Puffing Style and Human Exposure Minimally Altered by Switching to a Carbon-Filtered Cigarette

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Abstract

Objective: **Potential Reduced Exposure tobacco Products (PREP) are intended to lower human exposure to toxic constituents of tobacco smoke, but rigorous clinical evaluations are required to assess such claims. The present study assessed human smoking behavior and short-term exposure to a new carbon-filtered PREP, Marlboro UltraSmooth (MUS). Two MUS prototypes with filter carbon loads of 120 and 180 mg were compared with low and ultralow-yield conventional cigarettes.**

Methods: **After a 48-hour baseline period, 32 adult Marlboro Lights smokers were switched in a counterbalanced order, to MUS and Marlboro Ultra Lights for 48 hours each. Measures of smoking topography, subjective response, change in cardiac response, and carbon monoxide boost were obtained under supervised test conditions on separate days. After each test, topography measures were obtained via a 48-hour free smoking phase for each brand. Salivary cotinine was measured at the end of each 48-hour period.**

Results: **Although MUS was generally smoked in a style similar to conventional cigarettes, compensatory smoking was observed with 1 MUS prototype ($P = 0.003$). Carbon monoxide boost was lower for MUS compared with Marlboro Lights, but salivary cotinine and cardiac function measures after smoking of MUS did not vary from conventional brands.**

Conclusions: **Smoking MUS produced few differences in smoking topography and exposure compared with conventional low and ultralow-yield cigarettes. Results suggest that the manner in which MUS is smoked by humans is unlikely in the short term to reduce exposure among smokers who switch from a conventional brand.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):2995–3003)

Introduction

Tobacco products and nicotine delivery devices known as Potential Reduced Exposure Products (PREP) are designed to lower human exposure to toxic constituents of tobacco smoke using technological innovation. Limited evidence suggests that some PREPs may have the capacity to reduce human exposure to cancer-causing compounds, at least in the short term (e.g., refs. 1, 2). Ultimately, a tobacco product regarded as ''reduced exposure'' should have the capacity to lower not only exposure and thus individual risk but population health risks or harms associated with long term use. The Institute of Medicine has reviewed strategies for assessing PREPs (3). Recommended strategies included long-term research to understand the dose-response relationship between constituent exposure and health outcomes, and measurement of validated disease biomarkers among smokers of PREPs. In the shorter term, substantial research strategies can be used to assess the likelihood that a new PREP has exposure reducing capacity. Such strategies may include measurement of mainstream smoke yields of carcinogens and other toxic constituents, *in vitro* and *in vivo* toxicity testing, and clinical switching studies of smoker behavior and exposure (4). The importance of evaluating PREPs is reinforced by the missed historical opportunity to adequately assess and communicate harms associated with ''lights'' cigarettes. These low-yield cigarettes were perceived by smokers as safer, and this may have contributed to continued smoking and no significant reductions in disease after their introduction in the 1970s (5).

Marlboro UltraSmooth (MUS) is a recently developed PREP that resembles a conventional cigarette, but its filter has been modified by the addition of activated carbon (6). Carbon acts as a chemical adsorbant and is used in cigarettes to enhance smoking sensory characteristics such as ''smoothness.'' MUS is novel in that it contains far greater carbon used previously in U.S. cigarettes, and thus, its potential to reduce toxic smoke constituents may be enhanced. Three MUS prototypes of differing physical design entered commercial test market in mid-2005, in U.S. cities Salt Lake City, Tampa, and Atlanta. The Salt Lake City prototype has unique features, which include 180-mg vitreous carbon beads arranged in a pocket within the filter tow material, as well as an embedded filter fiber that carries a chemical flavorant. Tampa (120 mg carbon) and Atlanta (45 mg carbon) prototypes use ''dalmatian'' style filters, in which the carbon granules are distributed throughout the filter tow material. Standard (FTC) machine testing of mainstream smoke of Salt Lake City and Tampa prototypes has shown lowered gas phase constituent yields compared with a conventional low yield cigarette (7). However, the FTC method potentially underestimates cigarette actual

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mainstream smoke yields because low tar and nicotine yield conventional cigarettes tend to be smoked with a more intensive puffing style (8, 9). The FTC method calls for 35 mL puffs of 2-second duration, taken once per minute (10). In comparison, the so-called ''intensive'' Health Canada method is designed to mimic human puffing more closely and calls for 55 mL puffs of a 2-second duration and 30-second interval (11). The Health Canada method also requires 100% vent hole blocking to mimic the tendency for a smoker's fingers or lips to occlude the vent holes, whereas the FTC protocol has no vent hole blocking requirement.

The capacity of MUS to reduce gas phase constituent yields is considerably less effective when smoked under more intensive (Health Canada) smoking conditions compared with standard (FTC) conditions (7, 12). Particulate phase constituents, including polycyclic aromatic hydrocarbon and tobacco-specific nitrosamine carcinogens, are not reduced by the MUS carbon filter under either standard or intensive machine smoking regimens (7, 12). However, machine yield toxic smoke emission measures may be somewhat arbitrary and do not provide information about human toxicant exposure. Variability in human smoking behavior, including smoking patterns that are typically more intensive than a standard machine testing protocol and possible metabolic differences, may contribute to poor concordance between smoke machine constituent yields and human exposure (13, 14). Design features that lower machine smoking yields, such as increased filter ventilation, paper porosity, and lower tobacco rod nicotine, tend to encourage stronger puffing in human subjects (15, 16). This helps to ensure delivery of an amount of nicotine that is satisfactory to the smoker (13), whereas also increasing delivery of toxic smoke constituents.

