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Addiction potential of combustible menthol cigarette alternatives: a randomised cross-over trial

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ABSTRACT

Introduction The Food and Drug Administration (FDA) has issued proposed product standards banning menthol as a characterising flavour in cigarettes and cigars. The public health benefits of these product standards may be attenuated by the role of plausible substitutes in the marketplace. Therefore, the present study examined the addiction potential of plausible combustible menthol alternatives compared with usual brand menthol cigarettes (UBMC).

Methods Ninety-eight adult menthol cigarette smokers completed four visits, smoking their UBMC at the first session and three menthol cigarette alternatives in random order at the subsequent visits: (1) a preassembled menthol roll-your-own (mRYO) cigarette using menthol pipe tobacco and mentholated cigarette tube, (2) a menthol filtered little cigar (mFLC) and (3) a non-menthol cigarette (NMC). Measures of smoking topography, exhaled carbon monoxide (CO), craving and withdrawal, subjective effects and behavioural economic demand indices were assessed.

Results Compared with UBMC, menthol cigarette alternatives resulted in different puffing topography and CO exposure (except mRYO), and lower levels of positive subjective experience and behavioural economic demand indices. Among the alternative products, participants reported the highest level of positive subjective experience and higher demand for mRYO, compared with mFLC and NMC. Similarly, participants were significantly more likely to want to try again, purchase and use the mRYO product regularly compared with mFLC and NMC.

Conclusions and relevance mRYO cigarettes were the most highly rated cigarette alternative among study products, suggesting their potential appeal as a menthol cigarette substitute and needed inclusion of menthol pipe tobacco and cigarette tubes in FDA's proposed ban.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Menthol cigarettes are associated with increased smoking initiation, higher nicotine dependence and decreased adult cessation, particularly among vulnerable populations. To address this public health issue, the Food and Drug Administration announced in April 2021 its intention to issue product standards banning menthol as a characterising flavour in both cigarettes and cigars within a year. However, the public health benefits of these product standards may be attenuated by the role of plausible substitutes available in the marketplace.

WHAT THIS STUDY ADDS

⇒ In this randomised cross-over design study that included 98 adult menthol cigarette smokers, each of the alternative products demonstrated the ability to significantly reduce nicotine craving and withdrawal symptoms, but the combination of mentholated pipe tobacco and tubes in a menthol roll-your-own cigarette resulted in the highest behavioural economic demand and positive subjective experience.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To maximise the benefits of a menthol cigarette ban, restrictions should extend to plausible substitutes, particularly menthol pipe tobacco and cigarette tubes.

INTRODUCTION

The decreasing prevalence of cigarette smoking in the USA[1] has been driven by decreases in non-menthol cigarette (NMC) use.[2 3] In contrast, menthol cigarette consumption has remained largely stable since 2000, resulting in a more than 10% increase in menthol cigarette market share over the past two decades[2] and reaching 37% market share in 2020.[4] Menthol cigarettes are associated with increased smoking initiation and progression to regular use,[5 6] higher nicotine dependence and decreased adult cessation.[7–9] People who smoke menthol cigarettes are also more likely to be of low socioeconomic status, female, black or Hispanic, and identify as lesbian, gay, bisexual and transgender compared with non-menthol smokers.[10 11] Menthol cigarette smoking is estimated to have caused 10.1 million extra smokers, 3 million life years lost and 378 000 premature deaths between 1980 and 2018.[12]

The 2009 Family Smoking Prevention and Tobacco Control Act granted the US Food and Drug Administration (FDA) broad authority to regulate tobacco products, leading to bans of flavoured cigarettes, excluding menthol, and some flavoured e-cigarette devices. In May 2022, the FDA issued proposed rules for product standards banning menthol as a characterising flavour in both cigarettes and cigars.[13 14] While evidence from systematic reviews,[7 15–17] evaluations of Ontario's menthol cigarette ban[18–20] and simulation studies strongly support the likely positive public health impact of a menthol ban on cigarette and cigars,[21–23] experimental evidence is also needed to bolster these findings to withstand tobacco industry lawsuits.

Even with regulation, tobacco companies frequently exploit regulatory loopholes to maintain sales of their products.[24 25] Djarum, for example, launched clove filtered cigars in the USA in anticipation of the 2009 ban on flavoured cigarettes, and sales of clove filtered cigars increased by more than 1400% between 2009 and 2012.[26] Similarly, following the 2009 Children's Health Insurance Programme Reauthorization Act, which levied large increases in federal excise tax rates on cigarettes, cigars and roll-your-own (RYO) tobacco, tobacco companies repackaged and labelled RYO tobacco as pipe tobacco to avoid these policies.[27] As a result, while the market share of pipe tobacco declined from 30.4% in 2002 to 13.6% in 2008, it increased significantly to 89.6% in 2012.[27] This reflects an increase of approximately 25.49 million pounds of loose tobacco (ie, RYO and pipe tobacco) sold per year from 2002 to 2012.[27] These examples highlight how the potential public health benefits of regulation, such as a product standard, can be attenuated and suggest that estimating the impact of a potential ban on menthol in cigarettes requires accounting for likely substitutes in the marketplace that may also need to be restricted to effectively protect public health.

Current tobacco products, including menthol filtered little cigars (mFLCs), menthol pipe tobacco and cigarette tubes for menthol roll-your-own (mRYO) cigarettes, and NMC, are relevant targets as potential menthol cigarette substitutes.[28] Neither mRYO nor NMC will be affected by the proposed FDA ban on menthol cigarettes and cigars. NMC, mFLC and mRYO are all comparable to menthol cigarettes with respect to shape, size and filters,[25 29] and both mFLCs and mRYO are increasing in use.[30–32] While no single study has compared all of these products, findings are mixed in terms of differences in user puffing topography, nicotine delivery and toxicant exposure.[31–35] The limited research does suggest that each of these products are capable of delivering significant levels of nicotine and harmful tobacco-related toxicants. With important FDA menthol regulation under way, it is critical to assess their potential as substitutes to help guide effective FDA regulation, closing any pertinent loopholes (eg, mentholated pipe tobacco and cigarette tubes), and to provide support for further regulation of NMCs (eg, reducing nicotine to non-addictive levels).

With the ultimate goal of informing FDA menthol regulations by identifying potential market substitutes that may attenuate the positive public health effects of the proposed regulation, the purpose of this study was to assess the addiction potential of other plausible combustible menthol cigarette alternatives in adults who smoke menthol cigarettes by examining the impact of these alternatives on subjective effects, behavioural economic demand indices, smoking topography and resultant toxicant exposure compared with the participants' usual brand menthol cigarette (UBMC). We hypothesised that, compared with UBMC, alternatives would result in similar smoking topography and carbon monoxide (CO) exposure, but fewer positive subjective effects and lower demand.

METHODS

Setting and participants

Menthol cigarette smokers from the Columbus, Ohio metropolitan area, were recruited via internet advertisements, flyers and word-of-mouth advertising from January 2020 to August 2021. Potential participants were screened for eligibility via an online questionnaire and then over the telephone. Eligibility criteria included (1) current menthol cigarette smoker (>90% menthol cigarette use, ≥5 cigarettes per day) for at least the past 6 months; (2) between 21 and 50 years old; (3) willing to abstain from tobacco, nicotine and marijuana use for at least 12 hours prior to each of the study visits; (4) access to a smartphone or email, and (5) ability to read and speak in English. Exclusionary criteria included (1) self-reported diagnosis of lung disease; (2) cardiac event or distress within the past 3 months; (3) pregnancy, breast feeding or planning to become pregnant; (4) use of other tobacco products (eg, e-cigarette, cigar, etc) >5 days in the past month; (5) currently using one of the study products; (6) any reported use of illicit drugs (other than marijuana) during the last 30 days; and (7) currently engaging in smoking cessation treatment.

Procedure

Using an in-laboratory and outpatient mixed design, participants completed a three-phase study lasting approximately 3 weeks. In phase I, the participants completed four smoking session visits, smoking their UBMC or one of the three menthol cigarette alternatives at each visit. Each visit was separated by a 48-hour washout period. This phase used multiple methods of assessing addiction potential in a lab-based setting, including measurements of drug self-administration, suppression of craving and withdrawal, measures of drug liking and behavioural economic measures.[36] In phase II, the participants were instructed to completely substitute their preferred product from phase I for their UBMC for 1 week and to complete daily assessments of their use behaviour. In phase III, the participants completed a final in-lab visit to assess the substitutability of their preferred product, under simulated ban conditions using a progressive ratio task. We report the results of phase I further.

All participants completed sociodemographic measures and provided their tobacco use history including their years of smoking, usual cigarette brand, smoking frequency and quantity, number and recency of previous quit attempts, and their level of cigarette dependence (Fagerstrom Test for Nicotine Dependence).[37] Then, over four visits, the participants completed standardised smoking sessions, smoking a different product each session. During each session, a research assistant with a stopwatch instructed the participants to take a puff every 30 s, resulting in 10 puffs during the first 5 min. Participants sampled their UBMC during the first session; the order of subsequent products was randomised at the time of enrolment from a prespecified block randomisation table with blocks of size 6. Products included a preassembled (by study staff), machine-injected RYO cigarette using a mentholated cigarette tube and mentholated pipe tobacco (mRYO; OHM menthol pipe tobacco, hot rod tubes, menthol king size), an mFLC (Cheyenne 100's menthol) and a NMC (Newport Non-Menthol Red). For mRYO assembly, the Powermatic III was used to insert 1 g of tobacco into the rod to fill. See online supplemental table 1 and figure 1 for additional product characteristics. When machine-smoked, NMC had the greatest nicotine emissions (mg/rod) (M=2.51, SD=0.13), followed by mRYO (M=2.11, SD=0.08) and then mFLC (M=0.99, SD=0.11); mFLC had the highest menthol emissions (mg/rod) (M=3.04, SD=0.30), followed by mRYO (M=2.25, SD=0.16) and NMC with the least (M=0.003, SD=0.000); and mFLC had the highest resistance to draw (mm H_2O) (M=193.0, SD=13.0), followed by NMC (M=123.0, SD=6.9) and mRYO with the least (M=103.0, SD=8.3). All products were provided in plain boxes without brand or identifying information. Brand name was present, however, on the NMC filter wrapper. The participants were instructed to abstain from smoking (biochemically confirmed with exhaled CO ≤10 ppm),[38 39] as well as from

nicotine and marijuana for 12 hours before the sessions (abstinence from nicotine and marijuana was not confirmed).

During the smoking session, participant puffing topography was collected using the eTop (American University of Beirut), which includes mouthpiece adaptors to accommodate cigarettes of different diameters and provides valid measurements at puff flow rates as low as 3 mL/s.[40 41] Puffing topography measures collected included average flow rate, interpuff interval, puff volume, puff duration, maximum puff volume and total inhaled volume. Measures of cigarette craving (Tiffany-Drobes Questionnaire of Smoking Urges (QSU): Brief Form[42] and withdrawal (Minnesota Nicotine Withdrawal Scale (MNWS)[43]) were also administered immediately before (0) and after the smoking session (5 min), and at 15, 30, 60 and 90 min. The QSU is a 10-item self-report measure with items rated from 1 (strongly disagree) to 7 (strongly agree). Items are summed and have been shown to load on two factors—'desire to smoke' and 'anticipated relief from withdrawal'. For the MNWS, participants completed the 15-item version, but for analysis, we used the nine-item version assessing the *Diagnostic and Statistical Manual of Mental Disorders* symptoms for Tobacco Withdrawal and the 'craving to smoke' item; items were rated on a 5-point scale from 0 (none) to 4 (severe) and summed. We did not include sleep problems in our analysis since this item was not expected to change during the smoking sessions. Exhaled breath carbon monoxide level (eCO), a biomarker of smoke exposure, was assessed using a handheld monitor (Smokerlyzer Micro, Bedfont Scientific) at time 0 and 5 min to determine eCO boost (eCO at time 5 min minus eCO at time 0).

After each smoking session, measures of subjective effects were completed. The 11-item modified Cigarette Evaluation Questionnaire (mCEQ)[44 45] includes five subscales: Smoking Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations and Craving Reduction, with items rated from 1 (not at all) to 7 (extremely likely). Five visual analogue scale items ranging from 0 ('not at all') to 100 ('extremely') assessed wanting to smoke the product again, liking the product, enjoying the product, and finding the product pleasurable and satisfying.[46 47] Behavioural intentions to use the menthol cigarette alternatives were also collected. Participants reported how likely they were to 'try this product again', 'purchase this product for personal use' and 'use this product regularly' if menthol cigarettes were no longer available to be purchased; responses were rated on a 5-point scale (1, extremely unlikely; 2, unlikely; 3, neutral; 4, likely; 5, extremely likely). For analysis, answers were collapsed into 'unlikely' for users who responded 'extremely unlikely' or unlikely, 'neutral' for those who answered neutral, and 'likely' for those who answered extremely likely or likely. Participants also completed the Cigarette Purchase Task,[48 49] a behavioural economic task that assesses hypothetical tobacco product consumption across varying prices. Demand indices include demand intensity (Q_0; the number of products consumed per day when free), essential value (EV, a measure of reinforcing efficacy that measures the rate of change in demand elasticity across the range of prices), P_{max} (the price associated with the maximal expenditure, ie, the highest price before the curve changes from inelastic to elastic) and breakpoint (the last price in which consumption is greater than 0), with higher scores indicating greater abuse liability. Finally, following the completion all of smoking sessions, the participants selected their most preferred menthol alternative product to completely substitute for their UBMC for 1 week.

