FDA should implement its proposed rule that manufacturers must present scientific evidence demonstrating that any flavored tobacco product is appropriate for the protection of the public health before receiving marketing authorization to use that flavor

Docket No: FDA-2017-N-6565

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FDA's advance notice of proposed rulemaking (ANPRM) requesting comments on the role that flavors, including menthol, play in initiation, use, and cessation of tobacco products, especially among youth, and whether and how certain flavors may help adult cigarette users switch to potentially less harmful products appropriately recognizes the role flavors may play in youth initiation, that youth and young adult smokers are disproportionately more likely to smoke menthol than nonmenthol cigarettes, that youth who initiate smoking with menthol cigarettes may be at greater risk of progression from experimentation to established smoking and nicotine dependence, and that flavors are identified as one of the top three reasons why middle and high school students initiate and continue to use e-cigarettes. However, while it is appropriate for FDA to take "a closer look at flavors in tobacco products to better understand their level of impact...,"¹ *FDA already knows the answer*.

¹ FDA, Statement from FDA Commissioner Scott Gottlieb, MD, on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors – including menthol – in tobacco products. March 20, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601690.htm

The draft of the Deeming Rule published in May 2016² that was submitted for approval to the Obama administration's Office of Management and Budget (OMB) included a well-reasoned and scientifically justified rule³ that would have *allowed manufacturers to receive a marketing order from FDA to market menthol flavored and other flavored products if the manufacturer provided scientific evidence to the FDA that the marketing of the flavored product actually benefits the public health.*

This is a sensible and appropriate policy because it focuses the discussion on specific flavors that specific manufacturers wish to use rather than attempting to forge a general policy that would apply to the tens of thousands (or more) of flavors and flavor combinations that could hypothetically be used. It also avoids an outright ban on flavors while grounding the rule firmly in the legal standard of protecting public health established in the Family Smoking Prevention and Tobacco Control Act (TCA).

TCA section 907 gives FDA the authority to establish tobacco product standards "where appropriate for the protection of the public health," including "provisions respecting the construction, components, ingredients, additives" and other constituents of the tobacco product, in particular flavors (TCA section 907(a)(4)(B)(i)), and provisions restricting their sale and distribution (TCA section 907(a)(4)(B)(v)). In determining whether the tobacco product standard is "appropriate for the protection of the public health," FDA must consider scientific evidence concerning the risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products, and the increased or decreased likelihood that

² Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. Final Rule. 81 FR 28974, May 10, 2016. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-82904

³ TAB B 2014-850 Deeming Final Rule Redline Changes, pp. 167-183. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

existing users will stop using the products and that nonusers will start using the products. (TCA section 907(a)(3)(B)(i)) Additionally, if FDA determines that it is appropriate for the protection of public health to require the reduction or elimination of an additive or constituent (such as a flavor) because it is or may be harmful, any party objecting to the proposed standard may provide FDA with scientific evidence demonstrating that the proposed standard will not reduce or eliminate the risk of illness or injury. (TCA section 907(a)(3)(B)(i))

The draft Deeming Rule submitted to OMB was consistent with the law, because it specifically gave manufacturers the opportunity to provide evidence that restricting the marketing of a particular flavored product would not reduce harm.

In particular, it would also allow manufacturers to use flavors if they could demonstrate that a specific flavor helped adult smokers quit without attracting youth.

Unfortunately, under the Obama administration, the OMB deleted FDA's well-conceived evidence-based regulation, resulting in flavored e-cigarettes, cigars, hookah and other newly deemed tobacco products (including menthol flavored tobacco products) that especially appeal to youth and young adults continuing to be sold today. Indeed, had the Obama OMB allowed the FDA to move forward, the March 2018 ANPRM would be unnecessary. Prior to the long rule-making process for the Deeming Rule, FDA's own scientists and Tobacco Products Scientific Advisory Committee had already determined the public health impact of menthol in cigarettes and concluded that the removal of menthol cigarettes from the marketplace would benefit public health.⁴

⁴ FDA Tobacco Products Scientific Advisory Committee, Report on the public health impact of menthol in cigarettes. March 2011. Available at: <u>https://wayback.archive-</u> it.org/7993/20170405201750/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/T obaccoProductsScientificAdvisoryCommittee/UCM247689.pdf Scientific evidence supporting FDA's initial and correct conclusion that flavors in tobacco products appeal to youth and young adults and may contribute to initiation and continuation of tobacco use continues to grow, and is documented below. This new information further strengthens the FDA's original proposed rule. *FDA should prohibit the use of all flavors unless manufacturers submit scientific evidence demonstrating that a particular flavored tobacco product appropriately protects the public health, considering its health impacts on current users, non-users, and former users, as the law requires.*

FDA's Deeming Rule originally stated, "Given the attractiveness of flavors, especially to youth and young adults, and the impact flavored tobacco products may have on youth initiation, the Agency is not extending its compliance policy for premarket review to flavored new tobacco products.... Consequently, as of 180 days after publication of the rule, any non-grandfathered, newly deemed flavored tobacco products on the market will be subject to enforcement."⁵ Further, FDA stated, "menthol-flavored products will be treated the same as products with characterizing flavors other than tobacco for the purpose of this policy, because when it is used as a characterizing flavor, menthol has a similar impact on a product's appeal to youth and young adults as such other characterizing flavors."⁶ FDA recognized the import of its proposal, stating, "FDA recognizes that this will result in numerous flavored newly deemed products (that are not grandfathered) coming off the market within 180 days after the publication date of this final rule and that this will significantly impact the availability of flavored tobacco products at least in the short term. This rule and its associated compliance policies are not banning flavored newly deemed products; a manufacturer of a flavored newly deemed product can market the product

⁵ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 167. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

⁶ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 169. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

after receiving marketing authorization [which requires demonstrating that the product is appropriate for the protection of the public health] or if the product is grandfathered.⁷⁷

This rule should be extended to all tobacco products and favors, including menthol in cigarettes and smokeless tobacco, as well as all forms of electronic cigarettes currently on the market and those coming to market.

Flavors and Characterizing Flavors in Tobacco Products

With the exception of menthol, the 2009 Family Smoking and Prevention Tobacco Control Act (TCA) banned use of characterizing flavors in cigarettes.⁸ Use of characterizing flavors in other tobacco products (e.g., electronic cigarettes [e-cigarettes], cigars, and smokeless tobacco) continues to be permitted and is widespread. Moreover, flavors are still allowed in cigarettes as long as they are not used to "characterize" the products.

The FDA noted in the version of its Deeming rule submitted to the Obama OMB⁹ and posted in May 2016 that flavored tobacco products have the potential to lower barriers to nicotine addiction for youth and young adults. At page 170, FDA stated, "Flavoring also can make these products easier to use and increases their appeal among new users, most notably among young people (Ref. 9, Carpenter; Ref. 10, Cummings; Ref. 11, Manning)"¹⁰; at page 176 FDA reported, "a study of youth and young adults found that flavored tobacco use facilitates nicotine dependence among young smokers, despite low smoking frequency (Ref. 15A, Huh)."¹¹ After reporting data from the 2011-2014 National Youth Tobacco Surveys showing that in 2014,

⁷ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 169. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

⁸ Public Law 111-31(June 22, 2009): HR 1256.