The importance of assessing actual human smoking behavior of MUS is further emphasized, considering the potential for low machine–yield cigarettes to show brand elasticity. Compensatory smoking of an elastic cigarette brand may result in nonlinear increases in toxic constituent yields as the intensity of puffing increases (13). Compensatory smoking involves greater smoke intake arising from puffs that are larger, longer, or more frequent than an established smoking baseline (17, 18). Previous research has shown that MUS is elastic, and that a higher intensity machine puffing protocol (Health Canada) produces constituent yields that are disproportionately greater than those observed under a standard (FTC) protocol (7, 12). Under the FTC protocol, yields of MUS gas-phase volatile organic and carbonyl compounds were as low as 6% of that of a conventional ultralow-yield brand, but increase to as much as 60% of the conventional brand when tested under the Health Canada machine smoking regimen. A reasonable inference from these machine yield tests is that smoking of MUS by human subjects could produce smoke constituent deliveries that approach those of a conventional cigarette as smoking intensity increases. This may lessen the exposure reduction potential of MUS. Measures of actual human puffing behavior are therefore required to determine whether smokers puff MUS in a manner that is more consistent with the ''intensive'' Health Canada protocol than the FTC protocol. Furthermore, because compensatory smoking is one important means by which a PREP might fail to lower exposure, smoking behavior with MUS should be compared with subjects' own brand and a comparison ultralow-yield brand.

The present study aimed to assess human smoking behavior (puff topography) and short-term measures of exposure resulting from switching to MUS, compared with an ultralow-yield conventional cigarette, Marlboro Ultra Lights (MUL). The two MUS test market prototypes with the highest carbon load and thus greatest poten tial for exposure reduction, Salt Lake City (180 mg) and Tampa (120 mg), were used. Marlboro Lights (ML) smokers were recruited and switched, in a random counterbalanced order, to either MUS or MUL, before the final switch to MUL or MUS. Smoking topography measures were obtained from 2 cigarettes smoked under supervision and multiple cigarettes smoked over a 48-hour period under naturalistic conditions. Short-term exposure was determined by carbon monoxide (CO) boost presmoking to postsmoking, changes in simple cardiac function (heart rate and blood pressure), and salivary cotinine. Subjective response measures were also used to compare smokers' perceptions of MUS with a conventional cigarette. It was hypothesized that switching to MUS would result in a puffing style more similar to the intensive Health Canada smoking regimen than the lower intensity FTC regimen. MUS puffing style, puff topography (number of puffs, puff volume, puff duration, and interpuff interval) was compared with subjects' usual ML cigarette, and the ultralow-yield conventional control, MUL. It was further hypothesized that switching to MUS would result in lowered measures of exposure compared with the control cigarette, MUL. Finally, subjective responses to MUS were compared with conventional control brands to determine whether the design modifications of MUS influenced perceived liking and effect and whether these subjective effects were related to smoking behavior.

Materials and Methods

Subjects. Participants were daily smokers who reported a daily smoking minimum of five cigarettes and whose brand of choice was ML. Further eligibility criteria included having no intention to quit for at least the next 3 mo and (if female) self-reported nonpregnant status. The study was advertised through a local online notice board,[1] which posts notices for casual employment, including research volunteer opportunities. The final sample comprised 32 participants (21 female). Participants were paid $120 for a total of 6 d of research participation.

Cigarettes. MUS cigarettes were obtained from retail outlets in the test market cities of Salt Lake City, UT, and Tampa, FL, during May to June, 2005, and shipped to the research site in Massachusetts. Conventional control (ML) and comparison (MUL) cigarettes were obtained from local retail outlets in Massachusetts. All cigarette types (MUS, ML, and MUL) were provided without cost to subjects for the study duration. The nicotine and tar levels of brands used in this study, as reported to the Federal Trade Commission (10), were as follows: MUS,

[1] http://www.craigslist.org

5 mg ''tar'' and 0.4 mg nicotine; ML, 11 mg tar and 0.8 mg nicotine; and MUL, 6 mg tar and 0.5 mg nicotine.

Measures

Subject Characteristics. Basic demographic, smoking status, and smoking history were recorded using a standardized interview. Nicotine dependence was measured using the Fagerstrom Test for Nicotine Dependence (19). The Fagerstrom Test for Nicotine Dependence is a six-item scale, which produces nicotine dependence scores on a scale from 0 to 10, with higher scores representing greater nicotine dependence.

Smoking Topography. Behavioral measures of smoking were made using a portable CReSSmicro topography device (Plowshare Technologies). The device is slightly smaller than a cigarette pack and weighs about 90 grams. Because CReSSmicro measurements are acquired automatically after cigarette insertion, it can be used by study participants without supervision. A flow meter in the device measures pressure change related to the flow rate of smoke through the mouthpiece. Puffing variables obtained for each cigarette included puff number, puff volume (total draw for each individual puff, mL), puff duration (millisecond per puff), and interpuff interval (ms) per cigarette.