Data analytical plan

The study was powered based on a laboratory study examining the abuse liability of cigarettes containing different doses of nicotine,[50] such that with 80 participants, there was over 80% power to detect decreases in product satisfaction of up to 50% as compared with UBMC and decreases of 68%–72% in the cigarette purchase task indices of maximum expenditure, maximum price and price sensitivity.

Topography measures were winsorised at the 1st and 99th percentiles and analysed using repeated measures analysis of variance (ANOVA) with Tukey's adjustment for all pairwise comparisons between products. Subjective smoking experiences were similarly analysed using repeated measures ANOVA models with Tukey's adjustment, while the categorical behavioural intentions data were modelled with mixed effects multinomial logistic regression. For QSU, which was measured repeatedly within each visit, linear mixed effects models with Holm's procedure to adjust for post hoc comparisons were used to assess differences between products. Further, logistic regression was employed to assess the association of demographic and tobacco use characteristics with selection of mRYO as the preferred product. For all models, log transformations were employed as necessary to satisfy assumptions. All analyses were conducted in SAS V.9.4.

Demand data were fit to the normalised zero-bound model of demand using the freely available GraphPad Prism template provided by the Institute for Behaviour Resources (https://ibrinc.org/behavioral-economics-tools/). To assess normality for all demand indices, we conducted the D'Agostino-Pearson omnibus normality test using GraphPad Prism V.9. Results indicated the distributions for all demand indices deviated from a Gaussian distribution; therefore, we used the non-parametric Friedman test with Dunn's correction for multiple comparisons for all analyses (see online supplemental appendix for detailed methods).

RESULTS

Participant demographics and smoking history

A total of 98 participants enrolled in the study and were included in the analysed sample. The participants had a mean age of 37.0 years (SD=7.4) were predominantly female (74.5%), white (69.4%) and non-Hispanic or Latino (93.9%, table 1). The participants reported smoking an average of 11.9 cigarettes per day (SD=5.5) and smoking at this frequency for the last 15.9 years (SD=9.8), with a mean FTND (Fagerstrom Test for Nicotine Dependence) score of 3.44 (SD=2.16), indicating a moderate level of dependence. The participants reported minimal past 30-day use of other tobacco products (table 1).

Smoking topography and eCO boost

Table 2 compares all four products on topography and exposure measures. Compared with smoking UBMC, the participants demonstrated greater puff duration and eCO boost when smoking mFLC, as well as a lower flow rate, average puff volume, total inhaled volume and maximum puff volume. When smoking NMC, the participants had smaller average puff volume and total inhaled volume than any of three mentholated products. No significant differences in topography were seen between UBMC and mRYO.

Cigarette craving and withdrawal

Mean values for QSU–brief desire and relief factors for all four products over time are depicted in figure 1A,B, respectively. Significant within-participant reduction was observed in both subscales for all products following the initial directed puffing

Table 1 Demographics and tobacco use history (n=98)

	Analysed sample (n=98)	
Demographics		
Age (years), mean (SD)	37.04	7.43
What term below best describes your ethnicity? n (%)		
Hispanic or Latino	6	6.12
Not Hispanic or Latino	92	93.88
What term(s) below best describe your race? n (%)		
Black or African–American	19	19.39
White or Caucasian	68	69.39
Biracial or multiracial	11	11.22
Below is a list of terms that people often use to describe their sexuality or sexual orientation. Please check the term that best applies to you. n (%)		
Gay	3	3.06
Bisexual	17	17.35
Straight/eterosexual	77	78.57
Queer	1	1.02
What sex were you assigned at birth (what the doctor put on your birth certificate)? n (%)		
Male	25	25.51
Female	73	74.49
What is the highest level of school you have completed? n (%)		
12th grade, no diploma	3	3.06
High school graduate/GED	17	17.35
Some college, no degree /associates degree	53	54.08
Bachelor's degree/master's degree	25	25.51
Which of the following categories best describes your total household income in the past 12 months? n (%)		
Less than $35 000	42	42.86
$35 000–$149 999	56	57.14
On average, about how many cigarettes do you currently smoke *each day*? (one pack usually equals 20 cigarettes) (mean, SD)	11.90	5.49
Years smoked at this frequency (mean, SD)	15.85	9.83
Usual brand of store-bought cigarettes, n (%)		
Marlboro	23	23.47
Newport	28	28.57
Camel	23	23.47
Maverick	8	8.16
American Spirit	4	4.08
Other	12	12.24
Years smoked this brand of cigarettes (mean, SD)	10.16	8.02
Fagerstrom Test for Nicotine Dependence Score (mean, SD)	3.44	2.16
Other tobacco product use in past 30 days (n, %)		
Any	21	21.43
Pipe (with tobacco, not including hookah)	2	2.04
Cigars (like Cohiba or Romeo y Julieta)	4	4.08
Cigarillos	4	4.08
Little cigars or filtered cigars	2	2.04
e-cigarette or vaping device (like JUUL, blu, Vuse, MarkTen or Suorin)	17	17.35
Smokeless tobacco (like chewing tobacco, snuff or dip)	2	2.04
Snus (like Camel Snus)	0	0.00
Hookah/shisha/waterpipe/hookah tobacco	2	2.04

segment, supporting the ability of each of the four products to reduce craving. Significant differences comparing UBMC to the study products were not observed for desire or anticipated relief (see online supplemental table 3A,B for p values). Similarly, significant within-participant reduction was observed in withdrawal symptoms for all products following the initial directed puffing segment, but no significant differences were observed between any of the products (figure 1C,D; see online supplemental table 3online supplemental appendix 1 for p values).

Product demand indices

Demand curves for four participants (5%) were determined to be non-systematic and were removed from analyses. Post hoc analyses for multiple comparisons indicated significantly greater addiction potential of UBMC when compared with all three alternative products for measures of demand intensity, EV and breakpoint ($p<0.05$; figure 2). Among alternative products, mRYO indicated the greatest addiction potential, with significantly higher intensity and EV than both mFLC and NMC, significantly higher P_{max} than NMC, and significantly higher breakpoint than mFLC ($p<0.05$). There were no significant differences between NMC and mFLC.

Subjective smoking experience, behavioural intentions and product selection

Figure 3 depicts mean ratings for all subjective smoking experience items, and online supplemental table 4 provides p values for all comparisons. Compared with UBMC, the participants reported significantly lower levels of wanting to smoke the product again, liking, enjoyment, pleasure and satisfaction for each of the alternative products ($p<0.001$, figure 3A). Among the alternative products, the participants reported the most favourable subjective experience when smoking mRYO ($p<0.001$) compared with mFLC and NMC, with no significant differences between mFLC and NMC (figure 3A). Similarly, on the mCEQ, UBMCs were rated as more satisfying, rewarding and had more enjoyable sensations in the throat and chest than the alternative products ($p<0.05$, figure 3B). However, UBMC had similar levels of aversion to NMC and higher levels compared with mRYO and mFLC ($p<0.05$, figure 3B). Similarly, UBMC had similar levels of craving reduction to mRYO but higher levels compared with mFLC and NMC ($p<0.05$, figure 3B). The participants were also significantly more likely to want to try again ($p<0.001$), purchase ($p<0.001$) and use the mRYO product regularly ($p<0.001$) compared with mFLC and NMC, with no significant differences between mFLC and NMC (figure 3C). Consistent with these findings, 65.0% (n=52) of the participants chose mRYO as their preferred menthol alternative to use during phase II; 22.5% (n=18) chose NMC; and 12.5% chose mFLC (n=10). In a supplementary analysis to examine potential predictors of mRYO as the preferred menthol alternative, neither UBMC, ever use of other tobacco products, sexual orientation nor race was significantly associated with mRYO preference (see online supplemental appendix 1).

DISCUSSION

Using a large within-subjects study of adults who smoke menthol cigarettes and multiple methods of assessing addiction potential, our study expands prior cross-over studies of menthol and NMCs[33–35] to include other potential menthol cigarette substitutes, specifically mFLCs and the combination of mentholated pipe tobacco and tubes in a mRYO. The variability in the physical attributes and mainstream emissions of the mRYO cigarette

Table 2 Smoking topography for UBMCs and menthol cigarette alternatives (n=98)

	UBMC	mRYO cigarette	mFLC	NMC
	M (SD)	M (SD)	M (SD)	M (SD)
Average puff duration* (s)	1.99 (0.56)†	2.06 (0.64)†‡	2.65 (0.90)§¶‡	1.87 (0.60)¶†
Average flow rate (ml/s)	23.77 (6.98)†	24.89 (7.53)†‡	16.97 (5.42)§¶‡	22.07 (7.22)¶†
Average interpuff interval (s)	27.54 (1.71)†	27.54 (1.22)†	26.35 (2.64)§¶‡	27.77 (1.58)†
Average puff volume (mL)	45.74 (13.49)†‡	48.19 (12.40)†‡	42.53 (12.77)§¶‡	38.96 (12.10)§¶†
Maximum puff volume (mL)	63.16 (18.81)†‡	63.94 (15.23)†‡	56.59 (18.71)§¶	55.92 (16.16)§¶
Total inhaled volume (mL)	462.56 (138.46)†‡	484.78 (124.38)†‡	434.66 (127.95)§¶‡	389.33 (122.21)‡§†
CO boost (ppm)	8.10 (3.92)†	7.36 (2.98)†	9.30 (4.35)§¶‡	7.71 (2.91)†

Mean (M) and SDs for topography measures. P values estimated from repeated measures analysis of variance with Tukey adjustment for all pairwise comparisons. All measures were winsorised at the 1st and 99th percentiles. Superscripts denote differences in pairwise comparisons between study products at the p<0.05 level.
*Variable log transformed for analysis. See online supplemental table 2 for specific p values.
†Differs from mFLC.
‡Differs from NMC.
§Differs from UBMC.
¶Differs from mRYO.
mFLC, menthol filtered little cigar; mRYO, menthol roll-your-own; NMC, non-menthol cigarette; UBMC, usual brand menthol cigarette.

was similar to the other study products, indicating the by-hand preparation of this product was carried out with a reproducibility similar to that obtained by commercial machines. All products suppressed craving and withdrawal, with few differences over time across the four study products. Findings on subjective effects of each product were similar to other studies,[33 34] with participants reporting the most favourable subjective effects for their UBMC, with mRYO cigarettes rated next highest and outperforming the other two menthol cigarette alternatives. In line with behavioural intention data on likelihood of trying,

