Review

ENDS Tobacco Flavors, Public Health, and Toxicity

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ENDS Tobacco Flavors, Public Health, and Toxicity

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Abstract: On Feb. 6th, 2020, FDA implemented the enforcement priorities against all flavored, cartridge-based e-cigarettes other than menthol and tobacco flavors. This ban undermined the products' attraction to vapers, so e-cigarette manufacturers added flavorants of other attractive flavors into tobacco-flavored e-cigarettes and re-established attractions. Both the sales of e-cigarettes and posts on social media suggested that the manufacturers' strategies are likely "successful". The re-established attraction causes not only a public health issue, but also threats to the health of individual vapers. Research has shown an increase in toxicity associated with the flavorants commonly used in flavored e-cigarettes that are likely added in tobacco-flavored e-cigarettes based on tobacco-derived and synthetic tobacco free nicotine, and these other flavors are associated with higher clinical symptoms not often induced by only natural traditional tobacco flavors. The additional health risks posed by the flavorants are pronounced even without considering the interactions of toxicology of the different tobacco flavorants, and more research should be done to understand the health risks thoroughly and to take proper actions accordingly for regulation of these emerging products.

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Introduction

Tobacco flavors are a type of flavor added in e-cigarettes to make them appealing to vapers, specifically by mimicking the taste of traditional cigarettes. Tobacco-flavored e-cigarettes are often advertised as a safer alternative to traditional cigarettes that allow smokers to enjoy the taste they are familiar with more conveniently and smoothly.[1] Tobacco-flavored e-cigarettes are very popular among various subpopulations of adults in the US with around 30% of vapers using these products.[2] However, the prevalence seems to be lower in dual users (vapers who also use traditional cigarettes) and vapers who used e-cigarettes as an attempt to quit smoking, the percentages being 28.5% and 20.5%, respectively.[3,4]

Although the taste of tobacco-flavored e-cigarettes mimics that of traditional cigarettes, the type of nicotine they contain may differ from traditional cigarettes. Recently, e-cigarette products have begun to contain synthetic nicotine or tobacco-free nicotine (TFN), a racemic mixture of both R- and S-nicotine isomers, which is different from the traditionally used tobacco-derived nicotine (TDN) composed of pure S-nicotine.[5] Initially e-cigarette products began to utilize TFN since TFN was not regulated by the food and drug administration (FDA) and products were able to be brought to the market since these products did not need to go through the premarket tobacco product application for e-cigarettes.[5] Although initially brought to the market without government regulation, in 2022, new legislation has expanded the authority of the FDA to regulate TFN.[6] Currently, limited data is available regarding the health effects of TFN, but studies have found that messaging by e-cigarette companies leads to a belief in e-cigarette users that TFN has a lower health risk compared to TDN and a higher intention to use TFN products.[7] Young adults that were interested in trying TFN

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believed it to be less addictive than those who were uninterested, and young adults that have tried TFN reported that TFN products have flavors that taste better and products that taste smoother.[8] Similarly, young adults who were likely to purchase TFN pouches believed that TFN pouches were less harmful to a person's health, less addictive, and tastes smoother, cleaner, and better compare to young adults who would not purchase TFN pouches.[9] Due to the perception in young adults that TFN is less harmful and addictive, there is a need for more research on the health effects of exposure to TFN in order to aid government regulation and to properly educate the public about any potential risks of using TFN.

Besides the use of TFN in tobacco-flavored e-cigarettes, another important modification to these products is the addition of flavorants commonly used in other flavors. On Feb 6th, 2020, the FDA implemented the enforcement priorities against all flavored, cartridge-based e-cigarettes other than tobacco- and menthol-flavored products.[10] Data has shown that most youth vapers started vaping with a flavored e-cigarette and that the motivation for vaping among those who are still vaping is primarily the flavors.[11] It was also indicated that youth vapers preferred fruit and mint flavors to tobacco or menthol flavors.[12] Therefore, the ban on flavors other than tobacco and menthol undermined the e-cigarette products' attraction to youth vapers, largely decreasing the manufacturers' profit. In order to reverse the impacts brought by the regulations, e-cigarette manufacturers started to blend other flavors into tobacco-flavored e-cigarettes, recreating the attraction for youth vapers.[13,14] For example, "Monster Puff 3500 Disposable – Smooth Tobacco" is a fourth-generation e-cigarette with a combination of tobacco flavor and cream flavor, while "Tobacco Monster Salt Rich" is an e-liquid with tobacco flavor, smokey vanilla flavor, and creamy caramel flavor.[13,14]

Toxicology of Tobacco-Flavored E-Cigarettes

Besides the re-establishment of interest in e-cigarettes among youth vapers, the addition of other flavorants into tobacco-flavored e-cigarettes may inevitably change the toxicology of these products.