⁹ TAB B 2014-850 Deeming Final Rule Redline Changes, pp. 167-183. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

¹⁰ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 170. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

¹¹ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 176. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

about 2.2 million students currently used more than two tobacco products, and of current tobacco users, 2.4 million used e-cigarettes, FDA noted at page 173, "These figures are particularly concerning given the attractiveness of flavored e-cigarettes to youth and young adults and the potential for youth e-cigarette users to move on to the use of combustible tobacco products."¹² FDA further recognized that while flavors attract youth to tobacco products, removing flavors may reduce the attraction. FDA stated at page 176, "Focus group data also has suggested that removing flavors from tobacco products may reduce young adults" intentions to try these products and subsequently use them (Ref 13, Choi)."¹³

Today the evidence supports a stronger conclusion: Flavored tobacco products directly

contribute to youth tobacco initiation, continued use, and nicotine addiction.

In its version of the Deeming Rule submitted to the Obama OMB, FDA provided four

pages of scientific evidence supporting its conclusion that youth and young adult tobacco users

are more likely to use flavored tobacco products than adult tobacco users:¹⁴

4. Youth and Young Adult Tobacco Users are More Likely to Use Flavored Tobacco Products Than Adult Tobacco Users

Many comments provided data and information regarding youth and young adult use of flavored tobacco products in recent years, including examples of the different flavors used in many of the newly deemed products including:

- Cigar products: Strawberry, Blueberry, Grape, Peach, Cherry, Cream, Vanilla, Chocolate, Honey, Mango, Piña Colada, Tequila, Rum, Sour Apple, Watermelon
- Waterpipe tobacco products: Chocolate, Cherry, Champagne, Cinnamon, Clove, Grape, Mango, Lemonade, Piña Colada, Pineapple, Watermelon, Raspberry, Cola, Irish Cream, Key Lime Pie, Peach, Root Beer, Hazelnut, Butter Scotch, Chai

¹² TAB B 2014-850 Deeming Final Rule Redline Changes, p. 173. Available at:

https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

¹³ TAB B 2014-850 Deeming Final Rule Redline Changes, p. 176. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

¹⁴ TAB B 2014-850 Deeming Final Rule Redline Changes, pp. 177-180. Available at: https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

• E-cigarette products: Peppermint Party, Piña Colada, Very Vanilla, Cherry Crush, Peach Passion, Bazooka Joe Bubble Gum, Cotton Candy, Mojito, Chocolate, Mango, Strawberry, Gummy Bear, Peanut Butter

Researchers have concluded that flavored products are likely to influence patterns of tobacco use, particularly among youth and young adults (Ref. 12, Villanti). For example, the American Legacy Foundation's Young Adult Cohort Study reported that 18.5 percent of young adults (aged 18-25) in a national sample were currently using a flavored tobacco product, and the prevalence of flavored brand tobacco use when examined by product type was most common for waterpipes (59 percent). Waterpipe tobacco smoking is becoming more popular among youth and young adults, and it is believed that the waterpipe smoking experience (i.e., less physically harsh and easier to inhale compared to cigarette smoke) coupled with the appeal of flavored tobacco are some of the reasons for the growing popularity of waterpipe tobacco (Ref. 14, Primack). After waterpipe tobacco, the prevalence of flavored brand use was followed closely pipes (50 percent) and little cigars, cigarillos, and bidis (47 percent) (id.). The prevalence of flavored brand tobacco use was reported as 20 percent for cigarette smoke 17 percent of young adults reported using flavored e-cigarette brands (id.).

Researchers also have concluded that youth and young adults are more likely to use little cigars and cigarillos that have flavors (Ref. 12, Villanti) and are more likely to use such products than adults. For example, an analysis of the 2009-2010 National Adult Tobacco Survey found that flavored cigar use decreases with increasing age, with 9.1 percent of respondents aged 18-24 using flavored cigars and cigarillos, and only 1.4 percent of adults aged 45-64 using flavored cigars and cigarillos (Ref. 12A King). The CDC also has found the prevalence of flavored cigar use among cigar smokers decreases with increasing age, with 57.1 percent of 18-24 year old cigar smokers reporting use of flavored cigars in comparison to 43.2 percent of cigar smokers age 25-44, 28.9 percent of cigar smokers age 45-64, and 13.4 percent of cigar smokers over age 65 (Ref. 16A, King).

Data from the 2010 and 2011 NSDUH also illustrates this flavor preference for youth and young adults. Black & Mild, a brand which includes both flavored and non-flavored cigars and is well-known for its flavored little cigars (including cherry and vanilla), was the most popular cigar brand among 12 to 17 year olds participating in these national surveys (Ref. 21, SAMHSA 2010; Ref. 22, SAMHSA 2011). The two other top youth cigar brands, Phillies (available in flavored and nonflavored varieties) and Swisher Sweets, come in flavors such as grape, sweet chocolate and strawberry (Ref. 21, SAMHSA 2010; Ref. 22, SAMHSA 2010; Ref. 21, SAMHSA 2010; Ref. 22, SAMHSA 2011). Additionally, reporting usual use of a brand that makes flavored cigars decreased significantly with age in this survey, with 95 percent of 12 to 17 year olds reporting a usual brand that makes flavored cigars compared with 63.2 percent of cigar smokers aged 35 years and older (Ref. 16, Delnevo). Results from the 2009-2010 National Adult Tobacco Survey (NATS) also indicated that prevalence of flavored cigar use was highest among 18 to 24 year olds compared to all other adult age groups (Ref. 15, King, 2012). The Surgeon General has noted that, with one exception, the top cigar brands preferred by adolescents and young adults "include various

flavorings, such as peach, grape, apple, and chocolate" (Ref. 141 at 164, 12 SG). Given that cigar smoking was the second most common form of tobacco use among youth in 2013, with 11.9 percent of high school students reporting smoking cigars in the past 30 days (Ref. 20, Arrazola), FDA remains concerned about the impact of these flavored products on youth initiation and use.

Further, e-cigarettes are available in numerous flavors including candy, fruit, peach schnapps, bubblegum, and cola (Ref. 23A, ACS; Ref. 23B, AAP), all of which may be particularly attractive to youth and young adults. Following the release of research from the 2011 and 2012 National Youth Tobacco Survey noting the increased prevalence of e-cigarette use in middle school and high school students, students have been quoted as noting that classmates use e-cigarettes and prefer flavors like gummy bears "because it tastes really good" (79 FR 23142 at 23157; Ref. 23C, Bolario). A focus group study conducted with young adults (18-26 years old) on new tobacco products (e-cigarettes, snus, dissolvable tobacco products) found that participants generally reported positive perceptions of the new products, particularly because they came in flavors (Ref. 13, Choi).

