ENDS Tobacco Flavors, Public Health, and Toxicity

Yehao Sun, Prital Prabhu Prital Prabhu, Ryan Rahman, Dongmei Li, Scott McIntosh, Irfan Rahman

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Yehao Sun[1]; Prital Prabhu Prital Prabhu[1]; Ryan Rahman[1]; Dongmei Li[1]; Scott McIntosh[1]; Irfan Rahman[1] PhD

[1]University of Rochester Medical Center Rochester US

Corresponding Author:
Irfan Rahman PhD
University of Rochester Medical Center
601 Elmwood Avenue
Rochester
US

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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Original Manuscript

ENDS Tobacco Flavors, Public Health, and Toxicity

Yehao Sun[1], Prital Prabhu[1], Ryan Rahman[1], Dongmei Li, PhD[2], Scott McIntosh, PhD[3] and Irfan Rahman, PhD[1*]

1. Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY, USA.
2. Department of Clinical & Translational Research, University of Rochester Medical Center, Rochester, NY, USA.
3. Department of Public Health Sciences, University of Rochester Medical Center, Rochester, NY, USA.

***Correspondence**: Irfan_Rahman@urmc.rochester.edu

Irfan Rahman, Ph.D.
Department of Environmental Medicine
University of Rochester Medical Center
Box 850, 601 Elmwood Avenue
Rochester 14642, NY, USA
Tel: 1 585 275 6911
E-mail: irfan_rahman@urmc.rochester.edu

ORCID #

Yehao Sun: 0009-0008-7030-6749 [ysun82@u.rochester.edu]

Prital Prabhu: 0009-0000-4415-1781 [pprabhu4@u.rochester.edu]

Ryan Rahman: 0009-0002-9949-9464 [rrahman@hamilton.edu]

Dongmei Li, PhD: 0000-0001-9140-2483 [Dongmei_Li@urmc.rochester.edu]

Scott McIntosh, PhD: 0000-0002-5776-9617 [Scott_McIntosh@urmc.rochester.edu]

Irfan Rahman, PhD: 0000-0003-2274-2454 [Irfan_Rahman@urmc.rochester.edu]

Short running title: *E-cigarette tobacco flavors toxicity*

Abstract

Background:
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.

Objective:
This review aims to provide information to inform authorities about the public health issue of the addition of other flavorants in tobacco-flavored e-cigarettes and to propose routes for further research and potential interventions.

Methods:
Searches for relevant literature published between 2018 and 2023 were performed. Cited articles about the toxicity of e-cigarette chemicals include ones published before 2018, and governmental websites/documents were also included for crucial information.

Results:
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.

Conclusion:
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 flavoring is added to 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. 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 it was not regulated by the US 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 products as well [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 between 18 and 25 years of age who were interested in trying TFN believed it to be less addictive than those who were uninterested, and those who have tried TFN reported that TFN products have flavors that taste better and products that taste smoother [7]. Similarly, young adults (18-25 years) 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 compared 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 properly educate the public about any potential risks of using these compounds.

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]. According to Rostron et al. in 2020, as much as 93.2% of youth vapers started vaping with a flavored e-cigarette, and among those who are still vaping, 71.0% reported the flavors of e-cigarettes as a reason for use [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 including Classic Tobacco, Smooth/Bold Tobacco, and Virginia 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 difference in regulations, e-cigarette manufacturers started to blend other flavors into tobacco-flavored e-cigarettes, re-creating the attraction for youth vapers [13, 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, smokey vanilla, and creamy caramel flavors. 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 volatile organic compounds (VOCs), reactive oxygen species, and other compounds present in the tobacco-flavored e-liquids can pose further health risks.

Objective

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, characteristics, sales, and social media perception 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**).