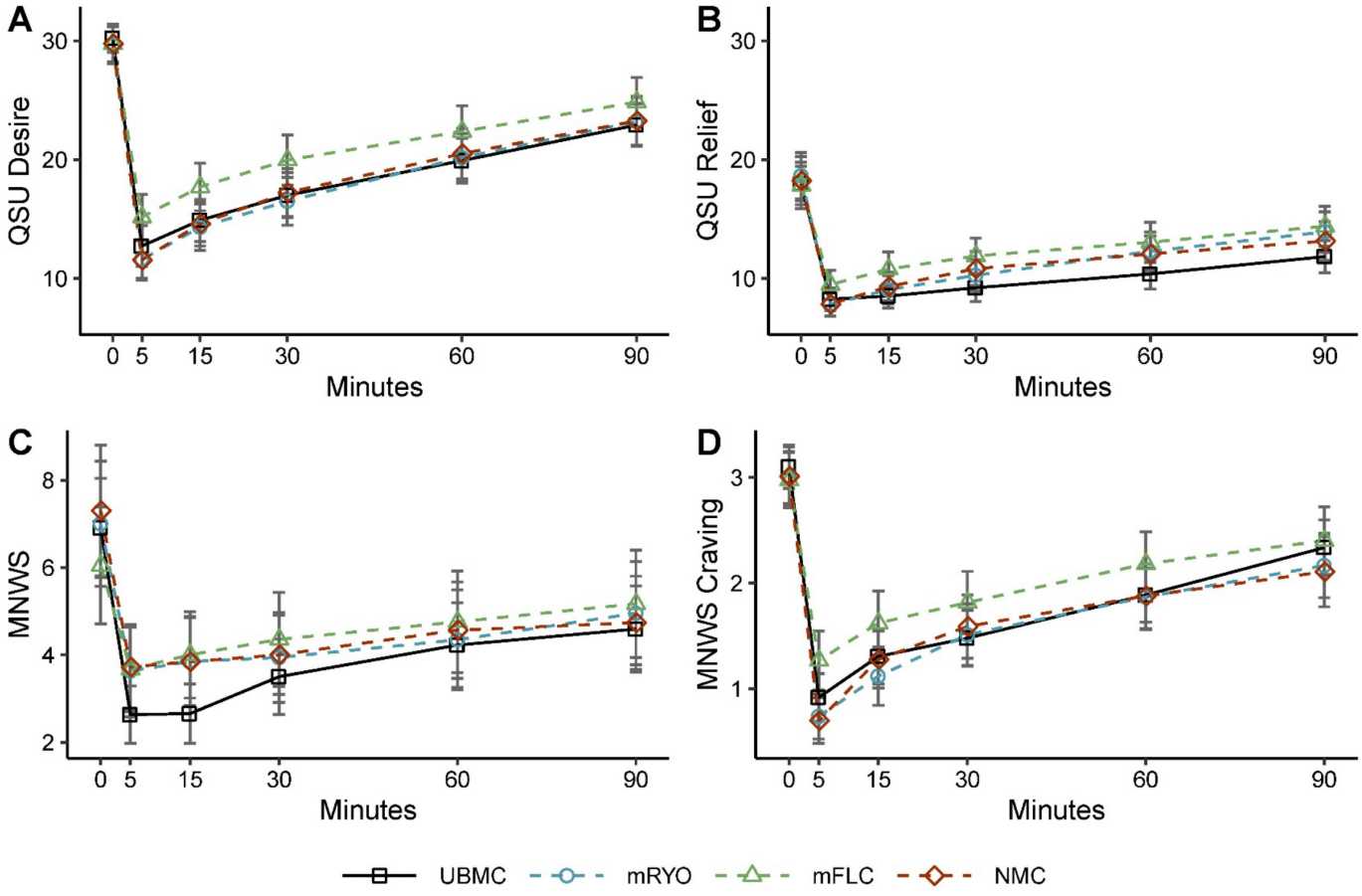

Figure 1 Measures of cigarette craving (Tiffany-Drobes QSU) and withdrawal (MNWS) for each product (n=98). (A) QSU–Desire, (B) QSU–Relief, (C) MNWS withdrawal symptoms and (D) MNWS craving. Mean and 95% CI estimated immediately before (0) and after the smoking session (5 min), and at 15, 30, 60 and 90 min; QSU–Relief and MNWS were log transformed for analysis. mFLC, menthol filtered little cigar; MNWS, Minnesota Nicotine Withdrawal Scale; mRYO, menthol roll-your-own; NMC, non-menthol cigarette; QSU, Questionnaire of Smoking Urges; UBMC, usual brand menthol cigarette.

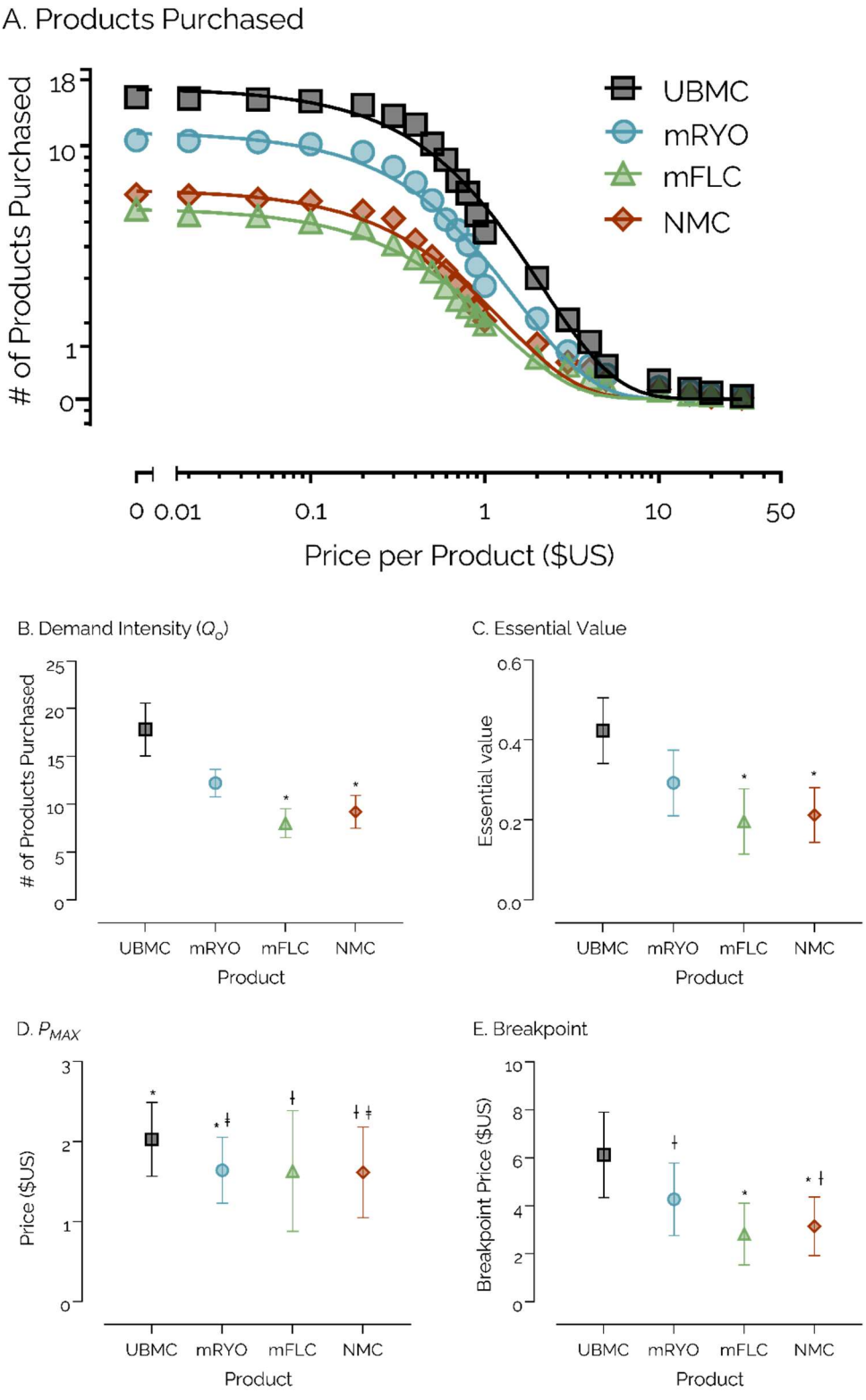

Figure 2 Behavioural economic measures of addiction potential by study product (n=76). (A) Overall demand across all four products. Data points indicate estimated daily consumption (y-axis) across varying price points per cigarette ranging from $0 (free) to $30 (x-axis) for all participants. (B–E) Demand indices across all four products. Data points represent mean scores across participants with 95% CIs. Along the x-axis is product type, and along the y-axis are the respective scores or price (in US$). For all indices, a higher score or price indicates greater abuse liability. Data points that do not share a symbol differ significantly (p <0.05). Note: four participants were removed from analyses due to non-systematic data. mFLC, menthol filtered little cigar; mRYO, menthol roll-your-own; NMC, non-menthol cigarette; UBMC, usual brand menthol cigarette.

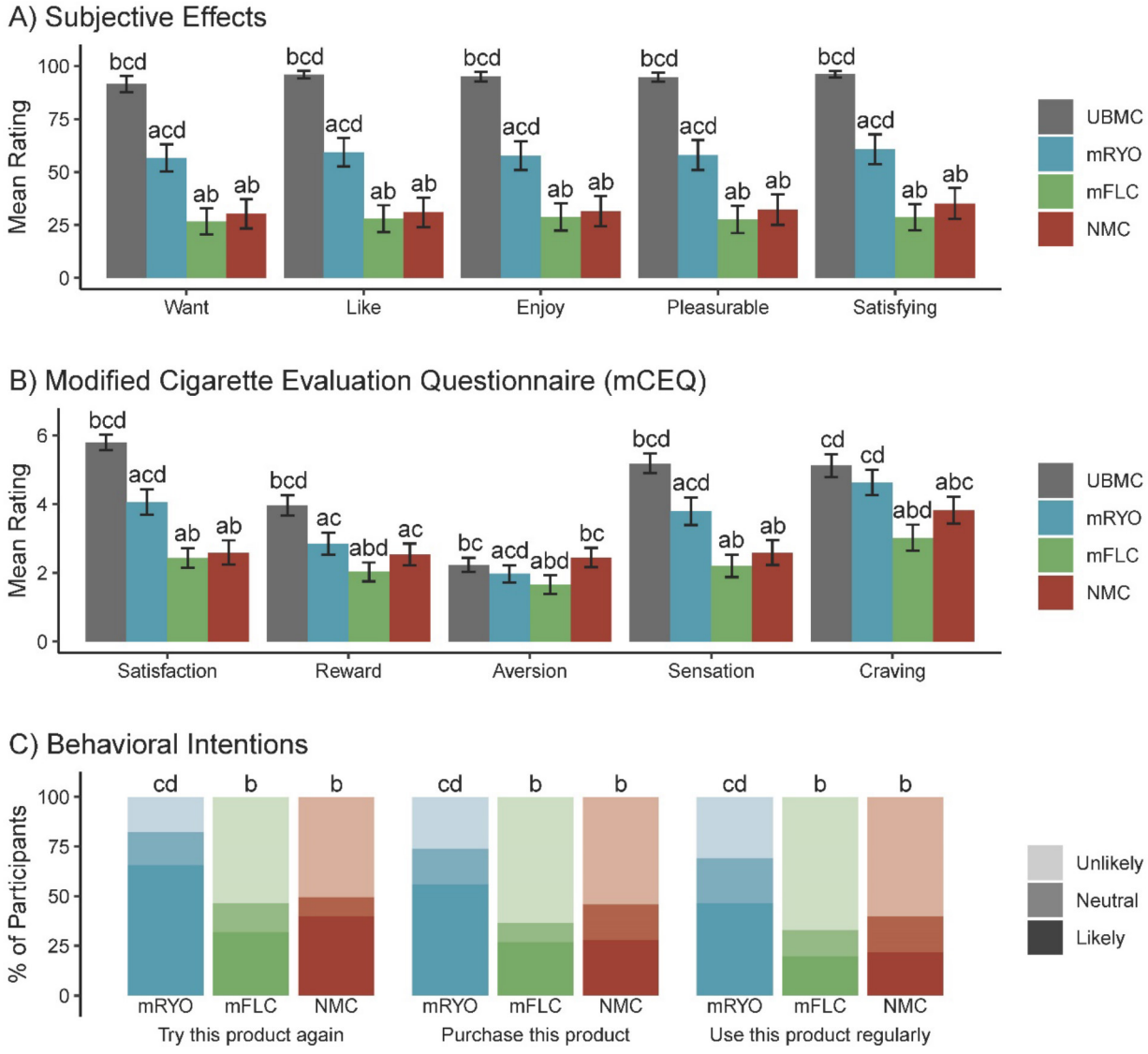

Figure 3 Subjective effects, mCEQ and behavioural intentions by study product (n=98). P values estimated from mixed effects models accounting for repeated measures, mCEQ-Aversion was log transformed for analysis; superscripts denote differences in pairwise comparisons between study products at p<0.05. a, differs from UBMC; b, differs from mRYO; c, differs from mFLC; d, differs from NMC. mCEQ, modified Cigarette Evaluation Questionnaire; mFLC, enthol filtered little cigar; mRYO, menthol roll-your-own; NMC, non-menthol cigarette; UBMC, usual brand menthol cigarette.

purchasing and using the product regularly, prefilled mRYO cigarettes were the products chosen by most participants to be used in a subsequent 1-week trial at home and the most highly rated cigarette alternative, suggesting their potential appeal as a menthol cigarette substitute. These findings are of particular importance, given the components of this product: pipe tobacco, which now comprises most of the loose tobacco market,[27] and cigarette tubes, which have been authorised by the FDA in prior substantial equivalence applications. While the FDA used its enforcement authority in 2013 to call out misbranding of RYO cigarette tobacco as pipe tobacco,[51] retailer education in 2021 embraced slippage between the product categories and encouraged convenience store owners and operators to promote both to their clients.[52] Given the 2020 court order vacating the FDA's health warning requirement for pipe tobacco,[53] continued ambiguity in differentiating pipe from RYO tobacco, and anticipated FDA action on menthol cigarettes and cigars, our findings suggest that components of mRYO products, including menthol rolling papers, cigarette tubes and pipe tobacco, be considered for inclusion under a menthol cigarette ban.

