Nicotine and Tobacco Research, 2023, **XX**, 1–7
https://doi.org/10.1093/ntr/ntad216
Advance access publication 1 November 2023
Original Investigation

Chemicals in Cigarette Flavor Capsules From Guatemala and Mexico

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Abstract

Background: The global market share for cigarettes with flavor capsules has grown exponentially over the last decade, particularly in Latin America. When smoking, consumers crush a liquid capsule in the filter that flavors the smoke. Little is known about the chemical constituents of the liquids in capsules or their potential health risks.

Methods: Based on consumer data and availability in Mexico and Guatemala, 31 flavor capsule brands were purchased (19 and 12, respectively) in 2020. Since some cigarettes included multiple capsules in a stick (up to 2) or pack (up to 4), the final analytic sample included 50 capsules. We conducted qualitative and quantitative analyses using gas chromatography with mass spectrometry (GC-MS, Agilent Technologies, Inc)

Results: The qualitative analysis detected 296 compounds (range = 9–67 per capsule), and all capsules contained menthol. Among the compounds detected in more than half the sample were limonene, menthone, benzaldehyde, eucalyptol, and triacetin. Traces of nicotine were found in 22% of the capsules. In the quantitative analysis, menthol concentrations were 33 times greater than the next most common compound (limonene). Benzyl alcohol and vanillin were also found in high concentrations. Comparing same-brand varieties across countries showed substantial variability in the concentration of menthol and other compounds.

Conclusions: Menthol is an omnipresent constituent in capsule cigarettes, perhaps because of its anesthetizing and reinforcing addictive properties. Other compounds found are toxic, potentially carcinogenic, and may enhance addictiveness. Variance in the presence and concentrations of such compounds highlights the importance of product standards to regulate capsule content.

Implications: This study evaluated the chemical content of capsule cigarettes from two Latin American countries that have two of the highest market shares for capsule cigarettes worldwide. Compared to other studies, our assessment included brand varieties from two countries to compare the differences in chemical content by country. Our results yield that menthol is found in all capsules, and that other chemicals found may prolong nicotine exposure and therefore reinforce the addictive properties of cigarettes.

Background

Flavor capsule cigarettes, first introduced in 2007, embed a liquid-filled capsule in the filter that the user can crush to flavor tobacco smoke.[1] Filters can contain one or more capsules and brand descriptors can communicate specific flavors, like beverages, cocktails, or fruits (eg, strawberry, blueberry). They might also use "concept" descriptors that do not explicitly identify flavors (eg, Mega Ice Express, Tokyo midnight, Ruby Fusion).[2–4] According to tobacco industry documents, capsule cigarettes were created to reduce harm perceptions, improve cigarette aftertaste, and increase appeal to youth.[5] Indeed, consumers associate flavor capsule cigarettes with greater appeal and taste, lower harm, greater smoothness, and reduced odor compared to regular cigarettes.[6–10] Youth and susceptible nonsmokers also find them more appealing[11] and less harmful than noncapsule cigarettes.[12]

Since 2007, flavor capsule cigarette use has increased worldwide, especially in low- and middle-income countries (LMICs).[9] By 2014, according to Euromonitor worldwide data, Latin America had become the region where capsule cigarettes account for the largest market share.[2,13] Among people who smoke, preference for flavor capsule cigarettes has been documented in 11 countries,[11] with prevalence being highest in Mexico (43%) and Chile (40%), far higher than in South Korea (18%), the third highest prevalence.[3,14,15] Greater preference for flavor over nonflavor capsule cigarettes has also been found among adolescents in Mexico, Chile, South Korea, the United States, the United Kingdom, and Australia.[3,8,14–18] In Mexico, women and younger smokers are more likely to prefer and use brands with flavor capsules than noncapsule cigarettes.[8,15] There are no data on capsule use among adults in Guatemala, though

Received: April 30, 2023. Revised: September 6, 2023. Accepted: October 22 2023.

data from adolescents indicate that it is a popular first tobacco product used.[19]

