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July 13, 2018
Scott Gottlieb MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Regulation of Flavors in Tobacco Products (FDA-2017-N-6565-0001).

Commissioner Gottlieb:

On behalf of the 16,000 members of the American Thoracic Society, I want to thank FDA for the opportunity to comment on the Advanced Notice of Proposal Rule Making regarding Regulation of Flavors in Tobacco Products (docket number FDA-2017-N-6565-0001). As chair of the ATS Tobacco Action Committee, I appreciate the opportunity to comment on this important public health issue.

The ATS is comprised of over 16,000 physicians, scientists, nurses, respiratory therapists and allied health professionals dedicated to the prevention, detection, treatment, cure and research of pulmonary disease, critical care illness and sleep disordered breathing. Our members seek to improve health through research, education, clinical care and advocacy. As respiratory experts, our members are all too familiar with disease, death and emotional destruction caused by tobacco products, including cigars. As researchers, we are well aware of the extensive scientific evidence base that documents the known adverse health effects of tobacco products – including the role flavoring agents play in enhancing tobacco initiation and the nascent, but growing literature base describing the adverse health effects from inhaled flavoring agents. It is with this expertise that the ATS offers the following comments:



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General Comments:

The ATS strongly recommends the agency use its full range of authority to regulate all aspects of all tobacco products, including flavorings, both at the characterizing and sub-characterizing level. Further, the ATS is extremely frustrated that FDA is engaging in the advanced notice of proposed rule making process. Many of the issues raised in this notice and comment exercise were raised and responded to in the 2016 Deeming rule process. Based on information contained in FDA's own final Deeming rule, the agency is fully aware of the role that flavoring agents play in the initiation and habituation of tobacco use in all of its forms. The agency's insistence on engaging in another round of public notice and comments, coupled with its postponement in implementing pre-market review authority, adds needless delay to the regulatory process, is detrimental to public health, and runs counter to the public health mission of the agency.

Flavoring Impact on Tobacco Initiation

While the ATS is pleased that the public law Family Smoking Prevention and Tobacco Products took immediate action to ban flavored cigarettes (with the notable exception of menthol cigarettes) failure to act on other flavored tobacco products has led to a predictable rise in the number and use of other flavored tobacco products. The tobacco industry has expanded flavored tobacco product options and marketing of new products including cigars (large cigars, small cigars and cigarillos), e-cigarettes, smokeless tobacco and hookah products. From 2011-2015, when overall sales for tobacco products were decreasing, sales for menthol cigarettes, flavored cigarillos and flavored chewing tobacco increased.¹ Further, the growth of the e-cigarette market continues and is estimated to reach 5.5 billion U.S. dollars in 2018.² Despite industry claims, it is clear that flavored tobacco products play a central role in the tobacco industry's deliberate efforts to recruit new tobacco users – particularly among our nation's youth. It is not coincidence that the flavoring agents used in kid-friendly candies (LifeSavers, Kool-Aid and Jolly Ranchers) are the same flavoring agents used in flavored tobacco products.

Flavored tobacco products play a pervasive role in tobacco initiation. This finding is supported by extensive research. Dr. Hoffmann and colleagues in a systematic review of related articles found that, "Children have a strong, likely innate, preference for sweet tasting substances such as sugar and artificial sweeteners...Sweet tastes and sweet odours form a powerful sweet flavour mix that can be particularly attractive to children."³

¹ Kuiper, NM, et al., "Trends in sales of flavored and menthol tobacco products in the United States during 2011-2015," *Nicotine & Tobacco Research*, published online June 1, 2017.

² Wells Fargo Securities. *Nielsen: Tobacco 'All Channel' Data 3/24*. Equity Research. San Francisco (CA): Wells Fargo Securities, April 3, 2018.

³ Hoffman, AC, et al., "Flavour preferences in youth versus adults: a review," *Tobacco Control*, published online September 15, 2016.



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The tobacco industry is well aware of this information and has been preying on youth's susceptibility to flavored tobacco products.