Home Smoking Diary. Subjects recorded the number of cigarettes smoked for each brand over each 48-h period, using a brief daily smoking checklist. This checklist also recorded time of each cigarette smoked and total number of number of cigarettes smoked per day. Diary reports were compared against cigarettes returned unsmoked, which helped to guard against overreporting (but not under reporting).

Exposure Measures. A behavioral measure of mainstream smoke exposure, total smoke intake per cigarette, was determined by summing puff volumes for all puffs, per cigarette. Cotinine, the major metabolite of nicotine, is more stable than nicotine and therefore was used for assessing exposure to tobacco smoke. Cotinine was obtained from a 1-mL saliva sample and analyzed by rapid gas-liquid chromatographic method. The assay used is sensitive to 0.6 ng/mL (Department of Laboratory Medicine, Children's Hospital Boston). Cotinine level arising from the use of each brand was the level recorded immediately after smoking that product over the 48-h period. Expired air CO level was measured using a Micro III Smokerlyzer (Bedfont). CO boost (parts per million of exhaled air) was determined by the difference between pre and postsmoking levels. Postsmoking changes in simple cardiac function were determined by subtracting presmoking from postsmoking measurements obtained using an HEM-737AC Blood Pressure Monitor (Omron).

Subjective Assessment. Self-reported subjective responses after smoking was assessed with two questions derived from Zacny (20). On the ''Feel Drug Effect'' question, subjects are asked to rate the intensity of the drug effect as they currently experience it [from 1 (''I feel no effect from it at all'') to 5 (''I feel a very strong effect'')]. On the ''Like Drug Effect'' question, subjects are asked how much they like the drug effect on a visual analogue scale of 0 to 100 with the following descriptors: 0, dislike a lot; 50, neutral; 100, like a lot.

Design and Procedures. Subjects were randomly assigned to receive either Tampa (MUS-Tampa) or Salt Lake City (MUS-SLC) prototype cigarettes. The study used a brand switching design in which a 48-h smoking baseline using ML was obtained before participants were switched for 48 h to either MUS (either MUS-Tampa or MUS-SLC) or control cigarette MUL, in a random counterbalanced order. Selection of MUS prototype and order of switching was made using customized random allocation software. The 48-h period was selected because it offers an opportunity to examine smoking behavior in the field with sufficient time to allow subjects to adjust to each new cigarette. Each 48-h period commenced at the conclusion of each supervised laboratory smoking session. During the final 48 h, subjects smoked the alternate cigarette—either MUL or MUS. This design therefore comprised 3 phases, each of 48-h duration (see Table 1).

Within each phase, two research components were conducted: a ''test'' component in which subjects smoked the study cigarettes and completed questionnaires in the presence of a researcher, and an ''*ad lib*'' component in which subjects smoked freely over a 48-h period. The test component required subjects to participate in study session of ~60 min duration in which two cigarettes were smoked and questionnaires completed before and after smoking. Physical measures (1 mL saliva sample for cotinine, expired air sample for CO, heart rate, and blood pressure) also were obtained presmoking and postsmoking.

The *ad lib* component required subjects to continue to use the designated experimental cigarettes (ML, MUS, or MUL) for ~ 48 h after each supervised session. Subjects recorded smoking topography for a minimum of 5 cigarettes on each 24-h period during this time, while smoking at home. Subjects self-monitored number and time of all cigarettes smoked on each of these 48-h periods. All procedures involving human subjects were done after approval by the Harvard School of Public Health's institutional review board and in accordance with an assurance filed with and approved by the Department of Health and Human Services.

Table 1. Study design

	Part 1			Part 2			Part 3	
	Test	*Ad Lib*		Test	*Ad Lib*		Test	*Ad lib*
	Day 1	Days 1-2		Day 3	Days 3-4		Day 5	Days 5-6
Order 1:	ML	ML	*Switch*	MUS	MUS	*Switch*	MUL	MUL
Order 2:	ML	ML	*Switch*	MUL	MUL	*Switch*	MUS	MUS

Informed consent was obtained from all participants before participation.

Data Analysis. Topography data were analyzed separately as supervised and unsupervised (*ad lib*) smoking sessions. Topography and exposure measures were analyzed using repeated measures ANOVA, with between-groups factor MUS prototype (Tampa, SLC) and within-subjects factor brand (ML, MUS, and MUL). Both main effects and interactions of these factors were explored. To determine whether significant effects were the result of differences between MUS and the control cigarette MUL, an analysis of simple comparisons was applied, which preserves per comparison type I error by using orthogonal contrasts (21). Because multiple measures were obtained from each subject, strategies to control familywise type I error, such as a Bonferroni correction, were considered. Adoption of such a control necessarily results in an increase in type II error (i.e., reducing power to detect significant effects). Given the relatively small sample size, and the exploratory nature of this new area of inquiry, a decision was made to use no correction to α (21). Effects of Order of switching (MUS-MUL or MUL-MUS) were evaluated for each measure by inclusion of a between-subjects term. If no main effects or interactions were observed with this term, data from the two order were collapsed for subsequent analysis.

