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THE INFLUENCE OF FLAVOR ON THE ABUSE LIABILITY OF A HEATED TOBACCO PRODUCT AND ITS FEASIBILITY AS A MENTHOL CIGARETTE SUBSTITUTE

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (PhD) at Virginia Commonwealth University

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bpm	Beats per minute
CC	Combustible Cigarettes
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPE	Cross Price Elasticity
CSTP	Center for the Study of Tobacco Products
CTP	Center for Tobacco Products
EMA	Ecological Momentary Assessment
ENDS	Electronic Nicotine Delivery System
ETM	Experimental Tobacco Marketplace
EU	European Union
FDA	Food and Drug Administration
HPHC	Harmful or Potentially Harmful Constituents of tobacco
HTP	Heated Tobacco Products
IOM	Institute of Medicine
IPI	Inter-Puff Interval
IQOS-M	IQOS 2.4 paired with Fresh Menthol HeatSticks
IQOS-T	IQOS 2.4 paired with Regular/Tobacco HeatSticks
IQR	Interquartile range
IRB	Institutional Review Board

ITC	International Trade Commission
mg	Milligrams (0.001 grams)
min	Minute(s)
mL	Milliliter
mmHG	Millimeters of mercury
MNWS	Minnesota Nicotine Withdrawal Scale
MRTP	Modified Risk Tobacco Product
ng	Nanograms (0.0000000001 grams)
NNAL	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
NRT	Nicotine Replacement Therapy
NVP	Nicotine Vaping Products (includes ENDS, HTPs, and ONPs)
OB	Own Brand (cigarette)
ONP	Oral Nicotine Products
PEQ	Product Evaluation Questionnaire
PMI	Philip Morris International
PNS	Peripheral Nervous System
ppm	Parts per million
PROMIS	Patient Reported Outcomes Measurement Information System
QSU-B	Questionnaire of Smoking Urges – Brief
sec	Second(s)
TLFB	Timeline Follow Back
US	United States
VAS	Visual analog scale

VTA	Ventral Tegmental Area
WHO	World Health Organization

Abstract

THE INFLUENCE OF FLAVOR ON THE ABUSE LIABILITY OF A HEATED TOBACCO PRODUCT AND ITS FEASIBILITY AS A MENTHOL CIGARETTE SUBSTITUTE

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (PhD) at Virginia Commonwealth University

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Heated Tobacco Products (HTPs) purport to expose people that use cigarettes to fewer of the harmful or potentially harmful constituents of tobacco while still delivering reinforcing amounts of nicotine (Auer, Concha-Lozano et al., 2017). An exemplar of the HTP class, IQOS, and its three varieties of "HeatSticks" have been authorized by the Food and Drug Administration (FDA) as "Modified Risk Tobacco Products" (MRTP). However, as the FDA is planning to ban menthol as a characterizing flavor in cigarettes, questions remain regarding whether characterizing flavors should be permitted in HTPs (FDA, 2022e). New evidence regarding HTP abuse liability (i.e., the likelihood that a tobacco product will produce and maintain dependence and long-term use) is needed now to inform regulatory action (Carter, Stitzer et al., 2009). This study aimed to measure the abuse liability of IQOS as a function of its available flavors (menthol and regular/tobacco) among adults that smoke menthol cigarettes across five dimensions: nicotine delivery, puff topography, self-reported effects (sometimes referred to as "subjective effects"), behavioral economic demand, and naturalistic use.

Thirty adults that smoke menthol cigarettes completed a two-week, parallel group pilot clinical trial. During week 1, participants used their own brand (OB) menthol cigarettes in clinical laboratory sessions (Mon, Fri; two hours each day) and at home (Tues-Thurs). During week 2, participants were randomized to receive IQOS 2.4 with either Fresh Menthol (IQOS-M) HeatSticks or Tobacco/Regular (IQOS-T) HeatSticks to use in clinical laboratory sessions (Mon, Fri; two hours each day) and at home as a substitute for OB menthol cigarettes (Tues-Thurs). During each of the four clinical laboratory sessions, participants completed a 10-puff directed use bout with that week's designated product. Each clinical laboratory visit involved measurement of the session product's plasma nicotine delivery, puff topography, and self-reported effects as well as completion of a behavioral economic task known as the Experimental Tobacco Marketplace (ETM). Electronic daily-diary ecological momentary assessments (EMA) measured participant's tobacco consumption while at home during the two-week study period.

IQOS served as a stronger substitute for OB menthol cigarettes in the ETM task when Fresh Menthol HeatSticks were available for purchase compared to a "restricted market" that did not offer Fresh Menthol HeatSticks ($p < 0.05$). When participants were given IQOS products to use at home during week 2, the median participant in IQOS-M group reduced their daily cigarette consumption by 80% (relative to consumption during week 1) and the median participant in the IQOS-T by 37% ($p < 0.05$). Clinical laboratory results following acute self-administration procedures suggested that IQOS-M may suppress cravings for cigarettes ($p < 0.10$) as well as urges to smoke ($p < 0.05$) to a greater extent than IQOS-T among adults that use menthol cigarettes. Participants also reported enjoying the taste and overall flavor sensation associated with using IQOS-M more than IQOS-T (each $p < 0.05$). Differences in puff topography parameters and nicotine delivery across participants that used IQOS-M and

participants that used IQOS-T in the clinical laboratory were relatively minor and not statistically significant (each $p > 0.05$). OB menthol cigarettes delivered more nicotine and were rated more favorably by participants with respect to flavor enjoyment, positive reinforcement, and negative reinforcement than either flavor of IQOS (each $p < 0.05$).

Results of this investigation suggest that IQOS-M may have greater abuse liability and be a more compelling substitute for cigarettes than IQOS-T among people that use menthol cigarettes. The enhanced abuse liability of IQOS-M (relative to IQOS-T) among people that use menthol cigarettes might be the result of menthol-associated positive reinforcement or menthol's possible role as a conditioned-stimulus of smoking behavior (Ahijevych & Garrett, 2010). Importantly though, OB menthol cigarettes appeared to have greater abuse liability than IQOS-M and IQOS-T, raising questions about whether IQOS could substitute for menthol cigarettes completely. This study contributes new evidence to the HTP literature that menthol flavor may increase HTP abuse liability but be *insufficient* to support complete substitution for people that smoke menthol cigarettes when both products are available. Tobacco regulatory policies that restrict access to menthol-flavored HTPs may reduce substitution with HTPs following a menthol cigarette ban but might promote attempts at complete smoking cessation in the post-ban period.

The influence of flavor on the abuse liability of a heated tobacco product and its feasibility as a menthol cigarette substitute

Despite significant reductions in the prevalence of smoking from its peak in the mid-1960s, use of combusted tobacco products remains the leading cause of preventable morbidity and mortality in the United States (US; CDC, 2023). Though rapid and consistent declines in smoking were realized in the latter half of the 20th century, the prevalence of smoking in the US has stabilized between 10-20% since the mid-2000s; as of 2021, the US adult smoking prevalence was estimated at 11.5% (CDC, 2023). The resilience of smoking in the face of its established harms can be attributed in part to the dependence induced by tobacco product use as well as to a lack of effective and accessible cessation strategies.

The persistence of smoking has led some to advocate for "tobacco harm reduction" – a clinical and political perspective that encourages people that smoke and are unable to quit to instead switch to a less harmful nicotine delivery vehicle than cigarette smoke (Hatsukami & Carroll, 2020). Tobacco harm reduction has been seen as a business opportunity by the tobacco industry in recent years (Peeters and Gilmore, 2013), contributing to the rise of product classes such as electronic nicotine delivery systems (ENDS; also known as "e-cigarettes" or "vapes"), oral nicotine products (ONPs), and heated tobacco products (HTPs). The utility of ENDS, ONPs, and HTPs to support tobacco harm reduction for people that smoke relies on whether these products are truly "lower harm" than cigarettes and their capacity to facilitate *complete substitution* away from a higher harm product (Abrams, Glasser et al., 2018; Hatsukami & Carroll, 2020; Martin, Warner et al., 2004). Additional considerations for evaluating the public health utility of tobacco harm reduction products include whether ENDS, ONPs, and HTPs maintain tobacco use among people that would otherwise quit or could be used to attract

tobacco-naïve individuals to prolonged nicotine/tobacco use (Cobb, Byron et al., 2010; Martin, Warner et al., 2004; Chen, Grigg et al., 2024).

The complexity associated with managing the US tobacco marketplace contributed to Congress' action to grant regulatory authority over tobacco products to the Food and Drug Administration (FDA) as part of the 2009 Family Smoking Prevention and Tobacco Control Act. The Act charged the FDA with taking actions "appropriate for the protection of the public health" and the agency was equipped with the power to create product standards, conduct premarket review, and enforce regulations associated with the manufacture, distribution, and marketing of tobacco products (Carvajal, Clissold et al., 2009). Alongside these developments, the field of *tobacco regulatory science* has burgeoned so that regulatory activity could be guided by an empirical evidence-base (Ashley, Backinger et al., 2014).

In recent years, the role of *characterizing flavors* has become an important target of tobacco regulatory policies (Bansal-Travers, Price et al., 2023; Higgins, Kurti et al., 2019; Patten & De Biasi, 2020). In April 2022 the FDA issued a proposed product standard that would ban *menthol* as a characterizing flavor in cigarettes (FDA, 2022e). FDA did not propose a formal definition of "characterizing flavor" in its proposed rule, but noted the following factors would be considered when determining if a product or any of its components (e.g., filter, tobacco, paper) has a characterizing flavor other than that of "tobacco": the presence and amount of artificial or natural flavor additives/ingredients, the multisensory experience (e.g., taste, aroma, cooling, burning, etc.) associated with a flavor during use of a tobacco product, flavor representation in product messaging or advertising, or other means to impart flavor to a tobacco product (FDA, 2022e). In contrast, the European Union's (EU) Tobacco Product Directive provides a more formal definition of a characterizing flavor as: "a clearly noticeable smell or

taste other than one of tobacco, resulting from an additive or a combination of additives which is noticeable before or during the consumption of the tobacco product" (European Commission, 2014; Talhout, van de Nobelen et al., 2016).

FDA's proposed regulatory action banning menthol as a characterizing flavor in cigarettes sold in the US has the potential to bring about profound public health benefits (Levy, Meza et al., 2021). However, the realized gains of a menthol ban will depend upon how people that smoke menthol cigarettes respond: will they quit, continue smoking, or switch to other tobacco products (Fong, Chung-Hall et al., 2022)? Complicating this discussion, whether characterizing flavors should be retained in non-combusted tobacco products (including those championed under the banner of "tobacco harm reduction" and/or that are designated as "modified risk tobacco products" [MRTPs] by the FDA) is yet to be resolved. Apart from two very low nicotine cigarettes and several snuff/snus products, the only other product to achieve MRTP status in the US is an HTP called IQOS (FDA, 2022c).

In FDA's proposed product standard banning the sale of menthol cigarettes, it was noted that "HTPs which meet the regulatory definition of a cigarette" would be subject to the ban (FDA, 2022e). Recent judicial review has concluded that IQOS does meet the regulatory definition of a cigarette and thus would be subject to the proposed menthol ban (*United States v. Philip Morris USA Inc, et al.,* 2023). However, in the proposed product standard, FDA stated that they would consider exemptions to the ban on a "case-by-case basis" for products that "present unique public health considerations" (FDA, 2022e). Under a tobacco harm reduction framework, the strongest case for an exemption from the menthol ban would be made by an HTP that can demonstrate strong health risk reduction potential and sufficient appeal to facilitate complete substitution from combustible cigarettes (Abrams, Glasser et al., 2018). This work focuses on the

latter consideration in the context of HTPs/IQOS and as a function of HTP flavor availability (menthol versus "regular" [i.e., tobacco-flavored]) among adults that use menthol cigarettes.

Earlier work with individuals that use menthol cigarettes suggests that responses to a menthol ban may be sensitive to the availability of non-tobacco characterizing flavors in products such as ENDS, ONPs, and HTPs (Denlinger-Apte, Cassidy et al., 2021; White, Goden et al., 2023). Yet, important unanswered questions regarding the availability of characterizing flavors like menthol in HTPs remain, such as: do flavors alter the nicotine delivery, use behaviors, subjective experiences, and purchasing patterns associated with HTPs among people that use menthol cigarettes (FDA, 2022d)? Prospectively understanding how tobacco use behaviors following a menthol ban may differ across alternative flavor availability policy scenarios for non-combusted tobacco products (e.g., HTPs), utilizing techniques to index abuse liability (i.e., the likelihood that a tobacco product will produce and maintain dependence and long-term use), holds enormous utility in guiding regulatory action (Carter & Griffiths, 2009; Carter, Stitzer et al., 2009). The abuse liability of tobacco products can be measured using validated assessments (e.g., drug self-administration studies, self-reported effects [sometimes referred to as "subjective effects"] questionnaires, behavioral economic tasks) in the controlled-environment of the clinical laboratory as well as in the more externally valid setting of a participant's natural (i.e., at home) environment (Carter & Griffiths, 2009).

By leveraging validated abuse liability assessments in the clinical laboratory as well as in naturalistic settings among a sample of adults that use menthol cigarettes, this work endeavors to provide novel evidence on the tradeoffs associated with *including* or *not including* IQOS in the broader menthol ban. Moreover, the present investigation intends to generate needed evidence to inform understanding of the abuse liability of modern HTPs. The following sections describe the

literature surrounding: the role that menthol plays in tobacco products, HTPs as a class of tobacco products with possible unique considerations for public health, and how abuse liability assessments are used as a tool for tobacco regulatory science.

Cigarette Design and the Role of Menthol in Tobacco Products

The modern cigarette is best understood as a highly-engineered drug delivery system (Talhout, Richter et al., 2018). Combustible cigarettes consist of a rod of processed tobacco that is wrapped in paper and capped with a filter (Talhout, Richter et al., 2018). When a cigarette is lit (via the chemical processes of combustion, pyrolysis, and distillation), smoke containing nicotine and other compounds known to be harmful to human health is generated then inhaled by the user (Baker, 1981, 2006; Forster, Liu et al., 2015). For decades, the tobacco industry has manipulated the constituents of cigarettes to reduce the negative experiences (e.g., irritation) and increase the positive experiences (e.g., taste) associated with smoking while also optimizing the speed and dose of nicotine delivered to the blood stream (Talhout, Richter et al., 2018).

While nicotine has been established as the primary pharmacologic reinforcer (i.e., a drug that will "increase the future occurrence of a responses [i.e., smoking] if its administration is contingent upon that responses" [Meisch & Lemaire, 1993]) associated with smoking (Henningfield & Goldberg, 1983; Henningfield & Keenan, 1993; Palmatier, Liu et al., 2007), it is far from the only compound contained within cigarettes that may contribute to dependence (Caggiula, Donny et al., 2009). For example, *menthol* is a naturally-occurring compound that tobacco manufacturers often add to tobacco products. Menthol can be added either in small amounts (0.002-0.07 mg/cigarette) or in sufficient levels to become the characterizing flavor (2.9-19.6 mg/cigarette) of a tobacco product (Ai, Taylor et al., 2015). The addition of menthol to

tobacco products has important implications for dependence and sustaining the health-related burdens associated with tobacco use (Ai, Taylor et al., 2015). Menthol has been the only characterizing flavor permitted in cigarettes sold in the US since passage of the 2009 Tobacco Control Act. Here, "menthol cigarettes" are defined as those combustible cigarettes that feature menthol as a characterizing flavor of the product and all other cigarettes are considered "nonmenthol cigarettes."

Menthol's Chemistry and Biological Activity

In nature, menthol is found in the highest concentrations in peppermint plants but the compound can also be derived synthetically. Menthol (5-methyl-2-(propan-2-yl)cyclohexan-1-ol) is a monoterpenoid with a waxy appearance and a wide-range of biological activity (Wishart, Knox et al., 2006). In the context of combustible cigarette smoking, menthol has been shown to mask tobacco's harshness with a "minty and cooling" sensation (Ahijevych et al., 2010), facilitate longer and more voluminous puffs (Ahijevych & Parsley, 1999; Lawrence, Cadman et al., 2011), and increase the bioavailability of nicotine (Benowitz, Herrera et al., 2004; Henderson, Wall et al., 2017) through a variety of mechanisms.

Owing to the intrinsic properties of nicotine and other tobacco constituents, the sensory experience of using tobacco products can be aversive (e.g., bitter tastes, throat irritation, burning sensations, coughing; Carstens & Carstens, 2022). Menthol can ameliorate some of these aversive effects. Via its interaction with TRPM8 receptors in the epithelial linings of the upper airway, menthol carried in smoke has "anti-tussive, anti-irritant, and cooling properties" (Wickham, 2020). The interaction with the TRPM8 receptor is also believed to mask the natural bitterness of nicotine as preclinical studies involving mice and rats have shown that menthol

increases consumption of nicotine containing liquids (Bagdas, Cam et al., 2020; Fait, Thompson et al., 2017; Wang, Wang et al., 2014). Additionally, menthol is an agonist of kappa-opioid receptors which can reduce the pain associated with throat irritation (Galeotti, Di Cesare Mannelli et al., 2002). Menthol's sensory effects are thought to be most pronounced in people that started smoking recently or are inexperienced users of nonmenthol cigarettes that switch to using a mentholated product, potentially contributing to larger puff volumes and greater exposure to nicotine (Watson, Richter et al., 2017; Wickham, 2020).

Once inhaled and absorbed into the blood stream across oral mucosa and pulmonary capillaries, menthol crosses the blood-brain-barrier and influences the activity of the central nervous system (CNS). The primary effects of menthol in the CNS involve alterations of the expression, structure, and activity of nicotinic acetylcholine receptors (nAchRs; Wickham, 2020). One study interrogated the expression level of nAchRs isoforms in people that smoke and found elevated levels of $\alpha 4\beta 2$ subunits but noted that the elevation was greater among people that used menthol cigarettes (Brody, Mukhin et al., 2013). Similarly, a preclinical murine model demonstrated that coadministration of menthol alongside nicotine caused elevations in the $\alpha 4$ and $\alpha 6$ subunits of nAchRs in the ventral tegmental area (VTA; Henderson, Wall et al., 2017). The preferential expression of $\alpha 4\alpha 6\beta 2$ nAChR subunits may increase glutameterigic drive on dopaminergic neurons, increasing neuronal excitability to nicotine (Berry, Engle et al., 2015; Liu, Zhao-Shea et al., 2012). Menthol also appears to exert allosteric modulation over nAchRs by reducing the amount of time the receptors spend in the "open" state (Ashoor, Nordman et al., 2013; Hans, Wilhelm et al., 2012) and preventing desensitization to nicotine (Henderson, Wall et al., 2016). The sum of these data suggest that nicotine is acting on a more sensitive subtype of

nAchR receptors in the VTAs of people that use menthol versus nonmenthol cigarettes (Wickham, 2020).

Apart from its sensory and CNS activity, menthol has peripheral activity with important implications for tobacco use and dependence. For example, menthol decreases the metabolic clearance of nicotine as much as two-fold via inhibition of CYP2A6 in the liver (Alsharari, King et al., 2015; Benowitz, Herrera et al., 2004; Pérez-Stable, Herrera et al., 1998). In humans, inhibition of CYP2A6 could explain why people that use menthol cigarettes are slower metabolizers of nicotine than people that use nonmenthol cigarettes (Valentine, DeVito et al., 2018). The precise mechanism of this inhibition is believed to result from CYP2A6 metabolizing menthol in place of nicotine when the two compounds are co-administered (Miyazawa, Marumoto et al., 2011). The result of the preferential hepatic metabolism of menthol is that the bioavailability of nicotine is increased. Counterintuitively though, slower metabolism of nicotine has been associated with *lower* cigarette dependence scores (Johnstone, Benowitz et al., 2006; Lerman, Tyndale et al., 2006). Apart from its metabolic effects, menthol can also increase salivary flow, dilate bronchial pathways, and increase transbuccal drug absorption (Squier, Mantz et al., 2010). Much work remains to be done to understand the complex interaction observed with menthol's effects on nicotine metabolism/bioavailability and subsequent CNS activity.

Apart from its inclusion in tobacco products, menthol has been incorporated into other consumer products including "vaporubs," shampoos, throat lozenges, and balms (Kamatou, Vermaak et al., 2013; Patel, Ishiuji et al., 2007; Wickham, 2020). Menthol is desirable in various consumer products because its cooling and anesthetic properties are conserved across different routes of administration (Kamatou, Vermaak et al., 2013; Patel, Ishiuji et al., 2007; Wickham, 2020). In part because of the widespread incorporation of menthol into other consumer products,

there is a misperception among people that use menthol cigarettes that such cigarettes are somehow “safer” or “healthier” than nonmenthol cigarettes (Allen, Cruz et al., 2010; Anderson, 2011). For example, people that smoke menthol cigarettes were more likely to agree with the statements that “menthols are … better for a sore throat… healthier … contain fewer chemical additives …. less harmful … than nonmenthol cigarettes” (Keller, D'Silva et al., 2020). The misperception of safety afforded by menthol has been cultivated and exploited in tobacco industry marketing for decades (Allen, Cruz et al., 2010; Anderson, 2011; Wailoo, 2022). Elevated harm perceptions of smoking are believed to have a positive influence on cessation (Kaufman, Persoskie et al., 2018; Land, Baker et al., 2023; Magnan, Koblitz et al., 2009), so the perception of “safety” offered by menthol is concerning.

The complex set of physiologic and psychologic effects of menthol manifest in the observation that people that use menthol cigarettes use fewer cigarettes per day (Fagan, Pohkrel et al., 2015) but exhibit higher levels of nicotine dependence (Bover, Foulds et al., 2008; Wackowski & Delnevo, 2007). Moreover, people that use menthol cigarettes have been shown to have a greater difficulty quitting than people that use nonmenthol cigarettes (Foulds, Hooper et al., 2010). One exemplar study from this body of literature followed a prospective cohort (N=1500) over a 15-year period and found people that used menthol cigarettes had 0.71 times the adjusted odds of sustained cessation and 1.89 times the adjusted odds of smoking relapse compared to those that used nonmenthol cigarettes (Pletcher, Hulley et al., 2006). Poorer cessation outcomes for people that use menthol compared to nonmenthol cigarettes are most evident among minoritized racial/ethnic groups, such as individuals identifying as African American/Black or Hispanic (Gundersen, Delnevo et al., 2009; Smith, Assefa et al., 2020). The menthol-related disparity in cessation is troublesome considering people that use menthol

cigarettes attempt to quit at similar-to-higher rates than people that use nonmenthol cigarettes (Talluri & Shete, 2023) and that both types of cigarettes exhibit similar lethality (Hoffman, 2011) despite popular beliefs to the contrary (Allen, Cruz et al., 2010).

The Menthol Cigarette Market: Historical Roots and Present Landscape

Per tobacco industry lore, menthol was first added to cigarettes in 1925 after tobacconist Lloyd "Spud" Hughes left his cigarettes in a tin containing menthol crystals for several days (Gardiner, 2004). When Spud smoked the menthol imbued tobacco, he found the cigarettes took on a distinctive flavor and sensory profile. Recognizing the novelty of this combination, Spud began selling menthol cigarettes before being acquired by the Axton-Fisher company (later acquired by Philip Morris), thus ushering in the era of commercially-produced menthol cigarettes.

Menthol cigarettes were considered a novelty product from the 1920s through the 1950s, being marketed primarily towards women as a "health cigarette" or as a "palate cleanser" (Wailoo, 2022). Menthol cigarettes constituted 2% of the cigarette market in the US from 1933-1957, growing to 5% with the introduction of *Salem* and *Newport* in 1957 then to 16% by 1963 (Gardiner, 2004). The commercial success of mentholated products took a fateful turn in 1963 once the tobacco industry – in particular, the manufacturers of *Kool* - identified another potential market for their mentholated products: African American/Black (AA/B) communities.

From 1963 to 1978 the market share of menthol cigarettes grew to 28% then stabilized for around 40 years (Gardiner, 2004). The rise in the popularity of menthol cigarettes was fueled by uptake from AA/B individuals, achieved through a variety of marketing practices implemented with the intent of making menthol cigarettes the "Black cigarette" (Gardiner, 2004;

Wailoo, 2022). For example, the tobacco industry financed the National Association for the Advancement of Colored People, civil rights leaders, and historically Black colleges and universities while positioning menthol cigarettes as a cultural icon of these broader social movements (Gardiner, 2004; Wailoo, 2022; Yerger, 2002). Menthol cigarette manufacturers were one of the largest purchasers of advertising space in publications and billboards that catered to AA/B communities (Wailoo, 2022), often sending readers coupons to buy menthol cigarettes at discounted prices (Richardson, Ganz et al., 2015; Yerger, Przewoznik et al., 2007). Purchasing of menthol cigarettes was enhanced further by the disproportionate concentration of menthol cigarette retailers in urban areas and AA/B communities (Mills, Henriksen et al., 2018). These efforts were effective and have been replicated in recent years to include individuals identifying as LGBTQIA+ and/or as a sexual and gender minority (Fallin, Goodin et al., 2015; Offen, Smith et al., 2003).

Menthol cigarettes constitute 37% of the $60 billion/year modern-day US cigarette market and are used by 18.5 million Americans (CDC, 2023; FDA, 2022b, 2022e; FTC, 2023). Significant disparities exist in the prevalence of menthol cigarette use among people that smoke, in accordance with those groups that have been targeted by the tobacco industry historically. Most strikingly, among AA/B individuals that smoke, an estimated 85% use a menthol cigarette as their normal brand (CDC, 2022). Menthol cigarette use prevalence is also higher among women (44% versus 35% for men; CDC, 2022), Hispanic (48% versus 30% for non-Hispanic; CDC, 2022), and LGBTQIA+ (36% versus 29% for heterosexual; American Lung Association, 2022) individuals that smoke. Greater use of menthol (relative to nonmenthol) cigarettes is also associated with being an individual with a psychiatric condition (Cohn, Johnson et al., 2016; White, Barnes et al., 2023) and youth initiation into prolonged tobacco use (Nonnemaker,

Feirman et al., 2019; Nonnemaker, Hersey et al., 2013). In sum, menthol cigarettes constitute a considerable portion of the US cigarette market, contribute to the health burdens of combusted tobacco use, and their associated use patterns may be driving disparities in tobacco related morbidity and mortality (Cadham, Sanchez-Romero et al., 2020; Delnevo, Ganz et al., 2020; FDA, 2021b).

Menthol Cigarette Bans

In response to the history and harms associated with menthol cigarettes, in 2022 the FDA announced its intent to ban menthol as a characterizing flavor for cigarettes sold in the US (FDA, 2022e). This proposed regulatory action follows on the heels of menthol being banned as a characterizing flavor for cigarettes sold in Massachusetts (2020) and California (2022) as well as the adoption of similar policies in over 100 localities in the US (Campaign for Tobacco Free Kids, 2023). Evidence from the first month of Massachusetts' menthol ban showed a significant reduction in menthol cigarette sales that partially was offset by increases in nonmenthol cigarette purchasing (Asare, Majmundar et al., 2022). Moreover, at one-year post-ban, a convenience sample of people that used menthol cigarettes in Massachusetts reported one-third had quit smoking but two-thirds continued to access menthol cigarettes from neighboring states (McGinnes, Kingsley et al., 2023). Massachusetts' menthol ban also applied to menthol-flavored ENDS products (Asare, Majmundar et al., 2022). Experiences with Massachusetts' menthol ban suggest that for menthol cigarette bans to be most effective, consideration must be given to alternative access points for menthol cigarettes as well as to whether menthol-flavored alternative products (e.g., HTPs) should remain available.

The sale of menthol cigarettes has been banned in multiple international markets. In 2020 the EU banned the sale of menthol cigarettes in its 28 member nations (European Network for Smoking and Tobacco Prevention, 2020). The sale of menthol cigarettes also has been banned in Canada, Brazil, Ethiopia, Senegal, Turkey, and Moldova (Erinoso, Clegg Smith et al., 2020). Evidence from Canada's menthol ban, which took effect between 2015 and 2018, revealed 22.3% of people that used menthol cigarettes were able to quit smoking following the ban's implementation compared to 15.0% of people that used nonmenthol cigarettes (Fong, Chung-Hall et al., 2022). Moreover, 64% of people that used menthol cigarettes attempted to quit smoking after Canada's menthol ban took effect compared to 43% of people that used nonmenthol cigarettes (Chaiton, Papadhima et al., 2020; Fong, Chung-Hall et al., 2022). Extrapolating these results to a possible US menthol ban may translate to 1,337,988 Americans who are daily or non-daily users of cigarettes quitting (Fong, Chung-Hall et al., 2022).

Mapping the experiences of individual states and international peers to what we might expect from a US federal menthol ban, however, is difficult for a number of reasons. Foremost, menthol cigarette use is far more popular among people that smoke in the US than in other countries (e.g., 5% in Canada compared to 37% in the US; Bird, May et al., 2017; Chaiton, Schwartz et al., 2018; Federal Trade Commission, 2023) and features a more racialized disparity in use patterns (Chaiton, Nicolau et al., 2019; Fong, Chung-Hall et al., 2022). A federal ban on menthol cigarettes could also reduce issues posed by the neighboring market problem that were observed in Massachusetts. One set of studies attempted to address these limitations in the literature by modeling the anticipated effects of a federal menthol ban in the US using a mix of empirical data and an expert elicitation approach (Levy, Cadham et al., 2021; Levy, Meza et al., 2021). The resulting compartmental model suggested that adoption of a menthol ban in 2021

could save 650,000 lives by 2060 because of people either quitting or switching to nicotine vaping products (NVPs), a category encompassing ENDS, HTPs, and ONPs (Levy, Meza et al., 2021). The public health gains of a menthol cigarette ban are expected to depend on maximizing quitting following the ban or, for those who are unable or unwilling to quit, switching to NVPs instead of continuing to use combusted tobacco products (Levy, Meza et al., 2021). Importantly, two of the biggest sources of uncertainty in these estimates is how much NVPs reduce tobacco-related harms and how many people that use menthol cigarettes will substitute with an NVP completely (Levy, Meza et al., 2021). The likelihood of an individual that smokes achieving complete substitution with an ENDS, HTP, or ONP may depend on the availability of appealing alternatives (e.g., flavored products) in a post-ban marketplace (Denlinger-Apte, Cassidy et al., 2021; White, Patev et al., 2024; White, Goden et al., 2023).

Now is not the first time the FDA has considered banning menthol as a characterizing flavor in cigarettes sold in the US. The FDA's Tobacco Product Scientific Advisory Council (TPSAC) recommended banning menthol cigarettes in 2011 (Samet, Pentz et al., 2016). However, the tobacco industry sued FDA alleging that three members of TPSAC had conflicts of interest that were managed inappropriately (*Lorillard v. United States Food and Drug Administration,* 2014). As a result, the TPSAC and its report on menthol were determined to be "fatally tainted" and FDA was barred from relying on the report to support a menthol ban (*Lorillard v. United States Food and Drug Administration,* 2014). As with previous efforts to ban menthol, we can expect the current effort to be mired by legal challenges, lobbying efforts, and changes in regulatory priorities.

To survive legal challenges FDA must defend that its actions are neither arbitrary nor capricious by citing evidence from the scientific community. In its proposed rule, FDA has asked

for information on the possible "intended and unintended consequences" of a menthol ban, seeking information on how people that use menthol cigarettes may respond (FDA, 2022). Ultimately, the public health benefit of a menthol ban will depend on the likelihood that people who smoke menthol cigarettes will quit after the ban and, for those who do not quit, that they switch to a lower harm product. Thus, three broad classes of responses may be expected with differing possibilities for public health benefits (Levy, Cadham et al., 2021; Levy, Meza et al., 2021; Levy, Pearson et al., 2011): *cessation* from all tobacco and nicotine products (highest benefit), *switching* to a non-combusted alternative product (intermediate benefit), *continuation* of combusted tobacco use (no benefit). Some public health benefit of a menthol ban would also be realized by reducing initiation into prolonged tobacco use by individuals that do not smoke currently (Levy, Meza et al., 2021).

Nearly half of people that use menthol cigarettes in the US say that a menthol ban would lead them to quit smoking but 20-30% report they would switch to nonmenthol cigarettes; meanwhile, 10-20% report intentions to switch to a non-cigarette alternative like ENDS (D'Silva, Amato et al., 2015; O'Connor, Bansal-Travers et al., 2012; Wackowski, Delnevo et al., 2015). However, these earlier surveys did not include HTPs in their menu of possible cigarette alternatives. Omission of HTPs from the list of possible cigarette alternatives is problematic because HTPs may substitute for cigarettes more effectively than other alternatives due to their use of reconstituted tobacco (as opposed to the liquid solutions that define ENDS), feeling more like a cigarette in the mouth and hands of the user, and their ability to make FDA-authorized reduced exposure claims (Duan, Wysota et al., 2022; East, Miller et al., 2023; Tompkins, Burnley et al., 2020).

In studies involving hypothetical responses to a menthol ban, flavor availability in alternative nicotine delivery systems has emerged as a potential determinant of substitution behaviors for people that use menthol cigarettes (Denlinger-Apte, Cassidy et al., 2021; White, Goden et al., 2023; Yang, Lindblom et al., 2022). The Experimental Tobacco Marketplace (ETM) is a behavioral economic task that measures participant's purchasing of alternative tobacco products as access to their preferred tobacco product is restricted (Bickel, Moody et al., 2017; Quisenberry, Koffarnus et al., 2016). The ETM permits the researcher to manipulate salient features (e.g., flavor availability) of products within a potentially-real marketplace (Bickel, Moody et al., 2017). The ETM is thus a compelling paradigm for studying substitution for menthol cigarettes with products such as HTPs. One study that used the ETM task (HTPs were not included) among a sample of people that use menthol cigarettes concluded "…menthol flavoring, whether in other combusted or non-combusted products, was an important factor for purchasing decisions among people that smoke menthol cigarettes. However, menthol flavoring, depending on the mode of delivery, may be insufficient for fully addressing menthol cigarette cravings. Thus, dual purchasing of e-cigarettes and nonmenthol cigarettes was common" (Denlinger-Apte, Strahley et al., 2023, p. 5). Others have argued that the availability of menthol-flavored ENDS may minimize switching to nonmenthol cigarettes following a ban on menthol cigarettes (Buckell, Marti et al., 2019; Denlinger-Apte, Cassidy et al., 2021; Kotlyar, Shanley et al., 2022). Our own analysis of AA/B people that use menthol cigarettes suggested that a menthol ban would be associated with higher intentions to quit smoking as well as to substitute with alternative product classes relative to maintenance of the status quo (White, Goden et al., 2023). However, compared to a policy scenario where flavors were restricted in cigarettes and cigars only, if flavors were banned in *all* tobacco products (e.g., ENDS, HTPs, ONPs) switching to non-

cigarette alternative products would decrease (White, Goden et al., 2023). In follow-up semi-structured interviews, participants from that same study discussed how current smoking cessation aids and strategies are not sufficient for many people that use menthol cigarettes (White, Patev et al., 2024). Relatedly, many people that use menthol cigarettes expressed interest in switching to alternative nicotine delivery systems like HTPs if menthol cigarettes were banned (White, Patev et al., 2024; White, Goden et al., 2023).

Tobacco manufacturers seem to view a menthol cigarette ban as an opportunity to promote alternative tobacco products, having used the United Kingdom's (UK) ban on menthol cigarettes to position HTPs as a menthol cigarette substitute (Brink, Glahn et al., 2022; Hiscock, Silver et al., 2020; Simpson, 2020). HTPs were exempted from the UK's menthol ban and Philip Morris International (PMI) packaged "menthol switching kits" at a discounted price to get people that used menthol cigarettes to switch to menthol-flavored IQOS products (Birch, 2020). Viewing FDA's proposed menthol ban as a "catalyst" for IQOS' eventual national rollout in the US, some market analysts have recommended purchasing PMI stock (Gorham, 2017; Rivas, 2023). As further indication of impending growth in the US HTP market, in December 2023 British American Tobacco submitted an application for its flagship HTP (*Glo Hyper Pro*) to the FDA for MRTP authorization (Rumney, 2024) and PMI announced that revenue from sales of IQOS products exceeded Marlboro cigarettes in non-US markets for the first time (Maloney, 2024). Absent additional regulation, we should expect considerable growth in the number of products offered as well as overall purchasing in the HTP sector of the US tobacco marketplace in the short- to medium-term. Thus, new evidence is needed *now* to understand whether HTPs may be a compelling alternative for people that smoke menthol cigarettes in the US, how these products are used, and to what extent flavor availability might influence substitution behaviors.

Heated Tobacco Products

HTPs are a re-emerging tobacco product class marketed as a way for people that smoke to reduce toxicant exposure while continuing to consume inhaled tobacco/nicotine products (Simonavicius, McNeill et al., 2019). In theory, HTPs *heat* tobacco (≤350^{o}C), eliciting a nicotine-containing aerosol via the chemical processes of "distillation" and "evaporation" (Auer, Concha-Lozano et al., 2017). The method HTPs use to produce aerosol contrasts with the chemical processes of "combustion" and "pyrolysis" (~800^{o}C) used by combustible cigarettes. However, some independent (i.e., non-tobacco industry) investigators have documented zones of "pyrolysis" in HTPs such as IQOS (Davis, Williams et al., 2019). The central idea underpinning the "reduced exposure" claims made by HTP manufacturers is that the temperatures in HTPs are *too low* to generate many of the harmful and potentially harmful constituents (HPHCs) of tobacco that are created during combustion/pyrolysis (e.g., volatile organic compounds, carbon monoxide) but are *high enough* to deliver reinforcing amounts of nicotine to the user (Auer, Concha-Lozano et al., 2017).

The heating technology featured in HTPs has evolved since the product class was developed in the 1960s and first marketed in the 1980s (O'Connor, Schneller et al., 2022; Risi, 2017). Earlier HTPs (e.g., Eclipse, Accord, Premier) failed as consumer products because of their "poor taste, smell, and user experience" and were withdrawn from most markets within 5-10 years of introduction (Elias, Dutra et al., 2018; O'Connor, Schneller et al., 2022). Modern HTP designs can now be grouped into four distinct categories (World Health Organization, 2023): carbon tipped devices studded with tobacco capsules that are lit (e.g., Premier, Eclipse), devices with a coil or blade that are resistance-heated by electricity and situated within a tobacco plug

(e.g., IQOS, Accord, Glo), devices with a coil that are resistance-heated by electricity to aerosolize a liquid that passes through tobacco (e.g., iFuse, PloomTech), and devices with tobacco situated in a mini-oven heated by electricity (e.g., Pax).

The change in the market fortunes of newer age HTPs (e.g., IQOS) suggest that some of the deficiencies of earlier HTPs have been ameliorated. Still, considerations of taste, cigarette substitution (e.g., nicotine delivery, feel), and smell remain central to the market success of HTPs as these themes feature in advertising materials heavily (Berg, Romm et al., 2021; Henderson, Van Do et al., 2022). There are now several HTPs marketed around the world (>75 countries) and global HTP sales are forecasted to exceed $68 billion by 2027, a seven-fold increase from 2020 (Upadhyay, Rahman et al., 2023). The leading brand in most markets where it is sold is PMI's IQOS tobacco heating system (Cheng, Noggle et al., 2023; University of Bath, 2023). These market dynamics suggest that HTPs, like IQOS, are poised to become major players in the global and US tobacco marketplaces.

The IQOS Heated Tobacco System

PMI first introduced the IQOS line of HTPs in Japan and Italy in 2014 (PMI, 2023). According to PMI, IQOS is most popular in Asia, the Mediterranean region, and eastern Europe (PMI, 2020). From 2008-2018 the US was without a meaningful HTP presence in its tobacco marketplace as older products failed and the industry prioritized newer products for international markets (O'Connor, Schneller et al., 2022). The lack of an HTP market presence in the US began to change in 2018 when IQOS 2.4 and its tobacco- and two varieties of menthol-flavored ("Smooth Menthol" and "Fresh Menthol") HeatSticks were the first HTPs authorized by FDA as MRTPs (FDA, 2020).

The IQOS 2.4 and its “Regular” (tobacco-flavored), “Fresh Menthol,” and “Smooth Menthol” Marlboro HeatSticks (known as “HEETS” elsewhere) are shown in Figure 1. HeatSticks are single-use consumables resembling a miniature cigarette and contain reconstituted tobacco pressed into rods using propylene glycol and glycerin (Zuck, 2018). The IQOS 2.4 device (a rechargeable, multi-use heating system) operates as a “Type 2” HTP under the World Health Organization (WHO) framework. Specifically, the IQOS device passes an electrical current through a blade situated within the HeatStick’s tobacco plug and the resistance from the blade generates heat that produces an aerosol containing nicotine, flavorings, and other byproducts (Lasseter, Bansal et al., 2017). The products of IQOS’ heating reaction are then passed through a polymer-film and filter on the mouth-end of the HeatStick to the user.

Figure 1. IQOS 2.4 tobacco heating system (left) and device schematic (right)

Note: The lefthand side of the image depicts the IQOS tobacco heating system and HeatSticks (Regular/Tobacco [grey box on left] and Fresh Menthol [green box on right]) that were used in this study. The righthand side of the image depicts the components of the IQOS holder and the HeatSticks and demonstrates how they are used together (Lasseter, Bansal et al., 2017).

The primary difference between the two varieties of menthol HeatSticks authorized by the FDA is that the "Smooth Menthol" HeatSticks contain an average of 6.98 mg menthol/HeatStick and the "Fresh Menthol" HeatSticks contain an average of 13.23 mg menthol/HeatStick; commercial menthol cigarettes range from 2.9-19.5 mg menthol/cigarette (FDA, 2017b). When standardized by gram of tobacco, nicotine levels are similar between unused HeatSticks and commercial cigarettes (Bekki, Inaba et al., 2017; Farsalinos, Yannovits et al., 2018). The IQOS 2.4 aerosolizes an estimated 1.29 mg of nicotine per Tobacco/Regular HeatStick, 1.19 mg of nicotine per Smooth Menthol HeatStick, and 1.17 mg of nicotine per Fresh Menthol HeatStick; commercial cigarettes aerosolize 1-3 mg of nicotine (Zuck, 2018). Other non-tobacco industry funded assessments of IQOS using machine-based puffing protocols have concluded that a single IQOS HeatStick generates about 50-70% the amount of nicotine as a combustible cigarette (Davigo, Klerx et al., 2023; Li, Luo et al., 2019; Mallock, Böss et al., 2018). Differences between the nicotine emissions from various flavors of IQOS are believed to be negligible when assessed under machine-based puffing protocols (El-Kaassamani, Yen et al., 2022; Farsalinos, Yannovits et al., 2018; Uchiyama, Noguchi et al., 2018).

The newest version of IQOS, *Iluma*, uses a novel heating system involving magnetic induction to heat a blade that is self-contained within the HeatStick (now called a "Terra"). While this version of IQOS is available in some international markets, IQOS 2.4 is the focus here as it was the only IQOS product available at the time of study conceptualization and has been granted MRTP authorization to be marketed under claims of "reduced exposure" (FDA, 2020). A functionally similar version of IQOS 2.4, known as IQOS 3 Duo, also received MRTP authorization to be marketed under claims of "reduced exposure" in April 2022 (FDA, 2022a). The MRTP designation that FDA authorized for IQOS 2.4 was based on evidence that "…

[IQOS] could help addicted adult smokers transition away from combusted cigarettes and reduce their exposure to harmful chemicals, but only if they completely switch" from cigarettes to IQOS (FDA, 2020). FDA authorized PMI to market IQOS under claims of "reduced exposure" but denied PMI's request to market IQOS with "reduced risk" claims (FDA, 2020; Lempert, Bialous et al., 2022). FDA's decision on the MRTP claims that could be used in marketing IQOS highlight the fact that *reducing* exposure to HPHCs does not lower associated health risks necessarily (FDA, 2020; Lempert, Bialous et al., 2022; St Helen, Jacob III et al., 2018; Chen, Grigg et al., 2024).

From October 2019 to November 2021, IQOS 2.4 was sold in four test markets in the US: Richmond, VA, Charlotte, NC, Charleston/Myrtle Beach, SC, and Atlanta, GA (Abroms, Levine et al., 2022). The IQOS 2.4 was only sold in "IQOS boutiques" (i.e., physical storefronts and kiosks), though HeatSticks could be purchased at local convenience stores (Churchill, Weaver et al., 2020). The IQOS boutiques took on a high-tech, minimalist, and modern appearance, drawing comparison to the retail environments of the technology company Apple (Churchill, Weaver et al., 2020). When a prospective customer entered an IQOS boutique they were age-verified (21+) and asked if they smoked cigarettes before being paired with an employee that provided personalized information about IQOS, instructions for use, and an opportunity to sample the product (Churchill, Weaver et al., 2020). From 2019 to 2021 the IQOS 2.4 device retailed for $100 and each pack of HeatSticks cost $5-6 (Churchill, Weaver et al., 2020).

PMI planned to begin selling IQOS across the US in 2021; however, those plans were interrupted when the International Trade Commission (ITC) ruled that PMI had infringed upon two patents held by RJ Reynolds/British American Tobacco (Abroms, Levine et al., 2022). The Commission barred the importation of IQOS products into the US, halting PMI's planned rollout

of the product (Lucas, 2021). PMI was not successful in appealing the Commission's ruling and IQOS products have not been available for purchase in the US since late 2021 (Yasiejko, 2023); however, in February 2024 PMI and British American Tobacco ceased litigation concerning several HTP- and ENDS-related patents (Carver, 2024). Settlement of the IQOS patent dispute nullifies the ITC's import ban and PMI has stated it plans to reintroduce IQOS in four undisclosed cities across two states in the US as early as May 2024 (Carver, 2024; Rumney, 2023a). In October 2023 PMI submitted a Premarket Tobacco Product Application (PMTA) for IQOS *Iluma* and national availability of IQOS is not expected until *Iluma* receives FDA authorization (McDonald, 2023; Rumney, 2023a).

Prevalence of Heated Tobacco Product Use and Current Regulatory Landscape

Due to the supply-side issues mentioned above, ever use of HTPs in the US is estimated at less than 2% among adults that have ever smoked cigarettes (Berg, Romm et al., 2021; Wang, 2019). However, HTPs are popular in other countries with IQOS being the leading brand in most markets (University of Bath, 2023). For instance, IQOS has been sold in Japan since 2014 and now represents 20-25% of the entire Japanese tobacco market (Vorster, 2017). Cigarette sales in Japan began declining concurrent with the introduction of IQOS, suggesting that many people that smoked cigarettes were switching to IQOS partially or completely (Stoklosa, Cahn et al., 2019). Menthol is the most popular (>40%) IQOS flavor in Japan (Sutanto, Miller et al., 2020; Sutanto, Miller et al., 2019) though IQOS HeatSticks/HEETS are now sold in over a dozen flavors including: Amber ("a rounded rich tobacco"), Blue ("deep menthol flavour"), Sienna ("intense and full bodied tobacco"), Turquoise ("smooth menthol blend"), Green ("lightly toasted tobacco blend providing a balanced menthol cooling sensation"), Sienna Caps ("woody and light

tea aroma which in a click delivers a cooling menthol breeze"), Teak ("balanced, roasted tobacco with a creamy note and nutty aroma"), Russet ("roasted tobacco with malty aromas"), and Mauve Wave ("crisp menthol tobacco blend with a taste of dark forest fruit"; Vapour Core, 2023).

The rise in popularity of HTPs in the EU after a ban on the sale of menthol cigarettes was implemented in May 2020 may be relevant to the US (European Network for Smoking and Tobacco Prevention, 2020). A post-menthol ban survey found that 6.5% of respondents in the EU had tried HTPs, up from 1.5% the year prior (Laverty, Vardavas et al., 2021). The EU exempted HTPs and ENDS from its menthol cigarette ban initially. After witnessing a >2000% increase in sales of heated tobacco sticks and a 2.5% growth in the HTP market share from 2018 to 2020, however, EU regulators have moved to include HTPs within the larger flavor ban regulation beginning October 2023 (European Commission, 2022). In an attempt to circumvent the EU's flavored tobacco regulations PMI has started manufacturing IQOS HeatSticks using a nicotine-infused "non-tobacco substrate" in place of tobacco, suggesting the industry's perspective on the importance of flavors to the economic viability of HTPs (Rumney, 2023b).

Evidence on the Health Effects of HTPs

With regard to harm reduction potential, IQOS may expose users to lower levels of *some* toxicants than combusted cigarettes (but not all) and may increase exposure to other harmful compounds (Upadhyay, Rahman et al., 2023). An exemplar study from this literature evaluated PMI's reported levels of HPHCs in its MRTP application to the FDA for the IQOS 2.4 tobacco heating system (St Helen, Jacob III et al., 2018). PMI reported that for mentholated HeatSticks, the levels of HPHCs were reduced >88% after normalizing for nicotine content compared to a

menthol Kentucky Research (3R4F) cigarette. Emissions for all 58 of the constituents reported by PMI were lower than for a 3R4F cigarette (St Helen, Jacob III et al., 2018). However, this list of 58 compounds only covered 40 of the 93 HPHCs that FDA tracks (St Helen, Jacob III et al., 2018). Moreover, 22 of the omitted HPHCs were found to be >200% higher and seven were >1000% higher for IQOS emissions relative to a 3R4F cigarette (St Helen, Jacob III et al., 2018). For example, unlike in cigarettes, IQOS emissions contained higher levels of the humectants glycerol and propylene glycol that may harm the human respiratory system (Bhat, Kalathil et al., 2021; Irina & Alistair, 2018; St Helen, Jacob III et al., 2018). Moreover, exposure to HTP emissions has been associated with potential antecedents to compromised cardiovascular and lung health including acute increases in heart rate, blood pressure, endothelial stiffness, and lung dysfunction (Chen, Grigg et al., 2024; Paulina, Mateusz et al., 2023; Sohal, Mathew et al., 2019; Fried & Gardner, 2020).

Tobacco industry data suggest that people that are able to switch from menthol cigarettes to IQOS may reduce their toxicant exposure (Haziza, de La Bourdonnaye et al., 2020). The strongest such industry-funded evidence involved a study of 160 healthy adults that used menthol cigarettes and were randomized as part of a three-arm (IQOS-menthol, continued menthol cigarette use, smoking abstinence) parallel group clinical trial. After 5 days of inpatient observation, biomarkers of exposure were reduced between 51% (o-toluidine) and 96% (1-aminoapthalene) for those who switched to IQOS-menthol relative to those that continued to smoke menthol cigarettes (Haziza, de La Bourdonnaye et al., 2020). Greater reductions in biomarkers of exposure for participants that used IQOS instead of cigarettes were also observed after a 90-day ambulatory use period (Haziza, de La Bourdonnaye et al., 2020). Responses to research instruments that assess the self-reported effects associated with tobacco use and

abstinence, including the Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal Scale, did not differ at each timepoint in the study between the IQOS-menthol and menthol cigarette groups (Haziza, de La Bourdonnaye et al., 2020).

In another industry-funded study conducted in the US, 962 people that smoked could use cigarettes, IQOS (provided for free), and other tobacco products in an ambulatory setting for 6 weeks (Roulet, Chrea et al., 2019). Adoption of IQOS (defined as >70% of total tobacco consumption being IQOS) was highest among participants that reported using regular- and menthol-HeatSticks together. Moreover, the odds of "adopting" IQOS were more than four times higher among participants that liked the HTP's smell and taste, making sensory effects the strongest predictor of adoption (Roulet, Chrea et al., 2019)

Four non-industry funded systematic reviews have addressed the health effects of HTPs (Drovandi, Salem et al., 2020; Jankowski, Brozek et al., 2019; Simonavicius, McNeill et al., 2019; Znyk, Jurewicz et al., 2021). Each of these reviews concluded that improvements in some biomarkers of exposure were realized for people that used HTPs relative to people that used combusted cigarettes. Moreover, each review found evidence of improvements in clinical biomarkers including cholesterol, FEV1, ICAM-1, and HDL for individuals that used HTPs instead of combustible cigarettes (Drovandi, Salem et al., 2020; Jankowski, Brozek et al., 2019; Simonavicius, McNeill et al., 2019; Znyk, Jurewicz et al., 2021). Evidence that IQOS exposure may exacerbate airway inflammation, result in oxidative stress, and enhance microbial adhesion to the respiratory track was also identified (Znyk, Jurewicz et al., 2021). A recent Cochrane systematic review on the health effects of HTPs reached similar conclusions, finding "moderate-certainty evidence for lower NNAL, exhaled carbon monoxide (eCO), and carboxyhemoglobin for those using HTPs rather than cigarettes" (Tattan-Birch, Hartmann-Boyce et al., 2022). For

example, pooled data from five studies showed greater lung function at follow-up for people that used HTPs compared to people that used cigarettes (Tattan-Birch, Hartmann-Boyce et al., 2022). All of these systematic reviews are limited, however, by the fact that available data (particularly those involving human participants) were generated by tobacco-industry funded studies. Overreliance on industry generated data in the extant literature is problematic because papers published by the tobacco industry are more likely to conclude that HTPs are at least as appealing as cigarettes, often rely on surrogate outcomes to justify their conclusions, and have suppressed findings that may challenge their commercial interests (Brandt, 2011; Braznell, Akker et al., 2022; Hammond, Collishaw et al., 2006; Rees, Kreslake et al., 2009; Suzuki, Aono et al., 2023). Last, there is emerging preclinical evidence that dual use of IQOS with cigarettes harms human airway epithelial cell viability and increases levels of oxidative stress relative to comparable levels of exclusive cigarette smoking or IQOS use (Saha, Jain et al., 2023).

Industry-funded studies suggest that IQOS may be an acceptable cigarette substitute and a viable exposure reduction tool for people who are unable and unwilling to quit smoking; though whether or not harm is reduced is as yet to be determined. Importantly though, these industry studies involve conflicts of interest and do not use established methods for investigating tobacco product substitution. Concerningly, there are no randomized and controlled clinical trials of IQOS in the current literature that were not funded by the tobacco industry.

Evidence on the Tobacco Use Behaviors Associated with HTPs and IQOS

Outside of controlled trials, there is a growing body of evidence demonstrating how IQOS products are used under real-world conditions. One industry-funded study conducted among individuals that were registered users of IQOS reported that 52% in Italy, 78% in Japan,

and 37% in Germany were “predominant” (>70% of total tobacco) users of IQOS (AlMoosawi, Bajec et al., 2022). A non-industry funded meta-analysis estimated pooled prevalence (2015-2022) in Italy, Japan, Germany of lifetime, current, and daily HTP use at 4.87%, 1.53%, and 0.79%, (Sun, Anandan et al., 2023). The prevalence of HTP use increased in the European and Western Pacific regions from 2015 to 2020 with 5% of the included populations having ever tried HTP and 1.5% identifying as a current user, though only about half of current users consumed HTPs daily (Sun, Anandan et al., 2023). There is also non-industry funded evidence from Japan and Spain that the introduction of IQOS was responsible for a decline in cigarette sales, though combined cigarette and IQOS sales remained stable from before to after IQOS’ introduction in both countries (Golpe, Martin-Alvarez et al., 2022; Stoklosa, Drope et al., 2016).

Epidemiologic data from the International Tobacco Control policy evaluation project suggests that the predominant pattern of HTP use in South Korea and Japan is dual use with cigarettes as only 10% of HTP users are exclusive HTP users (Kim & Friedman, 2022; Satomi, Kanami et al., 2023; Seo, Xu et al., 2023). Furthermore, use of HTPs in Japan and South Korea has been associated with lower cigarette cessation and increased smoking relapse risk (Satomi, Kanami et al., 2023; Seo, Xu et al., 2023). In South Korea, 35.4% of HTP consumers reported using HTPs to quit smoking, 14.7% to reduce smoking but not quit, and half for reasons other than quitting or reducing smoking (Seo, Xu et al., 2023). One cross-sectional survey of people that use tobacco products in South Korea suggested that HTPs were not substitutes to cigarettes but rather complementary goods (Hwang, Ryu et al., 2019).

In sum, objective evidence from non-US markets indicate that while HTP use is growing, considerable variability remains across different regions. Differences in HTP use patterns observed across international markets could be explained by variations in regulatory frameworks,

marketing, and the availability of HTP flavors within each country (Sun, Anandan et al., 2023). Despite this variability, the predominant pattern of use for HTPs is that of *dual use* with cigarettes and not complete substitution from combustible cigarettes.

Though much less is known about HTP use in the US compared to other countries, a cross-sectional study involving an online convenience sample in the US suggested that 97% of current IQOS users also smoked cigarettes (Levine, Duan et al., 2023). A series of surveys from 2019-2020 sampled young adults that smoke and found 10-20% had ever heard of HTPs, 3-5% had ever used an HTP, and 1-3% reported past year purchasing of an HTP (Berg, Romm et al., 2021; Duan, Wysota et al., 2022; Karim, Talluri et al., 2022). Moreover, people that smoke cigarettes in a US-based online convenience sample viewed IQOS as an ENDS substitute more so than as a cigarette substitute (Duan, Wysota et al., 2022).

Altria recently published findings from its first postmarketing surveillance study of IQOS in the US, interrogating the sociodemographic and tobacco use characteristics of adults that use IQOS (Cheng, Noggle et al., 2023). Data were collected using Altria's *IQOS Consumer Database* and analyses were restricted to Americans aged 21 and older that had used at least 100 IQOS HeatSticks in their lifetime (Cheng, Noggle et al., 2023). The results of this industry-funded study suggested ~28,000 individuals had purchased IQOS in the US prior to November 2021 (Cheng, Noggle et al., 2023). Of the ~700 respondents (response rate: 2.5%), most current and former users of IQOS in the US were male (61%), non-Hispanic white (73%), had a mean age of 45, and 69% had not used smoking cessation aids in the past year (Cheng, Noggle et al., 2023). The average number of days using IQOS over the past month among Altria's sample was 26 days and the median respondent used 15 HeatSticks/day (Cheng, Noggle et al., 2023). On average, IQOS was perceived as less harmful than cigarettes by respondents (Cheng, Noggle et

al., 2023). Nearly all (99%) respondents had ever smoked cigarettes and after an average of one year of IQOS use, half were still smoking cigarettes (Cheng, Noggle et al., 2023). Among people that used IQOS at the time of the survey, 34% used IQOS exclusively while 43% used at least one additional tobacco product and 23% used at least two additional tobacco products (Cheng, Noggle et al., 2023). Of those individuals who continued smoking cigarettes while using IQOS, Altria reported that 83.6% were using fewer cigarettes compared to before they tried IQOS (Cheng, Noggle et al., 2023). Most people in the US that used IQOS had tried all three varieties of HeatSticks but 48% preferred to use Regular/Tobacco HeatSticks, 30% preferred Smooth Menthol HeatSticks, and 23% preferred Fresh Menthol HeatSticks (Cheng, Noggle et al., 2023). Among the 122 people that used menthol cigarettes in the sample, 95.1% reported a preference for using a menthol HeatStick (Cheng, Noggle et al., 2023). Around 20% of respondents that used nonmenthol cigarettes also preferred a menthol variety of HeatSticks (Cheng, Noggle et al., 2023). According to this industry-funded study, IQOS use patterns were similar between people that used menthol and nonmenthol HeatSticks (Cheng, Noggle et al., 2023).

Four things are important to note from the current HTP literature: 1) nearly all of the available clinical trial data on IQOS was funded by the tobacco industry, 2) HTP and IQOS use is rare but growing in many international markets, 3) dual use of HTPs with cigarettes is the prevailing norm and is a pattern of use that may undermine tobacco harm reduction potential and, 4) the bulk of the epidemiological evidence on HTPs comes from markets outside the US or from the tobacco industry. This assessment of the existing literature is consistent with the European Respiratory Society Tobacco Control Committee's recent position statement on the role HTPs, ENDS, and ONPs play in "tobacco harm reduction" (Chen, Grigg et al., 2024). Owing to differences in the products, regulatory environments, cultures, and marketing practices

found in the US compared to its international peers, how results from prior HTP studies will extrapolate to the US experience is unclear. Fortunately, tools exist to help guide regulatory decision-making on HTP flavor availability *before* widespread availability of HTPs in the US.

Abuse Liability

Established methods exist for evaluating whether one tobacco product will substitute for another (Berman, Connolly et al., 2015; Carter, Stitzer et al., 2009). Methods for measuring the substitution potential of one tobacco product for another involve "abuse liability" assessments and can include work done in a clinical laboratory or in naturalistic settings (Carter & Griffiths, 2009; Carter, Stitzer et al., 2009; Henningfield, Hatsukami et al., 2011). Abuse liability and its related construct of "appeal" are of paramount importance to understanding the substitution feasibility of a MRTP for people that use cigarettes (Breland, Kleykamp et al., 2006; Fearon, 2023; Henningfield, Hatsukami et al., 2011; Vansickel, Baxter et al., 2021); *the more closely an alternative nicotine delivery system matches the abuse liability profile of a cigarette, the more likely complete substitution is to occur (Abrams, Glasser et al., 2018; Fearon, 2023).* This perspective offers an explanation for why nicotine replacement therapy (NRT) products are often ineffective smoking cessation tools even though they deliver nicotine (Theodoulou, Chepkin et al., 2023; Wadgave & Nagesh, 2016); cessation success rates with NRT are estimated at ~17% (Stead, Perera et al., 2012). The drug delivery, behavioral, and social reinforcement profiles (i.e., abuse liability) of NRT products are incongruent with that of combustible cigarettes making complete, lasting substitution difficult for people that smoke (Abrams, Glasser et al., 2018; Henningfield & Keenan, 1993; West, Hajek et al., 2000).

What is Abuse Liability?

Abuse liability refers to the likelihood that a tobacco product will produce and maintain dependence and long-term use (Balster & Bigelow, 2003; Carter, Stitzer et al., 2009). Others have postulated that pharmacologic (e.g., nicotine dose, drug delivery rate, route of administration), behavioral (e.g., puff volume, subjective and sensory effects), and social/political (e.g., economic and regulatory) factors are important determinants of abuse liability (Balster & Walsh, 2010; Carter, Stitzer et al., 2009; Jaffe & Jaffe, 1989). These pharmacologic, behavioral, and social/political factors exert independent and interactive effects to define the abuse liability of a tobacco product (Figure 2).

