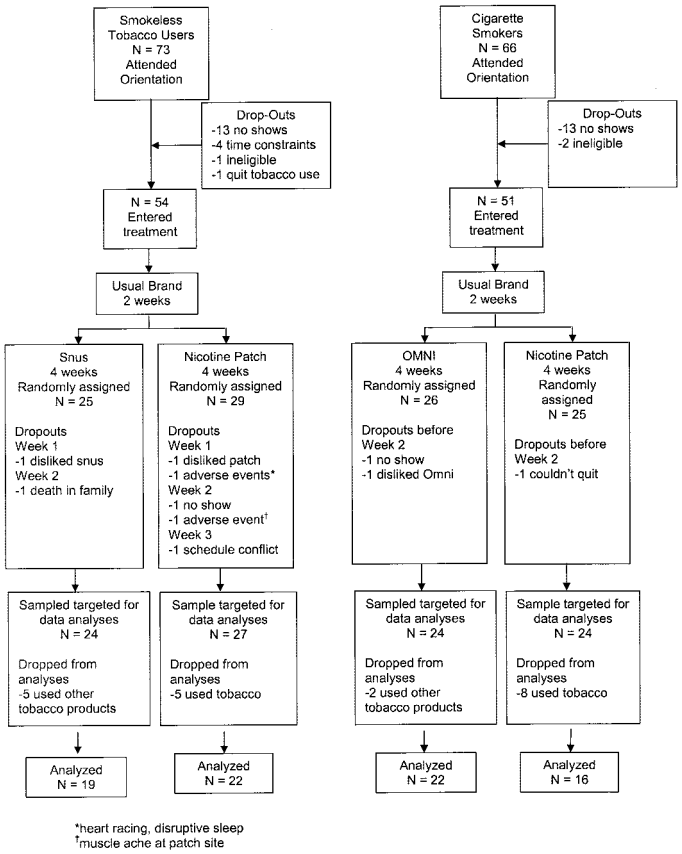

Fig. 1. Study design and participant flowchart for users of smokeless tobacco and cigarette smokers.

attend weekly clinic visits, during which the study products were distributed and outcome measures were assessed. Participants assigned to the nicotine patch groups received brief (5–10 minute) tobacco cessation counseling. Two participants who smoked cigarettes and two who used smokeless tobacco were unable to quit by using the 21-mg nicotine patch; thus, their nicotine patch doses were increased to 42 mg (two 21-mg patches). Participants assigned to the snus or OMNI cigarette treatment groups were encouraged to use the same amount of these tobacco products as they had of their usual brand of tobacco.

Participants were paid $150 for completing the study and received a $100 bonus if they used only the assigned products during the 4-week treatment period. Total potential compensation was therefore $250.

After completing the study, participants assigned to the snus or OMNI cigarette treatment groups were given a 4-week supply of the nicotine patch and behavioral counseling to help them quit. All procedures were approved by the University of Minnesota Institutional Review Board and were in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Measures

Tobacco and nicotine patch use. Throughout the study, participants were required to keep daily records of their tobacco use. Participants recorded the total number of cigarettes smoked or dips of snuff taken per day, the opening of a new cigarette pack or tin of oral tobacco, and the use of other tobacco products. Participants who used the nicotine patch were required to write down the time that each new patch was placed on the body.

Tobacco alkaloids. Levels of cotinine and its glucuronide, metabolites of nicotine, were analyzed to provide a measure of daily nicotine exposure and to verify compliance with study products. Urinary cotinine and its glucuronide were quantified as total cotinine (referred to herein as cotinine) as described *(21)*. To verify abstinence from tobacco in the nicotine patch treatment group, we determined anatabine levels. Anatabine, a tobacco alkaloid that is present in tobacco products but not in medicinal nicotine *(22)*, was determined with a modification of a published method, using 5-ethylnornicotine as an internal standard *(23,24)*.

Carbon monoxide. To verify that participants assigned to the nicotine patch treatment were not smoking during treatment and to measure carbon monoxide (CO) exposure in participants who smoked OMNI cigarettes, we analyzed expired breath samples by using a Bedfont Micro III Smokerlyzer CO monitor. A carbon monoxide level of 8 parts per million (ppm) or less was required to verify compliance with abstinence in the nicotine patch group *(25)*.

Biomarker of NNK uptake. NNK is metabolized to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-Gluc). These two metabolites of NNK can be detected in urine and are accepted biomarkers of NNK uptake *(26)*. Total NNAL (the sum of NNAL and NNAL-Gluc) was quantified as described previously *(27)*. Participants whose NNAL levels were below the limit of detection of the method were assigned NNAL levels that were one-half the limit of detection for data analysis.