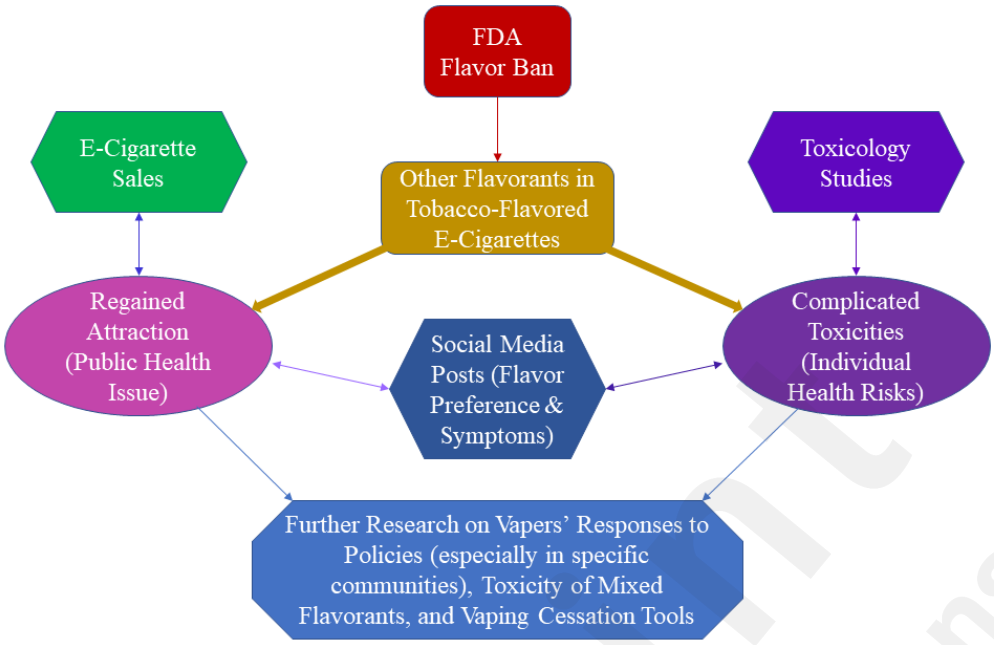

Figure 1. A schematic of the discussion of the new tobacco-flavored e-cigarettes and its associated problems.

Methodology

Searches on Google Scholar and PubMed for papers published between 2018 and 2023 related to e-cigarette use patterns, toxicity of e-cigarette chemicals, social media posts about e-cigarettes, and public health interventions regarding e-cigarettes were done for data collection. Toxicity information was also included from articles published before 2018, and e-cigarette sales data and related policies were extracted from government websites/documents. The keywords for searching these sources of information include "tobacco-flavored e-cigarettes", "e-cigarette use", "synthetic nicotine", "flavorants", "e-cigarette policy", "social media and vaping", "vaping cessation", and chemical names mentioned in this review.

With the extracted information, a discussion was done to figure out the attraction of tobacco-flavored e-cigarettes from sales data, the toxicity complications from toxicology studies, and to confirm these impacts of the addition of other flavorants in tobacco-flavored e-cigarettes by analyzing studies on related social media posts (**Figure 1**).

Results

E-liquid Constituents Inhaled during Vaping

Tobacco-flavored e-cigarettes have a wide range of chemicals in the e-liquid, and different tobacco flavors have different flavoring agents. However, in general, tobacco-flavored e-cigarettes contain propylene glycol, glycerol, and 0 mg/mL to 50 mg/mL (free base and salt nicotine) 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 and their combustion and degradation products that are inhaled during vaping.

Cellular Toxicities of Tobacco-flavored E-cigarette Aerosols

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 induce mucus hypersecretion by goblet cells and decrease mucociliary clearance in the lung by suppressing alpha7 nicotinic acetylcholine receptor activity and cystic fibrosis transmembrane conductance regulator, resulting in a greater risk for chronic lung diseases [19]. It was revealed that tobacco flavorants can induce oxidative stress, inflammation, DNA damage, and higher levels of cell death in lung epithelial cells and inflammatory responses in types of cells including fibroblasts [20, 21]. 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 [22].

Mechanisms of Disease Pathogenesis Related to Toxicities of Tobacco-flavored E-cigarette Aerosol

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 [23]. 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 [23]. Moreover, the

heating of glycerol found in tobacco-flavored e-liquids can produce formaldehyde, which can act as a carcinogen when inhaled [23]. 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, interleukin-6 (IL-6), and chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) [16]. The combination can also increase the level of plasminogen activator inhibitor-1 (PAI-1), a higher level of which is a risk factor for thrombosis and atherosclerosis [16, 24]. Additionally, the ROS and VOCs present in tobacco-flavored e-cigarettes can increase exposure to free radicals, resulting in oxidative stress and lung inflammation [19]. 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 chronic lung diseases ranging from COPD to cardiovascular disease (**Figure 1**).

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 [25, 26]. Generally, e-cigarette devices are divided into 4 generations, all of which can support tobacco flavors [26].