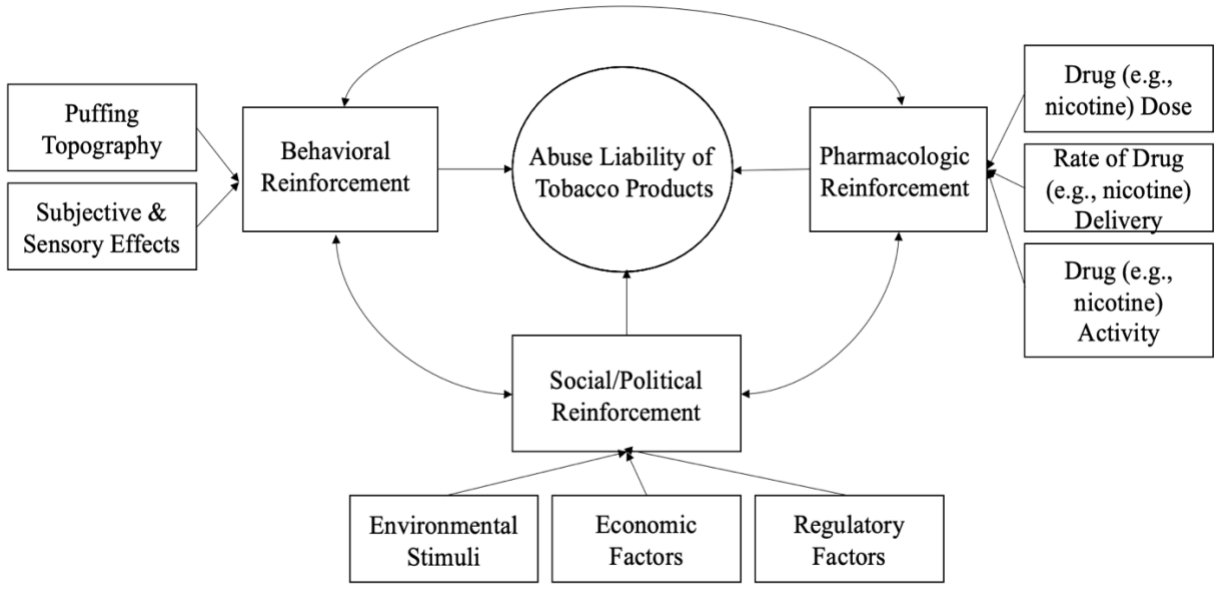


Figure 2. Conceptualization of the factors that influence the abuse liability of tobacco products and their potential interactions

Combustible cigarettes have very high abuse liability (Carter & Griffiths, 2009). In the context of MRTPs and the tobacco harm reduction framework, the goal is to elevate a lower risk product's abuse liability profile so that it can produce and maintain dependence and long-term use among people that use cigarettes and thereby allow for *complete* substitution from combustible products (Abrams, Glasser et al., 2018; Hatsukami & Carroll, 2020; Vansickel, Baxter et al., 2021). The FDA relies upon established methods (e.g., nicotine delivery, puff topography, self-reported effects, behavioral economic tasks, and naturalistic use studies) for indexing the abuse liability of new tobacco products to determine their regulatory status (FDA, 2017a). Understanding tobacco product abuse liability within and across products, as well as across distinct user groups, is an issue of increasing importance in tobacco regulatory science (Berman, Connolly et al., 2015; Wipfli, Berman et al., 2017).

Do Flavors Influence Abuse Liability in Tobacco Products?

Flavors influence abuse liability in cigarettes, cigars, and ENDS (Audrain-McGovern, Strasser et al., 2016; Barnes, Bono et al., 2017). The term "flavor" is a concept that integrates multiple sensory experiences including smell, taste, and chemesthasis (i.e., chemical reactivity of mucosal surfaces to produce sensations of temperature, touch, and pain [e.g., TRPM8 receptor activation in the oral cavity eliciting a "cooling" sensation]) that interact and are integrated in the orbotiofrontal cortex (Hayes & Baker, 2022; Krishnan-Sarin, O'Malley et al., 2019). Flavor can alter the abuse liability of tobacco products by influencing nicotine's bioavailability, user behavior, self-reported effects, and how hard an individual will work to earn product access (Bono, Cobb et al., 2020; Kostygina, Glantz et al., 2016; Wickham, 2020). In this way, flavors such as menthol may increase the rewarding effects of nicotine and be reinforcing on their own.

The use of menthol in cigarettes is perhaps the best studied example of how flavors can influence abuse liability in tobacco products (Ahijevych & Garrett, 2004; Ahijevych & Garrett, 2010; Cohn, Alexander et al., 2022; Kreslake & Yerger, 2010; Yerger & McCandless, 2011). For example, among an online sample of young adults, menthol (relative to nonmenthol) smoking was rated as more appealing and corelated with increased smoking intensity as well as lower harm perceptions (Cohn, Johnson et al., 2016). The heightened appeal associated with menthol smoking may be explained by people that use menthol cigarettes reporting greater psychological reward, satisfaction, and throat hit from smoking their usual brand than people that use nonmenthol cigarettes (Cohn, Alexander et al., 2022). Tobacco industry documents suggests that manufactures were knowledgeable of menthol's cooling and anesthetic properties, manipulated menthol content to enhance palatability as well as reduce the harshness associated with smoking, and knew that menthol's sensory qualities altered cigarette puff topography (Lee & Glantz, 2011; Yerger & McCandless, 2011). One tobacco industry executive observed that "menthol is a sensation in which menthol taste and cooling are indistinguishable" (Yerger & McCandless, 2011, p. 38). As early as 1974, PMI knew people that used menthol cigarettes took larger puffs from menthol than nonmenthol cigarettes (Yerger & McCandless, 2011). Moreover, the tobacco industry had data suggesting people that used menthol cigarettes took larger puff, longer puffs, and higher puff counts from their usual brand than from other menthol brands (Yerger & McCandless, 2011). As a result, people that use menthol cigarettes tend to have higher blood cotinine levels throughout the day, suggesting that they may smoke with greater intensity or that menthol is slowing nicotine's metabolism (Ahijevych & Parsley, 1999; Clark, Gautam et al., 1996; Gan, Cohen et al., 2008; Williams, Gandhi et al., 2007). This body of literature suggests that menthol is an active compound that increases the abuse liability of cigarettes.

Mechanistically, how flavors influence tobacco product abuse liability can be understood through direct and indirect effects. Flavors such as menthol can influence nicotine yields by altering the chemical properties of smoke (e.g., pH) and thereby nicotine's absorption, distribution, metabolism, and bioavailability (Kreslake & Yerger, 2010; Megerdichian, Rees et al., 2007). Indirectly, flavorings such as menthol can alter the sensory experience associated with using a tobacco product (e.g., enhancing palatability or reducing harshness) to influence puffing behaviors as well as nicotine delivery (Nemeth-Coslett & Griffiths, 1984). Thus, flavors such as menthol can influence the pharmacologic and behavioral reinforcement domains of abuse liability. From an environmental, regulatory, and economic perspective there is ample evidence that mentholated tobacco products have been marketed towards specific demographic groups (Wailoo, 2022), have persisted as the only characterizing flavor of cigarettes sold in the US (FDA, 2021b), and are often discounted in minoritized communities (White, White et al., 2006). The sum of these "menthol effects" is to enhance the abuse liability of cigarettes (Delnevo, Ganz et al., 2020; Lee & Glantz, 2011; FDA, 2022f). If and how menthol impacts the abuse liability of non-cigarette tobacco products, however, is an active area of research.

Early evidence suggests that non-tobacco flavors in ENDS products, such as mint/menthol and fruity flavors, may appeal to people that smoke cigarettes and are trying to quit or reduce smoking as well as to people that are tobacco-naïve (Zare, Nemati et al., 2018). A recent systematic review summarized the available literature regarding the role of flavors in ENDS and how they influenced intentions to quit smoking and smoking cessation attempts (Liber, Knoll et al., 2023). This systematic review concluded that there were "very low levels of certainty" that non-tobacco flavored ENDS use was *not* associated with smoking cessation, resolving that more evidence was needed to understand if flavored ENDS are superior to their

unflavored counterparts to encourage smoking cessation (Liber, Knoll et al., 2023). There have not yet been systematic investigations of the role flavors might play in determining HTP abuse liability or the likelihood that an HTP could serve as a cigarette substitute. More evidence is needed to understand the role of flavors in influencing abuse liability and substitution behaviors in emerging product classes such as HTPs (FDA, 2022d).

Methods for Assessing Abuse Liability in the Clinical Laboratory

Abuse liability assessments conducted in a clinical laboratory setting have been used for decades to evaluate the effects of tobacco products that are combusted (Cobb, Shihadeh et al., 2011; Cox, Tiffany et al., 2001; Ossip-Klein, Martin et al., 1983), orally-administered (Cobb, Weaver et al., 2010; Gritz, Baer-Weiss et al., 1981; Lunell, Fagerström et al., 2020), or heated (Breland, Buchhalter et al., 2002; deBethizy, Robinson et al., 1988; Rezk-Hanna, Doering et al., 2018). Many different measures have been developed to assess abuse liability in the clinical laboratory context including: drug discrimination studies, acute dose-effect comparisons, examination of self-reported effects, indices of tobacco withdrawal and craving suppression, self-administration procedures, choice procedures, clinical trials, and behavioral economic tasks (Bickel, Moody et al., 2017; Carter, Stitzer et al., 2009; Fischman & Foltin, 1991; Maloney, 2022). Strengths of the clinical laboratory for abuse liability assessment include rigorous control over product administration, well-established control conditions, and a variety of well-validated outcome measures (Breland, Kleykamp et al., 2006; Carter & Griffiths, 2009; Institute of Medicine, 2012). Because abuse liability is a multifactorial construct, when possible, multiple assessments should be integrated within the context of a single investigation (Wall, Bono et al., 2018). Fundamental abuse liability outcome measures relevant to understanding whether one

inhaled tobacco product will substitute for another include assessment of nicotine delivery, user behavior, self-reported effects, response to behavioral economic tasks, and naturalistic use patterns (Carter & Griffiths, 2009; Carter, Stitzer et al., 2009; Institute of Medicine, 2012).

Nicotine Delivery

One outcome relevant to characterizing the abuse liability of any tobacco product involves measuring the product's ability to deliver nicotine (Foulds, Ramstrom et al., 2003; Henningfield & Keenan, 1993; Lee, Malson et al., 2004). Typically, venous blood is sampled before and either once or several times during and after tobacco product use (Bullen, McRobbie et al., 2010; Pomerleau, Pomerleau et al., 1989; Russell, Feyerabend et al., 1976). Plasma can then be separated out from the blood sample and analyzed via gas chromatography-mass spectroscopy or similar methods to determine nicotine concentration (Jacob, Wu et al., 2000). Common outcomes from nicotine delivery studies include: changes in plasma nicotine levels from before to after product use (i.e., "nicotine boost"), the maximum nicotine concentration achieved during product use (C_{max}), the time to maximum nicotine concentration (T_{max}), and the area under the curve (AUC) of a plot of nicotine concentration over time (Hiler, Breland et al., 2017; Vansickel, Cobb et al., 2010; Voos, Smith et al., 2020).

Nicotine is the primary dependence-inducing drug delivered by a cigarette (Benowitz, 2008). Most commercial cigarettes contain between 10-14 mg of nicotine and 1-1.5 mg is delivered to the blood stream via absorption across pulmonary alveoli primarily (Benowitz, Hukkanen et al., 2009). Once in the blood stream, nicotine activates nAchRs in the CNS and PNS (Benowitz, 2010a, 2010b). Of primary interest is nicotine's activity in the CNS. Nicotine reaches the brain within 10-20 seconds of a puff being taken and, in the mesolimbic pathway,

binds to nAchRs in the VTA and nucleus accumbens to produce a phasic release of dopamine (Corrigall, Coen et al., 1994; Picciotto & Corrigall, 2002). Nicotine's binding in the mesolimbic pathway can induce mild euphoria (Pomerleau & Pomerleau, 1992). In humans that are dependent upon nicotine, aversive nicotine abstinence symptoms (e.g., irritability, frustration or anger, anxiety, depressed mood, dysphoria) emerge within 4-24 hours and peak within the first week of abstinence but can persist for 2-4 weeks (Buchhalter, Acosta et al., 2005; Hughes, 2007; Hughes & Hatsukami, 1986; Hughes, Higgins et al., 1994; McLaughlin, Dani et al., 2015). Larger doses and faster delivery of nicotine can produce more intense rewarding effects (Jensen, Valentine et al., 2020) and pronounced symptoms of abstinence (Benowitz, 2010a).

Nicotine's rapid delivery from a cigarette affords people that smoke the ability to alter their smoking behaviors to acquire desired effects (e.g., euphoria or relief of abstinence symptoms) by titrating plasma nicotine to tolerable concentrations (Benowitz, 2010b; Benowitz, Hukkanen et al., 2009). Acute administration studies conducted in a clinical laboratory setting with nicotine-deprived individuals that smoke suggest that 10-puffs of smoking, corresponding to use of about one cigarette, can increase baseline plasma (venous) nicotine concentration from 0-2 ng/mL to 13-24 ng/mL within a 5-minute window (Hajek, Pittaccio et al., 2020; Lopez, Hiler et al., 2016; Vansickel, Cobb et al., 2010; Yan & D'Ruiz, 2015). Assessing the nicotine delivery profile of a new tobacco product and drawing comparisons to the "benchmark" of a combustible cigarette is indispensable to determining abuse liability and substitution potential (Hajek, Pittaccio et al., 2020; Shihadeh & Eissenberg, 2015; Vansickel, Baxter et al., 2021).

One exemplar nicotine delivery study asked 18 individuals that smoked cigarettes to complete clinical laboratory sessions involving an ENDS device that differed by flavor: menthol, cherry, tobacco, espresso, and vanilla (Voos, Smith et al., 2020). One benefit to using an ENDS is

that the researcher can control the ENDS' liquid nicotine concentration and device power, factors that together define the rate nicotine is emitted from the mouth-end of the device (Shihadeh & Eissenberg, 2015). Control of nicotine emissions permits the influence of flavors on nicotine delivery, once puff duration is considered, to be better isolated. During clinical laboratory sessions, participants puffed on an ENDS for 10 minutes with blood sampling before, during, and after the use period (Voos, Smith et al., 2020). The menthol-ENDS produced a C_{max} more similar to participant's own brand (OB) combustible cigarettes than the tobacco-ENDS (Voos, Smith et al., 2020). These findings suggested, while holding ENDS nicotine concentration constant at 24 mg/mL, a menthol-flavored liquid made this particular ENDS a stronger cigarette substitute and that flavors can influence nicotine delivery (Voos, Smith et al., 2020). Evaluating a tobacco product's nicotine delivery profile is a requirement for understanding its potential for pharmacologic reinforcement (Lee, Nonnemaker et al., 2018; Spindle, Breland et al., 2015; Voos, Smith et al., 2020; Wadkin, Allen et al., 2023).

User Behavior and Puffing Topography

In abuse liability assessments of tobacco products, measuring user behavior (e.g., puff topography) is important because people that smoke are capable of manipulating the amount of nicotine they intake on a puff-by-puff basis (Blank, Disharoon et al., 2009; Felicione, Karaoghlanian et al., 2020). Puff topography studies adopt one of two structures (Perkins, Karelitz et al., 2012; Spindle, Breland et al., 2015): *ad libitum* (*ad lib*; i.e., participants are free to take puffs from the study product however they would like during a given time period) and *directed* (i.e., participants take puffs as instructed by the researcher according to a prescribed drug administration schedule). Regardless of the puffing structure adopted, typical outcomes

from topography assessments include: puff number, duration, volume, interpuff interval (IPI; i.e., the time between two puffs), and flow rate (Shihadeh, Azar et al., 2004). The directed bout paradigm is advantageous if the researcher wishes to standardize certain factors (e.g., puff number, IPI) across conditions (Spindle, Hiler et al., 2017). Puff topography parameters can be captured in real-time by attaching a mouthpiece connected to specialized equipment/software (Felicione, Karaoghlanian et al., 2020; Hiler, Breland et al., 2017; Spindle, Hiler et al., 2017) to the tobacco product under investigation. Puff topography outcomes can help contextualize nicotine delivery results and estimate toxicant exposure (Davigo, Klerx et al., 2023; Eissenberg & Shihadeh, 2009; Reilly, Goel et al., 2017; Soussy, El-Hellani et al., 2016).

In one example of the puff topography methodology, 31 ENDS-naïve individuals that smoked cigarettes and 33 experienced ENDS users completed clinical laboratory sessions that differed by ENDS liquid nicotine concentration (Hiler, Breland et al., 2017). At the highest liquid nicotine concentration (36 mg/mL), following a directed use bout the mean nicotine C_{max} was 6.9 ng/mL for the ENDS-naïve group and was 17.9 ng/mL for the experienced ENDS users (Hiler, Breland et al., 2017). Observed differences in plasma nicotine delivery were due to ENDS-naïve participants taking puffs of 2.9 seconds on average compared to ENDS-experienced participants that took puffs of 5.6 seconds on average as no other topography outcome was correlated with post-bout plasma nicotine concentration (Hiler, Breland et al., 2017). The fact that use behavior changes as people that smoke become more experienced with a tobacco product suggests that studies involving novel products like IQOS should measure this outcome over time to aid in interpreting nicotine delivery results (Farsalinos, Spyrou et al., 2015). Puff topography measures are an important set of outcomes to measure over time in clinical trials as increased puff duration with an ENDS from initial exposure to a two-week follow-up visit has been associated with

greater reductions in cigarette smoking (Wagener, Avery et al., 2021). The current literature is limited by a lack of data on if or how topography parameters change as people that smoke cigarettes gain experience with HTPs.

Most literature regarding the puff topography associated with HTP/IQOS use has been generated by the tobacco industry. According to two PMI-funded studies, people that smoke cigarettes and switch to IQOS take longer and more frequent puffs from the HTP than their OB cigarette (Haziza, de La Bourdonnaye et al., 2016; Lüdicke, Picavet et al., 2018). Other industry-funded cross-sectional studies have documented larger puff volumes among people that use HTPs than people that use cigarettes (Jones, Slayford et al., 2020) and that puff volumes were doubled upon switching to a Japanese HTP for people that smoke cigarettes (Yuki, Takeshige et al., 2018). The larger and longer puffs documented with use of HTPs compared to cigarettes may be a compensation for the lower concentration of nicotine found in HTP aerosol (Davigo, Klerx et al., 2023). People taking longer and more voluminous puffs from an HTP is concerning as it could ameliorate some of the toxicant reductions that form the basis of the "reduced exposure" claims made by HTP manufacturers (Ardati, Adeniji et al., 2023; Davigo, Klerx et al., 2023).

Flavors may affect tobacco product puff topography. In the context of cigarettes, menthol's cooling and anesthetic effects may encourage users to take a greater number of puffs, inhale larger volumes, puff longer durations, and encourage retention of smoke in the lungs (Ahijevych & Garrett, 2004; Anderson, 2011; Yerger & McCandless, 2011). For example, one study on puffing behaviors found that women that use menthol cigarettes had larger puff volumes than women that use nonmenthol cigarettes (Ahijevych & Parsley, 1999). Other studies have investigated the influence of menthol on cigarette smoking topography; findings from this literature are mixed as menthol has been shown to increase and decrease puff volume, count, and

duration (Ahijevych & Garrett, 2004; Ahijevych, Gillespie et al., 1996; Ahijevych & Parsley, 1999; Jarvik, Tashkin et al., 1994; McCarthy, Caskey et al., 1995; Moolchan, Hudson et al., 2004).

Flavors can influence the puff topography of ENDS (St Helen, Dempsey et al., 2017). For example, in one clinical laboratory study the average puff duration among adults that smoked cigarettes was 3.3 seconds when using a menthol-flavored ENDS compared to 2.8 seconds when using a tobacco-flavored ENDS ($p < 0.05$; Voos, Smith et al., 2020). In another study, participants with experience using ENDS took longer puffs when using a strawberry-flavored ENDS as opposed to a tobacco-flavored ENDS (St Helen, Shahid et al., 2018). The puffs of experienced ENDS users were longest when they used their usual brand of ENDS liquid though, suggesting that use of preferred flavors is associated with longer puffs and may increase aerosol/nicotine exposure (St Helen, Shahid et al., 2018). Flavors in ENDS may also impact puff volume and velocity (Maloney, 2022; Robinson, Hensel et al., 2018). To date, there have been no independent evaluations regarding how flavors might influence puff topography in HTPs among humans. This knowledge gap is important to fill because puff topography studies conducted with machines have demonstrated that puffing protocols with longer puff durations, higher puff volumes, and greater puff flow rates can increase the generation of carbonyl-compounds and phenols in IQOS (Ardati, Adeniji et al., 2023; Davigo, Klerx et al., 2023). Moreover, even when puffing behavior is standardized, certain flavors of IQOS HEETS (e.g., Amber, Bronze, and Green [i.e., menthol]) may increase exposure to toxicants such as formaldehyde and tobacco-specific nitrosamines (Davigo, Klerx et al., 2023). Thus, toxicant exposure from HTPs could be influenced by the intrinsic composition of the product (e.g., flavoring additives such as menthol) as well as by the impact that menthol has on puff

topography. More research is needed to evaluate the puffing behaviors of people that use IQOS, as well as the possible influence of flavors on HTP puff topography, to inform the design of machine-based topography studies of toxicant emissions and help regulators predict the health consequences of HTP use (Davigo, Klerx et al., 2023).

Self-Reported Effects

Another important set of clinical laboratory abuse liability assessments involves measuring the subjective experiences associated with tobacco product use (Buchhalter & Eissenberg, 2000; Butschky, Bailey et al., 1995; Carter & Griffiths, 2009). Self-reported effects assessments aim to capture individual's reports of their internal experiences before, during, and after tobacco product use (Fischman & Foltin, 1991). Self-reported effects assessments can evaluate the impact of a tobacco product on mood, abstinence symptoms, product liking, and the positive as well as negative aspects associated with tobacco use (Vansickel, Baxter et al., 2021). For example, in a study of 58 people that smoked cigarettes and were provided with an ENDS for 8 weeks, subjective measures of psychological reward associated with ENDS use were correlated with increased ENDS uptake and reduced cigarette consumption (Gades, Petersen et al., 2020). Several batteries have been validated to assess self-reported effects in the clinical laboratory setting including: the Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany et al., 2001), the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), and the Product Evaluation Questionnaire (PEQ; Hatsukami, Zhang et al., 2013).

For an MRTP like IQOS, a critical outcome is whether it suppresses abstinence symptoms (e.g., cravings for cigarettes) from before to after product use (Shiffman, Engberg et al., 1997). Abstinence symptom suppression is an important determinant of substitution from

combustible cigarettes that can be captured using the QSU-B and MNWS (Caponnetto, Campagna et al., 2013; Dawkins, Turner et al., 2013; Vansickel, Cobb et al., 2010). Prior work suggests that IQOS may be associated with greater tobacco abstinence symptom relief, including cigarette craving, than JUUL (a popular brand of ENDS) among people that smoke cigarettes (Maloney, Eversole et al., 2020). Results from a study examining the effects of a German HTP known as *Pulze* suggested that while HTP use suppressed cigarette cravings, its capacity to do so did not vary across its menthol- and tobacco-flavors (McDermott, Reichmann et al., 2023). However, among people that smoke cigarettes, no flavor of *Pulze* suppressed cigarette cravings as much as OB cigarettes (McDermott, Reichmann et al., 2023).

Literature on the self-reported effects associated with flavored ENDS use among people that smoke cigarettes may be instructive in predicting the influence that flavors have on HTP self-reported effects. Among a sample of people that smoked menthol cigarettes, use of an ENDS featuring apple or apple+menthol flavors was associated with greater reductions in cigarette craving compared to use of a menthol-only ENDS (MacLean, Gueorguieva et al., 2021). In a separate study involving people that smoked menthol cigarettes but abstained from smoking for 16 hours, use of a menthol-ENDS but not a tobacco-ENDS suppressed urges to smoke (Bello, Schulte et al., 2024). Apart from their influence on cigarette cravings and urges to smoke, flavors such as menthol have been shown to increase ratings of satisfaction, throat sensation, and pleasantness associated with ENDS use among people that smoke cigarettes (Bono, Barnes et al., 2019). The methods used to assess self-reported effects can help predict and explain substitution between cigarettes and emerging tobacco products (Gades, Petersen et al., 2020; Vansickel, Cobb et al., 2010) such as HTPs.

Behavioral Economic Tasks

The Institute of Medicine (IOM) and others have emphasized the importance of behavioral tasks in determining tobacco product abuse liability (IOM, 2012; Carter & Griffiths, 2009; Carter, Stitzer et al., 2009). Some of these tasks are related to abuse liability's economic determinants as they assess how much people are willing to pay to gain access to a tobacco product (Bickel, Moody et al., 2017; Gonzalez-Roz, Jackson et al., 2019). Several behavioral economic demand assessments are valid predictors of tobacco use, nicotine dependence, and transitions across products (Mackillop, Murphy et al., 2016; MacKillop, Murphy et al., 2008; Wilson, Franck et al., 2016). The fundamental assumption underlying behavioral economic tasks is that, subject to some constraint on time, effort, or money, consumers will allocate resources towards goods that confer the greatest utility (Bickel, Moody et al., 2017; Hursh & Silberberg, 2008; Reed, Naude et al., 2020). Abuse liability and behavioral economic demand are conceptualized to be related positively as participants demonstrate a willingness to expend more of their limited resources for product access (Bickel, Moody et al., 2017; Hursh & Silberberg, 2008; Reed, Naude et al., 2020).

Of particular policy relevance is whether demand for an HTP increases as cigarettes become more difficult to obtain, either because the price of cigarettes increases or access to cigarettes in the marketplace is restricted (Hursh & Roma, 2013). This economic relationship is known as the "cross-price elasticity of demand" (CPE) and is calculated by modeling changes in demand for an "alternative" product (e.g., IQOS) as a function of changes in the price of a "preferred" product (e.g., menthol cigarettes; Green, 1993; Hursh & Roma, 2013; Hursh & Roma, 2016). The sign of the CPE estimate describes the nature of the relationship between two goods (Hursh & Roma, 2016): a positive CPE suggests products are substitutes (i.e., the

alternative is consumed in place of the preferred product), a negative CPE suggests products are complements (i.e., the alternative is consumed alongside the preferred product), and a CPE of zero suggests the products are independent goods (i.e., demand for the alternative does not depend on demand for the preferred product). For example, if IQOS has a large, positive CPE with respect to menthol cigarettes, demand for IQOS is expected to rise as menthol cigarettes become more expensive or harder to obtain.

CPEs can be measured using the ETM task (Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2016). The ETM assesses changes in the demand for cigarettes and two or more price-constant alternatives as the price of OB cigarettes is raised incrementally (Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2016). Using the reported level of demand for each alternative at each cigarette price-point in the ETM permits product specific CPE calculation (Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2016). The ETM is a methodologic extension of the cross-product cigarette purchase task (CP-CPT) that has a long history of use in animal and human laboratory studies (Bickel, DeGrandpre et al., 1995; Bickel, Moody et al., 2017). The most important difference in ETMs and CP-CPTs is that in the ETM a wide array of tobacco products can be made available to the participant to purchase in place of a price-varying preferred product; in the CP-CPT, however, only one alternative is made available (Bickel, Moody et al., 2017). Allowing multiple alternatives to be available for purchase mimics the complex choices consumers make in the modern tobacco marketplace and guards against inflating demand for alternatives of interest artificially (Bickel, Moody et al., 2017; Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2016). The ETM also permits the researcher to manipulate the information available regarding a tobacco product's characteristics, description, availability, and price (Bickel, Moody et al., 2017; Quisenberry,

Koffarnus et al., 2016). The flexibility afforded by the ETM can be leveraged to mimic real-world market scenarios while providing tight experimental control (Bickel, Moody et al., 2017; Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2016).

An important consideration in designing behavioral economic tasks is whether responses are "reinforced" (i.e., the participant receives the products they select for purchase or incur some real-world consequence for their decisions) or hypothetical (Bickel, Moody et al., 2017). Previous comparisons of purchase tasks have found concordance in results originating from procedures involving hypothetical and real rewards (Wilson, Franck et al., 2016). Consequently, the ETM has developed to feature reinforced and hypothetical choice paradigms (Bickel, Pope et al., 2018; DeHart, Mellis et al., 2019; Denlinger-Apte, Cassidy et al., 2021).

In summary, behavioral economic demand assessments like the ETM offer a convenient and valid set of methods for assessing demand and the economic relationships between tobacco products. Thus, such tasks are a crucial component of a comprehensive assessment of substitution potential between cigarettes and alternative nicotine delivery systems like HTPs. Moreover, because demand is a multifactorial construct that underpins utility-maximization, consumers are required to balance receipt of reinforcing goods against constraints on that good's consumption (Bickel, Moody et al., 2017; Green & Srivastava, 1986). As a result of this balancing, behavioral economic tasks mimic real-world consumption and can provide important context to other abuse liability assessments that only measure a single domain of reinforcement (e.g., nicotine delivery) or are unable to impose constraints on consumption (e.g., *ad lib* product use). Unfortunately, the ETM task has not yet been used to characterize the abuse liability and substitution feasibility of HTPs such as IQOS for cigarettes.

Abuse Liability in Naturalistic Settings

Measuring consumption of tobacco products in naturalistic settings provides important external validation for clinical laboratory-based abuse liability studies (Carter, Stitzer et al., 2009; Ferguson & Shiffman, 2011; Hatsukami, Hanson et al., 2009; IOM, 2012; Shiffman, 2009a, 2009b). Measurement of tobacco product use while "at home" can be performed using techniques such as counting used and unused products (Ozga, Bays et al., 2021) and the "time line follow back" (TLFB) method (Sobell & Sobell, 1992; Sobell, 1996). The TLFB is a retrospective calendar-based assessment that asks participants to think back over a specific time period and estimate the number of "use episodes" that occurred on each of the days in the observation window (Sobell & Sobell, 1992; Sobell, 1996). TLFB assessments can be delivered by computer, interviewer, and self-administration methods and have a long history of use in the tobacco literature (Brown, Burgess et al., 1998; Sobell & Sobell, 1992). TLFB assessments allow researchers to measure changes in tobacco use over time and in response to experimental interventions (Cobb, Foulds et al., 2021). However, for individuals considered to be "heavy smokers," there is some concern that TLFB may overestimate cigarette consumption relative to "real-time" assessment methods (Griffith, Shiffman et al., 2009).

Another validated method, proven to reduce recall bias and improve compliance relative to TLFB and product counting (Blank, Breland et al., 2016; Serre, Fatseas et al., 2012; Shiffman, Brockwell et al., 2008) is ecological momentary assessment (EMA; Moskowitz & Young, 2006). EMA involves surveying participants in their natural environment using voice-, text-, or email-based prompts to capture daily tobacco product consumption and has been used to measure substitution in clinical trials (Blank, Breland et al., 2016; Cobb, Foulds et al., 2021; Mead, Chen et al., 2018). There are three general categories of EMA that differ based on the frequency of

sampling (Moskowitz & Young, 2006): daily diaries (i.e., behavior assessed at fixed intervals), experience sampling (i.e., random prompts sent to participant throughout the day to report on interval behaviors), and event-based sampling (i.e., participants report on behavior at the time of a particular event). The choice in EMA format is based on weighing the costs associated with sending prompts and training participants against the required resolution of data (Moskowitz & Young, 2006; Shiffman, Stone et al., 2008). More frequent sampling intervals are associated with greater validity at the cost of lower adherence (Cain, Depp et al., 2009). EMA is considered the "gold standard" of adherence assessments in clinical trials (Moskowitz & Young, 2006).

EMA techniques have been used to capture naturalistic use of alcohol, cocaine, tobacco products, and other substances of abuse (Epstein, Marrone et al., 2010; Piasecki, Jahng et al., 2011; Preston & Epstein, 2011; Shiffman, 2009a). There is a strong correlation between EMA records of cigarette consumption and biomarkers of tobacco exposure collected in clinical laboratories (Shiffman, 2009b). EMA can validate and extend clinical laboratory findings by capturing the "natural history" of tobacco use behaviors (e.g., adoption, cessation, substitution) via longitudinal data that are unobstructed by the artificial environment created in controlled settings (Beckham, Wiley et al., 2008; Ferguson & Shiffman, 2011). Daily diary EMA has been associated with high prompt-completion rates (>70%) for individuals receiving an app-based smoking cessation intervention (Businelle, Ma et al., 2016) and participants using a very low nicotine cigarette as a cigarette substitute in a 6-week clinical trial (Donny, Denlinger et al., 2015). Moreover, EMA based daily diaries have been used (78% prompt completion rate) to demonstrate greater reductions in cigarette smoking during a 6-week clinical trial for people that received a menthol-ENDS relative to those that received a chocolate-, cherry-, or tobacco-ENDS (Litt, Duffy et al., 2016).

EMA methods are important complements to clinical laboratory-based assessments of abuse liability as they can validate results externally as well as reveal social and environmental influences on tobacco use (Shiffman, 2009a). Moreover, techniques for assessing tobacco product use in a participant's natural environment can be used together (e.g., EMA with periodic TLFBs) to mitigate issues arising from missing data (Cobb, Foulds et al., 2021).

Previous Investigations of IQOS' Abuse Liability Involving Human Participants

Despite the utility of abuse liability assessments for informing tobacco product regulation, few independent studies have used these methods to index IQOS's abuse liability among people that smoke (Adriaens, Gucht et al., 2018; DeAtley, Stone et al., 2022; Leavens, Lambart et al., 2023; Funk, Nollen et al., 2023; Maloney, Eversole et al., 2020; Phillips-Waller, Przulj et al., 2021; Stone, DeAtley et al., 2022; Yingst, Bordner et al., 2023; Kale, Tattan-Birch et al., 2023). Furthermore, almost all of the current clinical trial data regarding IQOS has been funded by the tobacco industry. The following section summarizes the results from each of the independent human abuse liability assessments of IQOS conducted thus far.

In one independent study, the nicotine delivery profiles and self-reported effects of IQOS and OB cigarettes were compared using a within-participants design (Maloney, Eversole et al., 2020). The study involved 18 people that smoked cigarettes and completed three clinical laboratory sessions with the following products: OB cigarettes, JUUL, and IQOS. Following a 10-puff directed use bout, OB cigarettes boosted plasma nicotine concentrations on average from 2.1 ng/mL to 20.4 ng/mL and IQOS boosted plasma nicotine concentrations from 2.1 ng/mL to 12.7 ng/mL ($p < 0.05$). Differences in abstinence symptom suppression were not significant across the IQOS and OB cigarette conditions (Maloney, Eversole et al., 2020). Of the 18

participants, 10 (56%) used menthol cigarettes and IQOS flavors ("amber" [regular/tobacco] and "green" [menthol] HEETS) were matched to OB cigarette flavor but analyses did not consider the influence of flavor on study outcomes (Maloney, Eversole et al., 2020). In sum, results suggested that IQOS is a potential substitute for OB cigarettes, at least on par with the popular ENDS product "JUUL," though it may not be as psychologically rewarding as cigarettes (Maloney, Eversole et al., 2020).

Another clinical laboratory study involved 22 people that used ENDS every day and that used fewer than one cigarette per day (Phillips-Waller, Przulj et al., 2021). Following a 5-minute *ad lib* use period, IQOS delivered less nicotine than OB cigarettes (nicotine boost: ~12 ng/mL [IQOS] versus ~18 ng/mL [OB]) and JUUL (5.9% nicotine concentration; nicotine boost: ~20 ng/mL; Phillips-Waller, Przulj et al., 2021). IQOS use did not alleviate cravings for cigarettes/nicotine as much as JUUL (Phillips-Waller, Przulj et al., 2021). All participants used tobacco-flavored HEETS with IQOS and the "Virginia Tobacco" flavor of JUUL regardless of OB cigarette flavor preference. Results from this investigation suggest that IQOS may have sub-optimal abuse liability to encourage substitution among established ENDS users that smoke cigarettes occasionally and illustrates how restricting access to preferred flavors may reduce IQOS' abuse liability.

In another independent clinical laboratory study, 30 individuals in Belgium that smoked cigarettes were asked to use either IQOS, an ENDS, or their OB cigarette during a three-day inpatient observation study (Adriaens, Gucht et al., 2018). The study used a cross-over, counterbalanced, within-participants design and assessed eCO and self-reported effects (e.g., cigarette craving) before and after 5-minute *ad lib* use bouts with each product. IQOS use was associated with a small but reliable boost in eCO, suppressed a summary measure of tobacco

abstinence symptoms, and was rated as less aversive than OB cigarettes (Adriaens, Gucht et al., 2018). However, though IQOS did reduce cigarette craving, it did so less than OB cigarettes (Adriaens, Gucht et al., 2018). IQOS was rated higher with respect to subjective reward/satisfaction than the ENDS that was tested (Adriaens, Gucht et al., 2018). IQOS flavors were intended to be matched to OB cigarette flavor preference; however, no individuals that used menthol cigarettes enrolled in the study. Results from this study support the possible role of IQOS as a cigarette substitute within the context of other products promoted as lower harm alternatives (Adriaens, Gucht et al., 2018) but also highlight areas where IQOS use falls short of the OB cigarette smoking experience.

A more recent set of studies recruited nontreatment-seeking adults that smoked cigarettes every day (N=33) but were interested in quitting to complete a pilot study involving an at home OB cigarette smoking period (days 1-5), two clinical laboratory visits (days 6-7), and a two-week period of attempted switching from OB to IQOS (DeAtley, Stone et al., 2022; Stone, DeAtley et al., 2022). Roughly 67% of the participants (N=22) used menthol cigarettes and IQOS flavor was matched to OB cigarette flavor. During the laboratory visit on day 6, participants used IQOS in a 14-puff directed use bout following a 10-hour cigarette abstinence period and self-reported effects were evaluated before and after the bout (DeAtley, Stone et al., 2022; Stone, DeAtley et al., 2022). On day 7, following overnight abstinence, the reinforcing value of IQOS relative to cigarettes was assessed using a behavioral economic cross-product progressive ratio task. Clinical laboratory results suggested that IQOS reduced cigarette craving but did not alleviate other tobacco abstinence symptoms such as irritability, difficulty concentrating, or feelings of depression (Stone, DeAtley et al., 2022). Additionally, participants substituted 87% of their baseline consumption of cigarettes with IQOS by the end of the two-week switch period on

average (Stone, DeAtley et al., 2022). Participants who earned the fewest puffs from their OB cigarettes in the cross-product progressive ratio task (i.e., worked for more IQOS puffs) replaced more of their baseline cigarettes with HeatSticks while at home (Stone, DeAtley et al., 2022). Participants with higher risk perceptions of IQOS replaced fewer of their OB cigarettes with HeatSticks during the switch period (DeAtley, Stone et al., 2022). However, neither analysis from this set of studies considered the possible influence of menthol on the outcomes assessed.

Another independent abuse liability study focused on people that smoke menthol cigarettes and the menthol flavor of IQOS specifically (Yingst, Bordner et al., 2023). Eight adults that smoked at least four menthol cigarettes per day completed a directed puffing bout (14 puffs, 20 second IPI) with “Fresh Menthol” HeatSticks and IQOS 2.4 (Yingst, Bordner et al., 2023). Participants reported on self-reported effects and plasma nicotine was sampled before and after the directed puffing bout with IQOS. The mean nicotine boost for Fresh Menthol IQOS was 15.96 ng/mL, most participants reported enjoying using IQOS “a lot,” and 62.5% of participants reported reduced cigarette cravings following the directed use bout (Yingst, Bordner et al., 2023). However, participants did not consider IQOS to be as rewarding as OB cigarettes (Yingst, Bordner et al., 2023). This study provides important foundational information on the influence of flavors in HTPs among people that use menthol cigarettes but needs to be expanded upon with a larger sample size, the use of more than an acute IQOS exposure paradigm, addition of a control condition (e.g., OB menthol cigarettes), comparisons to regular/tobacco-flavored IQOS, as well as collecting collateral puff topography, behavioral economic, and naturalistic use data. Overall, results of this clinical laboratory study suggest that IQOS delivers a reinforcing amount of nicotine to people that use menthol cigarettes and the HTP’s use experience may be similar enough to OB menthol cigarettes to permit some substitution (Yingst, Bordner et al., 2023).

Another investigation asked 22 people that smoked cigarettes (two-thirds used menthol) to complete a three-session clinical laboratory study of OB, JUUL, and IQOS (Leavens, Lambart et al., 2023). Participants were allowed to choose the flavor of IQOS (i.e., Regular/Tobacco, Fresh Menthol, or Smooth Menthol HeatSticks) and JUUL they used throughout the study. OB cigarettes delivered higher levels of nicotine to the blood following a 5-minute directed use bout as well as a 60-minute *ad lib* use bout than IQOS (Leavens, Lambart et al., 2023). OB cigarettes, IQOS, and JUUL all reduced symptoms of tobacco abstinence after use but OB cigarettes decreased cravings for a cigarette to a greater extent than IQOS and JUUL following the directed use bout (Leavens, Lambart et al., 2023). A companion study found that participants were willing to substitute with IQOS as the work-requirement to earn puffs of OB cigarettes increased (Funk, Nollen et al., 2023). This set of studies demonstrate how plasma nicotine, self-reported effects, and behavioral economic abuse liability assessments can be integrated into a single experimental design and suggest that IQOS may substitute for OB at least well as JUUL; however, these investigations were not designed to evaluate flavoring effects (Leavens, Lambart et al., 2023; Funk, Nollen et al., 2023).

A final independent abuse liability assessment recruited individuals that smoked cigarettes to complete a multi-session clinical laboratory study in the UK concerning OB cigarettes, IQOS, and JUUL (Kale, Tattan-Birch et al., 2023). Participants (N=45) were allowed to choose the flavor of IQOS and JUUL they used during the study. IQOS reduced cravings to a greater extent and was perceived as more satisfying and similar to OB than JUUL (Kale, Tattan-Birch et al., 2023). Neither IQOS nor JUUL were rated as favorably on self-reported effects measures as OB cigarettes by participants (Kale, Tattan-Birch et al., 2023). Results of this investigation suggest that IQOS may be a more effective OB cigarette substitute than JUUL, but

that the HTP may not be reinforcing enough to facilitate complete substitution from cigarettes among people that smoke (Kale, Tattan-Birch et al., 2023).

Last, a WHO technical report aimed to summarize the literature on IQOS and other HTPs with respect to their abuse liability and compare findings from independent- and industry-funded studies (WHO, 2023). With respect to nicotine delivery, the report concluded: "Mainstream aerosol from IQOS delivers about 70% of the nicotine in the smoke of cigarettes. Relative nicotine delivery by IQOS is between 57% and 103%, with a median of 64.7% as compared with a reference cigarette… The median in studies funded by the tobacco industry is not statistically significantly different from the median in independent studies" (WHO, 2023, p. 61). The WHO report's conclusions demonstrate that IQOS' capacity to deliver nicotine approaches but does not match the drug delivery capacity of combustible cigarettes, thus IQOS may have a lower abuse liability than cigarettes (WHO, 2023). Whether or not IQOS' nicotine delivery is sufficient to support complete substitution and what effect flavors might have on nicotine delivery from IQOS among people that use menthol cigarettes remains undetermined.

In sum, the current literature supports the notion that IQOS can: deliver nicotine (though less than OB cigarettes on a puff-by-puff basis), reduce cravings for cigarettes (but not as much as OB cigarettes), be used in naturalistic settings as part of a clinical trial, and induce people that smoke cigarettes to exert some effort to access HTPs. This reading of the literature is consistent with a 2021 WHO report that concluded: "Thus, the abuse liability of at least some HTPs for which data are available is likely to be comparable to that of conventional cigarette. The liability may differ by HTP brand and type according to factors such as nicotine delivery, sensory properties (e.g., flavor) and ease of use" (WHO, 2021, p. 68). Similar sentiments were expressed by the FDA in their MRTP authorization of IQOS (FDA, 2020). Importantly though, prior studies

from the independent literature were not designed to determine whether IQOS substitutes for cigarettes among people that use menthol cigarettes nor whether flavor (i.e., menthol) influences HTP abuse liability. This project addresses those tobacco regulatory science evidence gaps.

Literature Gaps

There remain several gaps in the HTP/IQOS literature that may be relevant to regulators considering whether menthol-flavored HTPs should be available in the US. Foremost is that all of the HTP studies conducted to date have either allowed self-selection into flavor condition or matched HTP flavor with OB cigarette preference (Adriaens, Gucht et al., 2018; DeAtley, Stone et al., 2022; Leavens, Lambart et al., 2023; Funk, Nollen et al., 2023; Maloney, Eversole et al., 2020; Phillips-Waller, Przulj et al., 2021; Stone, DeAtley et al., 2022; Yingst, Bordner et al., 2023; Kale, Tattan-Birch et al., 2023). This design feature precludes prediction of what people might do if preferred flavors in HTPs are restricted from the marketplace. This limitation in the existing literature is important to address as FDA's proposed menthol ban could mean individuals that use menthol cigarettes will not have access to a menthol-flavored HTP following the ban's implementation. Moreover, the lack of random assignment to flavor conditions precludes assessing menthol's effect on puff topography, nicotine delivery, and self-reported effects in HTPs. One additional shortcoming of the experimental designs used in the existing independent literature is that all of the clinical laboratory experiments have involved acute exposure to HTPs among individuals that were HTP naïve (Adriaens, Gucht et al., 2018; DeAtley, Stone et al., 2022; Leavens, Lambart et al., 2023; Funk, Nollen et al., 2023; Maloney, Eversole et al., 2020; Phillips-Waller, Przulj et al., 2021; Stone, DeAtley et al., 2022; Yingst, Bordner et al., 2023; Kale, Tattan-Birch et al., 2023). Whether user behavior, subjective experiences, and the

reinforcing value of HTPs may change upon initial exposure to a later timepoint is not known. Furthermore, no behavioral economic data are available that focus on HTPs among participants that have actual experience with the product class. Lack of previous experience with HTPs may limit behavioral economic data if participants are unfamiliar with the products and thus unable to form stable preferences. As a result, new evidence is needed to determine whether HTPs are capable of serving as a substitute for menthol cigarette in the US and whether flavors in HTPs are necessary to support *complete substitution* for people that smoke cigarettes.

Another limitation of the literature is that most abuse liability studies of IQOS have captured only a few domains of reinforcement. To date, no studies have captured nicotine delivery, puff topography, behavioral economic demand, self-reported effects, and naturalistic use in one integrated design. The fracturing of these measures in the existing literature complicates a more comprehensive understanding of HTP abuse liability because of differences across study designs. The integration of multiple HTP abuse liability assessments would allow results from one abuse liability domain to be contextualized with findings from the other domains. Designs that feature multiple abuse liability assessments are commonplace in the study of other tobacco/nicotine products (Wall, Bono et al., 2018) but a comprehensive and independent investigation of modern HTP abuse liability is needed.

Last, there is a dearth of literature regarding whether the more internally-valid conditions of the clinical laboratory map to outcomes from the more externally-valid naturalistic use setting with respect to HTPs. The intertwining of these two experimental contexts would be an important development for the HTP literature by leveraging the strengths of both approaches and guiding the development of clinical laboratory-based abuse liability measurements.

Regulatory Implications

The 2009 Family Smoking Prevention and Tobacco Control Act granted FDA the authority to take actions with respect to the manufacture, distribution, and marketing of tobacco products that are deemed "appropriate for the protection of the public health" (Carvajal, Clissold et al., 2009). FDA asserts that its authority grants them power to regulate characterizing flavors and additives such as menthol in tobacco products (Carvajal, Clissold et al., 2009; FDA, 2021a, 2022e). To what extent HTPs that have been authorized as MRTPs should be subject to the same level of restriction as combustible cigarettes with respect to flavor availability is contentious (Theis, 2023). The decision regarding whether to permit characterizing flavors in HTPs is further complicated by a lack of non-industry funded empirical evidence on flavoring effects in HTPs. As the proposed menthol cigarette product standard stands, HTPs that meet the regulatory definition of a "cigarette" (e.g., IQOS) would be prohibited from using menthol as a characterizing flavor (FDA, 2022e; *United States v. Philip Morris USA, et al.,* 2023). However, FDA's proposed product standard also states that they would consider exemptions on a case-by-case basis (FDA, 2022e).

If IQOS-Menthol (IQOS-M; i.e., IQOS 2.4 with Fresh Menthol HeatSticks) is a stronger substitute for menthol cigarettes than IQOS-Tobacco (IQOS-T; i.e., IQOS 2.4 with Tobacco/Regulatory HeatSticks), regulatory policies that restrict access to menthol-flavored HTPs may have unintended consequences insofar as they might hinder people that use menthol cigarettes from switching to an MRTP. Setting aside legitimate unanswered questions surrounding the long-term health effects of HTPs as well as considerations for whether HTPs can function as complete cigarette substitutes, FDA might consider *exempting* some menthol-flavored HTPs from its proposed menthol cigarette ban. In the parlance of the "Regulatory

Stances" framework (Liber, 2022), the "prohibitionist" stance towards menthol in cigarettes may best be paired with a "permissive" or "expansionist" stance towards menthol in HTPs (Liber, 2022). A "permissive" or "expansionist" stance towards HTPs would create a relative market advantage for HTPs over cigarettes that may encourage substitution away from combusted products. However, if IQOS-M and IQOS-T are found to have similar abuse liability profiles and/or neither is a compelling substitute for menthol cigarettes, then menthol-flavored HTPs may not be adding sufficient public health benefit to offset their potential public health costs (e.g., flavors attracting youth users, sustaining nicotine dependence). In such a case, a "prohibitionist" or "contractionist" stance towards characterizing flavors in HTPs may be merited (Liber, 2022).

Statement of Problem

The tobacco industry has signaled its intent to invest in HTPs by capitalizing on the FDA's proposed ban on the sale of menthol cigarettes (Birch, 2020; Hiscock, Silver et al., 2020; PMI, 2020). However, the precise regulatory status of HTPs in the US has yet to be defined and a key, unresolved question will be to what extent regulators will allow HTPs with a characterizing flavor to be marketed. Answering this question will require balancing the ability for characterizing flavors (e.g., menthol) to attract youth/tobacco-naïve individuals or to sustain nicotine dependence among people that use combustible cigarettes and would otherwise quit *against* the potential public health utility of retaining MRTPs that are appealing enough to people that use combusted products to facilitate complete substitution (Krishnan-Sarin, O'Malley et al., 2019). Flavors are a well-established target in tobacco regulation and, given the lack of evidence on how flavors in influence HTP abuse liability, one that is ripe for empirical study.

Statement of Purpose

The current study aimed to characterize the abuse liability of IQOS as a function of its available flavors (menthol or regular/tobacco) via clinical laboratory and naturalistic abuse liability assessments among individuals that smoke menthol cigarettes. Studying the impact of flavors on HTP abuse liability among a policy-relevant population across multiple settings and beyond acute exposures will improve understanding of the pharmacologic, behavioral, subjective, and economic effects of HTPs and HTP flavors. Moreover, the combination of assessments employed here will make the present investigation one of the most thorough, independent abuse liability assessments of HTPs conducted to date.

Statement of Hypotheses

This study involves a two-week, parallel group randomized pilot clinical trial. During week 1, adults that smoke menthol cigarettes every day will use their OB menthol cigarettes in the clinical laboratory (Mon, Fri) and at home (Tues-Thurs). During week 2, participants will be randomized to receive IQOS with either the Fresh Menthol HeatSticks or Tobacco/Regular HeatSticks to use in the clinical laboratory (Mon, Fri) and at home as a substitute for OB menthol cigarettes (Tues-Thurs). The overarching hypothesis is that IQOS-M's abuse liability will exceed IQOS-T's, suggesting people that use menthol cigarettes may be more likely to substitute an HTP for OB menthol cigarettes when a menthol-flavored HTP is available. The specific aims and study hypotheses are summarized in Table 1:

Table 1. *Summary of study aims and hypotheses*

Aim 1: Assess IQOS' abuse liability among people that use menthol cigarettes in a clinical laboratory setting. In clinical laboratory sessions, participants will complete standard controlled product use episodes (10-puffs, 30-second inter-puff interval) with OB and IQOS (flavor randomly assigned). Blood will be sampled to assess nicotine/menthol delivery, puff duration and volume will be measured to assess use behavior, and self-reported effects (e.g., cigarette craving) and the Experimental Tobacco Marketplace (ETM) task will assess IQOS' substitutability for OB.			
H_{1A}***	Nicotine Delivery	Nicotine boost will be greater following use of IQOS-menthol than IQOS-tobacco.	[IQOS-M] > [IQOS-T]
H_{1B}	Puff Topography	Average puff duration will be greater for IQOS-menthol than IQOS-tobacco	[IQOS-M] > [IQOS-T]
H_{1C}	Subjective Effects	IQOS-menthol will suppress craving for cigarettes more than IQOS-tobacco.	[IQOS-M] > [IQOS-T]
H_{1D}***	Experimental Tobacco Marketplace	The cross-price elasticity of IQOS with respect to OB menthol cigarettes will be higher in a market with access to IQOS-menthol and IQOS-tobacco than it will be in a market with access only to IQOS-tobacco.	[IQOS-M] > [IQOS-T]
Aim 2: Measure tobacco use patterns across IQOS flavor availability conditions to assess clinical laboratory result validity. During two 7-day naturalistic evaluations outside of the clinical laboratory, participants will respond to daily ecological momentary assessment (EMA) prompts by reporting OB and IQOS use.			
H_{2A}***	Naturalistic Use	Those in the IQOS-menthol condition will have a larger percentage reduction in average daily cigarettes consumed per day (Tues-Thurs) from the baseline to the intervention week, than those in the IQOS-tobacco condition.	[IQOS-M] > [IQOS-T]
H_{2B}	Naturalistic Use	IQOS use per day will be higher during the intervention week (Tues-Thurs) in the IQOS-menthol condition compared to the IQOS-tobacco condition.	[IQOS-M] > [IQOS-T]

Note: *** designates primary outcome; all other hypotheses are considered secondary outcomes.

[OB] = Own brand menthol cigarette (purchased by laboratory staff), [IQOS-M] = IQOS 2.4 with Fresh Menthol HeatSticks, [IQOS-T] = IQOS 2.4 with Regular/Tobacco HeatSticks.

Methods

Participant Selection

Power analyses conducted at the time of study conceptualization determined that 50 participants would be sufficient to achieve 80% power (G*Power; Faul, Erdfelder et al., 2007). Sample size estimates were based on effect sizes observed in previous studies for the primary outcomes of this investigation: nicotine boost, CPE from the ETM, and percentage reduction in daily cigarette consumption from week 1 to week 2. Specifically, the main effect of condition (i.e., tobacco- versus menthol-flavored products) from previous studies (Ns~30) was medium-to-large for nicotine boost ($d>0.76$; Voos, Smith et al., 2020), large for CPE estimates in the ETM ($d>1.10$; Denlinger-Apte, Cassidy et al., 2021), and large for reductions in cigarette consumption ($d>1.24$; Litt, Duffy et al., 2016). The outcome measure with the smallest expected effect size (nicotine boost) was used to calculate the number of participants needed to complete the study.

In September 2023, after 30 individuals had completed the study, recruitment ended. The decision to end data collection prior to obtaining the sample size suggested by the power analyses was made for several reasons. Foremost, the products obtained for this study were deteriorating in quality. For example, participants reported that some HeatSticks tasted stale and that some IQOS devices were failing to hold a complete charge. The study team felt that further deterioration in product quality could compromise the integrity of the study design. Second, recruiting 20 additional participants before the end of 2023 was deemed impractical due to staffing and scheduling constraints. Third, the study team felt that the data collected as of September 2023 would be sufficient to publish as a pilot trial. Last, the study team believed rulemaking on menthol availability in HTPs was imminent and that the relevance of this work

may depend on timely publication. Due to the smaller than planned for sample size, statistical comparisons may be underpowered to detect true effects (type II errors).

Participants were recruited via word of mouth, IRB approved advertisements posted on Facebook and Craigslist, and the VCU Center for the Study of Tobacco Products' (CSTP) internal participant registry. All screening visits and clinical laboratory sessions took place in the clinical laboratory space at the CSTP in Richmond, Virginia. The "naturalistic use" periods were conducted in participant's home environments, monitored by daily EMA surveys.

Participants were required to satisfy the following inclusion criteria to be eligible for the study:

- be at least 21 years old,
- smoke an average of five or more cigarettes per day for at least one year,
- report using a "menthol or mint" cigarette as their usual brand,
- have an expired carbon monoxide concertation greater than five parts per million (ppm) at the time of screening,
- have a positive urine cotinine screen,
- have no intent to quit smoking within the next three months,
- be able to read and write in English,
- be willing to use IQOS in the laboratory and at home,
- be willing to comply with blood draw instructions,
- have access to a computer and/or smartphone and willing complete EMA surveys, and
- provide written informed consent to participate

Individuals were excluded from the study for the following reasons:

- reporting everyday use of any tobacco product other than cigarettes,

- having a systolic blood pressure exceeding 160 mmHG or diastolic pressure exceeding 100 mmHG at the time of screening,
- reporting > 25 days of alcohol use in the past 30 days, > 15 days of marijuana use in the past 30 days, or > 0 days of illicit drug use in the past 30 days at the time of screening,
- having a current and uncontrolled psychiatric condition,
- reporting a past year hospitalization or Emergency Room visit for a psychiatric indication,
- reporting any current heart related condition (e.g., recent heart attack/stroke, coronary heart disease), severe immune system disorder (e.g., HIV/AIDS, multiple sclerosis), respiratory disease (e.g., COPD, asthma), kidney or liver disease, seizure disorder,
- reporting of other medical conditions (e.g., diabetes, Lyme disease, thyroid disease) or use of a medication were considered for exclusion after consultation with the medical monitor and principal investigator,
- testing positive for pregnancy, and
- self-reporting breastfeeding.

Having made a previous attempt to quit smoking with an "evidence-based" cessation aid (e.g., NRT, counseling or self-help program, medication) was also an inclusion criterion at the start of recruitment for this study. After the first month of recruitment this criterion was dropped to increase the pool of potential participants to contact and out of recognition that individuals that had never attempted to quit smoking may search for a cigarette substitute following a menthol cigarette ban. One individual deemed ineligible due to never attempting to quit smoking in the past was recontacted after this change in the inclusion/exclusion criteria was adopted, screened again, and completed the study.

Screening and Informed Consent Procedures

Individuals interested in participating in the study were screened for eligibility using the CSTP's two-phase screening procedure. In phase 1, potential participants completed a "pre-screening" questionnaire available on the CSTP's secure website or by speaking on the phone with study personnel. All advertisements directed interested individuals to complete the pre-screening questionnaire. The pre-screening questionnaire assessed the potential participant's health status, tobacco use history, other substance use history, and availability. Individuals that appeared eligible were contacted by study personnel, provided with a description of the present study, and asked if they would like to complete an in-person screening visit at the CSTP.

When potential participants arrived at the CSTP for the in-person screening visit (phase 2), they were placed in a private session room with a computer and an unsigned copy of the consent form. The research assistant directed the participant to follow along as a video narrated the consent document. After viewing the video, participants were given a 5-minute period to generate questions they had about the study and consider whether they wished to participate. Following the rest period, the research assistant entered the room and addressed the participant's questions. The research assistant reviewed the main points of the consent document (e.g., study schedule, research purpose, participant expectations, compensation) then asked the potential participant if they would like to enroll in the study. Participants who agreed to enroll were asked to sign and date the consent form. After written and verbal consent was obtained, participants completed a baseline questionnaire that collected contact information, demographic information, health history, tobacco use history, substance use history, and nicotine dependence severity (Appendix 1). Individuals that were deemed "potentially eligible" at this stage provided a urine sample to test for cotinine (Accutest Cotinine test device, Jant Pharmaceutical Corp) and

pregnancy (Accutest Value hCG urine pregnancy test, Jant Pharmaceutical Corp), an eCO sample (BreathCO, Vitalograph), and had their heart rate (HR) and blood pressure (BP) measured (Vitalcare model 507, Criticare Systems). A second research assistant then confirmed that the participant satisfied all eligibility criteria. Eligible participants were told that they must begin the study on a Monday within two weeks then scheduled their four subsequent clinical laboratory sessions. At the end of the in-person screening session all eligible participants were asked to take four test puffs of the IQOS 2.4 with the Regular/Tobacco HeatSticks. Sampling of IQOS-T was done so that each participant had basic familiarity with IQOS before beginning the study. All individual that attended the screening session and watched the consent video were compensated ($25) for their time.

Reminder text messages were sent to each participant one-to-two days before each scheduled session as well as on the morning of their appointment. Appointment reminder messages also prompted participants about requirements for participation (e.g., bringing a pack of their OB cigarettes, eight hours of tobacco/nicotine abstinence prior to all clinical laboratory session, hydration to prepare for blood draws, returning loaned IQOS products) in the study.

Materials

During each of the four clinical laboratory sessions participants were provided with either their OB menthol cigarettes (Monday and Friday of week 1) or the IQOS 2.4 Tobacco Heating System with either “Regular” or “Fresh Menthol” HeatSticks (Monday and Friday of week 2). All products used in the clinical laboratory (Aim 1) were provided to participants for free. For the naturalistic use periods, participants supplied their OB cigarettes during weeks 1 and 2. During week 2, participants were provided with an IQOS 2.4 and their assigned flavor of

HeatSticks to use at home. Participants were given HeatSticks in packs of 20, in their original packaging, and in sufficient quantity to be used for the duration of the intervention week (i.e., equal to the number of cigarettes smoked during the baseline week plus 20%).

Most of the IQOS devices and HeatSticks used in this study were purchased in August 2020 for another study that was never implemented. In November 2021 five additional IQOS 2.4 tobacco heating systems and 50 additional packs of "Fresh Menthol" HeatSticks were purchased from Altria at full retail price. All study products were kept in their original sealed packaging, in an air-conditioned room, within a lockbox stored in a locked file cabinet. In July 2023, all unopened HeatSticks were moved to a refrigerator to preserve freshness. Unused HeatSticks were disregarded one week after a pack was opened. A new pack of cigarettes was purchased for each participant's use in the clinical laboratory following their screening visit from local retailers at full price. Packs of cigarettes were not opened until the first clinical laboratory session of the participant they were purchased for began. Opened packs of cigarettes were kept in a sealed zip-lock bag placed in a file cabinet in an air-conditioned room and were discarded after one week.

Procedures

Overview of Design

Eligible participants completed a two-arm, parallel group, two-week pilot clinical trial involving clinical laboratory and naturalistic use assessments of abuse liability for OB menthol cigarettes and IQOS. During week 1, participants completed OB menthol cigarette baseline assessments involving two clinical laboratory sessions (Mon and Fri) and naturalistic use assessments (daily). For the second week of the study, procedures from week 1 were repeated but participants were randomized (1:1 allocation) to receive IQOS 2.4 with either Fresh Menthol

HeatSticks or Regular/Tobacco HeatSticks to use in the clinical laboratory (Mon and Fri) and instructed to attempt to use their assigned IQOS product as an OB menthol cigarette substitute at home (daily).