Recent data, as well as studies included with comments, illustrate that youth are particularly attracted to flavored ENDS products. As a result, one tobacco company's website acknowledges that youth like flavors when it states, "kids may be particularly vulnerable to trying e-cigarettes due to an abundance of fun flavors such as cherry, vanilla, piña colada and berry" (Ref. 16D, Lorillard). According to 2014 NYTS data, 5.9 percent of U.S. middle and high school students reported using flavored e-cigarettes in the past 30 days (citation pending). Preliminary data from the national Population Assessment of Tobacco and Health (PATH) Study also demonstrate the popularity of flavored e-cigarettes in the past 30 days reported using flavored e-cigarettes (e.g., menthol, mint, clove, spice, candy, fruit, chocolate, wine, cognac, or other flavors) (Ref. 16E, Ambrose). Moreover, of those youth reporting having ever used an e- cigarette, 81 percent reported that their first e-cigarette was flavored (id.). This data also shows that 81.5 percent of current e-cigarette users (defined as those who used an e-cigarette in the past 30 days) stated that they used e-cigarettes because it "comes in flavors I like" (id.).

Results from small cross-sectional studies also suggest that flavored e-cigarette use is popular among youth. Several comments included a study that was under review for a peer- reviewed publication and has since published. In this survey conducted in four high schools and three middle schools in Connecticut in 2013, 25.2 percent of high school students reported trying e-cigarettes in their lifetime and 12 percent reported using e-cigarettes in the past 30 days, while among middle school students, 3.5 percent reported trying e-cigarettes in their lifetime and 1.5 percent reported using e-cigarettes in the past 30 days (Ref. 23, Krishnan). Among the 953 lifetime e-cigarette users interviewed, 71 percent reported having tried sweet flavors, and 22.1 percent reported having tried menthol-flavored e-cigarettes. In terms of preferred flavors, 56.8 percent reported preferring sweet flavors, while 8.7 percent preferred menthol e-cigarettes (Ref. 23, Krishnan).

Nothing published since FDA reached these conclusions contradicts this summary. The evidence on the importance of flavors being important factors in recruiting youth to nicotine addiction has only grown stronger.

Youth are Attracted to Flavored Tobacco Products

Nearly all tobacco users begin as an adolescent or young adults.¹⁵ In order to attract young and new users, the tobacco industry adds characterizing flavors like mint, menthol, fruit, and candy to tobacco, often using the same flavorants that are in fruit-flavored candy such as Jolly Ranchers, and sometimes used in higher doses.¹⁶ These flavors appeal to new users by masking the harsh taste of tobacco. Despite historic tobacco industry claims that menthol simply adds flavor, tobacco industry documents have revealed that the industry manipulates menthol levels to control a cigarette's intensity to cater to new and long-term smokers.¹⁷

Menthol and other characterizing flavors appeal to new users by masking the harsh taste of tobacco, and bright packaging associates flavored tobacco with candy and other appealing flavored products.^{18,19} Additionally, tobacco products with a characterizing flavor, including fruit-flavored e-cigarettes²⁰ and menthol cigarettes,¹⁴ are perceived to be less harmful than unflavored or tobacco-flavored products. Youth shown tobacco packages (primarily snus and dissolvable tobacco) with or without a flavor descriptor are more likely than older adults to

¹⁵ Ling PM, Glantz SA. Why and how the tobacco industry sells cigarettes to young adults: Evidence from industry documents. *Am J Public Health*. 2002;92(6):908-916. doi:10.2105/AJPH.92.6.908.

¹⁶ Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252.

¹⁷ Kreslake JM, Wayne GF, Alpert HR, Koh HK, Connolly GN. Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults. Am J Public Health. 2008;98(9):1685-1692. doi:10.2105/AJPH.2007.125542.

¹⁸ Yerger VB. Menthol's potential effects on nicotine dependence: a tobacco industry perspective. Tob Control. 2011;20(Suppl 2):ii29-i36. doi:10.1136/tc.2010.041970.

¹⁹ Lewis MJ, Wackowski O. Dealing with an innovative industry: A look at flavored cigarettes promoted by mainstream brands. Am J Public Health. 2006;96(2):244-251. doi:10.2105/AJPH.2004.061200.

²⁰ Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. Tob Control. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

associate the flavor descriptor with better taste, more appeal, and lower health risks.²¹ In addition, there is some evidence that menthol cigarettes are harder to quit.^{22,23}

Flavor or "taste" is one of the most common persuasive marketing techniques used to promote food (mostly candy and snacks) to children on TV.²⁴ Exposure to ads for flavored products is positively associated with youth consumption,²⁵ and most money spent by youth is on food or beverages, particularly sweets.²⁶ Research on e-cigarettes comports with these findings, concluding: flavors play an important role for online e-cigarette marketing and boosts user interaction and positive emotion;²⁷ flavored (vs. unflavored) e-cigarette ads elicit greater appeal and interest in buying and trying e-cigarettes and the appeal of ads for flavors is linked to rapid and persistent adoption of e-cigarettes among youth;²⁸ and 75% of US youth stated they would not use e-cigarettes without flavors.²⁹ In another recent study, middle and high school students who used flavored tobacco products were asked if they would continue to use those products if flavors were not available: most youth reported that they would no longer use the product if it

²¹ Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the U.S: findings from an internet-based cross-sectional survey. Harm Reduct J 2014;11:2

²² Pletcher MJ, Hulley BJ, Houston T, Kiefe CI, Benowitz N, Sidney S. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function. 2006;166.

²³ Trinidad DR, Pérez-Stable EJ, Messer K, White MM, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. Addiction. 2010;105(SUPPL.1):84-94. doi:10.1111/j.1360-0443.2010.03187.x.

²⁴ Jenkin G, Madhvani N, Signal L, Bowers S. A systematic review of persuasive marketing techniques to promote food to children on television. Obesity reviews. 2014;15(4):281-293.

²⁵ Cairns G, Angus K, Hastings G, Caraher M. Systematic reviews of the evidence on the nature, extent and effects of food marketing to children. A retrospective summary. Appetite. 2013;62:209-215.

²⁶ Kraak VI, Gootman JA, McGinnis JM. *Food marketing to children and youth: Threat or opportunity?* National Academies Press; 2006.

²⁷ Liang Y, Zheng X, Zeng DD, Zhou X. Impact of flavor on electronic cigarette marketing in social media. 2015:278-283.

²⁸ Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112.