Beyond measures of the subjective experiences of smoking, topography data provide useful information about how the product is likely to be used in the natural environment and can significantly influence uptake of nicotine in the body, both critical for the addiction potential and toxicity of menthol cigarette alternatives.[36] Findings showed that UBMC and mRYO cigarettes were used similarly. There were several topography measures that differed, however, between UBMCs and the other two study products, which may be related to the more negative subjective ratings of these products. Consistent with other studies,[34 35] participants had shorter puff duration, lower average puff volume and lower total inhaled smoke volume when using NMC compared with any of the mentholated products. The higher smoke volume seen for our three menthol products may result in higher exposure to nicotine, tobacco-specific nitrosamines and ultrafine particulates.[35] Novel findings

supported that compared with all other products, mFLC had a higher puff duration, lower average flow rate and higher CO boost. This finding likely reflects both the greater density of tobacco in the filtered cigar product and the much higher resistance to draw.[54] Increased puff duration may also be related to the mFLC's lower nicotine delivery, which was at most half that of the other two study products. The higher exhaled CO for mFLC is likely related to the incomplete combustion that comes from the narrower, longer and more densely packed column of tobacco and the lower flow rate of air through the burning end of the cigarette. The puffing behaviour data suggest that mFLCs, used as cigarettes,[30] may induce greater smoke exposure in their users.

Strengths of our study include use of a within-subjects design, multiple methods of estimating the addiction potential of menthol cigarette alternatives and a large clinical laboratory sample of adults who currently smoke menthol cigarettes. The fact that our sample had a high proportion of people who identified as white and female and of lower socioeconomic status is both a strength and a limitation of our study. Even though the prevalence of menthol cigarette use is highest among black adults who smoke,[3 11] there remains a larger absolute number of white adults who smoke menthol cigarettes in the USA. Our sample reflects the midwestern city in which it was recruited but is likely generalisable to a broader population of menthol cigarette smokers in the USA, including women and people of lower socioeconomic status who have a higher prevalence of menthol cigarette use.[3 11] While our study design is consistent with recommended methods to determine the comparative abuse liability of tobacco products,[36] the use of a longer ad libitum use period, in addition to a standardised puffing session, may have further elucidated differences in puffing topography and drug self-administration. Our study's use of a limited number of products to evaluate menthol cigarette alternatives does not reflect the range of alternative products that could be substituted for menthol cigarettes under a potential ban, but recent research using an online experimental tobacco marketplace to simulate product choice following a menthol cigarette ban supports menthol little cigars, NMCs, menthol cigarillos and menthol vapes as potential substitutes.[55] Expanding our multimethod design to a broader range of products, including menthol e-cigarettes and other mentholated smokeless tobacco products, may identify the most likely menthol cigarette alternative.

Our current findings suggest that menthol pipe tobacco and tubes should be a target for research and regulation. The FDA's current proposal to restrict the use of menthol in both cigarettes and cigars has the potential to significantly improve public health with a reduction in new smokers as well as increased cessation among current mentholated cigarette and cigar smokers. Recent announcements regarding a product standard for reduced nicotine content in cigarettes may also reduce the harms of NMCs,[56] studied in this trial. However, the present findings suggest that components of mRYO products, including menthol rolling papers, cigarette tubes and pipe tobacco, should also be included in the menthol cigarette and flavoured cigar product standards. Their absence from this restriction will result in a critical loophole that is already being exploited by the tobacco industry and has the potential to attenuate the potential public health benefits of the proposed menthol ban.

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Contributors TLW and ACV conceived of and designed the study and wrote the manuscript. TM managed the study and was overseen by TLW and ACV. AH, JAS and TGE conducted and are responsible for the data analysis. MCB and CW conducted tobacco product characterisation, including emissions testing. TM, AH, JAS, TGE, MCB, CW, and JT reviewed, edited and approved the final version. TLW, ACV and AH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TLW is responsible for the overall content as guarantor.

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Ethics approval This study involves human participants and was approved by the institutional review board (IRB) of Ohio State University (IRB protocol number 2019C0107). All participants provided written informed consent before taking part in the study.

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Data availability statement Data are available upon reasonable request. The corresponding author will make deidentified participant data and the data dictionary available following publication. Institutions and individuals wishing to access any resources or data must contact the corresponding author (theodore.wagener@osumc.edu). Data will only be made available to those whose proposed use of the data has been approved by the corresponding author. Data will be made available for the sole purpose of replicating the analyses reported in the manuscript. The recipient must agree to not transfer the data to other users and that the data are only to be used for research purposes. The private investigators will require requestors of data to sign a data sharing agreement that will ensure (1) use of the data is only for research purposes, (2) data security using appropriate technology/firewalls, (3) destruction of data after data analysis and (4) proper citation in publications or other written materials. A record of transfer of data and a copy of the dataset that was distributed will be kept by The Ohio State University.

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Addiction Potential of Combustible Menthol Cigarette Alternatives: A Randomized Crossover Trial

SUPPLEMENTARY APPENDIX

Contents

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Supplementary Tables & Figures

Supplementary Tables, Methods and Figure

Supplementary Table 1. Physical attributes, and mainstream emissions for the study products and certified reference cigarette.

	Study Products			Quality Control	
Measure	**Menthol Roll-Your-Own Cigarette (mRYO)**	**Menthol Filtered Little Cigar (mFLC)**	**Non-Menthol Cigarette (NMC)**	**Certified Reference Cigarette (1R6F)**	**1R6F within certified uncertainty? If "No" error (%) is provided**
	Physical Attributes, Mean (Standard Deviation), n=5 reps				
Rod[1] mass, g	1.059 (0.060)[c,d]	1.407 (0.035)[b,d]	0.881 (0.027)[b,c]	0.882 (0.029)	Yes
Tobacco mass, g	0.809 (0.06)[c,d]	0.992 (0.035)[b,d]	0.656 (0.030)[b,c]	0.625 (0.030)	Yes
Pressure Drop,[2] mm H_2O	103 (8.3)[c]	193 (13)[b,d]	123 (6.9)[c]	104 (3.6)	Yes
Circumference, mm	25.9 (0.14)[c,d]	24.3 (0.09)[b,d]	24.6 (0.24)[b,c]	24.3 (0.05)	Yes
Diameter, mm	8.24 (0.05)[c,d]	7.73 (0.03)[b,d]	7.85 (0.08)[b,c]	7.74 (0.01)	Yes
Rod length, mm	87.9 (0.79)[c,d]	98.8 (0.15)[b,d]	80.1 (0.13)[b,c]	83.2 (0.06)	Yes
Filter length, mm	20.3 (0.28)[c,d]	30.3 (0.22)[b,d]	21.0 (0.65)[b,c]	27.1 (0.13)	Yes
Packing density, g/cm^3	0.22 (0.02)[c]	0.31 (0.01)[b,d]	0.23 (0.01)[c]	0.24 (.01)	-cv-
	CI Mainstream Emissions, Mean (Standard Deviation), n = 5 reps				
Nicotine, mg/rod	2.11 (0.08) [c,d]	0.99 (0.11) [b,d]	2.51 (0.13) [b,c]	1.83 (0.16)	Yes
Menthol, mg/rod	2.25 (0.16)[c,d]	3.04 (0.30)[b,d]	0.003 (0.00)[b,c]	0.013 (0.00)	-na-
TPM, mg/rod	54.08 (2.61)[d]	48.14 (7.64)[d]	62.10 (2.43)[b,c]	37.94 (8.51)	No, -19%
Mass burned, mg/rod	0.903 (0.07)[d]	0.880 (0.02)[d]	0.680 (0.01) [b,c]	0.590 (0.02)	-na-
Puff Count	13.4 (1.5)[d]	12.4 (0.5)[d]	8.2 (0.4)[b,c]	7.6 (0.5)	No, -13%

[1] Rod = the total product

[2] Data shown for 16.7 mL/s flow rate

-na- = The 1R6F does not certify menthol content nor menthol mainstream emissions data nor mass burned

-cv- = calculated value; no uncertainty given

CI = Canadian Intense puffing regimen, 55 mL puff volume, 2 s duration, 2 puffs every 60 s, with 50% vent blocking

Alphabetical superscripts indicate pairwise comparisons between study products at the $p<0.05$ level:

[b] Differs from mRYO; [c] Differs from mFLC; [d] Differs from NMC

PHYSICAL AND CHEMICAL ANALYSIS METHODS

Products

To better simulate real-world use, all study products were not conditioned, but taken directly from freshly opened packages just prior to physical attribute, content and emissions testing. Study products were stored refrigerated (22 °C) and allowed to come to room temperature prior to testing. A certified reference cigarette, 1R6F, was obtained from the University of Kentucky Center for Tobacco Reference Products and included in all test methods.

Mass, Length, Pressure Drop, Packing Density

Mass was measured using a precision balance (0.0000 g, Metter AE 260-S). Length, circumference and diameter measurements were made with a digital caliper (Mitutoyo CD-6" ASX). Resistance to draw was measured with a digital manometer (Dwyer 4777AV-2) across four flow rates spanning 1–4 L/min. Packing density was calculated ats the mass of the tobacco filler divided by the volume of the tobacco column.

Mainstream Emissions

Mainstream smoke was generated using a single-port smoking machine (Gram Research, UVM) according to the Canadian Intense (CI) puffing regime: 55 mL puff volume, 2 s duration, 2 puffs every 60 s, with 50% vent blocking. CI was selected because this puffing regime more closely resembles the puffing done by participants compared to the ISO/FTC regime. Mainstream total particulate matter (TPM) was collected onto Cambridge filter pads (44 mm) and TPM per rod was calculated as the difference of the weight of the filter holder before and after smoking. Filters were recovered and extracted (10 mL of isopropanol with 0.1 mg/mL quinoline as internal standard) for 2 hours using a shaker table (180 RPM, New Brunswick Scientific™ Innova® 2100 platform shaker). Extracts were quantified using gas chromatography mass spectrometry equipped with a CP-WAX 51 column (20 m x 250 µm, x 0.2 µm); oven program was 80-230°C at 20°C/min, hold at 230°C for 4 minutes.

Quality Control

In general, overall variability across replicates was low in that relative standard deviations for all attributes for all products were <8%. The variability in physical attribute replicates was only slightly higher in the mRYO as compared to the other commercial and reference products, indicating the by-hand preparation of this product was carried out with a reproducibility similar to that obtained by commercial machines. All physical attributes obtained for the 1R6F fell within the certified uncertainty of the values reported in the 1R6F certificate of analysis (CoA), indicating the validity of our measurement procedures.

Mainstream nicotine obtained for the 1R6F fell within the certified uncertainty of the value reported in the 1R6F certificate of analysis (CoA), indicating the validity of our smoke generation, collection and quantification procedures. However, TPM and puff count for the 1R6F were low (-13 to -19% error from the certificated value), but still within -20% error from the certified values. This is probably due to the fact that the products were not conditioned prior to smoking, a choice made to better replicate real-world behavior, and thus these products were therefore dryer and likely burned more rapidly during the non-puffing periods of the smoking session.

Supplementary Table 2. Differences in smoking topography for Usual Brand menthol Cigarettes and Menthol Cigarette Alternatives. p-values are from repeated measures ANOVA with Tukey adjustment for all pairwise comparisons. All measures were winsorized at the 1st and 99th percentiles.

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
Average Puff Duration[1] (s)	0.994	<0.001	0.089	<0.001	0.001	<0.001
Average Flow Rate (ml/s)	0.077	<0.001	0.071	<0.001	<0.001	<0.001
Average Interpuff Interval (s)	1.000	<0.001	0.785	<0.001	0.843	<0.001
Total Number of Puffs	0.780	0.204	0.895	0.027	0.996	0.050
Inhaled Volume (mL)	0.215	0.033	<0.001	<0.001	<0.001	0.001
Average Puff Volume (mL)	0.264	0.044	<0.001	<0.001	<0.001	0.011
Max Puff Volume (mL)	0.991	0.004	0.002	<0.001	<0.001	0.997
CO Boost (ppm)	0.097	0.002	0.645	<0.001	0.682	<0.001

[1] Variable log transformed for analysis

Supplementary Table 3. Differences in QSU Desire **(A)**, Relief **(B)**, MNWS **(C)**, and MNWS Craving **(D)** for Usual Brand menthol Cigarettes and Menthol Cigarette Alternatives. p-values are from linear mixed effects models, those with an asterisk (*) are significant at the 0.05 level after Holm's adjustment for multiple comparisons between products at each time; relief and MNWS were log transformed for analysis.