Tobacco products contain chemicals and additives usually added to the tobacco rod or processed tobacco leaves, some of which are also used in capsule liquids.[4,20–22] A qualitative analysis of menthol and flavorings of 12 US cigarette brands, including 2 with capsules, found 11 chemical flavors (menthol and methyl acetate present in both capsules).[23] Another analysis of 22 capsule cigarettes from Mexico detected 101 compounds, although the average number of compounds per capsule was not reported.[4] The total cigarette menthol levels ranged from 2.97 to 11.9 mg/cig (mean 7.18) and triacetin from 4.38 to 19.4 mg/cig (mean 11.75).[4] The level of menthol reported in this study is higher than what is found on average in noncapsule mentholated cigarettes (4.75 mg/cig).[4,24] Two analyses of capsules have been conducted in South Korea. One in 2018, included 36 capsules and detected 86 compounds (mean = 9/capsule).[22] Another in 2022, analyzed 33 capsules that contained 128 compounds (mean = 14/capsule).[21] In both samples, methyl acetate, methyl octanoate, pulegone, and linalool were detected in almost all capsules.[21,22] All capsules had menthol.[21,22] The prominence of menthol across countries might be due to its anesthetic properties,[25,26] which, in conventional cigarettes, can make it easier to inhale the smoke. Mentholated tobacco in cigarettes appeals to and helps recruit new smokers, reinforces the addictive properties, and reduces harm perceptions.[25,27,28] Some other chemicals found in flavor capsules (eg, limonene, propionaldehyde, benzyl alcohol, cinnamaldehyde) have been classified by the Global Harmonized System as flammable, fatal if swallowed, and skin irritants.[29] Pulegone, also found in capsules, is a carcinogen in rodents, and banned by the U.S. Food and Drug Administration (FDA) from use as a synthetic food additive.[30–33]

Guatemala does not regularly collect data on smoking prevalence, with the last survey in 2015 indicating a 25.4% prevalence among men.[34] Despite ratifying the Framework Convention on Tobacco Control (FCTC) in 2004, smoke-free environment is the only FCTC policy implemented to date, largely due to strong tobacco industry interference.[35,36] Neighboring Mexico has one of the highest numbers of adult smokers in Latin America,[37] and, like Guatemala, industry interference is high.[35] As Mexico has adopted many FCTC policies (eg, smoke-free environments, pictorial warning labels, taxes, marketing bans), the prevalence of smoking has remained stable, although the frequency of smoking has decreased (eg, 60% of smokers are nondaily).[38]

The expanding marketing and popularity of flavor capsule cigarettes in Mexico are the primary explanation for why smoking prevalence has not declined.[10,17] Both Mexico and Guatemala are among the top five countries with the highest market share for flavor capsules (27.3% and 32.6%% in 2020, respectively).[13] Yet, neither has regulations for menthol cigarettes or flavor capsule cigarettes and their contents remain unknown.[39] Therefore, we sought to evaluate the chemical content of flavor capsule cigarettes in these countries to inform policy makers and tobacco control advocates.

Methods

Sample Selection

Between January and July 2020, we identified flavor capsule cigarettes available for purchase. In Guatemala, we searched the websites of supermarkets, grocery stores, and delivery apps to identify available capsule cigarettes. In Mexico, we used data from a 2018–2020 online consumer panel of adult smokers to identify the most popular brands with capsules.[10,40] We then visited supermarkets and convenience stores, in Guatemala City and Mexico City, to confirm their availability and identify other brands with capsules.[10] Cigarettes were grouped by brand and flavor category. Those available in both countries or brand varieties with similar flavors (eg, berries, menthol) were purchased (Table S1). Due to their prominence in one country but not the other, we also included L&M from Guatemala and Benson & Hedges from Mexico, as both brands were capsule cigarettes. A total of 31 cigarette brand varieties were purchased, 15 with two capsules in the filter (Table 1). In Guatemala and Mexico, Lucky Strike "Click and Mix" brand contains four different possible capsule flavors in a pack (albeit with only one capsule in each stick's filter). Our final analytic sample included 50 capsules.

Sample Preparation

Purchased cigarettes were stored at 4°C in a refrigerator. Using razor blades and forceps, capsules were removed from the filter. Each capsule was placed in a 1.5-mL microcentrifuge tube and punctured using a 22-gauge needle and 1-cc syringe to obtain the liquid to be stored until analyzed. Preparation for qualitative analysis included pipetting an aliquot of 10 µL and adding to 1.5-mL amber glass gas chromatography (GC) vials along with 1 mL of high-performance liquid chromatography grade dichloromethane, followed by vortexing for 15 minutes. Liquids were analyzed using gas chromatography

Table 1. Flavor Capsule Cigarettes Sample Characteristics From Mexico City and Guatemala City, 2021