First-generation e-cigarettes are designed to mimic the appearance of traditional cigarettes and thus are also known as cig-a-likes [25, 26]. The major components are a battery, an atomizing unit, and a fluid reservoir (cartridge) [26]. Although outdated, 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” installed in a pen-shaped device, so second-generation e-cigarettes are also called “vape pens” [25, 26]. Third-generation e-cigarettes, on the other hand, are highly customizable and contain sub-ohm tanks, which allow even higher wattage due to decreased resistance [25, 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 and are sold in large amounts.

Fourth-generation e-cigarettes are called “Pod-Mods”, indicating a modifiable pod cartridge that can be in various shapes [25, 26]. Fourth-generation e-cigarettes use nicotine salts instead of freebase nicotine in previous generations, allowing a higher concentration of nicotine to be present [25]. A popular variation named vape bars is the most popular product in online vape shops.

Tobacco-flavored products associated with all the generations discussed above are widely

available online vape shops for vapers, and the products are sold in large amounts. In online vape shops, 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/pods (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-cigarettes looks relatively old.

Public Perceptions 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 (sentiment score = -0.134) using sentiment analysis [27]. Meanwhile, it was also found that the public was positive toward fruit (sentiment score = 0.074) and sweets flavors (sentiment score = 0.156), and most of the discussions were about these two flavors (58.15% and 14.67%, respectively) [27]. Immediately after the flavor ban, only menthol and tobacco flavors were allowed on the market, and an increase in discussion about menthol flavors (from 16.4% to 37%) was observed [9, 28]. 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 [28]. In contrast, the discussion of fruits and sweets flavors remained high after the ban and even increased around five months later (from 41% and 22.3% before the ban to 57% and 28% five months 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 [28].

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 [29]. 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 [30].

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 FDA 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 loopholes 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 [31]. 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 Centers for Disease Control and Prevention (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 [31]. 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 rather than continuing to buy the tobacco and menthol-flavored cartridges still on the market [31]. 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% [31], 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

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 [12, 32].

Per the FDA "Deeming" regulations, the FDA can now regulate the presence and amount of

‘characterizing flavors’ in vaping products [33]. According to former FDA Commissioner Gottlieb, e-cigarette use among youth can be characterized as an epidemic [34]. 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 vendors [12, 33].

To address the vaping epidemic, especially among youth, in 2021 theFDA implemented a flavor enforcement policy to restrict the sales of all cartridge-based unauthorized flavored e-cigarettes other than tobacco and menthol flavors [35, 36]. 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 [35]. The proportion of tweets (and Twitter users’ mentions) concerning quitting vaping was compared before and after the implementation of the FDA flavor policy [35]. Compared to before the FDA flavor policy, the proportion of tweets and Twitter user mentions after the implementation of the policy was higher [35]. 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 [35]. 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 [35].

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 [37]. 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 [37].

Discussion

Toxicological Complexities Brought by the Addition of Other Flavorants

Besides the toxicities of tobacco-flavored e-cigarette constituents, the introduction of other previously irrelevant chemicals may inevitably complicate the toxicity of these products. The most commonly used flavorant (in 35% of e-liquids), vanillin, is responsible for vanilla flavors in e-liquids; is likely to be present in the “Tobacco Salt Rich” e-cigarette and was extracted from the de-

identified tobacco-flavored e-cigarette introduced earlier in this paper [16, 38, 39]. As shown, the presence of vanillin has a positive correlation with the toxicity of e-liquids (R^2 = 0.62) [38]. The vanillin in tobacco flavors is inflammatory and can irritate airways [19]. Another popular flavorant (in 32% of e-liquids) present in caramel flavors, ethyl maltol, was also present in the de-identified tobacco-flavored e-cigarette and has been shown to be a contributing factor for incidences of kidney lesions in rats and mild hemolytic anemia in dogs [15, 16, 39, 40]. Furthermore, inhalation of cinnamaldehyde and ethyl maltol, compounds found in tobacco flavors, cause oxidative stress 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 [38]. It was found that the more chemicals in the e-liquid, the higher the toxicity that e-liquid is likely to possess [38]. 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 are required to fully understand this complexity and take appropriate actions regarding the regulation.