Biomarker of PAH uptake. Levels of 1-hydroxypyrene (1-HOP), a urinary metabolite of pyrene and an established biomarker of PAH uptake *(26)*, were measured in smokers. 1-HOP occurs in urine predominantly in the form of its glucuronide. To quantify urinary 1-HOP levels, the glucuronide was hydrolyzed, and the total 1-HOP level (glucuronide and the hydrolyzed product), referred to in this paper as 1-HOP, was measured. The analysis was carried out as described *(28)*.

Records of tobacco use and carbon monoxide levels were obtained at all clinic visits. Other outcome measures (cotinine levels, 1-HOP [smokers only], and total NNAL levels) were obtained during both baseline visits and at weeks 2 and 4 of treatment. Anatabine levels were assessed for the two baseline visits and at week 4. The first urine void of the day was collected for the cotinine and carcinogen exposure analyses.

Statistical Methods

The use of 25 participants in each of two treatment conditions is sufficient to detect a difference of 1.25 standard deviation in mean outcomes, with a power of 80% using a two-tailed test at a 5% significance level. This sample size was determined based on previous studies *(21,29)* that showed statistically significant differences between baseline tobacco use and abstinence with or without use of nicotine patches using a sample size of approximately 13–14 subjects per condition. Participants who had five or more slips (defined as any use of their usual brand of cigarettes or smokeless tobacco) in the week before their clinic visit during treatment had their data excluded from all data analyses. These participants were excluded to minimize the confounding effects from the use of nonassigned tobacco products. Although this procedure affected the randomization process, the excluded subjects were from both treatment conditions, and analyses of the data including these subjects (not shown) resulted in virtually similar results. Participants who dropped out before the week 2 visit were also excluded from analyses because no urine samples were collected from these individuals during the product assignment phase. For the smokeless tobacco study, of the 54 participants randomly assigned, three participants (one in the snus treatment group and two in the nicotine patch group) dropped out before week 2, and 10 participants (five in the snus treatment group and five in the nicotine patch group) reported five or more slips or uses of other tobacco products during any one week of treatment. For the cigarette study, of the 51 participants randomly assigned to treatment, three participants (two in the OMNI cigarette group and one in the nicotine patch group) dropped out before week 2, and 10 participants (two in the OMNI cigarette group and eight in the nicotine patch group) reported five or more slips or uses of other tobacco products during any one week of treatment (Fig. 1).

Participants' self-reported baseline characteristics, including ethnicity, age, number of previous quit attempts, and years of tobacco use, were compared between the two treatment groups (reduced-exposure tobacco products and nicotine patch) for participants who used smokeless tobacco and for cigarette smokers. Discrete variables were analyzed using chi-square test or Fisher's exact test. Continuous variables were analyzed by using the two-sample *t* test, or, if normality and constant variances assumptions did not hold, by the Wilcoxon rank sum test. Characteristics with statistically significant differences between treatment groups were considered as covariates in the models when analyzing biomarkers and other outcome measures.

The baseline values of tobacco use, carbon monoxide, cotinine, anatabine, total NNAL, and 1-HOP levels were calculated as the average of the measurements from the two preassignment baseline visits. If one preassignment measurement was missing, then the baseline value was equal to the other nonmissing measurement.

After the randomization, two tobacco use variables—tins of smokeless tobacco per week and cigarettes per day—were measured at every clinic visit (week 1–4) among only the reduced-exposure tobacco product groups, that is, users of smokeless tobacco who were assigned to General Snus or smokers who were assigned to the OMNI Light cigarette. For each reduced-exposure tobacco product group, the analysis of variance (ANOVA) was applied to a mixed model to evaluate the fixed-visit effect and the random-subject effect on the amount of tobacco use.

The paired *t* test or Wilcoxon signed rank test was used to analyze the differences between the averaged baseline and week 4 anatabine levels to determine abstinence from tobacco in the two nicotine patch groups. For carbon monoxide, cotinine, total NNAL, and 1-HOP (smokers only) levels, a repeated-measure ANOVA for a linear mixed model *(30)* was used, in which the model contained a fixed-treatment effect, a random-subject effect (between-subject error), a fixed-visit effect, a fixed-interaction effect between treatment and visit, and a random error (within-subject error). The covariance structure was specified as compound symmetry, and variance components were estimated using the restricted maximum likelihood method. The multiple comparisons of mean outcomes under different treatment and/or visit conditions were adjusted by using Bonferroni's method.