Randomization was stratified by sex (male versus female) and race (AA/B versus non-AA/B). Within each of the four resulting strata, block randomization with random block sizes of 2 and 4 were used to allocate participants across experimental groups (i.e., IQOS-M group and IQOS-T group). The condition order sequence was generated on sealedenvelope.com (Singh, 2014) and saved in a password protected file. The randomization procedures adopted in this study ensured balance across sex and race in condition allocation but prevented the researcher from being able to predict the allocation sequence. This trial was conducted "open label" because the IQOS HeatSticks were distinguishable based on appearance, smell, and taste. Participants were randomized at the start of the first clinical laboratory session (Mon, week 1) but their condition assignment was not revealed to them until the puffing bout during the third clinical laboratory session (Mon, week 2). Randomization at the first clinical laboratory session was necessary to allow for the proper set of ETM alternative product choices to be displayed at clinical laboratory sessions that occurred during week 1.

The present study was divided into three phases: screening/enrollment, baseline week (use OB menthol cigarettes), and intervention week (use randomly-assigned IQOS products). In the screening/enrollment phase, participants completed the CSTP/BHRL registry and an in-person screening session at the CSTP as was described previously. During the baseline and intervention weeks, participants completed clinical laboratory sessions (see "Aim 1" below) and naturalistic use (see "Aim 2" below) assessments (Figure 3).

	Pre-screen	Screen	Mon	Tues -Thurs	Fri	Sat-Sun	Mon	Tues-Thurs	Fri	Sat-Sun
Study Day	NA	0	1	2, 3, 4	5	6, 7	8	9, 10, 11	12	13, 14
Phase	**Screening/Enrollment**		**Baseline Week (Week 1)**				**Intervention Week (Week 2)**			
Primary Product	**N/a**		**Own-Brand Menthol Cigarettes**				**IQOS-Menthol(M) or IQOS-Tobacco(T)**			
Main Activity	Online Survey	In-person screening + IQOS Sampling	Lab Visit 1 + Randomization	Natural Use (EMA)	Lab Visit 2	Natural Use (EMA)	Lab Visit 3 + IQOS Distribution	Natural Use (EMA)	Lab Visit 4	Natural Use (EMA)
Time	10 min	60 min	120 min	3 min/day	120 min	3 min/day	120 min	3 min/day	120 min	3 min/day
Relevant Measures	Baseline Demographics, Health, and Tobacco Use		Aim 1	Aim 2	Aim 1	Aim 2	Aim 1	Aim 2	Aim 1	Aim 2

Figure 3. Study timeline with relevant activities for each day of the observation window

Factors outside the participant's or the researcher's control sometimes impaired strict adherence to the study timeline. To handle missed sessions, the following procedures were adopted:

- If an in-person screening session was missed, the screening session was rescheduled at the participant's convenience.
- If the participant missed one of the baseline week visits, the missed session was not rescheduled. In these instances, the single baseline visit that was completed was taken as the control comparison in statistical analyses (n=6; all missed appointments occurred on Monday [session 1]). If two baseline visits were completed, the Friday (session 2) results served as the control comparison.
- If a participant missed their Monday intervention week visit (session 3), the session was rescheduled for the next Monday the participant was available (n=1).
- If a participant missed their Friday intervention week visit (session 4), that session was rescheduled for the next business day the participant was available (n=3).

These procedures were adopted to promote retention of participants throughout the study and minimize data loss without compromising the integrity of the experimental design.

Participants were compensated for their time: $25 for in-person screening, $2 for each complete EMA assessment (14 total), $50 for each of two Monday sessions, and $100 for each of two Friday sessions. The maximum possible compensation for a participant that completed this study was $353. Participants were also reimbursed up to $12/session for parking if needed.

Specific Study Procedures - Aim 1

Aim 1 involved four clinical laboratory sessions: the first two clinical laboratory sessions concerned participants' OB menthol cigarette and the second two clinical laboratory sessions concerned participants' randomly-assigned IQOS product (i.e., IQOS-M or IQOS-T). Each clinical laboratory session was two hours in length. Tasks performed during clinical laboratory sessions included: check-in, a series of self-reported effects questionnaires, a directed use bout with the session product and concurrent puff topography measurement, a nicotine delivery assessment, and the ETM (Figure 4).

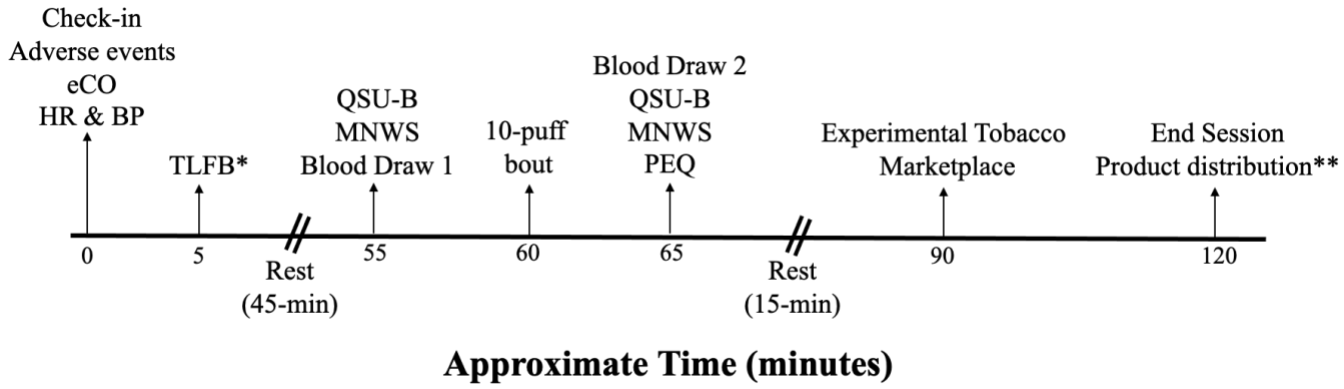


Figure 4. Timeline of measurements during clinical laboratory sessions

Note: *Three-day timeline follow back (TLFB) was only conducted during session 2 (Friday; study day 5) and session 4 (Friday; study day 12),

**IQOS product were only distributed at the end of session 3 (Monday; study day 8).

eCO = exhaled Carbon Monoxide,

HR = Heart Rate,

BP = Blood Pressure,

QSU-B = Questionnaire of Smoking Urges – Brief,

MNWS = Minnesota Nicotine Withdrawal Scale,

PEQ = Product Evaluation Questionnaire.

Check-in and Biomarker Assessment

Participants were asked, but not required, to abstain from using tobacco and nicotine products for the eight hours before each clinical laboratory session. Each clinical laboratory session began by obtaining an eCO sample and asking participants whether they had abstained from using tobacco or nicotine products over the preceding eight hours. Before beginning the rest of the clinical laboratory session, participant's HR and BP were taken and interval adverse events were assessed. During the two Friday sessions (sessions 2 and 4), participants completed a TLFB assessment to report on their usage of cigarettes, IQOS, and other tobacco products during the preceding three days (Tues-Thurs). After completing these check-in procedures, participants had a 45-minute supervised rest period before the acute self-administration portion of the session.

Acute Self-Administration Procedures (Nicotine Delivery, Puff Topography, Self-Reported Effects)

Following the 45-minute rest period participants completed two self-reported effects questionnaires (i.e., pre-puff self-reported effects): the QSU-B and MNWS (Appendix 2). All self-reported effects questionnaires were computer administered via REDCap.

- The QSU-B was developed to measure nicotine abstinence symptoms (Cox, Tiffany et al., 2001). The QSU-B is a measure of 10 smoking related items (e.g., "I have a desire for a cigarette right now") and each item is rated on a Likert-like discrete choice scale ranging from 1 (not at all) to 7 (extremely). The QSU-B's 10 items are collapsed into two factors in most analyses (Cox, Tiffany et al., 2001): factor 1 measures "the desire and intention to smoke with an anticipation of

pleasure from smoking" (mean response to questions 1, 3, 6, 7, and 10) and factor 2 describes "the relief from nicotine withdrawal or negative affect with an urgent and overwhelming desire to smoke" (mean response to questions 2, 4, 5, 8, 9).

- The MNWS is an 11-item measure used to assess nicotine/tobacco abstinence symptoms including cigarette cravings (Hughes & Hatsukami, 1986). Items are rated on a 100 mm visual along scale (VAS), bounded by "Not at all" (0) and "Extremely" (100) labels. Responses were recorded via a computerized VAS and were expressed as a percentage of total line length. Though some report a summed score of all questions on the MNWS (Bello, Schulte et al., 2024), reporting of individual items is preferred (Hughes & Hatsukami, 1998).

Following completion of the pre-puff self-reported effects questionnaires the research nurse collected a 7 mL blood sample (pre-puff blood sample) either from a venous catheter or with venipuncture. If venipuncture was used, at most three attempts were made to obtain a blood sample.

After the pre-puff blood sample was taken, participants completed a directed puffing bout with that session's designated product. All puffing bouts consisted of 10 puffs with a 30-second IPI. This puffing protocol is similar to the WHO's Intensive Smoking of Cigarettes regimen used in machine-based studies of topography and toxicant emissions, selected because it mimics the natural smoking behaviors of people that use cigarettes following a period of abstinence (Hammond, Wiebel et al., 2007). The IPI was defined as the time from the start of one puff to the beginning of the next and was thus inclusive of the puff itself (Hiler, Breland et al., 2017). All tobacco products were fitted with specialized mouthpieces, manufactured for this study at the American University of Beirut (AUB), that detected air flow-induced pressure changes across an

orifice as a result of inhalation. The mouthpieces were connected to puff topography instruments (software: eTOP) that converted the measured air flow-induced pressure changes to five outcome variables: puff duration, puff volume, flow rate, puff number, and inter-puff interval (Blank, Disharoon et al., 2009; Felicione, Karaoghlanian et al., 2020; Hiler, Breland et al., 2017). Prior work has established that these procedures are sensitive enough to measure puff velocities as low as 3 mL/second (Spindle et al., 2017). Mouthpieces were cleaned and calibrated using an automatic digital flow calibrator prior to each session. If the cigarette extinguished or the IQOS device turned off prior to the 10th puff, no further puffs were taken but the time set aside for the puffing bout was observed.

Following the 10-puff directed use bout an additional 7 mL blood sample was taken (post-puff blood sample) and the QSU-B and MNWS were repeated (post-puff self-reported effects). Participants then completed a modified PEQ and answered several study-specific questions (e.g., relative and absolute harm perceptions, enjoyment of flavor, harshness/irritancy) pertaining to that session's product (Appendix 3). The PEQ is a 21-item measure intended to capture self-reported subjective reinforcing and aversive experiences associated with tobacco use (Cappelleri, Bushmakin et al., 2007; Hatsukami, Zhang et al., 2013). Historically, the PEQ has been summarized by reporting on four factors: satisfaction, psychological reward, aversion, and relief (Hatsukami, Zhang et al., 2013). More recent work conducted among people that smoke cigarettes, however, proposes that the PEQ consists of four new subscales: stimulant effects, positive reinforcement, negative reinforcement, and aversion (Morean & Bold, 2022). Under this latter framework, adults that smoke menthol cigarettes have reported stronger stimulant and positive reinforcement effects associated with use of their OB cigarette than adults that smoke nonmenthol cigarettes (Morean & Bold, 2022). Question stems for the PEQ were modified to

specify “own brand menthol cigarette” (sessions 1 and 2) or “IQOS/IQOS HeatSticks” (sessions 3 and 4) as appropriate.

Blood samples obtained during each clinical laboratory session were centrifuged by the research nurse after collection. The resulting plasma from each blood sample was separated into two vials: one to analyze for plasma nicotine concentration and another to analyze for plasma menthol concentration. Serum samples were stored at -70^{o}C. Plasma samples were sent to VCU’s Department of Pharmaceutics and Bioanalytical Core Laboratories to analyze for nicotine concentration (Breland, Kleykamp, & Eissenberg, 2006). The limit of quantitation (LOQ) for nicotine concentration was 2.00 ng/mL. Values below the LOQ were replaced with 2.00 ng/mL to provide a conservative estimate of nicotine delivery (Vansickel, Cobb et al., 2010). Serum samples for plasma menthol concentration have not yet been analyzed (Jatlow, Valentine et al., 2018).

Experimental Tobacco Marketplace

After the acute self-administration portion of the session, participants had a 15-minute rest period then completed the ETM task (Appendix 4). At each clinical laboratory session instructions for the ETM were read aloud by the research assistant (Appendix 5) and the participant reviewed the task’s instructions on the computer. Participants were told they were being given a hypothetical budget to buy the tobacco/nicotine products they would use during a typical week. Each participant’s hypothetical budget in the ETM was set equal to the amount of money they reported spending on tobacco/nicotine products during a typical week during the in-person screening session. Participants were told that all purchases were hypothetical, that they should make selections as if the products displayed in the ETM were the only products available

to them, that they could not stockpile products for the future, that they possessed any equipment needed to use purchased products, that they did not have to spend their entire budget but could not spend more than their budget allowed, and that all products were offered in their preferred brand and flavor unless noted otherwise. Before submitting purchasing decisions when completing the ETM, participants had to confirm their intended purchase amount for each product. The minimum task time for the ETM was set to 20 minutes. Participants completed a novel version of the computerized ETM that was created in REDCap for this study.

Participants were asked to make purchasing decisions across an array of available tobacco/nicotine products, including IQOS and OB menthol cigarettes, as their OB menthol cigarettes became more expensive. The task involved a total of eight "price trials" of OB menthol cigarettes: $0.12, $0.50, $1.00, $1.50, $2.00, $4.00, $8.00, $16.00 per cigarette. The order of price trials was randomized for each clinical laboratory session but was held constant across participants. The price trial order for each session was determined using the random number generator function in Microsoft Excel. The prices of all alternative products (e.g., IQOS) were held constant at each price trial and were based on their 2022 market price in Richmond, Virginia or estimates from previous ETM studies (Bickel, Pope et al., 2018). All IQOS HeatSticks were $0.30/HeatStick in the ETM corresponding to a pack price of $6.00.

The ETMs were identical across the IQOS-M and IQOS-T groups with one exception: participants in the IQOS-M group could buy Regular/Tobacco HeatSticks and Fresh Menthol HeatSticks but participants in the IQOS-T condition could buy Regular/Tobacco HeatSticks only. Differing the HeatSticks available for purchase by group was done to mimic the policy alternatives of retaining menthol HTPs in the tobacco marketplace following a menthol cigarette ban (IQOS-M; "open" market) as opposed to including HTPs in the broader menthol ban (IQOS-

T; “restricted” market). Purchases of the two available flavors of IQOS HeatSticks were aggregated to determine total IQOS demand at each price trial in the “open” market condition (i.e., IQOS-M group). The primary outcome for the ETM was IQOS’ CPE with respect to OB menthol cigarettes.

Specific Study Procedures - Aim 2

Participants reported use of OB menthol cigarettes and their assigned IQOS product while at home by responding to EMA prompts (text or email, based on participant preference) sent each day of the two-week study period (Appendices 6 and 7). To avoid confounding from clinical laboratory sessions and weekends, primary outcomes concerned EMA prompts corresponding to consumption on Tuesday, Wednesday, and Thursday of each week. All EMA prompts instructed participants to report their tobacco use from the previous day (12:00 AM-11:59 PM) across three items: number of OB menthol cigarettes, number of IQOS HeatSticks, and any other tobacco product use (yes/no). Daily surveys were distributed via REDCap’s (Harris, Taylor et al., 2009) native email distribution feature or REDCap’s integration with the Twilio text messaging service. EMA prompts (Appendix 7) were sent at 8:00 AM each morning of the two-week observation window and if a participant failed to respond by 12:00 PM a reminder prompt (identical to the first) was sent. At the start of the two Friday clinical laboratory sessions participants completed a computerized three-day TLFB (Appendix 6) on REDCap covering their use of OB menthol cigarettes, IQOS HeatSticks, and other tobacco products from the preceding Tuesday, Wednesday, and Thursday.

On Monday of the intervention week (session 3), at the conclusion of the clinical laboratory session, participants were given an IQOS 2.4 and HeatSticks in their randomly-

assigned flavor. Participants received verbal and printed instructions regarding how to use IQOS (Appendix 8). IQOS products were distributed in their original packaging and placed in a solid black fabric bag. Before leaving the clinical laboratory, all participants demonstrated the proper technique for charging, using, and cleaning the IQOS device. Participants were provided with the same number of HeatSticks as cigarettes they reported consuming at home during the baseline week plus 20% (rounded up to the nearest whole pack) to account for potential product loss or increases in use. Participants were instructed "We are providing you with a heated tobacco product known as IQOS in the [condition] flavor over the next week to be used as a substitute or complete replacement for your own brand cigarettes. We want to understand how you use these specific heated tobacco products as well as your own brand cigarettes when they are the only products available to you. Therefore, please refrain from using all other nicotine/tobacco products and other heated tobacco product flavors for the duration of the study. If you use anything else, it is important that you tell us what you used. Additionally, please return all of the IQOS products and any unused HeatSticks at your laboratory visit on Friday."

Participant Safety and Rights

Study protocols and procedures were approved initially by the VCU Institutional Review Board (IRB) on August 5th, 2022 (HM20024873). IRB-approved staff members at the CSTP were trained to ensure that participant safety and rights were maintained throughout the study. During the screening process, eligible participants took four test puffs of IQOS to ensure their comfort with using the study product. Participants were instructed that they would receive *either* the tobacco or the menthol flavor of IQOS HeatSticks during the second week of the study but that their condition assignment would be determined randomly. The consent document explained

the state of IQOS' market availability and that participants would not have access to IQOS products after the study.

Participants were informed of the side-effects they might experience as part of study-related cigarette and HTP use (e.g., nervousness, nausea, lightheadedness, cough, throat irritation). Participants were also informed that they may experiences symptoms of nicotine abstinence (e.g., irritability, anxiousness, difficulty concentrating). While side-effects of tobacco use and abstinence may be uncomfortable, they are not considered medically dangerous. We assessed whether participants had experienced any adverse events since their last interaction with study staff at the beginning of each clinical laboratory session with a computerized questionnaire and participants were instructed to contact the medical monitor if they experienced any untoward event as a result of their participation in the study.

The CSTP's trained research nurse minimized risks and discomforts associated with blood draws by using sterile equipment and aseptic techniques. The medical monitor and principal investigator were notified if a participant's systolic BP exceeded 160 mmHg, diastolic BP exceeded 100 mmHg, or HR exceeded 120 bpm for a sustained period of time. Participants with abnormal BP or HR readings were assessed for symptoms of hypertensive emergency and/or urgency (e.g., changes in vision, headache, poor coordination, nausea/vomiting). Three participants had BP readings >160/100 mmHg after screening but after denying symptoms of hypertensive emergency/urgency, the medical monitor allowed all three participants to complete the study. One additional participant had elevated BP readings (>170/110 mmHg) and was removed from the study before the first clinical laboratory session was completed due to an inability to establish a BP below threshold. All hypertensive episodes were determined to be unrelated to the study intervention as they occurred during the baseline week at the beginning of

the first session (Mon, week 1). No serious side effects were reported during the study, no unanticipated adverse events were documented, and no adverse events were related to the intervention.

Potentially identifiable information was collected including participant's name, signature, social security number, birthdate, address, and other basic demographic information. Consent forms (Appendix 9) were stored apart from all other research data. All paper and computer-based research data were identified by an alphanumeric code and stored in locked cabinets in locked rooms only accessible to CSTP staff or saved on VCU's REDCap server. All computers with access to study data were password protected. One data breach occurred during the course of this study; a CSTP staff member who was unaffiliated with the study but responsible for handling payment-related tax documents sent information from eight participants to a third-party vendor inadvertently. The IRB was notified of this data breach, corrective action was taken, and all affected participants were offered one year of free credit monitoring.

Participants were allowed to stop participating in the study at any time without penalty and could keep all earned compensation. Participants could be withdrawn by the investigator without consent for a variety of reasons including: noncompliance with study procedures, failure to attend clinical laboratory sessions, and protection of participant's health/safety. Two participants withdrew from the study due to scheduling conflicts, one was withdrawn by the investigator due to health/safety concerns, and one participant was withdrawn by the investigator for failing to attend scheduled sessions.

Outcome Measures and Data Analysis Plan

The instruments (Table 2) used in this study and the statistical analysis plan for each outcome are described below. All statistical analyses were performed in Stata (version 17; College Station, Texas) and GraphPad Prism (version 9; Boston, Massachusetts). Primary and secondary study outcomes were compared across the IQOS-M and IQOS-T groups. Shapiro-Wilks tests for normality determined that all primary and secondary outcome measures (stratified by group assignment and measurement occasion) followed a non-normal distribution (each $p < 0.05$) and there were no conventional transformations that could be applied to the data to approximate normality. The non-normal distribution of the outcome data coupled with small subgroup sample sizes necessitated the use of non-parametric statistical tests (described below). To minimize the impact of outliers when reporting the central tendency of the outcome measures, sample medians and interquartile ranges (IQR) are reported for most outcomes instead of means and standard deviations. Two-sided tests with alpha set to 0.05 were used in all hypothesis testing.

Table 2. *Summary of measures and instruments for each phase of the study*

	Pre-screen	**In-Person Screening**	**Clinical Laboratory Sessions**	**Daily Surveys**
Study day	NA	0	1, 5, 8, 12	1-14
Demographics	X	X		
COVID-19 screening questionnaire		X	X	
Heart rate and blood pressure monitoring		X	X	
Urine pregnancy and cotinine tests		X		
Exhaled carbon monoxide		X	X	
Tobacco use history	X	X		
Drug and alcohol use history		X		
Health and medical history	X	X		
Reasons for flavored tobacco use		X		
Contact information		X		
Cigarette dependence		X		
Test puffs (4) of IQOS-Tobacco		X		
Adverse events			X	
Three-day timeline follow back			X	
Self-reported effects questionnaires (Questionnaire of Smoking Urges-Brief, Minnesota Nicotine Withdrawal Scale, Product Evaluation Questionnaire)			X	
Plasma nicotine & menthol delivery			X	
Puff topography			X	
Experimental Tobacco Marketplace			X	
Ecological momentary assessment (i.e., daily diaries)				X

Aim 1 Analyses.

Plasma Nicotine

The main plasma nicotine outcome was the change in plasma nicotine concentration from before the 10-puff bout to after (i.e., nicotine boost) at the final clinical laboratory session (Fri, week 2; session 4, study day 12). Plasma nicotine boost was calculated for each participant by subtracting their pre-puff plasma nicotine concentration from their post-puff plasma nicotine concentration at each session. Mann-Whitney U tests compared the participant-level nicotine boost estimates across the IQOS-M and IQOS-T groups (Stata 17).

Exploratory analyses compared within-group differences in nicotine boost between sessions 3 (Mon, week 2; study day 8) and 4 (Fri, week 2; study day 12) using Wilcoxon Signed Rank tests. Differences in nicotine boost between OB menthol cigarettes (Fri, week 1; study day 5) and IQOS (Fri, week 2; study day 12) were assessed within each group using Wilcoxon Signed Rank tests. Pre- and post-puff plasma nicotine concentrations at each session were compared within-group using Wilcoxon Signed Rank tests to determine if pre- and post-puff plasma nicotine concentrations differed.

Puff Topography

The main puff topography outcome was the average puff duration during the 10-puff directed use bout at the final clinical laboratory session (Fri, week 2; session 4, study day 12). Mann-Whitney U tests compared the mean puff duration during the 10-puff directed use bout across the IQOS-M and IQOS-T groups (Stata 17).

To assess whether puff topography patterns changed during the 5-day naturalistic exposure to IQOS, topography outcomes at session 3 (Mon, week 2; study day 8) and session 4

(Fri, week 2; study day 12) were compared within-group using Wilcoxon Signed Rank tests. Difference in topography outcomes between OB menthol cigarettes (Fri, week 1; study day 5) and IQOS (Fri, week 2; study day 12) were assessed within-group using Wilcoxon Signed Rank tests.

Self-Reported Effects

The main self-reported effects outcome was the change in self-reported "craving a cigarette/nicotine" on the MNWS from before the 10-puff directed use bout to after at the final clinical laboratory session (Fri, week 2; session 4, study day 12). The change in "craving a cigarette/nicotine" was calculated for each participant by subtracting the pre-puff measurement from the post-puff measurement (i.e., cigarette craving suppression). Mann-Whitney U tests compared differences in cigarette craving suppression across the IQOS-M and IQOS-T groups (Stata 17).

Differences across experimental groups in pre- to post-puff changes in QSU-B Factor 1, pre- to post-puff changes in QSU-B Factor 2, pre- to post-puff changes in all MNWS items, PEQ subscales, and the study specific questions were explored at session 2 (OB; Fri, week 1), session 3 (IQOS; Mon, week 2), and session 4 (IQOS; Fri, week 2) using Mann-Whitney U tests. Exploratory analyses compared within-group differences in all self-reported effects outcomes at session 3 (IQOS; Mon, week 2; study day 8) to session 4 (IQOS; Fri, week 2; study day 12) using Wilcoxon Signed Rank tests. Wilcoxon Signed Rank tests compared self-reported effects outcomes associated with use of OB menthol cigarettes (Fri, week 1; study day 5) to IQOS (Friday, week 2; study day 12) within each experimental group. Differences in the pre-puff and

post-puff values for items on the QSU-B and MNWS were explored within-group using Wilcoxon Signed Rank tests.

Experimental Tobacco Marketplace

The main ETM outcome was IQOS' CPE with respect to OB menthol cigarettes. Demand for all products in the ETM was converted to milligrams (mg) of nicotine to allow for cross-product comparisons (Bickel et al., 2018; Appendix 4) then log transformed (zero consumption values were converted to a nonzero integer by adding 0.1). CPE estimates for each alternative product in the ETM were estimated using an approach based on linear regression (Heckman, Cummings et al., 2017; Quisenberry, Koffarnus et al., 2017; Quisenberry, Koffarnus et al., 2016). CPE estimates were generated for each fixed-price alternative, for each individual, by creating a linear regression of log-transformed fixed-price alternative demand as a function of log-transformed OB menthol cigarette prices,

$$\log(Demand) = \beta_0 + \beta_1 \log(OB\ Menthol\ Cigarette\ Price) + e,$$

where β_0 represented the cross-price intensity of demand, β_1 represented the CPE of the fixed-price alternative as a function of OB menthol cigarette price (main outcome), and e was the error term. Mann-Whitney U tests compared the individual-level CPE estimates for IQOS across participants with access to both flavors of HeatSticks (IQOS-M group) to participants with access to only Regular/Tobacco HeatSticks (IQOS-T group) at the final clinical laboratory session (IQOS; Fri, week 2; session 4, study day 12). As an alternative strategy for calculating

CPE estimates, demand for each fixed-price alternative was averaged within-group at each price trial in the ETM then a single regression for each group was fit to Equation 1. The resulting β_1 coefficient estimates were compared across experimental groups using a linear combination of parameters approach.

To ensure data quality and that participants were responding to the price cues within the task, demand for OB menthol cigarettes in the ETM was modeled using an exponentiated demand equation (GraphPad Prism 9; Hursh & Silberberg, 2008),

$$Q = Q_0 + 10 * k\left(e^{(-\alpha(C*Q_0))}\right) - 1),$$

where *C* represented the cost of the OB menthol cigarettes, *Q* represented cigarette consumption at price *C*, Q_0 represented OB menthol cigarette demand intensity (i.e., cigarette consumption at the lowest price trial), *k* represented the range of cigarette demand across price trials in log units, and α was the free parameter that represented the rate of change in demand elasticity. *k* was set equal to 4.89 for all participants (Hursh & Roma, 2013; Hursh & Silberberg, 2008; Quisenberry, Koffarnus et al., 2016). Group-level averages for α and R^2 were the outcomes of interest; α was expressed in terms of log(α) because α values tend to be very small. OB menthol cigarette demand was also assessed for each participant using criteria (i.e., trend, bounce, reversal from zero) for identifying nonsystematic demand in purchase tasks (Stein, Koffarnus et al., 2015).

Exploratory analyses compared the observed *cross-price intensity* of IQOS (i.e., demand for IQOS at the lowest price of OB menthol cigarettes [$0.12/cigarette]) across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. CPE estimates for all other alternative products

were compared across experimental groups using Mann-Whitney U tests (individual-level analyses) and a linear combination of parameters (group-level analyses). Wilcoxon Signed Rank tests compared ETM outcomes (within-group) across sessions 2 (OB, Fri) and 4 (IQOS, Fri) as well as across sessions 3 (IQOS, Mon) and 4 (IQOS, Fri) to gauge if exposure to IQOS in the clinical laboratory or at home influenced purchasing decisions in the ETM.

Aim 2 Analyses.

Naturalistic Use

The main naturalistic use outcome was the percentage reduction in the mean number of cigarettes smoked per day from the baseline week (Tues-Thurs, week 1) to the intervention week (Tues-Thurs, week 2) based on responses to EMA prompts. The percentage reduction in mean number of cigarettes smoked per day was calculated for each individual as (Stone, DeAtley et al., 2022):

$$\%\ reduction\ in\ cigarettes\ consumed\ per\ day = 100 \times \left(\frac{Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 1,\ Tues-Thurs} - Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 2,\ Tues-Thurs}}{Avg\ \#\ menthol\ cigarettes\ per\ day_{Week\ 1,\ Tues-Thurs}}\right)$$

.

Percentage reductions in OB menthol cigarette consumption from the baseline week to the intervention week were compared across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. As sensitivity analyses, statistical comparisons were repeated using responses to the three-day TLFBs conducted at sessions 2 (OB, Fri) and 4 (IQOS, Fri) and by imputing missing EMA values with multiple imputation by chained equations (i.e., predictive mean matching

based on five nearest neighbors across 10 imputed datasets). Exploratory analyses compared mean daily use of IQOS HeatSticks (Tues-Thurs) during the intervention week across the IQOS-M and IQOS-T groups using Mann-Whitney U tests. Within-group differences in total tobacco consumption (i.e., sum of IQOS and OB consumption), OB cigarette consumption, and IQOS consumption during week 1 compared to week 2 were evaluated using Wilcoxon Signed Rank tests.

Results

Sample Description

Recruitment began on November 28th, 2022 and concluded on September 22th, 2023. A total of 119 community volunteers were contacted from the CSTP registry via phone, text, or email following review of phase 1 screening data. From this contact group, 51 individuals attended the in-person screening session.

Fifty individuals (Figure 5) consented to participate in the study and of that group, 34 (68%) were determined to be eligible. One individual who attended the in-person screening session but did not provide informed consent was compensated for their time but no data were collected. Of the 16 (32%) individuals that were deemed ineligible following phase 2 screening, the most common reasons for ineligibility were: reporting past 30-day use of illicit drugs (n=6), intending to quit smoking in the next 3 months (n=5), reporting > 15 days of marijuana use in the past month (n=5), disclosing a health condition exclusion (n=4), and reporting daily use of another tobacco product (n=2). Of participants that were eligible and enrolled, four (11.8%) did not complete the study: two participants (from the IQOS-T group) dropped out during the baseline week due to scheduling conflicts, one participant (IQOS-T group) was withdrawn by the researcher due to persistent post-screening hypertension, and one participant was withdrawn by the researcher prior to randomization for failing to attend or reschedule their first session. Thus, 30 individuals completed the study and were included in the final analyses (i.e., dropouts were not analyzed).

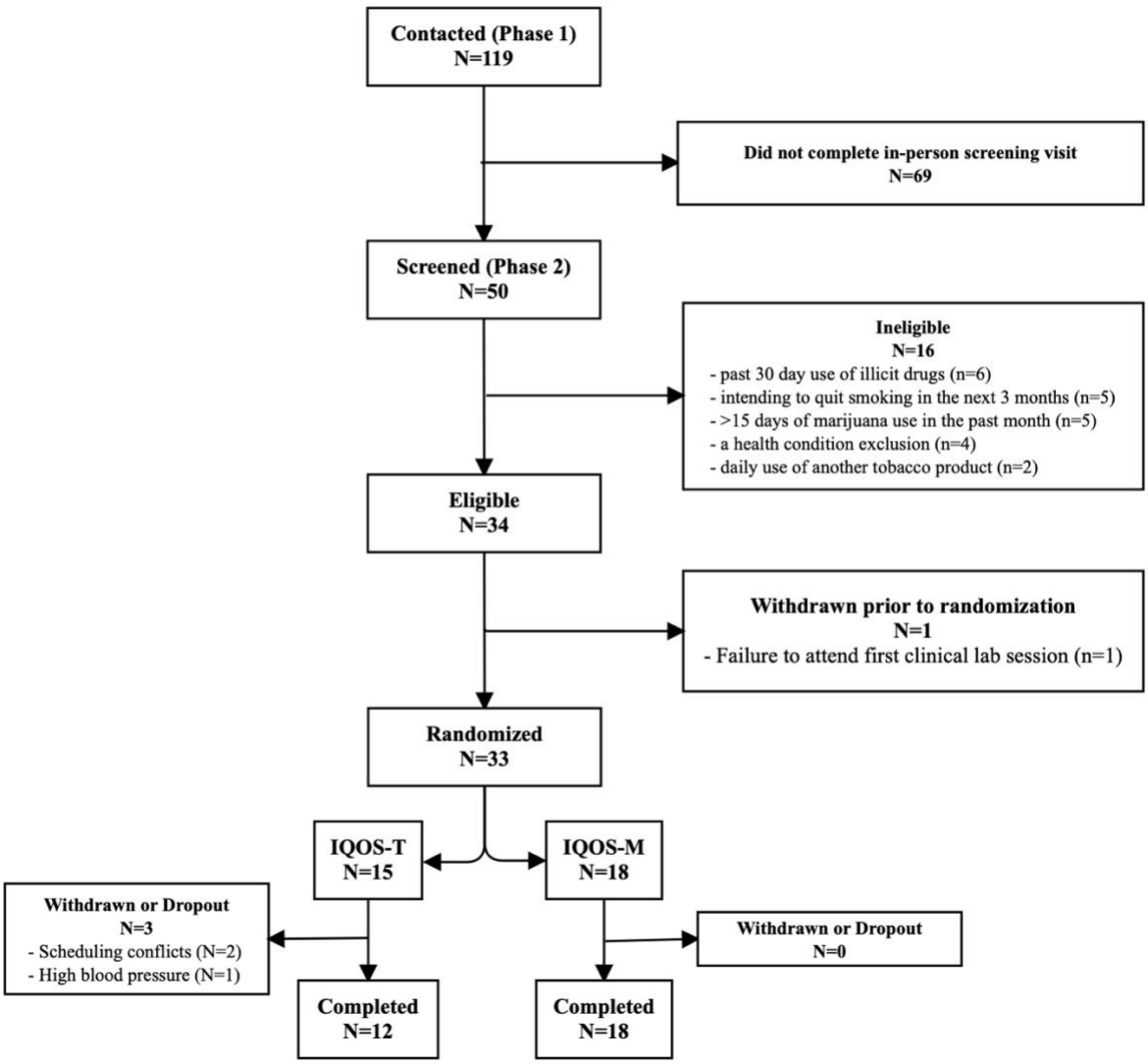


Figure 5. CONSORT diagram detailing study recruitment and retention

The mean (standard deviation [SD]) age of participants was 44.2 (10.1) years (Table 3). Twenty-two participants (73.3%) identified as African American or Black. With respect to ethnicity, three (10%) individuals identified as Hispanic or Latino. Most participants (66.7%) reported an annual household income below $50,000 and 70% reported attaining some post-secondary education or higher.

With respect to tobacco use behaviors, the mean (SD) number of cigarettes smoked per day was 13.9 (7.7) and participants had smoked for 15.6 (10.8) years on average. The mean (SD) eCO at the in-person screening session was 15.4 (8.1) ppm. The mean (SD) amount of spending on tobacco products during a typical week reported by participants was $44.50 (19.3). The mean (SD) score on the Penn State Cigarette Dependence Index was 12.4 (2.7), suggesting that participants in this sample had a moderate-to-high level of cigarette/nicotine dependence (Foulds, Veldheer et al., 2015). Twenty (66.7%) participants had attempted to quit smoking at some point in their lifetime. The tobacco products used most in the past month apart from cigarettes were e-cigarettes/ENDS (n=15) and cigarillos (n=13). Two participants reported past ever use of HTPs, with one reporting only a single prior use of an HTP and the other reporting 2-10 prior uses of an HTP.

Table 3. *Sample demographics*

	Overall (N=30)	IQOS-T group (n=12)	IQOS-M group (n=18)
Age in years	44.2 (10.1)	46.1 (12.6)	43.0 (8.3)
Sex			
Male	15 (50.0%)	6 (50.0%)	9 (50.0%)
Female	15 (50.0%)	6 (50.0%)	9 (50.0%)
Race			
African American/Black	22 (73.3%)	9 (75.0%)	13 (72.2%)
Non-African American/Black	8 (26.7%)	3 (25.0%)	5 (27.8%)
Ethnicity			
Hispanic or Latino	3 (10.0%)	0 (0.0%)	3 (16.7%)
Not Hispanic or Latino	27 (90.0%)	12 (100%)	15 (83.3%)
Employment			
Employed at least part-time	11 (36.7%)	3 (25.0%)	8 (44.4%)
Unemployed, looking for work, retired	12 (40.0%)	6 (50.0%)	6 (33.3%)
Student	2 (6.7%)	0 (0%)	2 (11.1%)
Permanent or temporary disability	1 (8.3%)	1 (8.3%)	0 (0.0%)
Other	4 (13.3%)	2 (16.7%)	2 (11.1%)
Education			
High school diploma or less	9 (30.0%)	4 (33.3%)	5 (27.8%)
At least some post-secondary education	21 (70.0%)	8 (66.7%)	13 (72.2%)
Annual self-report household income			
Less than $50,000	20 (66.7%)	9 (75.0%)	11 (61.1%)
At least $50,000	10 (33.3%)	3 (25.0%)	7 (38.9%)
Tobacco use history			
Exhaled carbon monoxide (ppm)	15.4 (8.1)	16.9 (8.6)	14.4 (7.9)
Average number of cigarettes per day	13.9 (7.7)	14.5 (6.6)	13.4 (8.5)
Years of smoking above number	15.6 (10.8)	11.7 (9.9)	18.2 (10.9)
Spending on tobacco products per week	$44.50 (19.3)	$43.75 (20.7)	$45.00 (19.0)
PROMIS Nicotine Dependence Scale	9.0 (3.1)	9.8 (2.5)	8.5 (3.4)
Penn State Cigarette Dependence Index	12.4 (2.7)	12.4 (2.2)	12.4 (3.1)
Prior attempt to quit smoking (yes)	20 (66.7%)	8 (66.7%)	12 (66.7%)
Past-month Electronic Nicotine Delivery System (ENDS) use (yes)	15 (50.0%)	6 (50.0%)	9 (50.0%)
Past-month cigarillo use (yes)	13 (43.3%)	5 (41.7%)	8 (44.4%)
Ever use of heated tobacco products	2 (6.7%)	1 (8.3%)	1 (5.6%)
Other substance use history			
Past-month marijuana use (yes)	16 (53.3%)	8 (66.7%)	8 (44.4%)
Past-month alcohol use (yes)	20 (66.7%)	6 (50.0%)	14 (77.8%)

Note: Categorical measures are presented as N (%) and continuous measures are presented as mean (standard deviation).

Study Outcomes Overview

Summary statistics and statistical comparisons for all study outcomes are described in the subsequent text, tables, and figures. All comparisons across experimental groups (IQOS-M group versus IQOS-T group; Mann-Whitney U tests) for Aim 1 (i.e., clinical laboratory based assessments) conducted at session 2 (OB, Fri), session 3 (IQOS, Mon), and session 4 (IQOS, Fri) are presented in Table 4. Differences in each outcome of Aim 1 across sessions 2 (OB, Fri) and 4 (IQOS, Fri) as well as across sessions 3 (IQOS, Mon) and 4 (IQOS, Fri) were assessed within-group using Wilcoxon Signed Rank tests and are presented in Table 5. Differences in the values of measures (e.g., plasma nicotine, QSU-B factors 1 and 2, and all MNWS items) collected before and after the 10-puff directed use bout in the clinical laboratory were evaluated within-group using Wilcoxon Signed Rank tests and are presented in Table 6. Group differences (IQOS-M group versus IQOS-T group; Mann-Whitney U tests) in tobacco product consumption during the at home portion of the study (Aim 2) are presented in Table 7. Differences in naturalistic use measures (e.g., average daily OB cigarettes smoked, average daily IQOS HeatSticks consumed, total tobacco consumption) collected during week 1 and week 2 (i.e., difference in the week 1 and week 2 values) were evaluated within-group using Wilcoxon Signed Rank tests and are presented in Table 8.

Table 4. *Summary of clinical laboratory outcomes (Aim 1), across group comparisons*

	Session 2 – Study Day 5 (Own brand cigarettes, Friday)			Session 3 – Study Day 8 (IQOS, Monday)			Session 4 – Study Day 12 (IQOS, Friday)		
	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p
Plasma Nicotine Delivery									
Nicotine Boost[a,b] (ng/mL)	11.01 (19.6)	8.75 (6.7)	z=0.634, p=0.548	4.19 (3.8)	3.41 (4.3)	z=-0.109, p=0.936	5.35 (6.5)	6.10 (7.2)	z=-0.683, p=0.516
User Behavior/Puff Topography									
Average Puff Duration (sec)[a]	1.65 (0.8)	1.70 (0.7)	z=-0.275, p=0.795	1.52 (0.7)	1.59 (1.0)	z=-0.339, p=0.755	1.34 (1.1)	1.64 (1.7)	z=-1.143, p=0.267
Average Puff Volume (mLs)	50.45 (21.1)	45.43 (22.3)	z=0.423, p=0.692	48.99 (34.2)	51.56 (29.6)	z=-0.720, p=0.491	50.59 (36.3)	60.15 (59.4)	z=-0.974, z=0.346
Puff Flow Rate (mLs/sec)	29.79 (13.0)	30.29 (9.9)	z=0.085, p=0.950	30.57 (14.1)	32.92 (10.3)	z=-0.466, p=0.662	33.99 (11.1)	37.75 (15.0)	z=0.042, p=0.983
Puff Number	10.00 (0.0)	10.00 (1.0)	z=-1.827, p=0.136	10.00 (0.0)	10.00 (3.5)	z=0.540, p=0.639	**10.00 (0.0)**	**10.00 (0.5)**	**z=2.571, p=0.019**
Average Interpuff Interval (sec)	28.94 (1.5)	28.66 (2.6)	z=1.693, p=0.095	28.95 (1.6)	29.50 (4.2)	z=0.677, p=0.518	28.70 (2.6)	28.54 (2.3)	z=-0.339, p=0.755
Self-Reported Effects									
QSU-B, Factor 1[b]	-3.00 (2.8)	-4.00 (3.0)	z=0.647, p=0.534	-2.00 (3.2)	-0.70 (3.8)	z=-1.569, p=0.120	-1.40 (2.8)	-1.20 (4.8)	z=-0.432, p=0.679
QSU-B, Factor 2[b]	-2.00 (1.6)	-1.80 (2.8)	z=0.563, p=0.587	-0.70 (2.6)	-0.40 (1.4)	z=-1.039, p=0.310	-1.30 (1.8)	-0.80 (1.3)	z=-0.662, p=0.522
MNWS, Urges to smoke[b]	-58.50 (58.0)	-50.00 (50.0)	z=-0.472, p=0.650	-45.30 (34.9)	-12.00 (50.0)	z=-1.609, p=0.111	**-34.50 (72.0)**	**-7.00 (45.0)**	**z=-1.991, p=0.047**
MNWS, Irritable/ Frustration/Anger[b]	-14.50 (37.0)	-5.00 (45.0)	z=-0.064, p=0.959	-1.50 (42.0)	-1.00 (10.5)	z=-0.798, p=0.437	-11.50 (49.0	-1.50 (18.5)	z=-1.610, p=0.110
MNWS, Anxious[b]	-34.00 (39.0)	-10.00 (23.5)	z=-0.847, p=0.409	**-28.00 (43.0)**	**-3.00 (23.0)**	**z=-2.101, p=0.035**	-22.00 (54.0)	-5.00 (33.5)	z=-0.834, p=0.416
MNWS, Difficulty Concentrating[b]	-4.00 (46.0)	-2.50 (5.5)	z=-0.536, p=0.606	-3.00 (31.0)	0.00 (8.5)	z=-1.834, p=0.068	-3.50 (35.0)	-4.50 (12.0)	z=-0.109, p=0.925
MNWS, Restlessness[b]	-14.50 (40.0)	0.00 (11.0)	z=-1.947, p=0.052	-13.00 (38.0)	0.00 (4.0)	z=-1.755, p=0.081	-15.00 (55.0)	-1.00 (15.5)	z=-0.751, p=0.465
MNWS, Hunger[b]	0.00 (21.0)	-1.00 (23.0)	z=1.223, p=0.235	-11.00 (34.0)	-2.50 (24.0)	z=-0.425, p=0.683	-2.50 (34.0)	-2.50 (10.0)	z=-0.385, p=0.713
MNWS, Impatient[b]	-14.00 (38.0)	-5.00 (30.0)	z=-0.181, p=0.868	-15.50 (46.0)	-7.50 (17.0)	z=-1.009, p=0.324	-2.00 (48.0)	0.00 (12.5)	z=-1.175, p=0.249
MNWS, Craving cigarette/nicotine[a,b]	-60.00 (69.0)	-32.00 (67.0)	z=-1.013, p=0.322	-59.00 (75.0)	-15.00 (54.0)	z=-1.207, p=0.236	-41.50 (46.0)	-9.50 (47.5)	z=-1.673, p=0.097

	Session 2 – Study Day 5 (Own brand cigarettes, Friday)			Session 3 – Study Day 8 (IQOS, Monday)			Session 4 – Study Day 12 (IQOS, Friday)		
	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p
MNWS, Drowsiness[b]	0.00 (17.0)	0.00 (25.0)	z=-0.695, p=0.508	-10.00 (46.0)	0.00 (8.0)	z=-1.446, p=0.153	-13.50 (28.0)	-1.00 (28.0)	z=-1.084, p=0.289
MNWS, Depression/ Feeling Blue[b]	0.00 (6.0)	0.00 (5.5)	z=0.046, p=0.972	-1.50 (24.0)	0.00 (1.0)	z=-1.525, p=0.131	0.00 (20.0)	0.00 (4.0)	z=-1.635, p=0.101
MNWS, Desire for Sweets[b]	0.00 (6.0)	-7.50 (25.5)	z=1.740, p=0.084	-2.00 (27.0)	0.00 (1.0)	z=-1.357, p=0.182	**-6.00 (12.0)**	**0.00 (2.5)**	**z=-2.566, p=0.009**
PEQ, Stimulant Effects	3.50 (2.3)	3.70 (2.0)	z=-0.204, p=0.850	2.70 (2.0)	2.20 (1.3)	z=1.778, p=0.077	2.50 (2.7)	1.70 (1.0)	z=0.961, p=0.347
PEQ, Positive Reinforcement	6.00 (1.7)	5.30 (2.2)	z=1.406, p=0.166	**5.00 (3.0)**	**2.50 (2.3)**	**z=2.785, p=0.004**	4.30 (3.7)	2.80 (2.0)	z=1.827, p=0.069
PEQ, Negative Reinforcement	5.80 (3.3)	4.80 (2.2)	z=1.296, p=0.202	**4.00 (2.3)**	**2.00 (2.7)**	**z=1.978, p=0.048**	3.50 (2.7)	2.00 (2.3)	z=1.128, p=0.269
PEQ, Aversion	1.30 (1.0)	1.00 (0.5)	z=1.030, p=0.314	1.00 (1.0)	1.00 (0.3)	z=0.835, p=0.438	1.00 (1.0)	1.00 (0.0)	z=1.070, p=0.339
SSQ, Easy to Use	7.00 (1.0)	6.00 (2.0)	z=0.898, p=0.403	6.00 (3.0)	6.50 (3.0)	z=-0.222, p=0.845	5.50 (4.0)	6.00 (3.5)	z=0.043, p=0.973
SSQ, Comfortable Using in Public	7.00 (2.0)	6.00 (2.5)	z=1.023, 0.317	6.00 (3.0)	4.50 (3.0)	z=0.960, p=0.350	6.00 (2.0)	5.50 (4.5)	z=1.407, p=0.175
SSQ, Enjoyment of Flavor Sensation	6.00 (1.0)	5.00 (2.5)	z=1.508, 0.141	**5.00 (2.0)**	**3.00 (2.0)**	**z=3.187, p=0.001**	**4.00 (4.0)**	**2.50 (2.5)**	**z=2.010, p=0.046**
SSQ, Harshness	2.50 (1.0)	2.00 (2.0)	z=0.261, 0.797	2.00 (1.0)	3.50 (1.5)	z=-1.386, p=0.170	2.00 (2.0)	3.50 (2.0)	z=-0.991, p=0.334
SSQ, Plan to use after the study	1.50 (1.0)	1.00 (1.0)	z=0.467, p=0.761	3.00 (0.0)	3.00 (1.0)	z=-0.157, p=0.849	4.00 (1.0)	3.50 (2.0)	z=0.441, p=0.697
SSQ, Absolute Harm Perception of IQOS	6.00 (2.0)	6.00 (2.0)	z=0.158, p=0.958	3.00 (3.0)	4.00 (2.0)	z=-0.237, p=0.825	4.00 (3.0)	3.00 (2.5)	z=-0.580, p=0.580
SSQ, Relative Harm of IQOS to OB Cigarettes	---	---	---	2.00 (2.0)	2.00 (1.0)	z=0.334, p=0.767	2.00 (2.0)	3.00 (1.0)	z=-1.118, p=0.274
Experimental Tobacco Marketplace									
OB menthol cigarettes (own-price elasticity)	-1.86 (0.7)	-1.90 (0.9)	z=0.550, p=0.602	-1.79 (0.8)	-1.95 (0.8)	z=0.550, p=0.602	-1.89 (0.8)	-1.66 (0.7)	z=-1.016, p=0.321
Non-menthol cigarettes (cross-price elasticity)	0.35 (0.7)	0.56 (1.0)	z=-0.343, p=0.665	0.17 (0.05)	0.48 (1.0)	z=-1.454, p=0.204	0.22 (0.6)	0.36 (0.9)	z=-0.430, p=0.816
IQOS (cross-price elasticity)[a]	0.34 (0.6)	0.18 (0.5)	z=0.871, p=0.397	0.45 (0.7)	0.38 (0.6)	z=0.043, p=0.984	**0.67 (0.8)**	**0.14 (0.4)**	**z=2.296, p=0.021**

	Session 2 – Study Day 5 (Own brand cigarettes, Friday)			Session 3 – Study Day 8 (IQOS, Monday)			Session 4 – Study Day 12 (IQOS, Friday)		
	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p	IQOS-M group	IQOS-T group	z p
IQOS (% menthol of total IQOS purchasing)	98.1% (6.9)	---	---	95.9% (12.2)	---	---	88.2% (31.4)	---	---
IQOS (cross-price intensity, mg of nicotine)	**42.67 (67.4)**	**0.67 (2.3)**	**z=2.247, p=0.015**	**81.78 (125.4)**	**6.67 (15.6)**	**z=2.529, p=0.009**	54.5 (115.8)	15.08 (30.9)	z=1.054, p=0.311
Traditional cigars (cross-price elasticity)	0.00 (0.0)	0.00 (0.0)	z=---, p=1.000	0.00 (0.0)	0.00 (0.0)	z=---, p=1.000	0.00 (0.0)	0.00 (0.0)	z=---, p=1.000
Cigarillos (cross-price elasticity)	0.32 (0.7)	0.32 (0.7)	z=0.526, p=0.620	0.20 (0.6)	0.38 (0.6)	z=-1.029, p=0.321	0.31 (0.8)	-0.07 (0.6)	z=1.732, p=0.092
Vape/E-cigarette pod (cross-price elasticity)	0.31 (0.5)	0.01 (0.0)	z=1.713, p=0.063	0.14 (0.6)	0.12 (0.4)	z=0.576, p=0.581	0.17 (0.5)	0.02 (0.1)	z=0.752, p=0.402
Vape/E-cigarette liquid (cross-price elasticity)	0.09 (0.4)	0.03 (0.1)	z=-0.245, p=1.000	0.12 (0.5)	0.06 (0.22)	z=-0.245, p=1.000	0.04 (0.2)	0.15 (0.5)	z=-0.343, p=0.800
Oral nicotine pouches (cross-price elasticity)	-0.05 (0.2)	0.00 (0.0)	z=-0.816, p=1.000	0.00 (0.0)	0.00 (0.0)	z=0.816, p=1.000	0.00 (0.0)	0.00 (0.0)	z=0.816, p=1.000
Chewing tobacco pouches (cross-price elasticity)	0.04 (0.2)	0.00 (0.0)	z=0.816, p=1.000	0.00 (0.0)	0.00 (0.0)	z=---, p=1.000	0.00 (0.0)	0.00 (0.0)	z=---, p=1.000
Nicotine gum (cross-price elasticity)	0.07 (0.4)	0.16 (0.4)	z=-0.652, p=0.703	0.00 (0.4)	0.08 (0.3)	z=-1.239, p=0.376	0.14 (0.4)	0.09 (0.3)	z=-0.107, p=0.949
Nicotine patches (cross-price elasticity)	-0.09 (0.3)	0.03 (0.1)	z=-0.860, p=0.525	-0.06 (0.1)	0.08 (0.3)	z=-1.827, p=0.179	-0.06 (0.2)	0.06 (0.2)	z=-2.152, p=0.076
Remaining budget at price point 8 ($16.00/OB menthol cigarette)	**$7.27 (15.4)**	**$24.09 (20.3)**	**z=-3.097, p=0.001**	**$10.21 (17.3)**	**$26.38 (23.9)**	**z=-2.210, p=0.026**	$13.23 (20.8)	$21.36 (17.9)	z=-1.679, p=0.096
Total unspent	$78.63 (110.6)	$159.76 (111.4)	z=-1.947, p=0.053	$91.12 (133.4)	$167.32 (142.6)	z=-1.799, p=0.073	$95.04 (136.9)	$154.13 (137.9)	z=-1.693, p=0.095

Note: Median (interquartile range) values are presented for all outcomes except for Experimental Tobacco Marketplace outcomes which show mean (standard deviation) values. Bolded red values indicate a statistically significant ($p < 0.05$) difference across groups at that session (U tests). QSU-B = Questionnaire of Smoking Urges-Brief, MNWS = Minnesota Nicotine Withdrawal Scale, PEQ = Product Evaluation Questionnaire, SSQ = Study Specific Questionnaire.

[a] Primary or secondary outcome of the study (at session 4), [b] Median difference in item from before to after (post-puff minus pre-puff) the 10-puff directed use bout of item is presented.

Table 5. *Summary of clinical laboratory outcomes (Aim 1), across session comparisons*

	Session 2 (OB Menthol Cigarettes, Fri) versus Session 4 (IQOS, Fri)		Session 3 (IQOS, Monday) versus Session 4 (IQOS, Fri)	
	IQOS-M group	**IQOS-T group**	**IQOS-M group**	**IQOS-T group**
Plasma Nicotine Delivery				
Nicotine Boost (ng/mL)	**8.15 (13.5) [z=3.181, p<0.001]**	4.29 (12.9) [z=1.177, p=0.266]	1.48 (5.7) [z=-0.384, p=0.735]	-1.00 (8.4) [z=-0.711, p=0.520]
Puff Topography				
Average Puff Duration (sec)	0.03 (0.6) [z=0.806, p=0.442]	-0.43 (1.3) [z=-1.412, p=0.176]	0.11 (0.4) [z=1.764, p=0.081]	-0.11 (1.1) [z=-1.334, p=0.204]
Average Puff Volume (mLs)	-0.45 (25.3) [z=0.196, p=0.865]	-18.45 (46.9) [z=-1.490, p=0.151]	-0.20 (11.8) [z=-0.414, p=0.702]	-7.90 (31.8) [z=-1.490, p=0.151]
Puff Flow Rate (mLs/sec)	-2.70 (10.2) [z=-0.501, p=0.640]	-1.99 (13.2) [z=-1.020, p=0.339]	-1.31 (6.5) [z=-1.372, p=0.182]	0.91 (5.6) [z=0.314, p=0.791]
Puff Number	0.00 (0.0) [z= -1.226, p=0.375]	0.00 (1.5) [z=2.215, p=0.063]	0.00 (0.0) [z=-0.390, p=0.938]	0.50 (2.0) [z=0.967, p=0.383]
Average Interpuff Interval (sec)	0.43 (1.9) [z=1.720, p=0.090]	-0.37 (3.8) [z=-1.098, p=0.301]	0.16 (1.85) [z=0.414, p=0.702]	-1.08 (5.4) [z-1.804, p=0.077]
Self-Reported Effects				
QSU-B, Factor 1 [a]	**0.60 (1.4) [z=2.178, p=0.028]**	1.60 (2.7) [z=1.540, p=0.148]	0.00 (1.6) [z=0.548, p=0.607]	-0.70 (1.4) [z=-1.274, p=0.234]
QSU-B, Factor 2 [a]	**0.40 (1.0) [z=2.353, p=0.016]**	**0.90 (2.2) [z=2.095, p=0.037]**	0.00 (0.6) [z=0.214, p=0.843]	-0.10 (0.8) [z=-0.716, p=0.520]
MNWS, Urges to smoke [a]	2.00 (31.0) [z=0.981, p=0.341]	**39.00 (26.0) [z=2.762, p=0.003]**	0.50 (30.0) [z=-0.022, p=0.991]	-3.00 (15.5) [z=-0.550, p=0.608]
MNWS, Irritable/ Frustration/Anger [a]	-0.50 (15.0) [z=-0.721, p=0.494]	11.00 (33.0) [z=1.260, p=0.225]	0.00 (13.0) [z=-0.802, p=0.439]	0.00 (23.0) [z=-0.278, p=0.805]
MNWS, Anxious [a]	-3.50 (39.0) [z=-0.697, p=0.502]	**4.5 (15.5) [z=2.082, p=0.035]**	1.00 (9.0) [z=0.722, p=0.493]	-6.50 (18.5) [z=-0.943, p=0.370]
MNWS, Difficulty Concentrating [a]	0.00 (18.0) [z=-0.860, p=0.407]	-1.50 (13.0) [z=-0.707, p=0.506]	0.00 (12.0) [z=0.557, p=0.597]	-5.00 (11.0) [z=-1.694, p=0.098]
MNWS, Restlessness [a]	0.00 (13.0) [z=0.328, p=0.758]	0.00 (17.0) [z=-0.223, p=0.863]	0.00 (9.0) [z=-0.263, p=0.807]	**-2.50 (7.5) [z=-2.246, p=0.025]**
MNWS, Hunger [a]	-3.00 (69.0) [z=-0.938, p=0.363]	0.00 (15.0) [z=1.037, p=0.320]	2.00 (22.0) [z=0.196, p=0.857]	-0.50 (31.0) [z=0.276, p=0.822]
MNWS, Impatient [a]	-0.50 [11.0] [z=-0.437, p=0.678]	2.00 (31.0) [z=1.564, p=0.133]	1.00 (8.0) [z=1.071, p=0.297]	4.00 (15.5) [z=0.297, p=0.193]
MNWS, Craving cigarette/nicotine [a]	**9.50 (27.0) [z=2.027, p=0.0418]**	**11.00 (41.0) [z=2.091, p=0.0352]**	3.00 (28.0) [z=0.893, p=0.387]	0.0 (40.0) [z=0.00, p=1.000]
MNWS, Drowsiness [a]	-4.50 (28.0) [z=-1.483, p=0.144]	-4.00 (21.0) [z=-1.112, p=0.299]	0.00 (22.0) [z=0.356, p=0.738]	0.00 (33.0) [z=-0.223, p=0.863]
MNWS, Depression/ Feeling Blue [a]	0.00 (8.0) [z=-1.759, p=0.081]	0.00 (6.0) [z=-0.983, p=0.348]	0.00 (4.0) [z=-1.447, p=0.155]	0.00 (6.0) [z=-1.474, p=0.160]
MNWS, Desire for Sweets	-1.00 (13.0) [z=-0.759, p=0.464]	**9.00 (27.0) [z=2.087, p=0.037]**	0.00 (9.0) [z=-0.119, p=0.917]	0.00 (4.0) [z=0.040, p=0.992]
PEQ, Stimulant Effects	0.00 (1.7) [z=0.525, p=0.616]	**1.00 (1.7) [z=2.539, p=0.008]**	0.00 (1.3) [z=0.437, p=0.677]	-0.30 (1.2) [z=-0.944, p=0.374]
PEQ, Positive Reinforcement	**1.00 (4.0) [z=2.831, p=0.003]**	**2.00 (2.2) [z=2.903, p=0.002]**	0.30 (1.3) [z=1.225, p=0.231]	0.00 (1.0) [z=-0.924, p=0.375]
PEQ, Negative Reinforcement	**0.50 (3.3) [z=1.989, p=0.047]**	1.30 (1.3) [z=1.918, p=0.055]	0.00 (1.7) [z=0.842, p=0.419]	-0.30 (1.3) [z=-1.175, p=0.273]
PEQ, Aversion	0.00 (0.5) [z=0.414, p=0.707]	0.00 (0.5) [z=0.941, p=0.500]	0.00 (0.5) [z=-0.700, p=0.555]	0.00 (0.0) [z=-1.000, p=1.000]
SSQ, Easy to Use	**0.00 (3.0) [z=2.437, p=0.016]**	1.0 (2.0) [z=2.022, p=0.063]	0.00 (2.0) [z=0.865, p=0.407]	0.00 (2.0) [z=0.243, p=0.836]
SSQ, Comfortable Using in Public	0.0 (1.0) [z=0.446, p=0.660]	1.0 (2.5) [z=1.973, p=0.055]	0.0 (3.0) [z=-0.384, p=0.735]	0.0 (2.0) [z=0.411, p=0.750]

	Session 2 (OB Menthol Cigarettes, Fri) versus Session 4 (IQOS, Fri)		Session 3 (IQOS, Monday) versus Session 4 (IQOS, Fri)	
	IQOS-M group	**IQOS-T group**	**IQOS-M group**	**IQOS-T group**
SSQ, Enjoyment of Flavor Sensation	**1.00 (4.0) [z=2.744, p=0.005]**	**1.50 (3.5) [z=2.966, p=0.002]**	0.50 (1.0) [z=1.1816, p=0.076]	0.00 (1.0) [z=-0.128, p=1.000]
SSQ, Harshness	0.00 (2.0) [z=-0.309, p=0.762]	-0.50 (3.0) [z=-1.439, p=0.195]	0.00 (2.0) [z=-0.179, p=0.898]	0.00 (2.0) [z=-0.081, p=1.000]
SSQ, Plan to use after the study	**-2.50 (2.0) [z=-3.461, <0.001]**	**-2.00 (2.0) [z=-2.765, p=0.005]**	**-1.00 (1.0) [z=-2.364, p=0.028]**	0.00 (0.5) [-0.400, p=0.938]
SSQ, Absolute Harm Perception of Session Product	**1.00 (3.0) [z=3.326, p<0.001]**	**2.00 (2.5) [z=2.258, p=0.025]**	0.00 (2.0) [z=-0.631, p=0.586]	0.50 (2.5) [z=-0.199, p=0.873]
SSQ, Relative Harm of IQOS to Own Brand Cigarettes	---	---	0.00 (2.0) [z=0.069, p=1.000]	0.00 (2.0) [z=-1.361, p=0.219]
Experimental Tobacco Marketplace				
IQOS (cross-price elasticity)	-0.11 (1.0) [z=-1.613, p=0.113]	0.00 (0.0) [z=-0.095, p=0.875]	-0.01 (0.6) [z=-1.071, p=0.302]	0.00 (0.15) [z=0.888, p=0.406]

Note: For all measures, the median (interquartile range) [z, p] within-subject difference in that outcome between the two sessions noted in the column heading are shown. Analyses were stratified by experimental group. Bolded red values indicate a statistically significant ($p < 0.05$) difference across sessions (Wilcoxon Signed Rank tests). Positive values suggest the outcome was larger at the first session noted in the column header than at the second session (i.e., in the "Session 2 versus Session 4" column a positive value for nicotine boosts suggests that the nicotine boost tended to be larger for that group when using OB menthol cigarettes than IQOS).