The role that flavorings play in luring youth tobacco users is noted in FDA's own public record. The FDA ANPRM (at 12296) notes that the tobacco industry has long used flavored tobacco products as part of its efforts to lure children into tobacco addiction. Tobacco industry documents show that as far back as 1972, the tobacco industry was consciously using flavored tobacco products to create "youth cigarettes."⁴

Flavors transcend product initiation and are a key part of product marketing. The US Surgeon General concluded, "E-cigarettes are marketed by promoting flavors and using a wide variety of media channels and approaches that have been used in the past for marketing conventional tobacco products to youth and young adults."⁵ Youth are uniquely vulnerable to tobacco industry e-cigarette marketing and its reliance on flavoring. The 2016 National Youth Tobacco Survey found that 78.2 percent of middle and high school students—20.5 million youth—had been exposed to e-cigarette advertisements from at least one source, an increase from 68.9 percent in 2014.⁶

The U.S. cigar market, including large cigars, cigarillos and small cigars, is growing. The cigar market doubled from 2000 to 2017 with over 13.3 billion cigars being sold. In general, cigar sales have increased while cigarette sales have declined.⁷ A large part of the growth in cigars has been driven by the introduction of candy, fruit or sweetened flavored cigars – a likely response to the banning of flavored cigarettes.

Flavored cigars appeal to kids. According the SAMSA data, the top five most popular cigar brands among 12- to 17-year olds who have used cigars – Black & Mild, Swisher Sweets, White Owl, Backwoods, and Dutch Masters – all come in flavor varieties, including apple, cherry, blueberry, chocolate strawberry, mango and peach – just to name a few.⁸ Flavored cigars are priced at a level youth can easily afford and are sold in eye catching packaging.

⁴ Marketing Innovations, "Youth Cigarette - New Concepts," Memo to Brown & Williamson, September 1972, Bates No. 170042014.

⁵ *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.*

⁶ Marynak, K., et al., "Exposure to Electronic Cigarette Advertising Among Middle and High School Students—United States, 2014-2016," *MMWR* 67(10): 294-299, March 16, 2018, <https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6710a3-H.pdf>.

⁷ U.S. Alcohol and Tobacco Tax and Trade Bureau (TTB), Tobacco Statistics. December 2000 & December 2017, <https://www.ttb.gov/tobacco/tobacco-stats.shtml>.

⁸ SAMHSA's public online data analysis system (PDAS), National Survey on Drug Use and Health, 2015, https://pdas.samhsa.gov/#/survey/NSDUH-2015-DS0001/crosstab/?row=CGR30BR2&column=CATAG2&weight=ANALWT_C&results_received=true.



Flavors are an essential part of the tobacco industry's effort to lure youth into nicotine addiction. Flavors in tobacco products increase youth initiation. Whether the tobacco product is a cigar, e-cigarette, chew tobacco or hookah tobacco, flavorings induce youth to try tobacco products.

As noted in FDA's ANPRM (at 12296), data from the government's 2013-2014 Population Assessment of Tobacco and Health (PATH) study found that 80.8 percent of 12-17 year olds who had ever used a tobacco product initiated tobacco use with a flavored product and 79.8 percent of current tobacco users had used a flavored tobacco product in the past month. Two-thirds of kids report they use the tobacco product, "because they come in flavors I like."⁹

Flavored tobacco products are prevalent in both middle and high school. 2014 NYTS found that 70 percent of current middle and high school tobacco users – a total of over 3.2 million youth (12 percent of all youth) – had used a flavored tobacco product in the past month.¹⁰ Another national study found that 18.5 percent of young adult (18-34 years old) tobacco users currently use a flavored tobacco product, with younger age being a predictor of flavored tobacco product use. In fact, the study found that those aged 18-24 years old had an 89 percent increased risk of using a flavored tobacco product compared to those aged 25-34 years old.¹¹

Adverse Health Effects of Flavoring Agents

While many of the chemicals that are currently used in flavored e-cigarettes and other new and emerging tobacco products have been examined for toxicity and adverse health effects as they relate to oral ingestion, most of these chemicals have not been examined for inhalational toxicity. There is now overwhelming evidence from numerous studies demonstrating the ability to cause cell death in different models of human lung cells, which would be the primary targets for these inhaled chemicals (1-8). These effects are usually observed in a dose-dependent manner, suggesting that the cytotoxic effects are related to the amount of the exposure. Therefore, regulation on the type and amount of flavoring chemicals contained in e-liquids and e-cigarettes is needed.

