ENDS Tobacco Flavors, Public Health, and Toxicity

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Abstract

Background: Recently, the FDA implemented the enforcement priorities against all flavored, cartridge-based e-cigarettes other than menthol and tobacco flavors.

Objective: 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.

Methods: 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.

Results: 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.

Conclusions: 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 the regulation of these emerging products. Clinical Trial: None

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Short running title: E-cigarette tobacco flavors toxicity

Abstract

Recently, the 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 the regulation of these emerging products.

Keywords: Vaping; e-cigarettes; tobacco flavors; toxicity; regulation.

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 give different flavors of tobacco, such as Virginia tobacco or Turkish tobacco which are recently emerged along with PG/VG and other additives. 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. Tobacco-flavored e-cigarettes are very popular among various subpopulations of adults in the US with around 30% of vapers using these products.[1] 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.[2,3]

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.[4] 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.[4] Although initially brought to the market without government regulation, in 2022, new legislation expanded the authority of the FDA to regulate TFN.[5] Currently, limited data are 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.[6] Young adults that were interested in trying TFN 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.[7] 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.[8] 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.[9] 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.[10] It was also indicated that youth vapers preferred fruit and mint flavors to tobacco or menthol flavors.[11] The tobacco flavors of e-cigarettes are made to mimic the flavor of traditional tobacco cigarettes with some variation. There are many different tobacco flavors made from hundreds of brands that can provide the user with different types of tobacco flavors. Such flavors include Virginia tobacco, Turkish tobacco, Smooth tobacco, and Cuban tobacco. Demographically, tobacco flavors are more popular among adults and less popular among youth.[12] The lack of appeal of tobacco-flavored e-cigarettes to the youth allows for fewer regulations. Therefore, we perceived that the ban on flavors other than tobacco and menthol undermined the e-cigarette products' attraction to youth vapers as their favorite flavors were removed from access, 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] However, flavoring agents are found in non-tobacco flavors into tobacco flavors due to the difference in regulations between tobacco and non-tobacco-flavored e-cigarettes.[14] For example, we found that an e-cigarette company has a fourth-generation e-cigarette product with "Smooth Tobacco" flavor which contains a combination of tobacco flavor and cream flavor. The same company also sells an e-liquid of "Tobacco Salt Rich" flavor, which is a mix of tobacco flavor, smokey vanilla flavor, and creamy caramel flavor. Studies have also extracted flavorants that represent sweet and caramel-like flavors in an e-liquid marked "Smooth & Mild Tobacco" and multiple flavorants that do not belong to tobacco flavors in another tobacco-flavored e-liquid that was de-identified.[13,15,16] Such compounds include ethyl maltol, vanillin, corylone, and ethyl vanillin which can lead to adverse health effects.[14] Additionally, the VOCs, reactive oxygen species, and other compounds present in the tobacco-flavored e-liquids can pose further health risks.

The emergence of these new tobacco flavors may serve as a source for public health issues, and information related to them is critical for the establishment of regulations and interventions. Therefore, by analyzing the toxicity, the characteristics, the sales, and the social media and public health aspects of tobacco-flavored e-cigarettes, this review aims to inform authorities about this issue and provide information for potential interventions (**Figure 1**).