OB = Own brand (menthol cigarettes), QSU-B = Questionnaire of Smoking Urges-Brief, MNWS = Minnesota Nicotine Withdrawal Scale, PEQ = Product Evaluation Questionnaire, SSQ = Study Specific Questionnaire.

[a] Difference in item from before to after the 10-puff directed use bout of item was calculated first and the difference across sessions in those differences (i.e., difference-in-differences) is presented. A positive value indicates that the pre- to post-puff change was larger at the first session indicated in the column than at the second and vice versa.

Table 6. *Summary of clinical laboratory pre-/post- 10-puff directed use bout outcomes*

	Session 2 – Study Day 5 (OB cigarettes, Friday)		Session 3 – Study Day 8 (IQOS, Monday)		Session 4 – Study Day 12 (IQOS, Friday)	
	IQOS-M group	**IQOS-T group**	**IQOS-M group**	**IQOS-T group**	**IQOS-M group**	**IQOS-T group**
Plasma Nicotine Delivery						
Nicotine Boost (ng/mL)	**11.01 (19.63) [z=3.351, p<0.001]**	**8.75 (6.7) [z=2.981, p=0.001]**	**4.19 (3.8) [z=2.764, p=0.0034]**	**3.41 (4.3) [z=2.934, p=0.001]**	**5.35 (6.4) [z=2.329, p=0.018]**	**6.10 (7.2) [z=2.903, p=0.002]**
Self-Reported Effects						
QSU-B, Factor 1	**-3.00 (2.8) [z=-3.621 p<0.001]**	**-4.00 (3.0) [z=-2.666, p=0.004]**	**-2.00 (3.2) [z=-3.664, p<0.001]**	-0.70 (3.8) [z=-1.610, p=0.115]	**-1.40 (2.8) [z=-3.595, p<0.001]**	**-1.20 (4.8) [z=-2.155, p=0.031]**
QSU-B, Factor 2	**-2.00 (1.6) [z=-3.665, p<0.001]**	**-1.80 (2.8) [z=-2.936, p=0.001]**	**-0.70 (2.6) [z=-3.359, p<0.001]**	-0.40 (1.4) [z=-1.972, p=0.063]	**-0.80 (1.6) [z=-3.020, p=0.001]**	-0.20 (1.4) [z=-1.834, p=0.078]
MNWS, Urges to smoke	**-58.50 (58.0) [z=-3.724, p<0.001]**	**-50.00 (50.0) [z=-2.892, p=0.002]**	**-40.00 (52.0) [z=-3.441, p<0.001]**	**-12.00 (50.0) [z=-2.049, p=0.039]**	**-34.50 (72.0) [z=-3.703, p<0.001]**	-7.00 (45.0) [z=-1.654, p=0.104]
MNWS, Irritable/ Frustration/Anger	**-14.50 (37.0) [z=-3.169, p=0.000]**	**-5.00 (45.0) [z=-2.731, p=0.008]**	**-1.50 (42.0) [z=-2.494, p=0.011]**	-1.00 (10.5) [z=-1.647, p=0.109]	**-11.50 (49.0) [z=-3.339, p=0.001]**	-1.50 (18.5) [z=-1.230, p=0.234]
MNWS, Anxious	**-34.00 (39.0) [z=-3.201, p=0.001]**	**-10.00 (23.5) [z=-2.868, p=0.002]**	**-28.00 (43.0) [z=-3.605, p<0.001]**	-3.00 (23.0) [z=-1.221, p=0.240]	**-22.00 (54.0) [z=-3.177, p=0.001]**	**-5.00 (33.5) [z=-2.303, p=0.020]**
MNWS, Difficulty Concentrating	-4.00 (46.0) [z=-1.910, p=0.057]	**-2.50 (5.5) [z=-1.984, p=0.047]**	**-3.00 (31.0) [z=-2.295, p=0.020]**	0.00 (8.5) [z=0.246, p=0.859]	**-3.50 (35.0) [z=-2.315, p=0.019]**	**-4.50 (12.0) [z=-2.584, p=0.016]**
MNWS, Restlessness	**-14.50 (40.0) [z=-3.050, p=0.001]**	0.00 (11.0) [z=-0.541, p=0.609]	**-13.00 (38.0) [z=-2.523, p=0.010]**	0.00 (4.0) [z=-0.323, p=0.773]	**-15.00 (55.0) [z=-2.781, p=0.004]**	**-1.00 (15.5) [z=-2.170, p=0.031]**
MNWS, Hunger	0.00 (21.0) [z=-0.634, p=0.550]	**-1.00 (23.0) [z=-2.568, p=0.016]**	-11.00 (34.0) [z=-1.788, p=0.075]	-2.50 (24.0) [z=-1.527, p=0.133]	**-2.50 (34.0) [z=-2.054, p=0.039]**	**-2.50 (10.0) [z=-2.584, p=0.016]**
MNWS, Impatient	**-14.00 (38.0) [z=-2.741, p=0.004]**	**-5.00 (30.0) [z=-2.706, p=0.008]**	**-15.50 (46.0) [z=-3.112, p=0.001]**	**-7.50 (17.0) [z=-2.330, p=0.016]**	**-2.00 (48.0) [z=-2.052, p=0.039]**	0.00 (12.5) [z=-0.635, p=0.555]
MNWS, Craving cigarette/nicotine	**-60.00 (69.0) [z=-3.680, p<0.001]**	**-32.00 (67.0) [z=-2.716, p=0.004]**	**-59.00 (75.0) [z=-3.201, p=0.001]**	**-15.00 (54.0) [z=-2.087, p=0.037]**	**-41.50 (46.0) [z=-3.680, p<0.001]**	-9.50 (47.5) [z=-1.536, p=0.133]
MNWS, Drowsiness	0.00 (17.0) [z=-1.645, p=0.106]	0.00 (25.0) [z=-0.402, p=0.727]	**-10.00 (46.0) [z=-2.821. p=0.003]**	0.00 (8.0) [z=-1.205, p=0.258]	**-13.50 (28.0) [z=-2.786, p=0.004]**	-1.00 (28.0) [z=-1.252, p=0.227]
MNWS, Depression/ Feeling Blue	0.00 (6.0) [z=-1.580, p=0.119]	0.00 (5.5) [z=-1.480, p=0.188]	**-1.50 (24.0) [z=-2.458, p=0.012]**	0.00 (1.0) [z=-0.127, p=0.906]	**-0.00 (20.0) [z=-2.623, p=0.016]**	0.00 (4.0) [z=-0.737, p=0.438]
MNWS, Desire for Sweets	0.00 (6.0) [z=-1.347, p=0.187]	**-7.50 (25.5) [z=-2.285, p=0.020]**	-2.00 (27.0) [z=-1.671, p=0.098]	0.00 (1.0) [z=0.593, p=0.656]	**-6.00 (12.0) [z=-2.491, p=0.010]**	0.00 (2.5) [z=0.041, p= 1.000]

Note: Group-level medians (interquartile range) [z, p] for the difference in pre- and post-puff value (post-puff minus pre-puff) for each measure are shown. Red boxes indicate a statistically significant difference ($p < 0.05$; Wilcoxon Signed Rank tests; positive sign: post value > pre value; negative sign: post value < pre value). OB = Own brand menthol cigarettes, MNWS = Minnesota Nicotine Withdrawal Scale, QSU-B = Questionnaire of Smoking Urges-Brief.

Table 7. *Summary of naturalistic use outcomes (Aim 2), across group comparisons*

	Week 1 (Tuesday-Thursday)			Week 2 (Tuesday-Thursday)			% change from Week 1 to Week 2		
Ecological Momentary Assessment (EMA; N=25; IQOS-M: n=15, IQOS-T: n=10)									
	IQOS-M group	**IQOS-T group**	**z p**	**IQOS-M group**	**IQOS-T group**	**z p**	**IQOS-M group**	**IQOS-T group**	**z p**
Daily OB Menthol Cigarettes	9.50 (5.0)	11.33 (5.7)	z=-1.086, p=0.288	**4.00 (3.8)**	**7.50 (4.3)**	**z=-2.719, p=0.005**	**80.36% (42.6)**	**36.81% (14.0)**	**z=2.332, p=0.019**
Daily IQOS HeatSticks	---	---	---	4.33 (6.3)	4.50 (5.0)	z=0.918, p=0.373	---	---	---
Daily total consumption (OB + IQOS)	9.33 (6.3)	11.83 (4.7)	z=-1.027, p=0.317	9.00 (9.7)	10.0 (8.7)	z=-0.777, p=0.453	---	---	---
Days of using another tobacco product	0.00 (0.0)	0.00 (0.0)	z=1.543, p=0.350	0.00 (0.0)	0.00 (0.0)	z=-1.183, p=0.833	---	---	---
Three-Day Timeline Follow Back (TLFB; N=30; IQOS-M: n=18, IQOS-T: n=12)									
	IQOS-M	**IQOS-T**	**z p**	**IQOS-M**	**IQOS-T**	**z p**	**IQOS-M**	**IQOS-T**	**z p**
Daily OB Menthol Cigarettes	10.00 (4.7)	11.00 (7.0)	z=-0.466, p=0.654	**3.67 (5.3)**	**7.17 (5.7)**	**z=-2.311, p=0.020**	76.86% (67.5)	30.81% (41.7)	z=1.652, p=0.101
Daily IQOS HeatSticks	---	---	---	4.00 (6.7)	4.67 (4.0)	z=0.455, p=0.669	---	---	---
Daily total consumption (OB + IQOS)	10.00 (4.7)	11.00 (7.0)	z=-0.466, p=0.654	9.50 (9.7)	10.33 (6.5)	z=-0.911, p=0.374	---	---	---
Days of using another tobacco product	0.00 (0.0)	0.00 (0.0)	z=1.463, p=0.402	0.00 (0.0)	0.00 (0.0)	z=-0.573, p=0.448	---	---	---

Note: Group medians (interquartile range) shown. The column "p" reports the significance level of the comparison in either the percentage reduction in daily cigarettes used from week 1 (Tues-Thurs) to week 2 (Tues-Thurs) or IQOS HeatStick consumption during week 2 (Tues-Thurs) across the two experimental groups (Mann-Whitney U tests). Bolded red values indicate a statistically significant ($p < 0.05$) difference across experimental groups. OB = Own brand (menthol cigarettes).

Table 8. *Summary of naturalistic use outcome measures (Aim 2), within-group comparisons*

	IQOS-M group			IQOS-T group		
Ecological Momentary Assessment (EMA; N=25, IQOS-M: n=15, IQOS-T: n=10)						
	Week 1	**Week 2**	**z p**	**Week 1**	**Week 2**	**z p**
Daily OB Menthol Cigarettes	**9.33 (6.3)**	**4.00 (3.8)**	**z=3.411, p=0.001**	**11.83 (4.7)**	**7.50 (4.3)**	**z=2.805, p=0.002**
Daily IQOS HeatSticks	**0.00 (0.0)**	**4.50 (6.3)**	**z=3.412, p<0.001**	**0.00 (0.0)**	**6.67 (5.0)**	**z=2.807 p=0.002**
Daily total consumption (OB + IQOS)	9.33 (6.3)	9.0 (9.7)	z=-0.057, p=0.967	11.83 (4.7)	10.00 (8.7)	z=0.764, p=0.492
Three-Day Timeline Follow Back (TLFB; N=30, IQOS-M: n=18, IQOS-T: n=12)						
	Week 1	**Week 2**	**z p**	**Week 1**	**Week 2**	**z p**
Daily OB Menthol Cigarettes	**10.00 (4.7)**	**3.67 (5.3)**	**z=3.724, p<0.001**	**11.00 (7.0)**	**7.17 (5.7)**	**z=3.024, p=0.001**
Daily IQOS HeatSticks	**0.00 (0.0)**	**4.00 (6.7)**	**z=3.726, p<0.001**	**0.00 (0.0)**	**4.67 (4.0)**	**z-3.024, p=0.001**
Daily total consumption (OB + IQOS)	10.00 (4.7)	9.50 (9.7)	z=0.044, p=0.976	11.00 (7.0)	10.33 (6.5)	z=0.981, p=0.359

Note: Group medians (interquartile range) for each naturalistic use outcome are shown by week. Wilcoxon Signed Rank tests (column "z, p") assessed the within-participant difference in the number of OB cigarettes, IQOS HeatSticks, and total tobacco consumption during week 1 compared to week 2, stratified by experimental group. Bolded red values indicate a statistically significant ($p < 0.05$) within-group difference in tobacco consumption across week 1 and week 2. OB = Own brand menthol cigarettes.

Plasma Nicotine Delivery

At session 2 (OB, Fri) all participants used their OB menthol cigarette and there was a statistically significant increase in plasma nicotine concentration from before the 10-puff bout to after within both groups (Figure 6; Table 6). The median (IQR) pre-puff plasma nicotine concentration in the IQOS-M group when using OB menthol cigarettes was 4.55 (7.8) ng/mL then 19.85 (6.6) ng/mL after the 10-puff bout, corresponding to a median nicotine boost of 11.01 (19.6) ng/mL ($z = 3.35$, $p < 0.001$). The median (IQR) pre-puff plasma nicotine concentration in the IQOS-T group when using OB menthol cigarettes was 5.51 (6.6) ng/mL then 15.86 (5.5) ng/mL after the 10-puff bout, corresponding to a median nicotine boost of 8.75 (6.7) ng/mL ($z = 2.98$, $p = 0.001$).

There was a statistically significant increase in plasma nicotine concentration from before to after the 10-puff directed IQOS use bout for both experimental groups at sessions 3 and 4 (each $p < 0.05$). At session 4 (IQOS, Fri), the median (IQR) pre-puff plasma nicotine concentration in the IQOS-M group was 7.90 (8.3) ng/mL then 8.91 (8.5) ng/mL after the 10-puff IQOS bout, corresponding to a median nicotine boost of 5.35 (6.4) ng/mL ($z = 2.33$, $p = 0.018$; Table 6). The median (IQR) pre-puff plasma nicotine concentration at session 4 (IQOS, Fri) in the IQOS-T group was 6.49 (8.9) ng/mL then 12.59 (12.5) ng/mL after the 10-puff IQOS bout, corresponding to a median nicotine boost of 6.10 (7.2) ng/mL ($z = 2.90$, $p = 0.002$; Table 6). There were not statistically significant differences across groups in the IQOS-associated nicotine boosts observed at session 3 ($z = -0.11$, $p = 0.936$; Table 4) or at session 4 ($z = -0.683$, $p = 0.516$). Differences in nicotine boosts observed at session 3 (IQOS, Mon) compared to session 4 (IQOS, Fri) were not statistically significant for the IQOS-M group ($z = -0.38$, $p = 0.735$; Table 5) or the IQOS-T group ($z = -0.71$, $p = 0.520$). Participants in the IQOS-M group received a

lower nicotine boost when using IQOS-M at session 4 (IQOS, Fri) compared to use of their OB menthol cigarette at session 2 (OB, Fri; $z = 3.181$, $p < 0.001$; Table 5); differences in the nicotine boosts observed in the IQOS-T group following use of OB menthol cigarettes at session 2 and IQOS-T at session 4 were not statistically significant ($z = 1.18$, $p = 0.266$).

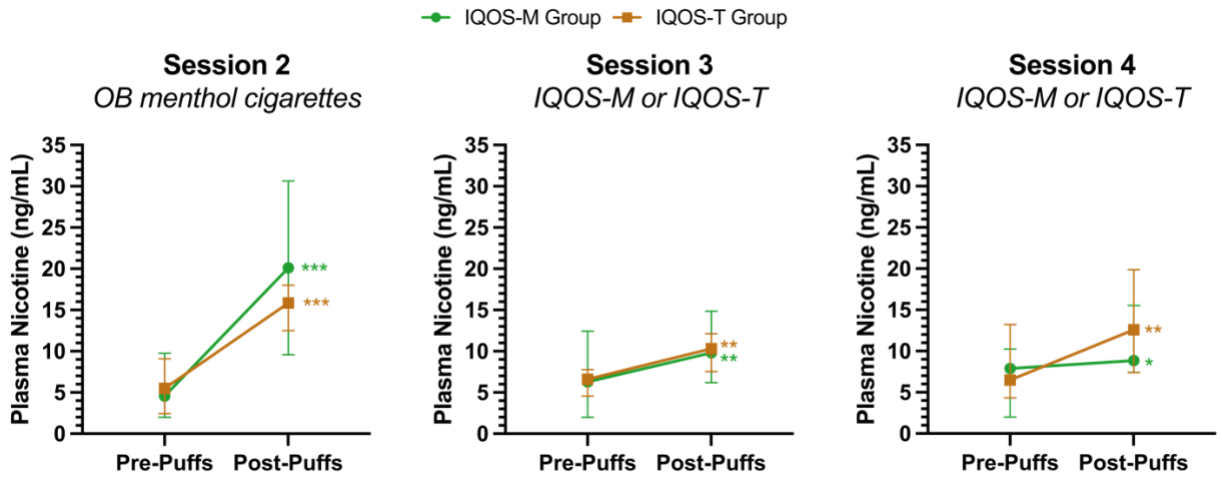


Figure 6. Plasma nicotine delivery at sessions 2 (own brand menthol cigarettes, Friday), 3 (IQOS, Monday), and 4 (IQOS, Friday).

Note: ***p < 0.001, **p < 0.01, *p < 0.05 for the within-group comparison of the post-puff value to the pre-puff value at each session. The median (symbols) and interquartile range (error bars) for plasma nicotine concentration measured before and after a 10-puff directed use bout with each product are shown, stratified by experimental group. Own brand (OB) menthol cigarettes data based on measurements taken at session 2 (Fri, study day 5) and IQOS data are based on measurements taken at session 3 (Mon, study day 8) and session 4 (Mon, study day 12).

Puff Topography

Puff Number. The median (IQR) number of puffs taken at sessions 2 (OB, Fri), 3 (IQOS, Mon), and 4 (IQOS, Mon) was 10.0 (0.0) puffs for both experimental groups. However, due to device malfunctions (e.g., IQOS battery dying before the 10^{th} puff) as well as participants sometimes taking multiple puffs when directed to take a single puff, the mean (SD) number of puffs at session 4 (IQOS, Fri) was 10.23 (0.6) puffs for the IQOS-M group and 9.42 (1.2) puffs for the IQOS-T group ($z = 2.57$, $p = 0.019$; Table 4).

Average Inter-puff Interval (seconds). The median of the participant-level average IPIs observed during the 10-puff directed use bouts performed at sessions 2 (OB, Fri), 3 (IQOS, Mon), and 4 (IQOS, Fri) ranged from 27.8 seconds to 29.4 seconds. No statistically significant differences in the IPI were observed across groups or sessions (each $p > 0.05$).

Average Puff Duration (seconds). At session 4 (IQOS, Fri), the median (IQR) of the average puff durations observed during the 10-puff bout was 1.34 (1.1) seconds for the IQOS-M group and 1.64 (1.7) seconds for the IQOS-T group ($z = -1.14$, $p = 0.267$; Table 4; Figure 7). At session 2 (OB, Fri), the median (IQR) of the average puff durations associated with use of OB menthol cigarettes in the IQOS-M group was 1.65 (0.8) seconds and in the IQOS-T group was 1.70 (0.7) seconds ($z = -0.275$, $p = 0.795$). No statistically significant differences were observed in average puff duration during the 10-puff directed use bout within either experimental group across session 3 (IQOS, Mon) and session 4 (IQOS, Fri; IQOS-M group: $z=1.76$, $p=0.081$; IQOS-T group: $z = -1.33$, $p = 0.204$; Table 5) nor across session 2 (OB, Fri) and session 4 (IQOS, Fri; IQOS-M group: $z = 0.81$, $p = 0.442$; IQOS-T group: $z = -1.41$, $p = 0.176$).

Average Puff Volume (mL). At session 4 (IQOS, Fri), the median (IQR) of the average puff volumes observed during the 10-puff IQOS directed use bout was 50.59 (36.3) mLs for the IQOS-M group and 60.15 (59.4) mLs for the IQOS-T group ($z = -0.97$, $p = 0.346$; Table 4; Figure 7). At session 2 (OB, Fri), the median (IQR) of the average puff volumes observed with use of OB menthol cigarettes for the IQOS-M group was 50.5 (21.1) mL and for the IQOS-T group was 45.43 (22.3) mL ($z = 0.42$, $p = 0.692$; Table 4).

Average Puff Flow Rate (mL/second). At session 4 (IQOS, Fri), the median (IQR) of the average puff flow rates observed during the 10-puff directed use bout for the IQOS-M group was 33.99 (10.3) mL/sec and for the IQOS-T group was 37.75 (15.0) mL/sec ($z = 0.04$, $p = 0.983$; Table 4; Figure 7). At session 2 (OB, Fri), the median (IQR) of the average puff flow rate observed during the 10-puff bout with OB menthol cigarettes was 29.79 (13.0) mL/sec for the IQOS-M group and 30.29 (9.9) mL/sec for the IQOS-T group ($z = 0.09$, $p = 0.950$).

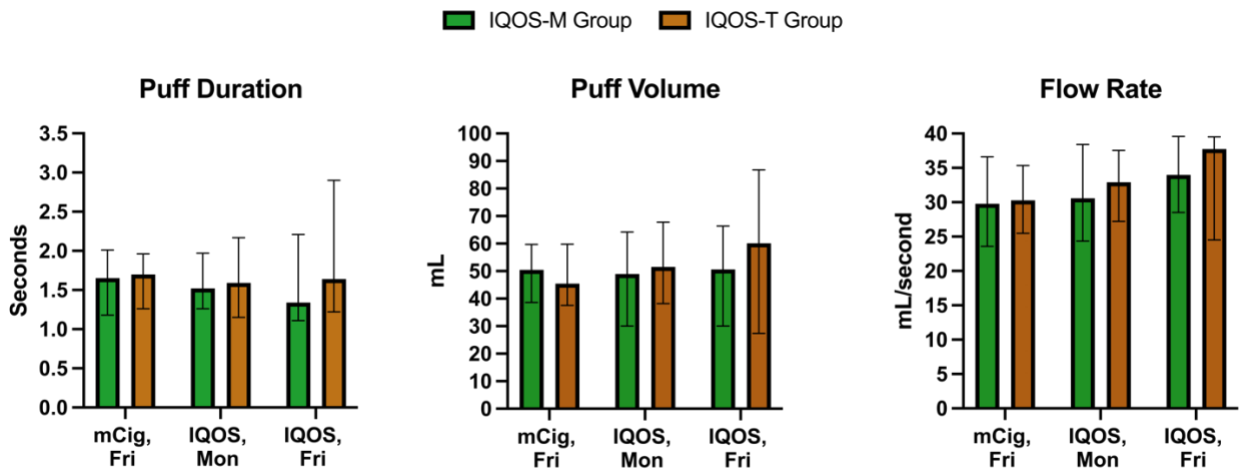


Figure 7. Select puff topography outcomes at sessions 2 (own brand menthol cigarettes, Friday), 3 (IQOS, Monday), and 4 (IQOS, Friday).

Note: ***p < 0.001, **p < 0.01, *p < 0.05. Bar height depicts the median and error bars represent the interquartile range (IQR). Results were based on a 10-puff (30-second inter-puff interval) directed use bout that occurred following 45 minutes of supervised abstinence. Medians and IQR were generated at the group level, after generating participant-level means for each topography outcome across all puffs taken at that clinical laboratory session. Colored bars in each panel correspond to group assignment (IQOS-M [N=18] or IQOS-T [N=12]). For each pair of bars corresponding to a single session, the IQOS-M group is presented first (i.e., left most) and the IQOS-T group is presented second (i.e., right most). Session 2 concerned own brand menthol cigarettes (mCigs) and took place on Friday of week 1, session 3 concerned participant's randomly-assigned IQOS flavor and took place on Monday of week 2, and session 4 concerned participant's randomly-assigned IQOS flavor and took place on Friday of week 2.

Self-Reported Effects

Select comparisons of interest in self-reported effects measures across groups (IQOS-M group versus IQOS-T group), as well as across products/sessions, are described below.

Questionnaire of Smoking Urges-Brief

Factor 1 (The Desire and Intention to Smoke with an Anticipation of Pleasure from Smoking). At session 4 (IQOS, Fri), the median (IQR) change in QSU-B factor 1 score from before to after the 10-puff directed IQOS use bout was -1.40 (2.8) for the IQOS-M group ($z = -3.60$, $p < 0.001$; Table 6) and -1.20 (4.8) for the IQOS-T group ($z = -2.16$, $p = 0.031$; Table 6). At session 4 (IQOS, Fri), there was not a statistically significant difference in the change in QSU-B factor 1 scores across experimental groups ($z = -0.43$, $p = 0.679$; Table 4). There was a larger pre- to post-puff reduction in QSU-B factor 1 following use of OB menthol cigarettes at session 2 (OB, Fri) compared to use of IQOS at session 4 (IQOS, Fri) for participants in the IQOS-M group ($z = 2.18$, $p = 0.028$; Table 5) but the difference among participants in the IQOS-T group was not statistically significant ($z = 1.54$, $p = 0.148$).

Factor 2 (The Relief from Nicotine Withdrawal or Negative Affect with an Urgent and Overwhelming Desire to Smoke). At session 4 (IQOS, Fri), the median (IQR) change in QSU-B factor 2 from before to after the 10-puff directed use bout was -1.30 (1.8) for the IQOS-M group ($z = -3.02$, $p = 0.001$; Table 6) and -0.80 (1.3) for the IQOS-T group ($z = -1.83$, $p = 0.078$; Table 6). At session 4 (IQOS, Fri), there was not a significant difference in the change in QSU-B factor 2 scores across groups ($z = -0.66$, $p = 0.522$; Table 4). There was a larger pre- to post-puff reduction in QSU-B factor 2 following use of OB menthol cigarettes at session 2 (OB, Fri)

compared to use of IQOS at session 4 (IQOS, Fri) for the IQOS-M group ($z = 2.35$, $p = 0.016$; Table 5) and the IQOS-T group ($z = 2.10$, $p = 0.037$).

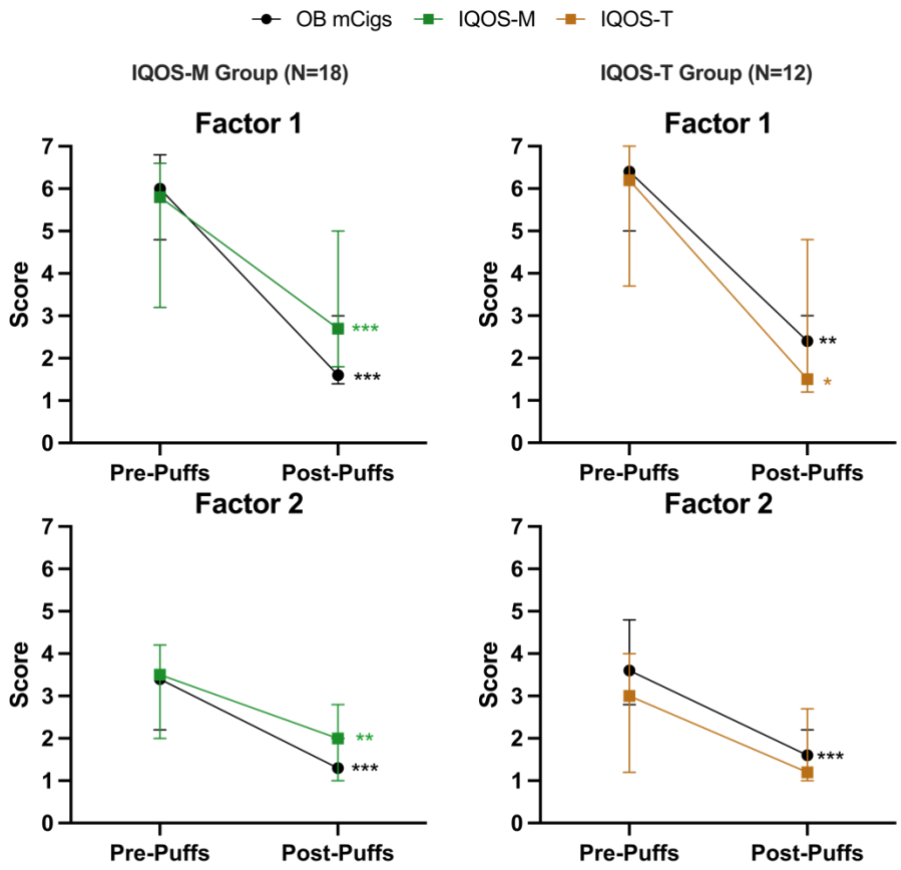


Figure 8. Select outcomes from the Questionnaire of Smoking Urges – Brief.

Note: ***p < 0.001, **p < 0.01, *p < 0.05 for the comparison of the post-puffs factor score to the pre-puffs factor score within each group and for each tobacco product. The median (symbols) and interquartile range (error bars) for QSU-B factor 1 (i.e., the desire and intention to smoke with an anticipation of pleasure from smoking) and factor 2 (i.e., the relief from nicotine withdrawal or negative affect with an urgent and overwhelming desire to smoke) before and after a 10-puff directed use bout with each product are shown, stratified by group. The lefthand column represents participants in the IQOS-M group (N=18) and the righthand column represents participants in the IQOS-T group (N=12). Own brand menthol cigarettes (OB mCigs) data are based on responses at session 2 (OB, Fri; study day 5) and IQOS data are based on responses at session 4 (IQOS, Fri; study day 12).

Minnesota Nicotine Withdrawal Scale

At session 4 (IQOS, Fri), IQOS-M use was associated with statistically significant pre- to post-puff reductions in all MNWS items (each $p < 0.05$; Table 6). Use of IQOS-T at session 4 (IQOS, Fri) was associated with statistically significant pre- to post-puff reductions in anxiousness ($z = -2.30$, $p = 0.020$), difficulty concentrating ($z = -2.58$, $p = 0.016$), restlessness ($z = -2.17$, $p = 0.031$), and hunger ($z = -2.58$, $p = 0.016$) but not "urges to smoke" ($z = -1.65$, $p = 0.104$) or "cravings for a cigarette/nicotine" ($z = -1.54$, $p = 0.133$). At session 2 (OB, Fri), use of OB menthol cigarettes was associated with statistically significant reductions in most MNWS items including "urges to smoke" (each $p < 0.01$) and "cravings for a cigarette/nicotine" (each $p < 0.01$) for participants in both groups.

Urges to Smoke. At session 4 (IQOS, Fri), the median (IQR) change in the "urges to smoke" item of the MNWS from before to after the 10-puff directed IQOS use bout was -34.50 (72.0) points for participants in the IQOS-M group and -7.00 (45.0) points for participants in the IQOS-T group ($z = 1.99$, $p = 0.047$; Table 4; Figure 9). There was a larger pre- to post-puff reduction in "urges to smoke" at session 2 (OB, Fri) compared to session 4 (IQOS, Fri) for the IQOS-T group ($z = 2.08$, $p=0.003$; Table 5) but the difference in "urges" suppression following use of OB menthol cigarettes compared to IQOS was not statistically significant among the IQOS-M group ($z = 0.98$, $p = 0.341$).

Anxious. There was a larger pre- to post-puff reduction in the "anxious" item of the MNWS following use of OB menthol cigarettes at session 2 (OB, Fri) compared to use of IQOS at session 4 (IQOS, Fri) for the IQOS-T group ($z = 2.08$, $p = 0.035$).

Craving a Cigarette/Nicotine. At session 4 (IQOS, Fri), the median (IQR) change in the "craving a cigarette/nicotine" item of the MNWS from before to after the 10-puff directed use bout was -41.50 (46.0) points for the IQOS-M group and -9.50 (47.5) points for the IQOS-T group ($z = 1.67$, $p = 0.097$; Table 4). There was not a statistically significant difference observed in the pre- to post-puff reductions in "craving a cigarette/nicotine" across session 3 (IQOS, Mon) and session 4 (IQOS, Fri) for either experimental group (IQOS-M group: $z = 0.89$, $p = 0.387$; IQOS-T group: $z = 0.00$, $p = 1.000$; Table 5). Pre- to post-puff reductions in "craving a cigarette/nicotine" were greater following use of OB menthol cigarettes at session 2 (OB, Fri) than following use of IQOS at session 4 (IQOS, Fri) for the IQOS-M group ($z = 2.03$, $p = 0.042$) and the IQOS-T group ($z = 2.091$, $p = 0.035$).

Desire for Sweets. At session 4 (IQOS, Fri), the median (IQR) change in the "desire for sweets" item of the MNWS from before to after the 10-puff directed IQOS use bout was -6.0 (12.0) points for those in the IQOS-M group and 0.0 (2.5) points for those in the IQOS-T group ($z = 2.57$, $p = 0.009$). There was a larger pre- to post-puff reduction in "desire for sweets" following use of OB menthol cigarettes at session 2 (OB, Fri) than following use of IQOS at session 4 (IQOS, Fri) for participants in the IQOS-T group ($z = 2.54$, $p = 0.037$).

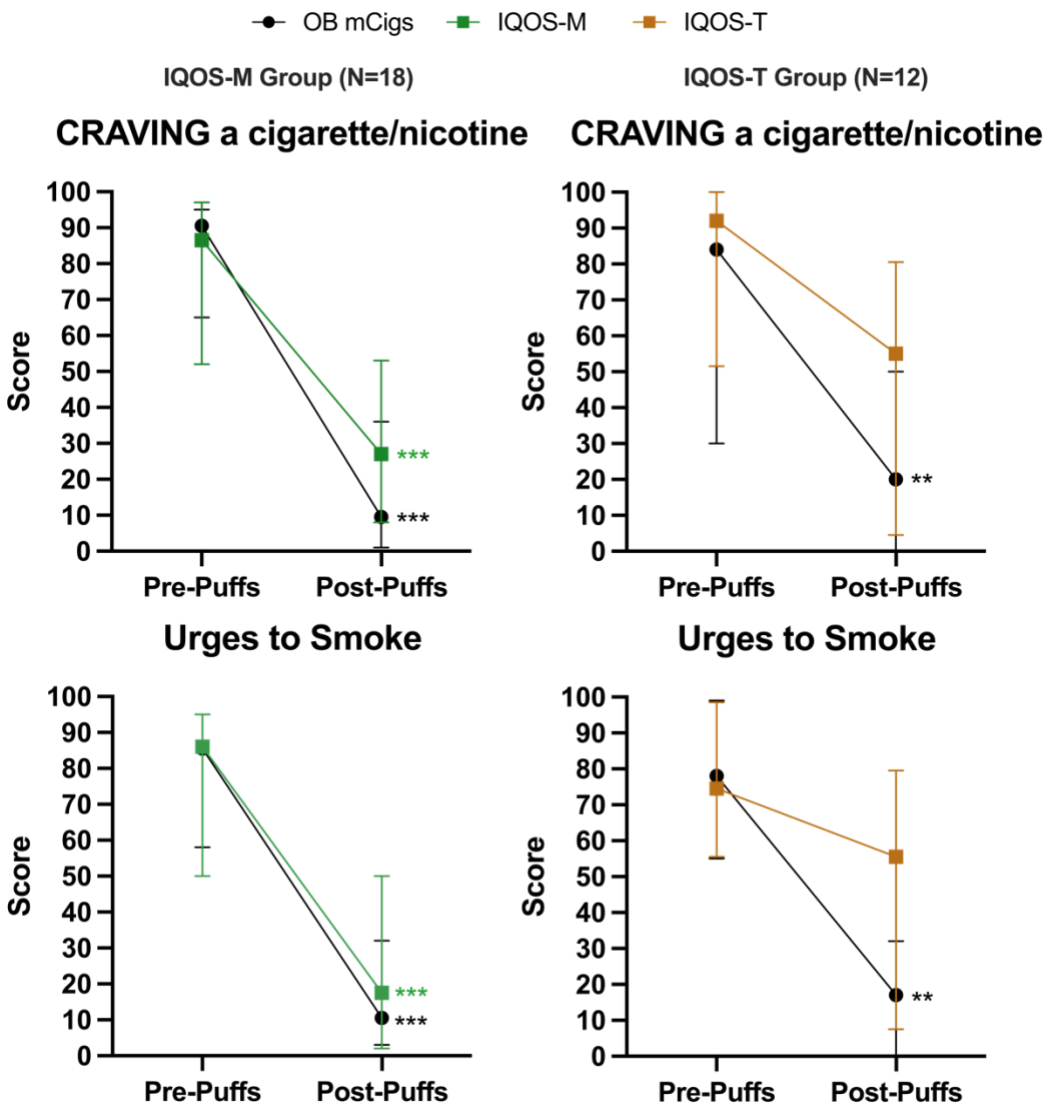


Figure 9. Select outcomes from the Minnesota Nicotine Withdrawal Scale

Note: ***p < 0.001, **p < 0.01, *p < 0.05 for the comparison of the post-puffs value to the pre-puffs value for each product within each group. Median (symbols) and interquartile range (error bars) for the MNWS' "urges to smoke" and "craving a cigarette/nicotine" items before and after a 10-puff directed use bout are presented. The lefthand column represents participants in the IQOS-M group (N=18) and the righthand column represents participants in the IQOS-T group (N=12). Own brand menthol cigarette (OB mCigs) data were based on responses at session 2 (Friday, study day 5) and IQOS data were based on responses at session 4 (Friday, study day 12).

Product Evaluation Questionnaire

Stimulant Effects. Following the directed IQOS use bout at session 4 (IQOS, Fri), the median (IQR) score for the "stimulant effects" subscale of the PEQ was 2.50 (2.7) for the IQOS-M group and 1.70 (1.0) for the IQOS-T group ($z = -0.96$, $p = 0.347$; Table 4; Figure 10). Stimulant effects were rated higher following the directed OB menthol cigarette use period at session 2 (OB, Fri) compared to the IQOS use bout at session 4 (IQOS, Fri) among participants in the IQOS-T group ($z = 2.54$, $p = 0.008$; Table 5).

Positive Reinforcement. Following the directed IQOS use bout at session 4 (IQOS, Fri), the median (IQR) score for the "positive reinforcement" subscale of the PEQ was 4.30 (3.7) for the IQOS-M group and 2.80 (2.0) for the IQOS-T group ($z = 1.83$, $p = 0.069$; Table 4; Figure 10). OB menthol cigarettes were rated as more "positively reinforcing" at session 2 (OB, Fri) than IQOS was at session 4 (IQOS, Fri) by participants in the IQOS-M group ($z = 2.83$, $p = 0.003$; Table 5) and the IQOS-T group ($z = 2.90$, $p = 0.002$).

Negative Reinforcement. Following the directed IQOS use bout at session 4 (IQOS, Fri), the median (IQR) "negative reinforcement" subscale score was 3.50 (2.7) for the IQOS-M group and 2.00 (2.3) for the IQOS-T group ($z = 1.13$, $p = 0.269$; Table 4; Figure 10). OB menthol cigarettes were considered to be more negatively reinforcing than IQOS among participants in the IQOS-M group ($z = 1.99$, $p = 0.047$; Table 5). Though the magnitude of the estimated effect was similar to the IQOS-M group, the difference with respect to perceived levels of negative reinforcement from OB menthol cigarettes compared to IQOS was not statistically significant among participants in the IQOS-T group ($z = 1.92$, $p = 0.055$).

Aversion. At session 4 (IQOS, Fri), the median (IQR) rating for the "aversion" subscale of the PEQ was 1.00 (1.0) for the IQOS-M group and 1.00 (0.0) for the IQOS-T group ($z = 0.04$, $p = 0.339$; Table 4; Figure 10). Differences in "aversion" between IQOS and OB menthol cigarettes were not statistically significant for either experimental group (IQOS-M group: $z = 0.41$, $p = 0.707$; IQOS-T: $z = 0.94$, $p = 0.500$; Table 5).

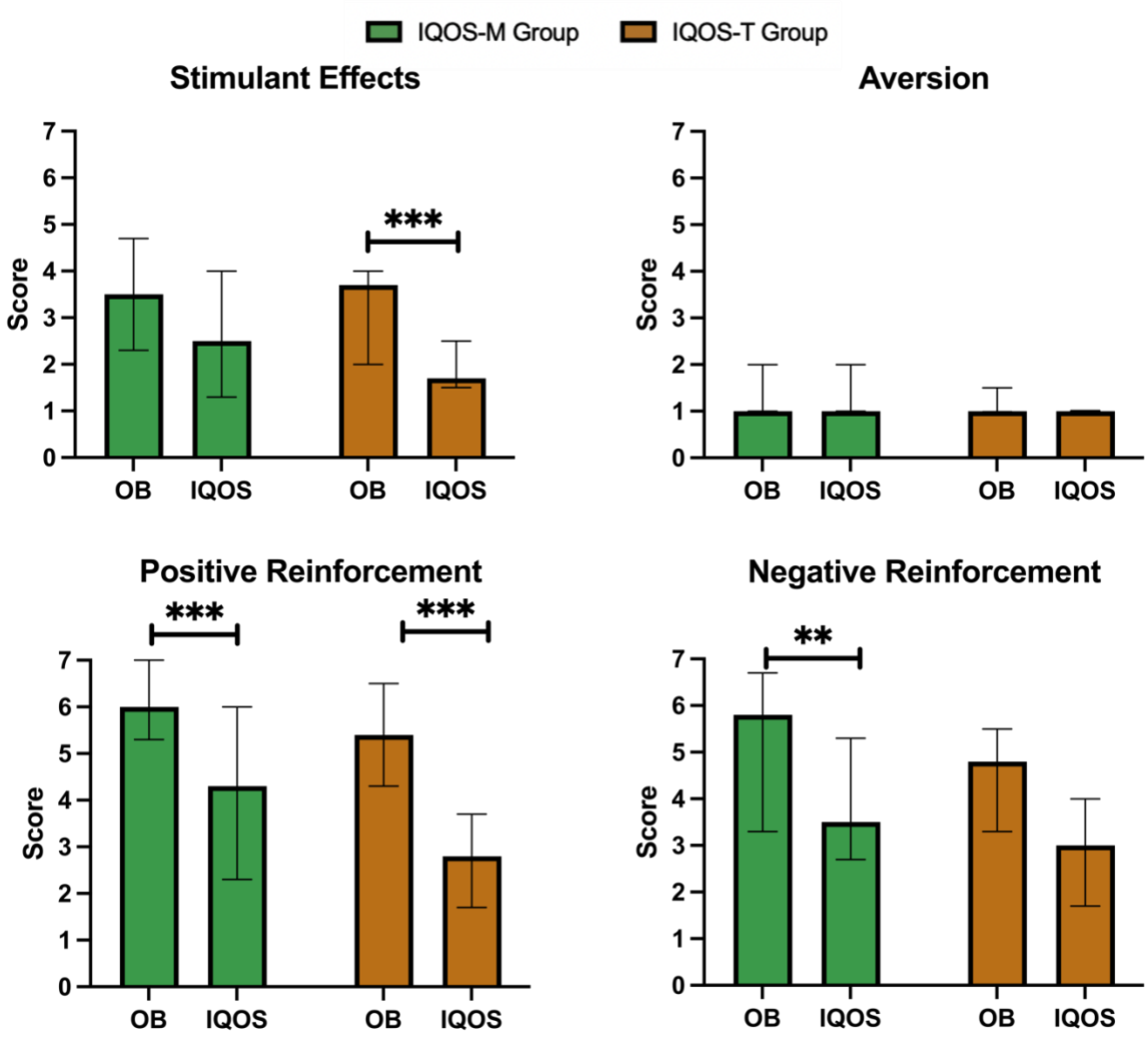


Figure 10. Select outcomes from the Product Evaluation Questionnaire (PEQ)

Note: ***p < 0.001, **p < 0.01, *p < 0.05. Bar height depicts median value for each PEQ subscale and the error bars represent the interquartile range. Own brand (OB) menthol cigarette data are based on responses at session 2 (Friday, study day 5) and IQOS data are based on responses at session 4 (Friday, study day 12). Statistical comparison across groups (for OB or IQOS) were based on Mann-Whitney U tests (Table 4); Wilcoxon Signed Rank tests compared OB to IQOS within each experimental group (Table 5). Within each panel of the above figure, the lefthand pair of bars present data from the IQOS-M group and the righthand pair of bars present data from the IQOS-T group.

Study Specific Questions

Easy to Use. Based on responses at session 2 (OB, Fri) and session 4 (IQOS, Fri), participants in the IQOS-M group considered OB menthol cigarettes to be easier to use then IQOS ($z = 2.44$, $p = 0.016$; Table 5). Participants in the IQOS-T group also tended to consider OB menthol cigarettes to be easier to use than IQOS but the difference between products was not statistically significant ($z = 2.02$, $p = 0.063$).

Enjoyment of the Overall Flavor Sensation. At session 4 (IQOS, Fri) the median (IQR) score for "enjoyment of the overall flavor sensation" item was 4.00 (4.0) for the IQOS-M group and 2.50 (2.5) for the IQOS-T group ($z = 2.01$, $p = 0.046$), indicating greater enjoyment of the flavor sensation afforded by IQOS-M than IQOS-T. Participants rated their "enjoyment of the overall flavor sensation" higher when using their OB menthol cigarette at session 2 (OB, Fri) than their randomly-assigned flavor of IQOS at session 4 (IQOS, Fri) in both groups (IQOS-M group: $z = 2.74$, $p = 0.005$, IQOS-T group: $z = 2.97$, $p = 0.002$; Table 5).

Plan to Use Product After the Study. Participants in the IQOS-M group reported less interest in using IQOS after the study at session 4 (IQOS, Fri) than at session 3 (IQOS, Mon; $z = -2.36$, $p = 0.028$; Table 5). Participants reported greater intent to use OB menthol cigarettes after the study than to use IQOS after the study in both experimental groups (IQOS-M group: $z = -3.46$, $p < 0.001$, IQOS-T group: $z = -2.77$, $p = 0.005$).

Absolute Harm Perceptions. At session 4 (IQOS, Fri), the median (IQR) score for the "in your opinion, how harmful are Heated Tobacco Products such as IQOS to general health"

question was 4.0 (3.0) for the IQOS-M group and 3.5 (2.0) for the IQOS-T group ($z = -0.58$, $p = 0.580$; Table 4). Participants in the IQOS-M group ($z = 3.33$, $p < 0.001$; Table 5) and the IQOS-T group ($z = 2.26$, $p = 0.025$) reported greater absolute harm perceptions for OB menthol cigarettes than for IQOS.

Experimental Tobacco Marketplace

Demand for Own Brand Menthol Cigarettes. Purchasing of OB menthol cigarettes in the ETM was well described by the exponentiated demand equation (Hursh and Silberberg, 2008) for both groups at each clinical laboratory session (Appendix 9, Table A9-1). At session 4 (IQOS, Fri), the mean (SD) R^2 value for the individual-fit demand curves was 0.96 (0.04) for the IQOS-M group and 0.97 (0.02) for the IQOS-T group. Estimates of the alpha parameter derived from the exponentiated demand equation suggested that OB menthol cigarette purchasing decreased as a function of increasing unit price (Appendix 9, Table A9-1). Two individuals were flagged as reporting non-systematic demand for OB menthol cigarettes possibly (Appendix 9, Table A9-2). One individual violated the "trend" assumption at sessions 3 and 4 due to null demand (i.e., zero demand for OB menthol cigarettes at all price points). A separate individual violated the "reversal from zero consumption" assumption at session 3. Due to allowance for violations of the "trend" assumption attributable to null-demand and violations of the "reversals from zero" assumption when randomized price trials are part of the purchase task's design, all observations were retained (Stein, Koffarnus et al., 2015). Overall, analyses of OB menthol cigarette purchasing suggest that participants were responsive to the pricing cues within the ETM.

Cross-Price Elasticity of IQOS. At session 4 (IQOS, Fri), a 10% increase in the price of OB menthol cigarettes was associated with a mean (SD) increase in demand for IQOS of 6.70% (0.9) when Fresh Menthol and Regular/Tobacco HeatSticks were available (i.e., "open-market" completed by the IQOS-M group; Figure 11; Table 4). Conversely, at session 4 (IQOS, Fri), a 10% increase in the price of OB menthol cigarettes was associated with a 1.4% (0.30) increase in demand for IQOS when only Regular/Tobacco HeatSticks were available (i.e., "restricted-market" completed by the IQOS-T group). IQOS's CPE with respect to OB menthol cigarettes was larger in the IQOS-M condition than in the IQOS-T condition under the individual-level ($z = 2.30$, $p = 0.021$) and group-level ($z = 5.85$, $p < 0.001$) analyses (Appendix 9, Table A9-3). For additional context, CPE estimates generated from national sales for non-cigarette tobacco products are presented in Appendix 10 (Huang, Gwarnicki et al., 2018). For example, the estimated CPE for IQOS in the open-market condition (+0.67) presented here was similar to the estimated CPE for nicotine lozenges (+0.65) derived from national sales data (Huang, Gwarnicki et al., 2018).

For the IQOS-M group at session 4 (IQOS, Fri), IQOS was a stronger substitute for OB menthol cigarettes than nonmenthol cigarettes ($z = 6.96$, $p < 0.001$), cigarillos ($z = 2.46$, $p = 0.014$), pod-based ENDS ($z = 5.19$, $p < 0.001$), refillable liquid-based ENDS ($z = 5.79$, $p < 0.001$), nicotine gum ($z = 4.63$, $p < 0.001$), and nicotine patches ($z = 5.97$, $p < 0.001$; Appendix 9, Table A9-4). For the IQOS-T group at session 4 (IQOS, Fri), nonmenthol cigarettes were a stronger substitute for OB menthol cigarettes than IQOS ($z = -5.51$, $p < 0.001$), but IQOS was a stronger substitute for OB menthol cigarettes than cigarillos ($z = 2.25$, $p = 0.025$) and pod-based ENDS ($z = 4.61$, $p < 0.001$; Appendix 9, Table A9-4).

Cross-Price Intensity of IQOS. The mean (SD) cross-price intensity of IQOS demand (i.e., IQOS demand at $0.12/OB cigarette) was 54.5 (115.8) mg of nicotine for the IQOS-M group and 15.08 (30.9) mg of nicotine for the IQOS-T group (Table 4). In the group-level analysis, the cross-price intensity of IQOS was higher for the IQOS-M group than for the IQOS-T group ($z = 18.63$, $p < 0.001$; Appendix 9, Table A9-3).

Substitution with non-IQOS Alternative Tobacco Products. At session 4 (IQOS, Fri), a 10% increase in the price of OB menthol cigarettes was associated with a mean (SD) increase in demand for nonmenthol cigarettes of 2.2% (0.5) in the open-market (i.e., IQOS-M group) condition and of 3.6% (0.3) in the restricted-market (i.e., IQOS-T group) condition ($z = -0.43$, $p = 0.816$; Table 4). Cigarillos ($z = 3.45$, $p < 0.001$) and pod-based ENDS ($z = 8.45$, $p < 0.001$) were stronger substitutes for OB menthol cigarettes at session 4 (IQOS, Fri) for the IQOS-M group than the IQOS-T group. ENDS with a refillable tank were stronger substitutes for OB menthol cigarettes at session 4 (IQOS, Fri) for the IQOS-T group than the IQOS-M group ($z = -2.50$, $p = 0.013$).

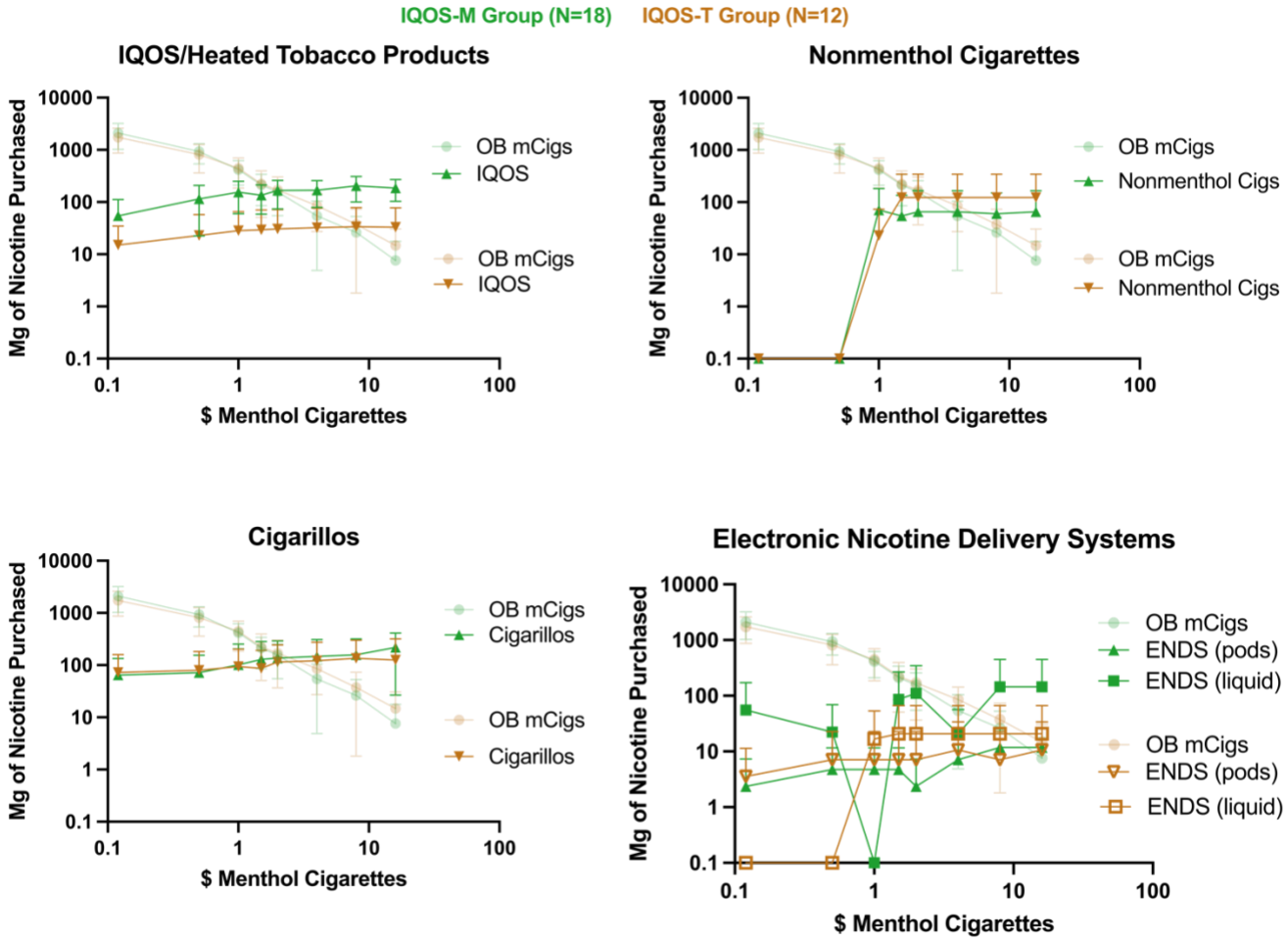


Figure 11. Select outcomes from the Experimental Tobacco Marketplace (ETM)

Note: Mean (symbol) and 95% confidence interval (error bars) for demand of each product at each price-point within the ETM task are shown, stratified by group. Opaque lines represent alternative products in the ETM while translucent lines represent demand of own brand menthol cigarettes (OB mCigs). Green-colored lines correspond to responses from the IQOS-M group and brown-colored lines correspond to responses from the IQOS-T group. The x- and y- axes are plotted in a logarithmic scale to match the Equation 1.

Substitution with Nicotine Replacement Therapy Products, Other Cessation Related Outcomes, and Total Nicotine Purchasing. Nicotine patches were stronger substitutes for OB menthol cigarettes at session 4 (IQOS, Fri) for the IQOS-T group than for the IQOS-M group ($z = -1.95$, $p = 0.049$; Figure 12). At session 2 ($z = -3.10$, $p = 0.001$) and session 3 ($z = -2.21$, $p = 0.026$), participants in the IQOS-T group left a larger portion of their hypothetical budget in the ETM unspent than participants in the IQOS-M group (Table 4). At session 4 (IQOS, Fri), participants in the IQOS-M purchased more nicotine (i.e., consumption summed across all available products) at the highest price trial ($16.00/OB menthol cigarette) than those in the IQOS-T group ($z = 2.01$, $p = 0.040$; Appendix 9, Table A9-5).

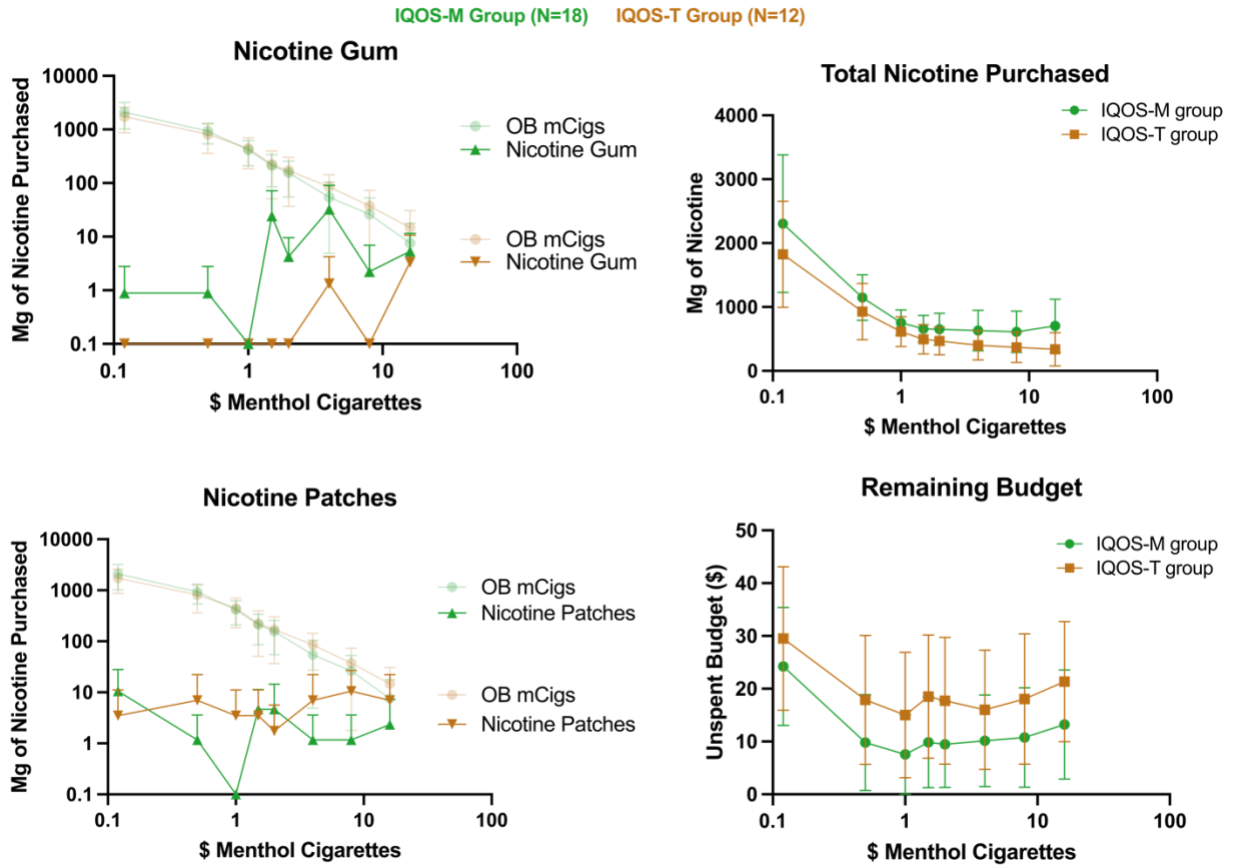


Figure 12. Cessation-related outcomes and total purchasing from the Experimental Tobacco Marketplace (ETM)

Note: Mean (symbols) and 95% confidence interval (error bars) for demand for each item at each price-point within the ETM task are shown. Opaque lines represent alternative products and translucent lines represent demand of own brand menthol cigarettes (OB mCigs). Green-colored symbols correspond to the IQOS-M group and brown-colored symbols correspond to the IQOS-T group; similarly, green circles correspond to the IQOS-M group and brown squares correspond to the IQOS-T group in the two righthand-side panels of the figure (Total Nicotine Purchased, Remaining Budget). The x- axes for all panels, and the y- axes for the nicotine gum and nicotine patches panels, are plotted in a logarithmic scale.