²⁹ Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*. 2014;23 Suppl 3:iii3-9.

were not flavored, including for cigarettes (54%), e-cigarettes (78%), cigars (81%), and hookah (74%).³⁰

The majority of youth in the US who try tobacco initiate with flavored tobacco products, including 81% of e-cigarette ever users, 65% of cigar ever users, and 50% of cigarette ever smokers.³¹ Adolescents are more likely to report interest in trying an e-cigarette from a friend if it is menthol-, candy-, or fruit-flavored than if unflavored.³² Most adolescent current tobacco users cite flavors as a reason for use (including 81% for past 30-day e-cigarette users; 74% for past 30-day cigar users).¹⁰ Youth and young adult tobacco users are more likely than older adult tobacco users to use flavored products, including menthol cigarettes,³³ flavored smokeless tobacco,³⁴ and flavored cigars.³⁵ Young smokers (age 12-17) are three times as likely to smoke menthol cigarettes as are smokers 35 and older.³⁶ Adolescents are more likely to report interest in trying an e-cigarette from a friend if it is menthol-, candy-, or fruit-flavored than if unflavored,³⁷ and *three quarters of adolescent and young adult flavored tobacco product users reported they would quit if flavors were unavailable*.³⁸

³⁰ Harrell MB, Loukas A, Jackson CD, Marti CN, Perry CL. Flavored Tobacco Product Use among Youth and Young Adults: What if Flavors Didn't Exist? Tob Regul Sci. 2017 Apr;3(2):168-173.

³¹ Ambrose B, Day H, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. *J Am Med Assoc.* 2015;314(17):1-3. doi:10.1001/jama.2015.13802.

³² Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control*.

^{2016;25(}Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

³³ Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tob Control*. 2016;25(Suppl 2):ii14-ii20. doi:10.1136/tobaccocontrol-2016-053329.

³⁴ Oliver AJ, Jensen JA, Vogel RI, Anderson AJ, Hatsukami DK. Flavored and nonflavored smokeless tobacco products: Rate, pattern of use, and effects. *Nicotine Tob Res*. 2013;15(1):88-92. doi:10.1093/ntr/nts093.

³⁵ Delnevo CD, Giovenco DP, Ambrose BK, Corey CG, Conway KP. Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tob Control*. 2014;24(4):389-394. doi:10.1136/tobaccocontrol-2013-051408.

³⁶ Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tob Control*. 2016:1-7. doi:10.1136/tobaccocontrol-2016-053329.

³⁷ Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control*. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

³⁸ Loukas A, Jackson CD, Marti CN, Perry CL. Flavored tobacco product use among youth and young adults: What if flavors didn't exist? *Tob Regul Sci.* 2017;3(2):168-173.

Youth Believe Ads for Flavored E-cigarettes Target Them

In a study³⁹ of California youth and young adults (mean age 17.5, SD = 1.7), participants were asked to indicate whether eight different ads for flavored e-cigarette products (Figure 1), randomly displayed, target someone younger than them, their age, someone a little older, or someone much older like their parents. Participants felt the ads were for someone just a little older than them (age 18 – 26; not for someone much older). More than half of participants felt ads for *cherry*, *vanilla cupcake*, *caramel*, and *smoothie* flavors were for someone their age. Ads were also seen as targeting an audience younger than them. These findings suggest that while the tobacco industry argues that flavored tobacco products, including sweet and fruit flavored products, are not meant to attract youth, they do. *These and similar findings indicate that the FDA should prohibit flavors in e-liquids and other products especially sweet (e.g., dessert, fruit) flavors, and prohibit marketing of these flavored products unless the manufacturers can provide specific evidence that allowing the use and marketing of that specific flavor avoids these problems with youth.*



Figure 1. Flavored e-cigarette ads shown to adolescents and young adults to elicit perceptions of the age of audience being targeted for each ad.²⁶

³⁹ McKelvey, K., Baiocchi, M., Halpern-Felsher, B. Youth Say Ads for Flavored

E-liquids are for Them. Presentation at the Pediatrics Academic Societies, Toronto, CA April 29, 2018.

Use of Menthol Attracts Youth, African Americans

In the general population, differences in menthol use exist across race, gender, age, and sexual orientation. Rates of use of menthol flavored tobacco products are often higher in marginalized and vulnerable populations. African American smokers consistently have the highest menthol use rate.⁴⁰ Menthol use is also higher among female smokers;²⁷ Lesbian, Gay, and Bisexual smokers⁴¹ (although see Rath et al 2013⁴²); people with severe psychological distress; people with fewer years of education and lower income; and those who are unmarried and uninsured people.⁴³ Use rates have increased among Hispanic, Asian, and white smokers.⁴⁴

Although less studied, there is some evidence that other flavored tobacco product use is also inequitably higher among marginalized groups. Among cigar smokers, women, high school graduates, and LGB and Transgender (LGBT) individuals have been found to have higher prevalence of flavored tobacco use than their male, more educated, or heterosexual counterparts,⁴⁵ although flavored little cigar use has been found to be higher among non-Hispanic white adolescent users than African American and Hispanic users.⁴⁶

⁴⁰ Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004-2014. Tob Control. 2016:1-7. doi:10.1136/tobaccocontrol-2016-053329.

⁴¹ Fallin A, Goodin AJ, King BA. Menthol cigarette smoking among lesbian, gay, bisexual, and transgender adults. *Am J Prev Med.* 2015;48(1):93-97. doi:10.1016/j.amepre.2014.07.044. ⁴² Rath JM, Villanti AC, Rubenstein RA, Vallone DM. Tobacco use by sexual identity among young adults in the

united states. Nicotine Tob Res. 2013;15(11):1822-1831. doi:10.1093/ntr/ntt062.

⁴³ Hickman NJ, Delucchi KL, Prochaska JJ. Menthol use among smokers with psychological distress: findings from the 2008 and 2009 National Survey on Drug Use and Health. Tob Control. 2014;23(1):7-13. doi:10.1136/tobaccocontrol-2012-050479.

⁴⁴ Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004-2014. Tob Control. 2016:1-7. doi:10.1136/tobaccocontrol-2016-053329.

⁴⁵ King BA, Dube SR, Tynan MA. Flavored cigar smoking among U.S. adults: Findings from the 2009-2010 national adult tobacco survey. Nicotine Tob Res. 2013;15(2):608-614. doi:10.1093/ntr/nts178.

⁴⁶ King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. J Adolesc Heal. 2014;54(1):40-46. doi:10.1016/j.jadohealth.2013.07.033.

The tobacco industry cultivated menthol use among African Americans by manipulating social factors of the civil rights era,⁴⁷ advertising menthol brand cigarettes, little cigars, and cigarillos in African American media and retail settings in African American neighborhoods,^{48,49} and donating to African American leadership organizations.⁵⁰ The strategy has been so successful that even by 6th grade, African American youth were three times more likely to recognize menthol brands than their peers.⁵¹ Such brand recognition helps initate new users; for example, young people who recognized the Newport brand were more likely to initiate smoking within the following 12 months.⁵² The tobacco industry has taken similar approaches in targetting the LGBT+ commuity. Industry documents reveal several campaigns to promote tobacco use among the LGBT media,⁵⁴ and funding LBGT and AIDS organizations.⁵⁵ For other flavors, tobacco products have been designed to graduate users from low nicotine, flavored products.

FDA had stated in its Deeming Rule submitted to the Obama OMB that menthol products would be treated the same as other flavored products, and therefore all newly deemed menthol

⁴⁷ Gardiner PS. The African Americanization of menthol cigarette use in the United States. *Nicotine Tob Res*. 2004;6 Suppl 1:S55-65. doi:10.1080/14622200310001649478.

