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Review

Sugars in Tobacco Products: Toxicity Research and Implications for Tobacco Product Regulation

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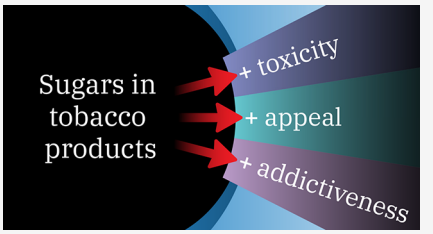
ABSTRACT: Sugars are naturally present in tobacco plants and are introduced as additives during the manufacturing of various tobacco- and nicotine-containing products. Product palatability and appeal are the primary reasons for manufacturers' attention to the sugar content in tobacco and nicotine products. However, because of the complex chemistry of sugars and their thermal decomposition, these versatile constituents are also contributing to the toxicity profile of tobacco and nicotine products. Using published empirical data, this non-systematic review summarizes the state of knowledge on the toxicologically relevant chemical transformations of sugars and artificial sweeteners in tobacco and nicotine products, including waterpipe tobacco, combustible and electronic cigarettes, heated tobacco products, and smokeless tobacco, and available research on the associated health effects of sugar-derived toxicants. Implications of sugar and sweetener content for abuse liability of various tobacco products are also discussed. Based on the findings of this review, research gaps are identified and policy recommendations are made for regulating sugars and artificial sweeteners in tobacco and nicotine products, including adding sugars and artificial sweeteners to the list of harmful and potentially harmful constituents (HPHCs).



INTRODUCTION

Chemical constituents present in tobacco and nicotine products and their emissions play an important role in product toxicity, carcinogenicity, and abuse liability (e.g., appeal, palatability, and addictiveness). In 2009, the Family Smoking Prevention and Tobacco Control Act (TCA) gave the U.S. Food and Drug Administration (FDA) authority to regulate the manufacture, distribution, and marketing of tobacco products.[1] Pursuant to the TCA, the FDA evaluated the available data on the known toxicants and carcinogens in tobacco and cigarette smoke and published a list of 93 constituents that cause or have the potential to cause harmful effects in people who use tobacco, referred to as "harmful and potentially harmful constituents" (HPHCs).[2] The TCA also allows the FDA to set product standards that limit the permissible levels of such constituents in tobacco products, which could serve as a powerful tool to protect public health.

This review focuses on sugars and sweeteners as constituents that have the potential to add to the toxicity and abuse liability of tobacco and nicotine products. Sugars and sweeteners, which are currently not included in the HPHC list, are virtually omnipresent in tobacco and nicotine products. Specific sugars and their amounts vary substantially across product types and brands. Some sugars, such as glucose and fructose, are formed in via enzymatic hydrolysis of starch during tobacco processing steps, such as drying and curing.[3,4] Sugars and sweeteners are also added by manufacturers to cigarette and waterpipe tobacco blends, smokeless tobacco, and other tobacco and nicotine products to achieve specific physicochemical (e.g., pH, product composition, and humidity) and chemosensory (e.g., smoothness and flavor) properties of the particular product brand.[5,6] As summarized in this review, the underlying mechanisms by which sugars affect these "desirable" product properties often involve the formation of known toxicants and carcinogens as the result of thermal degradation of sugars, which occurs during product use. Consequently, depending on the product type and the mode of use, naturally occurring and added sugars and sweeteners may contribute to increased toxicity and carcinogenicity of tobacco and nicotine products, in addition to their impact on product appeal. Given that sugars have a potential for a multidimensional impact on the morbidity and mortality associated with tobacco and nicotine products, their regulation would likely serve to protect public health.

This review synthesizes the current knowledge on sugars in tobacco and nicotine products, with a particular emphasis on

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Table 1. Levels of Commonly Reported Sugars in Various Tobacco and Nicotine Product Types[a]

product type	glucose	fructose	sucrose	total[b]	country (year)
cigarettes	6.5−33.5	18.2−57.6	5.2−47.2	33.7−122.9	U.S.A. (2006, 2017)[9,11]
	16−115	7−63	3−28	30−190	Netherlands (2020)[40]
	14.1−106.2	32.2−101.2	4−22.9	52.9−230.3	China (2007)[100]
				7−180	U.K. (1972)[10]
cigarillos	0.3−29.3	0.2−37.3	0.03−81.5	0.07−66.9	U.S.A. (2017)[11]
little cigars	0.2−4.1	0.2−6.5	0.03−0.2	0.6−11.1	U.S.A. (2017)[11]
cigars	0.02−3.5	LOD[c]−3.2	LOD−3.6	0.02−10.2	U.S.A. (2006)[9]
	0.3	LOD	0.4	0.7	China (2007)[100]
				6−7.5	U.K. (1972)[10]
pipe tobacco				66−256	U.S.A. (1980)[6]
				24−189	U.K. (1972)[10]
snuff	LOD−1.6	LOD−0.2	LOD	LOD−1.9	U.S.A. (2006)[9]
	7.8−9.2	9.8−14.2	LOD	9−26	U.S.A. (1980)[6,17]
chewing tobacco	LOD−104.3	18.9−209.6	0.26−224.6	59.6−407.1	U.S.A. (2006)[9]
	67.3−170.2	21.3−123.4	54.7−198.2	135−657	U.S.A. (1980)[6,17]
waterpipe tobacco	125−195	135−190	LOD−9		U.S.A. (2020)[13]
e-cigarette liquids	0.006−0.089	0.009−0.331	0.009−0.620		U.S.A. (2018)[15]