Naturalistic Use: Ecological Momentary Assessment & Timeline Follow Back

Ninety-five percent (95%) of all EMA prompts sent during the primary observation window (i.e., Tuesday, Wednesday, and Thursday of weeks 1 and 2) were completed. At least some use of "other products" was reported on 6.20% of observed days (most common products used: cigarillos and ENDS).

Own Brand Menthol Cigarette Consumption. The IQOS-M group reported a median (IQR) consumption of 9.33 (6.3) OB menthol cigarettes/day during week 1 and 4.00 (3.8) OB menthol cigarettes/day during week 2 ($z = 3.41$, $p = 0.001$; Tables 7 and 8; Figure 13). The IQOS-T group reported a median (IQR) consumption of 11.83 (4.7) OB menthol cigarettes/day during week 1 and 7.50 (4.3) OB menthol cigarettes/day during week 2 ($z = 2.81$, $p = 0.002$). The median (IQR) percentage reduction in daily OB menthol cigarette use from week 1 to week 2 was 80.36% (42.6) for the IQOS-M group and 36.81% (14.0) for the IQOS-T group ($z = 2.33$, $p = 0.019$; Table 7). The ordinal relationship across experimental groups with respect to the percentage reduction in daily OB menthol cigarette use was maintained when imputing missing EMA values ($z = 1.79$, $p = 0.054$) and analyzing data from the three-day TLFB ($z = 1.652$, $p = 0.101$; Table 7) though group differences were not statistically significant in these sensitivity analyses.

IQOS Consumption. The IQOS-M group used a median (IQR) of 4.33 (6.3) HeatSticks/day and the IQOS-T group used 4.50 (5.0) HeatSticks/day ($z = 0.92$, $p = 0.373$) during the second week of the study, however, mean (SD) daily IQOS consumption was 7.20 (6.1) HeatSticks/day for the IQOS-M group and 4.37 (3.1) HeatSticks/day for the IQOS-T group.

Total Consumption. There was not a statistically significant difference in total tobacco consumption during week 2 compared to week 1 among the IQOS-M group ($z = -0.06$, $p = 0.967$) or the IQOS-T group ($z = 0.76$, $p = 0.492$; Table 8). Differences in total tobacco consumption were not statistically significant across the two experimental groups during week 1 ($z = -1.03$, $p = 0.317$) or week 2 ($z = -0.78$, $p = 0.453$; Table 7).

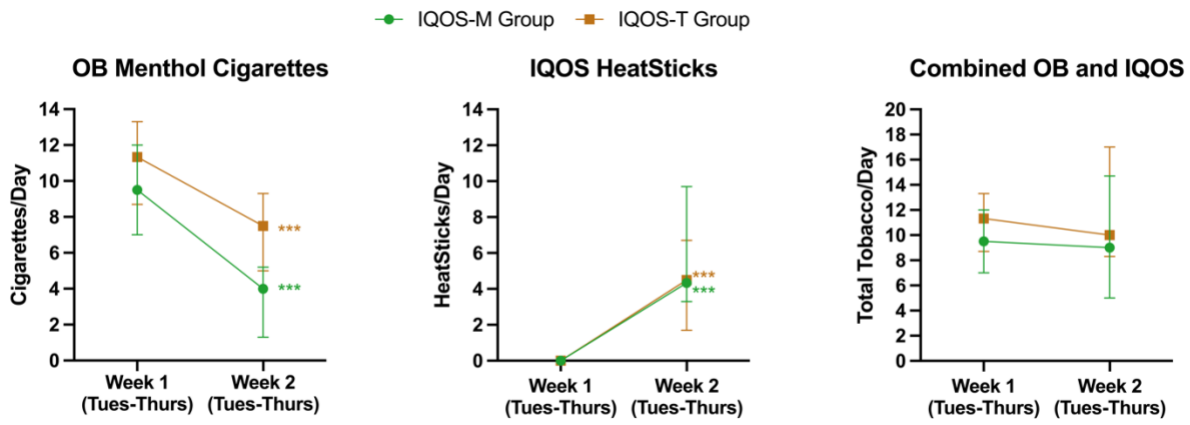


Figure 13. Select outcomes from the naturalistic use period

Note: ***p < 0.001, **p < 0.01, *p < 0.05 for the comparison of week 1 consumption to week 2 consumption within each group. Average daily consumption for own brand (OB) menthol cigarettes and IQOS across Tuesday, Wednesday, and Thursday of each week are shown as the median value (symbol) with interquartile range (error bar) by group. Data presented are based on responses to ecological momentary assessment prompts (i.e., daily diary; N=25 [IQOS-M group: n=15, IQOS-T group: n=10]).

Discussion

Overview

HTPs are marketed as a way for people that smoke cigarettes to reduce their exposure to the HPHCs of tobacco (FDA, 2020; PMI, 2020; Prochaska & Henriksen, 2019). The tobacco industry is investing in the US HTP market, a move that coincides with FDA's plan to ban the sale of cigarettes that feature menthol as a characterizing flavor (Abroms, Levine et al., 2022; Rumney, 2023a; Hiscock, Silver et al., 2020; Theis, 2023). However, the FDA has not yet defined the regulatory status of HTPs in the US fully. One relevant regulatory action for the FDA will be deciding whether to permit characterizing flavors (e.g., menthol) in HTPs with a MRTP authorization. To inform regulatory action, evidence from the scientific community regarding the influence of characterizing flavors such as menthol on HTP *abuse liability* (i.e., likelihood that an HTP will sustain long-term use) among adults that use menthol cigarettes is needed (Carter, Stitzer et al., 2009; FDA, 2022d).

FDA's proposed product standard banning menthol as a characterizing flavor of cigarettes may apply to the only HTP with MRTP authorization in the US: the IQOS tobacco heating system (FDA, 2022e; *United States v. Philip Morris USA, et al.,* 2023). However, FDA has noted its willingness to grant exemptions to the menthol ban on a case-by-case basis for products that present unique public health considerations (FDA, 2022e). Any exemption to the menthol ban must fulfill FDA's mission to promote public health, but no systematic and independent evaluations of the influence of flavors on HTP abuse liability are available to guide regulatory action. Fortunately, established methods exist that can be leveraged to fill the regulatory science evidence gap surrounding the influence of flavors on HTP abuse liability (Breland, Kleykamp et al., 2006; Carter & Griffiths, 2009; Carter, Stitzer et al., 2009; Henningfield, Hatsukami et al.,

2011; Vansickel, Baxter et al., 2021). Relevant assessments for determining HTP abuse liability include measuring the nicotine delivery, puff topography, self-reported effects, behavioral economic demand, and naturalistic use patterns associated with HTP use as a function of flavor availability (Carter, Stitzer et al., 2009). When integrated into a single experimental design, these measures can provide a multi-dimensional understanding of HTP abuse liability (Wall, Bono et al., 2018).

This study aimed to characterize the abuse liability of the IQOS 2.4 tobacco heating system as a function of its available flavors (Fresh Menthol or Regular/Tobacco) via clinical laboratory and naturalistic abuse liability assessments among adults that smoke menthol cigarettes. Results of this investigation inform understanding the influence of flavor on HTP abuse liability among a population of high policy-relevance.

Nicotine Delivery and User Behavior (Puff Topography)

Nicotine is an important reinforcer of smoking behavior (Benowitz, 2008) and prior work has demonstrated that a tobacco product's abuse liability increases with nicotine dose and delivery rate (Henningfield & Goldberg, 1983; Henningfield & Keenan, 1993; Jaffe & Jaffe, 1989). Understanding the nicotine delivery profile of HTPs (as compared to cigarettes) and how *menthol* may impact IQOS 2.4's nicotine delivery profile was of paramount importance to this investigation. Increases in plasma nicotine concentrations were observed following 10 puffs (with a 30-second IPI) from OB menthol cigarettes, as well as from IQOS-M and IQOS-T, by participants in this study suggesting that all products tested here delivered potentially reinforcing amounts of nicotine. Consistent with prior literature on the behaviors of people who smoke but are nicotine abstinent then given access to a cigarette, the median post-puff plasma nicotine

concentration among participants in this study following use of their OB menthol cigarettes was between 15-20 ng/mL (Hajek, Pittaccio et al., 2020; Lopez, Hiler et al., 2016; Vansickel, Cobb et al., 2010; Yan & D'Ruiz, 2015).

In this study, IQOS-M did not boost plasma nicotine levels as much as OB menthol cigarettes ($p < 0.05$) but differences between OB menthol cigarettes and IQOS-T were not statistically significant ($p = 0.266$). While the small and inconclusive differences noted here across the nicotine delivery of the menthol- and tobacco-flavored IQOS HeatSticks may be too small to carry much clinical significance, the lower post-puff plasma nicotine concentrations achieved following use of IQOS compared to OB menthol cigarettes could be clinically-relevant if this means that people who smoke and attempt to switch to IQOS do not receive the dose of nicotine required to suppress symptoms of nicotine abstinence adequately. Incomplete suppression of nicotine abstinence symptoms could compel people who smoke that attempt to switch to IQOS to continue supplementing their tobacco consumption with combustible cigarettes to achieve desired plasma nicotine concentrations.

The nicotine boost estimates observed here were comparable to other studies that have adopted similar puffing protocols for OB menthol cigarettes and IQOS (Leavens, Lambart et al., 2023; Maloney, Eversole et al., 2020). There was insufficient evidence to conclude that nicotine boosts were greater for participants that used IQOS-M than for participants that used IQOS-T at session 4 (Fri, week 2; $p = 0.516$), but the smaller than intended sample size raises the possibility of a type II error in this result.

The observation that median nicotine boosts associated with use of IQOS were 60-80% of boost values obtained following use of OB menthol cigarettes in this study is consistent with prior clinical laboratory studies of IQOS conducted among people that use cigarettes (Leavens,

Lambart et al., 2023; Maloney, Eversole et al., 2020; Phillips-Waller, Przulj et al., 2021) as well as machine-based puffing protocols (Davigo, Klerx et al., 2023; Li, Luo et al., 2019; Mallock, Böss et al., 2018). Participants using IQOS-M in this study appeared to receive less nicotine and reach a lower post-puff plasma nicotine concentration than individuals that used IQOS-M in a similar study that reported a median nicotine boost of 13.96 ng/mL, but differences in results across studies may be due to the more intense (14-puffs with 20 second IPI) puffing protocol as well as the requirement for 14-hours of pre-session abstinence adopted in the latter study (Yingst, Bordner et al., 2023). The contrast in nicotine boosts observed in this study and the nicotine boosts observed in prior work with a more intense puffing protocol demonstrates the potential sensitivity of nicotine delivery from IQOS to puffing behavior (Yingst, Bordner et al., 2023).

Nicotine delivery was hypothesized to differ across IQOS-M and IQOS-T due to menthol's potential impact on puff topography. Prior work suggested that menthol may encourage longer puffs from people that use menthol cigarettes and thus could increase nicotine delivery on a puff-by-puff basis (Ahijevych & Garrett, 2004; Ahijevych & Garrett, 2010; Davigo, Klerx et al., 2023). However, there was not a statistically significant difference in puff duration across participants using IQOS-M compared to participants using IQOS-T at any of the clinical laboratory sessions (Figure 7). The median (IQR) puff duration was 1.7 (0.7) seconds for participants when using their OB menthol cigarettes, 1.3 (1.1) seconds when using IQOS-M, and 1.6 (1.7) seconds when using IQOS-T. Tobacco-industry funded studies suggest people that smoke take longer puffs from HTPs than from cigarettes (Haziza, de La Bourdonnaye et al., 2016; Lüdicke, Picavet et al., 2018), though results reported here were inconclusive with respect to that behavior. With that said, while the difference could not be conclusively determined here, larger puff volumes for participants when using IQOS compared to OB menthol cigarettes were

observed in both groups. If true, this result would lend support to the theory that people that smoke cigarettes may need to take larger (if not longer) puffs from HTPs to compensate for lower nicotine delivery compared to a combustible cigarette (Davigo, Klerx et al., 2023; Jones, Slayford et al., 2020). No statistically significant differences in puff duration (or other puff topography measurements) were noted in either experimental group from the time of first exposure (study day 8) to final exposure (study day 12) with IQOS; thus, there is insufficient evidence reported here to conclude that participants may have "learned" to use IQOS more effectively during the at home use period. However, measuring changes in puff topography over time among participants that are introduced to HTPs may still be worthwhile in future studies, especially if a longer observation period than was used here (i.e., 3 days) can be accommodated.

Taken together and while acknowledging the underpowered analyses, the nicotine delivery and puff topography results presented did not support the hypotheses that menthol increases HTP abuse liability by increasing nicotine delivery or puff duration among people that use menthol cigarettes. A key takeaway from the acute self-administration portion of this study is that a single use of an IQOS HeatStick appears to deliver less nicotine than a combustible cigarette does, a finding that is consistent with prior literature from non-industry funded sources (Adriaens, Gucht et al., 2018; Leavens, Lambart et al., 2023; Maloney, Eversole et al., 2020). Thus, regardless of flavor, IQOS 2.4 may have insufficient pharmacologic reinforcement to support complete substitution from combustible cigarettes. The finding that IQOS delivers less nicotine than equivalent use of a combustible cigarette synergizes with observations from epidemiologic data suggesting that most people that use IQOS use the HTP alongside cigarettes (Cheng, Noggle et al., 2023; Satomi, Kanami et al., 2023; Sutanto, Miller et al., 2019). For example, PMI's post-marketing surveillance data of people that use IQOS in the US found that

two-thirds of its respondents used IQOS alongside at least one other tobacco product (Cheng, Noggle et al., 2023), and in Japan an estimated 63% of people that used an HTP also smoked cigarettes (Sutanto, Miller et al., 2020). Findings from this study suggest that the insufficient delivery of nicotine from IQOS in acute settings may, in part, be driving people that use HTPs to dual use combusted products to achieve desired blood nicotine concentrations (Benowitz, Zevin et al., 1997; Farsalinos, Romagna et al., 2013; Farsalinos, Romagna et al., 2015).

Self-Reported Effects of Tobacco Product Consumption

Measurement of the self-reported experiences associated with using OB menthol cigarettes and IQOS was another important line of inquiry in this study. The self-reported effects measures reported here sought to characterize how OB menthol cigarette and IQOS use influenced tobacco abstinence symptom suppression, product appeal, and behavioral intentions.

Nicotine is instrumental to the reinforcing effects of tobacco products and reductions in some tobacco abstinence symptoms can be documented following its administration (Buchhalter, Acosta et al., 2005; Hiler, Breland et al., 2017; Vansickel, Baxter et al., 2021). Consistent with the plasma nicotine findings described above, use of OB menthol cigarettes suppressed tobacco abstinence symptoms following a 10-puff directed use bout more so than IQOS-M or IQOS-T. For example, statistically significant suppression of QSU-B factors 1 and 2 were observed following use of OB menthol cigarettes as well as IQOS-M. However, greater suppression of QSU-B factors 1 and 2 was also reported by participants following use of their OB menthol cigarette than IQOS-M (each $p < 0.05$). The differences in tobacco abstinence symptom suppression between OB menthol cigarettes and IQOS-M presented here could be clinically meaningful as they might translate into people who smoke that attempt to switch to IQOS

continuing to experience the symptoms of tobacco abstinence even after use of a menthol-flavored HTP. The incomplete suppression of tobacco abstinence symptoms following use of IQOS-M could predispose to continued use of combustible menthol cigarette. Consequently, menthol-flavoring in IQOS 2.4 may be insufficient to suppress symptoms of tobacco abstinence enough to support complete substitution from combustible menthol cigarettes.

Statistically significant differences in tobacco abstinence symptom suppression were not observed across participants that used IQOS-M and participants that used IQOS-T except for two MNWS items: “urges to smoke” and “desire for sweets” (each $p < 0.05$). Participants that used IQOS-M reported a larger reduction in “urges to smoke” from before to after the directed puffing bout than participants that used IQOS-T ($p < 0.05$). Of principal interest was the difference in cigarette craving suppression across participants that used IQOS-M and participants that used IQOS-T. Though differences in “craving a cigarette/nicotine” across IQOS flavor conditions did not achieve statistical significance and thus were inconclusive, the pre- to post-puff change in “craving” may have been larger for participants following use of IQOS-M than for participants using IQOS-T (though there was considerable variability in these estimates). Specifically, at session 4 (IQOS, Fri), the IQOS-M group reported a median (IQR) reduction (on a 0-100 scale) in “craving a cigarette/nicotine” of 41.5 (46.0) points whereas participants in the IQOS-T group reported a median reduction of 9.5 (47.5) points ($p=0.097$). On the related question of “urges to smoke,” a median (IQR) reduction of 34.5 (72.0) points for participants in the IQOS-M group and 7.0 (45.0) points for participants in the IQOS-T group was observed ($p < 0.05$). Differences in the suppression of “craving” and “urges” to smoke between the two flavors of IQOS presented here may be large enough to suggest that people who smoke menthol cigarettes would be more

likely to continue smoking cigarettes alongside IQOS-T than IQOS-M, but such a conclusion cannot yet be established and further research into this possibility is merited.

The IQOS flavor condition differences in tobacco abstinence symptom suppression are intriguing when considered alongside the other self-reported effects and plasma nicotine data; despite not observing a statistically or clinically significant difference in nicotine delivery across the two flavors of IQOS, IQOS-M appeared to suppress cravings/urges for a cigarette to a greater extent among people that use menthol cigarettes than IQOS-T. Prior literature has identified cravings for cigarettes as a tobacco abstinence symptom that could be suppressed by non-nicotine stimuli (e.g., denicotinized cigarettes, citric acid inhalers, etc.) and concluded that nicotine administration *alone* does not suppress cigarette cravings (Behm, Schur et al., 1993; Buchhalter, Acosta et al., 2005; Henningfield & Goldberg, 1983). Viewed through this lens, menthol flavoring in HTPs may be operating as a conditioned-stimulus or non-nicotine reinforcer of smoking behavior among people that use menthol cigarettes (Ahijevych & Garrett, 2010). If so, menthol may be an important attribute of an MRTP to heighten abuse liability and support substitution from combustibles for people that use menthol cigarettes (Bello, Schulte et al., 2024). Indeed, repeated pairing of flavors (e.g., menthol) with nicotine has been hypothesized to create sensory cues and rewards through Pavlovian conditioning (Ahijevych & Garrett, 2010; Budworth, 2019), and menthol can reinstate nicotine-seeking behaviors in preclinical models (Harrison, Biswas et al., 2017). The present study is ill-suited to test whether menthol behaved as conditioned-stimulus or non-nicotine reinforcer but provides preliminary data that can be built upon in future studies.

The tobacco abstinence symptom suppression results from this study are similar to prior literature that found OB cigarettes and IQOS were capable of suppressing QSU-B factors 1 and 2

(Maloney, Eversole et al., 2020). In this investigation, observed reductions in "craving a cigarette/nicotine" and "urges to smoke" were greater following use of OB menthol cigarettes than either flavor of IQOS (each $p < 0.05$). Findings reported here are consistent with previous literature that found "urges to smoke" were suppressed to a greater extent following *ad lib* use of OB cigarettes than a flavor-matched IQOS product (Maloney, Eversole et al., 2020) as well as greater reductions in "craving a cigarette/nicotine" following use of OB cigarettes than a preferred-flavor IQOS (Adriaens, Gucht et al., 2018; Leavens, Lambart et al., 2023). In sum, menthol may enhance the ability of IQOS to suppress some symptoms of tobacco abstinence (e.g., craving and urges to smoke) for people that smoke menthol cigarettes but, even with a menthol flavor, the HTP still falls short of the abstinence suppressing capacity of OB menthol cigarettes.

At the final clinical laboratory session, there were no statistically significant differences in PEQ subscale scores across IQOS-M and IQOS-T (each $p >0.05$). However, group differences approached statistical significance for positive reinforcement (e.g., taste good, enjoy the sensation in your throat and chest, enjoy smoking; $p = 0.069$) suggesting that IQOS-M may be more positively reinforcing than IQOS-T among people that use menthol cigarettes. Consistent with potential differences in positive reinforcement between IQOS-M and IQOS-T, participants rated their overall "enjoyment of the flavor sensation" higher for IQOS-M than for IQOS-T ($p < 0.05$). Still though, OB menthol cigarettes appeared to be more positively and negatively reinforcing than either flavor of IQOS and more "stimulating" (e.g., more awake, help concentrate, reduce hunger) than IQOS-T.

Positive and negative (e.g., calm down, less irritable, relieves cravings) reinforcement scores were greater for IQOS-M than for IQOS-T among people that use menthol cigarettes at

session 3 (Mon, week 2; each $p < 0.05$), indicating that Fresh Menthol HeatSticks were more reinforcing than Regular/Tobacco HeatSticks during early exposure to IQOS. Thus, menthol may be important to determining *initial* appeal of HTPs for people that use menthol cigarettes, a sentiment also expressed in a qualitative study about initial use experiences with IQOS (Kim, Watkins et al., 2020). On a related note, flavors such as menthol have been well-documented to promote initiation into long-term use of cigarettes (Nonnemaker, Feirman et al., 2019; Nonnemaker, Hersey et al., 2013; Villanti, Collins et al., 2017) and ENDS (Cadham, Liber et al., 2022; Jones, Ashley et al., 2019; Landry, Groom et al., 2019) among nicotine-naïve individuals. Flavors may thus be most important in defining initial experiences with an MRTP such as IQOS, in turn influencing future use intentions (Yingst, Midya et al., 2024).

Most participants reported that they were not interested in using IQOS after the study ended in both experimental groups. Disinterest in continuing to use IQOS could be explained by the fact that participants rated IQOS as less easy to use than their OB menthol cigarettes. Anecdotally, many participants expressed frustration with using the IQOS device citing the need for the device to heat for 20-30 seconds before use, the need to charge the device in-between use episodes, and the limited number of puffs that could be taken before the device extinguished. Additionally, harm perceptions in absolute terms as well as relative to OB menthol cigarettes, for IQOS did not differ across IQOS flavors but participants in both groups felt that IQOS was less harmful to general health than OB menthol cigarettes (each $p < 0.05$).

In summary, the addition of menthol to IQOS HeatSticks may heighten the appeal of HTP use and make the subjective experiences associated with using an HTP more similar to a menthol cigarette. However, even with menthol, the subjective experience of using an HTP may differ from use of a combustible menthol cigarette in important areas such as positive and negative

reinforcement. Thus, regardless of flavor availability, HTPs may not be able to replicate the subjective reinforcement experience of combustible menthol cigarettes enough to support complete substitution.

Behavioral Economic and Naturalistic Assessments of Substitution

Participants completed the ETM at each clinical laboratory session to measure the relative reinforcing efficacy (i.e., substitution potential) of IQOS for OB menthol cigarettes. Participants in the IQOS-M condition completed an "open-market" task (Regular/Tobacco and Fresh Menthol HeatSticks were available) and participants in the IQOS-T condition completed a "restricted-market" task (only Regular/Tobacco HeatSticks were available). Results suggested that if menthol-flavored HeatSticks were available alongside tobacco-flavored HeatSticks, IQOS would be a stronger economic substitute for OB menthol cigarettes compared to a market that restricted access to menthol-flavored HeatSticks. Specifically, a 10% increase in the price of OB menthol cigarettes was associated with a 6.7% increase in the demand for IQOS when Fresh Menthol and Regular/Tobacco HeatSticks were available together and a 1.4% increase in the demand for IQOS when only Regular/Tobacco HeatSticks were available ($p = 0.019$). For context, a recent meta-analysis based on national sales data (funded by JUUL) suggested a 10% increase in the price of cigarettes raised ENDS demand by 9.8% (Selya, Foxon et al., 2023). Accounting for the costs associated with obtaining cigarettes from non-authorized suppliers, one could view the impending ban on menthol cigarettes as a sizeable-to-infinite increase in menthol cigarette price. Thus, FDA's decision to include or exclude HTPs from the menthol cigarette ban is likely to exert a meaningful impact on the potential market size of HTPs in the US and the overall economic viability of the product class. Findings presented here are consistent with previous literature that has used the ETM (Denlinger-Apte, Cassidy et al., 2021) or other choice-

tasks (White, Goden et al., 2023) to conclude that the availability of non-tobacco characterizing flavors in alternative nicotine delivery systems encourages at least partial substitution from combustible products among people that use menthol cigarettes.

The ETM also provided information on what people that smoke menthol cigarettes might do if their preferred product (i.e., OB menthol cigarettes) becomes difficult to obtain other than switch to IQOS. For example, in addition to IQOS, participants in the open-market condition substituted with cigarillos and pod-based ENDS to a greater extent than participants in the restricted-market condition (each $p < 0.05$). Switching to *nonmenthol* combustible cigarettes appeared to increase under both policy scenarios. Thus, an unintended consequence of banning menthol cigarettes might be to increase switching to nonmenthol cigarettes, but there was not sufficient evidence presented here to suggest that access to menthol-flavored HTPs influenced intentions to substitute with nonmenthol cigarettes. Still, monitoring of substitution with combusted alternatives to menthol cigarettes in the post-ban period will be critical work as such a pattern of substitution could undermine the public health benefits of the proposed ban. To gain prospective insight into the possibility of substitution with nonmenthol combusted alternatives further research is needed. For example, an inpatient study of the smoking behaviors of people that smoke menthol cigarettes but can only access non-menthol cigarettes or various flavors of IQOS products might provide useful information.

Complete substitution with an HTP in the ETM was not common in this sample of adults that smoke menthol cigarettes. At the final clinical laboratory session and at the highest price of OB menthol cigarettes, 38.9% (N=7) of participants in the IQOS-M group and 0% of participants in the IQOS-T group reported purchasing some IQOS products but no combustible tobacco product (e.g., cigarettes, cigars, cigarillos). The pattern of incomplete substitution with a

menthol-flavored alternative product (i.e., HTPs) documented here is consistent with prior literature that used the ETM to simulate flavor-restriction policies in ENDS among adults that use menthol cigarettes (Denlinger-Apte, Cassidy et al., 2021).

Another key finding from the ETM is that participants in the restricted-market (i.e., IQOS-T group) tended to spend less of their budgets and purchase fewer tobacco products across the span of price-points in the ETM. One interpretation of the lower purchasing activity among participants in the IQOS-T group is that restricting access to menthol-flavored alternative products like HTPs could promote cessation following a ban on the sale of menthol cigarettes, a conclusion that is consistent with previous work that investigated potential responses to a menthol ban (White, Goden et al., 2023). Coupling the suggestion of enhanced quit intentions with the theory that switching to a nonmenthol cigarettes could be a first step toward reducing or quitting smoking for people that use menthol cigarettes (Bold, Jatlow et al., 2020; Kotlyar, Shanley et al., 2021a, 2021b), the possibility that restricting access to HTPs with a characterizing flavor emerges as a possible strategy to promote cessation in the post-menthol ban period.

Findings from the ETM portion of this study were consistent with what was observed when participants took IQOS products home and attempted to switch from OB menthol cigarettes for five days. Relative to the level of cigarette consumption reported during the baseline week, during the intervention week the median (IQR) participant who received IQOS-M reduced their average daily cigarette consumption by 80.6% (42.6) whereas the median participant who received IQOS-T reduced their average daily cigarette consumption by 38.4% (14.0; $p < 0.05$). Reductions in daily cigarette smoking were statistically significant in both groups, but the clinical significance of these reductions would ultimately depend on the durability of the reduction and the marginal differences in long-term health risks from tobacco-

related disease of smoking fewer cigarettes alongside uptake of HTPs. Future research is needed to understand how much cigarette smoking might need to be reduced by to yield meaningful changes in health risk for people who smoke in the context of switching to an HTP and may require studies with longer observation periods and that collect relevant biomarkers of exposure.

The average daily consumption of IQOS HeatSticks during week 2 tended to be higher for the IQOS-M group (7.2 HeatSticks/day) than the IQOS-T group (4.4 HeatSticks/day) but group differences were not statistically significant ($p = 0.516$). The median consumption of IQOS HeatSticks for both groups during the intervention week was around 4.5 HeatSticks/day, suggesting that the mean value for daily HeatStick consumption in the IQOS-M group could be influenced by outliers on the upper-end of the distribution (i.e., right-skewedness). Tradeoffs between uptake of HTPs and commensurate reductions in cigarette smoking with respect to biomarkers of exposure and long-term health risk should be investigated in future work.

Despite instructions to attempt to "completely substitute [with IQOS]," only three participants (all part of the IQOS-M group) achieved complete substitution in the naturalistic use period (i.e., 100% reduction in cigarettes). The level of substitution documented in this study among the IQOS-M group was similar to the level of substitution seen in a previous study that allowed participants to substitute over a two-week period but allowed self-selection into IQOS flavor condition (59-87% reduction in cigarettes per day; Stone, DeAtley et al., 2022). The difference in substitution across the IQOS-M and IQOS-T groups observed here could thus be viewed as an estimate of the differential rate of substitution among adults that use menthol cigarettes that might be expected if menthol flavors are not available in HTPs sold in the US tobacco marketplace (i.e., 40-50 percentage points). Greater reductions in cigarette smoking may not translate to differences in long-term health risks from tobacco-related disease, however,

unless those reductions eventually lead to complete smoking cessation (Begh, Lindson-Hawley, and Aveyard, 2015). Early evidence on HTP use patterns suggests that complete smoking cessation is uncommon among individuals that smoke cigarettes but start using HTPs (Satomi, Kanami et al., 2023; Seo, Xu et al., 2023; Cheng, Noggle et al., 2023).

A final observation from the naturalistic use data is that despite IQOS delivering less nicotine on a per-unit basis than OB menthol cigarettes in the clinical laboratory, participants did not appear to be replacing each cigarette they reduced from week 1 to week 2 with more than one HeatStick. This observation runs counter to the idea that to switch from cigarettes to IQOS one would need to increase total tobacco consumption to compensate for the lower nicotine delivery of the HTP (Davigo, Klerx et al., 2023; Jarvis, Boreham et al., 2001). Why this is the case, despite the inferior nicotine delivery of IQOS, could be the subject of future investigations.

In sum, the results from the ETM and the naturalistic use periods suggest that menthol-flavored HTPs would support substitution from combustibles for people that smoke menthol cigarettes to a greater extent than tobacco-flavored HTPs. However, menthol flavor appears to be insufficient in supporting *complete substitution* from cigarettes to HTPs (at least in the context of IQOS 2.4) for most adults that smoke menthol cigarettes and it is unclear what health benefits may be realized from only partial substitution from combustible cigarettes. Additionally, people that smoke may be more likely to try to quit smoking following a ban on the sale of menthol cigarettes if menthol-flavored alternatives are not available.

Summary of Results

This primary focus of this study was to compare differences in the abuse liability of IQOS as a function of its available flavors (i.e., IQOS-M versus IQOS-T). The overarching pre-

study hypothesis that IQOS-M's abuse liability would be higher than that of IQOS-T's among people that use menthol cigarettes was supported by the data partially. A significant effect of menthol flavor in HTPs was noted on two of three primary outcomes for this study. Specifically, in the ETM, IQOS served as a stronger substitute for OB menthol cigarettes when menthol-flavored HeatSticks were available compared to a "restricted market" that did not offer menthol-flavored HeatSticks. Additionally, when participants were given IQOS products to take home and use as a substitute for OB menthol cigarettes, participants that were given IQOS-M reduced their daily cigarette consumption to a greater extent than participants that were given IQOS-T. The third primary hypothesis, that IQOS-M would boost plasma nicotine concentrations more so than IQOS-T following a 10-puff directed use bout, did not appear to be supported. Mechanistically, the hypothesized difference in nicotine delivery across IQOS products was believed to be the result of participants taking longer puffs from IQOS-M than IQOS-T. There was not sufficient evidence reported in this investigation that use of IQOS-M encourages longer puffs than use of IQOS-T. Still, IQOS-M suppressed urges to smoke (and possibly cravings for a cigarette/nicotine) to a greater extent than IQOS-T. This constellation of findings could be explained by menthol enhancing positive reinforcement (e.g., improved taste, flavor sensation, etc.) from HTP use or menthol's possible role as a conditioned stimulus of smoking. Future studies should further probe the mechanisms that menthol may exploit to enhance the abuse liability and substitution potential of alternative nicotine delivery systems among people that smoke menthol cigarettes.

Despite the enhanced appeal afforded by adding menthol flavor to IQOS HeatSticks, however, OB menthol cigarettes appeared to have greater abuse liability than either of the IQOS products tested. The conclusion that OB menthol cigarettes have greater abuse liability than

IQOS was based on the superior capacity of OB menthol cigarettes to boost plasma nicotine concentrations, suppress tobacco abstinence symptoms, create a reinforcing sensory experience associated with use, and the persistence of OB menthol cigarette consumption in the ETM as well as naturalistic use periods. The greater abuse liability of OB menthol cigarettes compared to IQOS 2.4 documented in this study calls into question the HTP capacity to function as a complete combustible menthol cigarette substitute regardless of flavor availability.

The results of this study suggest that among people that use menthol cigarettes, menthol flavoring heightens the abuse liability of HTPs such as IQOS. Thus, access to menthol-flavored HTPs may increase the likelihood that someone who uses menthol cigarettes could substitute with an HTP at least partially. The heightened abuse liability of HTPs with a menthol flavor may be attributable to the hedonic effects associated with the menthol flavoring itself. Still, even with menthol flavoring, it is unclear IQOS 2.4 possess sufficient abuse liability to sustain long-term use and support complete substitution among adults that use menthol cigarettes. Furthermore, retaining a menthol-flavored HTP in the marketplace following a ban on menthol cigarettes may deter attempts at complete cessation for some people that smoke menthol cigarettes.

Regulatory Implications

The 2009 Family Smoking Prevention and Tobacco Control Act granted FDA regulatory authority over tobacco products in the US and also banned the use of characterizing flavors in cigarettes sold in the US with the exception of menthol. FDA now appears poised to add menthol as a banned characterizing flavor for cigarettes sold in the US (FDA, 2022e). Today's tobacco marketplace features much greater complexity and variety than the one operating in the early 2010s. New products such as ENDS, ONPs, and HTPs are often championed under the banner of "tobacco harm reduction" and some, such as the HTP known as IQOS, have been granted

authorization by the FDA to be marketed as MRTPs based on evidence that they may expose people that smoke combustible cigarettes to fewer of the HPHCs of tobacco.

To maximize the potential public health benefit of FDA's proposed ban on the sale of menthol cigarettes, regulators must consider whether characterizing flavors such as menthol should be permitted in alternative tobacco product classes (e.g., HTPs). Any regulatory action on characterizing flavors in tobacco products must be defensible on the grounds that the action is appropriate for the protection of public health. In the context of characterizing flavors in tobacco products, determining the course of action that best protects public health has been framed as weighing the potential risks to youth/nicotine-naïve individuals of allowing flavors that may promote nicotine dependence against the potential tobacco harm-reduction role that appealing alternatives to cigarettes could play for people that smoke (Abrams, Glasser et al., 2018; Krishnan-Sarin, O'Malley et al., 2019). A key consideration in regulatory deliberations regarding characterizing flavors is defining a tobacco product's abuse liability. Combustible cigarettes have very high abuse liability and to achieve complete substitution it has been postulated that an MRTP (e.g., IQOS) must at least approximate a cigarette's abuse liability profile (Abrams, Glasser et al., 2018). An understanding of how flavors impact the abuse liability of HTPs would thus be useful to regulators at this critical time, but little existing literature can speak to that question directly.

This study attempted to address the evidence gap regarding the influence of flavors on HTP abuse liability and found that among people that use menthol cigarettes, menthol flavors appear to increase the abuse liability of HTPs. One conclusion for regulators to draw from this work is that, for most people that use menthol cigarettes to substitute with an HTP, retaining menthol-flavored HTPs may be an important market feature. However, even when paired with

menthol-flavored HeatSticks, the abuse liability of IQOS 2.4 appeared to be inferior to that of OB menthol cigarettes. At a behavioral level, the difference between the abuse liability of OB menthol cigarette and IQOS may manifest as a failure to achieve complete substitution and instead encourage dual use of IQOS alongside cigarettes or other combusted products.

Results of this investigation suggest that the decision to restrict flavors in HTPs within the context of a menthol cigarette ban could either encourage partial substitution with an MRTP (i.e., if IQOS-M retained) or promote attempts at cessation (i.e., if IQOS-M restricted) in the post-ban period. Given the lack of evidence that IQOS 2.4 is able to support complete substitution from OB menthol cigarettes (regardless of flavor), as well as IQOS' uncertain long-term health effects, it would seem appropriate to not grant an exemption from the menthol ban to IQOS 2.4 at this time. Moving forward, more research will be needed to understand the unique considerations posed by newer generations of HTPs (e.g., IQOS *Iluma*) and their abuse liability profiles among people that use cigarettes.

Limitations

There are several limitations that should be considered alongside the results of this investigation. The foremost limitation of this study is its underpowered sample. Power analyses conducted before beginning the study determined that 50 participants would be sufficient to detect effects of menthol flavoring in IQOS on the primary study outcomes. Because of challenges related to product availability and participant recruitment only 30 participants completed the study. Thus, some analyses presented here may have been underpowered to detect a true effect. Despite the smaller than intended sample size, significant effects in the hypothesized directions were still detected in two of the three primary study outcomes.

Second, the devices (IQOS 2.4) and HeatSticks (Fresh Menthol and Regular/Tobacco) used in this investigation were over three years old by the end of the study. The age of the study products presented challenges as IQOS devices would sometimes extinguish before the intended IQOS "use experience" (six minutes or 14 puffs) elapsed. Some participants reported a stale taste even when using HeatSticks taken out of new packs, potentially because of the age of the study products. Product quality issues could have made participants feel increased frustration when trying to use IQOS and created a less satisfying sensory experience. Whether product quality issues would have affected comparisons across IQOS-M and IQOS-T is uncertain, but product quality issues might explain some of the differences observed between OB menthol cigarettes and IQOS. A related limitation is that the device (IQOS 2.4) and HeatSticks tested here are now older versions of the IQOS line. Newer versions of IQOS (e.g., IQOS *Iluma*) use a different heating method and different HeatSticks than IQOS 2.4. PMI has submitted a pre-market tobacco approval application for IQOS *Iluma* in five flavor varieties, all featuring a characterizing flavor of either tobacco or menthol, to the FDA (McDonald, 2023; Tobacco Reporter, 2023). According to PMI, IQOS *Iluma* is demonstrating higher rates of "full switching" (not defined) by adults that smoke cigarettes and improved customer satisfaction (Tobacco Reporter, 2023). Future work should consider if and how the abuse liability profile of newer versions of IQOS differ from the version tested here to understand the relevance of this work to the products the tobacco industry appears committed to marketing in the future.

A third limitation is that the Fresh Menthol HeatSticks tested in this study are one of two menthol HeatSticks to receive MRTP authorization. To limit the number of groups in the experimental design, the Smooth Menthol HeatSticks were not tested. The main difference in the two varieties of menthol HeatSticks is that Fresh Menthol HeatSticks contain about twice as

much menthol as Smooth Menthol HeatSticks. Some participants in this study volunteered that they felt the menthol taste from the Fresh Menthol HeatSticks was too strong. Thus, it is possible that the lower menthol concentration found in Smooth Menthol HeatSticks would have been more appealing; Smooth Menthol HeatSticks are more popular than Fresh Menthol HeatSticks among people that use IQOS in the US according to PMI (Cheng, Noggle et al., 2023). Future studies could consider the *dose* of menthol delivered by different HeatSticks, as compared to menthol cigarettes, to ascertain whether there is a "sweet spot" of menthol delivery that may maximize HTP abuse liability and substitution. If a menthol "sweet spot" is found to be below the menthol delivery of the Fresh Menthol HeatSticks tested here, results of this investigation could be underestimating IQOS' abuse liability and substitution potential for menthol cigarettes.

Fourth, data from the naturalistic use periods were based on self-report and there were no tangible measures of tobacco product consumption collected (e.g., counting used and unused products, biomarkers of exposure). Though recall bias was minimized by sampling tobacco consumption every day and by performing three-day TLFB assessments, it is possible that asking participants to return used/unused products or using an event-based EMA sampling technique could have yielded different results. Substitution in the naturalistic use period of this investigation could also have been limited by the short timeframe (three full days) participants had access to IQOS while at home. If participants had more time to use IQOS at home there may have been more pronounced changes in how IQOS products were used in the clinical laboratory (e.g., puff topography) from initial to final exposure as has been demonstrated in some studies involving ENDS (Wagener, Avery et al., 2021). The only other independent study that asked people that smoke cigarettes to switch to IQOS in a naturalistic setting used a two-week switching period, but reported daily HTP consumption had stabilized within three days (Stone,

DeAtley et al., 2022). Thus, it is not certain that a longer exposure period to IQOS would have changed the results of this investigation.

Fifth, this study used a directed puffing bout in all clinical laboratory session. The puffing protocol adopted here was based on the observed behavior of people that smoke cigarettes after a period of abstinence. If the natural puffing behavior associated with IQOS use departs from the cigarette-norm, then puff topography and nicotine delivery results may be biased. However, other studies have used directed puffing bouts (five minutes) followed by ad-lib puffing bouts (one hour) and found that IQOS delivered less nicotine than OB cigarettes under each protocol (Leavens, Lambart et al., 2023; Phillips-Waller, Przulj et al., 2021). The lack of observational data on the natural puffing patterns associated with HTP use complicates the design of clinical laboratory studies of user behavior, drug delivery, and toxicant emissions.

Conclusions

This mixed clinical laboratory and naturalistic use study interrogated the abuse liability of the IQOS 2.4 tobacco heating system and its available flavors (Regular/Tobacco HeatSticks versus Fresh Menthol HeatSticks) among people that smoke menthol cigarettes. Study objectives were accomplished by measuring the nicotine delivery, puff topography, self-reported effects, behavioral economic demand, and naturalistic use patterns associated with IQOS-M and IQOS-T in the context of a parallel-group pilot clinical trial. The results of this study suggested that menthol enhances the abuse liability of HTPs among people that use menthol cigarettes. Thus, access to menthol-flavored HeatSticks may improve the feasibility of IQOS 2.4 to serve as a combustible cigarette substitute among people that smoke menthol cigarettes. The reason for the heightened abuse liability and substitution potential of IQOS-M (relative to IQOS-T) for people

that smoke menthol cigarettes did not appear to be due to differences in how the products were used (i.e., puff topography) or delivered nicotine. Rather, menthol-flavoring in the HTP may have functioned as a conditioned stimulus and/or non-nicotine reinforcer of smoking behavior that made IQOS 2.4 a more compelling menthol cigarette substitute (though these specific hypotheses were not tested). Importantly though, even IQOS-M's abuse liability lagged behind that of OB menthol cigarettes. The lower abuse liability of IQOS compared to OB menthol cigarettes calls into question the ability of HTPs to serve as *complete substitutes* for combustible cigarettes and thus their tobacco harm-reduction potential. This study adds support to the current literature surrounding the importance of nicotine delivery (Henningfield & Goldberg, 1983; Henningfield & Keenan, 1993; Jarvis, Boreham et al., 2001) and menthol (Ahijevych & Garrett, 2010; Henningfield, Benowitz et al., 2003; Voos, Smith et al., 2020) in determining the abuse liability of potentially lower harm products and the capacity of a MRTP to serve as a cigarette substitute. Federal regulators now must decide whether menthol-flavored HTPs should be permitted in the US tobacco marketplace. This study contributes new evidence to the HTP literature demonstrating that menthol increases HTP abuse liability (e.g., behavioral economic demand, substitution in naturalistic settings, positive reinforcement, suppression of cravings/urges to smoke) but may be *insufficient* to support complete substitution for people that smoke menthol cigarettes. Additionally, though more data is needed to affirm this conclusion, results reported here and in earlier work (White, Goden et al., 2023) suggest that including HTPs in FDA's proposed menthol ban may further promote smoking cessation in the post-ban period.

List of References

Abrams, D. B., Glasser, A. M., Pearson, J. L., Villanti, A. C., Collins, L. K., & Niaura, R. S. (2018). Harm minimization and tobacco control: Reframing societal views of nicotine use to rapidly save lives. *Annual Review of Public Health, 39*, 193-213. doi:10.1146/annurev-publhealth-040617-013849

Abroms, L., Levine, H., Romm, K., Wysota, C., Broniatowski, D., Bar-Zeev, Y., & Berg, C. (2022). Anticipating IQOS market expansion in the United States. *Tobacco Prevention & Cessation, 8*(04). doi:10.18332/tpc/144650

Adriaens, K., Gucht, D. V., & Baeyens, F. (2018). IQOS(TM) vs. e-cigarette vs. tobacco cigarette: A direct comparison of short-term effects after overnight-abstinence. *International Journal of Environmental Research and Public Health, 15*(12). doi:10.3390/ijerph15122902

Ahijevych, K., & Garrett, B. E. (2004). Menthol pharmacology and its potential impact on cigarette smoking behavior. *Nicotine & Tobacco Research, 6*(suppl 1), S17-28. doi:10.1080/14622200310001649469

Ahijevych, K., & Garrett, B. E. (2010). The role of menthol in cigarettes as a reinforcer of smoking behavior. *Nicotine & Tobacco Research, 12*(suppl 2), S110-S116. doi:10.1093/ntr/ntq203

Ahijevych, K., & Parsley, L. A. (1999). Smoke constituent exposure and stage of change in black and white women cigarette smokers. *Addictive Behaviors, 24*(1), 115-120. doi:https://doi.org/10.1016/S0306-4603(98)00031-8

Ahijevych, K., Gillespie, J., Demirci, M., & Jagadeesh, J. (1996). Menthol and nonmenthol cigarettes and smoke exposure in black and white women. *Pharmacology Biochemistry and Behavior, 53*(2), 355-360. doi:10.1016/0091-3057(95)02034-9

Ai, J., Taylor, K. M., Lisko, J. G., Tran, H., Watson, C. H., & Holman, M. R. (2015). Menthol content in US marketed cigarettes. *Nicotine & Tobacco Research, 18*(7), 1575-1580. doi:10.1093/ntr/ntv162

Allen, B., Cruz, T. B., Leonard, E., & Unger, J. B. (2010). Development and validation of a scale to assess attitudes and beliefs about menthol cigarettes among African American smokers. *Evaluation & the Health Proffessions, 33*(4), 414-436. doi:10.1177/0163278710383276

AlMoosawi, S., Bajec, M., Mainy, N., Kallischnigg, G., Zwisele, B., Fischer, K., Magnani, P., Roulet, S. (2022). Risk perception of IQOS and cigarettes: Temporal and cross-country comparisons. *SSM-Popululation Health, 18*, 101123. doi:10.1016/j.ssmph.2022.101123

Alsharari, S. D., King, J. R., Nordman, J. C., Muldoon, P. P., Jackson, A., Zhu, A. Z., Tyndale, R. F., Kabbani, N., & Damaj, M. I. (2015). Effects of menthol on nicotine pharmacokinetic, pharmacology and dependence in mice. *PLoS One, 10*(9), e0137070. doi: 10.1371/journal.pone.0137070

American Lung Association. (2022). *The Impact of Menthol Cigarettes on the Health of the LGBTQ+ Community.* https://www.lung.org/blog/menthol-lbgtq-community#:~:text=According%20to%20the%20CDC%2C%20approximately,visible%20at%20gay%20pride%20festivals

Anderson, S. J. (2011). Menthol cigarettes and smoking cessation behaviour: a review of tobacco industry documents. *Tobacco Control, 20(Suppl 2)*, 49-56. doi:10.1136/tc.2010.041947

Ardati, O., Adeniji, A., El Hage, R., Salman, R., El-Kaassamani, M., Yassine, A., Talih, S., Hourani, M., Karaoghlanian, N., Breland, A., Eissenberg, T., Saliba, N., Shihadeh, A., & El-Hellani, A. (2023). Impact of smoking intensity and device cleaning on IQOS emissions: comparison with an array of cigarettes. *Tobacco Control*. Published Online First. doi:10.1136/tc-2022-057802

Asare, S., Majmundar, A., Westmaas, J. L., Bandi, P., Xue, Z., Jemal, A., & Nargis, N. (2022). Association of cigarette sales with comprehensive menthol flavor ban in Massachusetts. *JAMA Internal Medicine, 182*(2), 231-234. doi: 10.1001/jamainternmed.2021.7333

Ashley, D. L., Backinger, C. L., van Bemmel, D. M., & Neveleff, D. J. (2014). Tobacco regulatory science: research to inform regulatory action at the Food and Drug Administration's Center for Tobacco Products. *Nicotine & Tobacco Research, 16*(8), 1045-1049. doi:10.1093/ntr/ntu038

Ashoor, A., Nordman, J. C., Veltri, D., Yang, K. H., Al Kury, L., Shuba, Y., Mahgoub, M., Howart, F., Sadek, B., Shehu, A., Kabbani, N., & Oz, M. (2013). Menthol binding and inhibition of α7-nicotinic acetylcholine receptors. *PLoS One, 8*(7), e67674. doi: 10.1371/journal.pone.0067674

Audrain-McGovern, J., Strasser, A. A., & Wileyto, E. P. (2016). The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug and Alcohol Dependence, 166*, 263-267. doi:10.1016/j.drugalcdep.2016.06.030

Auer, R., Concha-Lozano, N., Jacot-Sadowski, I., Cornuz, J., & Berthet, A. (2017). Heat-not-burn tobacco cigarettes: Smoke by any other name. *JAMA Internal Medicine, 177*(7), 1050-1052. doi:10.1001/jamainternmed.2017.1419

Bagdas, D., Cam, B., Gul, Z., Scott, M. M., Tyndale, R. F., Buyukuysal, R. L., Damaj, I., & Gurun, M. S. (2020). Impact of menthol on oral nicotine consumption in female and male sprague dawley rats. *Nicotine & Tobacco Research, 22*(2), 196-203. doi:10.1093/ntr/ntz019

Baker, R. R. (1981). Product formation mechanisms inside a burning cigarette. *Progress in Energy and Combustion Science, 7*(2), 135-153. doi:https://doi.org/10.1016/0360-1285(81)90008-3

Baker, R. R. (2006). Smoke generation inside a burning cigarette: Modifying combustion to develop cigarettes that may be less hazardous to health. *Progress in Energy and Combustion Science, 32*(4), 373-385. doi:https://doi.org/10.1016/j.pecs.2006.01.001

Balster, R. L., & Bigelow, G. E. (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug and Alcohol Dependence, 70*(3 Suppl), S13-40. doi:10.1016/s0376-8716(03)00097-8

Balster, R. L., & Walsh, S. L. (2010). Abuse Liability Evaluations. In I. Stolerman Editor, *Encyclopedia of Psychopharmacology.* New York, NY: Springer Link.

Bansal-Travers, M., Price, S. M., Bold, K. W., Villanti, A. C., Barnes, A., Chansky, M., Krishnan-Sarin, S., & Goniewicz, M. L. (2023). Common measures to evaluate flavored tobacco products: recommendationsfFrom the Tobacco Centers for Regulatory Science (TCORS) Flavored Tobacco Products Measurement Subcommittee. *Nicotine & Tobacco Research, 25*(1), 159-163. doi:10.1093/ntr/ntac171

Barnes, A. J., Bono, R. S., Lester, R. C., Eissenberg, T. E., & Cobb, C. O. (2017). Effect of flavors and modified risk messages on e-cigarette abuse liability. *Tobacco Regulatory Science, 3*(4), 347-387. doi: 10.18001/TRS.3.4.1

Beckham, J. C., Wiley, M. T., Miller, S. C., Dennis, M. F., Wilson, S. M., McClernon, F. J., & Calhoun, P. S. (2008). Ad lib smoking in post-traumatic stress disorder: An electronic diary study. *Nicotine & Tobacco Research, 10*(7), 1149-1157. doi:10.1080/14622200802123302

Begh, R., Lindson-Haelwy, N., & Aveyard, P. (2015). Does reduced smoking if you can't stop make a difference? *BMC Medicine*, *13(1)*, 257. doi: 10.1186/s12916-015-0505-2.

Behm, F. M., Schur, C., Levin, E. D., Tashkin, D. P., & Rose, J. E. (1993). Clinical evaluation of a citric acid inhaler for smoking cessation. *Drug & Alcohol Dependence, 31*(2), 131-138. doi:10.1016/0376-8716(93)90065-x

Bekki, K., Inaba, Y., Uchiyama, S., & Kunugita, N. (2017). Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *Journal of University of Occupational and Environmental Health, 39*(3), 201-207. doi:10.7888/juoeh.39.201

Bello, M. S., Schulte, A. R., Ring, C. R., Cho, J., Barrington-Trimis, J. L., Pang, R. D., Jao, N., Colby, S., Cassidy, R., & Leventhal, A. M. (2024). Effects of mint, menthol, and tobacco-flavored e-cigarettes on tobacco withdrawal symptoms in adults who smoke menthol cigarettes: A laboratory pilot study. *Drug and Alcohol Dependence*, in press. doi:https://doi.org/10.1016/j.drugalcdep.2024.111110

Benowitz, N. L. (2008). Clinical pharmacology of nicotine: Implications for understanding, preventing, and treating tobacco addiction. *Clinical Pharmacology & Therapeutics, 83*(4), 531-541. doi:https://doi.org/10.1038/clpt.2008.3

Benowitz, N. L. (2010a). Nicotine addiction. *New England Journal of Medicine, 362*(24), 2295-2303. doi:10.1056/nejmra0809890

Benowitz, N. L. (2010b). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annual Review of Pharmacology and Toxicology,* 49, 57-71. doi: 10.1146/annurev.pharmtox.48.113006.094742

Benowitz, N. L., Herrera, B., & Jacob, P. (2004). Mentholated cigarette smoking inhibits nicotine metabolism. *Journal of Pharmacology and Experimental Therapeutics, 310*(3), 1208-1215. doi:10.1124/jpet.104.066902

Benowitz, N. L., Hukkanen, J., & Jacob III, P. (2009). Nicotine chemistry, metabolism, kinetics and biomarkers. *Handbook of Experimental Pharmacology,* 192, 29-60. doi:10.1007/978-3-540-69248-5_2

Benowitz, N. L., Zevin, S., & Jacob III, P. (1997). Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *British Journal of Clinical Pharmacology, 43*(3), 259-267. doi: 10.111/j.1365-2125.1997.00566.x

Berg, C. J., Romm, K. F., Patterson, B., & Wysota, C. N. (2021). Heated tobacco product awareness, use, and perceptions in a sample of young adults in the United States. *Nicotine & Tobacco Research, 23*(11), 1967-1971. doi:10.1093/ntr/ntab058

Berman, M. L., Connolly, G., Cummings, K. M., Djordjevic, M. V., Myers, M., O'Connor, R. J., Parascandola, M., Rees, V., Rice, J., & Shields, P. G. (2015). Providing a science base for the evaluation of tobacco products. *Tobacco Regulatory Science, 1*(1), 76-93. doi:10.18001/TRS.1.1.8

Berry, J. N., Engle, S. E., McIntosh, J. M., & Drenan, R. M. (2015). α6-Containing nicotinic acetylcholine receptors in midbrain dopamine neurons are poised to govern dopamine-

mediated behaviors and synaptic plasticity. *Neuroscience, 304*, 161-175. doi: 10.1016/j.neuroscience.2015.07.052

Bhat, T. A., Kalathil, S. G., Leigh, N., Muthumalage, T., Rahman, I., Goniewicz, M. L., & Thanavala, Y. M. (2021). Acute effects of heated tobacco product (IQOS) aerosol inhalation on lung tissue damage and inflammatory changes in the lungs. *Nicotine & Tobacco Research, 23*(7), 1160-1167. doi: 10.1093/ntr/ntaa267

Bickel, W. K., DeGrandpre, R. J., & Higgins, S. T. (1995). The behavioral economics of concurrent drug reinforcers: a review and reanalysis of drug self-administration research. *Psychopharmacology, 118*(3), 250-259. doi:10.1007/bf02245952

Bickel, W. K., Moody, L., Snider, S. E., Mellis, A. M., Stein, J. S., Quisenberry, A. J. (2017). The behavioral economics of tobacco products. In Y. B. Hanoch, Barnes, A.J., & Rice, T. (Ed.), *Behavioral Economics and Healthy Behaviors: Key Concepts and Current Research.* New York, NY: Routledge.

Bickel, W. K., Pope, D. A., Kaplan, B. A., DeHart, W. B., Koffarnus, M. N., & Stein, J. S. (2018). Electronic cigarette substitution in the experimental tobacco marketplace: A review. *Preventative Medicine, 117*, 98-106. doi:10.1016/j.ypmed.2018.04.026

Birch, T. (2020). *IQOS menthol kits launched by Philip Morris Limited*. Better Retailing. Retrieved from https://www.betterretailing.com/product-news/vaping/iqos-menthol-kits/

Bird, Y., May, J., Nwankwo, C., Mahmood, R., & Moraros, J. (2017). Prevalence and characteristics of flavoured tobacco use among students in grades 10 through 12: a national cross-sectional study in Canada, 2012-2013. *Tobacco Induced Disease, 15*, 20. doi: 10.1186/s12971-017-0124-0

Blank, M. D., Breland, A. B., Enlow, P. T., Duncan, C., Metzger, A., & Cobb, C. O. (2016). Measurement of smoking behavior: Comparison of self-reports, returned cigarette butts, and toxicant levels. *Experimental & Clininical Psychopharmacology, 24*(5), 348-355. doi:10.1037/pha0000083

Blank, M. D., Disharoon, S., & Eissenberg, T. (2009). Comparison of methods for measurement of smoking behavior: mouthpiece-based computerized devices versus direct observation. *Nicotine & Tobacco Research, 11*(7), 896-903. doi:10.1093/ntr/ntp083

Bold, K. W., Jatlow, P., Fucito, L. M., Eid, T., Krishnan-Sarin, S., & O'Malley, S. (2020). Evaluating the effect of switching to non-menthol cigarettes among current menthol smokers: an empirical study of a potential ban of characterising menthol flavour in cigarettes. *Tobacco Control, 29*(6), 624-630. doi:10.1136/tobaccocontrol-2019-055154

Bono, R. S., Barnes, A. J., Lester, R. C., & Cobb, C. O. (2019). Effects of electronic cigarette liquid flavors and modified risk messages on perceptions and self-reported effects of e-cigarettes. *Health Education & Behavior, 46*(2), 197-203. doi:10.1177/1090198118806965

Bono, R. S., Cobb, C. O., Wall, C. S., Lester, R. C., Hoetger, C., Lipato, T., Guy, M. C., Eissenberg, T., Bickel, W. K., & Barnes, A. J. (2020). Behavioral economic assessment of abuse liability for Black & Mild cigar flavors among young adults. *Experimental & Clinical Psychopharmacology, 30*(1), 113-119. doi:10.1037/pha0000400

Bover, M. T., Foulds, J., Steinberg, M. B., Richardson, D., & Marcella, S. W. (2008). Waking at night to smoke as a marker for tobacco dependence: patient characteristics and relationship to treatment outcome. *International Journal of Clinical Practice, 62*(2), 182-190. doi:10.1111/j.1742-1241.2007.01653.x

Brandt, A. M. (2011). Inventing conflicts of interest: A history of tobacco industry tactics. *American Journal of Public Health, 102*(1), 63-71. doi:10.2105/AJPH.2011.300292

Braznell, S., Akker, A., Metcalfe, C., M. J. Taylor, G., & Hartmann-Boyce, J. (2022). Critical appraisal of interventional clinical trials assessing heated tobacco products: a systematic review. *Tobacco Control*, Published Online First. doi:10.1136/tc-2022-057522

Breland, A. B., Buchhalter, A. R., Evans, S. E., & Eissenberg, T. (2002). Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine & Tobacco Research, 4* (suppl 2), S131-140. doi:10.1080/1462220021000032780

Breland, A. B., Kleykamp, B. A., & Eissenberg, T. (2006). Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine & Tobacco Research, 8*(6), 727-738. doi:10.1080/14622200600789585

Brink, A. L., Glahn, A. S., & Kjaer, N. T. (2022). Tobacco companies' exploitation of loopholes in the EU ban on menthol cigarettes: a case study from Denmark. *Tobacco Control*, *32*(6), 809-812. doi:10.1136/tobaccocontrol-2021-057213

Brody, A. L., Mukhin, A. G., La Charite, J., Ta, K., Farahi, J., Sugar, C. A., Mamoun, M., Vellios, E., Archie, M., Kozman, M., Phuong, J., Arlorio, F., & Mandelkern, M. A. (2013). Up-regulation of nicotinic acetylcholine receptors in menthol cigarette smokers. *International Journal of Neuropsychopharmacology, 16*(5), 957-966. doi: 10.1017/s1461145712001022

Brown, R. A., Burgess, E. S., Sales, S. D., Whiteley, J. A., Evans, D. M., & Miller, I. W. (1998). Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors, 12*(2), 101-112. doi: 10.1037/0893-164x.12.2.101

Buchhalter, A. R., & Eissenberg, T. (2000). Preliminary evaluation of a novel smoking system: effects on subjective and physiological measures and on smoking behavior. *Nicotine & Tobacco Research, 2*(1), 39-43. doi:10.1080/14622200050011286

Buchhalter, A. R., Acosta, M. C., Evans, S. E., Breland, A. B., & Eissenberg, T. (2005). Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction, 100*(4), 550-559. doi:10.1111/j.1360-0443.2005.01030.x

Buckell, J., Marti, J., & Sindelar, J. (2019). Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment. *Tobacco Control, 28*(2), 168. doi:10.1136/tobaccocontrol-2017-054165

Budworth, L. (2019). Discussion Paper: Electronic cigarettes: Sensory cues in nicotine dependency. *PsyPag Quarterly, 1*(1), 34-37. doi:10.53841/bpspag.2019.1.110.34

Bullen, C., McRobbie, H., Thornley, S., Glover, M., Lin, R., & Laugesen, M. (2010). Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco Control, 19*(2), 98. doi:10.1136/tc.2009.031567

Businelle, M. S., Ma, P., Kendzor, D. E., Frank, S. G., Vidrine, D. J., & Wetter, D. W. (2016). An ecological momentary intervention for smoking cessation: evaluation of feasibility and effectiveness. *Journal of Medical Internet Research, 18*(12), e321. doi:10.2196//jmir.6058

Butschky, M. F., Bailey, D., Henningfield, J. E., & Pickworth, W. B. (1995). Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology, Biochemistry and Behavior, 50*(1), 91-96. doi:10.1016/0091-3057(94)00269-O

Cadham, C. J., Liber, A. C., Sánchez-Romero, L. M., Issabakhsh, M., Warner, K. E., Meza, R., & Levy, D. T. (2022). The actual and anticipated effects of restrictions on flavoured electronic nicotine delivery systems: a scoping review. *BMC Public Health, 22*(1), 2128. doi:10.1186/s12889-022-14440-x

Cadham, C. J., Sanchez-Romero, L. M., Fleischer, N. L., Mistry, R., Hirschtick, J. L., Meza, R., & Levy, D. T. (2020). The actual and anticipated effects of a menthol cigarette ban: a scoping review. *BMC Public Health, 20*(1), 1055. doi:10.1186/s12889-020-09055-z

Caggiula, A. R., Donny, E. C., Palmatier, M. I., Liu, X., Chaudhri, N., & Sved, A. F. (2009). The role of nicotine in smoking: a dual-reinforcement model. *Nebraska Symposium on Motivation, 55*, 91-109. doi:1007/978-0-387-78748-0_6

Cain, A. E., Depp, C. A., & Jeste, D. V. (2009). Ecological momentary assessment in aging research: a critical review. *Journal of Psychiatric Research, 43*(11), 987-996. doi: 10.1016/j.jpsychires.2009.01.014

Campaign for Tobacco Free Kids. (2023). *States & Localities that Have Restricted the Sale of Flavored Tobacco Products*. https://assets.tobaccofreekids.org/factsheets/0398.pdf

Caponnetto, P., Campagna, D., Cibella, F., Morjaria, J. B., Caruso, M., Russo, C., & Polosa, R. (2013). EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A prospective 12-month randomized control design study. *PLoS One, 8*(6), e66317. doi:10.1371/journal.pone.0066317

Cappelleri, J. C., Bushmakin, A. G., Baker, C. L., Merikle, E., Olufade, A. O., & Gilbert, D. G. (2007). Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addictive Behaviors, 32*(5), 912-923. doi:10.1016/j.addbeh.2006.06.028

Carstens, E., & Carstens, M. I. (2022). Sensory effects of nicotine and tobacco. *Nicotine & Tobacco Research, 24*(3), 306-315. doi: 10.1093/ntr/ntab086

Carter, L. P., & Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug and Alcohol Dependence, 105*(suppl 1), S14-S25. doi:10.1016/j.drugalcdep.2009.04.003

Carter, L. P., Stitzer, M. L., Henningfield, J. E., O'Connor, R. J., Cummings, K. M., & Hatsukami, D. K. (2009). Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiology, Biomarkers & Prevention, 18*(12), 3241-3262. doi:10.1158/1055-9965.EPI-09-0948 [doi]

Carvajal, R., Clissold, D., & Shapiro, J. (2009). The Family Smoking Prevention and Tobacco Control Act: An overview. *Food and Drug Law Journal, 64*(4), 717-732.

