R Street Policy Study
No. 298
February 2024

Flavor Can Save Lives:
The Neurobiological Rationale for Flavor in Reduced-Risk Nicotine Products

By Jeffrey S. Smith

If regulated appropriately, reduced-risk products can provide a wide variety of flavor selections that would increase the rate and sustainability of smoking cessation and greatly reduce the negative consequences of smoking on public health in a rapid and effective manner.

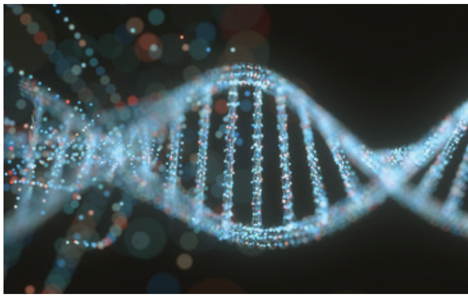
Table of Contents

Executive Summary

Although smoking rates have been declining in recent years, millions of individuals in the United States continue to smoke combustible cigarettes, and many experience health consequences—including death—from diseases associated with long-term use.

In 2009, in an effort to reduce negative tobacco-related health outcomes, the U.S. Food and Drug Administration established the Center for Tobacco Products (CTP) to develop regulatory guidelines to manage the tobacco marketplace (and, later, all nicotine products). A major aspect of the CTP's priorities has been attempting to understand the effects that the flavor of a tobacco or nicotine product might have on public health. From one perspective, flavor is viewed as a tool to help adult smokers move away from combustible cigarettes to alternative, reduced-risk products; from another perspective, flavor may attract nonsmokers to nicotine products and, eventually, lead to more individuals becoming smokers.

Determining the role that flavor might play in public health is not a simple task; it requires delving into the complex neurobiological processes involved. Flavors influence our actions and behaviors from the point of flavor detection through the integration of flavor information into cognitive processes. Moreover, our flavor preferences are influenced by our genetic heritage, lived experiences, and social interactions—all of which drive our decisions and act as powerful behavioral reinforcers. In fact, studies suggest that new flavors may be more reinforcing, helping to establish new behaviors.



Our flavor preferences are influenced by our genetic heritage, lived experiences, and social interactions—all of which drive our decisions and act as powerful behavioral reinforcers. In fact, studies suggest that new flavors may be more reinforcing, helping to establish new behaviors.

With an awareness of the neurobiological connection between flavor and behavior, one can better appreciate how novel and varied flavors might be leveraged as a tool in noncombustible tobacco and nicotine products to help transition combustible cigarette smokers to reduced-risk products. To demonstrate the public health value of doing so, this policy paper explores the neurobiological processing of flavor—both broadly and as it pertains to tobacco and nicotine products—and explains how flavor can influence behavioral choices. With this foundation in place, we discuss how seemingly simple regulatory decisions about flavored tobacco and nicotine products could have complex, significant implications on the CTP's goal of reducing the toll of smoking in the United States. Specifically, we explain the importance of opposing a broad range of rules that would limit flavor profiles for reduced-risk products, as doing so would diminish—or even eliminate—a powerful public health tool that can help adults move away from combustible cigarettes and their negative health effects.

Introduction

Currently, the most contentious debate in tobacco control and harm reduction is the role of flavored tobacco and nicotine products. Those against flavored products believe that they entice adults and minors to begin smoking and serve as a potential gateway to combustible cigarettes.[1] Those who support flavored products assert that they are a viable reduced-risk product that helps current combustible cigarette smokers switch from a dangerous habit to less harmful behavior that still meets or exceeds sensory desires while greatly reducing health risks.[2] Examples of reduced-risk products that use flavors include electronic nicotine delivery systems (ENDS, also known as vapes or e-cigarettes), heat-not-burn (HnB) products, and oral tobacco and nicotine products (snus, snuff, and nicotine pouches).

1. Andrea C. Villanti et al., "Association of Flavored Tobacco Use With Tobacco Initiation and Subsequent Use Among US Youth and Adults, 2013-2015," *JAMA Network Open* 2:10 (Oct. 23, 2019). https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2753396?utm_campaign=scite&utm_source=scite&utm_medium=referral.
2. Allison M. Glasser et al., "Patterns of E-cigarette Use and Subsequent Cigarette Smoking Cessation Over 2 Years (2013/2014–2015/2016) in the Population Assessment of Tobacco and Health Study," *Nicotine & Tobacco Research* 23:4 (April 2021), pp. 669-677. https://academic.oup.com/ntr/article-abstract/23/4/669/5906689?redirectedFrom=fulltext.

About a decade ago, scientific evidence demonstrating the importance of non-tobacco-flavored, reduced-risk products began to emerge. In 2015, researchers reported that 66 percent of those who independently chose to switch to novel ENDS products were able to completely stop smoking cigarettes.[3] Most of the study participants attributed their success, which was verified by exhaled carbon monoxide readings, to the availability of non-tobacco- and non-menthol-flavored ENDS products.[4] Unfortunately, around the same time, the underage use of vapes (both nicotine and non-nicotine) began to increase, which triggered an aggressive response from regulators and policymakers attempting to curb youth use via regulatory measures, educational campaigns, and laws limiting access to ENDS products.[5] This led to the current situation in which no non-tobacco-flavored ENDS product has been approved for sale in the United States by the Food and Drug Administration (FDA).[6]

In 2015, researchers reported that 66 percent of those who independently chose to switch to novel ENDS products were able to completely stop smoking cigarettes.

The lack of approved, non-tobacco-flavored ENDS products is problematic because of the way in which flavor can be leveraged to help individuals more easily transition to reduced-risk tobacco and nicotine products. Most of us tend to think of flavor as a useful perception that brings pleasure (or disgust) as we ingest food and beverages. The reality, however, is that flavor perception is an essential function that not only keeps us healthy and alive but also dramatically influences many of our activities and behaviors, whether we realize it or not.[7] To better understand the important role that flavor plays in our lives, this paper explains flavor perception from neuroscientific and psychological perspectives, describes how these influences consciously and subconsciously affect our behavior and thoughts, and explores how an understanding of these principles can be applied to influence smoking behavior and save the lives of millions of smokers across the globe.

500,000

To reduce the nearly 500,000 smoking-related deaths that occur each year in the United States, the FDA Center for Tobacco Products (CTP) must take a scientifically driven approach that recognizes the neurobiological rationale for allowing a wide variety of flavored, reduced-risk products to be available to adults (while minimizing youth access).

With this understanding of the underlying science and influence of flavor, we can better appreciate how flavor factors into a rational approach to the regulation of reduced-risk products. Simply put, to reduce the nearly 500,000 smoking-related deaths that occur each year in the United States, the FDA Center for Tobacco Products (CTP) must take a scientifically driven approach that recognizes the neurobiological rationale for allowing a wide variety of flavored, reduced-risk products to be available to adults (while minimizing youth access).[8] It is essential that the CTP approve non-tobacco-flavored, reduced-risk products.

3. Alayna P. Tackett et al., "Biochemically verified smoking cessation and vaping beliefs among vape store customers," *Addiction* 110:5 (May 2015), pp. 868-874. https://onlinelibrary.wiley.com/doi/abs/10.1111/add.12878.
4. Ibid.
5. Zainab Farzal et al., "The Adolescent Vaping Epidemic in the United States—How It Happened and Where We Go From Here," *JAMA Otolaryngology–Head & Neck Surgery* 145:10 (Aug. 22, 2019), pp. 885-886. https://jamanetwork.com/journals/jamaotolaryngology/article-abstract/2748897.
6. Karin A. Kasza et al., "Use of Electronic Nicotine Delivery Systems or Cigarette Smoking After US Food and Drug Administration–Prioritized Enforcement Against Fruit-Flavored Cartridges," *JAMA Network Open* 6:6 (June 30, 2023). https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2806715.
7. Gordon M. Shepherd, "Perspectives on Olfactory Processing, Conscious Perception, and Orbitofrontal Cortex," *Annals of the New York Academy of Sciences* 1121:1 (December 2007), pp. 87-101. https://nyaspubs.onlinelibrary.wiley.com/doi/10.1196/annals.1401.032.
8. Jonathan T. Macy et al., "Adolescent tolerance for deviance, cigarette smoking trajectories, and premature mortality: A longitudinal study," *Preventive Medicine* 119 (February 2019), pp. 118-123. https://www.sciencedirect.com/science/article/abs/pii/S0091743518304031?via%3Dihub; Vivek H. Murthy, "E-Cigarette Use Among Youth and Young Adults: A Major Public Health Concern," *JAMA Pediatrics* 171:3 (March 2017), pp. 209-210. https://jamanetwork.com/journals/jamapediatrics/article-abstract/2592300?utm_campaign=scite&utm_source=scite&utm_medium=referral.