[a]Levels in all products except for e-cigarette liquids are expressed as mg/g of product (converted from % weight-based data in some reports). Levels in e-cigarette liquids are expressed as mg/mL. [b]Sum of various sugars, including glucose, fructose, sucrose and other sugars, as measured in a given study. [c]LOD = limit of detection for a given study.

their levels, the evidence that sugars and sweeteners contribute to harmful emissions of products that are heated and used via inhalation (e.g., cigarettes, e-cigarettes, and heated tobacco products), and the toxicological implications. Cumulatively, the summarized data helps to inform future research directions and potential public health policies.

Sources and Variability of Sugar Levels across Various Tobacco Product Types. Levels of naturally occurring sugars (i.e., not introduced as additives) in the processed tobacco depend on the type of tobacco plant and the processing methods employed. For example, while sugars are formed via enzymatic hydrolysis of starch during tobacco drying and curing, their levels in Burley tobacco account for only <0.2% of tobacco weight.[3,4] This is because Burley is typically subjected to air-curing, a slow processing method that allows sugars to be enzymatically metabolized. In contrast, sugars may comprise 8−30% of tobacco weight in flue-cured Virginia tobacco and 10−20% in sun-cured Oriental tobacco because elevated temperatures prevent sugar metabolism. The amount and types of sugars and sweeteners introduced as additives during product manufacturing vary across product categories (e.g., cigarettes and smokeless tobacco) and brands. Such additives can be either individual compounds, such as sucrose, glucose, fructose, sucralose, acesulfame K, aspartame, and saccharin, or sugar- and sweetener-containing ingredients, such as honey, licorice, molasses, and corn syrup.[5,7,8]

Reports on the levels of specific sugars and sweeteners in U.S.-marketed tobacco products are limited. Table 1 illustrates representative measured levels of sugars in various tobacco product types. In addition to the latest available data for the U.S.-marketed products, levels of these sugars in earlier reports and/or in products from other countries are provided for reference.

Cigarettes, Cigars, and Cigarillos. Cigarettes manufactured in the U.S. are typically made with a blend of different tobacco types, including Burley, with blend "recipes" varying across product brands. To compensate for the lack of sugars in Burley tobacco, cigarette manufacturers typically use casings containing sugars and sweeteners. As a result, tobacco filler of U.S. cigarettes typically contains a mixture of sugars that are naturally occurring (e.g., glucose and fructose) and added (e.g., sucrose or artificial sweeteners), although some sugars, such as sucrose, can originate from both sources (Table 1). This is in contrast to the relatively low levels of sugars in cigars, which are mostly made with air-cured and fermented tobacco and often do not contain added sugars.[9] Based on previously published data,[6,10] sugar levels in pipe tobacco are likely to be similar to those in cigarette tobacco; however, there are no recent reports.

Insights into the relative trends in sugar content across cigarettes, little cigars, and cigarillos can be gained from a Centers for Disease Control and Prevention (CDC) laboratory's report on levels of sugars and humectants in 44 products representing various, unidentified U.S. brands.[11] The sum of all measured sugars (including glucose, fructose, sucrose, mannose, and other sugars) in various brands of little cigars was much lower than in cigarettes and was similar to levels reported in traditional, premium cigars. However, cigarillos had two distinct subgroups of brands, with the sugar content in one subgroup being similar to little cigars (i.e., low), while sugar content in the other group was as high as in cigarettes (Figure 1). The reasons for this variability of total sugar content across cigarillo brands

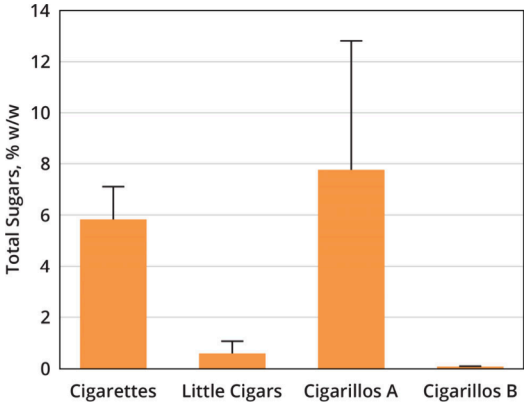

Figure 1. Total sugar content in the U.S.-marketed cigarettes, little cigars, and cigarillos.[11]

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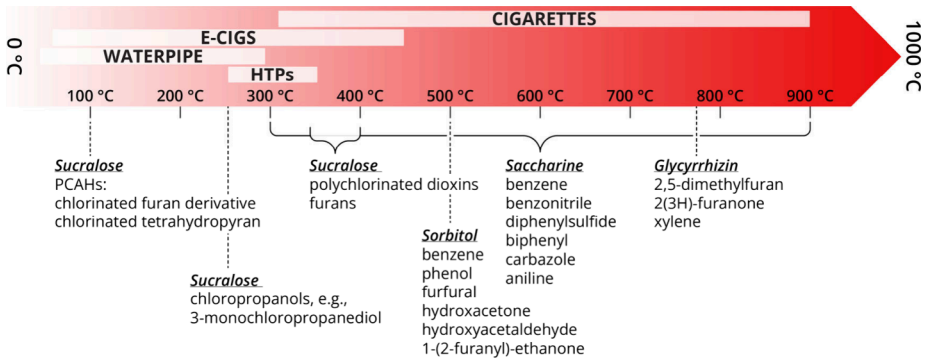