Pearson's partial correlations were calculated to explore potential relationships between exposure measures CO boost and salivary cotinine, and measures of smoke intake, smoking topography, and subjective responses. MUS prototype was controlled for to eliminate potential differential effects of between the SLC and Tampa versions.

Results

A total of 42 subjects were recruited and commenced the study procedure. Six subjects were discontinued due to noncompliance with the research protocol, and a further 4 subjects were discontinued owing to logistical problems. The proportions of discontinued subjects from each switching order were similar. The study procedure was completed by 32 subjects, of whom 15 received the MUS-SLC brand and 17 received the MUS-Tampa brand.

Demographic and smoking history data for each MUS group, and total sample, are presented in Table 2. The two MUS groups were well-matched on these basic descriptive variables. In general, the sample reflected demographic backgrounds comprising mostly young adults of White ethnicity with a high level of educational attainment and moderate nicotine dependence. Subjects reported having smoked for an average of 10.7 years and smoked a self-reported average of 16 cigarettes per day. The smoking history of MUS-SLC group seemed to have a slightly more extensive history of quitting than MUS-Tampa, as observed on number and length of previous quit attempts. Independent samples t tests found no significant differences between the groups in these quitting history variables [t's(30) < 1.4; $P > 0.10$]. There were no other demographic and smoking-related differences between the two groups (t test and χ^2 analyses, $P > 0.10$). Preliminary analyses using ANOVA revealed no main effects or interaction effects involving order of switching, and so data were collapsed across the two order groups for all further analyses.

Supervised Test Smoking

Smoking Topography. Several significant differences in smoking topography between MUS prototypes and conventional cigarettes were observed while smoking the two supervised test cigarettes (Table 3). Average number of puffs taken on 2 supervised cigarettes seemed to be marginally lower for MUS cigarettes compared with ML and MUL [F(1, 30) = 3.04; $P = 0.055$]. Analysis of simple comparisons suggested that this effect was the result of fewer puffs taken with MUS compared with MUL [F(1, 30) = 5.64; $P = 0.024$], and this effect was independent of MUS prototype. Puff volume differed significantly among the three study brands [F(2, 60) = 4.74; $P = 0.012$]. Analysis of simple comparisons revealed that MUS

Table 2. Sample characteristics (M, 95% CI)

	MUS-SLC	MUS-Tampa
n	17	15
Order 1 (ML-MUS-MUL; *n*)	9	10
Order 2 (ML-MUL-MUS; *n*)	8	5
Age	27.7 (24.3-31.0)	27.8 (23.5-32.1)
Female gender: *n* (%)	12 (70.6)	9 (60.0)
Ethnicity, *n* (%):		
White	16 (94.1)	11 (73.3)
Black	1 (5.9)	2 (13.3)
Asian	—	1 (6.7)
Hispanic/Latino	—	1 (6.7)
Highest school completed: *n* (%)		
High school	2 (11.8)	1 (6.7)
Some college	5 (31.6)	8 (53.3)
College graduate	9 (52.9)	5 (31.3)
Postgraduate	1 (5.9)	1 (6.7)
Age started smoking daily	17.1 (15.7-18.4)	17.4 (15.8-19.0)
Cigarettes/day	15.7 (12.0-19.3)	15.9 (9.5-22.2)
Months smoking at current level	78.0 (40.9-115.1)	72.5 (32.9-112.2)
Previous quit attempts	2.8 (1.6-4.0)	1.8 (1.0-2.6)
Longest quit attempt (mo)	3.2 (0.4-6.0)	2.8 (0.2-5.4)
Time since last quit attempt (mo)	25.6 (14.8-36.5)	30.2 (14.9-45.6)
Fagerstrom score	3.9 (2.5-5.4)	4.4 (3.0-5.8)

Abbreviations: M, Mean 95% CI, 95% confidence interval.

Table 3. Supervised topography, cardiac change, and subjective ratings (M, SD)

	Tampa group			Salt Lake City group		
	ML	MUS	MUL	ML	MUS	MUL
Puffs per cigarette	11.4 (3.0)	10.2 (2.9)	11.3 (2.6)	13.1 (4.8)	12.5 (5.0)	13.9 (5.6)
Puff volume (mL)	50.7 (19.6)	54.2 (19.4)	51.4 (19.0)	47.4 (16.9)	56.7 (15.2)	50.1 (15.6)
Puff duration(s)	1.35 (0.47)	1.39 (0.37)	1.32 (0.40)	1.29 (0.43)	1.47 (0.38)	1.38 (0.35)
Interpuff interval(s)	32. 1 (11.9)	28.4 (8.4)	33.0 (14.9)	24.8 (11.45)	23.9 (9.2)	21.8 (10.4)
Heart rate change (bpm)	2.5 (2.7)	1.6 (1.3)	2.9 (2.4)	3.4 (1.8)	1.6 (1.7)	2.9 (1.6)
Systolic BP change (mm Hg)	3.5 (3.6)	2.4 (2.7)	−0.23 (4.0)	0.47 (2.5)	−0.29 (2.7)	1.9 (3.3)
Diastolic BP change (mm Hg)	3.5 (2.9)	1.3 (1.0)	−2.1 (2.2)	1.0 (2.2)	1.5 (1.6)	2.1 (1.4)
Liking (1-100)	77.0 (17.5)	55.3 (30.2)	62.7 (21.7)	76.4 (18.5)	60.4 (19.8)	61.3 (15.1)
Effect (0-5)	3.7 (0.97)	3.1 (0.92)	2.9 (0.96)	3.8 (0.83)	3.2 (0.83)	3.2 (0.88)