Part of the toxicities is already known in existing studies about tobacco-flavored e-cigarettes.[15–19] It was revealed that tobacco flavorants can induce higher levels of cell death in lung epithelial cells and inflammatory responses in types of cells including fibroblasts.[15,16] Overall, reported in either *in vivo* or *in vitro* studies, increased reactive oxygen species (ROS)/oxidative stress and release of inflammatory cytokines are associated with tobacco flavors, and the conclusions included increased cell death, decreased cell viability, and increased inflammatory responses.[17] In another study, it is also shown that tobacco flavor accompanied by the presence of nicotine can induce an allergic inflammatory response characterized by elevated levels of eotaxin, IL-6, and RANTES (CCL5).[18] The combination can also increase the level of PAI-1, a higher level of which is a risk factor for thrombosis and atherosclerosis.[18,19]

By adding other flavorants into the mix, new toxic possibilities are introduced. The most commonly used flavorant (in 35% of e-liquids), vanillin, is responsible for vanilla flavors in e-liquids so is probably in "Tobacco Monster Salt Rich" introduced above.[14,20,21] As shown, the presence of vanillin has a positive correlation with the toxicity of e-liquids (R^2 = 0.62).[20] Another popular flavorant (in 32% of e-liquids) with caramel flavors, ethyl maltol, may also be present in "Tobacco Monster Salt Rich" and has been shown to be a cause of incidences of kidney lesions in rats and mild hemolytic anemia in dogs.[14,21–23] These are only two of the flavorants used in e-liquids, and generally the number of different flavorants in a single e-liquid product would be higher than 10.[20] It was found that the more chemicals in the e-liquid, the higher the toxicity that e-liquid is likely to possess.[20] Therefore, it is predicted that the additional flavorants in tobacco-flavored e-cigarettes that already contained many kinds of flavorants would increase the overall toxicity of the product, and it would be hard to figure out the interactions of the toxicity mechanisms related to flavorants that originally belonged to completely unrelated species. More studies need to be done for us to fully understand this complexity and take suitable actions regarding the issue.

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Tobacco-Flavored E-Cigarette Products

Although the flavors are limited to tobacco flavors, there is still a variety of e-cigarette devices with distinct characteristics associated with tobacco flavors.[24–30] Generally, e-cigarette devices are divided into 4 generations, all of which can support tobacco flavors.[24,25]

First-generation e-cigarettes are designed to mimic the appearance of traditional cigarettes and thus are also known as cig-a-likes.[24,25] They are neither rechargeable nor refillable and are intended to be used only once.[24] The major components are a battery, an atomizing unit, and a fluid reservoir (cartridge).[25] Usually, vapor is produced only when the device is sucked on, and there is no switch.[26] An example of tobacco-flavored cigalikes would be "ProSmoke Tobacco Disposable E-Cigarette".[27]

In second-generation e-cigarettes, the cartridge is replaced by a "clearomizer", which is larger in size and allows visualization of the liquid level in the tank.[25,26] The "clearomizer" typically comes with a pen-shaped device that contains the battery, so second-generation e-cigarettes are also called "vape pens".[24,25] Also, a button allows the vaper to decide to turn on/off the device.[26]

Third-generation e-cigarettes, on the other hand, adopted a completely different structure modified from flashlights and can be modified by the vapers, giving birth to its name "mods".[24–26] These devices are highly customizable in various aspects, while the most characteristic one is the adjustment of the wattage of the device by the vapers.[25,26] Another characteristic of some third-generation devices is that it contains sub-ohm tanks, which allow even higher wattage as a result of decreased resistance.[24–26] Both second- and third-generation e-cigarettes use e-liquids for aerosol generation, and tobacco-flavored e-liquids can be easily found in online vape shops.[28,29]