Figure 2. Spectrum of relevant temperature ranges that produce harmful constituents from various sugars and sweeteners.

are not known. However, examination of the levels of individual sugars suggests that various tobacco types and various amounts of added sugars both play a role in this variability. In addition to sugars, various high-intensity sweeteners are commonly added to cigarillos. A 2018 study[12] surveyed sweeteners added to top-selling U.S. cigarillo varieties. Sweeteners were found on the wrappers and mouth tips of 29 of the 31 varieties tested. Saccharin and glycyrrhizin (a sweet compound derived from the roots of the licorice plant) were the most common, detected in over 20 varieties. Other sweeteners identified in the cigarillos included acesulfame K, neotame, and sucralose.

Waterpipe Tobacco. Waterpipe tobacco, known as hookah or "shisha" tobacco, has the largest mass fraction of sugars, including fructose, glucose, and sucrose, compared to any other combustible tobacco product, typically accounting for more than half of the product mass (Table 1).[13,14] Limited data also suggests that levels of sugars are higher in flavored (e.g., fruit and desert flavors) compared to unflavored waterpipe tobacco.[13] Notably, sucrose accounts for a smaller proportion of total sugars in waterpipe tobacco compared to the tobacco filler of combustible products (Table 1).

E-Cigarettes and Heated Tobacco Products. Data on sugar content in e-cigarettes and heated tobacco products is limited. Reported levels are relatively low compared to combustible products and waterpipe tobacco (Table 1); however, significant variations have been reported. For example, in a study by Fagan et al.,[15] (Table 1), sucrose levels ranged from 9.3 to 620 μg/mL across 66 e-cigarette liquids and were significantly higher than glucose and fructose in flavored liquids. In some e-cigarette liquids, sugar alcohols are used as sweetening agents: Miao et al. detected trace amounts of sorbitol (<0.003%, w/w) and ethyl maltol (ranging from <0.003−0.089%, w/w) in some e-liquids.[7] Artificial sweeteners such as sucralose are also used in some e-liquids. In a recent study in Austria by Schlappack et al.[16] 43% of the screened 100 commercially available liquids contained sucralose, at concentrations ranging from 0.1 to more than 0.5% (w/v).

No published data exists on the levels of sugars and sweeteners in heated tobacco products. Research is needed to understand the levels, variability, and implications of sugars and sweeteners in e-cigarettes and heated tobacco products.

Smokeless Tobacco. Limited reports on the levels of sugars in smokeless tobacco indicate significant variations across products (Table 1). For example, levels of sugars in chewing tobacco are highly variable and are much higher than in moist snuff.[6,9,17] Such variability could be due to the use of different tobacco types. However, in the study by Clarke et al.,[9] sucrose levels varied nearly 1,000-fold across 11 brands of chewing tobacco, while fructose varied only 10-fold (Table 1). Given that naturally occurring sucrose is typically present in processed tobacco in relatively small amounts, its substantial variability across chewing tobacco brands suggests that sucrose or sucrose-containing additives are used in product manufacturing, with the likely purpose of modifying its taste and potentially other characteristics.

In addition to sugars, there is evidence that high intensity sweeteners are used in smokeless tobacco products. Miao et al.[7] evaluated five varieties of moist snuff and found saccharin in all samples, with the levels ranging from 0.0457 to 0.0895% (w/w), and sucralose in one of the products (0.0519%, w/w). Four snus products assessed in this study contained a relatively high level of sucralose (0.69−1.32%, w/w), and three of the four also contained aspartame (0.00759−0.0128%, w/w).

Oral Nicotine Pouches. Oral nicotine pouches are new "tobacco-free" products that are increasingly popular among people worldwide who use nicotine and tobacco. The global market size of these products is expected to grow to nearly $33 billion U.S. dollars by 2026.[18] Data on sugars or sweeteners in oral nicotine pouches is limited, but indicates that these products are frequently sweetened with high-intensity sweeteners, such as acesulfame K or sucralose.[19] In a 2024 study,[8] levels of acesulfame K measured in several oral nicotine pouch brands ranged from 0.32 to 0.94 mg per pouch, and one of the brands also contained sucralose at levels ranging from 0.64 to 1.2 mg per pouch. The sweetener levels were higher for varieties with a higher nicotine content, suggesting that higher levels of sweetener are used to mask the nicotine-related bitter taste.