SAS version 8.2 (SAS Institute, Cary, NC) was used for statistical analyses. All tests were two-sided, with statistical significance set at a P value of $<.05$.

Results

Users of Smokeless Tobacco

The participant flowchart is shown in Fig. 1. The primary data analysis was conducted on 41 participants: 22 participants assigned to the nicotine patch group and 19 participants assigned to the snus group. Of the 22 participants in the nicotine patch group, five had high anatabine levels (>1 ng/mL), and two had high cotinine levels while on the nicotine patch, suggesting noncompliance with the study design. Thus, after we excluded these participants, our secondary analysis included data from 34 participants: 15 participants in the nicotine patch group and 19 participants in the snus group. No statistically significant differences were observed in participant demographics and tobacco use history between the treatment groups at baseline ($P>.05$). Therefore, Table 1 shows the participant characteristics combined for both groups.

Tobacco use and cotinine levels. At baseline, the 41 participants used an average of 3.0 (standard deviation [SD] = 1.6, range = 1.0–10.0) tins per week of their usual brand of smokeless tobacco. No statistically significant differences in amounts used were found between the snus and nicotine patch groups ($P = .99$). Among participants assigned to the snus group, the amounts of smokeless tobacco used during baseline and after switching to snus were not statistically significantly different ($P = .67$; Table 2).The mean baseline urine cotinine level was 5960 ng/mL (SD = 3271 ng/mL, range = 1109–16 505 ng/mL), with no statistically significant differences between groups ($P = .63$). The overall mean cotinine level in the snus group (mean = 5525 ng/mL) was higher than the level in the nicotine patch group (mean = 4189 ng/mL), although the difference (1336 ng/mL, 95% CI = −68 to 2739) was not statistically significant ($P = .062$). Table 2 shows the cotinine levels across visits for the treatment groups. In the snus group, the mean cotinine level decreased from 6193 ng/mL at baseline to 4465 ng/mL at week 2 ($P = .020$) and then increased to 5926 ng/mL at week 4 ($P = .054$), resulting in a statistically significant overall visit effect on cotinine level ($P = .045$). In the nicotine patch group, the mean cotinine level decreased from 5759 ng/mL at baseline to 3661 ng/mL at week 2 ($P = .003$) and continued to decrease to 3204 ng/mL at week 4 ($P<.001$), resulting in a highly statistically significant overall visit effect on cotinine level ($P<.001$).

Biomarkers of NNK uptake. We determined the mean total NNAL levels under different treatment and visit conditions (Fig. 2). No statistically significant differences in baseline measures were found between the snus and nicotine patch treatment

Table 1. Demographic characteristics of participants*

Demographic variable	Users of smokeless tobacco (n = 41)		Smokers (n = 38)	
Mean age (SD), y	31.4 (5.9), range = 22–47		40.9 (9.7), range = 22–55	
Mean (SD) duration of use, y	12.9 (6.2), range = 3–29		22.3 (10.2), range = 1–39	
Brand/type of tobacco, No. of users				
	Copenhagen	13	Regular	15
	Kodiak	20	Medium	2
	Skoal Long Cut	6	Light	15
	Rooster	1	Ultra-light	5
	Red Seal	1	Self-rolled	1
Median No. of quit attempts	4.0, range = 0–100		4.0, range = 0–100	
Race/ethnicity				
Caucasian	39		36	
Asian	2		2	

*SD = standard deviation.

Table 2. Mean (95% confidence interval) number of tins used per week and urinary cotinine levels across visits by treatment (Snus or nicotine patch) groups among users of smokeless tobacco (N = 41)

Visit	No. of tins per week		Mean cotinine levels, ng/mL	
	Snus (n = 19)	Nicotine patch (n = 22)	Snus (n = 19)	Nicotine patch (n = 22)
Baseline	3.1 (2.1 to 4.1)	2.9 (2.4 to 3.3)	6193 (4579 to 7807)	5759 (4310 to 7208)
Week 1	3.9 (2.1 to 5.6)			
Week 2	3.8 (2.2 to 5.4)		4465 (3127 to 5803)	3661 (2524 to 4797)
Week 3	3.6 (2.1 to 5.0)			
Week 4	3.7 (2.2 to 5.1)		5926 (4415 to 7437)	3204 (2256 to 4152)

