Flavoured tobacco products in the USA: synthesis of recent multidiscipline studies with implications for advancing tobacco regulatory science

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Almost all tobacco products include flavour additives. As of 2014, over 1300 flavouring ingredients had been identified in cigarettes, smokeless and roll-your-own tobacco products.[1] The 2009 Family Smoking Prevention and Tobacco Control Act—which gave the US Food and Drug Administration (FDA) authority to regulate tobacco products in the USA—banned the inclusion of characterising flavours (eg, candy, fruit) other than tobacco and menthol in cigarettes, but not other tobacco products.[2] Additionally the FDA's Center for Tobacco Products (CTP) has conducted reviews[3–5] and requested information on the impact of menthol cigarettes on population health through the Federal Register and meetings of the Tobacco Product Scientific Advisory Committee.

While the US FDA has not yet asserted its authority to regulate flavours in non-cigarette tobacco products (eg, smokeless tobacco, cigars, hookah) or e-cigarettes to date, the FDA signalled in materials accompanying the May 2016 deeming regulations its intent to issue a product standard that would ban characterising flavours in cigars, cigarillos and little cigars.[6] Meanwhile, other countries are enacting more robust regulations regarding flavoured tobacco products, with bans on menthol flavoured products proposed and being passed in countries such as Brazil, Turkey, Germany and Ethiopia.[7]

Flavoured tobacco products are widely considered to be 'starter' products for young users and may encourage experimentation or reduce 'harshness' associated with more established products. Flavoured tobacco products are often perceived as less harmful than other products, facilitating tobacco use habits that can lead to a lifetime of addiction.[8] Like all tobacco products, flavoured tobacco products can have serious health risks in addition to those normally associated with tobacco use and should not be considered or perceived as less harmful than non-flavoured products. Little is known about the health consequences and patterns of initiation/use among emerging tobacco products many of which are marketed in flavoured varieties.[9–11]

The focus of this multidisciplinary collection of recent research by CTP-funded researchers within a themed issue is to advance empirical knowledge on the role of flavouring in tobacco products and implications for perceptions, use, dependence, appeal and toxicity that may inform tobacco regulation in the USA and other countries. This editorial provides an integrated synthesis of studies included in the issue and potential implications of findings from these studies for tobacco control.

Two studies describe the state of flavoured tobacco product use in the USA: one on flavoured non-cigarette tobacco product use in adults and the other on trends in menthol cigarette use among youth and adults. Using the National Adult Tobacco Survey, Bonhomme *et al*[12] show that in 2013–2014, flavoured non-cigarette tobacco product use was prominent among US adult tobacco users and present in 82% of hookah users, 68% of e-cigarette users, 51% of smokeless tobacco users and 36% of cigar users. Menthol, fruit-flavoured and sweet-flavoured product use was prevalent across products. Flavoured tobacco product use, in general, was higher among young adults aged 18–24 than older adults. Villanti and colleagues used the National Survey on Drug Use and Health to extend earlier work on menthol cigarette prevalence,[13] demonstrating a significant increase in menthol cigarette use among past-month smokers from 35% in 2008–2010 to 39% in 2012–2014, despite declines in the overall prevalence of cigarette smoking.[14] Of note, youth smokers remain the most likely group to use menthol cigarettes, menthol cigarette use is positively correlated with co-use of cigars over time in the full sample, and co-use of menthol cigarettes and smokeless tobacco increased from 2004 to 2014. A study by Sterling *et al*[15] provides greater support for the relationship between menthol cigarette and flavoured little cigar and cigarillo (LCC) use using a national probability sample of 964 young adult cigarettes smokers. In this sample, daily menthol cigarette use was strongly associated with flavoured LCC use. The highly flavoured nature of LCCs and smokeless products and appeal of flavoured products may explain co-use of menthol cigarettes with these products found in these two studies.

Four studies examine possible mechanisms for the appeal of flavoured products. Hoffman *et al*[16] conducted a systematic review of 474 articles to examine how children and adults differ in their preferences for flavours that may be used in tobacco products. Infants and children exhibited elevated sweet and salty preference relative to adults, with 'sweet' food odours highly preferred by children. The authors note that age-related changes in bitter, sour, umami and fat taste were not clear and represent areas in need of more research. Another review by Kostygina and Ling[17] highlights the rationale for marketing flavoured smokeless products found in tobacco industry documents. As shown for menthol in cigarettes,[18] the documents confirm that flavoured products have been consistently associated with young and inexperienced tobacco users. Internal industry studies demonstrated that candy-like sweeter milder flavours (eg, mint, fruit) could increase appeal to starters by evoking a perception of mildness, blinding the strong tobacco taste and unpleasant mouth feel; or by modifying nicotine delivery by affecting product pH. Two novel empirical studies in this issue support the findings of these reviews. The first, by Fan *et al*,[19] is a laboratory-based study in mice that found that in normal mice, oral menthol can reduce the aversive effects of oral nicotine and, at higher concentrations, acts as an irritant by itself. However, menthol's effects in relation to nicotine required the cold/menthol receptor (TRPM8), a cool temperature sensing ion channel that activates analgesic and counterirritant mechanisms. Mice without this receptor

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showed a strong aversion to the menthol and nicotine solution and preferred nicotine alone. The second, by Kim *et al*,[20] used a human laboratory-based study to rate liking/disliking, and intensities of flavour characteristics (ie, sweetness, coolness, bitterness, harshness and specific flavour) across multiple flavours of a standard e-cigarette with a common nicotine level. Across all flavours, liking was positively correlated with sweetness and coolness and negatively correlated with bitterness and harshness. In a multivariable model, sweetness had the greatest positive impact on liking followed by coolness; harshness had the greatest negative impact on liking.