puff volume was higher than both ML [F(1, 30) = 6.20; $P = 0.019$] and MUL [F(1, 30) = 16.74; $P < 0.001$]. There was no effect of MUS prototype on puff volume [F's < 2.0]. Although interpuff interval was lower overall among the MUS-Tampa group [F(1, 30) = 5.36; $P = 0.028$], this effect was not related to brand switching [F(2, 60) = 2.23; $P > 0.10$]. No statistically significant effects were observed on measures of puff duration. Topography results are summarized in Table 3.

Exposure Measures. After switching to MUS and MUL, total smoke intake per cigarette seemed to decrease among the MUS-Tampa group, and increase among the MUS-SLC compared with the baseline ML brand, although the effect was not significant [F(2, 60) = 1.92; $P = 0.216$; see Fig. 1, *left Y*-axis]. There were no main effects of brand or prototype on total smoke intake (F's < 2.0). Expired air CO boost was measured immediately presmoking and postsmoking two of each of the test cigarettes. At least one CO measurement was lost from a total of nine subjects owing to equipment malfunction. A significant main effect of brand on CO boost was observed [F(2, 42) = 4.34; $P = 0.019$]. Analysis of simple comparisons revealed that this was influenced by a marginally significantly lower CO boost for MUS compared with ML [F(1, 21) = 4.06; $P = 0.054$]. However, there was no difference in CO boost between MUS and the control brand MUL (F < 1.0). There were no significant effects of MUS prototype on CO boost [F < 1.0; Fig. 1, *right Y*-axis].

Heart rate and blood pressure increased significantly from resting baseline after smoking [F(1, 56) = 5.60; $P = 0.025$]. Heart rate increased similarly regardless of brand smoked or MUS prototype. Likewise, changes in systolic and diastolic blood pressure were not associated with brand smoked nor MUS prototype ($P < 0.10$).

Subjective Responses. Subjects reported significantly lower cigarette ''liking'' responses for the three test brands [F(2, 60) = 8.54; $P = 0.001$]. Comparison of simple differences showed that MUS was less well-liked than both ML [F(1, 30) = 11.48; $P = 0.002$] and MUL [F(1, 30) = 15.10; $P = 0.001$]. There was no difference in liking between the two MUS prototype groups [F(1, 30) < 1.0]. The test cigarette brands also differed in their perceived ''effect'' [F(1, 30) = 7.30; $P = 0.001$]. Although MUS was rated as having a lower effect than ML [F(1, 30) = 6.14; $P = 0.019$], its effect was rated as not different than the control brand MUL [F(1, 30) < 1.0; Table 3].

Correlations between Smoking Behavior and Exposure Measures. Partial correlations between salivary cotinine and measures of smoking behavior revealed significant associations between total smoke intake and CO boost, for MUS and MUL brands (r = 0.368 and 0.472; $P = 0.023$ and 0.006). The same partial correlation for the ML brand was not significant ($P = 0.15$). No significant correlations were observed between subjective measures, liking and effect, and measures of smoking topography. Results are presented in Table 5.

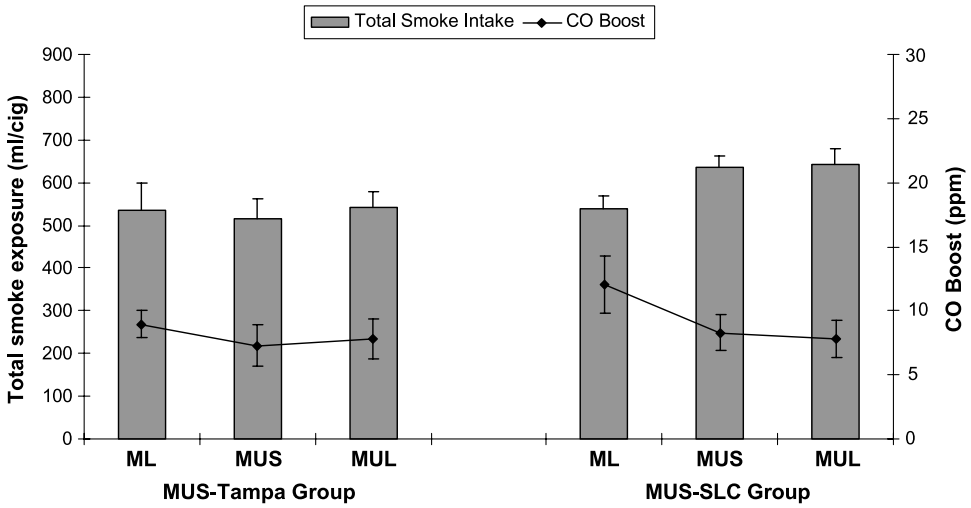

Figure 1. Mean smoke intake for two cigarettes smoked in laboratory (*bars*, *left Y*-axis) and presmoking to postsmoking CO boost (*lines*, *right Y*-axis). *Columns,* mean; *bars,* SE.

