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Commentary

Sugars and Sweeteners in Tobacco and Nicotine Products: Food and Drug Administration's Regulatory Implications

Mary Rezk-Hanna PhD[1], Reinskje Talhout PhD[2], Sven-Eric Jordt PhD[3]

[1]School of Nursing, University of California, Los Angeles, Los Angeles, CA, USA
[2]Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Utrecht, The Netherlands
[3]Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA

Corresponding Author: Mary Rezk-Hanna, PhD, School of Nursing, University of California, Los Angeles, 700 Tiverton Ave, 4-254 Factor Building, Los Angeles, CA 90095, USA. Telephone: 310-206-8654; Fax: 310-794-7482; E-mail: MRezk@ucla.edu

For the 5th National Institute of Health Tobacco Regulatory Science meeting, we participated in a plenary session focused on sugars and sweeteners profiles in tobacco and nicotine products and their related toxicity and abuse liability implications. The meeting was organized by the Tobacco Regulatory Science Program, a partnership between the National Institutes of Health (NIH) and the U.S. Food and Drug Administration's (FDA) Center for Tobacco Products. In this commentary, we wish to underscore the critical importance of this understudied topic and highlight potential regulatory implications for the FDA's Center for Tobacco Products.

While sugars are natural components of tobacco, tobacco companies manipulate consumers' sensory perceptions of the true noxiousness of cigarette smoke during inhalation by adding various sugars, including glucose, fructose, and sucrose, up to 4% of a cigarette's weight.[1] Because these manipulations also apply to other products, in the absence of adequate regulation, substantial differences in sugar content, and profiles will continue to exist across tobacco and nicotine products, including cigarettes, hookahs (ie waterpipes), electronic (e-) cigarettes, and smokeless products.

Sugars are key ingredients in tobacco, with total concentration levels up to 20% of a cigarette's weight.[1] Regardless of whether sugars are naturally present or added, studies have demonstrated their critical contributions to the adverse health effects associated with tobacco use. With oral use, ingested as food, sugars release dopamine and endogenous opioids, stimulating the brain similarly to effects from cocaine and other drugs.[2] With pyrolysis, sugars act as pro-addictive compounds by generating acetaldehyde, which increases the addictive potency of nicotine.[3] Pyrolysis of sugars also generates caramellic products and acids that decrease smoke pH, which results in a sweeter and milder smoke, masking the adverse harsh taste of smoke, and thus enhancing the appeal of cigarettes and nicotine products.[1] Emerging evidence shows that sugars affect the chemical composition of tobacco smoke and generate numerous toxicants and carcinogens.[4] Remarkably, studies performed by R.J. Reynolds demonstrated that sugars in tobacco increase the level of volatile toxicants, including formaldehyde and acrolein.[5] It remains to be established which sugar content (total or added) and combustion and heating conditions—heated versus unheated at high versus low temperatures and inhaled versus oral—influence toxicity and abuse liability. Despite mounting evidence for the contribution of sugars to smoking-associated morbidity and mortality, sugars in tobacco and nicotine products are neither regulated nor are part of the U.S. FDA harmful and potentially harmful constituents (HPHC) list.[6]

In addition to sugars, manufacturers are adding artificial and natural high-intensity sweeteners to oral tobacco and nicotine products. In the 1890s, the R.J. Reynolds company began adding saccharin to chewing tobacco.[7] Saccharin remains the most common sweetener additive in traditional smokeless products such as moist snuff.[8] More recently introduced oral smokeless products such as U.S. marketed snus contain high levels of sucralose (Splenda), an artificial sweetener 600 times sweeter than sucrose (table sugar).[8] The sweetness imparted by sucralose in snus products is more intense than the sweetness of the products' weights in table sugar, and more intense than the sweetness of sucralose-sweetened confectionary products.[8] The more recently introduced product categories of "tobacco-free" oral nicotine pouches, lozenges, and soft chews of the brands Zyn (Swedish Match), Velo (British American Tobacco), and On! (Altria) are either sweetened with sucralose, or with Acesulfame-K (AceK).[9,10] Flavored cigars were also found to contain sweeteners, both in the mouth sections and in the outside wrapper, suggesting deliberate addition to impart intense sweet taste, in combination with the sweet-associated characterizing flavors.[11] High-intensity sweeteners in cigars include saccharin, sucralose, AceK and Neotame, and also glycyrrhizin, the sweetener in licorice, 50 times sweeter than sucrose.[11] The tobacco industry is a major purchaser of licorice that is also added to combustible cigarettes.[12] Taken together, there is evidence for the increased sweetness of major tobacco product categories over time, with the newest products containing the most potent artificial sweeteners at levels exceeding the sweetness of