A Desire

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
0 Minutes	0.723	0.814	0.782	0.840	0.895	0.945
5 Minutes	0.500	0.118	0.474	<0.001*	0.943	<0.001*
15 Minutes	0.734	0.072	0.868	<0.001*	0.769	0.001*
30 Minutes	0.776	0.059	0.874	<0.001*	0.452	0.003
60 Minutes	0.858	0.114	0.704	0.017	0.732	0.042
90 Minutes	0.829	0.209	0.817	0.077	0.980	0.083

B Relief[1]

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
0 Minutes	0.617	0.250	0.306	0.393	0.492	0.866
5 Minutes	0.394	0.089	0.400	0.001*	0.990	0.001*
15 Minutes	0.626	0.003	0.290	0.001*	0.453	0.014
30 Minutes	0.206	0.001*	0.062	0.005	0.425	0.046
60 Minutes	0.036	0.003	0.060	0.254	0.774	0.155
90 Minutes	0.050	0.008	0.241	0.368	0.304	0.055

[1] Log transformed for analysis

C MNWS[1]

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
0 Minutes	0.776	0.058	0.939	0.045	0.653	0.014
5 Minutes	0.076	0.031	0.033	0.624	0.651	0.969
15 Minutes	0.019	0.003	0.015	0.458	0.909	0.531
30 Minutes	0.380	0.067	0.212	0.233	0.643	0.466
60 Minutes	0.928	0.273	0.499	0.210	0.465	0.600
90 Minutes	0.510	0.305	0.691	0.645	0.745	0.434

[1] Log transformed for analysis

D MNWS Craving

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
0 Minutes	0.709	0.613	0.740	0.842	0.952	0.796
5 Minutes	0.461	0.089	0.351	<0.001*	0.769	<0.001*
15 Minutes	0.442	0.123	0.961	0.001*	0.286	0.019
30 Minutes	0.802	0.100	0.549	0.039	0.605	0.123
60 Minutes	0.989	0.148	0.962	0.034	0.960	0.039
90 Minutes	0.491	0.701	0.330	0.112	0.672	0.045

Supplementary Table 4. Differences in subjective effects **(A)**, modified cigarette evaluation questionnaire **(B)**, and behavioral intentions **(C)** for Usual Brand menthol Cigarettes and Menthol Cigarette Alternatives. p-values from repeated measures ANOVA with Tukey adjustment for all pairwise comparisons (subjective effects, mCEQ) or multinomial logistic regression models (behavioral intentions).

A Subjective Effects

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
Want	<0.001	<0.001	<0.001	<0.001	<0.001	0.821
Like	<0.001	<0.001	<0.001	<0.001	<0.001	0.877
Enjoy	<0.001	<0.001	<0.001	<0.001	<0.001	0.905
Pleasurable	<0.001	<0.001	<0.001	<0.001	<0.001	0.706
Satisfying	<0.001	<0.001	<0.001	<0.001	<0.001	0.370

B Modified Cigarette Evaluation Questionnaire

	UBMC vs mRYO	UBMC vs mFLC	UBMC vs NMC	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
Smoking Satisfaction	<0.001	<0.001	<0.001	<0.001	<0.001	0.850
Psychological Reward	<0.001	<0.001	<0.001	<0.001	0.189	0.004
Aversion[1]	0.014	<0.001	0.741	0.014	0.001	<0.001
Enjoyment of Respiratory Tract Sensations	<0.001	<0.001	<0.001	<0.001	<0.001	0.306
Craving Reduction	0.110	<0.001	<0.001	<0.001	0.006	0.005

[1] Log transformed for analysis

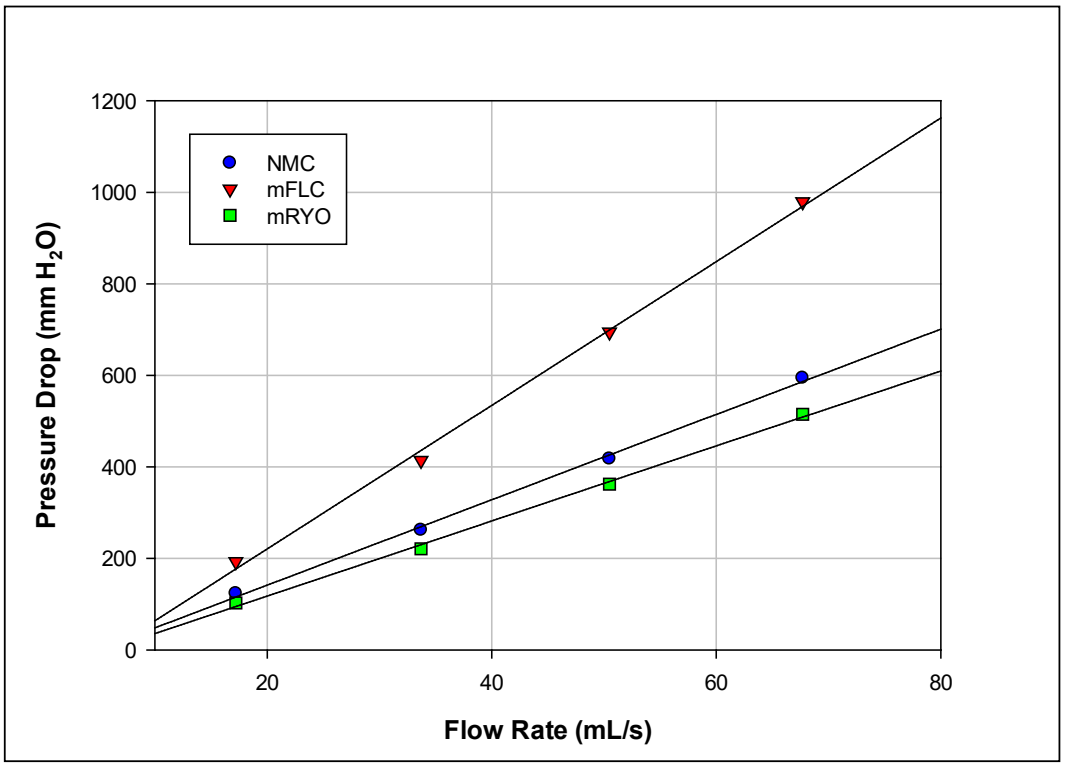
C Behavioral Intentions

	mRYO vs mFLC	mRYO vs NMC	mFLC vs NMC
Try this product again	<0.001	<0.001	0.442
Purchase this product for personal use	<0.001	<0.001	0.310
Use this product regularly	<0.001	<0.001	0.389

Supplementary Table 5. Logistic regression model for selection of mRYO.

	OR	95% CI	p-value
Race			
White	1.56	(0.51, 4.73)	0.4352
Non-White	Ref.		
Sexual Orientation			
LGBTQ	1.43	(0.43, 4.80)	0.5621
Straight/Heterosexual	Ref.		
Ever Use of Other Products			
Ever Used	2.66	(0.39, 18.22)	0.3184
Never Used	Ref.		
Usual Brand			
Not Newport	1.29	(0.41, 4.07)	0.6633
Newport	Ref.		

Supplementary Figure 1. Resistance to draw for study products.



Abstract

Recent changes in population patterns of tobacco use in youth and adults underscore the potential substitution of other menthol tobacco products for cigarettes in the face of a ban on menthol in cigarettes. The increased use of cigars and pipe tobacco in youth following the 2009 ban on flavored cigarettes is particularly important given that flavored filtered little cigars are often indistinguishable from cigarettes and flavored pipe tobacco can be used to make roll-your-own cigarettes. Mentholated pipe tobacco (for roll-your-own cigarettes, mRYO), menthol filtered little cigars (mFLC), and non-menthol cigarettes (nmC) appear to be plausible substitutes for menthol cigarettes. The goal of the current study is to examine the abuse liability and substitutability of these potential menthol cigarette substitutes using an in-laboratory and ad libitum outpatient mixed design. One hundred current menthol cigarette smokers (n=50 aged 18-24 years, n=50 aged 25+ years) will complete a three-phase study: in Phase 1, utilizing a randomized crossover design, participants' will complete 4 smoking sessions, smoking a different product each session to examine each product's abuse liability, demand, and topography. Products will include participants' usual brand menthol cigarette (UBMC) as well as 3 commercially-available alternatives, including mFLC, an mRYO product, and non-mentholated cigarette (nmC). Participants will complete one-week of daily diaries after smoking session 1 in phase 1 to assess their usage of usual brand menthol cigarette (UBMC). In Phase 2, to assess uptake, changes in subjective effects, and use over time, participants will select their preferred study product from Phase 1 and instructed to completely substitute the product for their UBMC for one week. Participants will complete daily diaries during this period to more accurately assess substitution and perceived effects in real-time. In Phase 3, participants will complete a final in-lab visit to assess the substitutability of their preferred product from Phases 1 and 2, under simulated ban conditions using a progressive ratio task. In all phases, multiple domains of abuse liability will be assessed, including product administration (in-lab topography and daily self-report measures), product liking/craving and withdrawal suppression (in-lab and daily diary self-report). This study will be the first to estimate the substitutability of potential menthol cigarettes substitutes in adult smokers, which could impact the health benefit of a public health standard banning menthol in cigarettes. It will evaluate characteristics and perceptions (e.g., satisfaction, taste) of these products that may increase the likelihood of substitutability. Findings from this study will provide key information on the potential unintended consequences of a ban on menthol in cigarettes (i.e., the extent to which these substitutes would appeal to and be used by existing menthol cigarette smokers). They may also inform how FDA treats other non-cigarette tobacco products used as menthol cigarette substitutes in future proposed rulemaking, for example, extending the ban to menthol filtered little cigars or menthol pipe tobacco.

Project Narrative/relevance to public health:
FDA has repeatedly indicated its intent to pursue a ban on menthol in cigarettes. However, estimating the impact of a potential ban on menthol in cigarettes requires accounting for likely substitutes in the marketplace that may also need to be restricted to effectively protect public health. The proposed study uses an in-laboratory and *ad libitum* outpatient mixed design to examine the abuse liability and substitutability of plausible menthol cigarette alternatives, including menthol filtered cigars, menthol roll-your-own cigarettes, and non-menthol cigarettes, in a sample of current adult menthol cigarette smokers.

A. Specific Aims

While the prevalence of cigarette smoking in the U.S. has continued to decrease,[7] the proportion of menthol cigarette users increased significantly from 35% in 2008-2010 to 39% in 2012-2014.[5] Menthol cigarettes are associated with increased youth smoking initiation, increased nicotine dependence, and decreased adult cessation.[6] Menthol smokers are also more likely to be of low socioeconomic status, female, black or Hispanic, and identify as LGBT compared to non-menthol smokers.[8] As these studies highlight, menthol is strongly associated with facilitating the initiation and maintenance of cigarette smoking, particularly among vulnerable populations.

The 2009 Family Smoking Prevention and Tobacco Control Act banned characterizing flavors in cigarettes and their components. Tobacco companies, however, exploited loopholes in this regulation to maintain sales of

their products. For example, Djarum, previously a clove flavored *cigarette*, launched clove filtered *cigars* in anticipation of the ban, and sales of their clove filtered cigars increased by more than 1400% between 2009 and 2012.[9] Moreover, menthol was not included in the ban, and the use of menthol cigarettes as well as flavored cigars and pipe tobacco increased in youth following the flavored cigarette ban, suggesting substitution of other available flavored tobacco products.[10] Thus, while manufactured flavored cigarettes are no longer available, the public health benefit of this product standard was attenuated by the presence of accessible commercially-available substitutes in the marketplace.

For any proposed regulatory action, the FDA must estimate the range of potential impacts on behavior and health. Estimating the impact of a potential ban on menthol in cigarettes, therefore, requires accounting for likely substitutes in the marketplace that may also need to be restricted to effectively protect public health. Current tobacco products, including menthol filtered little cigars (mFLC), menthol roll-your-own (mRYO) tobacco and cigarette tubes, and non-menthol cigarettes (nmC), are relevant targets.[11]

The goal of the proposed study is to examine the abuse liability and substitutability of plausible menthol cigarette alternatives. Using an in-laboratory and *ad libitum* outpatient mixed design, current menthol cigarette smokers (N=80) will complete a three phase, 3-week study: in ***Phase 1,*** utilizing a randomized crossover design, participants will complete [*4 smoking sessions*], smoking a different product each session to examine each product's abuse liability, demand, and topography. Products will include participants' usual brand menthol cigarette (UBMC) as well as 3 commercially-available alternatives, including mFLC, mRYO product, [*and non-mentholated cigarette (nmC)*.] Participants will complete one-week of daily diaries after smoking session 1 in phase 1 to assess their usage of usual brand menthol cigarette (UBMC). In ***Phase 2***, to assess uptake, changes in subjective effects, and use over time, participants will [*select their preferred study product from Phase 1*] and be instructed to completely substitute the product for their UBMC for one week. Participants will complete daily diaries during this period to more accurately assess substitution and perceived effects in real-time. In ***Phase 3,*** participants will complete a final in-lab visit to assess the substitutability of [*their preferred product from Phases 1 and 2*,] under simulated ban conditions using a progressive ratio task. In all phases, multiple domains of abuse liability will be assessed, including product administration (in-lab topography and daily diary self-report measures), product liking/craving and withdrawal suppression (in-lab and daily diary self-report).

Aim 1: To assess the abuse liability of menthol cigarette alternatives. H1a: Alternatives will [have similar use topography and significantly reduce nicotine craving/withdrawal similar to UBMC, but (H1b) UBMC will show significantly greater demand indices and liking/satisfaction compared to alternatives. H1c: Among alternatives, nmC will show the greatest demand and liking/satisfaction, followed by mFLC, and lastly mRYO.