Table 4. Unsupervised *ad lib* (48 h) topography (M, SD)

	Tampa group			Salt Lake City group		
	ML	MUS	MUL	ML	MUS	MUL
Cigarettes consumed	35.0 (5.4)	31.5 (5.2)	31.2 (5.8)	34.2 (4.5)	30.8 (3.8)	29.3 (4.0)
Cigarettes measured	8.6 (4.4)	9.0 (4.0)	8.3 (4.8)	9.8 (4.5)	8.4 (4.5)	10.0 (4.3)
Puffs per cigarette	11.9 (4.0)	9.3 (2.4)	10.5 (2.6)	11.9 (4.7)	11.7 (5.2)	12.1 (4.6)
Puff volume (mL)	51.2 (17.3)	53.5 (19.2)	49.9 (18.3)	41.0 (18.0)	54.6 (19.4)	52.2 (15.7)
Puff duration(s)	1.43 (0.53)	1.43 (0.48)	1.40 (0.48)	1.27 (0.48)	1.52 (0.46)	1.50 (0.47)
Interpuff interval(s)	37.3 (22.1)	33.6 (15.8)	35.1 (15.3)	26.8 (10.4)	24 6 (12.2)	24.7 (12.3)

Ad lib (48 Hour) Smoking

Smoking Topography. Subjects smoked each of three brands for 48 hours while monitoring a self-selected subsample of cigarettes with the topography device. Data were lost from two subjects owing to equipment malfunction. Subjects reported smoking 31.1 (SD, 16.7) MUS cigarettes over a 48-hour period, compared with 34.5 (SD, 18.7) for ML and 30.1 (SD, 18.1) for MUL. This main effect of brand was significant [$F(2, 58) = 3.23$; $P = 0.047$]. Analysis of simple comparisons suggested that significantly fewer MUS cigarettes compared with ML were smoked during the 48-hour period [$F(2, 58) = 5.91$; $P = 0.022$], but this decrease in consumption was not different to the control product, MUL [$F(2, 58) < 1.0$]. Total number of cigarettes smoked was not influenced by MUS prototype ($F < 1.0$).

Topography data were obtained for a mean of 25.9 cigarettes (MUS-Tampa group) and 28.2 cigarettes (MUS-SLC group) over the 6-day period. The number of cigarettes measured with the topography device did not differ among the three brands [$F(2, 58) < 1.0$], nor between the two MUS-prototype groups [$F(1, 30) < 1.0$; see Table 4]. Number of puffs taken per cigarette did not change when subjects were switched from ML to MUS and MUL ($F < 1.0$). Puff volume increased significantly when subjects were switched from ML [$F(2, 58) = 7.13$; $P = 0.002$], and analysis of simple comparisons showed that MUS was smoked with greater puff volume than both ML [$F(1, 29) = 8.91$; $P = 0.006$] and MUL [$F(1, 29) = 8.47$; $P = 0.007$]. Puff volume was further influenced by MUS prototype, as revealed by a significant prototype/brand interaction [$F(2, 58) = 5.34$; $P = 0.007$]. Analysis of simple comparisons showed that MUS-SLC produced a greater puff volume compared with ML [$F(1, 29) = 4.64$; $P = 0.04$] but did not differ from MUL. Interpuff interval was significantly lower among the MUS-SLC group overall [$F(1, 29) = 5.15$; $P = 0.031$], although this was not influenced by the brand smoked [$F(2, 58) < 1.0$]. No significant effects were observed on measures of puff duration. *Ad lib* (48 hours) smoking topography data are presented in Table 4.

Exposure Measures. Total smoke intake increased among subjects who were switched to MUS-SLC but decreased among subjects who switched to MUS-Tampa, as indicated by a significant interaction between brand and MUS prototype [$F(2, 58) = 6.64$; $P = 0.003$; see Fig. 2]. There were no main effects of brand or prototype ($F < 1.0$). Analysis of simple comparisons of this interaction suggested that there was significant variation in response between the MUS prototypes relative to ML [$F(1, 29) = 6.12$; $P = 0.018$] but not MUL [$F(1, 29) < 1.0$].

Salivary cotinine levels arising from 48 hours of smoking the study brands are presented in Fig. 2 (*right Y*-axis). There were no significant effects of MUS cigarette brand or prototype on cotinine level [$F < 1.84$; $P > 0.10$].

Correlations Between Smoking Behavior and Cotinine. Correlations between salivary cotinine and measures of smoking behavior revealed that total cigarettes consumed over the 48-hour period were significantly correlated with cotinine level for each brand. In contrast, total smoke consumed per cigarette was not significantly correlated with cotinine (see Table 5).