	Mexico		Guatemala		Compounds found per capsule		
Brand	Varieties	Capsules*	Varieties	Capsules*	Minimum	Maximum	Mean (SD)
Marlboro	5	7	2	3	14	61	41 (18)
Pall Mall	6	10	2	3	9	63	45 (15)
Lucky Strike	5	10	4	9	21	67	48 (13)
Benson & Hedges	3	3	—	—	20	53	31 (19)
L&M	—	—	4	5	24	58	43 (12)
Total	19	30	12	20			

*Capsule column represents the total capsules found by brand; varieties may have more than one capsule.
—Not present in that country.

with mass spectrometry (GC-MS, Agilent Technologies, Inc), using a modification of Agilent´s method for Qualitative Analysis of E-Cigarette Liquids.[41] All analyses were run in triplicate. Sample preparation for quantitative analysis included adding 30 µL of each extracted capsule to 3 mL of liquid chromatography–mass spectrometry grade methanol (MeOH) with internal standards. Each liquid was vortexed for 5 minutes and transferred to 1.5-mL amber glass GC vials for analysis with gas chromatography with quadrupole time-of-flight mass spectrometry (GC-qTOF-MS, Agilent Technologies, Inc). Additional dilutions using either reduced volumes of capsule liquid or increased MeOH volumes were prepared when necessary to quantify target compounds within acceptable calibration ranges. All analyses were conducted at Roswell Park Comprehensive Cancer Center in the United States.

Qualitative Analysis

Chemicals exceeding predetermined peak area thresholds from the GC-MS spectra were identified using three different libraries: NIST 17 MS,[42] the FFNSC 3,[43] and a laboratory-generated using Agilent Unknowns Analysis software (version 10.2). For the Unknowns Analysis, a minimum match factor of 70 between the spectral libraries and resolved peaks was used to identify larger flavoring peaks, where the largest match factor was used as the chemical identifier. Smaller peaks considered to be artifacts from the column and solvent were excluded either by falling below peak area thresholds or the acceptable match factor. A more detailed explanation of the acquisition and data processing method has been published elsewhere.[44]

Quantitative Analysis

Flavoring chemicals commonly found in electronic cigarette (e-cigarettes) liquids, including cinnamaldehyde, triacetin, benzaldehyde, and eugenol, are linked to inhalation toxicity and in vitro toxicity to respiratory cells, and thus were quantified using an established GC-qTOF-MS method.[45] Calibration curves for 20 targeted flavorings were prepared to cover a concentration range with a lower limit of quantification of 0.02 mg/mL to an upper limit of 10 mg/mL. Correlations of determination (r^2) for each chemical exceeded 0.985 with average response factors greater than 0.01 and relative standard error below 20%. Method validation results, following guidelines from the Scientific Working Group for Forensic Toxicology (SWGTOX) Standard Practices for Method Validation in Forensic Toxicology (SWGTOX, 2013) have been published elsewhere.[45] Nicotine peaks were detected through qualitative analysis; to further explore their presence in capsules, quantitative analysis was also performed.

Results

Qualitative Analysis

Our results show that a total of 296 compounds were detected in capsules (all had menthol). Flavoring compounds detected in more than half the sample included dl-limonene (citrus), 1-menthone (minty), benzaldehyde (fruity), eucalyptol (minty), propionaldehyde (musty), methyl acetate (minty), butanoic acid (sour), triacetin (creamy), and caryophyllene (spicy) (Table S2).[46] Lucky Strike capsules had the largest number of compounds (mean 48, min 21, and max 67; Table 1). Benson & Hedges (min 20 and max 53) had the lowest average number of detected compounds per capsule (31). Nicotine was detected in 22% (11) of the capsules.

Quantitative Analysis

In all capsules, menthol had the highest concentration, ranging from 6.74 to 374.85 mg/mL (Table 2). Most brands with high menthol concentration were not labeled accordingly, instead, they included other descriptors (Table S1). Those with the highest concentrations (Pall Mall Tokyo Midnight 360 mg/mL, and Lucky Strike After Hours Double Click Berry 302 mg/mL, Figure 1) did not include the term "menthol" on the packaging. For those brands found in both countries, menthol differed by country (Figure 2). Lucky Strike "Click and Mix"

Table 2. Chemical Concentration in a Sample of 50 Flavor Capsules From Mexico and Guatemala City, 2021