However, while the ability to cause overt toxicity and cell death is certainly of concern, there is increasing evidence that flavoring chemicals can have significant impact on lung health without causing overt cell death.

⁹ Ambrose, BK, et al., "Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014," *Journal of the American Medical Association*, published online October 26, 2015.

¹⁰ Corey, CG, et al., "Flavored Tobacco Product Use Among Middle and High School Students—United States, 2014," *MMWR* 64(38):1066-1070, 2015.

¹¹ Villanti, AC, et al., "Flavored Tobacco Product Use Among U.S. Young Adults," *American Journal of Preventive Medicine* 44(4):388-391, 2013.



Chemicals, such as benzaldehyde, which is used as a cherry or almond flavoring agent, are known to cause respiratory irritation or cough reflex responses (9, 10). While irritation of the airways or coughing may not be of significant concern in healthy individuals, in people with pre-existing conditions, such as asthma or COPD, inhalation of irritants and subsequent onset of reflex responses such as coughing, can exacerbate the underlying disease. In addition to benzaldehyde, other flavoring chemicals are also known to activate pulmonary neurogenic reflex responses, such as smooth muscle contraction, sneezing, coughing, and mucus secretion. Specifically, inhalation of compounds such as vanillin, a highly popular and abundant chemical found in flavored tobacco products, could lead to neurogenic inflammation (11,12), which includes the release of inflammatory mediators from neurons. Flavoring-induced activation of neurogenic inflammation could lead to adverse respiratory health outcomes and has been associated with the pathogenesis of asthma.

Additional flavoring chemicals that have been associated with the pathogenesis of asthma include cinnamaldehyde, a chemical often used to give flavored tobacco products a spicy flavor (13). Cinnamaldehyde has also been implicated in chronic cough and inflammation (14) and suppresses the function of critical immune cells in the lung in a dose-dependent manner (5). Implications resulting from these immune-suppressive effects of cinnamaldehyde likely include reduced ability to fight bacterial and viral infections in the lung, which are the most common causes for exacerbation of chronic lung diseases, such as asthma and COPD. Furthermore, cinnamaldehyde as well as other flavoring chemicals, such as eugenol, have been shown to be potential sensitizers for asthma and other allergic diseases, including allergic dermatitis (15-22). OSHA broadly defines sensitizers as “chemicals that cause a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical.” While cinnamaldehyde has been shown to have strong skin sensitizing activity, whether and to what extent repeated inhalation of flavoring chemicals such as cinnamaldehyde and eugenol in flavored tobacco products, could sensitize the airways to develop allergic reactivity and presents an unknown health risk.

Occupational exposure to diacetyl and other buttery flavors such as 2,3-Pentanedione and acetoin can cause obstructive lung disease (Bronchiolitis Obliterans or “Popcorn Lung”), which has been identified in workers of popcorn factories inhaling high concentrations of these flavoring chemicals. Buttery flavoring chemicals are contained in many e-cigarettes and e-liquids (23), thus presenting a risk of developing irreversible obstructive lung disease in e-cigarette users. The Flavor and Extract Manufacturers Association (FEMA) has now recognized the potential for these flavoring chemicals to cause respiratory irritation and other adverse respiratory health outcomes as a result of occupational exposures.



Consequently, FEMA has developed a list of “High Priority flavorings” that might be hazardous to respiratory health when inhaled (<https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/ResH%26S%202012%20FINAL.pdf>). This list includes several chemicals used as flavoring agents in tobacco products, such as benzaldehyde (cherry/almond flavor) and diacetyl/acetoin/2,3-Pentanedione (buttery flavor). Therefore, the potential health hazard caused by exposure to high concentrations of these flavoring chemicals, as would occur by inhaling flavored tobacco products, has been identified by the industry’s own trade association.