Contribution of Sugars to Harmful Emissions of Tobacco and Nicotine Products That Are Heated and Used via Inhalation. *Overview of the Thermal Degradation of Sugars and Sweeteners during Product Use.* Pyrolysis and other thermal transformations of sugars (e.g., caramelization) produce a broad range of reaction products, some of which are known toxicants and carcinogens. Sugars can also react with other compounds in tobacco and smoke, such as tobacco-derived amines, to form Maillard products.[20] Pyrolysis studies have simulated these processes,[21,22] screened for potential pyrolysis products, and characterized their thermal stability and formation temperatures.[22] The pyrolysis of fructose, glucose, and sucrose forms multiple aldehydes and ketones (e.g., formaldehyde, acetaldehyde, acrolein, diacetyl), as well as furans [e.g., furfural and 5-hydroxymethylfurfural (5-HMF)] and other volatiles [e.g., benzene, acrylamide, and polycyclic aromatic hydrocarbons (PAHs)], pyrazines, pyridines, and organic acids (e.g., formic and acetic acids).[20,23]

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Sugar pyrolytic profiles are heavily influenced by temperature, with furans and products that more closely resemble the original sugar structure prevailing at lower temperatures, aliphatic aldehydes increasing with temperature, and PAH resulting at much higher temperatures.[20,24,25] Therefore, sugar-related emissions can vary considerably across products heated to different temperatures, such as e-cigarettes (25−325 °C),[26] heated tobacco products (up to 350 °C),[27] waterpipe tobacco (25−300 °C),[28] and cigarettes (300−900 °C)[22] (Figure 2).

Heating of high-intensity sweeteners (e.g., saccharin, sucralose, and glycyrrhizin) and sugar alcohols (e.g., sorbitol) also produces a range of toxic chemical compounds. At temperatures as low as 98 °C, sucralose produces polychlorinated aromatic hydrocarbons, including a chlorinated furan derivative and a chlorinated tetrahydropyran.[29] At temperatures up to 250 °C, in the presence of the sugar alcohol glycerol (common in tobacco/nicotine products including e-cigarettes), sucralose generates several chloropropanols including the carcinogen 3-monochloropropanediol.[30,31] Sucralose degradation at 350−400 °C can yield polychlorinated dioxins and furans, with reactions catalyzed by metals (Al, Fe, Cu, etc.) and metal oxides, found in tobacco products including some e-cigarette and e-hookah heating coils.[32,33] Pyrolysis of sorbitol at 500 °C yielded hydroxyacetaldehyde, hydroxyacetone, furfural, 1-(2-furanyl)-ethanone, benzene, and phenol.[34] Pyrolysis of glycyrrhizin at 770 °C yielded numerous products including 2,5-dimethylfuran, 2(3*H*)-furanone, and xylene.[35]

As sugars and sweeteners are widely used in products that are heated and subsequently inhaled, systematic monitoring of the sugar content and its relationship with the relevant toxic emissions of tobacco/nicotine products is critical to informing meaningful regulation.

Research on the Contribution of Sugars to the Levels of Harmful Constituents in Product Emissions. *Combustion of Tobacco Cigarettes.* Approximately 0.5% of the sugars present in tobacco are transferred into mainstream smoke, whereas the major part will undergo pyrolysis or participate in pyrosynthesis (i.e., formation of new chemicals from multiple precursors).[20,36,37] A review by authors independent of the tobacco industry concluded that addition of sugars to cigarette tobacco increases levels of formaldehyde, acetaldehyde, acetone, acrolein, furfural and other furans, as well as certain acids.[20] Another study showed that adding sugars to Burley tobacco, containing virtually no natural sugars, resulted in an increase in acetaldehyde, acrolein, crotonaldehyde, propionaldehyde, and butanal levels in smoke, but not formaldehyde.[38] Differences in tobacco types can also affect the association between sugars and smoke chemistry, due to variable levels of polysaccharides (e.g., cellulose, pectin, and starch), which produce the same pyrolysis products as simple sugars.[20,39] In 50 brands of commercial Dutch cigarettes with different tobacco blends, emissions of formaldehyde, acetaldehyde, acrolein, and 2,5-dimethylfuran were related to the content of sugar and humectants in tobacco filler.[40]

Publications by tobacco industry researchers are not fully consistent with industry-independent findings summarized above. For example, tobacco industry reviews concluded that adding sugars to cigarette tobacco increases phenol, furans, organic acids, furfural, and formaldehyde, but did not mention acetaldehyde or acrolein emissions.[36,39] However, an industry study with added ^{14}C-labeled sugars, published in 1971, showed acetaldehyde among the products formed in the highest radiochemical yields.[37] More recent tobacco industry-sponsored studies that used isotopically labeled glycerol in cigarette tobacco have reported on the formation of acetaldehyde and acrolein, as well as formaldehyde and acetone during smoking.[41,42] The inconsistency of industry conclusions and their contradictions with some of the available independent data on the contributions of sugars to cigarette emissions emphasizes the need for industry independent research evidence to inform the FDA's regulatory decisions on tobacco products.