Compound	Number of capsules with compound (n = 50)	LLOQ (mg/mL)	Concentration measured (mg/mL)		
			Minimum	Maximum	Mean (SD)
L-menthol	50	0.08	6.74	374.85	192.2(77.65)
DL-limonene	37	0.08	0.1	35.45	5.82 (7.14)
Eucalyptol	33	0.08	0.08	9.87	4.21 (3.72)
Benzyl alcohol	21	0.02	0.02	18.8	2.25 (5.75)
(+)Pulegone	13	0.08	0.09	1.03	0.45 (0.34)
Triacetin	8	0.08	0.08	0.16	0.10 (0.02)
Vanillin	6	0.63	0.83	11.92	4.17 (5.13)
Ethyl maltol	5	0.63	2.78	7.34	5.13 (2.08)
Trans-Cinnamaldehyde	4	0.16	3.56	3.75	3.64 (0.08)
Benzaldehyde	3	0.04	0.29	0.61	0.48 (0.16)
Eugenol	2	0.04	0.04	0.05	0.04 (0.004)
Ethyl vanillin	2	0.31	10.85	17.18	14.01 (4.47)
Nicotine	11	0.039	0.018+	0.058	0.031(0.012)

LLOQ = lower limit of quantification.
+Values below LLOQ are considered estimated.