Fourth-generation e-cigarettes are called "Pod-Mods", indicating a modifiable pod cartridge.[24,25] The shapes of fourth-generation e-cigarettes vary from each other, including USB shapes and teardrop shapes.[24,25] Fourth-generation e-cigarettes use nicotine salts instead of freebase nicotine in previous generations, allowing a higher concentration of nicotine to be present in the product.[24] A very popular variation of fourth-generation e-cigarettes is vape bars, which are the most popular products in online vape shops.[29,30]

As shown in online vape shops, products associated with all the generations discussed above are widely available for vapers, and the products are sold in large amounts.[27–30] In "White Horse Vapor", the best-selling tobacco-flavored e-cigarette products are mostly vape bars (fourth-generation) followed by tobacco-flavored e-liquids (used by second and third-generation devices).[28–30] First-generation products can also be found in another vape shop where it claims that the product is the new #1 selling e-cigarette on the market.[27] The vape shop selling primarily fourth-generation e-cigarettes has a better website design with different fonts that may attract young vapers while the vape shop website that sells the first-generation e-cigarette looks relatively old.[27,29]

According to scientific studies, adult vapers tend to prefer first-generation e-cigarettes (cigalikes).[31] However, when taking adolescent vapers into consideration, the trend is reversed, and later-generation e-cigarettes are more favored by the whole vaper population.[32] The trend found by those studies is likely applicable to tobacco-flavored e-cigarettes as the characteristics of online vape shops discussed above match the trend.[31,32]

Public Perceptions and Discussions of Tobacco-flavored E-cigarettes on Social Media

An examination of the public perceptions of different e-liquid flavors on over two million e-cigarette-related Twitter posts from May 31 to August 22, 2019, showed the public had a more negative attitude toward the tobacco flavor using sentiment analysis.[33] Meanwhile, it was also found that the public was positive toward fruit and sweets flavors, and most of the discussions are about these two flavors.[33] After the flavor ban, only menthol and tobacco flavors are allowed on the market, and an increase in discussion about menthol flavors was observed.[10,34] However, there is no significant increase in discussion about tobacco flavors, meaning that vapers did not choose to shift to tobacco flavors immediately after the ban of their favorite flavors.[34] In contrast, the discussion of fruits and sweets flavors remained high immediately after the ban, signaling that the

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vapers were still craving for their favorite flavors even after they are banned.[34] Therefore, when their favorite flavors get integrated back into tobacco flavors, it is expected that they still like the mixed flavor. Since the availability of flavors was among the top reasons for vaping and its initiation, especially in adolescents and young adults, the addition of these flavors in tobacco flavors would inevitably resuscitate the motivation for vapers to continue to vape.[35,36]

Through applying generalized estimating equation (GEE) models on over 3,000 Reddit posts that co-mention e-cigarette use and health symptoms in the same Reddit posts from January 2013 to April 2019, it was found that tobacco flavor was more likely to be co-mentioned with respiratory and throat symptoms than other symptoms.[37] A specific examination of the JUUL pod tobacco flavor with health symptoms showed a high probability of co-mention of the JUUL tobacco flavor with the throat, respiratory, and cardiovascular symptoms using similar GEE models and Reddit posts from September 2016 to April 2019.[38]

These results are associated with the traditional tobacco-flavored cigarettes prior to the addition of new flavors, and the addition might cause more complicated symptoms. In the online vape shop we found the new tobacco-flavored e-cigarettes, the best-selling tobacco-flavored e-cigarettes often contained new flavors categorized as "sweets" flavors or "crème" flavors in JUUL products.[13,14,29,37,38] According to the same GEE models, "sweets" flavors are associated with throat and digestive symptoms while JUUL's "crème" flavor is associated with higher co-mention of neurological, digestive, and "other" symptoms, which are not observed in the corresponding tobacco flavors.[37,38] As a result, these new symptoms could emerge in vapers who use the new tobacco-flavored e-cigarettes, and even more concerning is that the toxicological effects of the flavorants may interact with each other, and the effects of such interactions are unknown. Therefore, more research should be done to further understand the symptom changes associated with the addition of other flavors into tobacco-flavored e-cigarettes.

Overall, as we observed more varieties of tobacco-flavored e-cigarettes sold in vape shops, the public perceptions of tobacco-flavored e-cigarettes and their associations with health symptoms mentioned on social media need to be revisited.