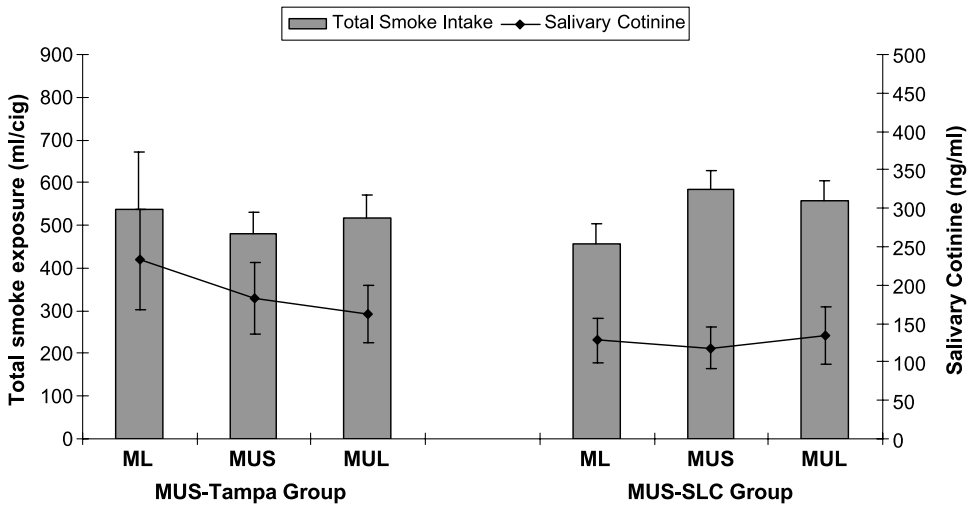

Figure 2. Mean unsupervised *ad lib* (48 h) smoke intake per cigarette (*bars, left Y*-axis) and 48-h salivary cotinine (*lines, right Y*-axis). *Columns,* mean; *bars,* SE.

Discussion

The results provide confirmation that that the two high-carbon load MUS prototypes, Tampa and SLC, when used freely by subjects in their own environment, are smoked in a manner that is more consistent with the Health Canada machine yield method. Puff volumes for MUS smoked *ad lib* were 53.5 mL (Tampa) and 54.6 mL (SLC) and were more similar to the 55 mL puff volume criterion for the Health Canada machine smoking regimen than that used by the FTC. *Ad lib* puff durations of 1.4 and 1.5 seconds (Tampa and SLC, respectively) were uniformly shorter than the 2.0-second Health Canada criterion, whereas interpuff intervals for MUS-Tampa and MUS-SLC (33.6 and 24.6 seconds, respectively) approximated the 30-second criterion Health Canada puff interval. Observed puffing topography in itself does not allow conclusions about human exposure to smoke constituents. Recent research has shown that MUS toxic gas phase yields are reduced to a far lesser extent when tested under the Canadian ''intense'' machine yield method compared with the FTC method (7, 12). The similarity of the human puffing profile for MUS with the Canadian intense machine yield method suggests that MUS smokers may receive exposure to toxic smoke constituent yields that are more like conventional products than suggested by the FTC smoke machine yield method.

These findings also show that, when switched from ML to MUS, participants maintained a generally similar smoking style. The two smoking conditions—test smoking while supervised and smoking *ad lib* at home over 48 hours—produced similar although not identical puffing profiles for MUS when compared with ML and MUL. Limited evidence for compensatory smoking of MUS compared with the baseline ML brand was observed for the MUS-SLC prototype. Under *ad lib* smoking conditions, MUS puff volume was higher than both ML and MUL, and this effect was most pronounced among the MUS-SLC prototype group. Total smoke intake was higher among the MUS-SLC group, although it was lower among MUS-Tampa compared with ML but did not differ from the MUL control. These data suggest that under free smoking conditions, MUS-SLC may promote a tendency toward compensatory smoking compared with a low-yield cigarette such as ML, but MUS-Tampa may influence a puffing style that results in total cigarette smoke intake that is not altered from such a low-yield brand. Nevertheless, the magnitude of this compensation was mild and was in line with the compensation observed with the conventional ultralow yield MUL cigarette.

Table 5. Correlations between exposure measures and smoking behavior

	CO Boost			Cotinine		
	r	df	*P*	r	df	*P*
MUS						
Mean Smoke Intake	0.368	28	0.023	0.085	31	0.319
Total cigarettes consumed	—	—	—	0.297	31	0.047
MUL						
Mean Smoke Intake	0.472	26	0.006	0.123	31	0.248
Total cigarettes consumed	—	—	—	0.449	31	0.005
ML						
Mean Smoke Intake	0.199	26	0.155	0.113	31	0.262
Total cigarettes consumed	—	—	—	0.332	31	0.029

Abbreviation: df, degrees of freedom.

The influence of the observed puffing style with MUS on short-term measures of exposure to mainstream smoke must be considered. Smoking either MUS prototype resulted in a lower precigarette to postcigarette CO boost compared with the conventional ML control brand but was similar to the ultralow yield MUL control. Although MUS puff volume for both prototypes increased compared with the control, the overall MUS smoke intake per cigarette remained similar to ML in the supervised smoking session. Recent research with PREPs has found that a low-nicotine-yield product may enhance compensatory smoking and correspondingly produce an increase in CO exposure (22). Although MUS exposure to CO was lower compared with the baseline ML brand, it did not differ from the conventional ultralow-yield MUL control cigarette. This suggests a failure for MUS to produce a reduction in CO when compared with a conventional cigarette with similar nicotine yield characteristics. The greater smoke intake may have offset any potential reduction in CO emissions.