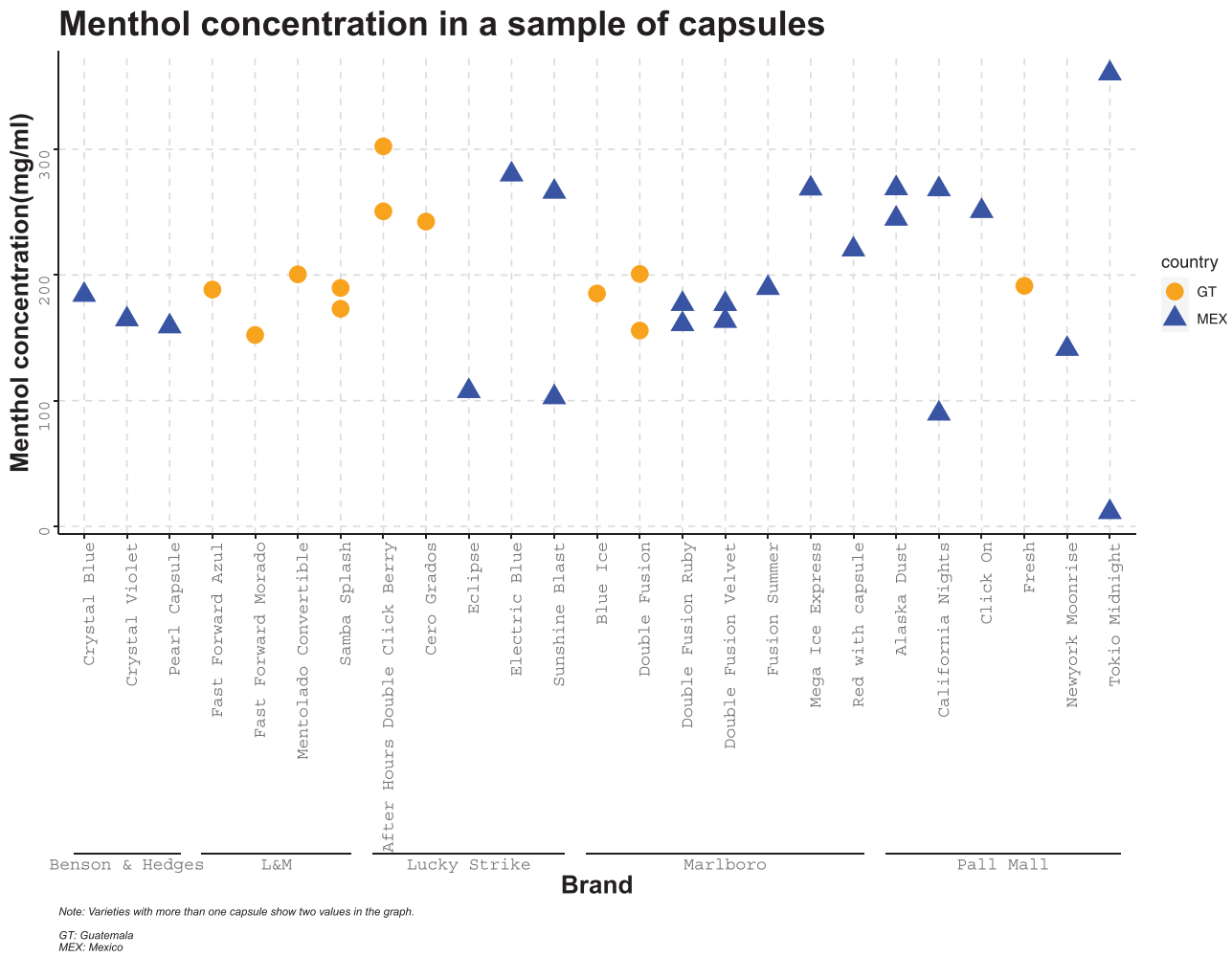

Figure 1. Menthol concentrations in flavor capsules by brand from Guatemala and Mexico, 2021. *Varieties with more than one capsule have two measures.

had the largest differences. Those from Mexico had higher concentrations than Guatemala in three of the four capsules analyzed. In the Mexican sample, concentrations ranged from 111.31 to 374.85 mg/mL, compared to the Guatemalan's which ranged from 6.74 to 257.60 mg/mL. Similarly, the menthol concentration for each of the two capsules in Pall Mall Mykonos Nightfall from Guatemala was lower (108.83 and 251.12 mg/mL) than those from Mexico (141.14 and 283.21 mg/mL, respectively). Other compounds with high concentrations in the total sample were dl-limonene (35.45 mg/mL), benzyl alcohol (18.8 mg/mL), and ethyl vanillin (17.18 mg/mL) (Table 2). In the quantitative analysis, nicotine was detected close to the lower limits of quantification (0.02–0.06 mg/mL).

Discussion

Our qualitative analysis of capsules in the Mexican and Guatemalan cigarette markets found nearly 300 compounds, on average 44 compounds per capsule, more than double of what has been reported in capsules sold in the United States and South Korea (on average 14 compounds per capsule).[4,21–23] Similar to other studies,[4,21–23] menthol was detected in all capsules. Other compounds we found have also been reported in samples from the United States, Korea, and Mexico such as benzaldehyde (Korea and Mexico), limonene (United States, Korea, and Mexico), menthone (United States, Korea, and Mexico), methyl acetate (United States and Korea), pulegone (United States and Korea), isopulegol (United States and Korea), linalool (Korea and Mexico), vanillin (Korea), and triacetin (Korea, Mexico). Furthermore, the presence of lactones (eg, gamma-decalactone, delta-decalactone, gamma-dodecalactone, deltaundecalactone) has a synergistic effect inhibiting nicotine metabolism, which might influence addiction by prolonging nicotine exposure.[20,21] Sugars (eg, ethyl vanillin, vanillin) increase the sweetness of tobacco smoke and menthol has anesthetic effects.[20] Given the evidence on menthol contributing to recruit smokers, including Hispanics and African Americans in the United States, and reinforcing tobacco use, our results highlight the importance of menthol in tobacco and other nicotine products.[5,27,28]

Our qualitative analysis detected nicotine in almost one-quarter of the samples, yet quantitative analysis yielded low concentrations. We believe that the presence of nicotine might not be intentional and could have been a result of leakage from the tobacco rod to the filter, contamination in the manufacturing process, or during the laboratory analysis.

Quantitative analysis also yields differences by compound type. Similar to what has been found in Korea,[21] menthol was in higher concentrations (average = 192 mg/mL) than other