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sugar, and sweeteners applied to critical parts of products interacting with the consumer.

Sweet flavors increase the palatability of tobacco and nicotine products and facilitate the initiation and continued tobacco use, particularly among youth.[13–16] Nationally representative U.S. adolescents and young adults report flavors as a primary reason for using a given tobacco product.[14] Among college-age youths, advertising of e-cigarettes with sweet flavors produced greater fMRI activity within the nucleus accumbens, as compared with tobacco flavors.[15] In addition to their potent behavioral effects, the presence of artificial sweeteners in tobacco products raises toxicological concerns. Sucralose was also detected in some commercial e-cigarette liquids and is sold as a sweetener additive for DIY mixing. Recent studies demonstrated that sucralose, a chlorinated sugar, can undergo chemical reactions when heated in e-cigarettes, forming toxic chloropropanols.[17,18] Frequent consumption of smokeless tobacco may lead to considerable artificial sweetener intake, raising concerns that the FDA-recommended Acceptable Daily Intake may be exceeded, especially when also consuming other artificially sweetened products.[8,19] Regular intake of artificial sweeteners may impact metabolism, resulting in increasing glucose tolerance, and affecting the intestinal microbiome.

Under current federal regulations, tobacco and vaping manufacturers are not required to disclose sugar and sweetener levels on their product packaging or marketing materials (Figure 1). To date, while the FDA mandates reporting added sugar levels on packaged foods and beverages "to make it easier for you to make informed choices",[20] this mandate does not extend to tobacco and nicotine products. It is plausible that manufacturers' reporting of sugar and sweetener levels (naturally present and added) in tobacco, which the FDA has the authority to require, would allow for more accurate characterization of harm potential with cigarette and nicotine products use and will allow consumers to make informed choices about smoking or vaping, similar to the choices they are encouraged to make with foods and beverages.

While the FDA has the authority to regulate "characterizing flavors" in tobacco products, sweetness per se, as imparted by sugars and sweeteners, has not been mentioned in any of the FDA's rulings and information materials as constituting a characterizing flavor. Sugars and high-intensity sweeteners are odorless and cannot be detected by the consumer through smell. However, the manufacturer often uses "sweet" as a brand moniker (eg "Swisher Sweets," "Sweet Fat Molly" cigars) or as part of flavor names (eg "Sweet Cream" cigar, "Sweet Cherry" e-liquids). It is likely the combination of sweet-associated flavor chemicals (vanillin, ethyl maltol, fruit, or chocolate flavorings) in combination with sugars and their caramelized combustion products, and sweeteners, attract users. Youth—shown to have a strong preference for sweetness—[16] and young adults are at especially high risk for initiating and continuing use of such products.[13,14] In smoked tobacco products, young adult hookah users report an enhanced smoking experience and greater interest in future use after smoking flavored versus unflavored tobacco.[13]

Addressing these loopholes is critical because despite the growing evidence of harm from added sugars and sweeteners in tobacco and nicotine products, consumers are unaware: (1) that sugar and related additives are added to tobacco and nicotine products, and (2) of their related harm. In their article in *Nicotine and Tobacco Research*, Seidenberg and colleagues examined public knowledge of added sugar in cigarettes and awareness of its effects.[21] This study included a convenience sample of 4351 adult current cigarette smokers (defined as having smoked ≥ 100 cigarettes in their lifetime and currently smoking every day or some days), who were asked to answer two questions about knowledge and awareness of added sugar in cigarettes. The findings show that only 5.5% of all participants responded "yes" to the question: "Is sugar added to cigarettes?" with only 3.8% of all participants indicated being aware that added sugar increases toxins in cigarette smoke.[21] Notably, more than half of the participants shared their interest in learning more about added sugars in cigarettes, and several expressed that learning about added sugars in cigarettes and their potential health effects may motivate them to quit or cut down on smoking.