groups (P = .275). The mean total NNAL levels statistically significantly decreased over visits for both the snus (P<.001) and nicotine patch (P<.001) groups, resulting in a highly statistically significant overall visit effect on total NNAL level (P <.001). The overall treatment group effect was also statistically significant (P = .008), with the mean total NNAL level of the snus group (2.0 pmol of NNAL/mg of creatinine) statistically significantly higher than that of the nicotine patch group (1.2 pmol of NNAL/mg of creatinine; mean difference = 0.9 pmol/mg of creatinine, 95% CI = 0.2 to 1.5). The decreasing NNAL levels in both treatment groups over visits were approximately parallel, resulting in a statistically nonsignificant treatment by visit interaction effect (P = .230). Similar results were observed when we limited the sample to participants in the nicotine patch group to include only those who were compliant with patch-only use based on anatabine results. The mean percent reduction in total NNAL (calculated as the mean of individual percent reductions) at week 4 was 48% (95% CI = 31% to 64%) for participants in the snus group and 90% (95% CI = 86% to 94%) and 89% (95% CI = 83% to 95%) for participants in the nicotine patch group without and with verification of patch-only use based on anatabine levels, respectively. At week 4, among the 19 participants who used snus, 11 participants had more than a 50% reduction in total NNAL levels, five participants had less than a 50% reduction (but at least a 15% reduction), and two participants had an increase of 17% and 28%, respectively, in total NNAL levels. One participant had missing values at both week 2 and week 4.

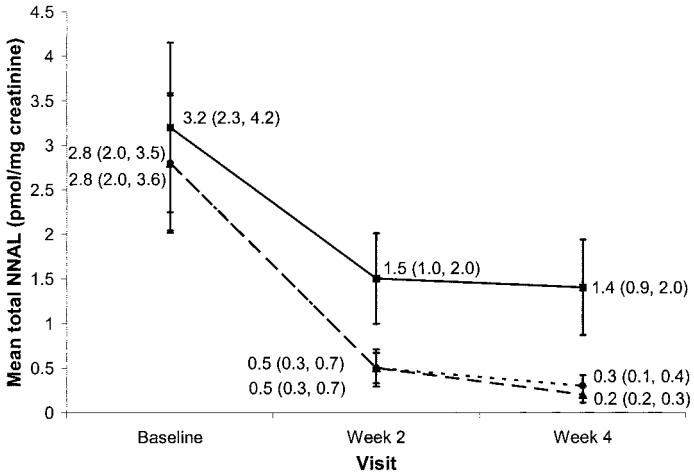

Fig. 2. Levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide (total NNAL) were measured in the urine of users of smokeless tobacco assigned to nicotine patch or snus groups at baseline and twice during the 4-week treatment period. Data are expressed as picomoles of total NNAL per milligram of creatinine. Each point represents the group mean (with 95% confidence intervals in parentheses). For participants in the nicotine patch group, data were analyzed for all participants (n = 22, **triangles and long-dashed line**) and for participants for whom levels of anatabine (an alkaloid present in tobacco but not in medicinal nicotine and thus a marker of study compliance) were below a level indicating tobacco use (n = 15, **circles and short-dashed line**). **Square marker and solid line** = snus group (n = 19).

Smokers

The participant flowchart is shown in Fig. 1. The primary analysis was conducted on 38 participants: 16 participants assigned to the nicotine patch group and 22 participants assigned to the OMNI cigarette group. Four participants in the nicotine patch group had high anatabine levels (>1 ng/mL) during patch use. Thus, after we excluded these participants, our secondary analysis included data from 34 participants: 12 participants in the nicotine patch group and 22 participants in the OMNI cigarette group. No statistically significant differences were observed in participant demographics and smoking history between treatment groups at baseline (P>.05). Table 1 shows the participant characteristics combined for both groups.

Tobacco use and cotinine levels. At baseline, the 38 participants smoked an average of 21.8 (SD = 6.2, range = 12.1–35.8) cigarettes per day, and no statistically significant differences in the number of cigarettes smoked per day were observed between treatment groups (P = .89). Statistically significant visit effects were observed for participants assigned to the OMNI cigarette group (P<.001). The pairwise comparisons showed that the number of cigarettes smoked per day at baseline was statistically significantly less than that for each of the four treatment visits (P<.01; Table 3).The mean baseline urine cotinine level of all smokers was 5233 ng/mL (SD = 2607, range = 1550–10690 ng/mL). Table 3 shows the cotinine levels across visits for the treatment groups. Participants in the OMNI cigarette group had statistically significantly lower baseline cotinine levels (mean = 4412 ng/mL) than did participants in the nicotine patch group (mean = 6364 ng/mL) (P = .03). Mean cotinine levels did not statistically significantly differ over visits among those assigned to the OMNI cigarette group (P = .88), whereas statistically significant decreases in mean cotinine levels over visits were observed in participants assigned to the nicotine patch group (P<.001).