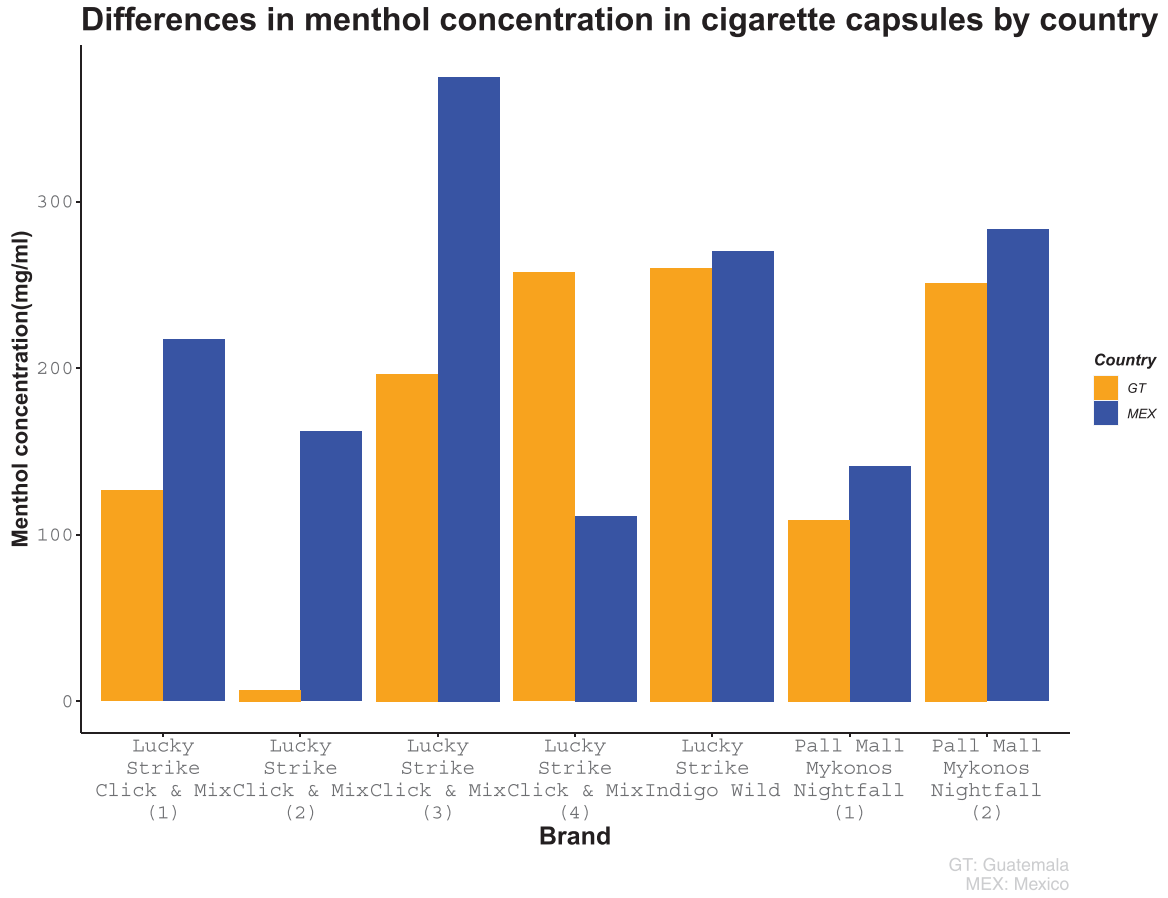

Figure 2. Differences in menthol concentration by varieties present in both countries, Guatemala and Mexico, 2021.

compounds. For instance, other compounds with relatively high concentrations were much lower than menthol (eg, ethyl vanillin = 14.00 mg/mL on average; limonene = 5.82 mg/mL on average). Many of the chemicals found in our sample are toxic if swallowed in larger quantities (eg, limonene, benzaldehyde, eucalyptol, pulegone, vanillin, ethyl maltol, ethyl vanillin), skin and eye irritants (eg, l-menthol, limonene, l-menthone, benzaldehyde, eucalyptol, propionaldehyde, triacetin, trans-cinnamaldehyde, eugenol, ethyl vanillin), and flammable (eg, limonene, l-menthone, eucalyptol, propionaldehyde) at relatively high exposure concentrations.[29] Some of these chemicals are certified Generally Recognized As Safe (GRAS) by the FDA, yet these are certified for oral consumption and not for heating and inhaling.[29,47] Others, such as limonene, linalool, pulegone, and menthone, may also damage the liver and kidneys.[29,30,48] Pulegone is also classified by the International Agency for Research on Cancer as a possible human carcinogen.[30]