Youth Vapers' Preferences

According to scientific studies, e-cigarette users' preferences for e-cigarette devices were shifting towards newer-generation devices: Fourth-generation devices (prefilled pod cartridges) are the most used devices, while third-generation devices still take up a considerable proportion of usage [41]. It was also observed that the shift towards newer generations is faster in youth users than in young adults or older adults [41]. Another study conducted by Lin et al. also agrees 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 (the percentage of users who usually use disposable/large-size rechargeable e-cigarettes dropped from 88.2% to 33.1% during the study) and prefer more innovative products (percentage of users who usually use pod-based e-cigarettes, which were only introduced into the market when the study was halfway through, was 22.3% by the end of the study) [42]. 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 [41, 42]. The fact that youth vapers shifted to pod-based e-cigarettes quickly also made the addition of other flavorants in these products a more significant public health issue.

Implications from Social Media Studies

According to results from the social media studies mentioned earlier, vapers demonstrated continued interest in fruit and sweets flavors immediately after the flavor ban while remaining uninterested in original tobacco flavors [27, 28]. Our online survey study also showed that most vapers continued using flavored e-cigarettes even after the flavor ban, as disposable e-cigarettes were not covered by the FDA flavor ban [43]. Therefore, when their favorite flavors get integrated back into tobacco flavors, it is expected that they would prefer 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 likely resuscitate the motivation for vapers to continue to vape [44, 45].

Social media research that focused on health issues co-mentioned with flavors discovered that tobacco flavors were generally more likely to be co-mentioned with respiratory and throat symptoms, and cardiovascular symptoms are also frequently co-mentioned if the tobacco-flavored e-cigarettes are from JUUL [29, 30]. These results are associated with the traditional tobacco-flavored cigarettes prior to the addition of new flavors, and the addition might be associated with 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 [29, 30]. According to the same GEE models, “sweets” flavors are co-mentioned with throat and digestive symptoms while JUUL’s “crème” flavor is co-mentioned with neurological, digestive, and “other” symptoms, which are not observed in the corresponding tobacco flavors [29, 30]. However, the co-mention of flavor with health symptoms does not indicate that vaping will cause these symptoms as it is also possible that vaping could reduce the health symptoms. Previous study showed that the toxicological effects of the flavorants may interact with each other and the effects of such interactions are unknown [46]. Therefore, more research should be done to further understand the symptoms 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]. Dual users usually only use e-cigarettes when they are engaging in activities or in places that encourage e-cigarette use, or when they use e-cigarettes as substitutes for traditional cigarettes [47]. This type of difference gets exceedingly important when there is a relatively high prevalence of vaping in the community (including minority youth) or when the community is our major target of protection (including age groups like adolescents) [48]. For instance, among young adult e-cigarette users, bisexual women were the most susceptible to e-cigarette use habits with a high-level cigarette use [49]. Such disparities are of importance when public health interventions are tailored, so knowing how specific communities respond to the addition of flavorants in tobacco-flavored e-cigarettes is critical. However, despite this importance, 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.

Conclusion

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 of 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) [41, 42].

Evidence from both the vaping market share and social media posts indicate that the manufacturers' strategy is likely successful [28, 31]. 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 motivated the vapers to switch to disposable e-cigarettes [31]. 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 [28]. 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, 38-40]. 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 [38]. 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 [29]. 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 issues 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 [36]. The use of the new vaping cessation apps is also a potentially important aspect of public health interventions [37]. 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/or premarketing approval, and emphasis should be placed on vulnerable communities regarding the vaping public health effects.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