The Complex Neurobiology of Flavor Perception

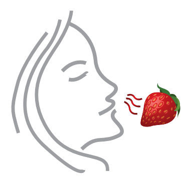
To demonstrate the degree to which our flavor preferences subconsciously drive a variety of choices we make every day, as well as the critical role flavor can play in helping combustible cigarette smokers transition to reduced-risk products, we must first appreciate the complex science of flavor.

The multisensory experience involves the cognitive mechanisms of sensory fusion, in which the brain combines and processes information from different sensory modalities to create a unified perception.

Flavor is a sensory perception that involves more than basic marketing descriptions and logos on a package. The perception of a flavor arises from the integration of various sensory inputs, including the taste, smell, texture, temperature, sight, and even sound of foods.[9] This multisensory experience goes beyond simply detecting basic taste qualities such as sweetness, saltiness, sourness, bitterness, and umami.[10] It involves the cognitive mechanisms of sensory fusion, in which the brain combines and processes information from different sensory modalities to create a unified perception.[11] Below, we explore some of the many systems and processes involved to illustrate how deeply rooted flavor perception is in the human experience.

The Detection of Chemicals Associated with Flavor

The olfactory system plays a crucial role in flavor perception. The sense of smell, or the detection of odor molecules, contributes to the overall flavor experience. When we eat or drink, volatile compounds are released in the oral cavity and travel to the olfactory receptors in the nasal cavity through the retronasal pathway. This process allows us to perceive the aroma and flavor of food and beverages; when olfactory function is disrupted, it can lead to an altered perception of flavors.[12]



The olfactory system plays a crucial role in flavor perception. The sense of smell, or the detection of odor molecules, contributes to the overall flavor experience.

Olfactory receptors contribute to the sense of smell and flavor perception by detecting and processing odor molecules. Olfactory receptor cells have two modes of signaling—excitation and inhibition—which add another level of complexity to olfactory perception.[13] These cells are responsible for detecting odorants in the environment. When odor molecules enter the nasal cavity, they bind to specific olfactory receptors located on the cilia of olfactory receptor neurons.[14] Each olfactory receptor neuron expresses only one type of olfactory receptor, and humans have hundreds of different types of olfactory receptors. These receptor cells are expressed not only in the olfactory system, but also in taste cells on the tongue, which reinforces their functional role in taste perception.[15]

9. Dana M. Small et al., "Experience-Dependent Neural Integration of Taste and Smell in the Human Brain," *Journal of Neurophysiology* 92:3 (September 2004), pp. 1892-1903. https://journals.physiology.org/doi/full/10.1152/jn.00050.2004.
10. Marco Francesco Mazzù et al., "Measuring the Effect of Blockchain Extrinsic Cues on Consumers' Perceived Flavor and Healthiness: A Cross-Country Analysis," *Foods* 10:6 (June 18, 2021), p. 1413. https://www.mdpi.com/2304-8158/10/6/1413.
11. Jérémy Roque et al., "Understanding Freshness Perception from the Cognitive Mechanisms of Flavor: The Case of Beverages," *Frontiers in Psychology* 8 (Jan. 11, 2018). https://www.frontiersin.org/articles/10.3389/fpsyg.2017.02360/full.
12. David Tianxiang Liu et al., "Retronasal olfactory function in patients with smell loss but subjectively normal flavor perception," *The Laryngoscope* 130:7 (July 2020), pp. 1629-1633. https://onlinelibrary.wiley.com/doi/full/10.1002/lary.28258.
13. Barry W. Ache and Janet M. Young, "Olfaction: Diverse Species, Conserved Principles," *Neuron* 48:3 (Nov. 3, 2005), pp. 417-430. https://doi.org/10.1016/j.neuron.2005.10.022.
14. Kensaku Mori et al., "The Olfactory Bulb: Coding and Processing of Odor Molecule Information," *Science* 286:5440 (Oct. 22, 1999), pp. 711-715. https://www.science.org/doi/abs/10.1126/science.286.5440.711.
15. Bilal Malik et al., "Mammalian Taste Cells Express Functional Olfactory Receptors," *Chemical Senses* 44:5 (June 2019), pp. 289-301. https://academic.oup.com/chemse/article/44/5/289/5470701.

The binding of an odorant to its specific receptor triggers a cascade of events that causes the olfactory receptor neuron to generate electrical signals. This influx of signals generates an electrical signal, known as an action potential, which is transmitted to the olfactory bulb in the brain. Individual glomeruli within the olfactory bulb receive inputs from specific types of odorant receptors. This allows for the identification of different odorants and contributes to the discrimination and identification of different smells. In addition to this classification, the olfactory bulb allows the axons of olfactory receptor neurons to synapse with other cells, which then project to higher brain regions involved in olfactory processing.

Taste also plays a fundamental role in flavor perception. The taste buds on the tongue detect basic taste qualities (sweetness, saltiness, sourness, bitterness, and umami) and transmit this information to the brain for further processing.[16] Molecules from the foods and beverages we consume interact with taste receptors on the taste buds to initiate a cascade of events that lead to the perception of taste. Each taste bud contains multiple taste receptor cells, and these cells express different types of taste receptors that detect specific taste qualities. For example, sweet taste receptors detect sugars, and bitter taste receptors detect bitter compounds. When a taste molecule binds to its corresponding taste receptor, it triggers a signaling pathway that leads to the generation of electrical signals in the taste receptor cell.[17] The taste information is relayed to the gustatory cortex, which is located in the insula and frontal operculum of the brain and involved in the perception and discrimination of taste qualities.[18] This information is integrated with olfactory information in the brain, contributing to overall flavor perception.[19]

Taste also plays a fundamental role in flavor perception. The taste buds on the tongue detect basic taste qualities (sweetness, saltiness, sourness, bitterness, and umami) and transmit this information to the brain for further processing.

Of note, neuroimaging studies have provided insights into the neural mechanisms underlying gustatory processing. The orbitofrontal cortex, in particular, has been implicated in the representation of the pleasantness of flavor.[20] These findings suggest that flavor perception is a complex cognitive process that integrates information from multiple sensory modalities. Indeed, other sensory inputs, such as texture, temperature, and visual cues also contribute to an overall flavor experience.[21]

Neurological Systems Involved in Flavor Perception

The motor system, specifically the muscles involved in chewing and swallowing, contributes to flavor perception. The act of chewing food helps release flavor

16. Joost X. Maier, "Single-neuron responses to intraoral delivery of odor solutions in primary olfactory and gustatory cortex," *Journal of Neurophysiology* 117:3 (March 10, 2017), pp. 1293-1304. https://journals.physiology.org/doi/full/10.1152/jn.00802.2016.
17. R. Matsuo, "Role of Saliva in the Maintenance of Taste Sensitivity," *Critical Reviews in Oral Biology & Medicine* 11:2 (2000), pp. 216-229. https://journals.sagepub.com/doi/10.1177/10454411000110020501.
18. Ivan E.T. De Araujo et al., "Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain," *European Journal of Neuroscience* 18:7 (Oct. 21, 2003), pp. 2059-2068. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1460-9568.2003.02915.x.
19. Small et al. https://journals.physiology.org/doi/full/10.1152/jn.00050.2004.
20. Ibid.
21. Ibid.

compounds and enhances the sensory experience.[22] The movement of the jaw and tongue during chewing exposes more taste buds to the food, allowing for greater taste perception. Additionally, the muscles involved in swallowing help distribute flavors throughout the oral cavity. [23]

Chewing exposes more taste buds to the food, allowing for greater taste perception.