Aim 2: To assess the substitutability of menthol cigarette alternatives. H2a: A significantly higher portion of product preference selections for Phase 2 will favor nmC than all other alternatives. H2b: Participants' use of study products will significantly increase over the one-week substitution period. H2c: Under simulated UBMC ban conditions, >80% of participants will substitute at least 50% of their UBMC use with study product.

Aim 3: To evaluate which product characteristics and perceived effects influence greater substitution. H3: Participants reporting higher product satisfaction, including "throat hit", menthol-specific sensory effects, craving reduction, improved mood with use, and ease of use [on daily diaries, will report the greatest substitution of study product for UBMC.

B. Significance

Menthol cigarette prevalence is increasing: In the face of historic declines in the prevalence of cigarette smoking in the U.S.,[7] the proportion of menthol cigarette users increased significantly from 35% in 2008-2010 to 39% in 2012-2014.[5] Significant increases in menthol cigarette prevalence occurred in all age groups, with youth (12-17 years old) and young adult (18-24 years old) smokers reporting the highest prevalence of menthol use among smokers (53.9% and 50.0%, respectively).[5] These findings were echoed by data from the 2013-2014 Population Assessment of Tobacco and Health (PATH) Study, with 60% of youth and 47% of young adult smokers using mentholated cigarettes.[4] These changes are consistent with growth in menthol cigarette market share[12-14] and menthol cigarette prevalence can only be expected to increase in youth and young adults given recent expansions in the distribution of menthol cigarettes by the largest U.S. cigarette companies.[15-18]

Role of menthol in smoking initiation and maintenance: Reviews of tobacco industry documents underscore the relationship between menthol cigarette use, youth smoking initiation and tobacco dependence, as understood and manipulated by the tobacco industry.[19-21] The appeal of menthol flavoring has been demonstrated to influence intention to smoke and initial smoking,[22,23] with youth more likely to experiment with menthol cigarettes than older age groups.[3,5,24,25] Additionally, young smokers who start with menthol cigarettes are more likely to increase or maintain their smoking behavior over time.[26,27] There are several mechanisms by which menthol in cigarettes has demonstrated to influence the initiation and maintenance of smoking, as indicated by tobacco industry documents as well as independent research: 1) menthol's cooling and analgesic properties mask the harshness and taste of cigarette smoke, making it more appealing; 2) menthol's refreshing sensory qualities increase the positive, or rewarding, properties associated with smoking[28,29]; 3) menthol inhibits nicotine metabolism, causing the smoker greater systemic exposure to nicotine[30]; and 4) menthol may change smokers' puff topography causing them to take more puffs.[31] These mechanisms, long known by the tobacco industry, allowed them to engineer a nicotine delivery device that would not only attract new smokers but also make it more difficult for established smokers to quit.

Menthol cigarettes, public health, and threats to the efficacy of a ban on menthol cigarettes: The 2009 Family Smoking Prevention and Tobacco Control Act banned certain characterizing flavors in cigarettes and their components (i.e., tobacco, filter, and paper). The law did not include menthol, nor did it address flavors in non-cigarette tobacco products.[32] However, the Act makes clear that the Food and Drug Administration (FDA) has the authority to issue a product standard to ban menthol in cigarettes, or any other tobacco product, to protect public health. Reviews of the scientific evidence by the FDA and its Tobacco Product Scientific Advisory Committee led to a report concluding that it is "likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes" [33] and "removal of menthol cigarettes from the marketplace would benefit public health in the United States."[34] FDA has continued to request information on the potential effects of a ban on menthol in cigarettes, including in the July 2017 announcement of its comprehensive approach to tobacco and nicotine regulation.[35] The 2009 ban on flavored cigarettes provides a key example of the potential intended and unintended consequences of such a ban. A recent study using data from the 1999-2013 National Youth Tobacco Surveys showed that the flavored cigarette ban was associated with reductions in the prevalence of past 30-day cigarette smoking and number of cigarettes smoked in youth, as intended.[10] However, youth prevalence of past 30-day flavored cigar, pipe, and menthol cigarette use increased following the 2009 ban, suggesting substitution of other flavored tobacco products for flavored cigarettes.[10] This is consistent with evidence of tobacco companies exploiting loopholes in tobacco regulation to maintain sales of their flavored products.[36,37] Djarum, for example, launched clove filtered cigars in the U.S. in anticipation of the 2009 ban on flavored cigarettes and sales of their clove filtered cigars increased by more than 1400% between 2009 and 2012.[9] Thus, while manufactured flavored cigarettes are no longer available, the public health benefit of this product standard was attenuated by the presence of accessible commercially-available substitutes in the marketplace.

Recent trend data highlight growth in U.S. sales of mentholated products, including filtered cigars from 2011 to 2015.[14] Population data show significant correlation between cigar use and menthol cigarette use.[5] These patterns of co-use may be related to the pervasiveness of characterizing flavors, including menthol, in these products.[38,39] Studies on effects of a hypothetical ban on menthol in cigarettes among menthol smokers support behavioral intentions to switch to another tobacco product[40,41] or to non-menthol cigarettes.[41,42] Importantly, these data suggest that poly-use of menthol tobacco products is already occurring, possibly enabling future substitution of other tobacco products for menthol cigarettes in response to an FDA ban. They also highlight non-menthol cigarettes as a possible substitute under such a ban.

Implications: Data on recent changes in the tobacco marketplace and population patterns of tobacco use in youth and adults underscore the potential substitution of other tobacco products for menthol cigarettes in the context of a ban. The increased use of cigars and pipe tobacco in youth following the 2009 ban on flavored cigarettes is particularly important given that flavored filtered cigars are often indistinguishable from cigarettes and flavored pipe tobacco is used to make roll-your-own cigarettes. Mentholated pipe tobacco (for RYO cigarettes), menthol filtered cigars, and non-menthol cigarettes appear to be plausible substitutes for menthol cigarettes. The goal of the current study is to examine the abuse liability and substitutability of these potential menthol cigarette substitutes in the

laboratory and in an extended observation period. Findings from this study will provide key information on the potential unintended consequences of a ban on menthol in cigarettes (i.e., the extent to which these substitutes would appeal to and be used by existing menthol cigarette smokers). They may also inform how FDA treats other non-cigarette tobacco products used as menthol cigarette substitutes in future proposed rulemaking, [for example, extending the ban to menthol filtered little cigars or menthol pipe tobacco. The scientific premise of this study is that examining abuse liability and substitutability of menthol cigarette substitutes will inform estimates of the public health impact of a ban on menthol in cigarettes. This information is required for FDA's regulatory impact analysis to pursue such a ban. This study will also provide a model for future research on the potential public health impact of flavor bans in non-cigarette products, noted as another priority by FDA in their plan for comprehensive nicotine regulation.[35]

C. Approach and Preliminary Studies

Our team brings combined expertise in all areas necessary for the successful implementation of a clinical/clinical laboratory study examining the substitutability of other combusted mentholated non-cigarette tobacco products for menthol cigarettes. Specifically, our team has strong expertise conducting survey and longitudinal cohort research examining the 1) the role of menthol in smoking initiation, dependence, and cessation,[3,5,6,8,12,27,51,52,55-57,59,97] 2) the impact of a menthol ban on population health including the substitutability of non-menthol and menthol cigarettes,[6,51,52,57 and 3]) the use of flavored and non-cigarette tobacco products among youth, young adults, adults.[3,4,60,65] We have also conducted five clinical/human laboratory studies examining the pharmacological, toxicological, and physiological effects of non-cigarette tobacco products including two ongoing studies examining the impact of flavors and sweeteners on waterpipe tobacco smoking (R03DA041928; R03DA041928-02S1). In each of these studies, we assessed the abuse liability, topography, nicotine delivery, toxicant exposure, and use behaviors of the non-cigarette tobacco product under investigation. All of these methods are very familiar to our team and we have experienced great success utilizing them. Our team has also conducted several short-term as well as long-term randomized trials assessing tobacco use behavior.[72-83] Lastly, our team has significant experience to collect daily diary data to examine tobacco use and behavioral correlates among smokers.[98-105] These studies have resulted in excellent retention (>80%) with high-rates of daily diary completion (80-88%).

Theoretical Framework: The proposed study is guided generally by behavioral economic theory[1] as well as an established framework for abuse liability assessment used by the FDA to assess drug products, including tobacco.[2] Specifically, abuse liability assessment involves determining the likelihood that use of a product will lead to persistent and problematic use through a series of specific tests across multiple domains (**Figure 1**) including: 1) self-administration tasks, to determine a product's rate of self-administration over time; 2) forced choice tasks, to determine if one product is preferred over another; 3) hypothetical purchase tasks, to determine how much of a product is consumed at different prices or changes in consumption relative to changes in the price of a different product; and 4) positive and negative subjective effects, to determine the psychoactive effects of a drug; and 5) suppression of withdrawal/craving with product use, to determine whether a product can prevent the effects of abstinence in nicotine dependent individuals. Products with a higher abuse liability will be self-administered at a relatively higher rate, preferred over the other product when forced to choose, less sensitive to higher costs to obtain it, greater positive effects/fewer side effects, and more effectively suppress craving and withdrawal symptoms. The proposed study will examine each of these domains.

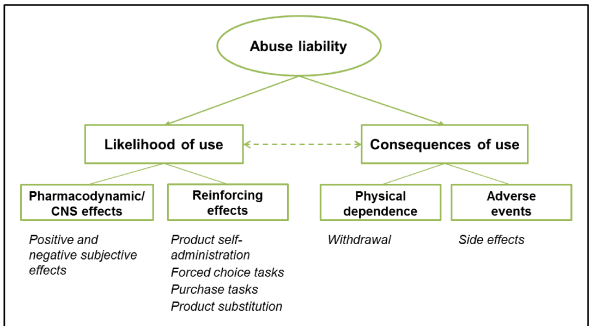


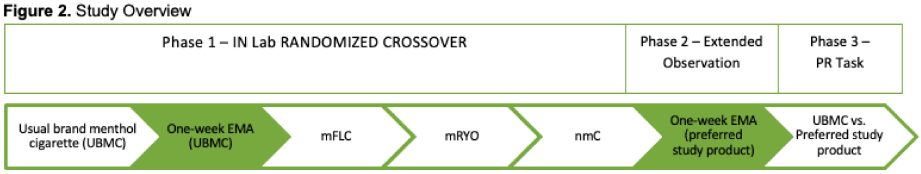
Figure 1. Abuse liability model and constructs (adapted from Carter et. al, 2009)

D. Research Design and Methods

1. Design Overview

Figure 2 depicts the sequence of the proposed study. Using an in-laboratory and *ad libitum* outpatient mixed design, 80 current menthol cigarette smokers will complete a three phase, 3-week study. Over the 3-week study time period, participants will attend 5 in-person lab visits. At the beginning of each visit, pregnancy tests will be completed to ensure that the participant is not pregnant. During visit 1, participants will complete a PROP taste test to measure a participants' perceived intensity to taste. In *Phase 1,* utilizing a randomized crossover design, participants will complete 4 smoking sessions, each session smoking a different product examining each participants' puff topography while sampling the product, the product's ability to suppress nicotine craving and withdrawal, and the product's demand indices. Products will include participants' usual brand menthol cigarette (UBMC) as well as 3 commercially-available alternatives, including an mFLC, a pre-assembled mRYO product (menthol tobacco + menthol tube), and an nmC. All sessions will occur following 12-hrs of nicotine abstinence and be separated by 48-hrs. Participants will complete daily diaries for one-week during this period to more accurately assess current use of their UBMC. In *Phase 2*, participants will *select their preferred study product from Phase 1* and be instructed to completely substitute the product for their UBMC for one week. Participants will complete daily diaries during this period to more accurately assess degree of substitution and perceived effects in real-time. In *Phase 3*, participants will complete a final in-lab visit to assess the substitutability of their preferred product, under simulated ban conditions using a progressive ratio task. In all phases, multiple domains of abuse liability will be assessed, including product administration (in-lab puff topography and daily diary self-report measures), product liking and craving and withdrawal suppression (in-lab and daily diary self-report), and hypothetical purchase tasks to simulate demand.

Figure 2. Study Overview



2. Study Procedures

Enrolled menthol smokers will complete four, 2-hr long counterbalanced smoking sessions that are preceded by 12 hours of overnight tobacco abstinence, biochemically verified by exhaled carbon monoxide (eCO≤10ppm). Sessions will be separated by a standard 48-hour washout period. Participants will smoke one cigarette ad libitum and a puff topography device will discretely record smoking behavior throughout the session, including puff duration, number of puffs, puff volume, and time between puffs. eCO, and self-report measures of craving and withdrawal will be recorded immediately before and at several times after the smoking session. Self-report measures of abuse liability will also be completed during the sessions. During the preferred study product observational use period, participants will be provided a weeks' worth of a potential menthol substitute at no cost. Consistent with our previous switching studies, study products will be provided in a 1.2 to 1 ratio based on self-reported use at the time of screening. This slight over appropriation helps to ensure that participants have enough study product available so to not artificially limit use, while also not oversupplying and potentially artificially increasing use behind what would be usual. Participants will be instructed to completely switch and exclusively use the study product during the 1-week time period. During this period, participants will complete daily diary once a day. Following the one-week use period, participants will come to the lab following 12-hr nicotine abstinence confirmed by eCO. To simulate the effect that restricting menthol in cigarettes would have on increasing (or not) preference for other alternative menthol substitutes, participants will complete a 90-minute concurrent choice task with differential cost (effort) required to earn 2 puffs from their UBMC (10 clicks increasing to 7200) versus their preferred study product (always 10 clicks) from Phase 2. This session will last approximately 3 hours.