⁴⁸ Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP. Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods. *Nicotine Tob Res.* 2012;14(1):116-121. doi:10.1093/ntr/ntr122.

 ⁴⁹ Kostygina G, Glantz SA, Ling PM. Tobacco industry use of flavours to recruit new users of little cigars and cigarillos. *Tob Control*. 2014:tobaccocontrol-2014-051830-. doi:10.1136/tobaccocontrol-2014-051830.
 ⁵⁰ Yerger VB, Malone RE. African American leadership groups: Smoking with the enemy. *Tob Control*.

³⁰ Yerger VB, Malone RE. African American leadership groups: Smoking with the enemy. *Tob Control*. 2002;11(4):336-345. doi:10.1136/tc.11.4.336.

 ⁵¹ Dauphinee AL, Doxey JR, Schleicher NC, Fortmann SP, Henriksen L. Racial differences in cigarette brand recognition and impact on youth smoking. *BMC Public Health*. 2013;13(1):170. doi:10.1186/1471-2458-13-170.
 ⁵² Dauphinee AL, Doxey JR, Schleicher NC, Fortmann SP, Henriksen L. Racial differences in cigarette brand

recognition and impact on youth smoking. *BMC Public Health*. 2013;13(1):170. doi:10.1186/1471-2458-13-170. ⁵³ Fallin A, Goodin AJ, King BA. Menthol cigarette smoking among lesbian, gay, bisexual, and transgender adults.

Am J Prev Med. 2015;48(1):93-97. doi:10.1016/j.amepre.2014.07.044.

⁵⁴ Smith EA, Malone RE. The outing of Philip Morris: Advertising tobacco to gay men. *Am J Public Health*. 2003;93(6):988-993. doi:10.2105/AJPH.93.6.988.

⁵⁵ Smith J, Thompson S, Lee K. "Public Enemy No. 1": Tobacco industry funding for the AIDS response. *SAHARA-J J Soc Asp HIV/AIDS*. 2016;13(1):41-52. doi:10.1080/17290376.2016.1164617.

products would have been ordered off the market by November 6, 2016. FDA presented overwhelming evidence, supported by comments it received on the then-proposed deeming rule, that menthol as well as candy and fruit-flavored tobacco products attract youth to tobacco use and deter quitting. In particular, FDA presented evidence in the draft submitted to the Obama OMB demonstrating the impact of menthol and other flavors in enticing African Americans to begin and continue smoking:

FDA expects that the tobacco flavor in a tobacco product need not be naturally inherent to the product in order for a manufacturer to fall within the compliance policy described here, but rather may result from the addition of ingredients or other measures by the manufacturer to result in the presence of tobacco as a characterizing flavor. However, menthol flavored products will be treated the same as products with characterizing flavors other than tobacco for the purpose of this policy, because when it is used as a characterizing flavor, menthol has a similar impact on a product's appeal to youth and young adults as such other characterizing flavors. We note that newly-deemed flavored tobacco products that are not grandfathered may still need to address the public health implications of any added flavors, including tobacco flavor, in their pre-market review submissions.⁵⁶

As noted above, the OMB deleted the provisions ending the use of menthol and other

flavors from the final Deeming Rule. *The FDA's conclusions were correct then and remain correct now. Precisely the same logic and even more scientific evidence should be used today to advance a rule eliminating menthol and other flavors from all tobacco products, except in cases where a manufacturer makes a good case that using a specific flavor would promote public health.*

The Evidence Against Flavors Attracting Youth is Weak

Shiffman et al.⁵⁷ reported the results of an online survey in which they concluded that "interest in e-cigarettes is very low among nonsmoking teens and is not affected by flavor

https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

⁵⁶ TAB B 2014-850 Deeming Final Rule Redline Changes, p.169. Available at:

⁵⁷ Shiffman S, Sembower MA, Pillitteri JL, Gerlach KK, Gitchell JG. The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. *Nicotine Tob Res* 2015:ntu333. doi:

descriptors." This conclusion is unlikely to be reliable because it is based on responses to a single question on interest in flavors that makes the results likely affected by floor (and ceiling) effects.^{58,59} This paper was funded by the NJOY e-cigarette company and whose authors all work for Pinney Associates on projects with Reynolds American Inc. on smoking cessation and reduced risk tobacco products.⁶⁰ The paper suffers from serious methodological problems that biased the results against finding an effect of flavors. Contrary to Shiffman et al.'s findings, the impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in e-cigarettes is not a reliable estimate of the effects of e-cigarette flavors on product desirability.

One of the largest problems with the findings from Shiffman et al was the measures used. Floor and ceiling effects occur when a measuring instrument is not sensitive enough to detect the real differences between participants when their answers are clumped at the low or high end of the possible range of values. An example of a floor effect would be testing mathematical knowledge using a problem that is so difficult that no one can solve it; thus, it will not reveal the true differences in mathematical knowledge. Shiffman et al. found almost no interest in any flavors of electronic cigarettes among teenagers who have never tried tobacco products (including e-cigarettes) and very low interest among adult smokers based on responses to a single question (albeit about 24 different flavors/products): "How interested would you be in using a [flavor] [product]?" The problem with just using a single question is that most people (especially those who are not yet tobacco users) are not interested in using a product even though they might be interested in trying it or using it in a specific situation, thus resulting in a floor effect.

^{10.1093/}ntr/ntu333

⁵⁸ Martin P, Bateson PPG. *Measuring behaviour: An introductory guide*: Cambridge University Press; 1993.

⁵⁹ Newman AB, Cauley JA. *The epidemiology of aging*: Springer; 2012.

⁶⁰ Pinney Associates. Tobacco harm reduction. http://www.pinneyassociates.com/our-practices/tobacco-harm-reduction/

To avoid the problem of a single question not measuring the variable of interest, surveys typically use more than one question to assess smoking behavior and intentions. For example, openness to smoking (or interest in smoking) is typically measured by at least two questions in most large surveys, such as the following questions from the National Youth Tobacco Survey:⁶¹

Do you think you will smoke a cigarette anytime during the next year? If one of your best friends offered you a cigarette, would you smoke it?

As a result, Shiffman et al.'s findings of limited interest in flavors, especially among youth, is likely to be the result of an insensitive measurement method rather than a real effect.

A study of smokers' interest in smokeless tobacco illustrates the importance of how the question is worded.⁶² Smokers reported very low interest in smokeless tobacco products (mean 1.5 on a 1-9 scale) when asked about use in general. However, when they were asked about smokeless tobacco use in specific situations, such as "How interested would you be in using this product when in a smokefree environment?" (mean=3.2) or for a specific reason, such as "to reduce health risk," they reported greater interest (mean interest=4.2 respectively).