As our scientific understanding expands in this critical, yet understudied, area of research, we wish to draw attention to three key points to consider, as efficient means to reduce use and initiation of tobacco and nicotine products: (1) setting

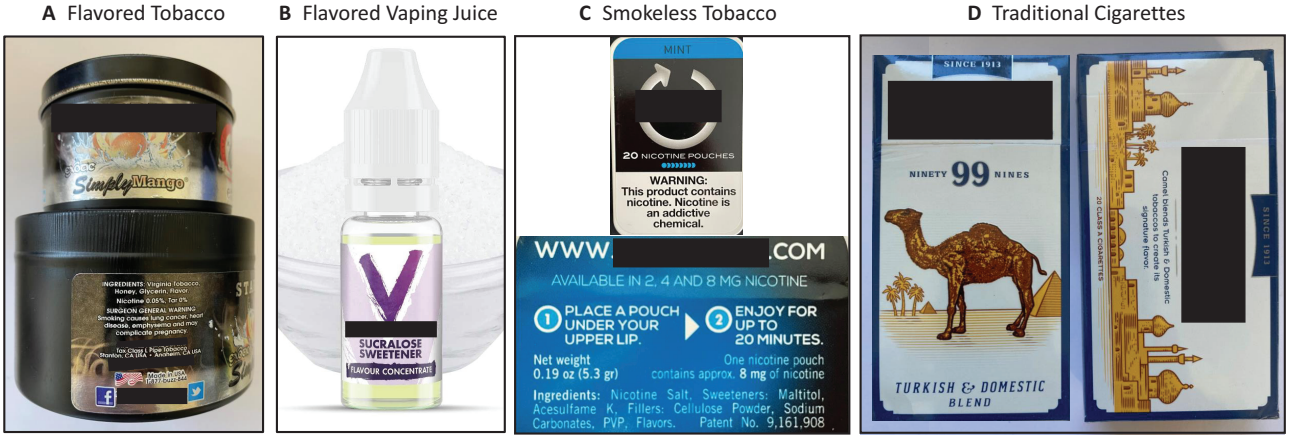

Figure 1. Tobacco and vaping product packaging. (**A**) Hookah (Waterpipe) flavored tobacco product manufactured by Starbuzz Tobacco listing honey as ingredients; (**B**) Flavored vaping juice manufactured by Vapable depicting a sucralose-based sweetener flavor concentrate, sold to add to vaping juice; (**C**) Nicotine pouches manufactured by On! (Altria) listing maltitol and acesulfame-K as sweeteners[22]; and (**D**) Traditional Cigarettes manufactured by Camel. While no ingredients are listed on the packaging, the following are listed on RJ Reynold's website: Tobacco, water, glycerol, high fructose corn syrup, propylene glycol, cellulose Fiber, cocoa, licorice, diammonium phosphate, ammonium hydroxide, and natural and artificial flavors.[23]

product standards relating to sugars and related sweeteners prohibiting their addition, particularly to smoked tobacco products, and ensuring accurate and comprehensible labeling displays on tobacco and nicotine products, (2) designating sugars and sweeteners as characterizing flavors in tobacco products, enabling FDA to regulate these additives with the goal to reduce youth initiation, diminish their reinforcing properties and lower daily sweetener intake, and (3) prioritizing educational efforts and advertisement campaigns on sugars in tobacco and nicotine products and their related health effects to increase public awareness and protect future generations by preventing them from becoming addicted to tobacco and nicotine products.

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Declaration of Interests

None declared: the views expressed herein are those of the authors and do not necessarily reflect those of the Tobacco Regulatory Science Program or other plenary session participants.

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