The Vaping Communities and the Flavor Addition to Tobacco Flavors

Since vapers can belong to a variety of different communities, the addition of other flavors into tobacco-flavored e-cigarettes may have different effects in those different communities, and we need to focus on the differences. For example, the vaping behaviors of dual users of both traditional cigarettes and e-cigarettes are different from vapers who only use e-cigarettes.[3] This difference gets exceedingly important when there is a relatively high prevalence of vaping in the community (including sexual minority youth) or when the community is our major target of protection (including age groups like adolescents).[39] Despite the importance of understanding the different effects that the flavor addition has on various communities, there is minimal data on this issue and the differential effects remain unknown to us. Further studies should be done on these specific communities for us to comprehensively understand how the new tobacco-flavored e-cigarettes impact the entire vaping population and establish regulations accordingly.

E-cigarette Sales after Flavor Ban Regulations and Flavorants' Attraction to Vapers

The vast variety of e-cigarette flavorings, such as banana, mango, and cotton candy, are extremely appealing to the younger generation, helping lead to the nicotine addiction epidemic amongst today's youth. However, the February 2020 Food and Drug Administration ban on flavored prefilled e-cigarette cartridges, while having the intention of curbing flavored e-cigarette use, also opened new doors for the vaping industry to continue making profits.[10] This was due to 2 keyholes in the FDA policy: the ban did not cover the sale of tobacco and menthol-flavored prefilled cartridges, or the sale of flavored disposable e-cigarettes.[40] For these reasons, e-cigarette users were able to find alternatives to flavored prefilled cartridges, such as the tobacco-flavored e-cigarettes outlined in this paper.

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The CDC Foundation's 2022 Data Brief shows that after the FDA policy enactment, the unit share of disposable e-cigarettes went from 29.9% to 49.6%, while the unit share of prefilled cartridges lowered respectively from 70.0% to 50.3% between February 2020 and July 2022.[40] This data shows the popularity of flavored e-cigarettes in the vaping population, with them quickly switching to disposable e-cigarettes once flavored prefilled cartridges became unavailable. Additionally, while the FDA ban was supposed to limit prefilled cartridge manufacturers like JUUL from profiting off of nicotine addiction, it allowed disposable vaping brands, such as Puff Bar, Elf Bar, and Blu, to achieve a massive increase in sales by developing products that filled the "flavoring hole" left by the prefilled cartridge ban. Data showed that in response to these holes, e-cigarette users largely switched to disposable devices than continuing to buy the tobacco and menthol-flavored cartridges still on the market.[40] After the 2020 ban up until July 2022, tobacco-flavored cartridge sales only increased by 11.9%, while all other flavor sales increased by 75.6%,[40] showing the preference of the vaping population for non-tobacco flavorings, which indicates that vapers are likely to be attracted by the new tobacco flavors that contain flavorants from other flavors.

Public Health Interventions Associated with Tobacco Flavors and New Technologies

Flavors have been cited as a key factor for the initiation of vaping by adolescents and young persons and facilitate the ongoing use of vaping products by those of all ages. Flavored vaping products are alluring to both new and established tobacco product users, and a wide variety of flavors are available. This wide variety and the ability to combine different flavors, in this case, the addition of other flavorants into tobacco flavors, could contribute to the ongoing vaping behavior among both youth and adults.[41,42]

Per the FDA "Deeming" regulations, the FDA can now regulate the presence and amount of 'characterizing flavors' in vaping products.[43] According to former FDA Commissioner Gottlieb, e-cigarette use among youth can be characterized as an epidemic.[44] Users must be at least 18 years of age to buy vaping products in most states, but those under 18 are still able to purchase from a variety of retailers and online.[41,43]