Temperature also influences flavor perception. The trigeminal nerve, which transmits sensory information from the face and mouth, provides information about temperature and other sensations. Temperature modulates the release of volatile compounds from food, which in turn affects aroma and flavor.[24] For example, warm or hot foods may release more volatile compounds, producing a more intense flavor perception, whereas cold foods may numb the taste buds and reduce the perception of certain flavors.

Temperature also influences flavor perception.

Cognitive factors play a significant role in flavor perception as well, influencing how we perceive and interpret sensory information from taste and smell. Cognitive processes, such as attention and expectation, can shape flavor perception, and a focus on specific sensory cues can enhance the perception of those flavors.[25] For example, directing attention to the taste or aroma of a particular ingredient in a dish can heighten the perception of that flavor. Additionally, expectations based on previous experiences or cultural influences can shape flavor perception. Moreover, studies have shown that the color of food or packaging can influence taste perception, with participants perceiving differently flavored foods as having different tastes based on color cues.[26] Finally, cognitive processes play a role in integrating sensory information from taste and smell, creating a unified flavor perception.[27]

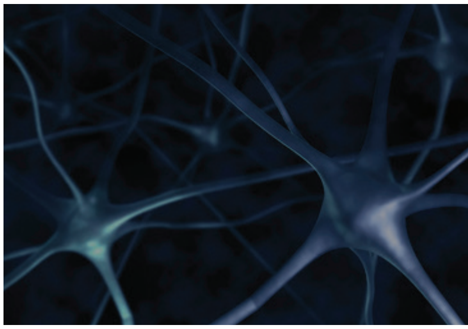
Cognitive factors influence how we perceive and interpret sensory information from taste and smell.

Similarly, emotions can influence how we perceive and evaluate the pleasantness or unpleasantness of flavors. For example, positive emotions can enhance the perceived pleasantness of flavors, and negative emotions can lead to a decreased perception of pleasantness.[28] In addition, emotional states such as stress or anxiety can affect taste perception, leading to alterations in flavor perception.[29] Emotions can also influence our food choices and preferences, with certain emotions leading to a preference for specific flavors or types of food.[30]

Emotions can influence how we perceive and evaluate the pleasantness or unpleasantness of flavors.

22. Malika Auvray and Charles Spence, "The multisensory perception of flavor," *Consciousness and Cognition* 17:3 (September 2008), pp. 1016-1031. https://www.sciencedirect.com/science/article/abs/pii/S1053810007000657.
23. Ibid.
24. Karel Talavera et al., "Heat activation of TRPM5 underlies thermal sensitivity of sweet taste," *Nature* 438 (Dec. 13, 2005), pp. 1022-1025. https://www.nature.com/articles/nature04248.
25. Charles Spence, "Mouth-Watering: The Influence of Environmental and Cognitive Factors on Salivation and Gustatory/Flavor Perception," *Journal of Texture Studies* 42:2 (April 2011), pp. 157-171. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1745-4603.2011.00299.x.
26. Charles Spence et al., "Does Food Color Influence Taste and Flavor Perception in Humans?," *Chemosensory Perception* 3 (2010), pp. 68-84. https://link.springer.com/article/10.1007/s12078-010-9067-z.
27. Roque et al. https://www.frontiersin.org/articles/10.3389/fpsyg.2017.02360/full.
28. Jessica I. Lake, "Recent advances in understanding emotion-driven temporal distortions," *Current Opinion in Behavioral Sciences* 8 (April 2016), pp. 214-219. https://www.sciencedirect.com/science/article/abs/pii/S2352154616300328?via%3Dihub.
29. Ibid.
30. Rani Andaleeb et al., "Cross-cultural sensory and emotions evaluation of chicken-spice blend by Chinese and Pakistani consumers," *Journal of Sensory Studies* 38:2 (April 2023). https://onlinelibrary.wiley.com/doi/abs/10.1111/joss.12815.

Research has shown that individual differences in cognitive and emotional factors can affect flavor perception. For example, individuals with higher levels of empathy may be more attuned to the emotional aspects of flavor perception, leading to a greater sensitivity to the emotional cues conveyed by food.[31] In addition, studies have suggested that individuals with better working memory performance may have enhanced flavor perception and discrimination abilities.[32] Understanding this interplay between cognitive, emotional, and sensory processes is essential for understanding flavor perception.



The evolutionary and biological basis of flavor preference is a complex topic that involves various factors such as taste, conditioning, learning, and neurobiology.

How Flavor Preference Develops and Influences Human Behavior

The evolutionary and biological basis of flavor preference is a complex topic that involves various factors such as taste, conditioning, learning, and neurobiology. Several studies have explored different aspects of flavor preference and have provided insights into the mechanisms underlying this phenomenon. For example, in one study, investigators found that hunger enhances the expression of calorie-mediated flavor preferences.[33] The study showed that flavor preferences mediated by a preferred taste, such as saccharin, were enhanced by hunger, whereas preferences mediated by positive outcomes, such as calories that provide the energy needed to survive, were not affected by hunger. This suggests that the biological drive for calories influences flavor preferences.

Another factor influencing flavor preference is the association between flavors and positive outcomes. Studies have shown that a glucose-conditioned flavor preference can be acquired.[34] In a study with rats, researchers determined that flavor preferences required the activation of dopamine D1-like receptors within the medial prefrontal cortex.[35] In this study, researchers distinguished between flavor-flavor conditioning, in which a preference developed for a cue flavor mixed with an already-preferred flavor, and flavor-nutrient conditioning, in which a preference developed for a cue flavor paired with the post-oral positive effects of a nutrient. This highlights the role of dopamine and the prefrontal cortex in the acquisition of flavor preferences.

Past Experiences, Evolution, and Learning

Early experiences with flavors have been shown to influence later preferences. Researchers have hypothesized that infants' early experiences with odors—a major component of flavor—in specific nursing behavior can result in long-term

31. Stephanie D. Preston and Frans B.M. De Waal, "Empathy: Its ultimate and proximate bases," *Behavioral and Brain Sciences* 25:1 (Jan. 23, 2002), pp. 1-20. https://www.cambridge.org/core/journals/behavioral-and-brain-sciences/article/abs/empathy-its-ultimate-and-proximate-bases/953E0D092176FEE351ED81E933FE646D.
32. Kumiko Hagiya et al., "Facial expression perception correlates with verbal working memory function in schizophrenia," *Psychiatry and Clinical Neurosciences* 69:12 (December 2015), pp. 773-781. https://onlinelibrary.wiley.com/doi/full/10.1111/pcn.12329.
33. Paul M. Fedorchak and Robert C. Bolles, "Hunger enhances the expression of calorie- but not taste-mediated conditioned flavor preferences," *Journal of Experimental Psychology: Animal Behavior Processes* 13:1 (1987), p. 73. https://psycnet.apa.org/record/1987-14890-001.
34. Khalid Touzani et al., "Acquisition of glucose-conditioned flavor preference requires the activation of dopamine D1-like receptors within the medial prefrontal cortex in rats," *Neurobiology of Learning and Memory* 94:2 (September 2010), pp. 214-219. https://www.sciencedirect.com/science/article/abs/pii/S1074742710001012.
35. Ibid.

preferences.[36] Investigators have also looked at the role of specific taste components in flavor preferences. For example, studies have shown that flavor preferences, like the preference for dashi (a fish stock with umami and other flavor components), are conditioned by dietary glutamate.[37] Additionally, some research has shown evidence of conditioned taste and flavor preferences in both children and adults.[38] Other research has suggested that the evolution of dietary preferences and the drive to seek food that improves one's health are key components of acquired flavor preferences.[39]

Some research has shown evidence of conditioned taste and flavor preferences in both children and adults. Other research has suggested that the evolution of dietary preferences and the drive to seek food that improves one's health are key components of acquired flavor preferences.