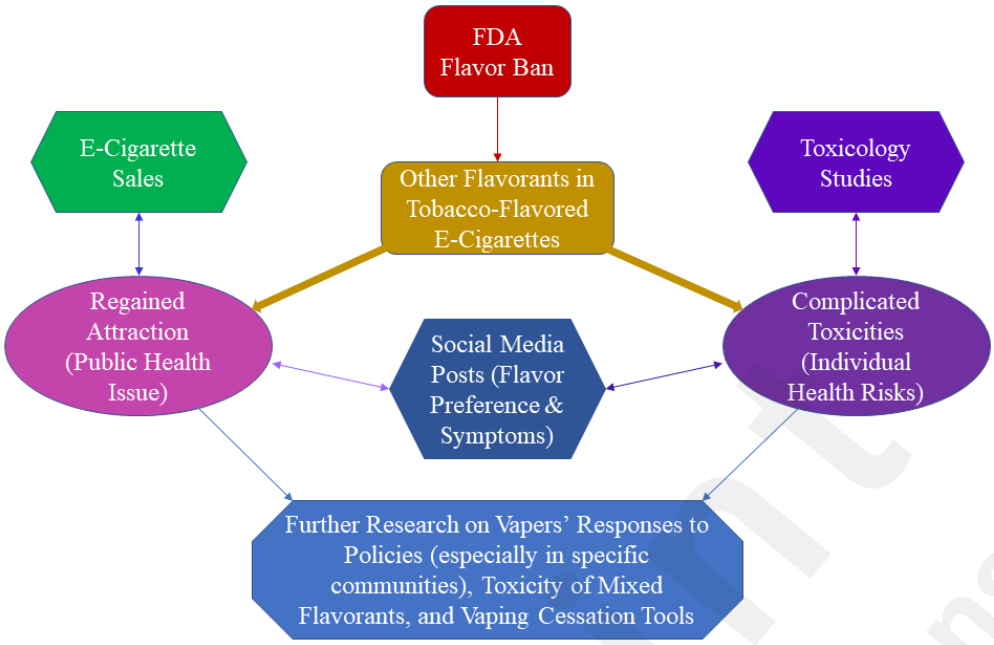

Figure 1. A schematic of the discussion of the new tobacco-flavored e-cigarettes and its associated problems.

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 toxicological mechanism of these products.

Tobacco-flavored e-cigarettes have a wide range of chemicals in the e-liquid, and different tobacco flavors have different flavor agents. However, in general, tobacco-flavored e-cigarettes contain propylene glycol, glycerol, and 0 mg/mL to 50 mg/mL of nicotine like most other e-cigarettes. Tobacco-flavored e-cigarettes have also been shown to have cinnamaldehyde.[17] Additionally, for the popular brands JUUL and Puff Bar, many other chemicals were frequently found to be in their tobacco-flavored e-cigarettes in greater than 1 mg/mL concentrations, including ethyl maltol, corylone, vanillin, and ethyl vanillin.[14] Another study found caffeine, isophorone, tributyl O-acetylcitrate, tributylphosphine oxide, triethyl citrate, and vanillin in tobacco-flavored e-liquids from popular brands like JUUL, Blu, Smok, and Vuse Alto.[18] There are also many volatile organic compounds (VOCs) present in tobacco flavors such as ethanol, toluene, ethylbenzene, and styrene.[17] Moreover, tobacco flavors would also produce reactive oxygen species that cause oxidative stress when used. Overall, there are many different carbonyls, citrates, phenols, VOCs, and other organic compounds present in tobacco-flavored e-liquids that are inhaled during vaping.

Existing studies have established some knowledge of the toxicities of tobacco-flavored e-

cigarettes.[16,19-24] The compounds present in the e-liquid and aerosol of tobacco-flavored e-cigarettes have many toxic effects on cells. For instance, nicotine in tobacco flavors can decrease mucociliary clearance in the lung by suppressing Alpha7 Nicotinic Acetylcholine Receptor activity and the CFTR, resulting in a greater risk for chronic lung diseases.[19] Additionally, the inhalation of compounds found in tobacco-flavored e-liquids can induce oxidative stress on cells, which can result in DNA, RNA, and protein damage. Beyond cells, tobacco-flavored e-cigarettes are harmful to the user's overall health. Inhaling nicotine from tobacco-flavored e-cigarettes can result in hypertension, chronic obstructive pulmonary disease (COPD), increased heart attack risk, and asthma.[20] Propylene glycol found in tobacco-flavored e-cigarettes can also pose health risks when inhaled where cough, difficulty breathing, and increased asthma risk are linked to inhalation of propylene glycol.[20] Moreover, the heating of glycerol found in tobacco-flavored e-liquids can produce formaldehyde, which can act as a carcinogen when inhaled.[20] 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.[21,22] 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.[23] Additionally, the ROS and VOCs present in tobacco-flavored e-cigarettes can increase exposure to free radicals, resulting in oxidative stress and lung inflammation that can increase the risk of COPD, asthma, and stroke.[19] 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).[16] The combination can also increase the level of PAI-1, a higher level of which is a risk factor for thrombosis and atherosclerosis.[16,24] Overall, inhalation of the compounds present in tobacco-flavored e-cigarettes poses a serious health risk and can increase lung toxicity and the likelihood of various diseases ranging from COPD to cardiovascular disease.

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; it is likely to be present in the “Tobacco Salt Rich” e-cigarette and was extracted from the de-identified tobacco-flavored e-cigarette introduced above.[16,25,26] As shown, the presence of vanillin has a positive correlation with the toxicity of e-liquids ($R^2 = 0.62$).[25] The vanillin in tobacco flavors is also inflammatory and can irritate airways.[19] Another popular flavorant (in 32% of e-liquids) with caramel flavors, ethyl maltol, was also present in the de-identified tobacco-flavored e-cigarette and has been shown to be a cause of incidences of kidney lesions in rats and mild hemolytic anemia in

dogs.[15,16,26,27] Furthermore, inhalation of cinnamaldehyde and ethyl maltol, compounds found in tobacco flavors, are oxidative and can lead to inflammation and epithelial barrier dysfunction, increasing the risk of diseases like COPD.[19] These are only two of the flavorants used in e-liquids, and the typical number of different flavorants in a single e-liquid product would be higher than 10.[25] It was found that the more chemicals in the e-liquid, the higher the toxicity that e-liquid is likely to possess.[25] 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.