References

1. Leventhal AM, Dai H. Prevalence of Flavored e-Cigarette Use Among Subpopulations of Adults in the United States. J Natl Cancer Inst. 2021 Apr 6;113(4):418-24. PMID: 32785659. doi: 10.1093/jnci/djaa118.
2. Zavala-Arciniega L, Hirschtick JL, Meza R, Fleischer NL. E-cigarette characteristics and cigarette smoking cessation behaviors among U.S. Adult dual users of cigarettes and e-cigarettes. Prev Med Rep. 2022 Apr;26:101748. PMID: 35256927. doi: 10.1016/j.pmedr.2022.101748.
3. Bold K, O'Malley S, Krishnan-Sarin S, Morean M. E-cigarette Use Patterns, Flavors, and Device Characteristics Associated With Quitting Smoking Among a U.S. sample of Adults Using E-cigarettes in a Smoking Cessation Attempt. Nicotine Tob Res. 2023 Apr 6;25(5):954-61. PMID: 36462196. doi: 10.1093/ntr/ntac276.
4. Jordt SE. Synthetic nicotine has arrived. Tob Control. 2023 Apr;32(e1):e113-e7. PMID: 34493630. doi: 10.1136/tobaccocontrol-2021-056626.
5. Stephenson J. FDA Gains Power to Regulate Synthetic Nicotine in e-Cigarettes. JAMA Health Forum. 2022 Apr 1;3(4):e221140. PMID: 36218961. doi: 10.1001/jamahealthforum.2022.1140.
6. Ratnapradipa K, Samson K, Dai HD. Randomised experiment for the effect of 'Tobacco-Free Nicotine' messaging on current e-cigarette users' perceptions, preferences and intentions. Tob Control. 2023 Jan 3. PMID: 36596708. doi: 10.1136/tc-2022-057507.
7. Camenga DR, Krishnan-Sarin S, Davis DR, Bold KW, Kong G, Morean ME. Curiosity, use, and perceptions of "tobacco-free nicotine" E-cigarettes among U.S. young adults. Prev Med. 2022 Nov;164:107296. PMID: 36216122. doi: 10.1016/j.ypmed.2022.107296.
8. Morean ME, Bold KW, Davis DR, Kong G, Krishnan-Sarin S, Camenga DR. "Tobacco-free" Nicotine Pouches: Risk Perceptions, Awareness, Susceptibility, and Use Among Young Adults in the United States. Nicotine Tob Res. 2023 Jan 1;25(1):143-50. PMID: 36000776. doi: 10.1093/ntr/ntac204.
9. Center for Tobacco Products. Enforcement priorities for electronic nicotine delivery system (ENDS) and other deemed products on the market without premarket authorization. U.S. Food & Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-priorities-electronic-nicotine-delivery-system-ends-and-other-deemed-products-market.

Published 2020. Accessed May 23, 2023.
10. Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017. Am J Health Behav. 2020 Jan 1;44(1):76-81. PMID: 31783934. doi: 10.5993/ajhb.44.1.8.
11. Leventhal AM, Miech R, Barrington-Trimis J, Johnston LD, O'Malley PM, Patrick ME. Flavors of e-Cigarettes Used by Youths in the United States. Jama. 2019 Dec 3;322(21):2132-4. PMID: 31688891. doi: 10.1001/jama.2019.17968.
12. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. 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). Int J Environ Res Public Health. 2019 Aug 20;16(16). PMID: 31434229. doi: 10.3390/ijerph16162991.
13. Lamb T, Muthumalage T, Meehan-Atrash J, Rahman I. Nose-Only Exposure to Cherry- and Tobacco-Flavored E-Cigarettes Induced Lung Inflammation in Mice in a Sex-Dependent Manner. Toxics. 2022 Aug 13;10(8). PMID: 36006150. doi: 10.3390/toxics10080471.
14. Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Ethyl maltol, vanillin, corylone and other conventional confectionery-related flavour chemicals dominate in some e-cigarette liquids labelled 'tobacco' flavoured. Tob Control. 2022 Nov;31(Suppl 3):s238-s44. PMID: 36328460. doi: 10.1136/tc-2022-057484.
15. Pittet AO, Rittersbacher P, Muralidhara R. Flavor properties of compounds related to maltol and isomaltol. Journal of Agricultural and Food Chemistry. 1970 1970/05/01;18(5):929-33. doi: 10.1021/jf60171a044.
16. Muthumalage T, Rahman I. Pulmonary immune response regulation, genotoxicity, and metabolic reprogramming by menthol- and tobacco-flavored e-cigarette exposures in mice. Toxicol Sci. 2023 May 31;193(2):146-65. PMID: 37052522. doi: 10.1093/toxsci/kfad033.
17. Eaton DL, Kwan LY, Stratton K. Chapter 5: Toxicology of e-cigarette constituents. In: Stratton K, Kwan LY, Eaton DL, eds. Public Health Consequences of E-Cigarettes. National Academies Press (US);2018:155-216. doi: 10.17226/24952
18. Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography-High-Resolution Mass Spectrometry. Chem Res Toxicol. 2021 Oct 18;34(10):2216-26. PMID: 34610237. doi: 10.1021/acs.chemrestox.1c00253.
19. Kaur G, Muthumalage T, Rahman I. Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products. Toxicol Lett. 2018 May 15;288:143-55. PMID: 29481849. doi: 10.1016/j.toxlet.2018.02.025.
20. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, et al. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. Oral Oncol. 2016 Jan;52:58-65. PMID: 26547127. doi: 10.1016/j.oraloncology.2015.10.018.
21. Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. Oncotarget. 2016 Nov 22;7(47):77196-204. PMID: 27791204. doi: 10.18632/oncotarget.12857.
22. Kaur G, Gaurav A, Lamb T, Perkins M, Muthumalage T, Rahman I. Current Perspectives on Characteristics, Compositions, and Toxicological Effects of E-Cigarettes Containing Tobacco and Menthol/Mint Flavors. Front Physiol. 2020;11:613948. PMID: 33329065. doi: 10.3389/fphys.2020.613948.
23. Hussam Z. Alshareef STO. Toxicology of Commonly Found Ingredients in E-Cigarettes: A Brief Review. Health. 2021 November 30, 2021;13(11):1396-409. doi: 10.4236/health.2021.1311100.
24. Vaughan DE. PAI-1 and atherothrombosis. J Thromb Haemost. 2005 Aug;3(8):1879-83. PMID: 16102055. doi: 10.1111/j.1538-7836.2005.01420.x.
25. Centers for Disease Control and Prevention. E-cigarette, or vaping, products visual