In contrast to the hypothetical interest Shiffman et al. assessed, real world behavior indicates that while under 10% of the of adults who ever tried e-cigarettes reported that they tried them because of "appealing flavors,"⁶³ 43.8% of youth listed "good flavors" as the reason they tried e-cigarettes.⁶⁴

There are also serious concerns about the ethics of the study. The authors state that the

⁶¹ Centers for Disease Control and Prevention. National Youth Tobacco Survey (NYTS).

Retrieved January 15, 2015 from http://www.cdc.gov/tobacco/data_statistics/surveys/nyts/index.htm.

⁶² Popova L, Ling P. Alternative tobacco product use and smoking cessation: A national study. Am J Pub Health. 2013;103:923-930. doi: 10.2105/AJPH.2012.301070

⁶³ Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. *Int J Environ Res Pub Health* 2014;11(10):10345-10361. doi: 10.3390/ijerph111010345

⁶⁴ Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2014:ntu257. doi: 10.1093/ntr/ntu257

work was "exempt" from human subjects because they were using de-identified data collected by a third-party internet survey firm. While subject confidentiality is certainly an issue, so is the fact that Shiffman et al. were subjecting youth (as well as adults) to stimuli that could increase the respondents' likelihood to try an e-cigarette, thereby possibly introducing them to nicotine addiction. There is no acknowledgement of this risk to the subjects or steps taken after the survey was completed to mitigate these risks. Further, there is no discussion that informed consent from the minors' parents or the adults participating in the study was not obtained. Such studies typically include anti-tobacco education at the end to try and blunt the effect of any pro-tobacco or pro-e-cigarette effects of collecting the data. Finally, even studies conducted using a thirdparty and with data collected using Internet-based surveys usually have some form of IRB approval and consent process.

For these the FDA should not rely on the results in Shiffman et al.'s paper for assessing the impacts of flavors on e-cigarette use.

Flavors in smokeless tobacco (ST) enhance perceived product acceptability among youth and likely contribute to youth ST initiation and continued use.

ST and other non-cigarette tobacco products frequently feature the same sweeteners and chemical flavorings found in popular candies.^{65,66} Most adolescent users of smokeless tobacco (ST) use flavored ST (69% of ever-users recall first starting with flavored ST; and 81% of

⁶⁵ Miao S, Beach ES, Sommer TJ, Zimmerman JB, Jordt SE. High-Intensity Sweeteners in Alternative Tobacco Products. Nicotine Tob Res. 2016 Nov;18(11):2169-2173. doi: 10.1093/ntr/ntw141.

⁶⁶ Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014 Jun 5;370(23):2250-2. doi: 10.1056/NEJMc1403015.

current users now use flavored ST).⁶⁷ However, among adult (age 25+) ST current users, less than half use a flavored product.⁶⁸

Smokeless tobacco, specifically conventional oral moist snuff and chewing tobacco, has a strong taste and odor. Potential and new ST users may need to overcome negative taste and sensation expectations before experimentation. Adding flavors to ST does just that. Adolescent users' preferences for flavored ST may relate to masking the tobacco taste or could correspond to stronger preferences for sweet flavors at younger ages.⁶⁹ Youth shown packages for ST with or without a flavor descriptor (primarily for snus and dissolvable tobacco) were more likely than older adults to associate the flavor descriptor with better taste, more appeal, and lower health risks.⁷⁰

Based on internal tobacco industry documents, tobacco manufacturers have consistently associated flavored ST products with inexperienced users,^{71,72} including as part of an industry strategy to position flavored, often lower-nicotine, ST "starter products" at the base of a graduation strategy for young or novice users.⁷³

⁶⁷ Ambrose BK, Day HR, Rostron B, Conway KP, Borek N, Hyland A, Villanti AC. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. JAMA. 2015 Nov 3;314(17):1871-3. doi: 10.1001/jama.2015.13802.

⁶⁸ Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, Rose SW, Feirman SP, Tworek C, Glasser AM, Pearson JL, Cohn AM, Conway KP, Niaura RS, Bansal-Travers M, Hyland A. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014). Am J Prev Med. 2017 Aug;53(2):139-151. doi: 10.1016/j.amepre.2017.01.026.

⁶⁹ De Graaf C, Zandstra EH. Sweetness intensity and pleasantness in children, adolescents, and adults. Physiol Behav. 1999 Oct;67(4):513-20.

⁷⁰ Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the U.S: findings from an internet-based cross-sectional survey. Harm Reduct J. 2014 Jan 17;11:2. doi: 10.1186/1477-7517-11-2.

⁷¹ Mejia AB, Ling PM. Tobacco industry consumer research on smokeless tobacco users and product development. Am J Public Health. 2010 Jan;100(1):78-87. doi: 10.2105/AJPH.2008.152603.

⁷² Kostygina G, Ling PM. Tobacco industry use of flavourings to promote smokeless tobacco products. Tob Control. 2016 Nov;25(Suppl 2):ii40-ii49. doi: 10.1136/tobaccocontrol-2016-053212.

⁷³ Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. Tob Control. 1995;4(1):73-79.

Beliefs regarding flavored ST are associated with youth susceptibility to ST use. Using data from the baseline wave of the nationally representative Population Assessment of Tobacco and Health (PATH) Youth Study, Chaffee et al. found US youth age 12-17 who had never tried any tobacco product (N=7,718) were more likely to report that flavored smokeless tobacco was "easier to use" compared to unflavored ST (20.2%) than to report that flavored ST was "harder to use" (5.8%).⁷⁴ Individuals who reported that flavored ST was easier to use were more likely to be susceptible to ST use than those who reported flavored ST was harder to use, about the same, or that they did not know. Adjusted for socio-demographic characteristics and other known tobacco initiation risk factors, such as receptivity to advertising, youth who viewed flavored ST as easier to use were at 1.5-times the odds of being susceptible to ST use than youth with any other perception regarding flavored ST and ease of use.

These findings show that regulation to limit or ban the use of smokeless tobacco characterizing flavors or non-characterizing sweeteners would reduce perceived product acceptability among adolescents as well as susceptibility to use, which in turn could result in fewer youth initiating ST use.⁷⁵

Couch et al. conducted a qualitative study examining with greater detail how flavors in smokeless tobacco potentially contribute to product appeal and initiation among youth. They interviewed 55 adolescent males at three rural high schools in the Western US, including 32 current or former users of smokeless tobacco. They found that particular flavors, packaging and other product characteristics appeared to enhance curiosity, experimentation, and peer

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⁷⁵ Chaffee BW, Urata J, Couch ET, Gansky SA. Perceived Flavored Smokeless Tobacco Ease-of-use and Youth Susceptibility. Tob Regul Sci. 2017 Jul;3(3):367-373. doi: 10.18001/TRS.3.3.12.

acceptance of ST products.⁷⁶ Specifically, participants often associated flavored ST with appealing attributes of non-tobacco products, such as chewing gum, breath mints, food, and alcohol. When discussing ST flavors, one 17 year-old participant said, "It smelled good. So like, I thought, you know, maybe it will taste good, too. I mean, like I said, it was basically the same as gum."⁷⁷

In addition to the flavors themselves, the wide selection of flavored ST varieties was described as a way to stimulate and maintain interest in ST, including among youth who reported experimental or intermittent ST use. Said one such 17-year old: "...my friend introduced me to the Copenhagen Wintergreen, and that was really what got me hooked on it. And then after that, mint came out and I started buying mint."⁷⁸

Seasonal and special offers promoted by the tobacco industry seem to stimulate interest in certain ST products. Many adolescent ST users discussed specific flavored varieties that were only available during a certain time of year, and cited limited availability as a source of urgency to buy ST products. Said another participant of a bourbon-flavored variety: "Some [friends] chew black [Copenhagen Black]. That's seasonal. But they'll get a lot of it so they can keep chewing it." Websites were mentioned as a way to stay in tune with ST product availability.