Biomarker of NNK uptake. We determined the mean total NNAL levels under different treatment and visit conditions (Fig. 3A). The baseline total NNAL levels were not statistically significant different between treatment groups (P = .396). Statistically significant decreases in total NNAL levels over visits were observed for both the OMNI cigarette (P = .003) and nicotine patch (P<.001) groups. The treatment group effect was statistically significant (P = .022), with the overall mean total NNAL levels of the OMNI cigarette group (1.9 pmol of NNAL/mg of creatinine) statistically significantly

Table 3. Mean (95% confidence intervals) of number of cigarettes smoked per day and cotinine levels across visits by treatment groups (OMNI cigarette and nicotine patch) among cigarette smokers (N = 38)

	No. of cigarettes per day		Cotinine levels, ng/mL	
Visit	OMNI cigarette (n = 22)	Nicotine patch (n = 16)	OMNI cigarette (n = 22)	Nicotine patch (n = 16)
Baseline	21.7 (18.9 to 24.4)	22.0 (18.6 to 25.4)	4412 (3468 to 5355)	6364 (4849 to 7878)
Week 1	25.1 (21.4 to 28.8)			
Week 2	26.9 (22.9 to 31.0)		4163 (3238 to 5089)	5156 (3142 to 7170)
Week 3	26.9 (22.1 to 31.7)			
Week 4	26.0 (21.8 to 30.2)		4450 (3452 to 5448)	3437 (1964 to 4910)

higher than that of the nicotine patch group (1.2 pmol of NNAL/mg of creatinine, mean difference = 0.6 pmol of NNAL/mg of creatinine, 95% CI = 0.1 to 1.1). The treatment group by visit interaction effect was also statistically significant ($P<.001$). Similar results were observed when the analysis was restricted to the participants from the nicotine patch group who were verified, based on anatabine levels, as not using any tobacco products. Because the number of cigarettes varied between baseline and during the use of OMNI cigarettes, we calculated the ratio of total NNAL/cigarettes per day and total NNAL/cotinine level. The ratios were observed to statistically significantly decrease over visits for both measures ($P<.001$ and $P = .009$, respectively). The mean percent reduction of total NNAL at week 4 was 21% (95% CI = 3% to 40%) for the OMNI cigarette group and 57% (95% CI = 21% to 92%) and 64% (95% CI = 21% to 107%) for the nicotine patch group without and with verification of patch-only use based on anatabine levels, respectively. According to the OMNI Web site, NNK levels decrease by slightly more than 50% using machine-determined methods developed by the FTC and Massachusetts Department of Public Health to assess toxic exposure. At week 4, among the 22 participants in the OMNI cigarette group, five participants had a greater than 50% decrease in total NNAL levels, 12 participants had between a 0 and 50% decrease, four participants had an increase in total NNAL levels (20%–84%), and one participant had a missing value. Of the participants who had increased NNAL levels, two had smoked light cigarettes, one had smoked ultralight cigarettes, and one had smoked regular cigarettes during the baseline smoking of their usual cigarette brands.

Biomarker of pyrene uptake. We measured mean 1-HOP levels under different treatment and visit conditions (Fig. 3B). There was no statistically significant difference in 1-HOP levels between treatment groups at baseline ($P = .51$). The 1-HOP levels statistically significantly decreased over visits among the nicotine patch ($P<.001$) but not the OMNI cigarette ($P = .27$) group. The overall treatment group effect on 1-HOP levels was not statistically significant ($P = .40$). The 1-HOP levels did not differ between treatment groups over visits ($P = .09$). Similar results were observed for the participants in the nicotine patch group who were verified, based on the anatabine data, as not using tobacco products. In addition, we calculated the ratio of 1-HOP level to the number of cigarettes smoked per day and 1-HOP level to total cotinine level for the OMNI cigarette group and found no statistically significant effects associated with visit for either measurement ($P = .10$ and $P = .76$, respectively). According to the OMNI Web site, pyrene levels decrease by between 20% and 30% using methods developed by the FTC and Massachusetts Department of Public Health. The mean percent reduction of 1-HOP at week 4 was 5% (95% CI = –27 to 38%) for the OMNI cigarette group and 27% (95% CI = –15% to 70%) and 52% (95% CI = 17% to 88%) for the nicotine patch group, without and with verification of patch-only use based on anatabine levels, respectively. Among the 22 participants in the OMNI cigarette group, six had a greater than 50% decrease in 1-HOP levels, five had between a 20% and 50% decrease, three had less than a 20% decrease, and eight had an increase or no change in 1-HOP levels. Among the eight participants who had an increase or no change, five had smoked light cigarettes during the baseline smoking of their usual cigarette brand.