Other reasons for flavoured tobacco product use and the impact of flavoured tobacco products on tobacco use behaviour are described in three recent studies included in this issue. Pepper *et al*[21] used a national phone survey in 1125 adolescents aged 13–17 to explore reasons for the appeal of specific e-cigarette flavours. They found that adolescents were more likely to report interest in trying an e-cigarette when offered by a friend if flavoured with menthol, candy or fruit compared with traditional tobacco flavour. In particular, adolescents believed that fruit-flavoured e-cigarettes were less harmful to health than tobacco-flavoured e-cigarettes. Litt *et al*[22] examined the appeal of e-cigarette flavours in 88 adult smokers with no intention to quit who agreed to substitute e-cigarettes for their current cigarettes; after being assigned to their preferred flavour or a control flavour, participants were followed for 6 weeks and their cigarette and e-cigarette consumption recorded. On average, cigarette consumption dropped from 16 cigarettes per day to 7 cigarettes per day over the 6-week follow-up; flavour had a significant effect, such that those assigned menthol e-cigarettes had the greatest decrease in cigarette consumption. The smallest drop in cigarette consumption occurred among those assigned chocolate-flavoured and cherry flavoured e-cigarettes. Smith *et al*[23] examined the relationship between first flavoured tobacco use and current tobacco use and the correlation between current flavoured tobacco use and quit attempts in a sample of 1443 adult tobacco users. First use of a flavoured tobacco product was associated with being a current tobacco user and polytobacco users were more likely than single-product users to currently use a flavoured product. Similar to existing evidence documenting lower cessation among menthol cigarette smokers,[3–5] those using flavoured non-cigarette tobacco products reported lower odds of making a past-year cigarette quit attempt compared with those using non-flavoured tobacco products.

Other potential health harms of flavoured tobacco products, particularly cigarettes and e-cigarettes, are noted in three laboratory studies in this issue. Leigh *et al*[24] tested aerosol from various types of electronic nicotine delivery system (ENDS) devices or a tank system prefilled with liquids of different flavours, nicotine carrier, variable nicotine concentrations and with modified battery output voltage. Cell viability and metabolic activity were more adversely affected by conventional cigarettes than most tested ENDS products. Product type, battery output voltage and flavours significantly affected toxicity of ENDS aerosol, with a strawberry-flavoured product being the most cytotoxic. More comprehensive studies are needed but these results are among the first to suggest that characteristics of ENDS products, including flavours, may induce inhalation toxicity. Another study by Soussy *et al*[25] examining e-cigarette aerosols, found that the addition of sweeteners to e-cigarette liquids exposes users to furans, a toxic class of compounds. Saccharides, which are commonly used to impart a sweet flavour to e-cigarette liquids, thermally degrade to produce toxic compounds, like aldehydes and furans. Soussy *et al* found that under certain conditions, the per-puff yield of 5-hydroxymethyl furfural and furfural in e-cigarette emissions were comparable to values reported for combustible cigarettes. Also included in this collection of recent studies on the constituents of e-cigarettes, Behar *et al*[26] evaluated the distribution, concentration and toxicity of cinnamaldehyde in 39 e-cigarette refill fluids plus 6 duplicates using gas chromatography and mass spectrometry. Cinnamaldehyde-containing refill fluids and aerosols were found to be cytotoxic, genotoxic, and anti-inflammatory, and low doses adversely affected cell processes and survival. These data indicate that cinnamaldehyde in e-cigarette refill fluids/aerosols may impair homoeostasis in the respiratory system. These studies add to the evidence base on e-cigarette flavouring ingredients that may have potentially harmful health effects under different vaping conditions.

Finally, a commentary by Samet *et al*[27] describes lessons learnt from research to date on menthol cigarettes and how research findings can be applied more broadly to the regulation of flavoured tobacco products. The menthol report developed by the CTP's Tobacco Products Scientific Advisory Committee elaborated a methodology for considering the public health impact of menthol in cigarettes that has relevance to flavourings generally. While menthol in cigarettes has growing evidence from related systematic reviews and evidence-based statistical models, consideration is needed to expand models and evaluate the existence of multiple flavourings across products.

SUMMARY AND IMPLICATIONS

This collection of recent US studies highlights that flavoured tobacco product use is high across products, particularly youth and young adults in the USA. Flavours are associated with polytobacco product use and fewer quit attempts reported in national survey data. Young tobacco users state the self-reported appeal of tobacco products is enhanced by sweet and palatable flavours and internal industry documents support that the products are marketed to take advantage of the powerful appeal of flavours to increase initiation and sustain use, particularly in young or inexperienced users. While users report misperceptions that flavoured tobacco products are safer than non-flavoured products, rigorous laboratory data are emerging that the degrading sweetening compounds themselves may have potentially detrimental health effects under certain conditions. The empirical literature is growing and further data across disciplines with rigorous methods are needed to inform policy decisions regarding the regulation of flavours in tobacco products that can reduce initiation of tobacco products, promote cessation of tobacco products among users and ultimately reduce exposure to harmful products to protect population health.

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