Waterpipe Tobacco Smoking. Although waterpipe tobacco does not burn self-sustainably due to the high concentrations of added syrups, indirect heating results in sugar decomposition.[43] Direct studies of sugar degradation has not yet been conducted for waterpipe tobacco smoke. However, the concentrations of glucose and sucrose in waterpipe tobacco are roughly ten times higher than those in cigarette tobacco (Table 1), and the existing data on sugar pyrolysis at various temperatures can be used to predict that the same degradation products identified in cigarette smoke are present in waterpipe tobacco smoke, albeit at different concentrations (Figure 2). For example, waterpipe tobacco smoke is likely to contain lower levels of certain low-molecular-weight carbonyls because a significant fraction of glycerol transfers to the smoke unchanged (due to lower temperatures).[43,44] In addition, a significant fraction of the carbonyls generated via sugar degradation dissolve into and are thus diluted by the water in the bowl, resulting in the corresponding dilution in the smoke.[43] The trend reverses for degradation products that form at lower temperatures, such as furans.[45,46] Further, people smoke over five times more waterpipe tobacco in a single setting than the amount of tobacco burned when smoking a cigarette (3.9 g/waterpipe session versus ∼0.73 g/cigarette).[43,47] Comparing maximum levels reported, for every gram of tobacco smoked, people who smoke waterpipe tobacco inhale 8 times less acetaldehyde, 16 times less acrolein, but roughly the same amount of formaldehyde, 250 times more 5-HMF, 6 times more furfural, and 3 times more furfuryl alcohol than people who smoke cigarettes.[28]

E-Cigarettes. As stated previously, high-intensity artificial sweeteners like sucralose may be present in commercial e-liquids and are also sold as additives for Do-It-Yourself e-liquids.[7,16,48] Under realistic e-cigarette use conditions, sucralose degrades to give hydrochloric acid that either reacts with propylene glycol or glycerol to produce chloropropanols and other chlorinated compounds, or enhances the degradation of propylene glycol and glycerol to produce toxic aldehydes and hemiacetals (formaldehyde-releasing agents).[49−51]

Studies examining the degradation of sugars that may be present in e-liquids are limited, although the experiments with laboratory-prepared e-liquids showed that during e-cigarette use sucrose and glucose could degrade to 5-HMF and furfural.[45] Under the same conditions, sorbitol did not degrade to give toxic furans.[45]

Heated Tobacco Products. Several studies assessing emissions of heated tobacco products reported the detection of compounds that could result from the pyrolysis of sugars. One study reported that furan levels tended to be higher in heated tobacco product aerosols compared to smoke from a reference cigarette.[52] The detection of furans and chloropropanols in heated tobacco product aerosols was also reported by a non-targeted chemical analysis funded by a tobacco product manufacturer.[53] A recent innovation in heated tobacco product design is the introduction of flavor capsules that may contain sugars or sweeteners in the mouthpiece of heated tobacco sticks.[54] Research is needed to determine whether such capsule

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ingredients will contribute to toxicant generation in heated tobacco product emissions.

Health Implications of Sugars in Tobacco and Nicotine Products. There is an overall lack of research directly assessing the sugar-attributed added toxicity of tobacco and nicotine products or specific health outcomes in people who use the products. However, there is extensive mechanistic, toxicological, and epidemiological evidence of the harmful effects of the numerous toxicants and carcinogens that are formed upon the thermal degradation of sugars and sweeteners in tobacco and nicotine products that are heated/combusted and used via inhalation. On the other hand, health effects of sugars in smokeless tobacco can be directly inferred from the existing evidence on the impact of sugars on oral health and the epidemiological data on the smokeless tobacco-associated oral and dental disease. Such evidence for the two types of products is summarized below.

Implications of Exposure to Products of Thermal Degradation of Sugars and Sweeteners. Most of the products of sugar decomposition are toxicants and carcinogens, and many are part of the FDA's HPHC list (Table 2). Exposure to carbonyls has been shown to play a key role in the pathogenesis of various diseases. For example, acrolein is an intense pulmonary irritant and toxicant, causes neurogenic inflammation, airway hypersensitivity, and is proposed to be a pulmonary carcinogen.[55,56] Reports also demonstrate a dose-dependent cardiovascular toxicity of acrolein.[57,58] Other carbonyls formed upon the thermal degradation of sugars also exhibit carcinogenic properties: formaldehyde and acetaldehyde cause respiratory tumors in laboratory animals,[59,60] and crotonaldehyde is a potent irritant and forms DNA adducts in the human lung.[61] An industry-funded study that employed theoretical calculations of risks associated with cigarette smoke constituents identified acrolein as the main constituent underlying non-cancerous cardiopulmonary diseases resulting from smoking, and acetaldehyde and formaldehyde as the second and third leading culprits of smoking-related cancers.[62] Other examples of sugar-relevant organic compounds with carcinogenic properties include furans, which are hepatic toxicants and carcinogens and can potentially contribute to renal carcinogenicity,[63] and acrylamide, which can damage DNA and can be carcinogenic toward multiple organs as well as genotoxic.[64] As a human carcinogen, benzene causes acute myeloid leukemia and acute non-lymphocytic leukemia and is associated with multiple myeloma and non-Hodgkin lymphoma.[60] Many PAH are widely accepted as major contributors to lung cancer in people who smoke, and are strongly implicated in cardiovascular disease and death.[65,66] Acute controlled exposure to acetic acid significantly increased self-reported ratings of nasal irritation among healthy individuals[67] and nasal obstructive responses among individuals with allergic rhinitis.[68]

Table 2. Sugar Degradation-Derived Constituents That Are Part of the FDA HPHC List

toxicant (class)	sugar sources[a]	FDA HPHC category[a]
carbonyls		
acrolein	S, F, G, SL	RT, CT
acetaldehyde	S, F, G	CA, RT, AD
formaldehyde	S, F, G	CA, RT
furans		
furfural	S, F, G	CA
5-hydroxymethylfurfural	S, F, G	CA
2,5-dimethylfuran	S, F, G	CA
volatile organic compounds		
benzene	S, F, G	CA, CT, RD
acrylamide	S, F, G	CA
polycyclic aromatic hydrocarbons	S, F, G	CA[b]
pyridines	S, F, G	CA[c]

[a]Sucrose (S), fructose (F), glucose (G), sucralose (SL), carcinogen (CA), respiratory toxicant (RT), cardiovascular toxicant (CT), reproductive or developmental toxicant (RDT), and addictive (AD). [b]Benzo[*a*]pyrene. [c]PhIP (2-amino-1-methyl-6-phenylimidazo-[4,5-*b*]pyridine).