Recruitment Feasibility and Retention

Recruitment: Based on our team's previous studies we conservatively assume a 20% attrition rate; thus, we will need to recruit 100 participants to have 80 complete the study. We are confident that our recruitment approaches will yield sufficient numbers given our successful history of recruitment for other tobacco-related research of similar design.[75,76,82] Menthol cigarette smokers will be recruited from advertisements through a variety of media outlets and the internet, including Study Search, as well as community events. Participants from other studies who have agreed to be contacted regarding other study opportunities will also be contacted. Staff from those studies will prepare contact letters/emails and call participants on behalf of this study. Participants interested will be referred to this study for screening. Participants will access the screening questionnaire using a public survey link generated by REDCap. Participants who meet the following eligibility criteria will be asked to take part in the study.

Inclusion Criteria: 1) a current menthol cigarette smoker (>90% menthol cigarette use; ≥5 cigarettes per day) for at least the past 6 months, 2) between 21-24 (young adult or 25-50 years old (aged 25+), 3) willing to provide informed consent and abstain from all tobacco and nicotine use for at least 12 hours prior to the five lab sessions, 4) willing to complete two weeks of daily dairies, 5) read and speak English, and 6) have access to a smart phone or email

Exclusion Criteria: 1) self-reported diagnosis of lung disease including asthma, cystic fibrosis, or chronic obstructive pulmonary disease, 2) history of cardiac event or distress within the past 3 months, 3) currently pregnant, planning to become pregnant, or breastfeeding (will be verified with urine pregnancy test), 4) use of other tobacco products (e.g., e-cig, cigar, etc.) >5 days in the past month, 5) current marijuana use >5 days per month, 6) any use of other illicit drugs during the last 30 days, 7) currently engaging in a smoking cessation attempt, and 8) currently using one of the alternative menthol study products, and 9) reside in the same household as a participant currently active (have not completed all study visits) in the study. If a participant is ineligible for the study at the time of screening, the participant can be reassessed at a later time to determine if they are now eligible i.e. A participant meets all other eligibility criteria, but is not eligible because they are currently pregnant or breastfeeding. The participant can submit a new screener after they are no longer pregnant or breastfeeding and can be reassessed for eligibility. Reassessment for eligibility will vary based on previous ineligibility criteria and will be determined on a participant by participant basis.

Participants' eligibility will be determined over the phone or via REDCap's online screener. Those who are eligible and willing to participate will be invited to sign an informed consent and complete their baseline visit in a private participant room at the Ohio State University. All participants will be given adequate time to review the informed consent with a trained research staff to help answer any questions that may arise during the consent process. Additionally, a copy of the informed consent will be given to all participants. A pregnancy test will be completed at the initial visit as well as before starting all the in-lab visits to ensure that the participant is not pregnant.

Retention: All participants will receive $50 per completed in-laboratory session, $7 for parking (when applicable), $50 bonus for completing all sessions (up to $335), and up to $30 for completing daily diaries over the two week ad-lib and observational use periods ($30 for 12 more diaries completed, $25 for 11 diaries completed, $20 for 9-10 diaries completed, $15 for 7-8 diaries completed and $0 for 1-6 diaries completed) for a total up to $365. Consistent with our previous studies, payments will be made using the Greenphire ClinCard to increase accountability and facilitate ease of payment. We will also facilitate study calls/visits by offering evening and weekend appointments as well as additional retention strategies (e.g., multiple sources of contact, reminder calls/texts/emails). Participants will receive reminder calls in addition to email or text reminders. Reminders will be sent by text or email based on a participant's preferred method of contact.

Study Products: Mentholated pipe tobacco in a roll-your-own cigarette tube (mRYO), menthol filtered little cigars (mFLC), and non-menthol cigarettes (nmC) were chosen as plausible menthol cigarette substitutes that are currently available on the commercial market. To produce the mRYO product, study staff will inject 1 gram of menthol OHM pipe tobacco (www.smokersoutletonline.com/ohm-pipe-tobacco-1-lb.html) into manufactured Hot Rod King (84 mm; www.smokersoutletonline.com/hot-rod-tubes.html) tubes using an electric rolling machine, as

described in online user forums. The menthol filtered cigar will be Cheyenne (Cheyennecigars.com) Seneca (senecacigars.com). The nmC will be Newport Non-Menthol Red. All products (mFLC, mRYO, nmC) will be provided to participants in plain boxes without brand or identifying information for the in-lab and *ad libitum* sessions; the box will include a study product ID number sticker for tracking purposes. Brand or identifying information may be present on the actual product.

Detailed Study Procedures

UBMC and Study Product Lab Sessions (Phase 1): Upon arrival at the lab, 12-hr tobacco abstinence will be assessed via self-report and confirmed with exhaled carbon monoxide testing (eCO≤10ppm). Pregnancy exclusion will also be confirmed with a urine test; and breath alcohol concentration (BrAC) tests will ensure BrAC <.01. Participants will not be allowed to eat or drink (other than water) during the session. Participants will be instructed to smoke one UBMC or study product *ad libitum* to completion through a puff topography device. eCO will be collected immediately pre- and post-smoking. Measures of subjective effects (see Table 1) will be collected immediately before the onset of puffing and at 1-min, 15-min, 30-min, 60-min, and 90-min after completion of the cigarette. The Cigarette Purchase Task will also be completed during the lab sessions. Sessions will last approximately 2 hours each. During this period, participants will complete one week of daily diaries to assess their usage of UBMC.

Preferred Study Product *Ad libitum*-Observational Use Period (Phase 2): During the preferred study product observational use period, participants will be provided products at no cost. Study products will be provided in a 1.2 to 1 ratio based on self-reported use at the time of screening. This slight over appropriation helps to ensure that participants have enough study product available so to not artificially limit use, while also not oversupplying and potentially artificially increasing use beyond what would be usual. Participants will be instructed to completely switch and exclusively use the study product during the 1-week time period. During this period, participants will complete one week of daily diaries. If the participant has not responded after 3 prompts, the assessment will be recorded as missed.

Final Lab Session – Simulated Menthol Cigarette Ban Using a Progressive Ratio Task (Phase 3): Following the one-week use period, participants will come to the lab following 12-hr nicotine abstinence confirmed by eCO. To simulate the effect that restricting menthol in cigarettes would have on increasing (or not) preference for other alternative menthol substitutes, participants will complete a 90-minute concurrent choice task with differential cost (effort) required to earn 2 puffs from their UBMC (10 clicks increasing to 7200) versus their preferred study product (always 10 clicks) from Phase 2. This session will last approximately 3 hours.

Data Management

All data collection will follow HIPAA guidelines. Data will be collected directly from the participant by a research assistant. Data will include participant responses to computer-based and phone-based survey Questionnaires, as well as exhaled carbon monoxide samples and progressive ratio task and puff topography readouts.

Access to Identifiable Information and Data Storage: Only research assistants who have completed training in the ethical conduct of research and the study MPIs (Drs. Wagener and Villanti) will have access to individually identifiable private information about human subjects. All data will be treated as confidential and will never be stored or reported in association with identifying information. Hard copies of signed informed consent and the patients cover sheet which includes contact information will be stored in locked filing cabinets separate from participants' study-related data. A common identification number will link identifiable forms (consent forms and contact information) and study-related data. Computer entered data will be de-identified and password-protected.

Quality Assurance

All research staff will have completed Human Subjects and HIPAA training. Standard operating procedures (SOP) have been developed for similar studies run by our lab; we will spend the first month developing the SOP for this

protocol. All staff will be trained to ensure adherence to the SOP. As is standard practice for our team's current studies, each visit will have its own checklist of specific measures to be completed and the order in which they are to be administered. On-site personnel will meet face-to-face weekly throughout the study, with Dr. Villanti joining all weekly meetings via Skype.

3. Measures

Questionnaire data will be collected over the phone or in-person by a trained research assistant and data will be entered into a secured and encrypted database using REDCap. See Table 1 for timing of measures. Sociodemographic measures will assess participant age, sex, marital status, ethnicity, employment status, occupation, years of education, and socioeconomic status. Tobacco use history will assess years of smoking, age of smoking onset, average number of cigarettes per day, number and recency of previous 24-hour quit attempts, number of smokers in the household, prior use of nicotine replacement therapy and other stop smoking medications, and history of receiving smoking cessation counseling. It will also assess tobacco type, brand, frequency, quantity, and duration of use all of nicotine/tobacco products including cigars, cigarillos, little cigars, pipe tobacco, chewing tobacco, snuff, snus, EC/vape/mod/APV/e-hookah, combusted tobacco hookah, and dissolvable tobacco. Cigarette Dependence will be measured with the 12-item Cigarette Dependence Scale.[118] Exhaled carbon monoxide will be assessed at the start of each study visit. Abuse liability of products will be measured across several domains 1) smoking puff topography, 2) subjective effects, 3) behavioral economic choice tasks, and 4) craving for and suppression of craving and withdrawal. Smoking puff topography will be measured using the eTOP which uses a pressure transducer integrated into a plastic cigarette holder to produce measures of puff count, puff duration, inter-puff-interval, puff flow rate, average puff volume, and total puff volume. Puff topography is a validated and sensitive behavioral measure of abuse liability, is highly stable and associated with level of dependence and predicts level of exposure to harmful tobacco-related toxicants.[119-121] An adapted version of the Drug Effects/Liking Questionnaire[122] will assess the desire and liking of UBMC and all three study products, positive and negative effects (i.e., side effects), and perceived strength and effectiveness. The modified Cigarette Evaluation Questionnaire (mCEQ) will also assess subjective responses to cigarettes (e.g., reward, satisfaction).[123,124] The Cigarette Purchase Task[125,126] will ask participants how much they would be willing to pay (ranging from 0¢ to $1,120) to smoke each product. Given that the study products will look similar to cigarettes, we will retain the original language (e.g., "1 cigarette") in the purchase task. Willingness to spend more will indicate greater abuse liability. Smoking urges/craving will be measured using the Tiffany-Drobes Questionnaire of Smoking Urges: Brief Form.[127] This is a 10-item measure where participants rate smoking-related items ("All I want right now is a cigarette.") on a 7-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. Similar to previous studies, we will collapse the items into two previously identified factors (Factor 1: strong desire and intention to smoke; Factor 2: anticipation of relief from withdrawal symptoms). Nicotine withdrawal will be assessed using the empirically validated 15-item version of the Minnesota Nicotine Withdrawal Scale.[128] This measure assesses smoking craving, anger/irritability, anxiety, depressed mood, restlessness/difficulty concentrating, increased appetite, sleep problems, and somatic symptoms (nausea, constipation, sore throat, dizziness, coughing). Subjective effects (daily diary) of the Phase 2 substitute product will be derived from daily diaries assessing product satisfaction and pleasure. Substitutability of products will be assessed using a Cross-Price Task, a Progressive Ratio (PR) Task and daily diaries. A Cross-Price Task in Phases 1 and 3 will estimate substitutability of the study product for the UBMC.[129,130] Participants will be asked how many study products and UBMCs they would consume when the price of the study product is fixed at $1 and the UBMC prices escalate. The data are then fit to an exponential equation that indicates whether the fixed-price product substitutes for the primary product, and the degree of substitution. Cross price elasticity (CPE) for each study product compared to UBMC > 0.2 indicates substitution, CPE < -0.2 indicates complementarity, and CPE between -0.2 and 0.2 indicate independence of the two products.[131] Consistent with previous studies conducted by Dr. Tidey,[89,93,94,132,133] the PR task will simulate the effect that restricting menthol in cigarettes would have on increasing (or not) preference for other alternative menthol substitutes. Participants will complete a 90-minute concurrent choice task with differential cost (effort) required to earn the reinforcement (2 puffs) from their UBMC and the study product (mFLC, mRYO or nmC). Puffs from the study product can be earned by clicking a computer mouse 10 times on a picture of the study product, but to earn two puffs of the UBMC, they will be required to make escalating response requirements (computer mouse clicks) according to the following schedule: 10, 160, 320,

640, 1280, 2400, 3600, 4800, 6000, 7200. A maximum of 10 reinforcers (20 puffs) per session will be allowed. The proportion of reinforcers earned is considered to provide an index of the strength of the reinforcing effects of the product. Participants will be informed of the differential sequence between products and instructed that the sessions are 3 hours in length no matter how much or how little they respond. Daily diaries will assess UBMC/study product smoked per day, product satisfaction and pleasure (see Table 1 for specific daily diary measures). Substitution assessed via use behavior during Phase 2 will be operationalized as the ratio of study product to UBMC used, with a ratio > 0 indicating any substitution and a ratio > 1 indicating substitution of study product for the UBMC at least 50% of the time.