⁷⁶ Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.

⁷⁷ Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.

⁷⁸ Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.

From another 17 year-old: "I follow a lot of pages that are dip-related. They keep me updated when like new flavors are coming out or when they come back into season and stuff."⁷⁹

Taken together, these findings show that flavors in smokeless tobacco are viewed favorably among adolescent ST users and potentially play a role in their motivation to initially try ST products and continue to use them.

For these reasons, FDA should prohibit the use of all flavors in smokeless tobacco

products, except when manufacturers can provide convincing evidence that the flavor will not

contribute to initiation and use of the product by youth and that the presence of the flavor will

provide public health benefits.

Toxicity of flavors

In 2016 FDA's original version of the final Deeming Rule before OMB's changes also

rested on scientific evidence that some chemical flavorings in newly deemed tobacco products

contain toxic compounds.⁸⁰

For example, one study tested 159 e-liquids with sweet flavors, such as toffee, chocolate, and caramel, and found that almost three-quarters of the samples (74 percent) contained diacetyl or acetyl propionyl,⁸¹ both of which pose known inhalation risks.⁸² And among those that tested positive, nearly half of the e-liquids in the study could expose users to levels that exceed recommended workplace limits for breathing these chemicals. Another study analyzed thirty e-cigarette liquids and found that many flavors, including cotton candy and bubble gum, contained aldehydes, a class of chemicals that can cause respiratory inrritation, airway constriction, and other effects.⁸³ Specifically, researchers

⁷⁹ Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.

⁸⁰ TAB B 2014-850 Deeming Final Rule Redline Changes, pp. 180-181. Available at:

https://www.regulations.gov/document?D=FDA-2014-N-0189-83193

⁸¹ Farsalinos, KE, Kistler, KA, Gillman, G et al. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. *Nicotine Tob. Res.* 2015 Feb;17(2):168-74.

⁸² U.S. Dept. of Labor, Occupational Safety & Health Admin., Occupational Exposure to Flavoring Substances: Health Effects and Hazard Control. SHIB10-14-2010, available at: https://www.osha.gov/dts/shib/shib10142010.html

⁸³ Tierney, PA, Karpinski, CD, Brown, JE, et al. Flavour chemicals in electronic cigarette liquids. Tob Control doi:10.1136/tobaccocontrol-2014-052175.

noted that two flavors, a dark chocolate and a wild cherry, would expose e-cigarette users to more than twice the recommended workplace safety limit for the aldehydes vanillin and benzaldehyde (id.). Similarly, researchers found that several cinnamon flavored e-liquids contained a chemical, cinnamaldehyde, which researchers stated was highly toxic to human cells in laboratory tests.⁸⁴ While some studies have found that lower levels of some toxicants are observed in e-cigarette aerosols than in combusted tobacco smoke,⁸⁵ evidence of toxicants in ENDS remains concerning. The potential dangers associated with chemical flavorings in newly deemed tobacco products provides additional supporting evidence not to extend the premarket review compliance policy to such products.

A March 2018 study tested the toxicity of the more than 7,700 e-liquid flavors that are available, and found that a large number are toxic, and the presence of vanillin (an example of a flavoring ingredient found in many e-liquids) was associated with higher toxicity values.⁸⁶

Adverse pulmonary effects

Inhaled flavorings have been associated with respiratory illness and life-threating

respiratory failure in humans. Diacetyl, a buttery flavoring agent used in microwave popcorn,

had long been designated by the FDA as Generally Recognized As Safe (GRAS) for oral

ingestion (i.e., eating it). In 2002, however, there was a cluster of cases of bronchiolitis

obliterans associated with workplace exposure to airborne diacetyl.⁸⁷ The effects of diacetyl

inhalation were recapitulated in a subsequent mouse study, which found that sub-chronic

exposures to diacetyl caused lymphocytic bronchitis and bronchiolitis.⁸⁸ Despite the widespread

⁸⁴ Behar, RZ, Davis, B, Wang, Y, et al. Identification of toxicants in cinnamon-flavored electronic cigarette refill liquids. Toxicol In Vitro. 2014 Mar;28(2):198-208.

⁸⁵ Goniewicz, M., L., J. Knysak, M. Gawron, et al. Levels of Selected Carcinogens and Toxicants in Vapour from Electronic Cigarettes. Tobacco Control, 23(2):133-139, 2014.

⁸⁶ Sassano MF, Davis ES, Keating JE, et al., Evaluation of e-liquid toxicity using an open-source high-throughput screening assay. PLOS Biology, March 27, 2018. https://doi.org/10.1371/journal.pbio.2003904

⁸⁷ Kreiss, K. *et al.* Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant. *New England Journal of Medicine* **347**, 330–338 (2002).

⁸⁸ Morgan, D. L., Flake, G. P., Kirby, P. J. & Palmer, S. M. Respiratory Toxicity of Diacetyl in C57BI/6 Mice. *Toxicol Sci* **103**, 169–180 (2008).

publicity surrounding "popcorn lung" in both the medical community and the lay press, a recent study reported the presence of diacetyl in 110 out of 159 tested "sweet" e-liquids.⁸⁹

Diacetyl inhalation is the most well-known case of artificial flavoring induced respiratory disease. However, a recent study of 367 workers at a flavoring manufacturing facility that had shifted toward usage of diacetyl substitutes found that time spent in production areas of one hour or greater per day predicted dyspnea and spirometric and diffusing capacity abnormalities.⁹⁰ Thus, inhalational exposure to flavoring additives beyond diacetyl may have dose-dependent pulmonary toxicity that may not manifest for many years. Additionally, a recent study reported that flavoring components of e-liquids were the main contributor in the production of toxic carbonyl species.⁹¹

The carbonyl compounds are formed by chemical reactions occurring during vaping, and this illustrates why *substances generally recognized as safe (GRAS) for oral consumption may not be safe if used in products that are vaped or smoked, because toxic substances could be formed from them by heating or during combustion.* Cinnamaldehyde, a reactive organic compound that gives cinnamon its flavor, has been shown to have cytotoxic and mutagenic effects in cell culture assays at concentrations found in cinnamon-flavored as well as a variety of fruit, tobacco, and sweet-flavored commercially available e-liquids.^{92,93} The UCSF TCORS has found than exposing primary human alveolar and bronchial epithelial cells to e-cigarette aerosol for 3 consecutive days, one hour daily reveals that cinnamon-containing e-cigarette aerosol

⁸⁹ Farsalinos, K. E., Kistler, K. A., Gillman, G. & Voudris, V. Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins. *Nicotine Tob Res* **17**, 168–174 (2015).