It is important to acknowledge that sugars contribute to only a fraction of the total concentrations of volatile toxicants and carcinogens in cigarette smoke, with significant amounts of these harmful agents being generated from the pyrolysis of the tobacco filler or other product ingredients. Nevertheless, as discussed above, the presence of sugars adds to exposures to such chemicals. Secondhand smoke and air pollution studies offer ample evidence that even incremental increases in exposure to sugar pyrolysis-relevant volatile toxicants are associated with cancer and respiratory and cardiovascular diseases.[69−74] Therefore, products of sugar degradation in tobacco product emissions are likely to contribute to the negative health outcomes associated with the use of these products. There is a need for risk assessment studies and for carefully designed human trials of product exposures and health effects to assess the sugar-attributed added toxicity in people who use tobacco and nicotine products.

Implications of Sugars in Smokeless Products for Oral Health. It is plausible to expect that high sugar content in some smokeless tobacco products may contribute to the high prevalence of dental caries, periodontal disease, and other non-carcinogenic oral and dental effects in people who use such products.[75] The use of smokeless tobacco has been clearly associated with such adverse outcomes in India.[76] However, the contribution of sugars to these effects may be difficult to assess because of the complexity of smokeless products in India, with many non-tobacco ingredients being often part of the product mix. Within the U.S., the potential association of sugars in smokeless products with oral health can be examined by comparing chewing tobacco and moist snuff, because chewing tobacco contains up to hundred-fold higher amounts of sugars than moist snuff (Table 1). For example, the National Health and Nutrition Examination Survey (NHANES) reported that adults who use chew tobacco had a higher adjusted mean number of decayed or filled coronal permanent tooth surfaces and decayed root surfaces than those who used moist snuff.[77] A dose−response relationship between the number of packages of chewing tobacco used per week and the odds of having root-surface caries was also found in that study. Further, chewing tobacco increased the in vitro growth of the cariogenic bacteria *Streptococcus mutans* and *Streptococcus sanguis*, while moist snuff did not have such effects.[78] However, such published literature is limited and outdated. There is a need for research to assess the potential oral health effects of sugars and sweeteners in current and emerging smokeless tobacco and nicotine products, including nicotine pouches.

Impact of Sugars on Abuse Liability of Tobacco and Nicotine Products. Palatability, appeal, and addictiveness are key attributes of a tobacco product's abuse liability which the FDA defines as "the likelihood that individuals will develop physical and/or psychological dependence on the tobacco

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product".[79] Given that tobacco manufacturers have been using sugars and sweeteners to enhance the taste and flavor characteristics of cigarette smoke for over a century,[5] the link between sugars and cigarette smoke palatability is incontestable. Furthermore, sugars may indirectly contribute to product addictiveness by affecting nicotine delivery and/or enhancing its addictive effects. The known and the potential mechanisms by which sugars contribute to these effects in various tobacco and nicotine products, and the relevant gaps, are briefly summarized below.

Contribution of Sugars to Palatability, Appeal, and Addictiveness of Cigarettes. Volatile basic components like ammonia, nicotine, and alkaloids give tobacco smoke a harsh taste, which makes inhalation more difficult.[20,80] Sugars increase the palatability of the smoke because the most abundant pyrolytic products of sugars are acetic and formic acids, which reduce smoke pH,[10] thus decreasing its harshness and irritation.[4,5] Sugars also contribute to the flavor of tobacco products.[4,20] In combusted products, sugar caramelization and Maillard reactions produce characteristic woody and caramel flavors and aromatic compounds with cocoa, nutty, or popcorn-type flavor notes, improving the taste and smell of the tobacco smoke for both the consumers and bystanders.[24,81] Indeed, an industry study has been referring to sugars as ameliorants and reported that tobacco smoke acceptance by people who smoke is proportional to the sugar level in tobacco.[20]

Sugars are likely contributing to the addictiveness of cigarettes. The reduced-pH, "smoother" smoke is easier to inhale, facilitating deliveries deep into the lung of higher nicotine levels than those from the low-sugar cigars and some cigarillos (Table 1). In addition, acetaldehyde has been shown to increase dopaminergic neuronal activity and enhance nicotine self-administration in laboratory animal studies.[82,83] However, quantitative and well-controlled studies with human participants on how sugars in combusted tobacco products may affect use behaviors and contribute to abuse liability are critically lacking.