The role of different brain regions in flavor preference has also been investigated from an evolutionary perspective. It has been suggested that flavor aversion and preference conditioning may share the same short-term flavor memory system, but the preference conditioning circuit is more fragile because of the biological importance of avoiding poisons.[40] This infers that different brain circuits are involved in flavor aversion and preference conditioning. An additional study has identified the role of amygdala dopamine D1 and D2 receptors in the acquisition and expression of fructose-conditioned flavor preferences in rats.[41] In this study, the researchers found that different brain regions, such as the amygdala and medial prefrontal cortex, mediate the acquisition and expression of fructose-conditioned flavor preferences. And yet another team of investigators suggested that sweet taste preferences are logical from an evolutionary standpoint because they offer a primary energy source.[42] This preference for sweetness may have evolved to identify and consume calorie-rich foods, which would have provided an advantage in terms of survival and energy acquisition. Taste has also been crucial in monitoring the quality and suitability of food and in sorting out harmful and toxic compounds.[43] Taken together, these studies suggest that our taste preferences have evolved to guide us toward nutritious and safe foods and away from potentially harmful substances.

Associative learning is another key factor flavor preference. One group of investigators studied the neuropharmacology of learned flavor preferences and the role of the endocrine system, learning, choice behavior, and the nucleus accumbens—a key brain region involved in reward processing—in the formation

36. Julie A. Mennella and Gary K. Beauchamp, "Flavor experiences during formula feeding are related to preferences during childhood," *Early Human Development* 68:2 (July 2002), pp. 71-82. https://www.sciencedirect.com/science/article/abs/pii/S0378378202000087.
37. Karen Ackroff and Anthony Sclafani, "Flavor Preferences Conditioned by Dietary Glutamate," *Advances in Nutrition* 7:4 (July 2016), pp. 845S-552S. https://advances.nutrition.org/article/S2161-8313(22)00772-4/fulltext.
38. Benjamin M. Seitz et al., "Eating behavior as a new frontier in memory research," *Neuroscience & Biobehavioral Reviews* 127 (August 2021), pp. 795-807. https://www.sciencedirect.com/science/article/abs/pii/S0149763421002347.
39. Akhila Hosur Shrungeswara and Mazhuvancherry Kesavan Unnikrishnan, "Evolution of dietary preferences and the innate urge to heal: Drug discovery lessons from Ayurveda," *Journal of Ayurveda and Integrative Medicine* 10:3 (July–September 2019), pp. 222-226. https://www.sciencedirect.com/science/article/pii/S0975947617302607.
40. Khalid Touzani and Anthony Sclafani, "Conditioned flavor preference and aversion: Role of the lateral hypothalamus," *Behavioral Neuroscience* 115:1 (2001), p. 84. https://psycnet.apa.org/record/2001-16476-007.
41. Sonia Bernal et al., "Role of amygdala dopamine D1 and D2 receptors in the acquisition and expression of fructose-conditioned flavor preferences in rats," *Behavioural Brain Research* 205:1 (Dec. 14, 2009), pp. 183-190. https://www.sciencedirect.com/science/article/abs/pii/S0166432809003945.
42. Michael Schaefer and Eileen Garbow, "Psychological Effects of Sweet Taste and Sweet Taste Preference," *Applied Sciences* 11:24 (2021). https://www.mdpi.com/2076-3417/11/24/11967.
43. Harald M. Eriksen and Vladimir Dimitrov, "The human mouth: oral functions in a social complexity perspective," *Acta Odontologica Scandinavica* 61:3 (July 2, 2009), pp. 172-177. https://www.tandfonline.com/doi/abs/10.1080/00016350310003297.

of flavor preferences.[44] Their research suggested that our flavor preferences may have evolved through a process of associative learning, whereby we learn to associate certain flavors with positive outcomes or rewards.[45]

Research suggests that our flavor preferences may have evolved through a process of associative learning, whereby we learn to associate certain flavors with positive outcomes or rewards.

Specific taste components in flavor are also important in our understanding of learned flavor preferences. As previously noted, flavor preferences are conditioned by dietary glutamate, which underscores the role of specific taste components, such as glutamic acid, in forming those preferences. Thus, our taste preferences may have evolved to favor certain taste components that are indicative of nutrient-rich foods.[46] Additionally, some research has suggested that the evolutionary psychological perspective on sex differences in human mate preferences is influenced by our flavor preferences and may have evolved as a way to signal genetic fitness and compatibility with potential mates.[47]

ENDS Products and Flavor Preferences

An early review evaluating the different flavor preferences of ENDS consumers identified that certain food-related flavors (e.g., fruit and cream-based flavors, which tend to be those we are exposed to early in life) were preferred over others (e.g., confectionary) and were rated much higher than traditional tobacco flavors.[48] Additionally, mixed-flavored ENDS products (more than one defining flavor characteristic) were more popular than single-flavor products. Critics of flavored ENDS products have suggested that the availability of food-related flavors might entice new (non-smoking) consumers to begin vaping or perhaps even eventually smoke traditional cigarettes.[49] But if we apply the evolutionary perspective of flavors, we can better understand how offering ENDS products with complex, preferred flavor profiles could help individuals effectively transition from combustible products to lower-risk products, as the flavors are more closely related to food products that they have experienced across their lifespan.[50] Thus, the most likely path for quitting smoking is often to first transition from combustibles to tobacco-flavored ENDS products and then to non-tobacco-flavored ENDS. This path of gradual behavior shifts improves the likelihood of long-term smoking cessation.[51]

The most likely path for quitting smoking.

Cultural Background and Heritage

Cultural norms, values, and flavor-related experiences can also shape flavor expectations, preferences, and choices. A systematic review of qualitative studies

44. Touzani et al. https://www.sciencedirect.com/science/article/abs/pii/S0091305710001887.
45. Ibid.
46. Ackroff and Sclafani. https://advances.nutrition.org/article/S2161-8313(22)00772-4/fulltext.
47. Kathryn V. Walter et al., "Sex Differences in Mate Preferences Across 45 Countries: A Large-Scale Replication," *Psychological Science* 31:4 (March 20, 2020), pp. 408-423. https://journals.sagepub.com/doi/abs/10.1177/0956797620904154.
48. Zhipeng Chen and Daniel D. Zeng, "Mining Online e-liquid reviews for opinion polarities about e-liquid features," *BMC Public Health* 17 (July 7, 2017), pp. 1-7. https://link.springer.com/article/10.1186/s12889-017-4533-z.
49. Samane Zare et al., "A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type," *PloS One* 13:3 (March 15, 2018). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194145.
50. Christopher Russell et al., "Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA," *Harm Reduction Journal* 15 (June 28, 2018), pp. 1-14. https://link.springer.com/article/10.1186/s12954-018-0238-6.
51. Yoonseo Mok et al., "Associations Between E-cigarette Use and E-cigarette Flavors With Cigarette Smoking Quit Attempts and Quit Success: Evidence From a U.S. Large, Nationally Representative 2018–2019 Survey," *Nicotine & Tobacco Research* 25:3 (March 2023), pp. 541-552. https://academic.oup.com/ntr/article-abstract/25/3/541/6761959.

on flavored tobacco products found that cultural factors influenced perceptions and experiences with these products.[52] Additionally, the cultural perceptions of a product have been shown to affect flavor perception and evaluation.[53] Other studies have identified that cultural differences can influence flavor perception and expectations. For example, young Taiwanese consumers expected a transparent blue drink to taste like mint, whereas young British consumers expected the same drink to have a raspberry flavor.[54] The impact of culture on flavor perception can extend to cross-cultural acceptance and preferences for specific foods as well. A study on the cross-cultural acceptance of sweet, ethnic food found that familiarity with the food influenced acceptance and preferences.[55]

A systematic review of qualitative studies on flavored tobacco products found that cultural factors influenced perceptions and experiences with these products.