Carbon monoxide. We measured mean carbon monoxide levels for the entire group of 38 smokers under different treatment and visit conditions (Fig. 3C). No statistically significant difference was observed between treatment groups on baseline measurements ($P = .92$). However, statistically significant visit effects were observed for the nicotine patch group ($P<.001$), with carbon monoxide levels decreasing sharply from baseline to week 1 and remaining at a low level through week 4. Visit effects were not statistically significant for the OMNI cigarette group ($P = .54$). The treatment effect was statistically significant ($P<.001$), with the overall mean carbon monoxide level of the OMNI cigarette group (24.2 ppm) statistically significantly higher than that of the nicotine patch group (7.4 ppm; mean difference = 16.8 ppm, 95% CI = 13.0 to 20.6). Similar results were observed for those participants in the nicotine patch group for whom we had verification that no tobacco was used based on anatabine levels. The mean percent reduction in carbon monoxide levels from baseline to week 4 was –1% (95% CI = –15% to 12%) for the OMNI cigarette group and 85% (95% CI = 78% to 92%) and 91% (95% CI = 88% to 94%) for the nicotine patch group, without and with verification of patch-only use based on anatabine levels, respectively. Among the 22 participants in the OMNI cigarette group, eight had a greater than 10% decrease in carbon monoxide levels, five had less than a 10% decrease in carbon monoxide, eight experienced increases in carbon monoxide levels (percent increase ranged from 5% to 91%), and one participant had a missing value.

DISCUSSION

The goals of this study were to examine human exposure to tobacco-related toxins in modified smokeless tobacco and cigarettes compared with that from medicinal nicotine. The principal results showed a statistically significant reduction in carcinogen uptake when users of smokeless tobacco switched from conventional brands of smokeless tobacco marketed in the United