dictionary. CDC Stacks. https://stacks.cdc.gov/view/cdc/103783. Published 2019. Accessed May 23, 2023.
26. Williams M, Talbot P. Design Features in Multiple Generations of Electronic Cigarette Atomizers. Int J Environ Res Public Health. 2019 Aug 14;16(16). PMID: 31416115. doi: 10.3390/ijerph16162904.
27. Lu X, Chen L, Yuan J, Luo J, Luo J, Xie Z, et al. User Perceptions of Different Electronic Cigarette Flavors on Social Media: Observational Study. J Med Internet Res. 2020 Jun 24;22(6):e17280. PMID: 32579123. doi: 10.2196/17280.
28. Gao Y, Xie Z, Li D. Investigating the Impact of the New York State Flavor Ban on e-Cigarette-Related Discussions on Twitter: Observational Study. JMIR Public Health Surveill. 2022 Jul 8;8(7):e34114. PMID: 35802417. doi: 10.2196/34114.
29. Chen L, Lu X, Yuan J, Luo J, Luo J, Xie Z, et al. A Social Media Study on the Associations of Flavored Electronic Cigarettes With Health Symptoms: Observational Study. J Med Internet Res. 2020 Jun 22;22(6):e17496. PMID: 32568093. doi: 10.2196/17496.
30. Luo J, Chen L, Lu X, Yuan J, Xie Z, Li D. Analysis of potential associations of JUUL flavours with health symptoms based on user-generated data from Reddit. Tob Control. 2021 Sep;30(5):534-41. PMID: 32709604. doi: 10.1136/tobaccocontrol-2019-055439.
31. CDC Foundation. National E-cigarette Sales Data Brief July 2022. https://www.cdcfoundation.org/National-E-CigaretteSales-DataBrief-2022-July22?inline. Published July 22, 2022. Accessed May 23, 2023.
32. Shi H, Tavárez ZQ, Xie Z, Schneller LM, Croft DP, Goniewicz ML, et al. Association of flavored electronic nicotine delivery system (ENDS) use with self-reported chronic obstructive pulmonary disease (COPD): Results from the Population Assessment of Tobacco and Health (PATH) study, Wave 4. Tob Induc Dis. 2020;18:82. PMID: 33082739. doi: 10.18332/tid/127238.
33. Department of Health and Human Services, Food and Drug Administration. Deeming Tobacco Products to be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Product Packages and Advertisements. https://www.fda.gov/media/97875/download. Published May 2016. Accessed May 23, 2023.
34. US Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on advancing new policies aimed at preventing youth access to, and appeal of, flavored tobacco products, including e-cigarettes and cigars. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-advancing-new-policies-aimed-preventing-youth-access. Published March 13, 2019. Accessed May 23, 2023.
35. Xie Z, Ruan J, Jiang Y, Zhang B, Chen T, Luo J, et al. Potential Impact of FDA Flavor Enforcement Policy on Vaping Behavior on Twitter. Int J Environ Res Public Health. 2022 Oct 7;19(19). PMID: 36232136. doi: 10.3390/ijerph191912836.
36. US Food and Drug Administration. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children. Published January 2, 2020. Accessed May 23, 2023.
37. Sanchez S, Kundu A, Limanto E, Selby P, Baskerville NB, Chaiton M. Smartphone Apps for Vaping Cessation: Quality Assessment and Content Analysis. JMIR Mhealth Uhealth. 2022 Mar 28;10(3):e31309. PMID: 35343904. doi: 10.2196/31309.
38. Sassano MF, Davis ES, Keating JE, Zorn BT, Kochar TK, Wolfgang MC, et al. Evaluation of e-liquid toxicity using an open-source high-throughput screening assay. PLoS Biol. 2018 Mar;16(3):e2003904. PMID: 29584716. doi: 10.1371/journal.pbio.2003904.