Because flavors can influence behavior, they are commonly used as a marketing tool to drive consumer purchases and improve how products are perceived. An earlier paper explored how taste can be altered by external influences such as physical attributes, brand names, product information, packaging, and advertising, which has also been observed in the context of tobacco products.[56] For example, the availability of sweet, fruity, and candy-like flavors has been identified as a key factor in attracting individuals to use e-cigarettes.[57]

The content of advertisements, which by their very nature are targeted to appeal to cultural norms, can impact taste perception by the way they frame the overall experience of the product.[58] Advertisements can also shape consumers' expectations and influence their sensory thoughts, which can subsequently affect their perception of taste. Similarly, packaging elements, including flavor descriptors, color, branding, and warnings, can influence consumers' perceptions of flavor, taste, smell, and appeal.[59] Flavors can also contribute to the perception that certain products are less harmful than others.[60]

Applying these culture-based findings to tobacco harm reduction, the importance of allowing flavor in reduced-risk nicotine products becomes clear: The wider variety of flavored products that are available, the greater number of cultures and individuals they will appeal to and the greater the potential to save lives.

52. Sarah D. Kowitt et al., "Perceptions and Experiences with Flavored Non-Menthol Tobacco Products: A Systematic Review of Qualitative Studies," *International Journal of Environmental Research and Public Health* 14:4 (March 23, 2017). https://www.mdpi.com/1660-4601/14/4/338.
53. Roque et al. https://www.frontiersin.org/articles/10.3389/fpsyg.2017.02360/full.
54. Charles Spence, "On the Relationship (s) Between Color and Taste/Flavor," *Experimental Psychology* 66:2 (March 2019). https://econtent.hogrefe.com/doi/full/10.1027/1618-3169/a000439.
55. Kowitt et al. https://www.mdpi.com/1660-4601/14/4/338; Christelle Chrea et al., "Culture and odor categorization: agreement between cultures depends upon the odors," *Food Quality and Preference* 15:7–8 (October–December 2004), pp. 669-679. https://www.sciencedirect.com/science/article/pii/S0950329303001307.
56. Aradhna Krishna, "An integrative review of sensory marketing: Engaging the senses to affect perception, judgment and behavior," *Journal of Consumer Psychology* 22:3 (July 2012), pp. 332-351. https://www.sciencedirect.com/science/article/pii/S1057740811000830; Kowitt et al. https://www.mdpi.com/1660-4601/14/4/338.
57. Nicholas Chadi et al., "Understanding the Implications of the "Vaping Epidemic" among Adolescents and Young Adults: A Call for Action," *Substance Abuse* 40:1 (Jan. 1, 2019), pp. 7-10. https://journals.sagepub.com/doi/abs/10.1080/08897077.2019.1580241.
58. Ryan S. Elder and Aradhna Krishna, "The Effects of Advertising Copy on Sensory Thoughts and Perceived Taste," *Journal of Consumer Research* 36:5 (February 2010), pp. 748-756. https://academic.oup.com/jcr/article-abstract/36/5/748/1788813.
59. Clare Meernik et al., "The effect of cigarillo packaging elements on young adult perceptions of product flavor, taste, smell, and appeal," *PLoS One* 13:4 (April 19, 2018). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0196236.
60. Jessica Liu et al., "What Does It Meme? A Qualitative Analysis of Adolescents' Perceptions of Tobacco and Marijuana Messaging," *Public Health Reports* 135:5 (Aug. 13, 2020), pp. 578-586. https://journals.sagepub.com/doi/abs/10.1177/0033354920947399.

Mood and Emotion

Several studies have explored the relationship between flavor and mood, providing insight into how different flavors can influence our emotional state. One study focused on flavor aversion and argued that this form of conditioning creates a feedback loop that can produce emotions such as disgust or distaste.[61] In contrast, the sensory properties of flavors, such as cooling, tingling, and mouth-watering sensations, have been found to have beneficial effects on attention, mood, and mental energy.[62] Researchers also conducted a study with an extruded snack product and found that the inclusion of spices affected emotions.[63] Similarly, other researchers have found that context can significantly influence several emotions and moods.[64] This suggests that environment and circumstances can influence flavor perception, which, in turn, can modulate emotional responses.

The neurobiological mechanisms underlying the relationship between flavor and mood have also been explored. For example, compounds in Baijiu, a Chinese alcoholic beverage, were found to have effects on both mood and alcohol stimulation.[65]

The sense of smell, which is intimately linked to flavor perception, has been found to play a role in mood regulation as well. Research has shown that a functioning sense of smell is important for emotional well-being, and individuals may develop mood and anxiety disorders without it.[66] The connection between olfactory perception, flavor, and mood has been investigated, and it has been determined that positive affect tends to have a stronger influence on mood congruency than negative affect. This suggests that positive mood states may be more likely to influence flavor preferences and evaluations. [67] For example, a recent exploratory study found that refreshing perception, which can be influenced by flavor, had an impact on mood, cognitive performance, and brain oscillations.[68]

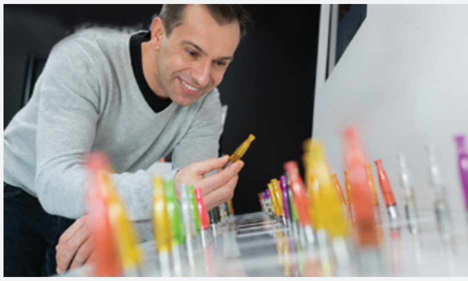
Thus, understanding the relationship between flavor and mood can provide insights into how flavors can be used to enhance positive emotional states and improve overall well-being.

Understanding the relationship between flavor and mood can provide insights into how flavors can be used to enhance positive emotional states and improve overall well-being.

61. Anthony Dickinson and Bernard Balleine, "Motivational control of goal-directed action," *Animal Learning & Behavior* 22 (1994), pp. 1-18. https://link.springer.com/article/10.3758/bf03199951.
62. Evelina De Longis et al., "The Matrix Matters: Beverage Carbonation Impacts the Timing of Caffeine Effects on Sustained Attention," *Nutrients* 14:11 (May 31, 2022). https://www.mdpi.com/2072-6643/14/11/2305.
63. Brandon Bell et al., "Spices in a Product Affect Emotions: A Study with an Extruded Snack Product," *Foods* 6:8 (Aug. 18, 2017). https://www.mdpi.com/2304-8158/6/8/70.
64. Jiyun Yang and Jeehyun Lee, "Current Research Related to Wine Sensory Perception Since 2010," *Beverages* 6:3 (July 27, 2020). https://www.mdpi.com/2306-5710/6/3/47.
65. Xuefeng Guo et al., "Study on the drunkenness of Chinese Baijiu with representative flavor based on behavioral characteristics," *Frontiers in Nutrition* 9 (Sept. 30, 2022). https://www.frontiersin.org/articles/10.3389/fnut.2022.1014813/full.
66. Emanuele Brai et al., "Smell, an Underrated Early Biomarker for Brain Aging," *Frontiers in Neuroscience* 14 (Aug. 25, 2020). https://www.frontiersin.org/articles/10.3389/fnins.2020.00792/full.
67. Klaus Fiedler and Mandy Hütter, "Memory and Emotion," in D. Stephen Lindsay and Timothy J. Perfect, eds., *The SAGE Handbook of Applied Memory* (Sage Publications Ltd, 2013), pp. 145-161. https://uk.sagepub.com/en-gb/eur/the-sage-handbook-of-applied-memory/book237290.
68. D. Labbe et al., "Impact of Refreshing perception on mood, cognitive performance and brain oscillations: An exploratory study," *Food Quality and Preference* 22:1 (January 2011), pp. 92-100. https://www.sciencedirect.com/science/article/pii/S0950329310001357.

ENDS Products and Emotional Changes

Flavored ENDS have been shown to induce emotional changes through various neurobiological, behavioral, and physiological mechanisms. For example, flavor additives such as menthol increase puff duration (which may indicate greater enjoyment) compared to non-flavored products, which in turn increase nicotine exposure and absorption.[69] Additionally, the flavor additives in ENDS can alter neurobiology and promote vaping-related behaviors independent of nicotine via the reinforcing properties of the flavor characteristics alone.[70] Similarly, flavor additives in food products have been found to evoke diverse emotional responses by which flavors reminiscent of those experienced in an individual's life may induce a positive emotional responses in some but no or even a negative emotional response in others.[71] Thus, the sensory properties of e-cigarettes, including flavorings, can make vaping more appealing to smokers than combustible cigarettes.[72]



The sensory properties of e-cigarettes, including flavorings, can make vaping more appealing to smokers than combustible cigarettes.