Contribution of Sugars to Abuse Liability of Other Tobacco/Nicotine Products That Are Heated and Used via Inhalation. The introduction of flavored waterpipe tobacco in the 1990s was a major factor in the resurgence of waterpipe use, particularly among youth.[84] The most popular flavored varieties of waterpipe tobacco worldwide are those to which sugar-containing ingredients are added. Flavored waterpipe tobacco, known as Moassel, or Maassel (which means "sweetened with honey") is available in a myriad of flavors.[14,85,86] In waterpipe research studies, the majority of participants reported the use of only flavored (sweetened) waterpipe tobacco, with appealing taste, aroma, and smoothness being cited as motivating factors to use flavored varieties.[84,87−89] Therefore, restricting the levels of sweetness and various flavors of waterpipe tobacco could be essential for reducing its appeal and curbing its use.

Sugars may also contribute to the palatability and appeal of e-cigarettes.[15] For example, because e-cigarettes operate at relatively low temperatures, a substantial proportion of dehydrated sugars is expected to transfer from e-cigarette liquid into the aerosol. Thus, sugars in e-cigarette liquids are likely to contribute to the palatability of aerosols by adding a sweet taste of sugars, in addition to alterations to the aerosol pH and/or contributing to aromatic compounds from the degradation of sugars. The latter two mechanisms are plausible based on what is known about the thermal transformations of sugars in cigarette smoke and are likely to be relevant to heated tobacco products. However, research is needed to better understand how, and to what degree such mechanisms contribute to the abuse liability of e-cigarettes and heated tobacco products.

Contribution of Sugars to Abuse Liability of Oral Tobacco and Nicotine Products. In the case of smokeless tobacco, no elevated temperatures are involved in product use, and the intact sugars and sweeteners serve as flavorants. The sweet taste in smokeless tobacco may stimulate saliva, and the sweetener-containing ingredients such as licorice may add appealing flavors. A recent study in laboratory animals examined the consumption of extracts of oral nicotine pouches and found that artificial sweeteners, at levels present in the pouches, increased nicotine consumption and decreased aversion to higher nicotine concentrations.[8] However, the research on the effects of sugars and sweeteners on the abuse liability of smokeless tobacco or novel nicotine pouches in people who use these products is virtually non-existent.

Consumer Perception of Sugars in Tobacco and Nicotine Products. Little is known about how people perceive the presence and the effects of sugars in tobacco and nicotine products. In the U.S., tobacco companies are not required to disclose added sugars on their product packaging or their marketing materials, and there are no known U.S. tobacco education programs focused on distributing such information. In 2019, the first known study assessed awareness and perceived toxicity of added sugars in 4,000 people who smoke cigarettes.[90] Very few (<6%) knew that there were added sugars in cigarettes and even less (<4%) knew that added sugars produce toxic chemicals during cigarette combustion. Few participants in that study mentioned that learning more about the toxicity concerns related to added sugars might impact their use patterns and quit attempts. Other studies reported that, while people who smoke believe that added sugars in products increase consumption and addictiveness of products, suppress bitter taste perceptions, and mask the odor of secondhand smoke, they are unaware of the potential contribution of sugars to smoke toxicity and health risks.[91,92] In the case of waterpipe tobacco, there has been explicit marketing of some sweet-flavored brands as a healthy and natural alternative to cigarettes.[44,93] Studies of people who smoke waterpipe tobacco also show that flavored waterpipe tobacco has been misperceived as a less harmful form of tobacco and entices people who do not use the product.[94]

The lack of empirical data, the absence of health campaigns educating the public on the deliberate use of sugars by manufacturers to make tobacco and nicotine products more palatable, false advertising, as well as the contribution of sugars and sweeteners to product palatability and appeal may impact perceptions of the safety of sugars in tobacco/nicotine products.

Potential Strategies for Regulating Sugars in Tobacco and Nicotine Products. The FDA considers sugar levels when making decisions regarding Substantial Equivalence (SE) and Premarket Tobacco Product Application (PMTA).[95,96] For example, in issuing Not Substantially Equivalent Orders prohibiting the sale of certain cigarette sub-brands, the FDA noted that differences in sugar levels contributed its decision because the effects on the product's palatability, abuse liability, and use behaviors,[97] as well as the mainstream smoke yields of toxicants.[98] In addition to carefully considering levels of sugars and sweeteners in new or modified product brands, there are several other strategies that could further the goal of protecting public health. Those suggested strategies are as follows:

1. Adding Sugars and Sweeteners to the HPHC List. According to the FDA, HPHCs include "any chemical or chemical compound in a tobacco product or in tobacco smoke

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that... causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products".[2] There is sufficient evidence that sugars, upon pyrolysis, produce previously listed HPHCs and other toxicants that are not on the HPHC list and therefore, at minimum, meet the criteria of "potentially harmful" constituents. Per the FDA's definition, compounds that facilitate initiation of the use of tobacco products constitute HPHCs as well, and sugars and sweeteners further qualify as HPHCs for that reason. Tobacco companies are already required to submit ingredient lists to the FDA, but if sugars are added to the HPHC list, which would trigger an additional obligation to report the quantity of such sugars in each product (and, if applicable, in its emissions). This information could provide the FDA with important evidence to support the other regulatory measures discussed below. In addition, if accompanied by sufficient public-facing communications, data on sugar and sweetener content in tobacco and nicotine products could help inform the public in a generalized way about the negative implications of sugars in such products.