39. Krüsemann EJZ, Havermans A, Pennings JLA, de Graaf K, Boesveldt S, Talhout R. Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category. Tob Control. 2021 Mar;30(2):185-91. PMID: 32041831. doi: 10.1136/tobaccocontrol-2019-055447.
40. Gralla EJ, Stebbins RB, Coleman GL, Delahunt CS. Toxicity studies with ethyl maltol. Toxicol Appl Pharmacol. 1969 Nov;15(3):604-13. PMID: 5353824. doi: 10.1016/0041-008x(69)90062-3.
41. Jiang N, Xu S, Li L, Cleland CM, Niaura RS. Use of electronic nicotine delivery system (ENDS) devices among U.S. Youth and adults: Findings from the Population Assessment of Tobacco and Health Study Waves 1-5. Addict Behav. 2023 Apr;139:107588. PMID: 36549101. doi: 10.1016/j.addbeh.2022.107588.
42. Lin C, Baiocchi M, Halpern-Felsher B. Longitudinal trends in e-cigarette devices used by Californian youth, 2014-2018. Addict Behav. 2020 Sep;108:106459. PMID: 32388394. doi: 10.1016/j.addbeh.2020.106459.
43. Li D, Ossip DJ, Bansal-Travers M, Xie Z. Impact of the FDA flavour enforcement policy on flavoured electronic cigarette use behaviour changes. Tob Control. 2022 Nov;31(Suppl 3):s176-s83. PMID: 36328457. doi: 10.1136/tc-2022-057492.
44. Lindpere V, Winickoff JP, Khan AS, Dong J, Michaud TL, Liu J, et al. Reasons for E-cigarette Use, Vaping Patterns, and Cessation Behaviors Among US Adolescents. Nicotine Tob Res. 2023 Apr 6;25(5):975-82. PMID: 36507903. doi: 10.1093/ntr/ntac278.
45. Landry RL, Groom AL, Vu TT, Stokes AC, Berry KM, Kesh A, et al. The role of flavors in vaping initiation and satisfaction among U.S. adults. Addict Behav. 2019 Dec;99:106077. PMID: 31437770. doi: 10.1016/j.addbeh.2019.106077.
46. Lu S, Liu SS, Huang P, Wang ZJ, Wang Y. Study on the Combined Toxicities and Quantitative Characterization of Toxicity Sensitivities of Three Flavor Chemicals and Their Mixtures to Caenorhabditis elegans. ACS Omega. 2021 Dec 28;6(51):35745-56. PMID: 34984305. doi: 10.1021/acsomega.1c05688.
47. Pokhrel P, Herzog TA, Muranaka N, Regmi S, Fagan P. Contexts of cigarette and e-cigarette use among dual users: a qualitative study. BMC Public Health. 2015 Sep 4;15:859. PMID: 26341634. doi: 10.1186/s12889-015-2198-z.
48. Azagba S, Ebling T, Shan L. Sexual Minority Youth E-Cigarette Use. Pediatrics. 2023 Mar 1;151(3). PMID: 36808534. doi: 10.1542/peds.2022-058414.
49. Romm KF, Cohn AM, Wang Y, Williams R, Berg CJ. Disparities in trajectories of cigarette and E-cigarette use across sexual orientation groups of young adult men and women in the US. Addict Behav. 2023 Oct;145:107763. PMID: 37295384. doi: 10.1016/j.addbeh.2023.107763.

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.