Of note, a study on the effects of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among smokers showed that individuals were willing to work harder to obtain flavored ENDS products than they were for non-flavored products, suggesting that flavored ENDS had stronger reinforcing properties.[73] Furthermore, the affective and emotional responses associated with flavored ENDS have been identified as crucial factors in developing lower-risk perceptions of flavored products and their effects on behavior.[74]

Clearly, the diverse emotional responses evoked by flavor additives in ENDS and food products underscore the complexity of flavor-induced emotional changes and the need for comprehensive research to understand their implications.

Social Behaviors and Product Preferences

Flavor perception has been shown to affect social cues and influence various aspects of social interactions and behaviors, including the choice of products. For example, one study found that young adults' preferences and use of certain flavored tobacco products could be influenced by their peers' opinions of those products.[75] In addition, as noted previously, adding sweet flavorings and nicotine to e-cigarettes increases their appeal and sensory properties for adult consumers, which could lead consumers to prefer them over combustible products.[76]

This has also been observed in the context of food and beverages when one sensory cue provides information that is integrated across different sensory systems to influence the overall perception of flavor and choice of product.[77]

69. Elise E. DeVito and Suchitra Krishnan-Sarin, "E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure," *Current Neuropharmacology* 16:4 (2018), pp. 438-459. https://www.ingentaconnect.com/content/ben/cn/2018/00000016/00000004/art00011.
70. Skylar Y. Cooper et al., "Chemical Flavorants in Vaping Products Alter Neurobiology in a Sex-Dependent Manner to Promote Vaping-Related Behaviors," *The Journal of Neuroscience* 43:8 (Feb. 22, 2023), pp. 1360-1374. https://www.jneurosci.org/content/43/8/1360.abstract.
71. Andaleeb. https://onlinelibrary.wiley.com/doi/abs/10.1111/joss.12815.
72. Nicholas I. Goldenson et al., "Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology," *Drug and Alcohol Dependence* 168 (Nov. 1, 2016), pp. 176-180. https://www.sciencedirect.com/science/article/pii/S0376871616309218.
73. Janet Audrain-McGovern et al., "The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers," *Drug and Alcohol Dependence* 166 (Sept. 1, 2016), pp. 263-267. https://www.sciencedirect.com/science/article/pii/S0376871616301788.
74. Amy L. Nyman et al., "Flavors and Risk: Perceptions of Flavors in Little Cigars and Cigarillos Among U.S. Adults, 2015," *Nicotine & Tobacco Research* 20:9 (September 2018), pp. 1055-1061. https://academic.oup.com/ntr/article-abstract/20/9/1055/3897087.
75. Kelvin Choi et al., "Young Adults' Favorable Perceptions of Snus, Dissolvable Tobacco Products, and Electronic Cigarettes: Findings From a Focus Group Study," *American Journal of Public Health* 102:11 (November 2012), pp. 2088-2093. https://ajph.aphapublications.org/doi/abs/10.2105/ajph.2011.300525.
76. Goldenson et al. https://www.sciencedirect.com/science/article/pii/S0376871616309218.
77. Charles Spence, "Multisensory Flavor Perception," *Cell* 161:1 (March 26, 2015), pp. 24-35. https://www.sciencedirect.com/science/article/pii/S0092867415002603.

In one study, investigators identified that the textures of certain foods influenced flavor perception, which indicates that the sensory properties of food can drive taste, enjoyment, and preferences.[78] In another, investigators found that color can affect flavor perception, suggesting that visual cues can shape behaviors and choices.[79]

How Flavor Characteristics and Restrictions Affect the Combustible Tobacco Industry

A primary concern of critics of reduced-harm, flavored tobacco products is that flavors boost the appeal and use of tobacco products, particularly among young people, because they are easier to use and mask tobacco's natural harshness and taste.[80] In 2009, to protect youth from the appeal of flavored tobacco products, the Family Smoking Prevention and Tobacco Control Act prohibited the sale of cigarettes with flavors other than menthol but did not restrict the use of flavors in other forms of tobacco.[81]

The tobacco industry has responded to these flavor bans and restrictions in various ways. They have used marketing strategies, such as direct mail and lifestyle magazines, to target young adults and maintain customer relationships.[82] The industry has also submitted evidence to government committees and used economic arguments to oppose flavor bans, claiming they would have detrimental economic effects and increase illicit tobacco trade.[83] However, looking to the example of the Canadian menthol cigarette ban, such measures do not appear to have led to a surge in illicit cigarette sales in that country (although most illicit product entry would be across an open border between the United States and Canada, which makes it difficult to accurately estimate).[84]

It has also been suggested that the tobacco industry strategically used flavors to meet the preferences of specific populations, such as African Americans, by manipulating the burgeoning Black, urban, segregated consumer market in the 1960s, although other factors beyond race may have influenced the growth of flavored product adoption.[85] Flavor additives and curing techniques have also been used to enhance the overall flavor profile of tobacco smoke and improve the smoking experience.[86]

In reality, flavor enhancement has been used to improve product acceptance by consumers in traditional tobacco products for a reason: It increases the likelihood of someone using the product. The same principle applies to reduced-risk products: Increasing the flavor options for consumers will increase the likelihood that those who smoke would potentially try and switch to a flavored, reduced-risk product. Ultimately, this means that—with appropriate regulatory oversight and protections to reduce underage access to such products—flavored tobacco products will lead to a public health win.

Flavor enhancement has been used to improve product acceptance by consumers in traditional tobacco products for a reason: It increases the likelihood of someone using the product.

78. Koen G.C. Weel et al., "Flavor Release and Perception of Flavored Whey Protein Gels: Perception Is Determined by Texture Rather than by Release," *Journal of Agricultural and Food Chemistry* 50:18 (Aug. 1, 2002), pp. 5149-5155. https://pubs.acs.org/doi/abs/10.1021/jf0202786.
79. Massimiliano Zampini et al., "The multisensory perception of flavor: Assessing the influence of color cues on flavor discrimination responses," *Food Quality and Preference* 18:7 (October 2007), pp. 975-984. https://www.sciencedirect.com/science/article/pii/S095032930700047X.
80. Brian A. King et al., "Flavored-Little-Cigar and Flavored-Cigarette Use Among U.S. Middle and High School Students," *Journal of Adolescent Health* 54:1 (January 2014), pp. 40-46. https://www.sciencedirect.com/science/article/pii/S1054139X13004151.
81. Andrea C. Villanti et al., "Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013–2014)," *American Journal of Preventive Medicine* 53:2 (August 2017), pp. 139-151. https://www.sciencedirect.com/science/article/pii/S074937971730065X.
82. M. Jane Lewis and Pamela M. Ling, "'Gone are the days of mass-media marketing plans and short term customer relationships': tobacco industry direct mail and database marketing strategies," *Tobacco Control* 25:4 (2016), pp. 430-436. https://tobaccocontrol.bmj.com/content/25/4/430.short; Daniel K. Cortese et al., "Tobacco Industry Lifestyle Magazines Targeted to Young Adults," *Journal of Adolescent Health* 45:3 (September 2009), pp. 268-280. https://www.sciencedirect.com/science/article/pii/S1054139X09001098.
83. K.A. Evans-Reeves et al., "'It will harm business and increase illicit trade': an evaluation of the relevance, quality and transparency of evidence submitted by transnational tobacco companies to the UK consultation on standardised packaging 2012," *Tobacco Control* 24:e2 (2015), pp. e168-e177. https://tobaccocontrol.bmj.com/content/24/e2/e168?itm_campaign=tc&itm_content=consumer&itm_medium=cpc&itm_source=trendmd&itm_term=0-A.
84. Michal Stoklosa, "No surge in illicit cigarettes after implementation of menthol ban in Nova Scotia," *Tobacco Control* 28:6 (2019), pp. 702-704. https://tobaccocontrol.bmj.com/content/28/6/702.abstract.
85. Phillip S. Gardiner, "The African Americanization of menthol cigarette use in the United States," *Nicotine & Tobacco Research* 6:Suppl_1 (February 2004), pp. S55-S65. https://academic.oup.com/ntr/article-abstract/6/Suppl_1/S55/1124544.
86. Tzu-Chien Kao et al., "Bioactivity and Potential Health Benefits of Licorice," *Journal of Agricultural and Food Chemistry* 62:3 (Dec. 30, 2013), pp. 542-553. https://pubs.acs.org/doi/abs/10.1021/jf404939f.