Evidence Linking E-cigarettes and Respiratory Health Effects in Humans

Over the past few years, several case reports have been published linking use of e-cigarettes with severe adverse respiratory health outcomes. Even though detailed analysis of which flavoring chemical(s) could have been associated with these observations is not available, it is assumed that in each case the patients used flavored e-cigarettes. We are providing a growing list of case reports documenting adverse clinical outcomes of e-cigarette use.

Case Report #1: An 18-year old woman who was admitted with signs of acute lung injury (ALI; dyspnea) reported to have started vaping e-cigarettes in the recent past. Upon further examination, the patient was diagnosed with hypersensitivity pneumonitis, lipid pneumonia, and eosinophilic pneumonia (24).

Case Report #2: A 40-year old female developed several signs of pulmonary toxicity, including symptoms of dyspnea, intermittent chest pain, and pneumonia, after using e-cigarettes (25).

Case Report #3: A 45-year old female e-cigarette user presented with abdominal pain and fever. Assessment of lung biopsies revealed an area with multinucleated cells suggestive of reaction to lipophilic material. Subsequent cessation of e-cigarette use caused disappearance of the lung nodules (26).

Case Report #4: A 20-year old male developed acute eosinophilic pneumonia after using e-cigarette (27).

Case Report #5: A 33-year old male with diabetes and seizure disorder and self-reported increased use of e-cigarettes over the past 2 months developed diffuse alveolar hemorrhage (2018 ATS meeting: Abstract #A3567)



Case Report #6: A 43-year old male developed acute dyspnea after switching from traditional smoking to e-cigarettes. The patient had a past history of pulmonary embolism and asthma and a CT scan revealed small bilateral nodules, which resolved after 6-months prednisone (2018 ATS meeting: Abstract #A3565)

Case Report #7: a 45-year old male, who was a former smoker and switched to e-cigarettes, developed sudden severe dyspnea. Assessment of pulmonary function showed severe obstructive airway disease. Analysis of e-liquid showed furfural, vanillin, aldehydes, but no diketones (e.g. diacetyl). ATS meeting 2018: Abstract #A3572)

Ban Flavoring Agents with known Nicotine enhancing effect

Flavoring chemicals contained in tobacco products can also modify nicotine metabolism, resulting in enhanced availability of the addictive chemical. For example, cinnamaldehyde and menthol have been shown to modify the activity of the enzyme CYP2A6 (28, 29), which is the predominant enzyme metabolizing nicotine. CYP2A6 plays a major role in the inactivation of nicotine to cotinine. Therefore, flavoring chemicals causing the inactivation of CYP2A6 would result in decreased inactivation of nicotine to cotinine and increased stability/availability of nicotine. Decreased activity of CYP2A6 has been shown to increase the risk of nicotine dependence (30), possibly due to increased availability of nicotine. In addition, flavoring chemicals, such as menthol can significantly affect the expression and abundance of nicotine-binding receptors in the brain, thus enhancing the addictive potential of nicotine (31-34). Consequently, inhaling flavors could affect the metabolism, availability, and activation of nicotine-binding receptors, which are all factors increasing nicotine dependence.

Policy Recommendations:

Ban Menthol as a Characterizing Flavor in Cigarettes

The ATS notes with concern that FDA has not yet taken action on menthol flavoring in cigarettes even after the 2011 report of the Tobacco Products Scientific Advisory Committee. The Family Smoking Prevention and Tobacco Control Act provided a decision pathway for the agency to collect information, report its findings and take action on menthol flavorings in cigarettes. In 2013 FDA released its report on menthol flavoring in cigarettes and additional studies documenting the adverse health effects have been published. The reports, and the science on which they are based, are clear and consistent. Menthol flavoring increases tobacco initiation, reduces cessation and therefore causes adverse individual and public health effects. Further, the agency is engaged in not one, but two public notice and comment periods regarding menthol as a characterizing flavor in cigarettes. The evidence on the role menthol plays in initiation, habituation and reduction of cessation efforts has remained consistent.



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Based on the available evidence, FDA should take immediate action to ban menthol flavorings from cigarettes. FDA action on this issue is long overdue.