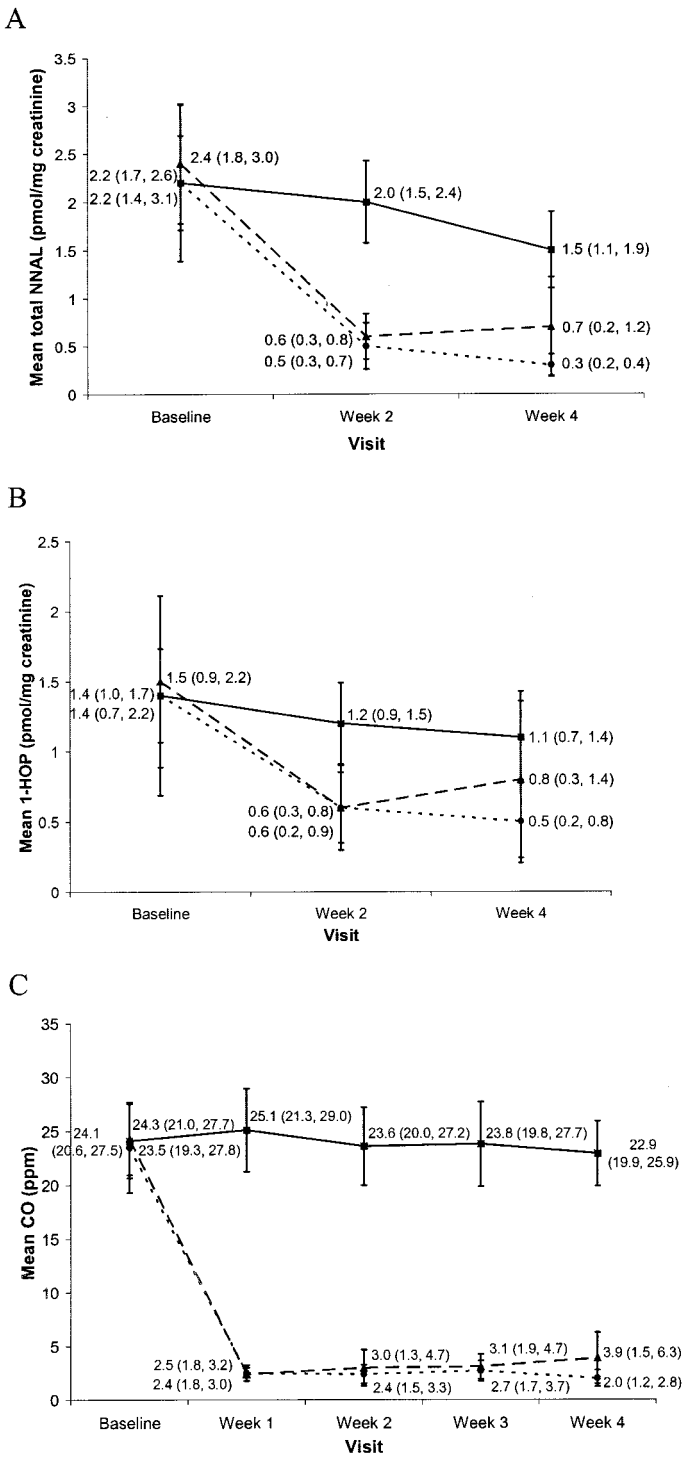

Fig. 3. Levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide (total NNAL) **(A)** and 1-hydroxypyrene (1-HOP) **(B)** were measured in the urine and alveolar carbon monoxide (CO) **(C)** of cigarette smokers assigned to the nicotine patch or OMNI cigarette groups at baseline and twice during the 4-week treatment period. Data are expressed as picomoles of total NNAL or 1-HOP per milligram of creatinine. Each point represents the group mean (with 95% confidence intervals in parentheses). For participants in the nicotine patch group, data were analyzed for all participants (n = 16, **triangles and long-dashed line**) and for participants for whom levels of anatabine (an alkaloid present in tobacco but not in medicinal nicotine and thus a marker of study compliance) were below a level indicating tobacco use (n = 12, **circles and short-dashed line**). **Square marker and solid line** = OMNI cigarette group (n = 22).

States to Swedish snus. Modest and statistically significant or minimal reductions in uptake in tobacco toxins were observed when smokers switched from their usual conventional cigarette brand to OMNI cigarettes. Statistically significantly greater reductions in toxins occurred with the use of medicinal nicotine compared with either of these two products.

The results of this study lead to four major conclusions. First, tobacco products are available that can statistically significantly reduce exposure to carcinogens. In particular, we found that users of Swedish snus, a smokeless tobacco product, had lower exposure to the carcinogen NNK than did users of smokeless tobacco products sold in the United States. In those who used snus for 4 weeks, total NNAL levels (biomarkers of NNK uptake) were decreased by approximately 50% relative to levels obtained during 2 weeks of *ad libitum* use of widely used brands of smokeless tobacco products in the United States. This decrease in total NNAL levels was not a result of decreased smokeless tobacco use because study participants used similar amounts of snus and, by the end of treatment, had similar cotinine levels as they had during use of their usual smokeless tobacco product.

Using the Swedish smokeless tobacco product rather than the smokeless tobacco products marketed in the United States may not only reduce carcinogen exposure but also may decrease cancer risk. The prevalence of oral cancer among individuals who use Swedish snus is no higher than that among individuals who do not use tobacco products *(31–33).* By contrast, in the United States, rates of oral cancer are higher among individuals who use oral smokeless tobacco products than that among individuals who do not use tobacco products *(34–38).* Although the reasons for these differences are not fully understood, lower levels of the carcinogenic nitrosamines in snus compared with those in brands widely used in the United States may be a contributing factor.

Our study has also shown that smoking OMNI cigarettes results in lower uptake of NNK, albeit only 20% lower than that from smoking conventional cigarettes sold in the United States. Nonetheless, considering that NNK is among the most important lung carcinogens in cigarette smoke, and given the magnitude of the smoking and lung cancer problem, reductions in exposure to this compound in cigarettes may have a public health impact, provided that other toxin exposures and rates of smoking do not increase by smoking OMNI cigarettes.

The second conclusion is that, even though the modified tobacco products we examined reduced exposure to some tobacco toxins, these products still contain substantial levels of carcinogens. Tobacco-specific nitrosamine levels in snus are 100 times greater than nitrosamine levels in other consumer products, such as beer and food *(8,9).* Although users of snus do not appear to have an increased risk of oral cancer, heavy smokeless tobacco users *(39)* and oral snus users [as cited in *(40)*] may have an increased risk of pancreatic cancer, which could likely result from NNK exposure. Other health effects such as increased incidence of oral pathologies, including gum recession and leukoplakia, increased cardiovascular disease risk factors, and potentially increased incidence of fetal toxicity, are associated with both snus and U.S. brands of smokeless tobacco *(41–43).* Therefore, snus should not be considered a safe product, even with its substantial reduction in tobacco-specific nitrosamines.