Leveraging the Science of Flavor in Tobacco Harm Reduction

The role of non-tobacco-flavored, reduced-risk products in tobacco harm reduction is a topic of significant interest and debate in public health. The use of flavored tobacco products, including non-menthol flavors, has been a subject of concern due to their appeal to various demographic groups, including youth.[87] The marketing of these products, particularly in the context of harm reduction, has raised questions about the potential impact on public health principles and the right to health.[88] Below, we apply what we have discussed about the complex science of flavor to tobacco harm reduction, focusing on flavor's impact on smoking behavior, youth use, and adult use of reduced-risk products.

The use of flavors in tobacco products has been found to increase the rewarding and reinforcing value of these products and make them more pleasurable and satisfying, leading to higher levels of use, nicotine exposure, and dependence.

How Flavor Reinforces Smoking Behavior

The use of flavors in tobacco products has been found to increase the rewarding and reinforcing value of these products and make them more pleasurable and satisfying, leading to higher levels of use, nicotine exposure, and dependence.[89] Flavors also have a significant impact on smoking initiation and cessation behaviors.[90] Furthermore, flavored tobacco products are often marketed as a remedy to the harshness and irritation of smoking, making them more appealing to specific groups, such as African Americans, women, and youth.[91]

Studies have shown that the impact of flavors on smoking behavior extends beyond cigarettes and e-cigarettes. Flavored hookah tobacco has been found to reduce the odds of hookah smoking cessation and increase the frequency of hookah smoking.[92] Similarly, flavored little cigars and cigarillos have been found to appeal to young adults and influence their smoking behavior.[93] The use of flavors in these tobacco products contributes to the maintenance of smoking behavior and the development of nicotine dependence.[94]

87. Kowitt et al. https://www.mdpi.com/1660-4601/14/4/338
88. Neil Sircar et al., "Does a human rights-based approach to harm reduction support commercialized harm reduction? Brief Research," *Frontiers in Public Health* 10 (Oct. 26, 2022). https://www.frontiersin.org/articles/10.3389/fpubh.2022.1001036/full?trk=public_post_main-feed-card_feed-article-content.
89. Audrain-McGovern et al. https://www.sciencedirect.com/science/article/pii/S0376871616301788; Kowitt et al. https://www.mdpi.com/1660-4601/14/4/338.
90. Ibid.
91. Guillermo Paraje et al., "The association between flavor capsule cigarette use and sociodemographic variables: Evidence from Chile," *PLoS One* 14:10 (Oct. 23, 2019). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0224217.
92. Samir Soneji et al., "Transitions in frequency of hookah smoking among youth and adults: findings from waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) study, 2013–15," *Addiction* 116:4 (April 2021), pp. 936-948. https://onlinelibrary.wiley.com/doi/abs/10.1111/add.15250.
93. Liane M. Schneller et al., "Use of Flavored E-Cigarettes and the Type of E-Cigarette Devices Used among Adults and Youth in the US—Results from Wave 3 of the Population Assessment of Tobacco and Health Study (2015–2016)," *International Journal of Environmental Research and Public Health* 16:16 (Aug. 20, 2019). https://www.mdpi.com/1660-4601/16/16/2991; Kymberle L. Sterling et al., "Appeal and Impact of Characterizing Flavors on Young Adult Small Cigar Use," *Tobacco Regulatory Science* 1 (April 2015), p. 42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5130284.
94. Ibid.

The role of flavors in smoking cessation is a complex issue. Some studies have found that flavors, especially sweet ones, can act as a positive reinforcer and increase the likelihood of quitting smoking.[95] However, other studies have produced mixed results, and more research is needed to understand the role of flavors in smoking cessation and relapse and to inform effective tobacco control policies.[96]

Flavor can also potentially influence smoking behavior by affecting preferences and perceptions of smoking products and cessation tools. Studies have examined the impact of flavor on smoking behavior in various contexts, including e-cigarettes, menthol cigarettes, and hookah. One study found that e-cigarettes with low nicotine content increased intentions to try them and were perceived as more effective for smoking cessation.[97] Another study compared the perceived efficacy of e-cigarettes to nicotine replacement therapy and found that the availability of a variety of flavors in e-cigarettes may contribute to their appeal.[98] Additionally, a scoping review suggested that a ban on menthol cigarettes may encourage smokers to switch to non-menthol cigarettes or alternative tobacco/nicotine products.[99] Of course, the impact of flavors on smoking behavior is complex and can vary depending on individual factors such as age, sex, and smoking habits.

The Importance of Preventing Youth Uptake of Flavored Products

Stakeholders agree that reducing youth access to any nicotine product—flavored or not—must be a priority.[100] Because certain flavors like fruit, candy, dessert, and menthol, are particularly appealing to young adults and adolescents (who are more likely to initiate and continue smoking products with these types of flavors), it is critically important that youth be deterred and prevented from using such products.[101] To help address this concern, on Dec. 20, 2019, Tobacco 21 (also called "T21") was signed into law as an amendment to the Federal Food, Drug, and Cosmetic Act.[102] This law made it illegal for anyone under the age of 21 to purchase any nicotine product, and it has helped decrease the use of nicotine products by underage individuals in the United States.[103]

On Dec. 20, 2019, Tobacco 21 was signed into law, making it illegal for anyone under the age of 21 to purchase any nicotine product and helping to reduce the underage use of these products in the United States.

95. Zare et al. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194145.
96. Luis Zavala-Arciniega et al., "E-cigarette characteristics and cigarette smoking cessation behaviors among U.S. Adult dual users of cigarettes and e-cigarettes," *Preventive Medicine Reports* 26 (April 2022). https://www.sciencedirect.com/science/article/pii/S2211335522000559; Mok et al. https://academic.oup.com/ntr/article-abstract/25/3/541/6761959; Nicholas I. Goldenson et al., "A Review of the Use and Appeal of Flavored Electronic Cigarettes," *Current Addiction Reports* 6 (2019), pp. 98-113. https://link.springer.com/article/10.1007/s40429-019-00244-4.
97. Zare et al. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194145.
98. Amanda M. Barbeau et al., "Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach," *Addiction Science & Clinical Practice* 8:1 (March 5, 2013), pp. 1-7. https://ascpjournal.biomedcentral.com/articles/10.1186/1940-0640-8-5.
99. Cadham et al. https://link.springer.com/article/10.1186/s12889-020-09055-z.
100. Vivek H. Murthy, "E-Cigarette Use Among Youth and Young Adults: A Major Public Health Concern," *JAMA Pediatrics* 171:3 (March 2017), pp. 209-210. https://jamanetwork.com/journals/jamapediatrics/article-abstract/2592300?utm_campaign=scite&utm_source=scite&utm_medium=referral.
101. Yvette van der Eijk et al., "Cross-sectional survey of flavored cigarette use among adult smokers in Singapore," *Tobacco Induced Diseases* 19 (June 3, 2021). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8173988.
102. "Tobacco 21," U.S. Food & Drug Administration, Sept. 1, 2021. https://www.fda.gov/tobacco-products/retail-sales-tobacco-products/tobacco-21.
103. Ibid.

Flavor's Role in Encouraging Adults to Switch to Reduced-Risk Products

With youth prevention laws and efforts in place, we can better assess the value of flavors for adults looking to transition from combustible cigarettes to reduced-risk products and ensure that a wide variety of these products are available to consumers.