Three brand varieties found in both countries contained seven different flavor capsules that had different chemical concentrations across countries. For example, menthol concentrations were higher in five out of the seven capsules for the same-brand variety in Mexico compared to Guatemala. This suggests that, either the industry tailors liquid formulations to different markets, or that manufacturing procedures are not standardized across manufacturers of same-brand varieties. Since menthol in other cigarette components (eg, tobacco rod, filter), as well as total contents per capsule were not measured, we cannot draw any conclusions on the total menthol delivered to a smoker. However, a previous analysis of capsule cigarettes reported total menthol concentration per cigarette, which, on average, is higher than what has been reported for noncapsule menthol cigarettes.[4,24] Further, capsule volume from our study is estimated to range from 0.02 to 0.04 mL, based on the average density among capsules ($n = 50$, 0.92 ± 0.01 g/mL), and weights of a subselection of capsules ($n = 7$, ranging 13.6–36.4 mg). Thus, the average menthol content is approximately 5.2 ± 3.2 mg/capsule, ranging between 0.2 and 10.7 mg/capsule. Observed differences in capsule volume may be attributed to the number of capsules contained in each filter, and content may be adjusted accordingly to deliver similar levels of menthol across products. Regardless, capsule cigarettes are customizable products that offer combinations of menthol and other flavorings that attract and engage adolescents and women.[10,11] Future research should address total menthol concentration in addition to that found in capsules, while also considering assessment of multiple samples of each brand within countries. While this study identified numerous chemicals among flavor capsules, the concentration of only 20 flavorings was determined. Although peak area thresholds were applied to reduce the background signal and contamination from the instrument, the relative amounts of the remaining identified compounds in each capsule are unknown. Further, identifications are considered tentative without parent standards to confirm instrument retention times and spectral patterns. Pharmacokinetic studies are needed to better understand the delivery of these chemicals under normal smoking conditions, including how delivery

relates to flavor concentrations and combinations for chemicals of concern, such as the lactones identified in this study.

The long-term health effects of heating and inhaling flavor capsule compounds are yet unknown and deserve further research. Nevertheless, many are also present in tobacco, and contribute to increase nicotine delivery and addictiveness.[20] Because menthol plays such an important role in facilitating use and maintaining an addiction to tobacco products, it should be banned in capsules, as well as its use in tobacco leaf, paper, and filter. The presence of compounds that reduce inflammatory response and therefore may conceal respiratory symptoms[20] is troubling. Thus, capsules might intensify the addictive properties of cigarettes.

Mexico has made considerable progress in the implementation of the FCTC compared to Guatemala. However, both countries experience weak enforcement of the current laws.[49] In 2022, Mexico banned the marketing of tobacco products at the POS. However, one of the largest convenience stores (Oxxo) was granted the exemption and is still allowed to advertise at the POS.[50] The importance of banning flavor capsules in cigarettes is based not only on its impact in reducing abuse liability and health impacts, but also these products are heavily marketed toward and appeal to youth and other vulnerable groups in countries with weak tobacco regulatory environments and may therefore reinforce existing health disparities.

Supplementary Material

Supplementary material is available at *Nicotine and Tobacco Research* online.

Funding

Research reported in this publication was supported by the Fogarty International Center of the National Institutes of Health under award number R01 TW010652 (Primary Investigators: JFT & JB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declaration of Interests

All authors declare no conflict of interest. None of the authors hold an economic, personal, political, or academic relationship that could influence the writing and publication of this manuscript.

Author Contributions

Sophia Mus (Formal analysis [Supporting], Investigation [Lead], Methodology [Supporting], Writing—original draft [Lead], Writing—review & editing [Supporting]), Inti Barrientos (Investigation [Lead], Methodology [Supporting], Writing—review & editing [Supporting]), Desirée Vidaña-Pérez (Data curation [Supporting], Visualization [Supporting], Writing—review & editing [Supporting]), Jose Monzon (Investigation [Supporting], Methodology [Supporting], Writing—review & editing [Supporting]), Joaquin Barnoya (Conceptualization [Lead], Investigation [Lead], Methodology [Supporting], Project administration [Lead], Supervision [Lead], Writing—review & editing [Supporting]), Michelle Page (Data curation [Lead], Formal analysis [Lead], Writing—review & editing [Supporting]), Ashleigh Block (Data curation [Lead], Formal analysis [Lead], Writing—review & editing [Supporting]), Maciej Goniewicz (Data curation [Lead], Formal analysis [Lead], Methodology [Lead], Writing—review & editing [Supporting]), Richard O'Connor (Data curation [Lead], Formal analysis [Lead], Methodology [Lead], Writing—review & editing [Supporting]), and James Thrasher (Conceptualization [Lead], Funding acquisition [Lead], Investigation [Equal], Methodology [Supporting], Project administration [Lead], Supervision [Supporting], Writing—review & editing [Supporting])

Data Availability

The data underlying this article are available in the article and in its Supplementary Material.

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