To address the vaping epidemic, especially among youth, in 2021 the U.S. Food and Drug Administration (FDA) implemented a flavor enforcement policy to restrict the sales of all cartridge-based unauthorized flavored e-cigarettes other than tobacco and menthol flavors.[45,46] Evaluation of the impact of FDA flavor enforcement policy on e-cigarette use behavior is in progress. One study assessed the potential impact of the flavor enforcement policy on a specific vaping-related behavior change—quitting vaping— using natural language processing strategies with data collected from the Twitter platform.[45] The proportion of tweets (and Twitter users' mentions) concerning quitting vaping was compared before and after the implementation of the FDA flavor policy.[45] Compared to before the FDA flavor policy, the proportion of tweets and Twitter user mentions after the implementation of the policy was higher.[45] They also reported that after the policy implementation (compared to before) there was an increasing trend in the proportion of females and young adults (18–35 years old) mentioning quitting vaping.[45] They concluded that, as observed on Twitter, the FDA policy did have a positive effect on quitting vaping and therefore a potential influence of the FDA flavor enforcement policy on broader definitions of vaping behavior.[45]

Another public health intervention for vaping cessation is the use of free vaping cessation apps, which have various content, features, and adherence to evidence-based approaches. In 2020, researchers conducted a systematic search of existing smartphone apps for vaping cessation.[47] A total of 8 apps were included in a quality assessment and content analysis. They concluded that the limited number of existing vaping cessation apps employ similar approaches to smoking cessation apps but are potentially valuable tools.[47]

Summary

After the FDA implemented the enforcement priorities against all flavored, cartridge-based e-cigarettes other than tobacco- and menthol-flavored products on Feb. 6th, 2020, most e-cigarette products became regulated, leaving only menthol and tobacco flavors widely and legally available

for vapers.[10] This ban on other flavors impaired e-cigarettes' attraction to vapers, so e-cigarette manufacturers decided to re-create similar flavors by blending the corresponding flavorants into tobacco-flavored e-cigarettes to form variant tobacco flavors including "Smooth Tobacco".[13,14] These mixed tobacco flavors are now widely available in online vape shops, and the products come as/be used in any generation e-cigarettes to accommodate the preference of vapers in different age groups (it is inferred that adult vapers would prefer first-generation tobacco-flavored e-cigarettes while adolescents would prefer ones in later generations).[27–32]

Evidence from both the vaping market share and social media posts indicate that the manufacturers' strategy is likely successful.[34,40] After the FDA regulation, the unit share of prefilled cartridges decreased, and the sales of disposable e-cigarettes of flavors other than tobacco flavors increased dramatically, indicating a strong preference for flavorants in other flavors that provided the vapers the motivation to switch to disposable e-cigarettes.[40] Therefore, the addition of these flavorants into the tobacco flavors may establish attraction of the new tobacco flavors. On the other hand, similar trends are found in social media posts that fruit and sweets flavors were still often discussed after the flavor ban policies.[34] The heated discussions indicate the vapers' strong craving for these flavors, so this further confirms that the addition of other flavorants into tobacco flavors may successfully attract the vapers.

This strategy by the manufacturers can not only bring public health issues but also new health risks and symptoms in individual users. The additional flavorants mixed in the new tobacco-flavored e-cigarettes may have unique toxicology mechanisms that are not observed in flavorants used in traditional tobacco flavors. For example, vanillin and ethyl maltol are likely found in "Tobacco Monster Salt Rich" and have been shown to increase the toxicity of e-liquids and induce incidences of kidney lesions in rats and mild hemolytic anemia in dogs, respectively.[14,20–23] Other flavorants may also be integrated into the recipe of tobacco-flavored e-cigarettes, and it has been shown that the toxicity of the e-liquids increases as the number of chemicals increases in its recipe.[20] Meanwhile, in the analysis of Reddit posts using GEE models, the "sweets" flavors in e-cigarettes are associated with higher co-mention of digestive and throat symptoms, which are not demonstrated in traditional tobacco flavors.[37] Therefore, the symptoms associated with e-cigarette use are likely to be more complicated in using the new tobacco-flavored e-cigarettes. However, our predictions of toxicology and symptoms are based on the simple addition of effects while the interactions between the flavorants were not taken into consideration. More research needs to be done in order to fully understand the interactions and the overall effects.

Besides the public health issue and personal health risks associated with the addition of flavorants in tobacco-flavored e-cigarettes, the FDA flavor ban policies overall did have a positive effect in helping vapers quit vaping.[45] The use of the new vaping cessation apps is also a potentially important aspect of public health interventions.[47] To further extend the positive effects, more research should be done to analyze the effects brought by the manufacturers' efforts in bypassing the regulations, and emphasis should be placed on vulnerable communities regarding the vaping issue.

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