For smokers of OMNI cigarettes, carcinogen uptake was reduced by approximately 20% for NNK and 5% for pyrene.

Whether this modest reduction confers a reduced cancer risk is unknown. The Web site for OMNI cigarettes, in fact, states that there is no proof that a reduction in toxin levels will actually result in a substantial decrease in the health risk associated with smoking. Moreover, it is important to consider exposure to a variety of toxins when assessing the effects of these cigarette products. For example, the FTC method for assessing the amount of toxin exposure indicates that there is a 170% increase in nitric oxide exposure associated with OMNI cigarettes, which may increase absorption of nicotine in the lungs *(44)* and could consequently increase the uptake of nicotine in the brain. Therefore, these modest reductions in toxins and increase in exposure to other toxins may be unlikely to reduce the risk for cancer or other tobacco-related diseases.

The third conclusion from this study is that information provided to consumers on the OMNI Web site that indicated a 53% reduction in NNK exposure and a 15–20% reduction in pyrene, as determined by the FTC analysis methods, is misleading and may not be directly applicable to the general smoking population. The results from our study highlight the limitations of machine-measured methods (i.e., FTC methods) and the importance of examining actual human smoking behavior to determine the extent of exposure *(45,46).* Furthermore, before switching to products that claim to have reduced toxin levels, smokers should consider the individual variability that occurs with the extent of exposure to tobacco toxins. Variability can arise from differences in how individuals smoke cigarettes and how quickly they metabolize tobacco toxins *(3).* Therefore, mean values from machine-determined methods of exposure do not accurately reflect levels of toxin exposure in all smokers. As we found in our study, although some smokers of OMNI cigarettes had reduced toxin levels, others had increased levels.

The fourth conclusion is that use of the nicotine patch resulted in substantially lower levels of NNK and pyrene uptake than did use of snus and OMNI cigarettes. These results demonstrate that use of medicinal nicotine therapy is a safer approach than switching to an alternative oral tobacco product or modified cigarette. The observation of statistically significant reductions in carcinogen levels is important to correct the misperception among smokers that medicinal nicotine may be carcinogenic *(47).* Medicinal nicotine, compared with snus and the OMNI cigarette, is less likely to lead to addiction, is not known to cause cancer, is likely to be associated with relatively lower cardiovascular disease risk, and reduces fetal toxicity *(48).* Compared with cigarettes, medicinal nicotine does not increase the incidence of pulmonary disease. Because the safety profile for medicinal nicotine is better than that for conventional or modified tobacco products, the use of long-term medicinal nicotine products is more likely to result in reduced disease risk.

Our study has several limitations. First, it is difficult to confirm whether individuals who were randomly assigned to the snus or OMNI cigarette groups used conventional products during the treatment period. The data from the nicotine patch group showed that some individuals were not entirely truthful regarding their tobacco use during the study. Consequently, we undertook data analyses excluding subjects who self-reported a specific level of exposure to a nonassigned product and a more stringent data analysis of individuals in the medicinal nicotine groups who, on the basis of anatabine levels, did not use any tobacco products. Ideally, this study would have been an inpatient study, in which access to tobacco products could be controlled. However, to have participants stay in an inpatient unit for 4 weeks was not feasible. In addition, the dual use of products may be more reflective of the pattern of use observed in the natural environment. Second, our sample size was small—a consequence of the number of individuals who experienced difficulty sustaining and using solely the assigned products. A small sample size may not accurately reflect the extent or variability of reductions observed in the general population of smokers.

The method of nicotine delivery by modified tobacco products and the types of these products are evolving. As such, independent testing and government regulation of these tobacco products is essential *(3,49).* The need for regulation of tobacco products is particularly evident when products with nonexistent levels of carcinogens and other tobacco toxins (i.e., medicinal nicotine) are under FDA regulation, whereas the products that contain higher levels of carcinogens—and which are more likely to lead to premature death and disease—are not. Regulation of tobacco products would permit standards to be established for allowable toxin levels of tobacco products. Furthermore, the public would be accurately informed about the extent to which they are exposed to tobacco toxins with the use of these products. It would also be important to assess the potential impact of claims of reduced carcinogen and toxin exposure on public perceptions of these products, which may influence the prevalence of tobacco use *(3,50),* before tobacco companies market their products. The past experiences with the "light," "mild," and "low-yield" cigarettes, which did not reduce morbidity and mortality as had been assumed and led to continued smoking among some smokers rather than quitting *(46),* should alert the public health community that consumers need to be better informed about these new tobacco products before accepting them as reduced-risk products.

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NOTES

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