2. Restricting or Prohibiting Sugar Additive. Adding sugars to cigarettes enhances the sensory attributes of cigarette smoke and encourages smoking initiation and maintenance, and the tobacco industry has long considered the addition of sugars to tobacco products to be a key part of its cigarette marketing strategy.[99] This knowledge alone is a strong argument in favor of considering a product standard that would restrict or prohibit the addition of sugars and sweeteners to tobacco products. It would clearly be "technologically achievable" for manufacturers to comply with such standard (a factor the FDA is required to consider when issuing a product standard). Any product standard must be written to ensure that manufacturers cannot circumvent it by modifying the tobacco blend or the product design, and manufacturers should be required to disclose any modifications made to their products in response to a regulation limiting or prohibiting sugar additives. Research on how the absence of sugar additives would affect product use behaviors, related exposures, and risk perceptions could assist with assessing the potential benefit of such product standard.

3. Setting Upper Limits for the Naturally Occurring Sugars. Policymakers could also consider issuing a product standard that sets upper limits for the levels of naturally occurring sugars in finished tobacco products. The levels of naturally occurring sugars can be reduced by altering the tobacco blend or through processing approaches that accelerate sugar metabolism. Such a standard could address the potential concern that tobacco product manufacturers would shift to tobacco blends high in natural sugars in response to restrictions on sugar additives. Further research could help inform the types of sugars for which a limit could be established, the appropriate upper limit value(s), and strategies to avoid or mitigate unintended consequences.

RECOMMENDED RESEARCH DIRECTIONS

In reviewing the existing evidence on sugars and sweeteners in tobacco and nicotine products, we identified several key research gaps. Addressing these gaps can help to strengthen the scientific basis for the potential regulatory decisions on whether to add sugars and sweeteners to the HPHC list, how to design potential product standards, and how to communicate the effects of sugars to people who use and do not use tobacco and nicotine products. Recommended research areas to help address the identified research gaps are listed below.

- Carry out brand-specific surveillance of sugars and sweeteners in various product types: Such data is extremely limited; however, there are apparent variations across products. The data on the levels and the variability of sugars across various product types and brands is key to informing studies of how such levels are related to product toxicity and abuse liability. This information is also needed to determine the achievable lowest level of added and natural sugars in various tobacco products, and to inform the potential product standards.
- Better characterization of the chemical profile of emissions (for products that are combusted or heated) as a function of sugar and sweetener content: In the case of combustible tobacco products, this is necessary because of the limitations of prior studies. The majority of such studies were conducted by tobacco industry researchers reporting inconsistent results and/or using experimental tobacco or cigarettes that are not representative of those on the U.S. market. Relevant research on e-cigarettes and HTPs is virtually lacking, as evident from this review. Addressing this research gap should also incorporate investigations of how a decrease in sugar content (a potential regulatory measure) may affect levels of HPHCs, to avoid unintended consequences.
- Human studies on toxicant exposures and biological effects associated with sugars in tobacco products: Studies employing relevant biomarkers are needed to determine whether there is a dose−response relationship between sugar content in products and the toxicant uptake and biological effects in people who use the products. This is important because product characteristics other than sugar content can have a profound impact on the levels of exposure to smoke constituents upon product use.
- Better characterization of the impact of sugars on palatability and appeal of various tobacco products: Both animal behavioral studies and human laboratory and observational studies of product use are needed to address this research gap. The human studies should focus on sensory attributes, puffing intensity, and other relevant subjective and behavioral measures.
- Investigation of the potential contribution of sugars to product addictiveness: Studies are needed to determine whether higher levels of sugars in tobacco products, particularly in cigarettes and other combusted products, are associated with higher nicotine intake. Animal and mechanistic studies are also needed to examine whether sugar coexposure modifies the addictive effects of nicotine in product emissions (due to sugar-derived increases in acetaldehyde yields).
- Communication research to address the potential misperceptions of sugars in tobacco products and of the potential sugar regulation: People who use and do not use tobacco are likely to have preconceived notions about the positive and negative effects of sugars (e.g., pleasant taste or weight gain) related to food or drinks, but not related to the toxicity of tobacco/nicotine products. It is important to develop effective communication strategies that account for such preconceived notions. If sugars are added to the HPHC list and limits are set, the public will need to be informed about the purpose and significance of the regulatory action.

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- Modeling studies to assess the population impact of a potential sugar standard for various tobacco products: As the research gaps above are being addressed, the accumulating evidence can be leveraged to develop models assessing the potential public health impact of sugar regulation in various tobacco product types.

CONCLUSION

Reducing the use of tobacco and nicotine products remains a public health priority in the U.S. and globally. Regulation of constituents and product characteristics that increase toxicity, appeal, and abuse liability of tobacco and nicotine products can serve as a powerful tool in efforts to protect public health. Based on the data presented in this review, we conclude that the evidence on toxicological risks posed by sugars in tobacco and nicotine products supports that sugar be added to the HPHC list. It will also be important to identify maximum thresholds of sugars and sweeteners in different products and employ those thresholds as a product standard. Future research directions are proposed that can inform tobacco/nicotine product regulation aimed at reducing the harm associated with sugars and sweeteners in these products.

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Notes

The authors declare no competing financial interest.

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