Carver, R. (2024). *BAT agrees to pivotal settlement on heated cigarette, vapor patents*. Winston-Salem Journal. https://journalnow.com/news/local/business/bat-agrees-to-pivotal-settlement-on-heated-cigarette-vapor-patents/article_ca6c0fe2-c1ca-11ee-835f-6b0fe1e9754e.html

Centers for Disease Control and Prevention. (2022). *Menthol Smoking and Related Health Disparities*. https://www.cdc.gov/tobacco/basic_information/menthol/related-health-disparities.html#:~:text=In%202018%2C%2051.4%25%20of%20non,of%20non%2DHispanic%20White%20youth.&text=In%202019%2C%20approximately%2085%25%20of,who%20smoked%20used%20menthol%20cigarettes.

Centers for Disease Control and Prevention. (2023). *Current Cigarette Smoking Among Adults in the United States*.

https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm#references

Chaiton, M. O., Nicolau, I., Schwartz, R., Cohen, J. E., Soule, E., Zhang, B., & Eissenberg, T. (2019). Ban on menthol-flavoured tobacco products predicts cigarette cessation at 1 year: a population cohort study. *Tobacco Control*, *29*(3), 341-347. doi:10.1136/tobaccocontrol-2018-054841

Chaiton, M., Papadhima, I., Schwartz, R., Cohen, J. E., Soule, E. K., Zhang, B., & Eissenberg, T. (2020). Product substitution after a real world menthol ban: A cohort study. *Tobacco Regulatory Science, 6*(3), 205-212. doi:10.18001/TRS.6.3.5

Chaiton, M., Schwartz, R., Cohen, J. E., Soule, E., & Eissenberg, T. (2018). Association of Ontario's ban on menthol cigarettes with smoking behavior 1 month after implementation. *JAMA Internal Medicine, 178*(5), 710. doi:10.1001/jamainternmed.2017.8650

Chen, D. T., Grigg, J., Filippidis, F., & Tobacco Control Committee of the European Respiratory Society. (2024). European Respiratory Society statement on novel nicotine and tobacco products, their role in tobacco control and "harm reduction". *European Respiratory Journal,* In press. doi:10.1183/13993003.01808-2023

Cheng, H. G., Noggle, B., Vansickel, A. R., Largo, E. G., Magnani, P., & Heremans, A. (2023). Tobacco use, perceptions, and characteristics of adults who use IQOS in the United States: Findings from a cross-sectional study. *Research Square (pre-print)*. doi:10.21203/rs.3.rs-3252865/v1. Retrieved from https://assets.researchsquare.com/files/rs-3252865/v1/df1559da-9dcd-4646-ba32-307c7e7e98c3.pdf?c=1693451240

Churchill, V., Weaver, S. R., Spears, C. A., Huang, J., Massey, Z. B., Fairman, R. T., Pechacek, T., Ashley, D., & Popova, L. (2020). IQOS debut in the USA: Philip Morris International's heated tobacco device introduced in Atlanta, Georgia. *Tobacco Control, 29*(e1), e152-e154. doi:10.1136/tobaccocontrol-2019-055488

Clark, P. I., Gautam, S., & Gerson, L. W. (1996). Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers. *Chest, 110*(5), 1194-1198. doi:10.1378/chest.110.5.1194

Cobb, C. O., Foulds, J., Yen, M.-S., Veldheer, S., Lopez, A. A., Yingst, J. M., Bullen, C., Kang, L., Eissenberg, T., Randomised Control Trial Methods Workgroup of the Center for the Study of Tobacco Products (2021). Effect of an electronic nicotine delivery system with 0, 8, or 36 mg/mL liquid nicotine versus a cigarette substitute on tobacco-related toxicant exposure: a four-arm, parallel-group, randomised, controlled trial. *The Lancet Respiratory Medicine, 9*(8), 840-850. doi:10.1016/S2213-2600(21)00022-9

Cobb, C. O., Shihadeh, A., Weaver, M. F., & Eissenberg, T. (2011). Waterpipe tobacco smoking and cigarette smoking: a direct comparison of toxicant exposure and self-reported effects. *Nicotine & Tobacco Research, 13*(2), 78-87. doi:10.1093/ntr/ntq212

Cobb, C. O., Weaver, M. F., & Eissenberg, T. (2010). Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tobacco Control, 19*(5), 367-373. doi:10.1136/tc.2008.028993

Cobb, N. K., Byron, M. J., Abrams, D. B., & Shields, P. G. (2010). Novel nicotine delivery systems and public health: the rise of the "e-cigarette". *American Journal of Public Health, 100*(12), 2340-2342. doi:10.2105/AJPH.2010.199281

Cohn, A. M., Alexander, A. C., & Ehlke, S. J. (2022). Affirming the abuse liability and addiction potential of menthol: differences in subjective appeal to smoking menthol versus non-menthol cigarettes across African American and White young adult smokers. *Nicotine & Tobacco Research, 24*(1), 20-27. doi:10.1093/ntr/ntab137

Cohn, A. M., Johnson, A. L., Hair, E., Rath, J. M., & Villanti, A. C. (2016). Menthol tobacco use is correlated with mental health symptoms in a national sample of young adults: implications for future health risks and policy recommendations. *Tobacco Induced Diseases, 14*(1). doi:10.1186/s12971-015-0066-3

Corrigall, W. A., Coen, K. M., & Adamson, K. L. (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Research, 653*(1-2), 278-284. doi:10.1016/0006-8993(94)90401-4

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research, 3*(1), 7-16. doi:10.1080/14622200020032051

D'Silva, J., Amato, M. S., & Boyle, R. G. (2015). Quitting and switching: Menthol smokers' responses to a menthol ban. *Tobacco Regulatory Science, 1*(1), 54-60. doi:10.18001/trs.1.1.6

Davigo, M., Klerx, W. N., van Schooten, F. J., Opperhuizen, A., Remels, A. H., & Talhout, R. (2023). Impact of more intense smoking parameters and flavor variety on toxicant levels in emissions of a Heated Tobacco Product. *Nicotine & Tobacco Research*, Online ahead of print. doi:10.1093/ntr/ntad238

Davis, B., Williams, M., & Talbot, P. (2019). iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tobacco Control, 28*(1), 34-41. doi:10.1136/tobaccocontrol-2017-054104

Dawkins, L., Turner, J., Roberts, A., & Soar, K. (2013). 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction, 108*(6), 1115-1125. doi:10.1111/add.12150

DeAtley, T., Stone, M. D., Strasser, A. A., & Audrain-McGovern, J. (2022). The role of IQOS risk perceptions on cigarette smoking behaviours: results from a prospective pilot study. *Tobacco Control,* online ahead of print. doi:10.1136/tc-2022-057461

deBethizy, J. D., Robinson, J. H., Davis, R. A., Doolittle, D. J., Burger, G. T., Reynolds, J. H., Fletcher, R., & Hayes, A. W. (1988). Absorption of nicotine from a cigarette that does not burn tobacco. *Pharmacology, 37*(5), 328-332. doi:10.1159/000138484

DeHart, W. B., Mellis, A. M., Kaplan, B. A., Pope, D. A., & Bickel, W. K. (2019). The Experimental Tobacco Marketplace: Narratives engage cognitive biases to increase electronic cigarette substitution. *Drug and Alcohol Dependence, 197*, 203-211. doi:10.1016/j.drugalcdep.2019.01.020

Delnevo, C. D., Ganz, O., & Goodwin, R. D. (2020). Banning menthol cigarettes: A social justice issue long overdue. *Nicotine & Tobacco Research, 22*(10), 1673-1675. doi:10.1093/ntr/ntaa152

Denlinger-Apte, R. L., Cassidy, R. N., Carey, K. B., Kahler, C. W., Bickel, W. K., O'Connor, R., Thussu, S., & Tidey, J. W. (2021). The impact of menthol flavoring in combusted tobacco on alternative product purchasing: A pilot study using the Experimental Tobacco

Marketplace. *Drug and Alcohol Dependence, 218*, 108390. doi:10.1016/j.drugalcdep.2020.108390

Denlinger-Apte, R. L., Strahley, A. E., Lockhart, D. E., Wiseman, K. D., Cassidy, R. N., Davis, D. R., O'Connor, R., & Tidey, J. W. (2023). Reactions to using other nicotine and tobacco products instead of menthol cigarettes: A qualitative study of people who smoke menthol cigarettes in the United States. *Preventive Medicine Reports, 34*, 102228. doi:10.1016/j.pmedr.2023.102228

Donny, E. C., Denlinger, R. L., Tidey, J. W., Koopmeiners, J. S., Benowitz, N. L., Vandrey, R. G., al'Absi, M., Carmella, S., Cinciripini, P., Dermody, S., Drobes, D., Hecht, S., Jensen, J., Lane, T., Le, C., McClernon, J., Montoya, I., Murphy, S., Robinson, J., Stitzer, M., Strasser, A., Tindle, H., & Hatsukami, D. K. (2015). Randomized trial of reduced-nicotine standards for cigarettes. *New England Journal of Medicine, 373*(14), 1340-1349. doi:10.1056/NEJMsa1502403

Drovandi, A., Salem, S., Barker, D., Booth, D., & Kairuz, T. (2020). Human biomarker exposure from cigarettes versus novel heat-not-burn devices: A systematic review and meta-analysis. *Nicotine & Tobacco Research, 22*(7), 1077-1085. doi:10.1093/ntr/ntz200

Duan, Z., Wysota, C. N., Romm, K. F., Levine, H., Bar-Zeev, Y., Choi, K., & Berg, C. J. (2022). Correlates of perceptions, use, and intention to use heated tobacco products among US young adults in 2020. *Nicotine & Tobacco Research, 24*(12), 1968-1977. doi:10.1093/ntr/ntac185

East, K. A., Miller, C. R., Hitchman, S. C., McNeill, A., & Tompkins, C. N. E. (2023). 'It's not what you'd term normal smoking': a qualitative exploration of language used to describe

heated tobacco product use and associated user identity. *Addiction, 118*(3), 533-538. doi:10.1111/add.16051

Eissenberg, T., & Shihadeh, A. (2009). Waterpipe tobacco and cigarette smoking: Direct comparison of toxicant exposure. *American Journal of Preventive Medicine, 37*(6), 518-523. doi:https://doi.org/10.1016/j.amepre.2009.07.014

El-Kaassamani, M., Yen, M., Talih, S., & El-Hellani, A. (2022). Analysis of mainstream emissions, secondhand emissions and the environmental impact of IQOS waste: a systematic review on IQOS that accounts for data source. *Tobacco Control,* online ahead of print. doi:10.1136/tobaccocontrol-2021-056986

Elias, J., Dutra, L. M., St Helen, G., & Ling, P. M. (2018). Revolution or redux? Assessing IQOS through a precursor product. *Tobacco Control, 27*(suppl 1), s102-s110. doi:10.1136/tobaccocontrol-2018-054327

Epstein, D. H., Marrone, G. F., Heishman, S. J., Schmittner, J., & Preston, K. L. (2010). Tobacco, cocaine, and heroin: Craving and use during daily life. *Addictive Behaviors, 35*(4), 318-324. doi:10.1016/j.addbeh.2009.11.003

Erinoso, O., Clegg Smith, K., Iacobelli, M., Saraf, S., Welding, K., & Cohen, J. E. (2020). Global review of tobacco product flavour policies. *Tobacco Control, 30*(4), 373-379. doi:10.1136/tobaccocontrol-2019-055454

European Commission. (2014). *Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC*. https://eur-lex.europa.eu/eli/dir/2014/40/oj

European Commission. (2022). *REPORT FROM THE COMMISSION on the establishment of a substantial change of circumstances for heated tobacco products in line with Directive 2014/40/EU*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022DC0279&qid=1655456179686.

European Network for Smoking and Tobacco Prevention. (2020). Ban on menthol cigarettes: European Union member states shall prohibit the placing on the market of tobacco products with a characterising flavour. *Tobacco Prevention & Cessation, 6*(July), 40. doi:10.18332/tpc/124164

Fagan, P., Pohkrel, P., Herzog, T., Pagano, I., Vallone, D., Trinidad, D. R., Sakuma, K., Sterling, K., Fryer, C., & Moolchan, E. (2015). Comparisons of three nicotine dependence scales in a multiethnic sample of young adult menthol and non-menthol smokers. *Drug and Alcohol Dependence, 149*, 203-211. doi:10.1016/j.drugalcdep.2015.02.005

Fait, B. W., Thompson, D. C., Mose, T. N., Jatlow, P., Jordt, S. E., Picciotto, M. R., & Mineur, Y. S. (2017). Menthol disrupts nicotine's psychostimulant properties in an age and sex-dependent manner in C57BL/6J mice. *Behavioural Brain Research, 334*, 72-77. doi: 10.1016/j.bbr.2017.07.027

Fallin, A., Goodin, A. J., & King, B. A. (2015). Menthol cigarette smoking among lesbian, gay, bisexual, and transgender adults. *American Journal of Preventive Medicine, 48*(1), 93-97. doi:10.1016/j.amepre.2014.07.044

Farsalinos, K. E., Romagna, G., & Voudris, V. (2015). Factors associated with dual use of tobacco and electronic cigarettes: A case control study. *International Journal of Drug Policy, 26*(6), 595-600. doi:https://doi.org/10.1016/j.drugpo.2015.01.006

Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. (2013). Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Substance Abuse, 7*, 139-146. doi:10.4137/SART.S12756

Farsalinos, K. E., Spyrou, A., Stefopoulos, C., Tsimopoulou, K., Kourkoveli, P., Tsiapras, D., Kourkoveli, P., Tsiapras, D., Kyrzopoulous, S., Poulas, K., & Voudris, V. (2015). Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). *Scientific Reports, 5*, 11269. doi:10.1038/srep11269

Farsalinos, K. E., Yannovits, N., Sarri, T., Voudris, V., & Poulas, K. (2018). Nicotine delivery to the aerosol of a heat-not-burn tobacco product: Comparison with a tobacco cigarette and e-cigarettes. *Nicotine & Tobacco Research, 20*(8), 1004-1009. doi:10.1093/ntr/ntx138

Farsalinos, K. E., Yannovits, N., Sarri, T., Voudris, V., Poulas, K., & Leischow, S. J. (2018). Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. *Addiction, 113*(11), 2099-2106. doi:10.1111/add.14365

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavioral Research Methods, 39*(2), 175-191. doi:10.3758/bf03193146

Food and Drug Administration. (2017a). *Assessment of Abuse Potential of Drugs Guidance for Industry*. Rockville, MD: U.S. Department of Health and Human Services

Food and Drug Administration. (2017b). *Scientific Review of Modified Risk Tobacco Product Appliction Under Secion 911(d) of the FD&C Act – Technical Project Lead.* https://www.fda.gov/media/139796/download

Food and Drug Administration. (2020). *FDA authorizes marketing of IQOS tobacco heating system with 'reduced exposure' information*. https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information

Food and Drug Administration. (2021a). *Family Smoking Prevention and Tobacco Control Act - An overview*. https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/family-smoking-prevention-and-tobacco-control-act-overview

Food and Drug Administration. (2021b). *Menthol and other flavors in tobacco products*. https://www.fda.gov/tobacco-products/products-ingredients-components/menthol-and-other-flavors-tobacco-products#reference

Food and Drug Administration. (2022a). *FDA authorizes reduced exposure claim for IQOS 3 system holder and charger*. https://www.fda.gov/tobacco-products/ctp-newsroom/fda-authorizes-reduced-exposure-claim-iqos-3-system-holder-and-charger

Food and Drug Administration. (2022b). *FDA proposes rules prohibiting menthol cigarettes and flavored cigars to prevent youth initiation, significantly reduce tobacco-related disease and death*. https://www.fda.gov/news-events/press-announcements/fda-proposes-rules-prohibiting-menthol-cigarettes-and-flavored-cigars-prevent-youth-initiation

Food and Drug Administration. (2022c). *Modified risk tobacco products*. https://www.fda.gov/tobacco-products/advertising-and-promotion/modified-risk-tobacco-products

Food and Drug Administration. (2022d). *Reserach priorities*. https://www.fda.gov/tobacco-products/research/research-priorities

Food and Drug Administration. (2022e). *Tobacco product standard for menthol in cigarettes*. Federal Register. https://www.federalregister.gov/documents/2022/05/04/2022-08994/tobacco-product-standard-for-menthol-in-cigarettes.

Food and Drug Administration. (2022f). *Scientific review of the effects of menthol in cigarettes on tobacco addiction 1980-2021*. https://www.fda.gov/media/157642/download.

Fearon, I. M. (2023). Human abuse liability assessment of e-cigarettes: Why, what and how? *Drug Testing and Analysis, 15*(10), 1211-1221. doi:https://doi.org/10.1002/dta.3251

Federal Trade Commission. (2023). *Cigarette Report for 2021*. https://www.ftc.gov/system/files/ftc_gov/pdf/p114508cigarettereport2021.pdf.

Felicione, N. J., Karaoghlanian, N., Shihadeh, A., Eissenberg, T., & Blank, M. D. (2020). Comparison of measurement methods for electronic cigarette puff topography. *Tobacco Regulatory Science, 6*(5), 318-330. doi:10.18001/TRS.6.5.2

Ferguson, S. G., & Shiffman, S. (2011). Using the methods of ecological momentary sssessment in substance dependence research - smoking cessation as a case study. *Substance Use & Misuse, 46*(1), 87-95. doi:10.3109/10826084.2011.521399

Fischman, M. W., & Foltin, R. W. (1991). Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *British Journal of Addiction, 86*(12), 1563-1570. doi: 10.1111/j.1360-0443.1991.tb01749.x

Fong, G. T., Chung-Hall, J., Meng, G., Craig, L. V., Thompson, M. E., Quah, A. C. K., Cummings, K. M., Hyland, A., O'Connor, R., Levy, D. , Delnevo, C., Ganz, O., Eissenberg, T., Soule, E., Schwartz, R., Cohen, J., & Chaiton, M. O. (2022). Impact of Canada's menthol cigarette ban on quitting among menthol smokers: pooled analysis of pre-post evaluation from the ITC Project and the Ontario Menthol Ban Study and

projections of impact in the USA. *Tobacco Control, 32*(6), 734-738. doi:10.1136/tobaccocontrol-2021-057227

Forster, M., Liu, C., Duke, M. G., McAdam, K. G., & Proctor, C. J. (2015). An experimental method to study emissions from heated tobacco between 100-200°C. *Chemistry Central Journal, 9*, 20. doi:10.1186/s13065-015-0096-1

Foulds, J., Hooper, M. W., Pletcher, M. J., & Okuyemi, K. S. (2010). Do smokers of menthol cigarettes find it harder to quit smoking? *Nicotine & Tobacco Research, 12* (suppl 2), S102-109. doi:10.1093/ntr/ntq166

Foulds, J., Ramstrom, L., Burke, M., & Fagerström, K. (2003). Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control, 12*(4), 349-359. doi:10.1136/tc.12.4.349

Foulds, J., Veldheer, S., Yingst, J., Hrabovsky, S., Wilson, S. J., Nichols, T. T., & Eissenberg, T. (2015). Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine & Tobacco Research, 17*(2), 186-192. doi:10.1093/ntr/ntu204

Fried, N. D., & Gardner, J. D. (2020). Heat-not-burn tobacco prodcuts: an emerging threat to cardiovascular health. *American Journal of Physiology – Heart and Circulatory Physiology, 319*(6), H1234-H1239. doi:10.1152/ajphheart.00708.2020

Funk, O. L., Nollen, N. L., Wagener, T. L., Ahluwalia, J. S., Mayo, M. S., Mahmud, K. M. F., Lambart, L., & Leavens, E. L. S. (2023). Concurrent choice assessment of preference and substitutability of e-cigarettes and heated tobacco products for combustible cigarettes among African American and White smokers. *Nicotine & Tobacco Research, 25*(8), 1505-1508. doi:10.1093/ntr/ntad052

Gades, M. S., Petersen, A., Meier, E., Lindgren, B. R., O'Connor, R. J., Shields, P. G., & Hatsukami, D. (2020). The role of subjective responses in electronic cigarette uptake and substitution in adult smokers. *Drug and Alcohol Dependence, 212*, 107999. doi: 10.1016/j.drugalcdep.2020.107999

Galeotti, N., Di Cesare Mannelli, L., Mazzanti, G., Bartolini, A., & Ghelardini, C. (2002). Menthol: a natural analgesic compound. *Neuroscience Letters, 322*(3), 145-148. doi:10.1016/s0304-3940(01)02527-7

Gan, W. Q., Cohen, S. B., Man, S. F., & Sin, D. D. (2008). Sex-related differences in serum cotinine concentrations in daily cigarette smokers. *Nicotine & Tobacco Research, 10*(8), 1293-1300. doi:10.1080/14622200802239132

Gardiner, P. (2004). The African Americanization of menthol cigarette use in the United States. *Nicotine & Tobacco Research, 6*(1), 55-65. doi:10.1080/14622200310001649478

Golpe, A. A., Martin-Alvarez, J. M., Galiano, A., & Asensio, E. (2022). Effect of IQOS introduction on Philip Morris International cigarette sales in Spain: a logarithmic mean divisa index decomposition approach. *Gaceta Sanitaria, 36*(4), 293-300. doi:10.1016/j.gaceta.2021.12.007

Gonzalez-Roz, A., Jackson, J., Murphy, C., Rohsenow, D. J., & MacKillop, J. (2019). Behavioral economic tobacco demand in relation to cigarette consumption and nicotine dependence: a meta-analysis of cross-sectional relationships. *Addiction, 114*(11), 1926-1940. doi:10.1111/add.14736

Gorham, P. (2017). *FDA's nicotine plan has limited impact on big tobacco*. Morning Star. https://www.morningstar.com/stocks/fdas-nicotine-plan-has-limited-impact-big-tobacco

Green, L. F. F., & Debra, E. (1993). The substitutability of reinforcers. *Journal of Experimental Analysis of Behavior*, *60*(1), 151-158. doi: 10.1901/jeab.1993.60-141

Green, R. C., & Srivastava, S. (1986). Expected utility maximization and demand behavior. *Journal of Economic Theory, 38*(2), 313-323. doi: 10.1016/0022-0531(86)90121-3

Griffith, S. D., Shiffman, S., & Heitjan, D. F. (2009). A method comparison study of timeline followback and ecological momentary assessment of daily cigarette consumption. *Nicotine & Tobacco Research, 11*(11), 1368-1373. doi: 10.1093/ntr/ntp150

Gritz, E. R., Baer-Weiss, V., Benowitz, N. L., Van Vunakis, H., & Jarvik, M. E. (1981). Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. *Clinical Pharmacology & Therapeutics, 30*(2), 201-209. doi: 10.1038/clpt.1981.149

Gundersen, D. A., Delnevo, C. D., & Wackowski, O. (2009). Exploring the relationship between race/ethnicity, menthol smoking, and cessation, in a nationally representative sample of adults. *Preventive Medicine, 49*(6), 553-557. doi:10.1016/j.ypmed.2009.10.003

Hajek, P., Pittaccio, K., Pesola, F., Myers Smith, K., Phillips-Waller, A., & Przulj, D. (2020). Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction, 115*(6), 1141-1148. doi:10.1111/add.14936

Hammond, D., Collishaw, N. E., & Callard, C. (2006). Secret science: tobacco industry research on smoking behaviour and cigarette toxicity. *The Lancet, 367*(9512), 781-787. doi: 10.1016/S0140-6736(06)68077-X

Hammond, D., Wiebel, F., Kozlowski, L. T., Borland, R., Cummings, M. K., O'Connor, R. J., McNeill, A., Connolly, G., Arnott, D., & Fong, G. T. (2007). Revising the machine smoking regime for cigarette emissions: implications for tobacco control policy. *Tobacco Control, 16*(1), 8-14. doi:10.1136/tc.2005.015297

Hans, M., Wilhelm, M., & Swandulla, D. (2012). Menthol suppresses nicotinic acetylcholine receptor functioning in sensory neurons via allosteric modulation. *Chemical Senses, 37*(5), 463-469. doi: 10.1093/chemse/bjr128

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42(2),* 377-381. doi:10.1016/j.jbi.2019.103208

Harrison, E., Biswas, L., Avusula, R., Zhang, M., Gong, Y., & Liu, X. (2017). Effects of menthol and its interaction with nicotine-conditioned cue on nicotine-seeking behavior in rats. *Psychopharmacology, 234*(23-24), 3443-3453. doi: 10.1007/s00213-017-4736-0

Hatsukami, D. K., & Carroll, D. M. (2020). Tobacco harm reduction: Past history, current controversies and a proposed approach for the future. *Preventive Medicine, 140*, 106099. doi:10.1016/j.ypmed.2020.106099

Hatsukami, D. K., Hanson, K., Briggs, A., Parascandola, M., Genkinger, J. M., O'Connor, R., & Shields, P. (2009). Clinical trials methods for evaluation of potential reduced exposure products. *Cancer Epidemiology, Biomarkers & Prevention, 18*(12), 3143-3195. doi:10.1158/1055-9965.EPI-09-0654 [doi]

Hatsukami, D. K., Zhang, Y., O'Connor, R. J., & Severson, H. H. (2013). Subjective responses to oral tobacco products: scale validation. *Nicotine & Tobacco Research, 15*(7), 1259-1264. doi:10.1093/ntr/nts265 [doi]

Hayes, J. E., & Baker, A. N. (2022). Flavor science in the context of research on electronic cigarettes. *Frontiers in Neuroscience, 16*, 918082. doi:10.3389/fnins.2022.918082

Haziza, C., de La Bourdonnaye, G., Donelli, A., Poux, V., Skiada, D., Weitkunat, R., Baker, G., Picavet, P., & Ludicke, F. (2020). Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 2.2 for 3 months (part 1). *Nicotine & Tobacco Research, 22*(4), 539-548. doi:10.1093/ntr/ntz013

Haziza, C., de La Bourdonnaye, G., Skiada, D., Ancerewicz, J., Baker, G., Picavet, P., & Lüdicke, F. (2016). Evaluation of the tobacco heating system 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. *Regulatory Toxicology and Pharmacology, 81*(suppl 2), S139-S150. doi:10.1016/j.yrtph.2016.11.003

Heckman, B. W., Cummings, K. M., Hirsch, A. A., Quisenberry, A. J., Borland, R., O'Connor, R. J., Fong, G. T., & Bickel, W. K. (2017). A novel method for evaluating the acceptability of substitutes for cigarettes: The Experimental Tobacco Marketplace. *Tobacco Regulatry Science, 3*(3), 266-279. doi:10.18001/TRS.3.3.3

Henderson, B. J., Wall, T. R., Henley, B. M., Kim, C. H., McKinney, S., & Lester, H. A. (2017). Menthol enhances nicotine reward-related behavior by potentiating nicotine-induced changes in nAChR function, nAChR upregulation, and DA neuron excitability. *Neuropsychopharmacology, 42*(12), 2285-2291. doi:10.1038/npp.2017.72

Henderson, B. J., Wall, T. R., Henley, B. M., Kim, C. H., Nichols, W. A., Moaddel, R., Xiao, C., & Lester, H. A. (2016). Menthol alone upregulates midbrain nAChRs, alters nAChR subtype stoichiometry, alters dopamine neuron firing frequency, and prevents nicotine reward. *The Journal of Neuroscience, 36*(10), 2957-2974. doi:10.1523/JNEUROSCI.4194-15.2016

Henderson, K. C., Van Do, V., Wang, Y., Duan, Z., Popova, L., Spears, C. A., Weaver, S., Ashley, D., Barker, D., & Huang, J. (2022). Brief report on IQOS point-of-sale marketing, promotion and pricing in IQOS retail partner stores in Atlanta, Georgia, USA. *Tobacco Control, 32*(e2), 057285. doi:10.1136/tc-2022-057285

Henningfield, J. E., & Goldberg, S. R. (1983). Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacology Biochemistry and Behavior, 19*(6), 989-992. doi: 10.1016/0091-3057(83)90405-7

Henningfield, J. E., & Keenan, R. M. (1993). Nicotine delivery kinetics and abuse liability. *Journal of Consulting and Clinical Psychology, 61*(5), 743-750. doi:10.1037/0022-006X.61.5.743

Henningfield, J. E., Benowitz, N. L., Ahijevych, K., Garrett, B. E., Connolly, G. N., & Wayne, G. F. (2003). Does menthol enhance the addictiveness of cigarettes? An agenda for research. *Nicotine and Tobacco Reserach, 5*(1), 9-11. doi:10.1080/1462220031000070543

Henningfield, J. E., Hatsukami, D. K., Zeller, M., & Peters, E. (2011). Conference on abuse liability and appeal of tobacco products: conclusions and recommendations. *Drug and Alcohol Dependence, 116*(1-3), 1-7. doi:10.1016/j.drugalcdep.2010.12.009

Higgins, S. T., Kurti, A. N., Palmer, M., Tidey, J. W., Cepeda-Benito, A., Cooper, M. R., Krebs, N., Baezconde-Garbanati, L., Hart, J., & Stanton, C. A. (2019). A review of tobacco regulatory science research on vulnerable populations. *Preventive Medicine, 128*, 105709. doi: 10.1016/j.ypmed.2019.04.024

Hiler, M., Breland, A., Spindle, T., Maloney, S., Lipato, T., Karaoghlanian, N., Shihadeh, A., Lopez, A., Ramoa, C., & Eissenberg, T. (2017). Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and self-reported effects: Influence of liquid

nicotine concentration and user experience. *Experimental and Clinical Psychopharmacology, 25*(5), 380-392. doi: 10.1037/pha0000140

Hiscock, R., Silver, K., Zatoński, M., & Gilmore, A. B. (2020). Tobacco industry tactics to circumvent and undermine the menthol cigarette ban in the UK. *Tobacco Control*, 29(e1), e138-e142. doi: 10.1136/tobaccocontrol-2020-055769

Hoffman, A. C. (2011). The health effects of menthol cigarettes as compared to non-menthol cigarettes. *Tobacco Induced Diseases, 9*(suppl 1), s1-s7. doi:10.1186/1617-9625-9-s1-s7

Huang, J., Gwarnicki, C., Xu, X., Caraballo, R. S., Wada, R., & Chaloupka, F. J. (2018). A comprehensive examination of own- and cross-price elasticities of tobacco and nicotine replacement products in the U.S. *Preventive Medicine, 117*, 107-114. doi: 10.1016/j.ypmed.2018.04.024

Hughes, J. R. (2007). Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine & Tobacco Research, 9*(3), 315-327. doi:10.1080/14622200701188919

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry, 43*(3), 289-294. doi: 10.1001/archpsyc.1986.01800030107013

Hughes, J. R., Higgins, S. T., & Bickel, W. K. (1994). Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction, 89*(11), 1461-1470. doi:10.1111/j.1360-0443.1994.tb03744.x

Hughes, J., & Hatsukami, D. K. (1998). Errors in using tobacco withdrawal scale. *Tobacco Control, 7*(1), 92. doi:10.1136/tc.7.1.92a

Hursh, S. R., & Roma, P. G. (2013). Behavioral economics and empirical public policy. *Journal of the Experimental Analysis of Behavior, 99*(1), 98-124. doi:10.1002/jeab.7

Hursh, S. R., & Roma, P. G. (2016). Behavioral economics and the analysis of consumption and choice. *Managerial and Decision Economics, 37*(4-5), 224-238. doi:10.1002/mde.2724

Hursh, S. R., & Silberberg, A. (2008). Economic demand and essential value. *Psychological Review, 115*(1), 186-198. doi:10.1037/0033-295X.115.1.186

Hwang, J. H., Ryu, D. H., & Park, S. W. (2019). Heated tobacco products: Cigarette complements, not substitutes. *Drug and Alcohol Dependence, 204*, 107576. doi:10.1016/j.drugalcdep.2019.107576

Institute of Medicine. (2012). *Scientific Standards for Studies on Modified Risk Tobacco Products*. http://www.nap.edu/catalog/13294/scientific-standards-for-studies-on-modified-risk-tobacco-products

Irina, S., & Alistair, W. (2018). Heated tobacco products: things we do and do not know. *Tobacco Control, 27*(suppl 1), s7-s8. doi:10.1136/tobaccocontrol-2018-054774

Jacob, P., Wu, S., Yu, L., & Benowitz, N. L. (2000). Simultaneous determination of mecamylamine, nicotine, and cotinine in plasma by gas chromatography-mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis, 23*(4), 653-661. doi: 10.1016/S0731-7085(00)00343-5

Jaffe, J. H., & Jaffe, F. K. (1989). Historical perspectives on the use of self-reported effects measures in assessing the abuse potential of drugs. *NIDA Reserach Monograph, 92*, 43-72. https://pubmed.ncbi.nlm.nih.gov/2512502/

Jankowski, M., Brozek, G. M., Lawson, J., Skoczynski, S., Majek, P., & Zejda, J. E. (2019). New ideas, old problems? Heated tobacco products - a systematic review. *International Journal of Occupational Medicine and Environmental Health, 32*(5), 595-634. doi:10.13075/ijomeh.1896.01433

Jarvik, M. E., Tashkin, D. P., Caskey, N. H., McCarthy, W. J., & Rosenblatt, M. R. (1994). Mentholated cigarettes decrease puff volume of smoke and increase carbon monoxide absorption. *Physiology & Behavior, 56*(3), 563-570. doi:10.1016/0031-9384(94)90302-6

Jarvis, M. J., Boreham, R., Primatesta, P., Feyerabend, C., & Bryant, A. (2001). Nicotine yield from machine-smoked cigarettes and nicotine intakes in smokers: evidence from a representative population survey. *Journal of the National Cancer Institute, 93*(2), 134-138. doi:10.1093/jnci/93.2.134

Jatlow, P., Valentine, G., Gueorguieva, R., Nadim, H., Wu, R., O'Malley, S. S., & Sofuoglu, M. (2018). Plasma menthol glucuronide as a biomarker of acute menthol inhalation. *Tobacco Regulatory Science, 4*(1), 586-591. doi: 10.18001/TRS.4.1.5

Jensen, K. P., Valentine, G., Gueorguieva, R., & Sofuoglu, M. (2020). Differential effects of nicotine delivery rate on subjective drug effects, urges to smoke, heart rate and blood pressure in tobacco smokers. *Psychopharmacology, 237*(5), 1359-1369. doi: 10.1007/s00213-020-05463-6

Johnstone, E., Benowitz, N., Cargill, A., Jacob, R., Hinks, L., Day, I., Murphy, M., & Walton, R. (2006). Determinants of the rate of nicotine metabolism and effects on smoking behavior. *Clinical Pharmacology & Therapeutics, 80*(4), 319-330. doi:10.1016/j.clpt.2006.06.011

Jones, D. M., Ashley, D. L., Weaver, S. R., & Eriksen, M. P. (2019). Flavored ENDS use among adults who have used cigarettes and ENDS, 2016-2017. *Tobacco Regulatory Science, 5*(6), 518-531. doi: 10.18001/TRS.5.6.4

Jones, J., Slayford, S., Gray, A., Brick, K., Prasad, K., & Proctor, C. (2020). A cross-category puffing topography, mouth level exposure and consumption study among Italian users of

tobacco and nicotine products. *Scientific Reports, 10*(1), 12. doi:10.1038/s41598-019-55410-5

Kale, D., Tattan-Birch, H., Brown, J., Cox, S., Dawkins, L., Goniewicz, M. L., Morris, K., & Shahab, L. (2023). Examining acute psychopharmacological effects of nicotine vaping versus heated tobacco products in a randomised crossover study of product naive adult smokers. *Scientific Reports, 13*(1), 22676. doi:10.1038/s41598-023-49602-3

Kamatou, G. P. P., Vermaak, I., Viljoen, A. M., & Lawrence, B. M. (2013). Menthol: A simple monoterpene with remarkable biological properties. *Phytochemistry, 96*, 15-25. doi: 10.1016/j.phytochem.2013.08.005

Karim, M. A., Talluri, R., Chido-Amajuoyi, O. G., & Shete, S. (2022). Awareness of heated tobacco products among US adults: Health information national trends survey, 2020. *Substance Abuse, 43*(1), 1023-1034. doi:10.1080/08897077.2022.2060440

Kaufman, A. R., Persoskie, A., Twesten, J., & Bromberg, J. (2018). A review of risk perception measurement in tobacco control research. *Tobacco Control*, *22*(11), 1937-1945. doi: 10.1136/tobaccocontrol-2017-054005

Keller, P. A., D'Silva, J., Lien, R. K., Boyle, R. G., Kingsbury, J., & O'Gara, E. (2020). Perceived harm of menthol cigarettes and quitting behaviors among menthol smokers in Minnesota. *Preventive Medicine Reports, 20*, 101269. doi:10.1016/j.pmedr.2020.101269

Kim, M., Watkins, S. L., Koester, K. A., Mock, J., Kim, H. C., Olson, S., Harvanko, A. M., & Ling, P. M. (2020). Unboxed: US young adult tobacco users' responses to a new heated tobacco product. *International Journal of Environmental Research and Public Health, 17*(21), 8108. doi:10.3390/ijerph17218108

Kim, S. C., & Friedman, T. C. (2022). A new ingenious enemy: Heat-not-burn products. *Tobacco Use Insights, 15*. doi:10.1177/1179173X221076419

Kostygina, G., Glantz, S. A., & Ling, P. M. (2016). Tobacco industry use of flavours to recruit new users of little cigars and cigarillos. *Tobacco Control, 25*(1), 66-74. doi:10.1136/tobaccocontrol-2014-051830

Kotlyar, M., Shanley, R., Dufresne, S. R., Corcoran, G. A., & Hatsukami, D. K. (2022). Effect of restricting menthol flavored cigarettes or E-cigarettes on smoking behavior in menthol smokers. *Preventive Medicine, 165*, 107243. doi: 10.1016/j.ypmed.2022.107243

Kotlyar, M., Shanley, R., Dufresne, S. R., Corcoran, G. A., Okuyemi, K. S., Mills, A. M., & Hatsukami, D. K. (2021a). Effects on Smoking Behavior of Switching Menthol Smokers to Non-menthol Cigarettes. *Nicotine & Tobacco Research, 23*(11), 1921-1927. doi:10.1093/ntr/ntab090

Kotlyar, M., Shanley, R., Dufresne, S. R., Corcoran, G. A., Okuyemi, K. S., Mills, A. M., & Hatsukami, D. K. (2021b). Effects on time to lapse of switching menthol smokers to non-menthol cigarettes prior to a cessation attempt: a pilot study. *Tobacco Control, 30*(5), 574-577. doi:10.1136/tobaccocontrol-2020-055689

Kreslake, J. M., & Yerger, V. B. (2010). Tobacco industry knowledge of the role of menthol in chemosensory perception of tobacco smoke. *Nicotine & Tobacco Research, 12*(suppl 2), S98-S101. doi:10.1093/ntr/ntq208

Krishnan-Sarin, S., O'Malley, S. S., Green, B. G., & Jordt, S. E. (2019). The science of flavour in tobacco products. *World Health Organisation Technical Report Series, 1015*, 125-142.

Land, S. R., Baker, L., Twesten, J., Reyes-Guzman, C. M., & Kaufman, A. R. (2023). Smoking cessation and tobacco-related risk perceptions among people with and without a

diagnosis of cancer. *Cancer Epidemiology, Biomarkers, & Prevention, 32*(2), 266-273. doi:10.1158/1055-9965.EPI-22-0651

Landry, R. L., Groom, A. L., Vu, T.-H. T., Stokes, A. C., Berry, K. M., Kesh, A., Hart, J., Walker, K., Giachello, A., Sears, C., McGlasson, K., Tompkins, L., Mattingly, D., Robertson, R., & Payne, T. J. (2019). The role of flavors in vaping initiation and satisfaction among US adults. *Addictive Behaviors, 99*, 106077. doi:10.1016/j.addbeh.2019.106077

Lasseter, T., Bansal, P., Wilson, T., Miyazaki, A., Wlison, D., & Kalra, A. (2017). *Scientists describe problems in Philip Morris e-cigarette experiments*. https://www.reuters.com/investigates/special-report/tobacco-iqos-science/

Laverty, A. A., Vardavas, C. I., & Filippidis, F. T. (2021). Prevalence and reasons for use of Heated Tobacco Products (HTP) in Europe: an analysis of Eurobarometer data in 28 countries. *The Lancet Regional Health - Europe, 8*. doi:10.1016/j.lanepe.2021.100159

Lawrence, D., Cadman, B., & Hoffman, A. C. (2011). Sensory properties of menthol and smoking topography. *Tobacco Induced Diseases, 9*(1), S3. doi:10.1186/1617-9625-9-S1-S3

Leavens, E. L. S., Lambart, L., Diaz, F. J., Wagener, T. L., Ahluwalia, J. S., Benowitz, N., & Nollen, N. L. (2023). Nicotine delivery and changes in withdrawal and craving during acute electronic cigarette, heated tobacco product, and cigarette use among a sample of Black and White people who smoke. *Nicotine & Tobacco Research,* Online ahead of print. doi:10.1093/ntr/ntad247

Lee, E. M., Malson, J. L., Moolchan, E. T., & Pickworth, W. B. (2004). Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine & Tobacco Research, 6*(1), 95-102. doi:10.1080/14622200310001656911

Lee, Y. O., & Glantz, S. A. (2011). Menthol: putting the pieces together. *Tobacco Control, 20*(suppl 2), 1-7. doi:10.1136/tc.2011.043604

Lee, Y. O., Nonnemaker, J. M., Bradfield, B., Hensel, E. C., & Robinson, R. J. (2018). Examining daily electronic cigarette puff topography among established and nonestablished cigarette smokers in their natural environment. *Nicotine & Tobacco Research, 20*(10), 1283-1288. doi:10.1093/ntr/ntx222

Lempert, L. K., Bialous, S., & Glantz, S. (2022). FDA's reduced exposure marketing order for IQOS: Why it is not a reliable global model. *Tobacco Control, 31*(e1), e83-e87. doi:10.1136/tobaccocontrol-2020-056316

Lerman, C., Tyndale, R., Patterson, F., Wileyto, E. P., Shields, P. G., Pinto, A., & Benowitz, N. (2006). Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clinical Pharmacology & Therapeutics, 79*(6), 600-608. doi:10.1016/j.clpt.2006.02.006

Levine, H., Duan, Z., Bar-Zeev, Y., Abroms, L. C., Khayat, A., Tosakoon, S., Romm, K., Wang, Y., & Berg, C. J. (2023). IQOS use and interest by sociodemographic and tobacco behavior characteristics among adults in the US and Israel. *International Journal of Environmental Research and Public Health, 20*(4), 3141. doi:10.3390/ijerph20043141

Levy, D. T., Cadham, C. J., Sanchez-Romero, L. M., Knoll, M., Travis, N., Yuan, Z., Li, Y., Mistry, R., Douglas, C., Tam, J., Sertkaya, A., Warner, K., & Meza, R. (2021). An expert elicitation on the effects of a ban on menthol cigarettes and cigars in the United States. *Nicotine & Tobacco Research, 23*(11), 1911-1920. doi:10.1093/ntr/ntab121

Levy, D. T., Meza, R., Yuan, Z., Li, Y., Cadham, C., Sanchez-Romero, L. M., Travis, N., Knoll, M., Liber, A., Mistry, R., Hirschtick, J., Fleischer, N., Skolnick, S., Brouwer, A., Douglas,

C., Jeon, J., Cook, S., & Warner, K. E. (2021). Public health impact of a US ban on menthol in cigarettes and cigars: a simulation study. *Tobacco Control, 32*(e1), e37-e44. doi:10.1136/tobaccocontrol-2021-056604

Levy, D. T., Pearson, J. L., Villanti, A. C., Blackman, K., Vallone, D. M., Niaura, R. S., & Abrams, D. B. (2011). Modeling the future effects of a menthol ban on smoking prevalence and smoking-attributable deaths in the United States. *American Journal of Public Health, 101*(7), 1236-1240. doi:10.2105/AJPH.2011.300179

Li, X., Luo, Y., Jiang, X., Zhang, H., Zhu, F., Hu, S., Hou, H., Hu, Q., & Pang, Y. (2019). Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. *Nicotine & Tobacco Research, 21*(1), 111-118. doi:10.1093/ntr/nty005

Liber, A. C. (2022). Using regulatory stances to see all the commercial determinants of health. *The Milbank quarterly, 100*(3), 918-961. doi:10.1111/1468-0009.12570

Liber, A. C., Knoll, M., Cadham, C. J., Issabakhsh, M., Oh, H., Cook, S., Warner, K., Mistry, R., & Levy, D. T. (2023). The role of flavored electronic nicotine delivery systems in smoking cessation: A systematic review. *Drug and Alcohol Dependence Reports, 16*(7), 100143. doi:10.1016/j.dadr.2023.100143

Litt, M. D., Duffy, V., & Oncken, C. (2016). Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. *Tobacco Control, 25*(suppl 2), ii67-ii72. doi:10.1136/tobaccocontrol-2016-053223

Liu, L., Zhao-Shea, R., McIntosh, J. M., Gardner, P. D., & Tapper, A. R. (2012). Nicotine persistently activates ventral tegmental area dopaminergic neurons via nicotinic

acetylcholine receptors containing α4 and α6 subunits. *Molecular Pharmacology, 81*(4), 541-548. doi:10.1124/mol.111.076661

Lopez, A. A., Hiler, M. M., Soule, E. K., Ramoa, C. P., Karaoghlanian, N. V., Lipato, T., Breland, A., Shihadeh, A., & Eissenberg, T. (2016). Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: A preliminary report. *Nicotine & Tobacco Research, 18*(5), 720-723. doi:10.1093/ntr/ntv182

Lucas, A. (2021). *Philip Morris, Altria banned from importing or selling IQOS tobacco device in the US.* CNBC News. https://www.cnbc.com/2021/09/30/philip-morris-altria-banned-from-selling-iqos-tobacco-device-in-the-us.html

Lüdicke, F., Picavet, P., Baker, G., Haziza, C., Poux, V., Lama, N., & Weitkunat, R. (2018). Effects of switching to the menthol tobacco heating system 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: A randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 2). *Nicotine & Tobacco Research, 20*(2), 173-182. doi:10.1093/ntr/ntx028

Lunell, E., Fagerström, K., Hughes, J., & Pendrill, R. (2020). Pharmacokinetic comparison of a novel non-tobacco-based nicotine pouch (Zyn) with conventional, tobacco-based swedish snus and american moist snuff. *Nicotine & Tobacco Research, 22*(10), 1757-1763. doi:10.1093/ntr/ntaa068

Mackillop, J., Murphy, C. M., Martin, R. A., Stojek, M., Tidey, J. W., Colby, S. M., & Rohsenow, D. J. (2016). Predictive validity of a cigarette purchase task in a randomized controlled trial of contingent vouchers for smoking in individuals with substance use disorders. *Nicotine & Tobacco Research, 18*(5), 531-537. doi:10.1093/ntr/ntv233

MacKillop, J., Murphy, J. G., Ray, L. A., Eisenberg, D. T., Lisman, S. A., Lum, J. K., & Wilson, D. S. (2008). Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers. *Experimental and Clinical Psychopharmacology, 16*(1), 57-65. doi:10.1037/1064-1297.16.1.57

MacLean, R. R., Gueorguieva, R., DeVito, E. E., Peltier, M. R., Parida, S., & Sofuoglu, M. (2021). The effects of inhaled flavors on intravenous nicotine. *Experimental and Clinical Psychopharmacology, 29*(6), 615-624. doi:10.1037/pha0000394

Magnan, R. E., Koblitz, A. R., Zielke, D. J., & McCaul, K. D. (2009). The effects of warning smokers on perceived risk, worry, and motivation to quit. *Annals of Behavioral Medicine, 37*(1), 46-57. doi:10.1007/s12160-009-9085-8

Mallock, N., Böss, L., Burk, R., Danziger, M., Welsch, T., Hahn, H., Pieper, E., Henkler-Stephani, F., Hutzler, C., & Luch, A. (2018). Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. *Archives of Toxicology, 92*(6), 2145-2149. doi:10.1007/s00204-018-2215-y

Maloney, S. (2022). *The abuse liability profile of an unflavored sucralose-sweetened* (Doctoral dissertation, Virginia Commonwealth University). VCU Scholars Compass. doi:10.25772/DFFZ-JV93

Maloney, S., Eversole, A., Crabtree, M., Soule, E., Eissenberg, T., & Breland, A. (2020). Acute effects of JUUL and IQOS in cigarette smokers. *Tobacco Control, 30*(4), 449-452. doi:10.1136/tobaccocontrol-2019-055475

Maloney, J. (2024). *Outside the US, Marlboro revenue exlipsed by sales of a cigarette alternative.* The Wall Street Journal. https://www.wsj.com/livecoverage/stock-market-

today-dow-jones-earnings-02-08-2024/card/outside-u-s-marlboro-revenue-eclipsed-by-sales-of-a-cigarette-alternative-EIUP4n4YZljvwPeSAoMa

Martin, E. G., Warner, K. E., & Lantz, P. M. (2004). Tobacco harm reduction: what do the experts think? *Tobacco Control, 13*(2), 123-128. doi:10.1136/tc.2003.006346

McCarthy, W. J., Caskey, N. H., Jarvik, M. E., Gross, T. M., Rosenblatt, M. R., & Carpenter, C. (1995). Menthol vs nonmenthol cigarettes: effects on smoking behavior. *American Journal of Public Health, 85*(1), 67-72. doi:10.2105/ajph.85.1.67

McDermott, S., Reichmann, K., Mason, E., Fearon, I. M., O'Connell, G., & Nahde, T. (2023). An assessment of nicotine pharmacokinetics and self-reported effects of the pulze heated tobacco system compared with cigarettes. *Scientific Reports, 13*(1), 9037. doi:10.1038/s41598-023-36259-1

McDonald, J. (2023). *IQOS: How does it work and where can you find one?* Vaping 360. https://vaping360.com/learn/iqos-phillip-morris/

McGinnes, H., Kingsley, M., Song, G., Rosewarne, J., Gonthier, S., Doane, J., & Henley, P. (2023). Evaluation of a statewide flavored tobacco restriction on use, access, and cessation among Black and White tobacco users in Massachusetts. *American Journal of Health Promotion*, *37*(7). doi:10.1177/08901171231183308

McLaughlin, I., Dani, J. A., & De Biasi, M. (2015). Nicotine withdrawal. *Current Topics in Behavioral Neuroscience, 24*, 99-123. doi:10.1007/978-3-319-13482-6_4

Mead, E. L., Chen, J. C., Kirchner, T. R., Butler, J., & Feldman, R. H. (2018). An ecological momentary assessment of cigarette and cigar dual use among African American young adults. *Nicotine & Tobacco Research, 20*(suppl_1), S12-S21. doi:10.1093/ntr/nty061

Megerdichian, C. L., Rees, V. W., Wayne, G. F., & Connolly, G. N. (2007). Internal tobacco industry research on olfactory and trigeminal nerve response to nicotine and other smoke components. *Nicotine & Tobacco Reseach, 9*(11), 1119-1129. doi:10.1080/14622200701648458

Meisch, R., & Lemaire, G. (1993). Methods in behavioral pharmacology: Ed. Haaren F., Elsevier Science Publishers. Amsterdam, Netherlands.

Mills, S. D., Henriksen, L., Golden, S. D., Kurtzman, R., Kong, A. Y., Queen, T. L., & Ribisl, K. M. (2018). Disparities in retail marketing for menthol cigarettes in the United States, 2015. *Health & Place, 53*, 62-70. doi:10.1016/j.healthplace.2018.06.011

Miyazawa, M., Marumoto, S., Takahashi, T., Nakahashi, H., Haigou, R., & Nakanishi, K. (2011). Metabolism of (+)- and (-)-menthols by CYP2A6 in human liver microsomes. *Journal of Oleo Science, 60*(3), 127-132. doi:10.5650/jos.60.127

Moolchan, E. T., Hudson, D. L., Schroeder, J. R., & Sehnert, S. S. (2004). Heart rate and blood pressure responses to tobacco smoking among African-American adolescents. *Journal of the National Medical Association, 96*(6), 767-771. https://pubmed.ncbi.nlm.nih.gov/15233486/

Morean, M. E., & Bold, K. W. (2022). The Modified Cigarette Evaluation Questionnaire: Psychometric properties of the originally-proposed five-factor structure and a novel four-factor structure for use with adults who currently smoke cigarettes. *Drug and Alcohol Dependence, 241*, 109684. doi: 10.1016/j.drugalcdep.2022.109684

Moskowitz, D. S., & Young, S. N. (2006). Ecological momentary assessment: what it is and why it is a method of the future in clinical psychopharmacology. *Journal of Psychiatry & Neuroscience, 31*(1), 13-20. https://pubmed.ncbi.nlm.nih.gov/16496031/

Nemeth-Coslett, R., & Griffiths, R. R. (1984). Determinants of puff duration in cigarette smokers: I. *Pharmacology Biochemistry & Behavior, 20*(6), 965-971. doi: 10.1016/0091-3057(84)90024-8

Nonnemaker, J., Feirman, S. P., Macmonegle, A., Ambrose, B. K., Jackson, K. J., Schroeder, M. J., Smith, A., Ridgeway, W., & Rass, O. (2019). Examining the role of menthol cigarettes in progression to established smoking among youth. *Addictive Behaviors, 98*, 106045. doi:10.1016/j.addbeh.2019.106045

Nonnemaker, J., Hersey, J., Homsi, G., Busey, A., Allen, J., & Vallone, D. (2013). Initiation with menthol cigarettes and youth smoking uptake. *Addiction, 108*(1), 171-178. doi:10.1111/j.1360-0443.2012.04045.x

O'Connor, R. J., Bansal-Travers, M., Carter, L. P., & Cummings, K. M. (2012). What would menthol smokers do if menthol in cigarettes were banned? Behavioral intentions and simulated demand. *Addiction, 107*(7), 1330-1338. doi:10.1111/j.1360-0443.2012.03822.x

O'Connor, R. J., Schneller, L. M., Felicione, N. J., Talhout, R., Goniewicz, M. L., & Ashley, D. L. (2022). Evolution of tobacco products: recent history and future directions. *Tobacco Control, 31*(2), 175-182. doi:10.1136/tobaccocontrol-2021-056544

Offen, N., Smith, E. A., & Malone, R. E. (2003). From adversary to target market: the ACT-UP boycott of Philip Morris. *Tobacco Control, 12*(2), 203-207. doi:10.1136/tc.12.2.203

Ossip-Klein, D. J., Martin, J. E., Danley Lomax, B., Prue, D. M., & Jo Davis, C. (1983). Assessment of smoking topography generalization across laboratory, clinical, and naturalistic settings. *Addictive Behaviors, 8*(1), 11-17. doi:10.1016/0306-4603(83)90049-7

Ozga, J. E., Bays, C., Haliwa, I., Felicione, N. J., Ferguson, S. G., Dino, G., & Blank, M. D. (2021). Measurement of cigarette smoking: Comparisons of global self-report, returned cigarette filters, and ecological momentary assessment. *Experimental and Clinical Psychopharmacology*, *30*(3), 365-370. doi:10.1037/pha0000449

Palmatier, M. I., Liu, X., Caggiula, A. R., Donny, E. C., & Sved, A. F. (2007). The role of nicotinic acetylcholine receptors in the primary reinforcing and reinforcement-enhancing effects of nicotine. *Neuropsychopharmacology, 32*(5), 1098-1108. doi:10.1038/sj.npp.1301228

Patel, T., Ishiuji, Y., & Yosipovitch, G. (2007). Menthol: A refreshing look at this ancient compound. *Journal of the American Academy of Dermatology, 57*(5), 873-878. doi: 10.1016/j.jaad.2007.04.008

Patten, T., & De Biasi, M. (2020). History repeats itself: Role of characterizing flavors on nicotine use and abuse. *Neuropharmacology, 177*, 108162. doi:10.1016/j.neuropharm.2020.108162

Paulina, M., Mateusz, J., & Grzegorz, M. B. (2023). Acute health effects of heated tobacco products – comparative analysis with traditional cigarettes and electronic cigarettes in young adults. *European Respiratory Journal Open Research, 9*(3), 00595-2022. doi:10.1183/23120541.00595-2022

Peeters, S., and Gilmore, A. B. (2013). Understanding the emergence of the tobacco industry's use of the term tobacco harm reduction in order to inform public health policy. *Tobacco Control, 24(2),* 182-189. doi: 10.1136/tobaccocontrol-2013-051502.

Pérez-Stable, E. J., Herrera, B., Jacob, P., 3rd, & Benowitz, N. L. (1998). Nicotine metabolism and intake in Black and White smokers. *JAMA, 280*(2), 152-156. doi:10.1001/jama.280.2.152

Perkins, K. A., Karelitz, J. L., Giedgowd, G. E., & Conklin, C. A. (2012). The reliability of puff topography and subjective responses during ad lib smoking of a single cigarette. *Nicotine & Tobacco Research, 14*(4), 490-494. doi:10.1093/ntr/ntr150

Philip Morris International. (2020). *Can innovative products like IQOS accelerate the decline of smoking?* https://www.pmi.com/sustainability/case-studies-and-market-stories/can-innovative-products-like-iqos-accelerate-the-decline-of-smoking#:~:text=Japan%2C%20the%20first%20country%20where,product%20users%20in%20the%20world.

Philip Morris International. (2023). *Japan: Philip Morris Japan Limited.* https://www.pmi.com/markets/japan/en/overview#:~:text=In%20November%202014%2C%20PMI%20officially,product%20is%20now%20available%20nationwide.