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.[28,29] Generally, e-cigarette devices are divided into 4 generations, all of which can support tobacco flavors.[28,29]

First-generation e-cigarettes are designed to mimic the appearance of traditional cigarettes and thus are also known as cig-a-likes.[28,29] They are neither rechargeable nor refillable and are intended to be used only once.[28] The major components are a battery, an atomizing unit, and a fluid reservoir (cartridge).[29] Usually, vapor is produced only when the device is sucked on, and there is no switch on the device. Currently, tobacco-flavored e-cigarettes of the first generation can still be found in some online and/or physical vape shops.

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.[29] The “clearomizer” typically comes with a pen-shaped device that contains the battery, so second-generation e-cigarettes are also called “vape pens”.[28,29] Also, a button allows the vaper to decide to turn on/off the device.

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”.[28,29] 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.[29] Another characteristic of some third-generation devices is that they contain sub-ohm tanks, which allow even higher wattage due to decreased resistance.[28,29] 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 and are sold in

large amounts.

Fourth-generation e-cigarettes are called “Pod-Mods”, indicating a modifiable pod cartridge.[28,29] The shapes of fourth-generation e-cigarettes vary from each other, including USB shapes and teardrop shapes.[28,29] 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.[28] A very popular variation of fourth-generation e-cigarettes is vape bars, which are the most popular products in online vape shops.

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. In a fashionable online vape shop, 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). First-generation products and prefilled cartridges (second-generation) can also be found in another vape shop where it claims that the first-generation product is the new #1 selling e-cigarette on the market. 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 first- and second-generation e-cigarette looks relatively old.

According to scientific studies, e-cigarette users’ preferences for e-cigarette devices were shifting towards newer-generation devices: Fourth-generation devices (prefilled pods) are the most used devices, while third-generation devices still take up a considerable proportion of usage.[30] It was also observed that the shift towards newer generations is faster in youth users than in young adults or older adults.[30] Findings from another study also agree with this as they found that adolescent and young adults’ preference is responsive to advancements in e-cigarette technology as they generally avoid using earlier-generation devices and prefer more inventive products.[31] 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.[30,31]

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.[32] 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.[32] After the flavor ban, only menthol and tobacco flavors are allowed on the market,

and an increase in discussion about menthol flavors was observed.[9,33] However, there is no significant increase in discussion about tobacco flavors, indicating that vapers likely did not choose to shift to tobacco flavors immediately after the ban of their favorite flavors.[33] In contrast, the discussion of fruits and sweets flavors remained high immediately after the ban, signaling that the vapers might have sought other sources for their favorite flavors after they are banned, which indicates continued interest in these flavors.[33] 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, it is likely that the addition of these flavors in tobacco flavors would resuscitate the motivation for vapers to continue to vape.[34,35]

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.[36] 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.[37]

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.[36,37] 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.[36,37] 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.[2] 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).[38] 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.[9] 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.[39] 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.

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.[39] 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.[39] 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%,[39] 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.[40,41]

Per the FDA "Deeming" regulations, the FDA can now regulate the presence and amount of 'characterizing flavors' in vaping products.[42] According to former FDA Commissioner Gottlieb, e-cigarette use among youth can be characterized as an epidemic.[43] 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.[40,42]

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.[44,45] 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.[44] The proportion of tweets (and Twitter users' mentions) concerning quitting vaping was compared before and after the implementation of the FDA flavor policy.[44] Compared to before the FDA flavor policy, the proportion of tweets and Twitter user mentions after the implementation of the policy was higher.[44] 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.[44] 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.[44]

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.[46] 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.[46]

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.[9] 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".[13,16] 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 younger vapers' preferences switch to more innovative products more easily and they generally use newer-generation devices).[30,31]

Evidence from both the vaping market share and social media posts indicate that the manufacturers' strategy is likely successful.[33,39] 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.[39] 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.[33] 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 a product with the flavor "Tobacco Salt Rich" and another de-identified tobacco-flavored e-cigarette, and these flavorants 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.[15,16,25-27] 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.[25] 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.[36] 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.[44] The use of the new vaping cessation apps is also a potentially important aspect of public health interventions.[46] 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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Figure legends:

Figure 1. A schematic of the discussion of the new tobacco-flavored e-cigarettes and its associated repercussions on toxicity and public health.