Ban Characterizing Flavors in All Tobacco Products

Flavors are an essential element of the tobacco industry's efforts to hook people on tobacco products. No one inherently wants to use tobacco-flavored tobacco. Candy, fruit or sweetened flavors lure youth to try tobacco products, mask the harshness of tobacco products and enable naive users to consume tobacco products until they become addicted. Without characterizing agents, the lure of tobacco products would be significantly reduced – much to the benefit of public health. A characterizing flavoring ban should be implemented across all tobacco products including cigars, e-cigarettes, chew tobacco, roll your own, pipe, hookah and other novel forms of tobacco.

Banning characterizing flavors in all tobacco products would greatly improve public health. Available evidence suggests youth and young adult tobacco initiation rates would drop significantly, helping to further reduce tobacco use and nicotine addiction in the U.S. The public health benefits, in terms of reducing tobacco-related death and disease, would be significant. Further, motivation for quit attempts would significantly increase as current users would no longer experience the masking effects of flavoring in tobacco products. Banning characterizing flavors is consistent with congressional intent. We note that the Family Smoking and Prevention Act explicitly banned flavors in cigarettes and established a firm deadline for FDA to enforce the flavoring ban. We also note that Congress directed FDA to study the impact of menthol flavoring and urged the agency to take action on available evidence. Congress clearly envisioned and encouraged FDA to take both immediate action on flavorings and further action as more information became available. Further, Congress gave FDA the explicit authority to ban flavoring agents. Banning characterizing flavorings across all tobacco products – similar to the ban on cigarette products, is consistent with congressional intent.

Ban Flavoring Agents with Known Respiratory Toxicity

In addition to a complete ban on characterizing flavors across all tobacco products, the ATS also recommends FDA implement a ban of flavoring agents at the sub-characterizing level for flavoring agents that have known respiratory toxicity efforts when inhaled directly, burned, heated or vaporized. As such, we recommend the immediate ban on diacetyl, 2,3 pentanedione, acetoin, cinnamaldehyde, benzaldehyde, eugenol, vanillin/ethyl vanillin, and menthol until proper inhalational safety assessments have been completed and NOAEL for inhalational exposures can be identified.



Require Testing of Flavoring Agents for Sub-characterizing Flavors

The ATS notes that the majority of flavoring agents used in tobacco products are categorized by FDA as “generally accepted as safe,” and that this indication was based on historical experience with the flavors as food additives. The majority of the tobacco flavoring agents have not been tested for their potential respiratory impacts. FDA should require that all ingredients used as sub-characterizing flavoring agents should be tested for respiratory and other health effects. A recent publication provides a ranking of flavoring chemicals based on oral toxicity as well as abundance in currently available e-liquids (3). All of these flavors should be evaluated for inhalational toxicity. Testing should be conducted for several types of exposures, including direct inhalation, combustion, heated and vaporized inhalation. We further recommend that qualified researchers who are not associated with the tobacco industry conduct testing.

In addition, all flavors should be modeled to predict adverse human health effects using new toxicology and risk assessment tools, such as high throughput assays and modified adverse outcome pathways (AOP). Flavoring chemicals could be tested for molecular initiation events, known to have broad adverse biological outcomes based on existing AOP models for respiratory toxicants (35).

Require Testing of Flavoring Agents for Stability and Reactivity with other Chemicals

Flavoring chemicals can undergo numerous different reactions, which are influenced by factors such as temperature, pH, storage period, existing enzymes, and oxygen. Some of the popular tobacco product flavoring chemicals that have been identified to undergo chemical reactions and degradation include: vanillin, furaneol, and citral (36). Other chemicals are known to directly interact with each other. For example, eugenol enhances thermal stability of cinnamaldehyde (36). Consequently, testing to guarantee quality assurance of flavoring chemicals, shelf-life stability, and potential expiration dates are needed.

The ATS appreciates the opportunity to comment on FDA’s Advanced Notice of Proposed Rulemaking regarding regulation of flavoring agents in tobacco products. We believe studies documenting the role flavoring agents play in youth and young adult tobacco initiation is compelling and the growing evidence base documenting the adverse health effects of the flavoring agents is concerning. FDA needs to exercise its existing regulatory authority to act quickly and decisively to regulate flavoring agents in tobacco products.



Sincerely,



Harold J. Farber MD MSPH ATSF
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