Phillips-Waller, A., Przulj, D., Pesola, F., Smith, K. M., & Hajek, P. (2021). Nicotine delivery and user ratings of IQOS heated tobacco system compared with cigarettes, JUUL, and refillable e-cigarettes. *Nicotine & Tobacco Research, 23*(11), 1889-1894. doi:10.1093/ntr/ntab094

Piasecki, T. M., Jahng, S., Wood, P. K., Robertson, B. M., Epler, A. J., Cronk, N. J., Rohrbaugh, J., Heath, A., Shiffman, S., & Sher, K. J. (2011). The self-reported effects of alcohol-tobacco co-use: an ecological momentary assessment investigation. *Journal of Abnormal Psychology, 120*(3), 557-571. doi:10.1037/a0023033

Picciotto, M. R., & Corrigall, W. A. (2002). Neuronal systems underlying behaviors related to nicotine addiction: Neural circuits and molecular genetics. *The Journal of Neuroscience, 22*(9), 3338. doi:10.1523/JNEUROSCI.22-09-03338.2002

Pletcher, M. J., Hulley, B. J., Houston, T., Kiefe, C. I., Benowitz, N., & Sidney, S. (2006). Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Archives of Internal Medicine, 166*(17), 1915-1922. doi:10.1001/archinte.166.17.1915

Pomerleau, C. S., & Pomerleau, O. F. (1992). Euphoriant effects of nicotine in smokers. *Psychopharmacology, 108*(4), 460-465. doi:10.1007/bf02247422

Pomerleau, O. F., Pomerleau, C. S., & Rose, J. E. (1989). Controlled dosing of nicotine: a review of problems and progress. *Annals of Behavioral Medicine, 11*(4), 158-163. doi:10.1207/s15324796abm1104_6

Preston, K. L., & Epstein, D. H. (2011). Stress in the daily lives of cocaine and heroin users: relationship to mood, craving, relapse triggers, and cocaine use. *Psychopharmacoloy, 218*(1), 29-37. doi:10.1007/s00213-011-2183-x

Prochaska, J. J., & Henriksen, L. (2019). PMI reduced-risk claims and upselling of IQOS via Reviti life insurance. *Tobacco Control, 29*(e1), e136-e137. doi:10.1136/tobaccocontrol-2019-055145

Quisenberry, A. J., Koffarnus, M. N., Epstein, L. H., & Bickel, W. K. (2017). The Experimental Tobacco Marketplace II: Substitutability and sex effects in dual electronic cigarette and conventional cigarette users. *Drug and Alcohol Dependence, 178*, 551-555. doi:10.1016/j.drugalcdep.2017.06.004

Quisenberry, A. J., Koffarnus, M. N., Hatz, L. E., Epstein, L. H., & Bickel, W. K. (2016). The Experimental Tobacco Marketplace I: Substitutability as a function of the price of conventional cigarettes. *Nicotine & Tobacco Research, 18*(7), 1642-1648. doi:10.1093/ntr/ntv230

Reed, D. D., Naude, G. P., Salzer, A. R., Peper, M., Monroe-Gulick, A. L., Gelino, B. W., Harsin, J., Foster, R., Nighbor, T., Kaplan, B., Joffarnus,M., & Higgins, S. T. (2020). Behavioral economic measurement of cigarette demand: A descriptive review of published approaches to the cigarette purchase task. *Experimental and Clinical Psychopharmacology, 28*(6), 688-705. doi:10.1037/pha0000347

Rees, V. W., Kreslake, J. M., O'Connor, R. J., Cummings, K. M., Parascandola, M., Hatsukami, D., Shields, P., & Connolly, G. N. (2009). Methods used in internal industry clinical trials to assess tobacco risk reduction. *Cancer Epidemiology, Biomarkers & Prevention, 18*(12), 3196-3208. doi:10.1158/1055-9965.EPI-09-0819

Reilly, S. M., Goel, R., Bitzer, Z., Elias, R. J., Foulds, J., Muscat, J., & Richie, J. P. (2017). Effects of topography-related puff parameters on carbonyl delivery in mainstream cigarette smoke. *Chemical Research in Toxicology, 30*(7), 1463-1469. doi:10.1021/acs.chemrestox.7b00104

Rezk-Hanna, M., Doering, L., Robbins, W., Sarna, L., Elashoff, R. M., & Victor, R. G. (2018). Acute effect of hookah smoking on arterial stiffness and wave reflections in adults aged 18 to 34 Years of Age. *American Journal of Cardiology, 122*(5), 905-909. doi:10.1016/j.amjcard.2018.05.033

Richardson, A., Ganz, O., Pearson, J., Celcis, N., Vallone, D., & Villanti, A. C. (2015). How the industry is marketing menthol cigarettes: the audience, the message and the medium. *Tobacco Control, 24*(6), 594-600. doi:10.1136/tobaccocontrol-2014-051657

Risi, S. (2017). On the origins of the electronic cigarette: British American Tobacco's Project Ariel (1962-1967). *American Journal of Public Health, 107*(7), 1060-1067. doi:10.2105/AJPH.2017.303806

Rivas, T. (2023). *Here's Why Philip Morris Stock Was Upgraded Twice in One Week*. Barrons. https://www.barrons.com/articles/philip-morris-stock-upgrade-tobacco-51674661059

Robinson, R. J., Hensel, E. C., al-Olayan, A. A., Nonnemaker, J. M., & Lee, Y. O. (2018). Effect of e-liquid flavor on electronic cigarette topography and consumption behavior in a 2-week natural environment switching study. *PLoS One, 13*(5), e0196640. doi:10.1371/journal.pone.0196640

Roulet, S., Chrea, C., Kanitscheider, C., Kallischnigg, G., Magnani, P., & Weitkunat, R. (2019). Potential predictors of adoption of the IQOS Tobacco Heating System by US adult smokers: An actual use study. *F1000Res, 8*, 214. doi:10.12688/f1000research.17606.1

Rumney, E. (2023a). *Philip Morris signals slower US roll out for IQOS*. Reuters. https://www.reuters.com/markets/us/philip-morris-expands-smoke-free-ambition-updates-targets-2023-09-28/

Rumney, E. (2023b). *Focus: Big Tobacco turns to roibos tea to counter upcoming ban*. Reuters https://www.reuters.com/business/retail-consumer/big-tobacco-turns-rooibos-tea-counter-upcoming-ban-2023-10-16/#:~:text=LONDON%2C%20Oct%2016%20(Reuters),on%20flavoured%20heated%20tobacco%20products.

Rumney, E. (2024). *BAT shores up US heated tobacco prospects as competition grows.* Reuters. *https://www.reuters.com/business/retail-consumer/cigarette-giant-bat-makes-move-us-heated-tobacco-market-2024-02-08/*

Russell, M. A., Feyerabend, C., & Cole, P. V. (1976). Plasma nicotine levels after cigarette smoking and chewing nicotine gum. *British Medical Journal, 1*(6017), 1043-1046. doi:10.1136/bmj.1.6017.1043

Saha, P., Jain, S., Mukherjee, I., Panda, S. R., Zeki, A. A., Naidu, V. G. M., & Sharma, P. (2023). The effects of dual IQOS and cigarette smoke exposure on airway epithelial cells: Implications for lung health and respiratory disease pathogenesis. *European Respiratory Journal Open Research, 9*(3), 00558-2022. doi:10.1183/23120541.00558-2022

Samet, J. M., Pentz, M. A., & Unger, J. B. (2016). Flavoured tobacco products and the public's health: Lessons from the TPSAC menthol report. *Tobacco Control, 25*(Suppl 2), ii103. doi:10.1136/tobaccocontrol-2016-053208

Odani, S., Kanami, T., Agaku, I., & Tabuchi, T. (2023). Heated tobacco products do not help smokers quit or prevent relapse: a longitudinal study in Japan. *Tobacco Control*, Online ahead of print. doi:10.1136/tc-2022-057613

Selya, A., Foxon, F., Chandra, S., & Nealer, E. (2023). Meta-analysis of e-cigarette price elasticity. *F1000Research, 12*(121). doi:10.12688/f1000research.129233.1

Seo, H. G., Xu, S. S., Li, G., Gravely, S., Quah, A. C. K., Lee, S., Lim, S., Cho, S., Kim, Y., Lee, E., Choi, Y., Miller, C., Goniewicz, M., O'Connor, R. J., & Fong, G. T. (2023). Reasons for initiation and regular use of heated tobacco products among current and former smokers in South Korea: Findings from the 2020 ITC Korea Survey. *International*

Journal of Environmental Reseach and Public Health, 20(6), 4963. doi:10.3390/ijerph20064963

Serre, F., Fatseas, M., Debrabant, R., Alexandre, J.-M., Auriacombe, M., & Swendsen, J. (2012). Ecological momentary assessment in alcohol, tobacco, cannabis and opiate dependence: A comparison of feasibility and validity. *Drug and Alcohol Dependence, 126*(1), 118-123. doi:10.1016/j.drugalcdep.2012.04.025

Shiffman, S. (2009a). Ecological momentary assessment (EMA) in studies of substance use. *Psychological Assessment, 21*(4), 486-497. doi:10.1037/a0017074

Shiffman, S. (2009b). How many cigarettes did you smoke? Assessing cigarette consumption by global report, Time-Line Follow-Back, and ecological momentary assessment. *Health Psychology, 28*(5), 519-526. doi:10.1037/a0015197

Shiffman, S., Brockwell, S. E., Pillitteri, J. L., & Gitchell, J. G. (2008). Use of smoking-cessation treatments in the United States. *American Journal of Preventive Medicine, 34*(2), 102-111. doi:10.1016/j.amepre.2007.09.033

Shiffman, S., Engberg, J. B., Paty, J. A., Perz, W. G., Gnys, M., Kassel, J. D., & Hickcox, M. (1997). A day at a time: predicting smoking lapse from daily urge. *Journal of Abnormal Psychology, 106*(1), 104-116. doi:10.1037/0021-843x.106.1.104

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology, 4*(1), 1-32. doi:10.1146/annurev.clinpsy.3.022806.091415

Shihadeh, A., & Eissenberg, T. (2015). Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. *Nicotine & Tobacco Research, 17*(2), 158-162. doi:10.1093/ntr/ntu175

Shihadeh, A., Azar, S., Antonios, C., & Haddad, A. (2004). Towards a topographical model of narghile water-pipe café smoking: a pilot study in a high socioeconomic status neighborhood of Beirut, Lebanon. *Pharmacology Biochemistry and Behavior, 79*(1), 75-82. doi:https://doi.org/10.1016/j.pbb.2004.06.005

Simonavicius, E., McNeill, A., Shahab, L., & Brose, L. S. (2019). Heat-not-burn tobacco products: a systematic literature review. *Tobacco Control, 28*(5), 582-594. doi:10.1136/tobaccocontrol-2018-054419

Simpson, G. G. (2020). *Philip Morris reveals RRP of its menthol ban-busting IQOS Kit*. Asian Trader. https://www.asiantrader.biz/philip-morris-reveals-rrp-of-its-menthol-ban-busting-iqos-kit/

Singh, J. (2014). Randomization and online databases for clinical trials. *Journal of Pharmacology and Pharmacotherapies, 5*(2), 173-174. doi:10.4103/0976-500X.130155.

Smith, P. H., Assefa, B., Kainth, S., Salas-Ramirez, K. Y., McKee, S. A., & Giovino, G. A. (2020). Use of mentholated cigarettes and likelihood of smoking cessation in the United States: A meta-analysis. *Nicotine & Tobacco Research, 22*(3), 307-316. doi:10.1093/ntr/ntz067

Sobell, L. C., Sobell, M. B., Buchan, G., Cleland, P. A., Fedoroff, I., & Leo, G. I. (1996). *The reliability of the timeline followback method applied to drug, cigarette, and cannabis use.* Presented at the 30th Annual Meeting of the Association for Advancement of Behavior Therapy. New York, NY. https://www.nova.edu/gsc/forms/TLFBDrugCigMJoverview.pdf

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R. Z. Litten & J. P. Allen (Eds.), *Measuring Alcohol Consumption* (pp. 41-72). Totowa, NJ: Humana Press.

Soussy, S., El-Hellani, A., Baalbaki, R., Salman, R., Shihadeh, A., & Saliba, N. A. (2016). Detection of 5-hydroxymethylfurfural and furfural in the aerosol of electronic cigarettes. *Tobacco Control, 25*(suppl 2), ii88-ii93. doi:10.1136/tobaccocontrol-2016-053220

Spindle, T. R., Breland, A. B., Karaoghlanian, N. V., Shihadeh, A. L., & Eissenberg, T. (2015). Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and self-reported effects. *Nicotine & Tobacco Research, 17*(2), 142-149. doi:10.1093/ntr/ntu186

Spindle, T. R., Hiler, M. M., Breland, A. B., Karaoghlanian, N. V., Shihadeh, A. L., & Eissenberg, T. (2017). The influence of a mouthpiece-based topography measurement device on electronic cigarette user's plasma nicotine concentration, heart rate, and self-reported effects under rirected and ad libitum use conditions. *Nicotine & Tobacco Research, 19*(4), 469-476. doi:10.1093/ntr/ntw174

Squier, C. A., Mantz, M. J., & Wertz, P. W. (2010). Effect of menthol on the penetration of tobacco carcinogens and nicotine across porcine oral mucosa ex vivo. *Nicotine & Tobacco Research, 12*(7), 763-767. doi:10.1093/ntr/ntq084

St Helen, G., Dempsey, D. A., Havel, C. M., Jacob III, P., & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug and Alcohol Dependence, 178*, 391-398. doi:10.1016/j.drugalcdep.2017.05.042

St Helen, G., Jacob III, P., Nardone, N., & Benowitz, N. L. (2018). IQOS: examination of Philip Morris International's claim of reduced exposure. *Tobacco Control, 27*(suppl 1), s30-s36. doi:10.1136/tobaccocontrol-2018-054321

St Helen, G., Shahid, M., Chu, S., & Benowitz, N. L. (2018). Impact of e-liquid flavors on e-cigarette vaping behavior. *Drug and Alcohol Dependence, 189*, 42-48. doi:10.1016/j.drugalcdep.2018.04.032

Stead, L. F., Perera, R., Bullen, C., Mant, D., Hartmann-Boyce, J., Cahill, K., & Lancaster, T. (2012). Nicotine replacement therapy for smoking cessation. *Cochrane Database Systematic Reviews, 11*, CD000146. doi:10.1002/14651858.CD000146.pub4

Stein, J. S., Koffarnus, M. N., Snider, S. E., Quisenberry, A. J., & Bickel, W. K. (2015). Identification and management of nonsystematic purchase task data: Toward best practice. *Experimental and Clinical Psychopharmacology, 23*(5), 377-386. doi:10.1037/pha0000020

Stoklosa, M., Cahn, Z., Liber, A., Nargis, N., & Drope, J. (2019). Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. *Tobacco Control, 29*(4), 381-387. doi:10.1136/tobaccocontrol-2019-054998

Stoklosa, M., Drope, J., & Chaloupka, F. J. (2016). Prices and e-cigarette demand: Evidence from the European Union. *Nicotine & Tobacco Research, 18*(10), 1973-1980. doi:10.1093/ntr/ntw109

Stone, M. D., DeAtley, T., Pianin, S., Strasser, A. A., & Audrain-McGovern, J. (2022). Switching from cigarettes to IQOS: A pilot examination of IQOS-associated reward, reinforcement, and abstinence relief. *Drug and Alcohol Dependence, 238*, 109569. doi:10.1016/j.drugalcdep.2022.109569

Sohal, S. S., Mathew, S. E., Vegi, G., & Pawan, S. (2019). IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. *European*

Respiraotry Journal Open Research, 5(1), 0015-02018. doi:10.1183/23120541.00159-2018

Sun, T., Anandan, A., Lim, C. C. W., East, K., Xu, S. S., Quah, A. C. K., Rutherfurd, B., Johnson, B., Qi, Y., Stjepanovic, D., Leung, J., Connor, J., Gartner, C., Hall, W., Vu, G., & Chan, G. C. K. (2023). Global prevalence of heated tobacco product use, 2015-22: A systematic review and meta-analysis. *Addiction, 118*(8), 1430-1444. doi:10.1111/add.16199

Sutanto, E., Miller, C., Smith, D. M., Borland, R., Hyland, A., Cummings, K. M., Quah, A., Xu, S., Fong, G., Ouimet, J., Yoshimi, I., Mochizuki, Y., Tabuchi, T., O'Connor, R., & Goniewicz, M. L. (2020). Concurrent daily and non-daily use of heated tobacco products with combustible cigarettes: Findings from the 2018 ITC Japan Survey. *International Journal of Environmental Research and Public Health, 17*(6), 2098. doi:10.3390/ijerph17062098

Sutanto, E., Miller, C., Smith, D. M., O'Connor, R. J., Quah, A. C. K., Cummings, K. M., Xu, S., Fong, G., Hyland, A., Ouimet, J., Yoshimi, I., Mochizuki, Y., Tabuchi, T., & Goniewicz, M. L. (2019). Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan Survey. *International Journal of Environmental Resrach and Public Health, 16*(23), 4630. doi:10.3390/ijerph16234630

Suzuki, H., Aono, N., Zhang, Y., Yuri, K., Bassole Epse Brou, M. A. M., Takemura, S., .Higashiyama, A., Tabuchi, T., & Fujiyoshi, A. (2023). Comparison of publications on heated tobacco products with conventional cigarettes and implied desirability of the products according to tobacco industry affiliation: A Systematic Review. *Nicotine & Tobacco Research,* Online ahead of print. doi:10.1093/ntr/ntad205

Talhout, R., Richter, P. A., Stepanov, I., Watson, C. V., & Watson, C. H. (2018). Cigarette design features: Effects on emission levels, user perception, and behavior. *Tobacco Regulatory Science, 4*(1), 592-604. doi:10.18001/TRS.4.1.6

Talhout, R., van de Nobelen, S., & Kienhuis, A. S. (2016). An inventory of methods suitable to assess additive-induced characterising flavours of tobacco products. *Drug and Alcohol Dependence, 161*, 9-14. doi:10.1016/j.drugalcdep.2015.12.019

Talluri, R., & Shete, S. (2023). Sociodemographic differences in menthol cigarette use in the United States. *Substance Abuse, 44*(1-2), 91-95. doi:10.1177/08897077231174683

Tattan-Birch, H., Hartmann-Boyce, J., Kock, L., Simonavicius, E., Brose, L., Jackson, S., Shahab, L., & Brown, J. (2022). Heated tobacco products for smoking cessation and reducing smoking prevalence. *Cochrane Database Systematic Review, 1*(1), CD013790. doi:10.1002/14651858.CD013790.pub2

Theis, L. (2023). *What role will heated tobacco products have if there is a menthol ban?* Scripps News. https://scrippsnews.com/stories/what-role-will-heated-tobacco-products-have-if-there-is-a-menthol-ban/

Theodoulou, A., Chepkin, S. C., Ye, W., Fanshawe, T. R., Bullen, C., Hartmann-Boyce, J., Lingstone-Banks, J., Hajizadeh, A., & Lindson, N. (2023). Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews 2023*(6), CD013308. doi:10.1002/14651858.CD013308.pub2

Tobacco Reporter. (2023). *PMI Applies to Sell IQOS ILUMA in the US.* https://tobaccoreporter.com/2023/10/21/pmi-applies-to-sell-iqos-iluma-in-the-u-s/

Tompkins, C. N. E., Burnley, A., McNeill, A., & Hitchman, S. C. (2020). Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of IQOS users and ex-users in the UK. *Tobacco Control, 30*(1), 16-23. doi:10.1136/tobaccocontrol-2019-055306

Uchiyama, S., Noguchi, M., Takagi, N., Hayashida, H., Inaba, Y., Ogura, H., & Kunugita, N. (2018). Simple determination of gaseous and particulate compounds generated from heated tobacco products. *Chemical Research in Toxicology, 31*(7), 585-593. doi:10.1021/acs.chemrestox.8b00024

United States v. Philip Morris USA Inc., et al. (2023). Civil Action No. 99-CV-2496. https://assets.tobaccocontrollaws.org/uploads/litigation/United%20States/US_20230714_US-v.-Philip-Morris_2023-07-17-142120_bicv.pdf

University of Bath. (2023). *Heated Tobacco Products*. Tobacco Tactics. https://tobaccotactics.org/article/heated-tobacco-products/

Upadhyay, S., Rahman, M., Johanson, G., Palmberg, L., & Ganguly, K. (2023). Heated tobacco products: Insights into composition and toxicity. *Toxics, 11*(8), 667. doi:10.3390/toxics11080667

Valentine, G. W., DeVito, E. E., Jatlow, P. I., Gueorguieva, R., & Sofuoglu, M. (2018). Acute effects of inhaled menthol on the rewarding effects of intravenous nicotine in smokers. *Journal of Psychopharmacology, 32*(9), 986-994. doi:10.1177/0269881118773972

Vansickel, A. R., Cobb, C. O., Weaver, M. F., & Eissenberg, T. E. (2010). A clinical laboratory model for evaluating the acute effects of electronic “cigarettes”: Nicotine delivery profile and cardiovascular and self-reported effects. *Cancer Epidemiology Biomarkers & Prevention, 19*(8), 1945-1953. doi:10.1158/1055-9965.EPI-10-0288

Vansickel, A., Baxter, S., Sherwood, N., Kong, M., & Campbell, L. (2021). Human abuse liability assessment of tobacco and nicotine products: Approaches for meeting current regulatory recommendations. *Nicotine & Tobacco Research, 24*(3), 295-305. doi:10.1093/ntr/ntab183

Vapour Core. (2023). *IQOS HEETS Mixed Carton - 200 Sticks*. https://www.vapourcore.com/products/iqos-heets-mixed-carton-200-sticks

Villanti, A. C., Collins, L. K., Niaura, R. S., Gagosian, S. Y., & Abrams, D. B. (2017). Menthol cigarettes and the public health standard: a systematic review. *BMC Public Health, 17*(1), 983. doi:10.1186/s12889-017-4987-z

Voos, N., Smith, D., Kaiser, L., Mahoney, M. C., Bradizza, C. M., Kozlowski, L. T., Benowitz, N. L., O'Connor, R. J., & Goniewicz, M. L. (2020). Effect of e-cigarette flavors on nicotine delivery and puffing topography: results from a randomized clinical trial of daily smokers. *Psychopharmacology, 237*(2), 491-502. doi:10.1007/s00213-019-05386-x

Vorster, P. M., Masahi, M; Mills, C., Erskine, A., Baig, F., & Eggleton, M. (2017). *Global Tobacco Equity Research*. https://research-doc.credit-suisse.com/docView?language=ENG&format=PDF&sourceid=emgpm&document_id=1074879641&serialid=a0FCDbxi6cVHayw5Rry84yUAqI4VKH8vmB2r7c3VMf8%3D&cspId=null

Wackowski, O. A., Delnevo, C. D., & Pearson, J. L. (2015). Switching to e-cigarettes in the event of a menthol cigarette ban. *Nicotine & Tobacco Research, 17*(10), 1286-1287. doi:10.1093/ntr/ntv021

Wackowski, O., & Delnevo, C. D. (2007). Menthol cigarettes and indicators of tobacco dependence among adolescents. *Addictive Behaviors, 32*(9), 1964-1969. doi:10.1016/j.addbeh.2006.12.023

Wadgave, U., & Nagesh, L. (2016). Nicotine replacement therapy: An overview. *International Journal of Health Sciences, 10*(3), 425-435. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003586/

Wadkin, R., Allen, C., & Fearon, I. M. (2023). E-cigarette puffing topography: The importance of assessing user behaviour to inform emissions testing. *Drug Testing and Analysis, 15*(10), 1222-1232. doi:https://doi.org/10.1002/dta.3322

Wagener, T. L., Avery, J. A., Leavens, E. L. S., & Simmons, W. K. (2021). Associated changes in e-cigarette puff duration and cigarettes smoked per day. *Nicotine & Tobacco Research, 23*(4), 760-764. doi:10.1093/ntr/ntaa211

Wailoo, K. (2022). *Pushing Cool*: *Big Tobacco, Racial Marketing, and the Untold Story of the Menthol Cigarette.* University of Chicago Press: Chicago, IL.

Wall, C. S., Bono, R. S., Lester, R. C., Hoetger, C., Lipato, T., Guy, M. C., Eissenberg, T., Bickel, W. K., Barnes, A. J., & Cobb, C. O. (2018). Triangulating abuse liability assessment for flavoured cigar products using physiological, behavioural economic and subjective assessments: a within-subjects clinical laboratory protocol. *British Medical Journal Open, 8*(10), e023850. doi:10.1136/bmjopen-2018-023850

Wang, T. W., Marynak, K. L., Gentzke, A. S., & King, B. A. (2019). *Awareness and ever use of heated tobacco products among US adults, 2018*. Paper presented at the Society for Reserach on Nicotine and Tobacco Annual Meeting. San Fransico, CA.

Wang, T., Wang, B., & Chen, H. (2014). Menthol facilitates the intravenous self-administration of nicotine in rats. *Frontiers in Behavioral Neuroscience, 8*, 437. doi:10.3389/fnbeh.2014.00437

Watson, C. V., Richter, P., de Castro, B. R., Sosnoff, C., Potts, J., Clark, P., McCraw, J., Yan, X., Chambers, D., & Watson, C. (2017). Smoking behavior and exposure: Results of a menthol cigarette cross-over study. *American Journal on Health Behaviors, 41*(3), 309-319. doi:10.5993/AJHB.41.3.10

West, R., Hajek, P., Foulds, J., Nilsson, F., May, S., & Meadows, A. (2000). A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology, 149*(3), 198-202. doi:10.1007/s002130000382

White, A. M., Goden, A. B., Rudy, A. K., Bajwa, H. K., Guy, M. C., Hood, K. B., Cobb, C. O., & Barnes, A. J. (2023). Responses of African American individuals who use menthol cigarettes to potential flavored tobacco bans. *American Journal of Preventive Medicine, 64*(6), 898-901. doi:10.1016/j.amepre.2022.12.005

White, A. M., Barnes, A. J., & Garner, W. (2023). Racial/ethnic differences in the association between menthol cigarette use and mental illness among adults who smoke in the United States. *Journal of Ethnicity in Substance Abuse*, Online ahead of print. doi:10.1080/15332640.2023.2196645

White, A. M., Patev, A., Imran, R., Goden, A., Bajwa, H., Hood, K., Guy, M., Cobb, C., and Barnes, A. J. (2024). Impact of smoking cessation motivations and barriers on quit intentions following a hypothetical flavor ban among African American/Black individuals that use menthol cigarettes: A mixed methods study. *Nicotine & Tobacco Research,* In press.

White, V. M., White, M. M., Freeman, K., Gilpin, E. A., & Pierce, J. P. (2006). Cigarette promotional offers: Who takes advantage? *American Journal of Preventive Medicine, 30*(3), 225-231. doi:https://doi.org/10.1016/j.amepre.2005.11.001

Wickham, R. J. (2020). The biological impact of menthol on tobacco dependence. *Nicotine & Tobacco Research, 22*(10), 1676-1684. doi:10.1093/ntr/ntz239

Williams, J. M., Gandhi, K. K., Steinberg, M. L., Foulds, J., Ziedonis, D. M., & Benowitz, N. L. (2007). Higher nicotine and carbon monoxide levels in menthol cigarette smokers with and without schizophrenia. *Nicotine & Tobacco Research, 9*(8), 873-881. doi:10.1080/14622200701484995

Wilson, A. G., Franck, C. T., Koffarnus, M. N., & Bickel, W. K. (2016). Behavioral economics of cigarette purchase tasks: Within-subject comparison of real, potentially real, and hypothetical cigarettes. *Nicotine & Tobacco Research, 18*(5), 524-530. doi:10.1093/ntr/ntv154

Wipfli, H. L., Berman, M., Hanson, K., Kelder, S., Solis, A., Villanti, A. C., Ribeiro, C., Meissner, H., & Anderson, R. (2017). Defining tobacco regulatory science competencies. *Nicotine & Tobacco Research, 19*(2), 222-230. doi:10.1093/ntr/ntw178

Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. (2006). Drugbank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Research*, D668-72. 16381955. https://go.drugbank.com/drugs/DB00825

World Health Organization. (2021). *Report on the scientific basis of tobacco product regulation (Vol. 8).* Geneva, SW: World Health Organization. https://www.who.int/publications/i/item/9789240022720

World Health Organization. (2023). *Heated tobacco products: summary of research and evidence of health impacts.* Geneva, SW: World Health Organization. https://www.who.int/publications-detail-redirect/9789240042490

Yan, X. S., & D'Ruiz, C. (2015). Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regulatory Toxicology and Pharmacology, 71*(1), 24-34. doi:10.1016/j.yrtph.2014.11.004 [doi]

Yang, Y., Lindblom, E. N., Ward, K. D., & Salloum, R. G. (2022). How smokers of menthol cigarettes and flavored cigars might respond to FDA's proposed bans. *Nicotine & Tobacco Research*, *24*(10), 1645-1653. doi:10.1093/ntr/ntac078

Yasiejko, C. (2023). *Philip Morris Loses Bid to Flip Ban of Its Heated-Tobacco Sticks*. Bloomberg Law. https://news.bloomberglaw.com/ip-law/philip-morris-loses-bid-to-flip-ban-of-its-heated-tobacco-sticks

Yerger, V. B. (2002). African American leadership groups: smoking with the enemy. *Tobacco Control, 11*(4), 336-345. doi:10.1136/tc.11.4.336

Yerger, V. B., & McCandless, P. M. (2011). Menthol sensory qualities and smoking topography: a review of tobacco industry documents. *Tobacco Control, 20*(suppl_2), ii37-ii43. doi:10.1136/tc.2010.041988

Yerger, V. B., Przewoznik, J., & Malone, R. E. (2007). Racialized geography, corporate activity, and health disparities: tobacco industry targeting of inner cities. *Journal of Health Care for the Poor and Underserved, 18*(suppl 4), 10-38. doi:10.1353/hpu.2007.0120

Yingst, J. M., Bordner, C., Hrabovsky, S., Hobkirk, A. L., Trushin, N., Richie, J. P., & Foulds, J. (2023). Nicotine delivery of a menthol-flavored heat-not-burn tobacco product during

directed use. *Nicotine & Tobacco Research,* Online ahead of print. doi:10.1093/ntr/ntad119

Yingst, J., Midya, V., White, A., Foulds, J., Cobb, C., Veldheer, S., Miao-Shan, Y., & Eissenberg, T. (2024). Effects of liquid nicotine concentration and flavor on the acceptability of electronic nicotine delivery systems (ENDS) among people who smoke participating in a randomized controlled trial to reduce cigarette consumption. *Tobacco Control,* In press.

Yuki, D., Takeshige, Y., Nakaya, K., & Futamura, Y. (2018). Assessment of the exposure to harmful and potentially harmful constituents in healthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence. *Regulatory Toxicology and Pharmacology, 96*, 127-134. doi:https://doi.org/10.1016/j.yrtph.2018.05.001

Zare, S. A., Nemati, M., & Zheng, Y. (2018). A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type. *Plos ONE, 13*(3), e0194145. doi:10.1371/journal.pone.0194145

Znyk, M., Jurewicz, J., & Kaleta, D. (2021). Exposure to heated tobacco products and adverse health effects, a systematic review. *International Journal of Environmental Research and Public Health, 18*(12), 6651. doi:10.3390/ijerph18126651

Zuck, K. (2018). *Evidence related to the health risk of IQOS use: evaluation of product chemistry*. Food and Drug Administration, Center for Tobacco Products. https://www.fda.gov/media/110744/download

Appendix 1. In-Person Screening Questionnaire

Demographics		
Today's date	MM/DD/YYYY	
Do you read and write in English?	1 = Yes 0 = No	
What is your date of birth?	MM/DD/YYYY	https://www.phenxtoolkit.org/protocols/view/10101
What is your gender identity?	Text	
What was your sex assigned at birth?	1 = Male 2 = Female 3 = Intersex	
What pronouns do you use?	Text	
Are you currently pregnant, breastfeeding, or intending to become pregnant in the next three months? [if sex assigned at birth = female or intersex]	1 = Yes 0 = No 2 = Does not apply to me	
Are you currently using birth control or other contraceptive methods (e.g., condoms) to prevent pregnancy? [if sex assigned at birth = female or intersex]	1 = Yes 0 = No 2 = Does not apply to me	
We would like to know what you do – are you working now, looking for work, retired, keeping house, a student or what?	1 = Working now 2 = Only temporarily laid off, sick leave or maternity leave 3 = Looking for work, unemployed 4 = Retired 5 = Disabled, permanently or temporarily 6 = Keeping house 7 = Student 8 = Other	https://www.phenxtoolkit.org/protocols/view/11301
What is the highest grade or level of school you have completed or the highest degree you have received?	0 = Never attended/ Kindergarten only 1 = 1st grade 2 = 2nd grade 3 = 3rd grade 4 = 4th graded 5 = 5th grade 6 = 6th grade 7 = 7th grade 8 = 8th grade 9 = 9th grade 10 = 10th grade	https://www.phenxtoolkit.org/protocols/view/11001

	11 = 11th grade 12 = 12th grade 13 = High school graduate 14 = GED or equivalent 15 = Some college, no degree 16 = Associates degree: occupational, technical, or vocational program 17 = Associates degree: academic program 18 = Bachelor's degree (example, BA, AB, BS, BBA) 19 = Master's Degree (example: MA, MS, MEng, MEd, MBA) 20 = Professional school degree (example: MD, DDS, DVM, JD) 21 = Doctoral degree (example, PhD, EdD)	
Are you...	1 = Married 2 = Divorced 3 = Widowed 4 = Separated 5 = Never married 6 = A member of an unmarried couple	https://www.phenxtoolkit.org/protocols/view/10903
Which race best describes you? (You can choose more than one.)	1 = White or Caucasian 2 = Black or African American 3 = Asian 4 = Middle Eastern 5 = American Indian or Alaskan Native 6 = Native Hawaiian or Other Pacific Islander 7 = Other (please specify): _____	
Do you consider yourself to be Hispanic, Latino, or of Spanish origin?	1=Yes 0=No 4 = Don't know	https://www.phenxtoolkit.org/protocols/view/10502
The next questions are about your total family income in the past year. Income is important in analyzing the health information we collect. Please be assured that, like all other information you have provided, these	Text (integer)	https://www.phenxtoolkit.org/protocols/view/11101

answers will be kept strictly confidential. When answering these questions, please remember that by "combined family income," I mean your income PLUS the income of all family members living in your household (including cohabitating partners, and armed forces members living at home). What is your best estimate of the total income of all family members from all sources, before taxes, in the last year?		
Was your total family income from all sources less than $50,000 or $50,000 or more? [if above income question is left blank]	1 = Less than $50,000 2 = $50,000 or more 3 = Don't know	https://www.phenxtoolkit.org/protocols/view/11101
Has anyone else in your household participated in this study?	1=Yes 0=No	

Health and Medical History		
Do you have a <u>recent</u> or <u>current</u> diagnosis from a doctor, nurse, or other healthcare provider for the following health conditions? Heart attack Angina or coronary heart disease Stroke Seizures Asthma COPD – chronic obstructive pulmonary disease Immune system disorder Cancer Diabetes Kidney disease Liver disease Low blood pressure High blood pressure Food/chemical allergies Any other medical conditions (please specify):____	0=No 1=Yes Asked for each condition listed	P3-Flux
For each condition: Date of Onset Ongoing Condition: Yes/No Please describe any current symptoms and/or treatment in the past week	text/date field (embedded fields table)	P50-P3 RCT
Do you have any current, diagnosed psychiatric conditions?	1 = Yes 0 = No	P3-Flux
If yes: Condition Name Date of Onset Ongoing Condition: Yes/No Please describe any current symptoms and/or treatment in the past week	text/date field (embedded fields table)	P50-P3 RCT
Have you been to the emergency room and/or been hospitalized for a psychiatric condition in the past year?	1 = Yes 0 = No	
Are you taking any prescription or over-the-counter medications on a regular basis?	1 = Yes 0 = No	P50-P3 RCT
For each medicine: Medication Name Indication Dose Frequency Start Date End Date Ongoing Use: Yes/No	text/date field (embedded fields table)	P50-P3 RCT

Non-Tobacco Drug & Alcohol Use		
In your entire life, have you had at least 1 drink of any kind of alcohol, not counting small tastes or sips?	1 = Yes 0 = No	https://www.phenxtoolkit.org/protocols/view/30101
Think specifically about the past 30 days, from [DATEFILL*], up to and including today. During the past 30 days, on how many days did you drink one or more drinks of an alcoholic beverage? [if yes to ever drinking]	# OF DAYS: ____ [RANGE: 0 - 30]	https://www.phenxtoolkit.org/protocols/view/30101
On the days that you drank during the past 30 days, how many **drinks** did you **usually** have each day? Count as a drink a can or bottle of beer; a wine cooler or a glass of wine, champagne, or sherry; a shot of liquor or a mixed drink or cocktail. [if yes to ever drinking]	# OF DRINKS: ____ [RANGE: 0 - 50]	https://www.phenxtoolkit.org/protocols/view/30101
Have you EVER used **Marijuana, including THC**, for example…weed, pot, dope, hashish, Mary Jane, joint, blunt?	1 = Yes 0 = No	https://www.phenxtoolkit.org/protocols/view/30101
Think specifically about the past 30 days, from [DATEFILL**] up to and including today. During the past 30 days, on how many days did you use marijuana? [if yes to ever marijuana]	# OF DAYS: _____ [RANGE: 0-30]	https://www.phenxtoolkit.org/protocols/view/30101
Have you used any other recreational drugs within the past 30 days?	1 = Yes 0 = No	
Please identify which drug or drugs: (If yes to past 30 day recreational drug use)	text	

Tobacco Use History		
Cigarette Smoking		
Have you ever tried cigarette smoking, even one or two puffs?	1 = Yes 0 = No	https://www.phenxtoolkit.org/protocols/view/30604
Have you smoked cigarettes in the past 30 days? (If yes to ever cigarette use)	1 = Yes 0 = No	https://www.phenxtoolkit.org/protocols/view/741401
Do you now smoke cigarettes every day, some days, or not at all? (If yes to past 30 days and yes to ever use)	1 = Every day 2 = Some days 3 = Not at all	https://www.phenxtoolkit.org/protocols/view/30604
On average, on the days that you smoke, about how many cigarettes do you smoke per day? (Every day/some day smokers)	____ cigarettes per day	
For how long have you smoked this number? (Every day/ some day smokers)	1= Days 2= Months 3= Years	
Please provide the number of [cig_dmy]:	Text (integer)	
Are currently smoking at least 5 cigarettes per day on average, and have smoked this amount for at least 1 year?	1 = Yes 0= No	
What brand of cigarettes do you use most often? (If yes to past 30 days and yes to ever use)	_____Brand Name _____Size (short, regular, 100, etc.) _____Pack Color	
Is your regular brand you smoke flavored to taste like menthol or mint? [If yes to past 30 days and yes to ever use]	1 = Yes 0 = No	PATH
Do you intend to quit smoking anytime within the next 3 months?	1 = Yes 0 = No	
Have you EVER made a serious attempt to stop smoking because you were TRYING to quit -- even if you stopped for less than a day?	1 = Yes 0 = No	CPS-TUS
During any of your past quit attempts, did you use any of the following: • telephone help line or quit line	1 = Yes 0 = No	2018-2019 CPS-TUS

• one-on-one counseling by a health professional • a stop smoking clinic, class, or support group • internet or web-based program • smartphone apps and text messaging programs • nicotine patch • nicotine gum/lozenge • nicotine nasal spray • nicotine inhaler • Chantix or Varenicline • Zyban, Buproprion or Wellbutrin	Asked for each individual item	
Other Tobacco/Nicotine Use		
Which, if any, of the following tobacco or nicotine products have you **ever** used or tried? Please select all that apply. For cigars/cigarillos, pipe, hookah/shisha, and heated tobacco products, count even one puff. Please note these questions only regard your use of tobacco products alone NOT in combination with marijuana, cannabis, or hashish.	1 = Electronic cigarettes or e-cigarettes/vapes (JUUL, Blu, Avail) 2 = Traditional cigars (Macanudo, Romeo y Julieta, or Arturo Fuente) 3 = Pipe (with tobacco) 4 = Cigarillos/filtered cigars (like Black & Mild, Swisher Sweets, or Phillies Blunt) 5 = Smokeless tobacco, such as chewing tobacco, dip, snuff, or snus (like Levi Garrett, Red Man, or Beech Nut, Skoal or Copenhagen) 6 = Hookah/shisha (hookah tobacco) 7 = Nicotine replacement products (like gum, patches, lozenges) 8 = Heated tobacco products (IQOS/Heatsticks)	P3-Flux
During the **last 30 days**, on how many days have you used any of the following tobacco/nicotine products? For cigars/cigarillos, pipe, hookah/shisha, and heated tobacco products, count even one puff. Please note these questions only regard your use of tobacco products alone NOT in combination with marijuana, cannabis, or hashish.	[each product indicated above]:number of days ___ (range 0-30) 1 = Electronic cigarettes or e-cigarettes/vapes (JUUL, Blu, Avail) 2 = Traditional cigars (Macanudo, Romeo y Julieta, or Arturo Fuente) 3 = Pipe (with tobacco)	P3-Flux

	4 = cigarillos/filtered cigars (like Black & Milds, Swisher Sweets, or Phillies Blunt) 5 = Smokeless tobacco, such as chewing tobacco, dip, snuff, or snus (like Levi Garrett, Red Man, or Beech Nut, Skoal or Copenhagen) 6 = Hookah/shisha (hookah tobacco) 7 = Nicotine replacement products (like gum, patches, lozenges) 8 = Heated tobacco products (IQOS/Heatsticks)	
How many times in your lifetime have you used a heated tobacco product like IQOS? [If ever use to Heated Tobacco Products]	0=1 time 1=2-10 times 2= >10 times	
In the past 30 days, were any of the non-cigarette tobacco products you used flavored to taste like menthol, mint, clove, spice, fruit, chocolate, alcoholic drinks, candy or other sweets? (logic = only if used other tobacco products 1 or more days)	1 = Yes 0 = No	https://www.phenxtoolkit.org/protocols/view/720601
Which flavors have you used in the past 30 days? Choose all that apply. (if yes to above)	• Menthol • Mint • Clove or spice • Fruit • Chocolate • An alcoholic drink (such as wine, cognac, margarita or other cocktails) • Candy or other sweets • Tobacco flavor • Some other flavor Specify :_____ (if selected participant is prompted to write in name)	https://www.phenxtoolkit.org/protocols/view/720601
During a typical week how much do you spend on all tobacco/nicotine products (US Dollars [$]))?	[free text – numbers only]	
Reasons for flavored tobacco use		

Preamble Text: The next questions are about the reasons people use flavored tobacco products (including menthol or mint flavored cigarettes). Please select which reasons apply to you. I use flavored tobacco products because…		Andrew CASEL Flavors Working Group – updated 01/20/21
1. They comes in flavors I like.	1 = Yes 0 = No	
2. Flavored tobacco products are easier to smoke compared to the same product that is tobacco flavored or unflavored.	1 = Yes 0 = No	
3. Flavored tobacco products might be less harmful to me compared to the same product that is tobacco flavored or unflavored.	1 = Yes 0 = No	
4. I like the way flavored tobacco products smell.	1 = Yes 0 = No	
5. Flavored tobacco products are more affordable than other tobacco products.	1 = Yes 0 = No	
6. Using flavored tobacco products helps people quit smoking cigarettes.	1 = Yes 0 = No	
7. Flavored tobacco products don't er non-tobacco users.	1 = Yes 0 = No	
8. I find flavored tobacco products more appealing than the tobacco flavored or unflavored version.	1 = Yes 0 = No	

PROMIS: Smoking: Nicotine Dependence of Daily and Nondaily Smokers- Short Form 4a		https://www.rand.org/health-care/projects/promis-smoking-initiative/item-banks-short-forms.html
When I haven't been able to smoke for a few hours, the craving gets intolerable	0 = Never 1 = Rarely 2 = Sometimes 3 = Often 4 = Almost Always	
I find myself reaching for cigarettes without thinking about it.	0 = Never 1 = Rarely 2 = Sometimes 3 = Often 4 = Almost Always	
I drop everything to go out and buy cigarettes.	0 = Never 1 = Rarely 2 = Sometimes 3 = Often 4 = Almost Always	
I smoke more before going into a situation where smoking is not allowed.	0 = Never 1 = Rarely 2 = Sometimes 3 = Often 4 = Almost Always	

Penn State Dependence Index		
How many cigarettes per day do you usually smoke?	0 = 0-4 time/day 1 = 5-9 2 = 10-14 3 = 15-19 4 = 20-29 5 = 30 or more	https://research.med.psu.edu/smoking/dependence-index/
On days that you can smoke freely, how soon after you wake up do you smoke your first cigarette of the day?	5 = less than 5 minutes 4 = 6-15 minutes 3 = 16-30 minutes 2 = 31-60 minutes 1 = 61-120 minutes 0 = more than 121 minutes	

Do you sometimes awaken at night to have a cigarette?	1 = Yes 0 = No	
If yes, how many nights per week do you typically awaken to smoke?	0 = 0-1 nights 1 = 2-3 nights 2 = 4 or more nights	
Do you smoke now because it is really hard to quit?	1 = Yes 0 =No	
Do you ever have strong cravings to smoke?	1 = Yes 0 = No	
Over the past week, how strong have the urges to smoke been?	0 = None/Slight 1 = Moderate/Strong 2 = Very Strong/Extremely Strong	
Is it hard to keep from smoking in places where you are not supposed to?	1 = Yes 0 = No	
When you haven't used tobacco for a while or when you tried to stop smoking: Did you feel more irritable because you couldn't smoke?	1 = Yes 0 = No	
When you haven't used tobacco for a while or when you tried to stop smoking: Did	1 = Yes 0 = No	

you feel nervous, restless, or anxious because you couldn't smoke?		

Contact Information		
Instructions: Please note all of this information is kept confidential and is only used for study-related purposes.		
What is your first name?	Text	
What is your last name?	Text	
Do you have a preferred name or nickname? If so please provide.	Text	
What is your primary phone number?	Text	
Is your primary telephone number a...?	1 = Cell phone 2 = Home phone 3 = Work phone	
Is it okay to leave a message at your primary number?	1 = Yes 0 = No	
Is it okay to text you at your primary number?	1 = Yes 0 = No	
Would you like to also give us a secondary phone number we could reach you at if we are unable to get a hold of you on the primary number you gave us?	1 = Yes 0 = No	
What is your secondary phone number?	Text	
Is your secondary number a...?	1 = Cell phone 2 = Home phone 3 = Work phone	
Is it okay to leave a message at your secondary number?	1 = Yes 0 = No	
Is it okay to text you at your secondary number?	1 = Yes 0 = No	
When is the best time to call you?	1 = 8 am – 10 am 2 = 10 am – 12 pm 3 = 12 pm – 2 pm 4 = 2 pm – 4 pm 5 = 4 pm – 6 pm 6 = Other (text box)	
Would you prefer to receive daily surveys via text or email?	1 = Email 2 = Text	
What is your primary email address? (If you do not have an email address please fill cstp@vcu.edu as the email address)		
May we use your primary email address to contact you during the study?	1 = Yes 0 = No	
Are you willing and able to respond online surveys sent via text/email?	1 = Yes 0 = No	
Who may we contact in case of emergency (first and last name)?		
What is your emergency contact's phone number?		
Would you like to receive information about the study results when it is completed (via email)?	1= Yes 0 = No	
Do you have access to a computer and/or smartphone that you would be willing to	1 = Yes 0 = No	

receive daily surveys regarding your tobacco use on? All surveys will be sent at 8 AM each day of the baseline and intervention weeks.		

Appendix 2. Subjective Effects and Product Evaluation Questionnaire

Subjective Effects Questionnaires (asked pre- and post- puffing bout)		
Questionnaire of Smoking Urges - Brief (QSU-B)		
Indicate how much you agree or disagree with each of the following statements by placing a single checkmark (like this: [✓]) by a number ranging from 1 (strongly disagree) to 7 (strongly agree). The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling right now as you are filling out this questionnaire.		
I have a desire for a cigarette right now	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
Nothing would be better than smoking a cigarette right now	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
If it were possible, I probably would smoke right now	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
I could control things better right now if I could smoke	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf

All I want right now is a cigarette	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
I have an urge for a cigarette	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
A cigarette would taste good now	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
I would do almost anything for a cigarette now	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf
Smoking would make me less depressed	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf

I am going to smoke as soon as possible	1, Strong disagree 2, 3, 4, 5, 6, 7, Strongly agree	https://www.phenxtoolkit.org/toolkit_content/PDF/PX520306.pdf

Minnesota Nicotine Withdrawal Scale

Instructions: Please rate yourself as you feel right now:		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1747694/pdf/v011p00376.pdf
Urges to smoke	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Irritability/Frustration/Anger	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Anxious	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Difficulty concentrating	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Restlessness	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Hunger	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Impatient	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
CRAVING a cigarette/nicotine	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Drowsiness	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Depression/Feeling blue	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	
Desire for sweets	Visual Analog Scale: 0 [Not at all] – 100 [Extremely]	

Study Product Evaluation (Week 1 [own brand menthol cigarette] and Week 2 [IQOS HeatSticks])		
Study Product Evaluation		
Please choose the answer that describes you best. How much did you like the overall flavor sensation of the [own brand menthol cigarettes/IQOS HeatSticks]? How would you rate the overall harshness/irritancy of the [own brand menthol cigarettes/IQOS HeatSticks]??	1= Not at all ; 2= Very little ; 3= A little ; 4= Moderately ; 5= A lot ; 6= Quite a lot ; 7= Extremely	Created specifically for study
Were the [own brand menthol cigarette/IQOS HeatSticks] satisfying?	1= Not at all 2= Very little 3= A little 4= Moderately 5= A lot 6= Quite a lot 7= Extremely	Hatsukami, D. K., Zhang, Y., O'Connor, R. J., & Severson, H. H. (2013). Subjective responses to oral tobacco products: scale validation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 15(7), 1259–1264. https://doi.org/10.1093/ntr/nts265
Did the [own brand menthol cigarette/IQOS HeatSticks] taste good?		
Did you enjoy the sensations in your throat and chest while using the [own brand menthol cigarette/IQOS HeatSticks] ?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] calm you down?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] make you feel more awake?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] make you feel less irritable?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] help you concentrate?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] reduce your hunger for food?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] make you dizzy?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] make you nauseous?		
Did using the [own brand menthol cigarette/IQOS HeatSticks] immediately relieve your craving for a cigarette?		

Did you enjoy using the [own brand menthol cigarette/IQOS HeatSticks] ?		Product Evaluation Questionnaire (mCEQ+)
Did the [own brand menthol cigarette/IQOS HeatSticks] relieve withdrawal symptoms?		
Did the [own brand menthol cigarette/IQOS HeatSticks] relieve the urge to smoke cigarettes?		
Did the [own brand menthol cigarette/IQOS HeatSticks] give enough nicotine?		
Did the [own brand menthol cigarette/IQOS HeatSticks] give too much nicotine?		
Were the [own brand menthol cigarette/IQOS HeatSticks] easy to use?		
Did the [own brand menthol cigarette/IQOS HeatSticks] have ersome side effects?		
Were you comfortable using the [own brand menthol cigarette/IQOS HeatSticks] in public?		
Did you still have a craving for a cigarette after using the [own brand menthol cigarette/IQOS HeatSticks] ?		
Are you concerned that you would become dependent on the [own brand menthol cigarette/IQOS HeatSticks] ?		
Do you plan on continuing to use the [own brand menthol cigarette/IQOS HeatSticks] when this study is over?	1=Definitely 2=Probably 3=Possibly 4=Probably not 5=Definitely not	
Compared to smoking your own-brand cigarettes, using Heated Tobacco Products, such as IQOS, is…	-3 = a lot less harmful -2 -1 0 = Equally as harmful 1 2 3 = a lot more harmful	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828048/
In your opinion, how harmful are heated tobacco products, such as IQOS, to general health?	1 = Not at all harmful 2 3 4 5 6 7= Extremely harmful	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828048/
In your opinion, how harmful is smoking cigarettes to health?	1 = Not at all harmful 2 3 4 5 6 7= Extremely harmful	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828048/

Appendix 3. Experimental Tobacco Marketplace

Experimental Tobacco Marketplace (pre-task instructions)

Please pay attention to the instructions below.

For the following questions, you will be presented with an Experimental Tobacco Marketplace from which you can purchase tobacco/nicotine products. We will give you a budget to spend on products and you should purchase enough products to last you 1 week (7 days).

The Experimental Tobacco Marketplace contains the following commercially available products:

- conventional cigarettes,
- heated tobacco products,
- cigars,
- cigarillos,
- vape/e-cigarette pods/cartridges,
- vape/e-cigarette liquid,
- oral nicotine pouches,
- chewing tobacco,
- nicotine gum,
- nicotine patches

As you go through the rest of the survey, you will be presented with several different independent trials, meaning that every time you have the opportunity to purchase items, you should assume it is a completely new purchasing scenario. That is, imagine none of your previous purchases in this survey affect how you are purchasing now.

When making purchases in the marketplace, please assume the following:

- Imagine a TYPICAL WEEK during which you smoke and use tobacco/nicotine products.
- The following questions ask how many nicotine products you would purchase and consume for the next 7-day period if they cost various amounts of money. Remember, make these purchases for use during the next 7 days.
- Please make your choices based on the following assumptions:
- Assume that you have NO ACCESS to any other cigarettes or nicotine products other than those offered at these prices.
- Assume that you have all necessary equipment to use any purchased products (i.e., you already have the IQOS tobacco heating system to use with any purchased HeatSticks).
- Assume all products offered are in your preferred brand unless noted otherwise
- Assume you can smoke without any restrictions and without factoring in what might occur in the next 7 days related to your participation in the study.
- Assume that you cannot save or stockpile products for longer than the next 7 days. In other words, assume that any of the products you purchase will expire after 7 days if you did not use them.
- Assume that you cannot give away any of the products you purchase.

Please make your choices based on the following instructions:

- You will be a given a budget. You may use as much or as little of the budget as you'd like, however you cannot exceed this budget.
- Although you will not actually receive any of the choices you make, please make your choices as if you were actually receiving the products for use during the next 7 days.
- At the bottom of the ETM, you will be asked to confirm your purchasing amounts for ALL products regardless of if you purchased any. It is required that you answer these questions before submitting.
- Please respond to these questions honestly.

WELCOME TO THE EXPERIMENTAL TOBACCO MARKETPLACE

Please make purchases for the next week (7 days). Also, make sure the total amount to purchase falls within the budget you are given (see below).

You are about to begin making a new set of purchases. Please treat this set of purchases as if you have not made any previous purchases.

For this set of purchases, please note that the price of each of your own-brand menthol cigarettes in the Experimental Tobacco Marketplace is: $____.

BUDGET: $[budget amount]

X (price of menthol cigarettes)	**Y own-brand menthol cigarettes**	**Z1 IQOS HeatSticks (Flavor: Menthol; $0.30 each)** **(Available to those in the IQOS-M group ONLY)**	**Z2 IQOS HeatSticks (Flavor: Tobacco; $0.30 each)**	**B (other products*)**
$0.12 (P1)				
$0.50 (P2)				
$1.00 (P3)				
$1.50 (P4)				
$2.00 (P5)				
$4.00 (P6)				
$8.00 (P7)				
$16.00 (P8)				

*other products include: tobacco-flavored cigarettes ($0.40 each), preferred-flavored cigars ($2.00 each), preferred-flavored cigarillos ($1.00 each), vape/e-cigarette pod in preferred flavor (5% nicotine; $4.50 each), vape/e-cigarette liquid in preferred flavor (50 mg/mL; $0.50/mL), oral nicotine pouches in preferred flavor (6 mg; $0.25/pouch), chewing tobacco pouches in preferred flavor ($0.10/pouch), nicotine gum in preferred flavor (4 mg; $0.40 each), and nicotine patch (21 mg; $2.25 each).

Each item in the ETM has a picture, description, price, purchase quantity selection, and total cost calculation associated with it (see screenshots below).

PRICE ORDER BY SESSION:
Session 1: P2, P3, P5, P4, P6, P7, P8, P1
Session 2: P8, P5, P3, P6, P4, P1, P2, P7
Session 3: P8, P4, P7, P1, P3, P2, P6, P5
Session 4: P1, P2, P3, P7, P4, P5, P6, P8

ORDER SUMMARY:
List amount and total cost for each item in ETM with confirmation (YES-NO) question in table

Starting Budget: $___
Total Spent: $ ___
Remaining Budget: $___

Submit?

**SEE BELOW FOR SCREENSHOTS OF TASK AS THEY WERE DISPLAYED TO PARTICIPANTS

The ETM for each of the two experimental groups was identical EXCEPT that those in the IQOS-Tobacco condition will have no access to the IQOS menthol-flavored HeatSticks.

WELCOME TO THE EXPERIMENTAL TOBACCO MARKETPLACE

Please make purchases for the next week (7 days). Also, make sure the total amount to purchase falls within the budget you are given (see below).

You are about to begin making a new set of purchases. Please treat this set of purchases as if you have not made any previous purchases.

For this set of purchases, please note that the price of each of your own-brand menthol cigarettes in the Experimental Tobacco Marketplace is: $0.12

Budget: $10

CIGARETTES	
	
Own-Brand Cigarettes (Flavor: Menthol)	Cigarettes (Flavor: Tobacco)
Description: A single menthol cigarette in your normal brand.	Description: A single tobacco-flavored (i.e., non-menthol) cigarette.
Price: $0.12/cigarette	Price: $0.40/cigarette
Quantity: 0 cigarettes	Quantity: 0 cigarettes
Cost: $0	Cost: $0

HEATED TOBACCO PRODUCTS	
	
IQOS HeatSticks (Flavor: Menthol)	IQOS HeatSticks (Flavor: Tobacco)
Description: A single HeatStick (14 puffs). Assume you already have the heating device required or that it is available for free.	Description: A single HeatStick (14 puffs). Assume you already have the heating device required or that it is available for free.
Price: $0.30/HeatStick	Price: $0.30/HeatStick
Quantity: 0 HeatSticks	Quantity: 0 HeatSticks
Cost: $0	Cost: $0

CIGARS/CIGARILLOS	
	
Traditional Cigars (Flavor: Tobacco)	Cigarillos (Flavor: Tobacco)
Description: A single traditional cigar.	Description: A single cigarillo.
Price: $2.00/cigar	Price: $1.00/cigarillo
Quantity: 0 cigars	Quantity: 0 cigarillos
Cost: $0	Cost: $0

VAPES/E-CIGARETTES	
	
Vape/E-Cigarette Pod (Flavor: Preferred)	Vape/E-Cigarette Liquid (Flavor: Preferred)
Description: A one-time use pod or cartridge compatible with specific devices. Assume you have access to the device required or that it is availabe to you for free.	Description: A 1 milliliter (mL) bottle of nicotine liquid for use in refilliable vapes/e-cigarettes. Assume you have access to the device required or that it is avaible to you for free.
Price: $4.50/pod	Price: $0.50/mL
Nicotine dose: 5%	Nicotine dose: 50 mg/mL
Quantity: 0 pods	Quantity: 0 mLs
Cost: $0	Cost: $0

Oral Nicotine Products	
	
Oral Nicotine Pouches (Flavor: Preferred)	Chewing Tobacco Pouches (Flavor: Preferred)
Description: A spitless smoke-free and tobacco-free product that the user places under the upper lip, near the corner of the mouth.	Description: A single pouch of chewing tobacco (i.e., dip).
Price: $0.25/pouch	Price: $0.10/pouch
Nicotine Dose: 6 mg/pouch	
Quantity: 0 pouches	Quantity: 0 pouches
Cost: $0	Cost: $0

NICOTINE REPLACEMENT THERAPY	
	
Nicotine Gum (Flavor: Preferred)	Nicotine Patches
Description: A single piece of nicotine gum.	Description: A single dermal nicotine patch.
Price: $0.40/piece	Price: $2.25/patch
Nicotine dose: 4 mg/piece	Nicotine Dose: 21 mg/patch
Quantity: 0 pieces of gum	Quantity: 0 patches
Cost: $0	Cost: $0

Order Summary

Cart	Purchase Confirmation
Own Brand Menthol Cigarettes ($0.12 each): 0 cigarettes for $0.	Correct? Yes No reset
Tobacco-flavored Cigarettes ($0.40 each): 0 cigarettes for $0.	Correct? Yes No reset
IQOS Menthol HeatSticks ($0.30 each): 0 HeatSticks for $0.	Correct? Yes No reset
IQOS Tobacco HeatSticks ($0.30 each): 0 HeatSticks for $0.	Correct? Yes No reset
Cigars ($2.00 each): 0 cigars for $0.	Correct? Yes No reset
Cigarillos ($1.00 each): 0 cigarillos for $0.	Correct? Yes No reset
Pod/Cartridge vapes/e-cigarettes ($4.00 each): 0 pods for $0.	Correct? Yes No reset
Liquid vapes/e-cigarettes ($0.50/mL): 0 mLs of liquid for $0.	Correct? Yes No reset
Oral nicotine pouches ($0.25 each): 0 pouches for $0	Correct? Yes No reset
Chewing tobacco pouches ($0.10 each): 0 pouches for $0	Correct? Yes No reset
Nicotine gum ($0.40 each): 0 pieces of gum for $0.	Correct? Yes No reset
Nicotine patches ($2.25 each): 0 patches for $0.	Correct? Yes No reset

Starting Budget: $10
Total Spent: $0
Remaining Budget: $10

Appendix 4. Verbal Instructions for Study Instruments

Adverse Events Questions

To start these session, we're just going to have you answer 3 quick questions to gauge whether you've had any negative experiences with the study or your health since your last visit. If there's anything you'd like to tell us though about your involvement in the study, but don't want to write into the survey, just let me know. Once you answer those questions we'll continue with the rest of the session.

Timeline Follow-Back Assessment

For this next set of questions, we're interested in getting an understanding of which tobacco products you used over the past 3 days. Specifically, we're interested in your tobacco use on Tuesday, Wednesday, and Thursday of this week. To the best of your ability, please try to remember how many cigarettes, HeatSticks, and other tobacco products you used on each of these three days. We totally understand that your memory might not be perfect, but just try your best.

Additionally, there may be a few questions where you need to respond by typing in some text – please share as much information as you are comfortable sharing, but don't feel a need to write a novel. We're most interested in your overall impressions of these products and why you did or did not want to use them.

Once you finish answering these questions, you'll have a 45 minute break then we'll get on with the rest of the session for today. Any questions?

Subjective Effects Questionnaires

This next set of questions will ask you about how you're feeling in this particular moment in time. Be sure to follow the directions on the screen, read each item carefully, and answer honestly. You'll answer this set of questions now and then again after you use today's session product.

Do you have any questions before you begin?

Blood Draws and Puff Topography

For this portion of the study, we're going to start by having our research nurse – Nicoleta – take a small blood sample.

After Nicoleta has gotten that first blood sample, I'm then going to hand you the **[SESSION PRODUCT]** which will be connected to the computer by some special sensors. We're going to ask that you take 10-puffs from this product and each puff will be separated by 30 seconds. I'll be keeping time on this stopwatch and tell you when to take each puff. There's no need to puff in a particular way or do anything special on your end – just use the product as you would normally, but be careful not to knock the tubing off if you can. If you need to stop at any point or start to feel bad, just let us know.

After you take those 10-puffs, Nicoleta will take one more small blood sample. After that, we'll leave the room, let you answer those self-reported effects questions again, then you'll have a 15 minute break.

Do you have any questions before we begin?

Experimental Tobacco Marketplace

This is the last task you'll complete today and its known as the "Experimental Tobacco Marketplace." The way this tasks works is that you'll be given a hypothetical budget with which you can buy the tobacco and nicotine products that you would use over the course of a typical 7-day period.

For example, each market has cigarettes, heated tobacco products, e-cigarettes, and nicotine replacement therapy available. On the screen, you'll see a picture and description of each item, as well as its price, and there will be a drop down menu you can open to designate how many of each product you'd like to purchase. Keep in mind, you'll be purchasing in units such as "individual cigarettes" not "packs of cigarettes" – all that information will be clearly on the screen though.

After you submit your responses, you'll then complete the task again but the price of certain products may be a little different. You'll complete the task a total of 8 times during each session.

A few points to keep in mind while you complete the task:

- Responses are purely hypothetical – you won't receive any of the products you select for purchase. Even still please respond as if you WOULD receive these products to use during a typical week and as if you do not have access to any other products other than those offered at these prices
- Each time you make purchasing decisions, respond as if none of your prior purchasing decisions are in play. For example, if you purchased 5 cigarettes in the first market – disregard that information when you enter the second market… in other words, each time you start a new price-level, pretend as if you have a full budget and no tobacco products currently.
- Additionally, you can use as much or as little of your budget as you'd like – but you cannot spend over your budget. Error messages will pop up to let you know if you are over budget.
- Products are designed to look generic, but pretend that they are in your preferred brand and flavor unless noted otherwise. Also assume you already have all equipment needed to use any products you purchased.
- At the bottom of the page, you'll need to confirm all of your purchasing decisions for each product – even if you opted to purchase none.