Other measures of exposure revealed no differences between MUS and conventional products. There were no differences between MUS prototypes and conventional brands on measures of simple cardiac function (heart rate and blood pressure). Similarly, 48 hours of *ad lib* smoking resulted in no differences in salivary cotinine level between MUS prototypes and conventional brands. Although subjects reported smoking fewer MUS cigarettes over 48 hours than ML, this reduction in smoking behavior did not differ from the control MUL brand. Differences in subjects' smoking style of the ultralow-yield MUS and MUL brands may have helped to adjust for the fewer cigarettes smoked, and so help to maintain similar cotinine levels among all brands smoked.

Subject self-reports indicated that MUS was less well-*liked* than the conventional counterpart brands. Carbon filters tend to reduce flavor characteristics desired by consumers, and previous research has shown that MUS-SLC has an added artificial flavorant to address this flavor deficit (7). This innovation seems not to have succeeded in enhancing smoker liking, and the present data showed that MUS-SLC was liked no more than MUS-Tampa. Both MUS prototypes were rated as having less *effect* than ML, suggesting that immediate nicotine-like effects may not have been as salient as with subjects' brand of choice, ML. Although sensory characteristics of cigarette products have been shown to influence smoking behavior (23), the current study found no relationship between MUS liking or effect on smoking topography. It is also noteworthy that low subjective ratings of MUS seemed to correspond with lowered measures of exposure. Further research is required to determine whether subjective and sensory characteristics may modify smoking behavior of low-yield, carbon-filtered PREPs.

This study has important limitations. Biomarkers of exposure to carcinogens were not obtained, and so conclusions regarding exposure to tobacco toxins instead rely on a limited array of measures including CO boost and salivary cotinine. Recent research has suggested that CO exposure may provide an index for mainstream

smoke constituent exposure for conventional cigarettes, by correlating with lung carcinogen biomarkers 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and 1-hydroxypyrene (24). It is interesting to postulate on whether CO boost can provide such a proxy measure for mainstream smoke toxicant exposure arising from a carbon-filtered cigarette, whose purpose is to selectively reduce the relative proportions of gas phase smoke constituents. Second, in contrast with many brand switching studies in which smoking occurs over 1 week or more, subjects smoked each brand only for a 48-hour period. Although 48 hours may be a sufficient period to achieve a valid cotinine measure (25), it is unknown whether a longer period of time may have been required for subjects to completely adjust to a new smoking style with each brand switch. An incomplete adjustment of smoking style could have implications for accuracy of measures of total smoke intake and other measures of exposure. Longer term studies of MUS are required to address such questions.

These findings underscore the importance of exploring in tandem the related factors of product design, smoking behavior, and human exposure, and support the use of integrated PREP evaluation strategies. Optimal evaluation of the harm reduction capacity of new PREPs requires research strategies that are not immediately available, such as measurement of validated disease biomarkers and long-term epidemiologic studies of disease outcomes. Shorter-term strategies, which include mainstream emissions testing and smoking topography measurement, provide important preliminary data on a capacity of PREP to reduce exposure. Further investigation and refinement of human behavioral and exposure assessment strategies, using smokers of a range of products and smoking styles, may provide more sensitive tools by which ''potentially'' harmful tobacco products may be assessed.

This study has shown that MUS lends itself to a style of puffing behavior that is closer to the Health Canada machine yield method than the FTC machine yield method. Evidence of a mild trend toward compensatory smoking—larger puffs and, in the case of MUS-SLC, greater smoke intake—was seen with MUS compared with conventional baseline and control brands. Because MUS has been shown in earlier research to show elasticity in toxic smoke constituent yields (7), this puffing style has the potential to produce mainstream MUS toxicant yields that are more, rather than less, similar to conventional low-yield cigarettes. Short-term exposure measures did not show differences between MUS and a conventional ultralow-yield control cigarette. These observations suggest that MUS was smoked about as intensely as current conventional Light and Ultra Light cigarettes and resulted in similar exposures to CO and cotinine. It is possible that MUS could decrease or increase toxicity, depending on the details of smoke composition and delivery. Because the observed puffing behavior for MUS is likely to make the composition of MUS mainstream smoke more like a conventional cigarette (7), it is unlikely that this product will produce substantially altered exposure to toxic mainstream smoke constituents. In being designed as a reduced exposure product, MUS could erroneously be perceived by current and potential smokers not just as ''safer,'' but as ''safe.'' This could have negative public health consequences, as smokers delay quitting or new smokers are recruited in the belief that smoking risks are lessened, as was the case when lights cigarettes were marketed to an uninformed public two decades ago (5). The present data also support the use of assessment strategies for PREPs that reach beyond simple machine smoke yield measures. Strategies such as measurement of human smoking topography and exposure to cancer biomarkers may also provide more meaningful tools for government regulation of PREPs and new tobacco products.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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