The CTP recently funded an initiative to develop and apply standardized measures to evaluate flavored tobacco products, with the goal of building a more robust evidence base to inform regulatory decisions and reduce tobacco and ENDS use at the population level.[104] Additionally, the influence of electronic cigarette characteristics on susceptibility, perceptions, and abuse liability indices among combustible tobacco cigarette smokers and non-smokers has been a focus of research, with a former FDA commissioner announcing plans to investigate the role of ENDS in tobacco harm reduction and the current director of the FDA CTP acknowledging the existence of the tobacco/nicotine products continuum of harm.[105]

Although much of the focus has been on ENDS products, these concepts are applicable to other forms of reduced-risk products. Oral products such as snus have been viewed as a key tool in greatly reducing smoking rates in Sweden.

Although much of this focus has been on ENDS products, these concepts are applicable to other forms of reduced-risk products. For example, the effect of oral, tobacco-derived nicotine pouches on cigarette smoking and smokeless tobacco product use behaviors has been studied, illustrating the potential for harm reduction if adult tobacco consumers fully switch from more harmful tobacco products.[106] Oral products such as snus have been viewed as a key tool in greatly reducing smoking rates in Sweden.[107] In addition, a recent systematic review highlighted the increasing adoption of HnB products as an alternative to smoking conventional cigarettes.[108] The review emphasized the potential of HnB products to reduce health risks associated with smoking combustible tobacco products.

104. Maansi Bansal-Travers et al., "Common Measures to Evaluate Flavored Tobacco Products: Recommendations From the Tobacco Centers for Regulatory Science (TCORS) Flavored Tobacco Products Measurement Subcommittee," *Nicotine & Tobacco Research* 25:1 (January 2023), pp. 159-163. https://academic.oup.com/ntr/article-abstract/25/1/159/6650862.

105. Cosima Hoetger et al., "Influence of Electronic Cigarette Characteristics on Susceptibility, Perceptions, and Abuse Liability Indices among Combustible Tobacco Cigarette Smokers and Non-Smokers," *International Journal of Environmental Research and Public Health* 16:10 (May 23, 2019). https://www.mdpi.com/1660-4601/16/10/1825; Brian A. King and Benjamin A. Toll, "Commentary on Wackowski *et al*.: Opportunities and Considerations for Addressing Misperceptions About the Relative Risks of Tobacco Products among Adult Smokers," *Addiction* 118:10 (October 2023), pp. 1892-1594. https://onlinelibrary.wiley.com/doi/abs/10.1111/add.16296.

106. Daniel Stjepanović et al., "Efficacy of smokeless tobacco for smoking cessation: a systematic review and meta-analysis," *Tobacco Control* 32:6 (2023), pp. 757-768. https://tobaccocontrol.bmj.com/content/32/6/757.abstract.

107. Hans Gilljam and M. Rosaria Galanti, "Role of *snus* (oral moist snuff) in smoking cessation and smoking reduction in Sweden," *Addiction* 98:9 (September 2003), pp. 1183-1189. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1360-0443.2003.00379.x.

108. Aleksandra Ratajczak et al., "Heat Not Burn Tobacco Product—A New Global Trend: Impact of Heat-Not-Burn Tobacco Products on Public Health, a Systematic Review," *International Journal of Environmental Research and Public Health* 17:2 (Jan. 8, 2020). https://www.mdpi.com/1660-4601/17/2/409.

A study examining the effects of switching to an HnB tobacco product on biologically relevant biomarkers found favorable changes when cigarette smokers switched to the Tobacco Heating System 2.2.[109] Furthermore, a comparative study demonstrated that aerosols from HnB tobacco products contain lower levels of harmful and potentially harmful constituents than smoke from conventional cigarettes.[110] This finding supports the premise that HnB products may offer reduced exposure to harmful compounds compared to traditional smoking. Additionally, a study on the cytotoxic effects of HnB products on human bronchial epithelial cells indicated that HnB products produced lower levels of these effects than combustible tobacco products.[111] The appeal and likelihood of use of multiple flavor varieties of ENDS among adult current, former, and never-tobacco users has also been investigated, suggesting potential benefits for current cigarette users without posing a substantial risk of initiation by tobacco non-users, including young adults.[112]

The synthesis of evidence from various studies underscores the need for continued research and evidence-based policy development to address the challenges and opportunities associated with flavored, reduced-risk tobacco products.

Overall, the role of non-tobacco flavored reduced-risk products in tobacco harm reduction is a complex and multifaceted issue that requires a comprehensive understanding of consumer perceptions, marketing strategies, regulatory policies, and potential public health implications. The synthesis of evidence from various studies underscores the need for continued research and evidence-based policy development to address the challenges and opportunities associated with flavored, reduced-risk tobacco products. However, the current body of science suggests that, if regulated appropriately, reduced-risk products can provide a wide variety of flavor selections that would increase the rate and sustainability of smoking cessation and greatly reduce the negative consequences of smoking on public health in a rapid and effective manner.

Challenges and Future Directions

Switching away from an established behavior is challenging but not impossible. There are key factors associated with any behavior that maintains them. In the simplest of terms, one has to identify the characteristics of the behavior one wishes to modify, identify what reinforcers are mediating those behaviors, and find other sources for those reinforcers that are either stronger, easier to obtain, or associated with behaviors that are easier to engage in.

109. Frank Lüdicke et al., "Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial," *Cancer Epidemiology, Biomarkers & Prevention* 28:11 (Nov. 1, 2019), pp. 1934-1943. https://aacrjournals.org/cebp/article-abstract/28/11/1934/167343.
110. Mikhail Shein and Gunnar Jeschke, "Comparison of Free Radical Levels in the Aerosol from Conventional Cigarettes, Electronic Cigarettes, and Heat-Not-Burn Tobacco Products," *Chemical Research in Toxicology* 32:6 (April 1, 2019), pp. 1289-1298. https://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.9b00085.
111. Noel J. Leigh et al., "Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells," *Tobacco Control* 27:Suppl1 (2018), pp. s26-s29. https://tobaccocontrol.bmj.com/content/27/Suppl_1/s26.abstract.
112. Elliott H. McDowell et al., "Appeal and Likelihood of Use of Multiple Flavor Varieties of BIDI® Stick Electronic Nicotine Delivery Systems among Adult Current, Former, and Never Tobacco Users in the United States," Research Square, Aug. 19, 2022. https://www.researchsquare.com/article/rs-1962398/latest.

A number of common reinforcing aspects drive smokers to engage in the behavior. For some, it is the physical response to nicotine. For others, it is a means of relaxation, time socializing with others, the way the product feels in the mouth, or the flavor itself. Any strategy that hopes to successfully move smokers away from cigarettes should address a wide variety of these reinforcers.

Replacement products should look, feel, and function similarly to combustible cigarettes. Additionally, to have a larger influence on behavioral change, reduced-risk products should have attributes that act as stronger reinforcers than those of combustible cigarettes.

Replacement products should look, feel, and function similarly to combustible cigarettes. Additionally, to have a larger influence on behavioral change, reduced-risk products should have attributes that act as stronger reinforcers than those of combustible cigarettes. These include the option of products with higher nicotine levels; a wider, more desirable variety of flavors; and delivery devices of different formats, shapes, and sizes. All of these characteristics combine to influence consumers of combustible cigarettes to be more attracted to reduced-risk products.

Finally, changing policy (from both the industry and regulatory sides) to make reduced-risk products more affordable and less costly than combustible cigarettes by lowering both initial cost and the taxes applied to the product purchase itself would lower the barrier of entry. This would prime behavioral change in a manner that strengthens the motivation to switch from the established smoking behavior to a new, less risky alternative.

There is no "one size (or one product) fits all" approach that will work to mitigate the centuries-old problems associated with smoking behavior. We have seen medically approved products (e.g., nicotine patches) fail to solve the problem. We have seen attempts to block access through prohibition-like activities fail to solve the problem. The only approach that has had any real impact on moving smokers away from combustible cigarettes has been the alternative nicotine marketplace, which provides a multitude of reduced-harm options for smokers. Now that legislation is in place to help curb youth uptake and use, the FDA-CTP should move quickly to approve a wide variety of products so that those who smoke combustible cigarettes have a multitude of options available to help them switch from a behavioral choice that carries significant health risks to one that confers much lower risks.

About the Author

Jeffrey S. Smith is a behavioral neuroscientist and resident senior fellow in the R Street Institute's integrated harm reduction program.