These instructions will be on the screen in front of you and printed out in the room for you to review. Don't start until you feel comfortable that you understand the task.

Do you have any questions before we begin?

Daily Surveys
We will be sending you a [**TEXT/EMAIL**] every morning for the next two weeks at 8 AM. That message will have a link in it, which you will be able to click and it will open a survey. This survey will ask about your tobacco use over the PRIOR day (from midnight to 11:59 PM). Only report those tobacco products you used in that 24 hour period – we will ask for the exact number of cigarettes and HeatSticks you used, as well as if you used any other products. These surveys should take less than 2 minutes and are worth $2 each. It is very important that you respond to these surveys each day. You can complete the survey at any point that day, however, if you forget to do a survey one day do NOT attempt to do it at a later date.

Do you have any questions?

Just to confirm your [**phone number/email address**] is …. ?

Product Distribution and Instructions
We are providing you with a heated tobacco product known as IQOS in [**condition-specific flavors**] over the next week to be used as a substitute or complete replacement for your own brand cigarettes. We want to understand how you use these specific heated tobacco products as well as your own brand cigarettes when they are the only products available to you. Therefore, please refrain from using all other nicotine/tobacco products and other heated tobacco product flavors for the duration of the study. If you use anything else, it is important that you tell us what you used. Additionally, please return all of the IQOS products and any unused HeatSticks at your laboratory visit on Friday.

Do you have any questions about these instructions?

[Take device out of box]

[Step through the instruction sheet, demonstrating how to charge the device, how to turn it on, how to use it, and how to store and clean it]

You are being given each of the components shown on this graphic [pull out each element in the labeled image on the instruction sheet]. A few things to keep in mind…

- The IQOS device does need to charge – you'll be able to see the charge status on the side of the pocket holder. The device holds enough power to use about 20 HeatSticks, so we recommend you completely charge the device every single night. It takes about 90 minutes for a full charge.
    - Point out charging status cheat sheet on the back of the instruction sheet
- [Step through how to use a HeatStick] … As a reminder, each use period will last for 14 Puffs OR 6 minutes – whichever comes first (unless you end the session early by holding the power button)
- You can dispose of a HeatStick in the same manner you would a cigarette

- You may need to clean the device at some point if you notice debris in the Heater, though the device should clean itself every 20 uses or so.

[Put device back in box and hand participant bag with IQOS device, HeatSticks, and product instructions printed out].

If you have any questions about how to use the device, be sure to consult this sheet or watch the YouTube video at the top. There's also a "user guide" in the box. You are also welcome to call or email us at any point if you run into any issues.

Appendix 5. Ecological Momentary Assessment and Timeline Follow Back

Ecological Momentary Assessment (EMA) Daily Survey Text		
Instructions: Remember we are asking about your tobacco use YESTERDAY. Please note that yesterday includes any tobacco products used between 12:00am-11:59pm (24-hr period).		
How many menthol cigarettes did you smoke yesterday?	0-60	
How many IQOS Heatsticks did you use yesterday?	0-60	
Did you use any IQOS Heatsticks not provided to you by the study? [if >0 to above]	1=Yes 0=No	
Did you use any other tobacco/nicotine products yesterday?	1 = Yes 0 = No	
Which of the following did you use? Please select all that apply.	1 = Electronic cigarettes or e-cigarettes/vapes (JUUL, Blu, Avail) 2 = Traditional cigars (Macanudo, Romeo y Julieta, or Arturo Fuente) 3 = Pipe (with tobacco) 4 = Cigarillos/filtered cigars (like Black & Milds, Swisher Sweets, or Phillies Blunt) 5 = Smokeless tobacco, such as chewing tobacco, dip, snuff, or snus (like Levi Garrett, Red Man, or Beech Nut, Skoal or Copenhagen) 6 = Hookah/shisha (hookah tobacco) 7 = Nicotine replacement products (like gum, patches, lozenges) 8 = Non-menthol cigarettes	

Three-Day Timeline Follow Back		
What is today's date?	[date button]	
Have you used any tobacco or nicotine containing products in the last 8 hours? (asked verbally at start of each session)	1 = Yes 0 = No	
Cigarettes		
Have you smoked even one puff of a menthol cigarette in the past 24 hours?	1 = Yes 0 = No	
How many menthol cigarettes did you smoke on [DATE yesterday]? How many menthol cigarettes did you smoke on [DATE two days ago]? How many menthol cigarettes did you smoke on [DATE three days ago]?	0-60	
It looks like you did not smoke menthol cigarettes on one or more days this week. Why didn't you smoke cigarettes? [if 0 for any day of cigarette use]	1 = I was sick 2 = I didn't have any cigarettes 3 = I tried to quit smoking 4 = Other	
You selected other. Please describe.	[text field]	
IQOS		
Have you inhaled even one puff of an IQOS HeatStick in the past 24 hours?	1 = Yes 0 = No	
How many IQOS HeatSticks did you use on [DATE yesterday]? How many IQOS HeatSticks did you use on [DATE two days ago]? How many IQOS HeatSticks did you use on [DATE three days ago]?	0-60	
It looks like you did not use your IQOS Heatsticks on one or more days this week. Why didn't you use your IQOS Heatsticks? [if 0 for any day of IQOS use]	1 = I was sick 2 = I didn't have any IQOS Heatsticks 3 = I tried to quit my IQOS Heatsticks 4 = I don't like using my IQOS Heatsticks 5 = Other	
You selected other. Please describe.	[text field]	
Other tobacco products		

Have you used any other tobacco/nicotine products in the past 24 hours?	1 = Yes 0 = No	
Did you use any other tobacco/nicotine products on [DATE yesterday]? Did you use any other tobacco/nicotine products on [DATE two days ago]? Did you use any other tobacco/nicotine products on [DATE three days ago]?	1 = Yes 0 = No	
What other tobacco/nicotine product(s) did you use from [DATE yesterday] to [DATE three days ago]? For cigars/cigarillos, pipe, hookah/shisha, and heated tobacco products, count even one puff. Please note these questions only regard your use of tobacco products alone NOT in combination with marijuana, cannabis, or hashish. Please select all that apply. [If yes to any of the above]	1 = Electronic cigarettes or e-cigarettes/vapes (JUUL, Blu, Avail) 2 = Traditional cigars (Macanudo, Romeo y Julieta, or Arturo Fuente) 3 = Pipe (with tobacco) 4 = Cigarillos/filtered cigars (like Black & Milds, Swisher Sweets, or Phillies Blunt) 5 = Smokeless tobacco, such as chewing tobacco, dip, snuff, or snus (like Levi Garrett, Red Man, or Beech Nut, Skoal or Copenhagen) 6 = Hookah/shisha (hookah tobacco) 7 = Nicotine replacement products (like gum, patches, lozenges) 8 = Non-menthol cigarettes	

Appendix 6. Ecological Momentary Assessment Prompts

Text or Email (Daily)
Daily survey/reminder (sent at 8 AM each day, with reminder sent at 12 PM if no response)
Hello! Please complete your daily survey for the IQOS-Flavors study. REMEMBER: We are asking questions about your tobacco use YESTERDAY (12:00 AM – 11:59 PM). Daily surveys are worth $2 each. Call 804-827-3562 if you have any questions.
Please complete your survey by clicking on the following link: [LINK]
This link is unique to you and should not be forwarded to others. If you are no longer interested in participating in this study, please let us know or reply STOP to this message.

PHONE SCRIPTS (if miss 2 days in a row)

Hello, may I please speak to [name].

Hi [name], my name is [name] and I am calling from the IQOS-FLAVORS project at VCU.
I was just calling today to ask about your daily surveys. I noticed you had only completed X out of Y surveys. I was wondering if you were receiving the daily surveys, or if you were having issues accessing the surveys?

a) [If they are having issues] I'm so sorry to hear that. We can double check to make sure your surveys are going to the correct phone number. Can I double check your number with you? Is it [#]. Okay, I'm going to send you a test survey now. Can you let me know if you receive it?
b) [If they are not having issues] Okay, I'm glad to hear you can access the surveys. Is there anything we can do to support you in completing the surveys?

[name], it's been great talking to you today. Please let us know if you have any questions or concerns about the surveys.

Appendix 7. IQOS Use Instruction Sheet Given to Participants

Heated Tobacco Product (HTP) – IQOS Instruction Manual

Watch a video explanation by scanning the QR code or visiting:
https://tinyurl.com/32h7edr4

The **IQOS**, (pronounced EYE-kose) is made up of three primary parts: the tobacco or menthol HeatStick, the device (holder), and the charger. The Heatsticks, device, and charger will be provided to you for the duration of the study. You will get either **tobacco-only** or **menthol-only** flavors of Heatsticks, depending on your randomly selected study condition.

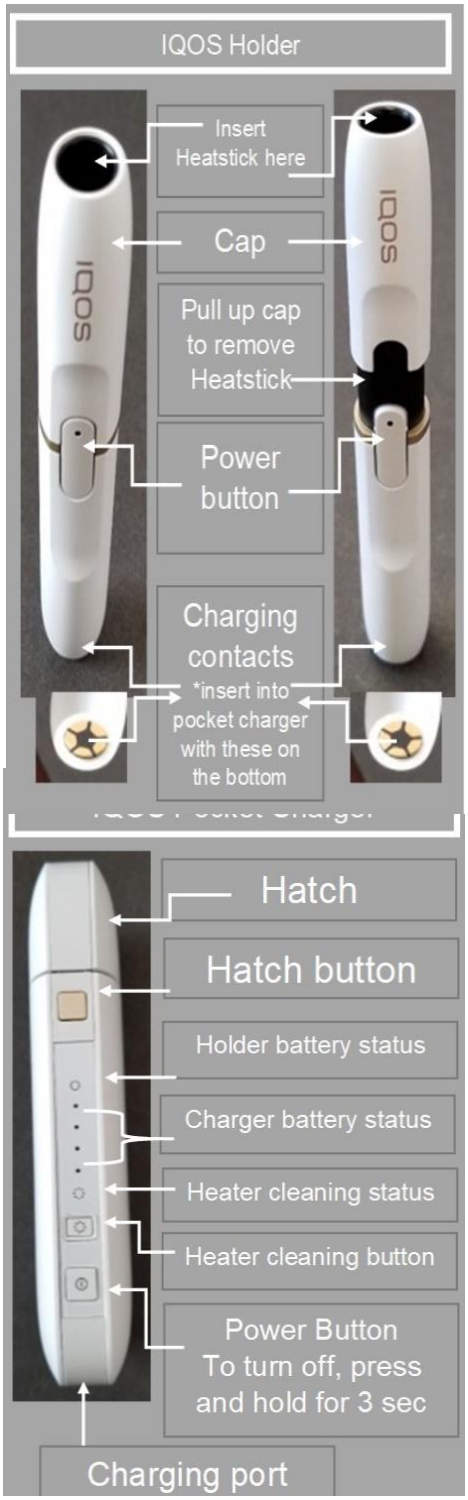
This guide will give you summary of directions on how to use the IQOS device kit. Your kit comes with a User Guide and a Quick Start Guide, have useful information, if you choose to read it but please read all of this information sheet.

The charger takes about **90 minutes to fully charge** and stores enough power to use ~ **20 Heatsticks**. We encourage you to charge your device nightly, even if you have only used the device a few times, to avoid your device running out of power.

About every 20 uses the IQOS will run a 'cleaning' process but if you notice loose tobacco in the holder, please use the cleaning tool to remove the tobacco. More cleaning details are available in the Quickstart Guide and/or the User Manual, inside the device box. Most IQOS users report using the cleaner tool about once a week.

What you are given

Pocket Charger and Holder (device)



To use a Heatstick:

- Gently insert it into the holder (to the line), tobacco down
- Press and hold the power button for two seconds
  - Blinking green light – still heating up
  - Solid green light – ready to use
- After ~ 6 min or 14 puffs the Heatstick needs to be disposed.
  - Green status light will go off
  - Press + hold the power button for 5 sec to end use early

To dispose of Heatstick:

- Pull up on the IQOS holder cap until you hear a 'click'
- Then pull the Heatstick out of the holder and dispose

Important tips:

- Do **not** twist the Heatstick on or off of the device
- Do **not** reuse the Heatstick, even if you end use early.
- Do **not** remove the Heatstick mid-heat cycle
- Do **not** use cigarettes in the IQOS
- Do **not** preheat the IQOS
- Remove Heatstick before charging the holder

IQOS Holder Battery Status:

* holder takes about 6 minutes to charge

- Blinking green – charging
- Green circle – charged
- Blinking orange – charging but with poor contact
- Blinking red – charging but malfunctioning

IQOS Pocket Charger Battery Status:

- Blinking green – charging
- Four green dots – fully charged
- Single green dot – will run out of battery charge soon

Cleaning:

* See QuickStart Guide/User Manual for cleaning tips

- Blinking green – cleaning in progress
- Solid orange – automatic cleaning will start once charged
- Heater battery status, cleaning status/button blinking red – pocket charger malfunction

Appendix 8. Consent Form

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: The Abuse Liability of a Novel Heated Tobacco Product (IQOS) and Its Feasibility as a Menthol Cigarette Substitute (HTP-FLAVORS)

VCU INVESTIGATOR: Dr. Andrew Barnes, Associate Professor of Health Behavior and Policy

SPONSOR: National Institutes of Health/Food and Drug Administration (FDA)

ABOUT THIS CONSENT FORM
You are being invited to participate in a research study lead by VCU's Dr. Andrew Barnes. **It is important that you carefully think about if being in this study is right for you and your situation.**

This consent form is meant to assist you in thinking about whether or not you want to be in this study. **Please ask the study staff to explain any information in this document that is not clear to you.** We will email you an unsigned copy of this consent form to think about and discuss with family or friends before making your decision.

Your participation is voluntary. You may decide to not participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

AN OVERVIEW OF THE STUDY AND KEY INFORMATION
This study aims to understand how the flavors ("Tobacco" and "Menthol") for a *heated tobacco product* called "IQOS" impact tobacco use, nicotine exposure, and the chance someone might use these products. IQOS was authorized by the U.S. FDA as a product that exposes smokers to less harmful chemicals than cigarettes. This study focuses on menthol smokers because they have been shown to have a harder time quitting than non-menthol smokers. Additionally, FDA is considering banning menthol in cigarettes and heated tobacco products. This study will help us to understand heated tobacco product flavors and their potential to reduce harm among smokers.

In this study, you will be asked to do the following things:

1. **To begin**, we will ask you to complete a brief online "pre-screener" where we will ask about your background, medical history, and tobacco use.
2. **If your responses indicated that you are potentially eligible for the study**, we will contact you to schedule an in-person screening session at VCU's Center for the Study of Tobacco Products (CSTP). At this session we will confirm your identity, review study procedures, and discuss your consent to participate.

   You may skip any survey questions administered (at any point in the study) except for those required to determine your eligibility.
3. **If you consent to participate in the study**, you will complete a survey during the in-person screening session. If you are eligible, we will ask that you return to the CSTP on a Monday (within 2 weeks) to begin the study. If you are not eligible, you will be paid for

screening ($25) but removed from the study. During this session, we will ask for a urine sample to test for pregnancy (pregnant individuals are not eligible) and the presence of cotinine to confirm your status as a smoker. We will also collect a breath sample to test for carbon monoxide, by having you breathe through a specialized instrument for 10 seconds. You will also have an opportunity to take up to 4 test puffs of the study product in the tobacco flavor. This session may last about 1 hour.

4. **If you complete the screening session**, the first full-week of the study is called the "baseline week." You will come to the CSTP on Monday and Friday of this week for about 2 hours. We ask that you refrain from using nicotine containing products for the 8 hours before the session. However, not refraining from using nicotine containing products will not stop you from being able to complete a session. During the course of these sessions, you will use your own brand menthol cigarettes (provided for free).

   During these laboratory sessions you will complete a series of activities to measure your tobacco use. First, you will answer questions about how you feel in that moment. Next, you will take 10-puffs of your cigarette during which we will monitor the length of the puffs you take and collect 2 blood samples. Last, you will complete an "experimental tobacco marketplace" where you will tell us how many cigarettes and other tobacco products you would buy if they cost varying amounts of money.

   You will report the number of cigarettes and other tobacco products you use while at home. These surveys will be sent using text message or email (your preference). Messages will be sent every morning at 8 AM and ask about your tobacco use over the prior day.

5. **If you successfully complete the baseline week laboratory sessions**, you will be randomized to receive one of two flavors of IQOS: menthol or tobacco. This means your condition assignment (i.e., which products you will receive) will be determined purely by chance, like flipping a coin. You will have an equal chance to be in a condition where you will receive the heated tobacco product in:

   Tobacco flavor

   OR

   Menthol flavor

6. **Beginning on the Monday of the intervention week**, this will mark the start of the "intervention week". This week follows the same procedure as the baseline week but instead of using your own brand menthol cigarettes, we will ask you to replace some or all of your normal cigarette use with IQOS products. We will give you these products to take home. We will continue to send you daily surveys. We will ask that your return all IQOS products on the following Friday.

Brief "pre-screener"	In-Person Screening Session and Informed Consent	Week 1 (Baseline week; Use your own brand menthol cigarettes)	Week 2 (Intervention week; Use your randomly assigned IQOS products)

• Answer demographic and tobacco use questions • Schedule an in-person screening session and review an unsigned copy of this consent form	• Review informed consent document and provide consent • Complete screening survey and provide urine and breath samples • Complete baseline survey • Confirm eligibility • Take 4 tests puffs of the study product	• Use your own brand menthol cigarettes as you normally would • Respond to daily surveys • Participate in clinical laboratory sessions on Monday and Friday (2 blood draws, 10-puffs of your own brand menthol cigarette, hypothetical purchasing task, answering survey questions about subjective feelings and tobacco use)	• Attempt to replace some or all of your normal menthol cigarette use with IQOS (menthol OR tobacco flavor) • Respond to daily surveys • Participate in clinical laboratory sessions on Monday and Friday (2 blood draws, 10-puffs of IQOS, hypothetical purchasing task, answering survey questions about subjective feelings and tobacco use)

WHAT WILL HAPPEN IF I PARTICIPATE IN THE STUDY?

Your participation in this study will last about 3 weeks. The brief online screener and in-person screening session should take about 1 hour total. Each clinical laboratory session during the baseline and intervention weeks will take about 2 hours. The daily surveys will take <3 minutes per day over two weeks. Total study involvement is expected to be about 10 hours. About 50 individuals will participate in this study. Below, we provide a brief description of all study measures:

1. **Blood Plasma Nicotine/Menthol Levels and Puff Topography (Clinical Laboratory Sessions ONLY):** At the start of the 4 clinical laboratory sessions, our research nurse will prepare your arm to obtain a blood sample – either via venipuncture (“a stick”) or (if necessary) by placing a catheter. Once your arm has been prepared, a 7 mL (about 1.5 tsp) sample of blood will be taken by a registered nurse. You will then complete a “puffing bout” with that session’s designated product (own brand menthol cigarettes [baseline week] or IQOS [intervention week]), in which research staff will direct you to take 10-puffs of the product with a 30-second break between puffs. Your tobacco product will be connected to a machine that measures how long you are puffing and the volume of air you inhale. After the puffing bout, another 7 mL blood sample will be taken (14 mL/session).

2. **Subjective Effects Questionnaires (Clinical Laboratory Sessions ONLY)**: Immediately before and after the puffing bout described above, you will complete a short set of questions about how you are feeling in that moment regarding cigarette cravings, mood, and nicotine withdrawal symptoms.

3. **Experimental Tobacco Marketplace (Clinical Laboratory Sessions ONLY):** After the self-reported effects questions, you will have a 15-minute rest period. You will then complete the "Experimental Tobacco Marketplace." In this task, you will be provided with a (hypothetical) budget and asked how you would spend that money across multiple tobacco products at various prices. You will not receive any of the products you select for purchase.

4. **Daily Tobacco Use Questionnaires (Every day, at home):** Beginning on Monday of the baseline week and continuing until Sunday of the intervention week, you will receive a text- or email-based invitation to complete a short survey. The survey will ask about the type and amount of tobacco products you used over the prior day. Surveys will be sent at 8 AM each day.

WHAT ALTERNATIVES ARE AVAILABLE?
This is not a therapeutic study. You have the alternative not to participate.

WHAT RISKS AND DISCOMFORTS COULD I EXPERIENCE FROM BEING IN THE STUDY?
There are risks and benefits of participating in research studies.

Most Common Risks and Discomforts
Physical Risks:
1. Frustration - You may experience mild frustration while completing some of the study-related questionnaires.
2. Breath sampling for carbon monoxide - You may find giving breath samples uncomfortable but using a special collection device should reduce this risk. Moreover, it is possible that holding one's breath and breathing out for 10 seconds could cause some temporary lightheadedness and discomfort. However, such effects should resolve spontaneously for participants that meet inclusion standards for physical health.
3. Nicotine-related side effects - You may experience side effects from products that contain nicotine such as acute increases in heart rate and blood pressure, sweating, lightheadedness, dizziness, nausea, and nervousness. These side effects are unlikely in individuals who use cigarettes regularly.
4. Heated tobacco product side effects - The use of heated tobacco products may include other side effects/risks such as cough, headache, and syncope (fainting). Available data indicates side effects from these products are similar to other tobacco exposures.
5. Nicotine withdrawal symptoms – Some participants may experience nicotine withdrawal symptoms when they reduce their own brand cigarette consumption. Common withdrawal symptoms are irritability, anxiety, depressed mood, increased appetite, fatigue, or difficulty concentrating. These effects may also be experienced by individuals when adhering to the 8-hour abstinence period preceding each clinical laboratory session. These effects are seldom clinically-significant but will be monitored by the researchers.
6. New pregnancy or want to become pregnant – Nicotine, either from cigarettes or heated tobacco products, is known to be harmful to the developing human fetus. Women who are

pregnant or are nursing a child may not participate in this research study. You must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation. The investigator will discuss appropriate precautions with you. If at any point during the research you believe there is any possibility that you may be pregnant, you must notify the research assistant or research nurse immediately.

7. The researchers will let you know about any significant new findings (such as additional risks or discomforts) that may make you change your mind about participating in the study.

8. Blood draws - there is possible risk of bruising, infection, and discomfort resulting from the two blood draws that will be conducted during each clinical session. These are routine medical procedures and we attempt to mitigate these risks by having trained personnel (research nurse) perform all blood draws using aseptic techniques. Such adverse effects of blood draws are typically minor and/or uncommon when performed with proper technique by a trained professional. Our medical monitor is available to evaluate and provide necessary referrals in the event that any adverse complication arises from these blood draws.

Non-physical Risks

1. Privacy - Participation in research might involve some loss of privacy. There is a small risk that someone outside the study could see and misuse information about you.
2. Sensitive questions - The study questionnaires ask personal questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable.

Benefits to You & Others

1. You will derive no personal benefits from this study. Your participation will help us to better understand the effects of flavors in heated tobacco products.
2. In general, we will not give you any of your individual results from this study.

WILL I BE PAID TO PARTICIPATE IN THE STUDY?

Payments from this study will be paid out in cash in US Dollars.

Following the brief online "pre-screener" and obtaining of informed consent, you will be asked to complete the screening session for $25. If your responses indicate you are eligible, you will be asked to participate in 4 clinical laboratory sessions over a 2 week period (2 sessions/week). Laboratory sessions will take place on Monday ($50/session) and Friday ($100/session) of each week. Additionally, you will be asked to complete daily surveys (<3 min) reporting your tobacco use from the previous day ($2/day for 2 weeks = $28 total). The total possible payment if you complete all study activities (in-person screening, 4 clinical laboratory sessions, 14 daily surveys) is $353. You will be paid all money due for study activities completed to-date at 5 times: after the in-person screening session and after the 4 in-person clinical laboratory sessions. We can also reimburse you up to $12 per visit for parking, if needed.

If you decide to stop participating, you are entitled to compensation for all study activities completed to that point. This partial compensation can either be paid out in cash (USD) by coming to the CSTP or by requesting a gift card be sent to your email account (Amazon gift cards ONLY).

How you are paid for completing each activity in this study

	In-Person Screening Session	Monday Laboratory Sessions (x2)	Friday Laboratory Sessions (x2)	Daily Surveys (x14)
Amount	$25 for completing the in-person screening session.	$50 during Weeks 1 and 2	$100 during Weeks 1 and 2	$2 per day during Weeks 1 and 2
Total Possible: $353	$25	$100	$200	$28

Total payments within one calendar year that exceed $600 will require the University to annually report these payments to the IRS and you. This may require you to claim the compensation you receive for participation in this study as taxable income. VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THE STUDY?

If you are injured by, or become ill, from participating in this study, please contact the main study site (804-827-3562) and/or your study doctor (Dr. Thokozeni Lipato; thokozeni.lipato@vcuhealth.org) immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness, it is very important to follow all study directions.

CAN I STOP BEING IN THE STUDY?

You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health. Tell the study staff if you are thinking about stopping or decide to stop.

If you leave the study before the final regularly scheduled assessment, you will be able to keep any money that you have earned in the study up to that point.

Your participation in this study may be stopped at any time by the investigator without your consent. The reasons might include:

- the investigator thinks it necessary for your health or safety
- you are found to not be eligible for the study
- the sponsor has stopped the study
- you have not followed study instructions
- administrative reasons require your withdrawal

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your

information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed. While you are participating in this study, only IRB-approved study staff performing study-related tasks will be permitted to view identifiable information – except where required by law.

Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study (as required by law):

- The study sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System
- Officials of the Department of Health and Human Services

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

This study will **not** use your blood samples to sequence all or part of your DNA.

There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value.

In the future, identifiers might be removed from the information you provide in this study (including results of the urine, blood, and breath analyses described above), and after that removal, the information could be used for other research studies by this study team or another researcher without asking you for additional consent.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Important information about the availability of IQOS in the United States:

IQOS products have not been available in the United States since November of 2021 because of a patent dispute. IQOS is expected to be available for purchase in early 2023 (https://tinyurl.com/2s3a366f). At the conclusion of your participation in this study, if you express an interest in continuing to use IQOS, we will debrief you regarding the current (off the market) availability and expected near term availability (on the market) of IQOS. We will not provide any IQOS products for you to use apart from those require for completing the activities described in this study.

WHO SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

If you have any questions, complaints, or concerns about your participation in this research, contact:

Dr. Andrew Barnes at 804-827-4361 / email: andrew.barnes@vcuhealth.org

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study.

The medically responsible investigator is Dr. Thokozeni Lipato thokozeni.lipato@vcuhealth.org

If you have general questions about your rights as a participant in this or any other research, you may contact:

Virginia Commonwealth University Office of Research
800 East Leigh Street, Suite 3000
Box 980568
Richmond, VA 23298
Phone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

STATEMENT OF CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will have the opportunity to download a copy of the consent form for my records and/or receive a paper copy.

_____	
Adult Participant Name (Printed)	
_____	_____
Adult Participant's Signature	Date
_____	
Name of Person Conducting Consent Discussion (Printed)	
_____	_____
Signature of Person Conducting Consent Discussion	Date
_____	_____
Principal Investigator Signature (if different from above)	Date

Appendix 9. Supplementary Tables Supporting ETM results

Table A9-1. *Own Brand Menthol Cigarette Demand in the Experimental Tobacco Marketplace*

	log(alpha)		R^2	
	IQOS-M	IQOS-T	IQOS-M	IQOS-T
Session 1	-4.40 (0.4)	-3.97 (0.4)	0.96 (0.05)	0.89 (0.10)
Session 2	-4.33 (0.4)	-4.18 (0.3)	0.96 (0.03)	0.93 (0.08)
Session 3	-4.29 (0.6)	-4.11 (0.4)	0.95 (0.06)	0.95 (0.06)
Session 4	-4.22 (0.3)	-4.03 (0.4)	0.96 (0.04)	0.97 (0.02)

Note: Mean (standard deviation) for estimates based on the results of fitting individual demand curves to the exponential demand function in equation 2 are shown. Alpha represents the *rate of change* in the own-price elasticity of own brand (OB) menthol cigarettes and is inversely proportional to the drug's essential value. The R^2 is the generated from the line of best fit, based on equation 2, drawn through the OB menthol cigarette demand curve for each individual. One participant's data (IQOS-M group) were excluded from sessions 3 and 4 in this analysis because they reported constant null-demand for OB menthol cigarettes. As a result of this pattern of demand, a line of perfect fit was drawn (horizontal line through 0, $R^2 = 1$) but alpha could not be estimated as elasticity did not change over the price scale.

Table A9-2. *Summary of Potential Violations in Systematic Demand of Own Brand Menthol Cigarettes in the Experimental Tobacco Marketplace*

	Trend[A]		Bounce[B]		Reversal from Zero[C]	
	IQOS-M group	IQOS-T group	IQOS-M group	IQOS-T group	IQOS-M group	IQOS-T group
Session 1	0	0	0	0	1	0
Session 2	0	0	0	0	0	0
Session 3	1*	0	0	0	1	0
Session 4	1*	0	0	0	0	0

Note: This chart adopts the criteria set forth in to characterize violations in systematic demand in ETM purchasing data for own brand menthol cigarettes (Stein, Koffarnus et al., 2015).

*Participant demanded a consistent amount of own-brand (OB) menthol cigarettes (0 mg) at all price-points (i.e., null demand) – both violations of the trend assumption were committed by the same participant. Participant was asked in session to verbally confirm intent to not consume any OB menthol cigarettes and they assented stating that they would rather use IQOS regardless of OB menthol cigarette price.

A = Participant reported negligible reductions, no change, or increased consumption from the lowest (P_1) to the highest (P_n) price point. Trend = $[(\log Q_1 - \log Q_n)]/[(\log P_n - \log P_1)$; Trend values below 0.025 were flagged as nonsystematic.

B = Bounce is calculated as the percentage of price points increments with an *increase* in consumption >25% of the consumption reported when price was $0.12/cigarette (lowest price). Bounce criterion was set to 0.2 to be flagged as nonsystematic. This cutoff is slightly higher than the suggested cutoff of 0.10 because only 8 price points were used and thus, a single incidence of "bounce" would have flagged the data as nonsystematic (Stein, Koffarnus et al., 2015).

C = Flagged for participants who reported >0 demand at two prices greater than a price at which they said they would purchase nothing. Note that ETM price points were randomized and this criteria may not be relevant when price-points are randomized (Stein, Koffarnus et al., 2015).

Table A9-3. *Demand for Own Brand Menthol Cigarettes and Possible Alternative in the Experimental Tobacco Marketplace at Session 4 (group-level analyses)*

	IQOS-M group	IQOS-T group	Group Difference
Own-Brand Menthol Cigarettes			
Own-price elasticity estimate	-1.89*** (0.02)	-1.66*** (0.18)	-0.22 (0.20)
Model R^2	0.9424	0.9231	
Nonmenthol Cigarettes			
Cross-price elasticity estimate	0.22*** (0.05)	0.36*** (0.06)	-0.14 (0.08)
Model R^2	0.5446	0.6680	---
IQOS – Cross Price Elasticity			
Cross-price elasticity estimate	0.67*** (0.09)	0.14** (0.03)	0.52*** (0.09)
Model R^2	0.8780	0.6754	---
IQOS – Cross Price Intensity			
Cross-price intensity estimate	2.38*** (0.15)	-0.38*** (0.06)	2.76*** (0.14)
Model R^2	0.8780	0.6754	---
Cigars			
Cross-price elasticity estimate	---	---	---
Model R^2	---	---	---
Cigarillos			
Cross-price elasticity estimate	0.31* (0.09)	-0.07 (0.09)	0.38** (0.11)
Model R^2	0.5893	0.0856	
Pod Vapes			
Cross-price elasticity estimate	0.17* (0.05)	0.02** (0.01)	0.16*** (0.02)
Model R^2	0.6005	0.6446	---
Refillable Liquid Vapes			
Cross-price elasticity estimate	0.04 (0.05)	0.15* (0.05)	-0.12* (0.05)
Model R^2	0.0891		
Oral Nicotine Pouches			
Cross-price elasticity estimate	0.00 (0.00)	---	---
Model R^2	0.3992	---	---
Chewing Tobacco Pouches			
Cross-price elasticity estimate	---	---	---
Model R^2	---	---	---
Nicotine Gum			
Cross-price elasticity estimate	0.14	0.09	0.06

	(0.09)	(0.04)	(0.06)
Model R^2	0.1357		
Nicotine Patches			
Cross-price elasticity estimate	-0.06 (0.06)	0.06 (0.05)	-0.11* (0.06)
Model R^2	0.009	0.059	---

Note: ***p < 0.001, **p < 0.01, *p < 0.05. Cross price elasticity (CPE) estimates were generated by collapsing consumption to price-point averages within each group then regressing the log of average consumption on log of own brand cigarette price for each group (beta coefficient [standard error] shown). All data come from clinical laboratory session 4 (IQOS, Friday). "---" means no demand was reported by any participant at any price-point or an inability to perform statistical comparison between groups.

Table A9-4. *Comparison of IQOS' Cross-Price Elasticity to Other Cigarette Alternatives at Session 4 by Experimental Group*

	IQOS-M group (N=18) *IQOS CPE: 0.67 (0.09)*	**IQOS-T group (N=12)** *IQOS CPE: 0.14 (0.03)*
Nonmenthol cigarettes	0.45*** (0.06)	-0.22*** (0.04)
Cigars	---	---
Cigarillos	0.36* (0.14)	0.23* (0.09)
Pod-Based ENDS	0.50*** (0.10)	0.13*** (0.03)
Refillable Liquid-Based ENDS	0.63*** (0.11)	-0.01 (0.01)
Oral Nicotine Pouches	---	---
Chewing Tobacco	---	---
Nicotine Gum	0.53*** (0.11)	0.06 (0.06)
Nicotine Patches	0.73*** (0.12)	0.09 (0.05)

Note: ***p < 0.001, **p < 0.01, *p < 0.05. Differences in Cross-Price Elasticity (CPE) for IQOS *relative to each alternative product* are presented based on the group level analyses presented in Table A9-3. CPE estimates for each product were generated by collapsing consumption to price-point averages for each group then regressing the log of average consumption on log of own brand cigarette price for each group. Comparisons between product-specific CPE estimates were based on a linear combination of parameters (beta coefficient [standard error] shown above) – a positive value indicates that IQOS was a stronger substitute for own brand menthol cigarettes than the comparator product, a negative value indicates that IQOS was a weaker substitute for own brand menthol cigarettes than the comparator product. All data come from clinical laboratory session 4 (IQOS, Friday). IQOS-M group completed an open-market (i.e., IQOS-M and IQOS-T available) and the IQOS-T group completed a restricted-market (i.e., only IQOS-T available) task. "---" means no demand was reported by any participant at any price-point or an inability to perform statistical comparison between products.

Table A9-5. *Total Nicotine Purchased at Each Price Point in the Experimental Tobacco Marketplace, Clinical Laboratory Session 4*

Own Brand Menthol Cigarette Price	**IQOS-M group (N=18)**	**IQOS-T group (N=12)**	**z, p-value**
$0.12	2304.91 (2166.2) mg	1826.20 (1307.0) mg	z=0.678, p=0.510
$0.50	1147.97 (717.6) mg	928.60 (695.1) mg	z=1.017, p=0.320
$1.00	753.4 (403.2) mg	614.71 (369.5) mg	z=0.804, p=0.433
$1.50	657.05 (425.0) mg	493.71 (366.2) mg	z=1.016, p=0.325
$2.00	652.22 (503.2) mg	467.12 (340.4) mg	z=0.995, p=0.330
$4.00	630.70 (640.4) mg	402.56 (362.0) mg	z=1.439, p=0.158
$8.00	612.41 (653.0) mg	367.37 (372.8) mg	z=1.397, p=0.168
$16.00	705.35 (836.2) mg	336.82 (412.6) mg	z=2.054, p=0.040
Cumulative	7463.98 (4773.2) mg	5437.08 (3014.5) mg	z=1.058, p=0.305

Note: Table shows the sum of all consumption, expressed in terms of milligrams (mg) of nicotine, at each price point in the ETM as well as cumulatively. Mean (standard deviation) values for total tobacco purchasing in the ETM at the group level are shown, along with the p-value from a between-groups Mann-Whitney U test.

Appendix 10. Cross-Price Elasticity (CPE) of Other Tobacco Products with respect to Cigarette Prices, Based on National Sales Data

Tobacco Product	Estimated Cross-Price Elasticity with Respect to Cigarettes
Cigars	-0.652** [-1.16, -0.143]
Cigarillos	0.287 [-0.279. 0.852]
Little Cigars	0.861** [0.122, 1.599]
Roll Your Own Loose Tobacco	1.567** [0.376. 2.759]
Pipe Tobacco	1.749*** [0.676, 2.822]
Moist Snuff	-0.119 [-1.063, 0.826]
Dry Snuff	-0.545 [-1.834, 0.743]
Chewing Tobacco	-0.566 [-1.413, 0.281]
Snus	-0.114 [-0.968, 0.740]
Reusable Electronic Cigarettes	1.983 [-2.238, 6.205]
Disposable Electronic Cigarettes	0.149 [-2.199, 2.497]
Nicotine Replace Therapy Gum	0.267 [-0.242, 0.777]
Nicotine Replace Therapy Patch	0.399 [-0.114, 0.913]
Nicotine Replace Therapy Lozenges	0.648** [0.006, 1.289]

Note: This table is a recreation of Table 3 from Huang et al. (2018). ***p<0.01, p<0.05, *p<0.10, [95% CI]. Models estimates controlled for market, year, and quarter fixed effects. Estimates presented are from the combined "Food, Drug, and Mass Merchandizing Stores" and the "Convenience Stores" model based on Nielsen Sales data (2007-2014). Negative CPE estimates indicate a complement relationship to cigarettes, a zero estimate indicates an independent relationship to cigarettes, and a positive estimate indicates a substitute relationship to cigarettes.

AUGUSTUS MICHAEL WHITE
GOOGLE SCHOLAR PROFILE | LINKEDIN PROFILE

Education

MD Virginia Commonwealth University, School of Medicine — Present
Estimated Graduation Date: May 2026

PhD Virginia Commonwealth University, *Healthcare Policy and Research* — Present
Estimated Graduation Date: May 2024

BA University of Tennessee-Knoxville, College Scholars — May 2018
Emphasis in Health Economics and Policy
Graduated *Summa Cum Laude*
Minor: Public Policy Analytics

Funding History

NRSA Ruth Kirschstein Pre-Doctoral Fellowship (F30DA057047) July 2022- Present
Funding Agency: National Institute on Drug Abuse
PI: Augustus White, BA
Role: Principal Investigator

Wright Scholar of Clinical and Translational Research July 2022-Present
Funding Agency: Virginia Commonwealth University Wright Center for Clinical and Translational Research (UL1TR002649)
PI: Augustus White, BA
Role: Principal Investigator

Virginia Commonwealth University Pre-Doctoral V30 Fellowship July 2022-July 2022
Funding Agency: Virginia Commonwealth University School of Medicine
PI: Augustus White, BA
Role: Principal Investigator
Award was returned upon receipt of F30DA057047 per terms of fellowship

Center for the Study of Tobacco Products (U54DA036105) March 2020- Present
Funding Agency: National Institute on Drug Abuse and FDA Center for Tobacco Products
PI: Thomas Eissenberg, PhD and Allison Breland, PhD
Role: Graduate Research Assistant/Trainee

Peer- Reviewed Publications

Yingst, J., Midya, V., **White, A.,** Foulds, J., Cobb, C., Veldheer, S., Miao-Shan, Y., & Eissenberg, T. (2024). Effects of liquid nicotine concentration and flavor on the acceptability of electronic nicotine delivery systems (ENDS) among people who smoke participating in a randomized controlled trial to reduce cigarette consumption. *Tobacco Control,* In press.

Hoetger, C., **White, A.**, Bono, R., Hall, C., Hood, K., Everhart, R., Nana-Sinkham, P., Barnes, A., and Cobb, C. (2023). Perceptions of African American youth and adults regarding tobacco use-related factors in their community: A mixed-methods approach in Richmond, Virginia. *Family and Community Health*. In press.

Bono, R., **White, A.,** Bickel, W., Lipato, T., Cobb, C., and Barnes, A. (2023). Beyond Cross-Price Elasticity: What Else Can We Learn from the Cross-Price Purchase Task? *Journal of Experimental Analysis of Behavior*. In press.

White, A., Patev, A., Imran, R., Goden, A., Rudy, A., Bajwa, H., Hood, K., Guy, M., Cobb, C., and Barnes, A. (2023). Health-Related Benefits of Quitting and Ex-Smoker Testimonials May Help African American/Black Menthol Smokers Quit: Implications for Flavor Bans from a Mixed Methods Study. *Nicotine and Tobacco Research.* In press.

White, A., Garner, W., and Barnes, A. (2023). Racial/Ethnic Differences in the Association Between Menthol Cigarette Use and Mental Illness Among Adults Who Smoke in the United States. *Journal of Ethnicity in Substance Abuse.* In press.

White, A., Goden, A., Rudy, A., Bajwa, H., Hood, K., Guy, M., Cobb, C., and Barnes, A. (2022). Responses of African American/Black Individuals who use Menthol Cigarettes to Potential Flavored Tobacco Bans. *American Journal of Preventative Medicine*. In press. doi:10.1016/j.amepre.2022.12.005.

White, A., Bono, R., Lester, R., Underwood M., Hoetger, C., Cobb, C., and Barnes, A. (2022). The Electronic Nicotine Delivery System (ENDS) Purchase Task: Are Results Sensitive to Price Framing? *Experimental and Clinical Psychopharmacology.* Advance online publication. doi:10.1037/pha0000631

Hoetger, C., Bono, S., **White, A**., Barnes, A., and Cobb, C. (2021). Limits on E-cigarette Nicotine Concentration in Markets with Open-system Devices: The Interaction of Nicotine Concentration and Device Power on E-Cigarette Abuse Liability. *Experimental and Clinical Psychopharmacology, 30(6),* 973-982. https://doi.org/10.1037/pha0000523

White, A., Li, D., Snell, L.M., O'Connor, R., Hoetger, C., Croft, D., Lester, R., McIntosh, S., Underwood, M., Schneller, L., Breland, A., Barnes, A., Cobb., C, and Ossip, D. (2021). Perceptions of Tobacco Product-Specific COVID-19 Risks and Changes in Tobacco Use Behaviors Among Smokers, E-Cigarette Users, and Dual Users. *Nicotine and Tobacco Research*, *23(9),* 1617-1622. doi:10.1093/ntr/ntab053.

White, A., Ossip, D., Li, D., Snell, L.M., O'Connor, R., Hoetger, C., Croft, D., Lester, R., McIntosh, S., Underwood, M., Schneller, L., Breland, A., Cobb., C, and Barnes, A.

(2021). Tobacco Product Access Scenarios Influence Hypothetical Use Behaviors. *Tobacco Regulatory Science*, *7(3)*, 184-202. doi:10.18001/TRS.7.3.4.

Non-Peer-Reviewed Publications

Barnes, A., **White, A.,** and Shadowen, H. (2022). Chapter 4: The Demand for Health. In Rice, T., Barnes, A., and Unruh, L. (Eds.), *The Economics of Health, Reconsidered (5th Edition).* Health Administration Press.

- I authored the initial draft of one-third of the chapter, performed the requisite literature review for all sections, designed all figures, wrote the discussion questions, and created a supplementary PowerPoint for instructors.

Barnes, A., and **White, A**. (2022). Chapter 10: Behavioral Economics. In Rice, T., Barnes, A., and Unruh, L. (Eds.), *The Economics of Health, Reconsidered (5th Edition).* Health Administration Press.

- I authored the initial draft of the entire chapter, performed the requisite literature review for all sections, designed all figures, wrote the discussion questions, and created a supplementary PowerPoint for instructors.

White, A. (2021). The Medicaid Expansion: Modeling of Important Factors in State Decision Making. *Haslam Scholars Projects.* https://trace.tennessee.edu/utk_haslamschol/21

- I was responsible for study conceptualization, authored the first draft the entire manuscript, downloaded and managed the dataset, and performed all analyses.

Policy and Community Briefs

White, A., Patev, A., Imran, R., Goden, A., Rudy, A., Bajwa, H., Hood, K., Guy, M., Cobb, C., and Barnes, A. (2022). What do Black/African American menthol smokers living in Richmond say they will do after menthol cigarettes are banned? Community brief.

Sheng, Y., Cunningham, P., **White, A.**, Walker, L., and Barnes, A. (2019). "Opioid Prescribing for Medicaid Members Drops Sharply after 2016," VCU ARTS Evaluation Update – Policy Analysis Brief. https://hbp.vcu.edu/media/hbp-dev/pdfx27s/policy-briefs/arts/HBP_ARTSIssue03_ACC.pdf

Teaching experience

White, A. (2022). IBMS 653: Medical Scientist Training Program Seminar (VCU; Instructor: Dr. Gretchen Neigh). Teaching Assistant. Hybrid.

White, A. (2022). *Behavioral Economics*. Healthcare Policy and Research 731: Principles of Health Economics (VCU; Instructor: Dr. Michael Preston). Invited Guest Lecture. Virtual.

White, A. (2021). *COVID-19 Vaccines: Insights for Experimental Design*. Psychology 317: Experimental Methods (VCU; Instructor: Dr. Caroline Cobb). Invited Guest Lecture. Virtual.

Research Experience

Center for the Study of Tobacco Products, VCU July 2022- Present
Principal Investigator, Advisor: Dr. Andrew Barnes, Richmond, VA

- Completing a NIDA-supported dissertation project entitled: The Abuse Liability of a Novel Heated Tobacco Product (IQOS) and Its Feasibility as a Menthol Cigarette Substitute.
- The aims of this project, for which I am the principal investigator, are to understand how flavors influence the nicotine delivery, puff topography, subjective use experience, and substitution feasibility of heated tobacco products among individuals that use menthol cigarettes.

Center for the Study of Tobacco Products, VCU May 2019- July 2022
Graduate Research Assistant, Advisor: Dr. Andrew Barnes, Richmond, VA

- Employed and designed behavioral economic tasks in a clinical laboratory setting to assess abuse liability of cigarettes and alternative nicotine delivery systems (e.g., electronic cigarettes). Aims of this research included understanding how nicotine concentration, device wattage, and nicotine flux influence measures of abuse potential among individuals who use tobacco products.
- Responsibilities included administering sessions in the experimental lab, performing demand curve and other statistical analyses, creating computerized progressive and fixed ratio responding tasks, and creating presentations of findings for submission to academic conferences/journals
- Helped develop, administer, and lead a multi-site research team in conducting online experiments related to tobacco use behaviors, including responses to the COVID-19 pandemic and potential changes in tobacco regulatory policies

Department of Family Medicine, VCU May 2019- October 2019
Student Research Assistant, Advisor: Dr. Alex Krist, Richmond, VA

- Created a theoretical framework to aide in the use of the Virginia All-Payer Claims Database for assessing the quality of care provided to insured patients in Virginia
- This work was eventually paired paired with community health and SES data to augment the Virginia HealthLandscapes project, a publicly-available geospatial analysis tool that provides information on health trends at the zip code level.

Department of Health Behavior and Policy, VCU June 2018 – August 2018
Student Research Assistant, Advisor: Dr. Andrew Barnes, Richmond, VA

- Collected data and drafted a report which detailed the ways in which other states had evaluated the effectiveness of their Medicaid expansion programs in order to aid in the planning of the evaluation for Virginia's own Medicaid expansion

Department of Health Behavior and Policy, VCU June 2018 - August 2018
Student Research Assistant, Advisor: Dr. Peter Cunningham, Richmond, VA

- Analyzed data from the Virginia All Payer Claims Database to prepare a policy brief that detailed trends in opioid prescribing patterns among Virginia Medicaid beneficiaries, as well as assessed the effectiveness of state-level prescribing policies which aimed to combat the opioid epidemic

Department of Public Health, University of Tennessee January 2016 – May 2018
Student Research Assistant, Advisor: Dr. Robert Lieberthal, Knoxville, TN

- Proposed, designed, and executed a research project that used econometric techniques (e.g., event-history analysis, survival analysis) to evaluate state-level political and economic factors which influenced adoption of the Affordable Care Act's Medicaid expansion

Project Sisyphus, Oak Ridge National Laboratory May 2014 – December 2015
*Undergraduate Research Assistant***,** Advisor: Dr. Jerome Baudry, Oak Ridge, TN

- Created a database potential therapeutic drug targets that could be used in high-throughput drug candidate screening performed on the Titan supercomputer

Honors and Awards

Outstanding Student Award (Dept Health Behavior and Policy) December 2023
Awarded by the faculty of VCU Department of Health Behavior and Policy to the top overall student in the Healthcare Policy and Research PhD program ($500).

Sherman Master Memorial Scholarship (Best Overall Poster) November 2023
Awarded to the best overall poster, based on an expert judging panel's evaluation, at the Virginia Society of Addiction Medicine Annual Meeting.

Dissertation Completion Award May 2023
Awarded on a merit basis to a graduate student in the Department of Health Behavior and Policy to support completion of their dissertation project ($800)

School of Medicine Travel Award February 2023
Awarded on a merit-basis to graduate students within the VCU School of Medicine to support travel to academic conferences to present their research ($750).

National Research Service Award Ruth Kirchstein Fellowship (F30) July 2022
Nationally-competitive award from the National Institute on Drug Abuse for a 5-year award period ($240,000) on a merit basis to pre-doctoral level MD-PhD candidates to support their training as a physician-scientist (award number F30DA057047).

Wright Scholar for Clinical and Translational Research May 2022
Awarded once annually to MD-PhD students at Virginia Commonwealth University with exceptional promise to conduct clinical and translational research ($3,300/year to support training and research project).

Charles C. Clayton Scholar April 2022
Awarded once annually to the top (second-year or higher) PhD student within each department of the Virginia Commonwealth University Graduate School ($1,000).

Department of Health Behavior and Policy's "Amazing Addition" December 2020
Awarded by the VCU Department of Health Behavior and Policy, based on a vote of the current students and faculty, to the new student who most demonstrates tremendous promise in research and academic achievement.

SRNT Annual Meeting – Competitive Travel Award December 2020
A competitive, full-cost of registration grant to attend and present research at the 2021 Society for Research on Nicotine and Tobacco (SRNT) annual meeting ($125)

Chancellor's Citation for Academic Excellence May 2018
Presented to graduating seniors who have displayed a "true commitment to academic excellence, in the classroom and out, while at the University of Tennessee."

Phi Kappa Phi Award for Outstanding Undergraduate Research April 2018
Presented to the undergraduate student with the best overall social-science related research project at the University of Tennessee.

Gold Award at Eureka Research Conference April 2018
Presented to the student with the top research project and poster presentation in the field of social science at the University of Tennessee's annual undergraduate research conference.

1st Place – 3 Minutes to Win It Video Competition April 2018
Presented to the student who produces the best 3-minute video presentation explaining their thesis research and encouraging other undergraduate students to pursue research opportunities.

Fred J. Holly Award for Outstanding Undergraduate Research January 2018
Presented to the undergraduate student with the top overall research project in Econometrics for the academic year.

College Scholar Excellence Award May 2017
Award is given to annually to a member of the College Scholars Program to financially support the execution of a proposed research project ($2,500).

Baker Scholar April 2016
Designation given to select undergraduate students who display a strong interest and aptitude in the field of public policy or policy research.

College Scholar October 2016
Designation given to select undergraduate students who wish to pursue a degree program not offered by the University of Tennessee with permission to work with a faculty mentor to develop a unique curriculum, course of study, and honors thesis project.

Haslam Scholar May 2014
Designation given to the top 15 entering students of each class at the University of Tennessee, associated with a full tuition/fees/stipend scholarship, curricular and research enrichment opportunities, and study abroad support (~$100,000 over 4 years).

Invited Talks, Podium Presentations, Symposiums

White, A., Imran, R., Cobb, C., Perera, R., Eissenberg, T., Barnes, A. (2024). The Acute Effects of a Menthol- and Tobacco-Flavored Heated Tobacco Product (IQOS) Among Individuals Who Use Menthol Cigarettes. Society for Research on Nicotine and Tobacco. Podium Presentation. Edinburgh, Scotland.

White, A. (2023). Understanding Youth Tobacco Use II: Implications for Prevention. Virginia Foundation for Healthy Youth Annual Meeting. Moderator. Richmond, VA.

White, A. (2023). Insomnia is Associated with Neurofunctional Differences among Females Treated for OUD. Virginia Commonwealth University IVY Lab. Invited Talk. Virtual.

White, A. (2022). Predicting the Effect of American/Black Individuals who use Menthol Cigarettes to Potential Flavored Tobacco Bans. Virginia Commonwealth University Center for the Study of Tobacco Products. Invited Talk. Richmond, VA.

White, A. (2022). Prevalence and Risk Factors for Medical Debt and Subsequent Changes in Social Determinants of Health in the United States by Himmelstein et al. AcademyHealth Student Chapter at VCU Journal Club. Invited Talk. Richmond, VA.

White, A., Goden, A., Rudy, A., Bajwa, H., Hood, K., Guy, M., Cobb, C., and Barnes, A**.** (2022). Predicting the Effects of Potential Tobacco Product Flavor Regulations Among African American/Black Menthol Cigarette Smokers. *NIH Tobacco Regulatory Science Meeting.* Oral Podium Presentation. Virtual.

White, A. and Eversole, A. Using Crowdsourcing to Study the Differential Effects of Cross-Drug Withdrawal for Cigarettes and Opioids in a Behavioral Economic Demand Framework. *CASEL Journal Club.* Invited Presentation. Virtual.

White, A. (2022). Strategies for Crowdsourcing Data in Cancer Prevention and Control Research. *T32 Postdoctoral Training Seminar Series.* Invited Talk. Richmond, VA.

White, A. (2022). Peering Through the Smoke and Mirrors: A Primer on Tobacco Regulatory Science. *Virginia Commonwealth University MD-PhD Seminar.* Invited Talk. Richmond, VA.

White, A. (2021). Learning to Lead in a Technical World. Technology Student Association National Conference. Keynote Speaker. Virtual.

White, A. (2021). The Association of Menthol Cigarette Use with Any Mental Illness (AMI) and Serious Mental Illness (SMI) Among Smokers. 24th Annual VCU Graduate Student Symposium. Oral Podium Presentation. Virtual.

White, A., Barnes, A, and Garner, W. (2021).The Association of Menthol Cigarette Use with Any Mental Illness (AMI) and Serious Mental Illness (SMI) Among US Smokers. VCU Center for the Study of Tobacco Products Scientific Meeting. Invited Presentation. Virtual.

White, A., Ossip, D., Snell, L.M., Li, D., Hoetger, C., O'Connor, R., Lester, R., Croft, D., Underwood, M., McIntosh, S., Breland, A., Schneller, L., Cobb, C., and Barnes, A. (2021). Restricted Access to Tobacco Products and Smoking Cessation Therapies Influences Hypothetical Tobacco Use Behaviors Among Smokers and E-Cigarette Users: Results from an Online Experiment. Society for Research on Nicotine and Tobacco. Baltimore, MD. Oral Podium Presentation. Virtual.

White, A., Ossip, D., Snell, L.M., Li, D., Hoetger, C., O'Connor, R., Lester, R., Croft, D., Underwood, M., McIntosh, S., Breland, A., Schneller, L., Cobb, C., and Barnes, A. (2020). Restricted Access to Tobacco Products Influences Hypothetical Tobacco Use Behaviors Among Smokers and E-Cigarette Users: Results from an Online Experiment. Tobacco Centers for Regulatory Science Grantee Meeting. Virtual. Oral Podium Presentation. Virtual.

White, A. (2020). COVID-19 and its Effects on Users of Tobacco Products. VCU Center for the Study of Tobacco Products Scientific Meeting. Richmond, VA. Invited Presentation. Virtual.

White, A. and Westfall, M. (2019). Integrating *HealthLandscapes* and Virginia's All-Payer-Claims-Database (APCD): A Framework for Evaluating the Quality of Care Provided to Insured Patients in Virginia. Department of Family Medicine and Population Health's Summer Medical Student Research Day. Oral Podium Presentation. Richmond, VA.

White, A. (2018). The Medicaid Expansion: Modeling of Important Factors in State Decision Making. Haslam Scholar Research Colloquium. Oral Podium Presentation. Knoxville, TN.

White, A. (2018). The Medicaid Expansion: Modeling of Important Factors in State Decision Making. Public Health Research Day. Oral Podium Presentation. Knoxville, TN.

Poster Presentations

White, A., Imran, R., Cobb, C., Perera, R., Eissenberg, T., Bickel, W., Barnes, A. (2024). Substitution of Menthol- and Tobacco-Flavored Heated Tobacco Products (IQOS) For Menthol Cigarettes: Insights from a Randomized Clinical Trial and the Experimental Tobacco Marketplace. Society for Research on Nicotine and Tobacco. Poster. Edinburgh, Scotland.

White, A., Wu, J., Hurley, J., Brown, T., Lemay, M. (2023). Brugada Think About it! ECG Monitoring in the Addiction Clinic. Virginia Society of Addiction Medicine Annual Meeting. Poster. Virginia Beach, VA.

White, A., Imran, R., Gaitan, N., Cobb, C., Perera, R., Eissenberg, T., Barnes., A. (2023). The Potential Role of Heated Tobacco Products as a Menthol Cigarette Substitute. Virginia Society of Addiction Medicine Annual Meeting. Poster. Virginia Beach, VA.

White, A., Eglovitch, M., Parlier-Ahmad, A.B., Dzierzewski, J., Moeller, F.G., Martin, C. (2023). Insomnia is Associated with Neurofunctional Differences among Females Treated for Opioid Use Disorder. College on Problems of Drug Dependence Annual Meeting. Poster. Denver, CO.

White, A., Golden, A., Rudy, A., Bajwa, H., Guy, M.C., Hood, K.B., Cobb, C.O., Barnes, A.J. (2023) Predicting the Effects of Proposed Tobacco Product Standards Among African American/Black Menthol Cigarette Smokers. AcademyHealth Annual research Meeting. Accepted Poster. Seattle, WA.

White, A., Eglovitch, M., Parlier-Ahmad, A.B., Dzierzewski, J., Moeller, F.G., Martin, C. (2023). Insomnia is Associated with Neurofunctional Differences among Females Treated for Opioid Use Disorder. American Society of Addiction Medicine. Accepted Poster. Washington, DC.

White, A., Eglovitch, M., Parlier-Ahmad, A.B., Dzierzewski, J., Moeller, F.G., Martin, C. (2023). Insomnia is Associated with Neurofunctional Differences among Females Treated for Opioid Use Disorder. MD-PhD Second Look Research Symposium. Poster. Richmond, VA.

White, A., Golden, A., Rudy, A., Bajwa, H., Guy, M.C., Hood, K.B., Cobb, C.O., Barnes, A.J. (2023) Predicting the Effects of Proposed Tobacco Product Standards Among African American/Black Menthol Cigarette Smokers. Society for Research on Nicotine and Tobacco Annual Research Meeting. Poster. San Antonio, TX.

White, A., Golden, A., Rudy, A., Bajwa, H., Guy, M.C., Hood, K.B., Cobb, C.O., Barnes, A.J. (2023). Health-related benefits of quitting and ex-smoker testimonials may help African American/Black Menthol Smokers Quit: Implications for flavor bans. Society for Research on Nicotine and Tobacco Annual Research Meeting. Poster. San Antonio, TX.

White, A., Cobb, C., and Barnes, A. (2022). Crowdsourcing Tobacco Research on Amazon's Mechanical Turk (mTurk): Strategies to Collect Valid Data Quickly and Conduct Online Experiments. Society for Research on Nicotine and Tobacco Annual Meeting. Baltimore, MD. Poster.

White, A., Bono, R., Scholtes, R., Underwood, M., Hoetger, C., Cobb, C., and Barnes, A. (2022). The Electronic Cigarette Purchase Task: Are Results Sensitive to Price Framing? Society for Research on Nicotine and Tobacco Annual Meeting. Baltimore, MD. Poster.

White, A., Bono, R., Scholtes, R., Underwood, M., Hoetger, C., Cobb, C., and Barnes, A. (2021). The Electronic Cigarette Purchase Task: Are Results Sensitive to Price Framing? National Institutes of Health Tobacco Regulatory Science Meeting. Virtual. Poster.

White, A., Barnes, A., and Garner, W. (2021).The Association of Menthol Cigarette Use with Any Mental Illness (AMI) and Serious Mental Illness (SMI) Among US Smokers. AcademyHealth Annual Research Meeting. Poster. Virtual.

White, A., Li, D., Snell, L.M., O'Connor, R., Hoetger, C., Croft, D., Lester, R., McIntosh, S., Underwood, M., Schneller, L., Breland, A., Barnes, A., Cobb., C, and Ossip, D. (2021). Perceptions of Tobacco Product-Specific COVID-19 Risks and Changes in Tobacco Use Behaviors Among Smokers, E-Cigarette Users, and Dual Users. Society for Research on Nicotine and Tobacco. Baltimore, MD. Poster.

White, A., Bono, R., Lester, R., Barnes, A., and Cobb, C. (2019). Effects of E-Cigarette Power and Nicotine Content on Indices of Abuse Liability Among Dual Users and Exclusive E-Cigarette Users. National Institutes of Health Tobacco Regulatory Science Meeting. Bethesda, MD. Poster.

White, A. (2018). The Medicaid Expansion: Modeling of Important Factors in State Decision Making. AcademyHealth Annual Research Meeting. Seattle, WA. Poster.

Professional Affiliations

College on Problems of Drug Dependence 2023-Present
Student member

American Society of Addiction Medicine 2023-Present
Student member

Ad Hoc Peer Reviewer 2019-Present
Nicotine and Tobacco Research
American Journal of Pathology
Substance Abuse Treatment, Prevention, and Policy
Journal of Lung Health and Disease

Society for Research on Nicotine and Tobacco (SRNT) 2018-Present
Student member
Operations Coordinator, Policy Research Network (Nov 2022 – Present)

Student Family Medicine Association 2018-Present
Student member

AcademyHealth Student Chapter at VCU 2018-Present
Co-President, responsible for planning and executing monthly chapter events (2019-2022)
Chapter Treasurer, responsible for proposing and managing budget of $4,200 (2018-2019, 2022 - 2023).