Supplementary Files

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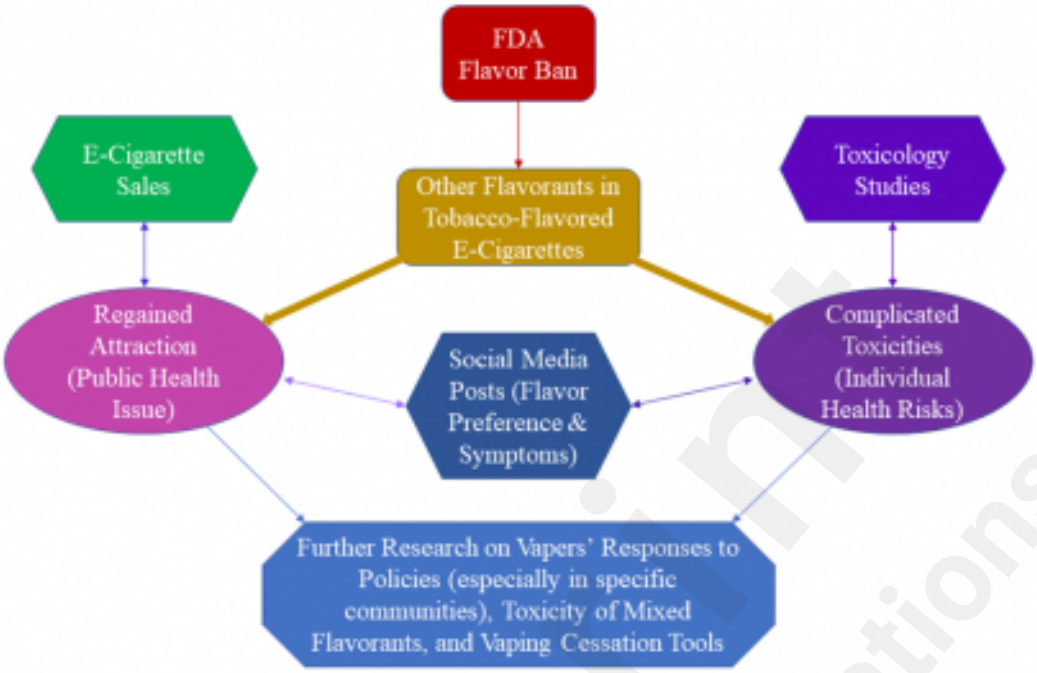

Figure 1. A schematic of the discussion of the new tobacco-flavored e-cigarettes and its associated problems.

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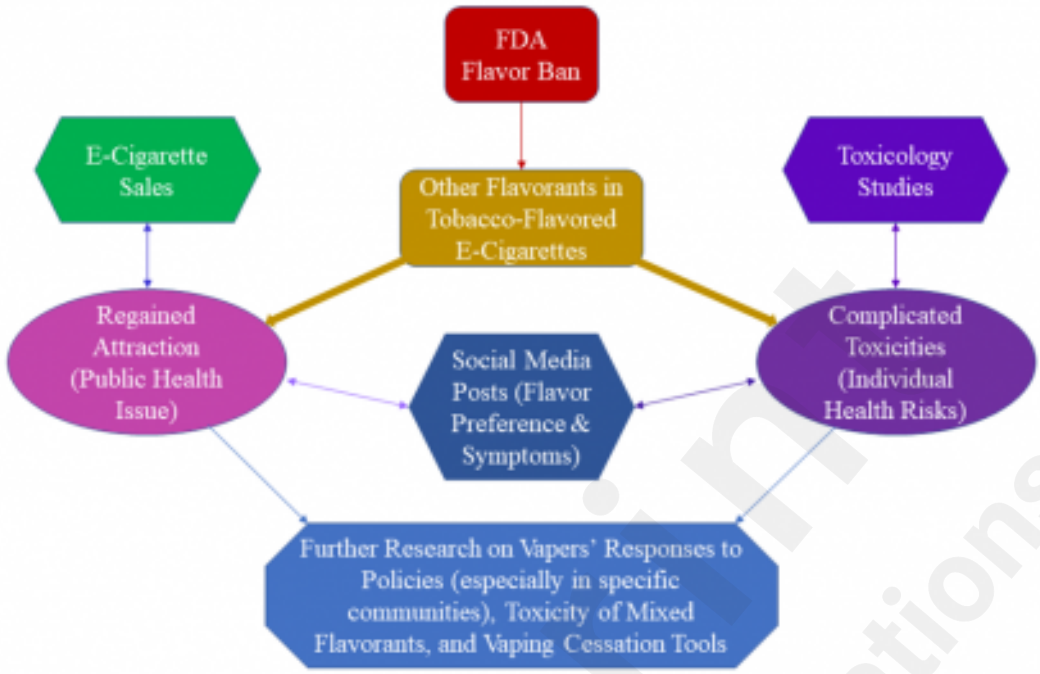
Figures

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



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