Table 1. Measures

Measures	**Phase 1:**			**Phase 2:**	**Phase 3:**
	3 in-lab visits			**1-week**	***Final Lab***
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Background Measures					
Exhaled CO Abstinence verification	X	X	X	X	X
Pregnancy Test	X	X	X	X	X
Exhaled carbon monoxide	X	X	X	X	X
Breath Alcohol Concentration (BrAC)	X	X	X	X	X
Taste testing strips (PROP)	X				
Sociodemographic measures	X				
Cigarettes Use/Tobacco Use Hx (EDSHC)	X				
Menthol Subscales	X				
Readiness Rulers	X				
Product Use Status	X				
Product Use Detailed Assessment	X				
Fagerstrom	X				
Abuse liability					
Smoking topography	X	X	X	X	
Drug Effects/Liking Questionnaire	X	X	X	X	X
Modified Cigarette Evaluation Questionnaire (mCEQ)	X	X	X	X	X
Tiffany-Drobes Questionnaire of Smoking Urges: Brief Form (modified)	X	X	X	X	X
MNWS	X	X	X	X	X
Cigarette Purchase Task	X	X	X	X	X
Subjective effects	X	X	X	X	X
Substitutability					
Cross Price Elasticity Task		X	X	X	X
Progressive ratio task (UBMC vs. study product - computer task)					X
Record final product selected				X	
Use behavior (Daily Diary)	X			X	
Daily diary					
· # Study products smoked				X	
· # Non-study products smoked	X			X	

· Other tobacco use	X			X	
Modified Cigarette Evaluation Questionnaire (mCEQ)	X			X	
Drug Effects/Liking Questionnaire	X			X	
Behavioral Intentions				X	
Tiffany-Drobes Questionnaire of Smoking Urges: Brief Form (modified)	X			X	
MNWS	X			X	

E. Statistical Methods

1. Power Analysis

Since our main goal is to evaluate the substitutability of menthol alternatives in the context of a menthol cigarette ban, statistical power is based on differences in abuse liability measures (Hypothesis 1a) and product substitution (Hypothesis 2c). Sample size estimates relied on means and standard deviations of data collected as part of a University of Vermont laboratory study examining the abuse liability of cigarettes containing different doses of nicotine.[89] A sample size of 80 subjects has 81% power to detect decreases in product satisfaction of up to 50% compared to their usual brand (mean for UBMC 5.5, SD 1.3). In addition, a sample size of 80 participants has greater than 80% power to detect decreases of 68%-72% in the cigarette purchase task indices of maximum expenditure, maximum price and price sensitivity. This sample size also provides 81% power to estimate 80% use of the preferred alternate product more than half the time during Phase 2 with a 95% confidence interval of 66%-94%.

2. Data Analytic Plan

Statistical analyses will be performed using SAS 9.4 and an alpha of .05. Background measures will be summarized by product (UBMC, mFLC, mRYO, nmC), as appropriate. Continuous variables will be presented as mean ± SD; categorical variables will be presented as counts and proportions. We will apply a transformation to normalize the distribution and stabilize the variance of the residuals where appropriate.

Hypotheses 1a and 1c: We will use Repeated Measures Analysis of Variance with Tukey-adjustment to examine differences between the alternatives and the UBMC in abuse liability assessed at each product lab session. Assuming statistically significant product differences, this post-hoc test will allow us to not only compare each product to the UBMC, but will also allow comparison of the alternative products with each other. Because product introduction in Phase 1 will be randomized using a Latin Square, a fixed effect for session and a random effect for sequence will be included in all analyses.

Hypothesis 2a: Product preference will be examined using a Chi-Square Test, comparing the proportions of participants choosing each alternate product for further use.

Hypothesis 2b: We will examine the trajectory of use behavior outcomes using Linear Mixed Model (LMM) regression analysis. We will employ a random intercept or slope parameter, as appropriate, and model the covariance structure for the repeated outcome measures, while accounting for potential confounders, including gender and baseline cigarettes/day.

Hypothesis 2c: This aim will be analyzed as a Chi-Square Test of Goodness of Fit to test the proportion of use compared to 80%.

Hypothesis 3: We will examine whether differences in product characteristics and changes in perceived effects collected via daily diary are associated with increased substitution of the alternate product over the seven-day period using generalized LMM regression analysis, similar to that outlined in H2b.

Exploratory analyses regarding moderation: For both lab session measures in phase 1 and product substitution in phase 2, we will examine whether age moderates the differences in abuse liability measures and perceived effects of the abuse liability on use behavior outcomes by including an age-by-predictor effect in all analyses. Age will be dichotomized at less than 25 years of age compared to age 25 or older to conform to the recruitment strategy.

3. Missing Data

In the event of missing data, we will contact participants immediately or censor at the point of loss if they cannot be contacted. If the combined missing rate is very small (<5%) and the data are confirmed to be missing at random, then we may safely perform the data analysis on the available data using maximum likelihood procedures. If the missing rate is high, then we will explore sequential multiple imputation (SMI).

F. Gender/Minority/Pediatric Inclusion for Research

1. Inclusion of Women and Minorities

According to 2018 US Census estimates, 51.3% of Columbus residents are female. We expect that the proportion of female participants will likely be somewhat larger given our previous studies with smokers (55-62% female). According to 2018 US Census estimates, the racial composition of individuals living in Columbus is 60.5% White, 28.3% Black or African American, 5.2% Asian, 0.2% American Indian/Alaska Native, 0.0% Native Hawaiian/Other Pacific Islander, and 4.1% two or more races. The ethnic composition of individuals living in Columbus is 6.0% Hispanic/Latino and 94.0% Non-Hispanic/Latino. We expect that our distribution will be similar to these but may potentially have a larger distribution of ethnic and racial minorities, given our previous studies and that menthol smokers tend to more often be black or Hispanic. However, we will continuously monitor enrollment in order to ensure that we are meeting recruitment goals to avoid under-recruiting minorities. If the targeted enrollment for minorities is not met because they do not respond to the advertisements, we will make special efforts to solicit their participation by advertising in community newspapers, local church organizations, and community centers.

2. Inclusion of Children

Participation in the proposed study will be restricted to individuals 21 to 50 years of age. This exclusion is for two primary reasons: 1) the use of tobacco products by minors is illegal, and 2) the concern of introducing and potentially addicting children and adolescents to another tobacco product.

G. Human Participants

1. Recruitment and Informed Consent

At first contact, all participants will be screened according to the study's inclusion/exclusion criteria. Those who are eligible will be given a brief verbal overview of the study and invited to participate. Informed consent (including a description of the nature, purpose, risks, and benefits of the study) will take place through both oral and written explanation of the study. The voluntary nature of the study and the participant's right to withdraw at any time will be stressed during the consent process; a copy of the informed consent will be provided to the

participant in written form at the time of consent for them to keep. Informed consent will be collected by IRB approved study personnel. Recruitment script and materials, consent forms and all study procedures will be approved by the OSU Institutional Review Board. All participants will provide written consent before any study data is collected.

1. Potential Risks and Protections Against Risk

There are minimal risks associated with this protocol. The protocol requires menthol smokers 21 to 50 years of age and older to undergo 12 hours of tobacco/nicotine abstinence on six occasions and to attempt to substitute another combusted mentholated nicotine product for their current combusted mentholated nicotine product. Tobacco/nicotine abstinence can lead to withdrawal symptoms that include irritability, anxiety, restlessness, hunger, and difficulty sleeping.[126] The effects can be uncomfortable but are not dangerous. Risks and side effects related to the cigarette products that are commercially available include:

- Nicotine addiction: Nicotine is a highly addictive chemical found in cigarettes, and toxic at certain doses. It negatively affects the brain, nervous system and heart, and excessive exposure can result in poisoning, particularly in young children and pets. It also causes blood vessels to contract, increasing your blood pressure and pulse rates.
- Chronic diseases including COPD, bronchitis, emphysema, coronary heart disease, stroke and cancer.
- Smoking can also cause infertility and peptic ulcer disease, as well as slow the healing of wounds. It's the leading cause of preventable illness and death in the U.S.

The risk associated with substituting one combustible menthol product for another is also low. It is very unlikely that there is any difference in the level of harm between the participants' usual brand and the study products; therefore, substitution is unlikely to increase participants' exposure to harmful constituents over their usual brand. We are also attempting to mitigate the risk of artificially increased use due to receiving product by only giving participants study products in a 1.2 to 1 ratio.

We will withdraw participants who become pregnant, begin to breastfeed or receive diagnosis for a cardiovascular disease during the course of the study.

The risk of undermining smoking cessation is also potential risk; however, we will only recruit smokers not currently engaged in a smoking cessation attempt, and we will provide all participants at the end of the study with a referral to the Ohio Tobacco Quit Line (1-800-QUIT-NOW).

Protection against loss of confidentiality and privacy will be maintained by numerically coding all data, disguising identifying information, and keeping data locked in file drawers or in a secure, password-protected database. Only study research assistants and the PI will have the information that connects participant's name and ID number. All electronic data will be numerically coded and stored in a password protected database, on a password protected computer in a secure research space. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical conduct of research (i.e., both HIPAA and CITI trainings). Identifying information will not be reported in any publication.

2. Potential Benefits of the Proposed Research

Whereas no assurance can be made to an individual participant that s/he will personally benefit from this research, the experience should be beneficial. The immediate benefits of this research are scientific in nature, which in the long-term should benefit society as a whole. The study will also benefit menthol smokers as a group by providing information as to the abuse liability of other mentholated products; and serve as evidence to inform regulatory action that improves public health. Overall, it is expected that the potential benefits to

participants in the proposed study outweigh the potential risks.

H. Data and Safety Monitoring Plan

Data will be analyzed initially after 20 participants are accrued, to ensure electronic data capture systems employed (i.e., REDCap) are accurately capturing data and to ensure the format and completeness of all data collected.

1. Adverse events

Adverse events will be assessed by study staff at each follow-up visit via participant self-report and managed immediately. All adverse events will be reported to the OSU IRB. We will monitor for risk of smoking by screening participants for general medical precautions (pregnancy, cardiovascular disease). Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be discussed immediately between study personnel and Dr. Wagener. Dr. Wagener will be responsible for completing an Adverse Events Form should an event occur. Dr. Wagener will report Serious Adverse Events to the OSU IRB within 24 hours of having received notice of the event. Dr. Wagener will gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the OSU IRB and the Program Officer at NIH. Adverse event reports will be reviewed annually with the OSU IRB to ensure participant safety.

Collection of Adverse Events

The collection of adverse events will be on a self-report basis and logged within an electronic data capture system (REDCap) or collected using standardized paper forms and will only be identified with the study's ID of the participant.

Addendum

COVID-19 Related Procedures

Due to the COVID-19 pandemic, processes and procedures have been implemented to help protect participants and research staff. These processes and procedures are to be followed as long as social distancing requirements are necessary for conducting study visits.

Only one study participant per study coordinator will attend study visits at the CTR at any given time. All study participants will be provided with a face mask upon entry. Only one coordinator will meet the participant at their car for a temperature check**,** direct the participant into the building, and the two of them will ride the elevator to the 4th floor physically distanced at least 6 ft apart, both wearing masks. No more than 2 persons may ride the elevator at any given time. The participant will be immediately escorted to a private exam/draw room. Therefore, there will be no waiting in open lobby/waiting areas.

When in the exam room, the study coordinator will stand at least 6 feet away from the study participant to give instructions. Afterwards, the study coordinator will leave the exam room to allow the study participant to conduct the instructed procedures. The study coordinator and study participant will be at least 6 feet away from one another and wearing protective masks at all times during each visit.

Each study coordinator will have a designated exam/draw room and smoking room in which to conduct their designated research study. Each smoking room is separated from the staff control station in the hallway by its own door and contains a large window for the study coordinator to be able to see in and monitor study participant activity within the room. There is also a speaker and microphone system within each smoking room

along with the Genetech software system on the outside of each room at the smoking room computer stations. Therefore, the study coordinator and study participant can communicate without being in the room together.

For study measures which cannot be physically distanced, appropriate PPE will be worn at all times by research staff during these procedures including goggles, face masks, gloves, and isolation gowns or lab coats.

After each participant visit is complete, there will be at least a 45-minute period for cleaning and air exchanges in the negative pressure rooms and for cleaning exam rooms and equipment before the next participant visit. All smoking rooms are under negative pressure with a ventilation rate of 36.8 – 44.1 air changes per hour (ACH).

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