⁹⁰ Cummings, K. J. *et al.* Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility. *Occup Environ Med* **71**, 549–554 (2014).

⁹¹ Khlystov, A. & Samburova, V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. *Environ. Sci. Technol.* **50**, 13080–13085 (2016).

⁹² Behar, R. Z. *et al.* Identification of Toxicants in Cinnamon-Flavored Electronic Cigarette Refill Fluids. *Toxicol In Vitro* (2013). doi:10.1016/j.tiv.2013.10.006

⁹³ Behar, R. Z. *et al.* Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tobacco Control* tobaccocontrol-2016-053224 (2016). doi:10.1136/tobaccocontrol-2016-053224

demonstrated more cytotoxicity than unflavored aerosol, as assessed by the concentration of lactate dehydrogenase in the culture media (unpublished data). Investigators have also reported cytotoxic effects from specific e-cigarette aerosols with the flavor of coffee,⁹⁴ cinnamon-cookie,⁹⁵ "swiss dark," "menthol arctic," and butterscotch.⁹⁶ Furthermore, a recent report has shown high levels of the irritant compound benzaldehyde in cherry-flavored e-liquids.⁹⁷

Flavors have negative effects outside the lung

Carbonyl species elaborated by flavored e-cigarettes increase oxidative stress and inflammatory cytokine release in cultured gingival epithelial progenitors,⁹⁸ suggesting the potential for increased periodontal disease.⁹⁹ Flavors may also have broad effects on immune function. A recent study revealed that monocytes exposed to commonly used e-cigarette flavoring chemicals including diacetyl, cinnamaldehyde, acetoin, pentanedione, o-vanillin, maltol and coumarin demonstrated dose-dependent toxicity and inflammatory responses.¹⁰⁰ Conversely, flavorants related to cinnamon have also been shown to impair the innate immune functions of alveolar macrophages, neutrophils, and NK cells,¹⁰¹ suggesting major impacts on the host response to invading pathogens. The UCSF TCORS has found evidence that mice exposed

⁹⁴ Romagna, G. *et al.* Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. *Inhal Toxicol* **25**, 354–361 (2013).

⁹⁵ Farsalinos, K. E. *et al.* Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *Int J Environ Res Public Health* **10**, 5146–5162 (2013).
⁹⁶ Bahl, V. *et al.* Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models.

⁹⁶ Bahl, V. *et al.* Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod. Toxicol.* **34**, 529–537 (2012).

⁹⁷ Kosmider, L. *et al.* Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax* (2016). doi:10.1136/thoraxjnl-2015-207895

⁹⁸ Sundar, I. K., Javed, F., Romanos, G. E. & Rahman, I. E-cigarettes and flavorings induce inflammatory and prosenescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget* **7**, 77196–77204 (2016).

 ⁹⁹ Javed, F., Kellesarian, S., Sundar, I., Romanos, G. & Rahman, I. Recent updates on electronic cigarette aerosol and inhaled nicotine effects on periodontal and pulmonary tissues. *Oral Dis* n/a-n/a (2017). doi:10.1111/odi.12652
 ¹⁰⁰ Muthumalage, T. *et al.* Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. *Front Physiol* 8, 1130 (2017).

¹⁰¹ Clapp, P. W. *et al.* Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am. J. Physiol. Lung Cell Mol. Physiol.* **313**, L278–L292 (2017).

to cinnamon-flavored e-cigarette aerosol may have a longer duration of influenza viral shedding (unpublished data).

Flavors have not been shown to help adult smokers quit

FDA notes the existence of preliminary data that some adults may use flavored noncombusted tobacco products (e.g., flavored e-cigarettes) to transition away from combusted tobacco, and believes that "under a properly regulated framework that protects youth," flavors may help some currently addicted adult cigarette smokers switch to non-combustible forms of tobacco products.

In a nationally-representative sample of US tobacco users, Smith and colleagues found that among current users of non-cigarette tobacco products, those who reported using a flavored a flavored tobacco product were less likely to have made a past-year quit attempt than those who used unflavored tobacco.¹⁰²

FDA should not assume that e-cigarettes help adult smokers quit

Before discussing the evidence related to FDA's presumption that flavorings help adult tobacco smokers quit smoking combustible tobacco products, it is important to emphasize that, while some smokers have successfully quit smoking using e-cigarettes (notably daily users of high nicotine delivery systems), most smokers who use e-cigarettes are *less* not more likely to quit smoking. A meta-analysis of existing studies reports that the odds of quitting cigarettes are significantly reduced (OR 0.77, 95% CI 0.06-0.99) among smokers who use e-cigarettes

¹⁰² Smith DM, Bansal-Travers M, Huang J, Barker D, Hyland AJ, Chaloupka F. Association between use of flavoured tobacco products and quit behaviours: findings from a cross-sectional survey of US adult tobacco users. Tob Control. 2016 Nov;25(Suppl 2):ii73-ii80.

compared to smokers who do not use e-cigarettes.¹⁰³ In other words, the overall effect of ecigarette use is to depress smoking cessation, and thus flavored e-cigarettes do not increase likelihood of cigarette cessation.

Evidence on the effect of flavors on actual smoking cessation behavior is weak and mixed

Tackett et al¹⁰⁴ conducted a cross-sectional study of a convenience sample of 215 adult ecigarette users recruited in vape shops in "a large metropolitan city in the Midwestern United States" in 2013. They found that most customers (86%) started using e-cigarettes as an aid to stopping smoking. While most started with tobacco flavored e-liquids, the authors found that those using non-tobacco and non-menthol flavored e-liquids (fruity, coffee, candy, etc.) were significantly more likely to have stopped smoking cigarettes (OR 2.95, 95% CI 1.04-8.40) compared to e-cigarette users who used tobacco or menthol flavored e-liquids. Strengths of this study are that it observed the relationship between smoking behavior and flavors, and that most participants had their smoking status verified with exhaled CO. Weaknesses are that the study was cross-sectional and that there was no control group of smokers who did not use e-cigarettes. In addition, the authors note that "specialty vapor stores may be serving individuals with vaping characteristics distinct from those purchasing their products from convenience stores, gas stations, or online."

A PubMed search using "(e-cigarette or ENDS) and flavor and (quit or cessation)" conducted on May 1, 2018 identified 32 papers. Only two included evidence on the

 ¹⁰³ Glantz S. While several studies have been published showing some e-cig users quit more, the overall picture remains negative. <u>https://tobacco.ucsf.edu/while-several-studies-have-been-published-showing-some-e-cig-users-quit-more-overall-picture-remains-negative</u>. April 9, 2018.
 ¹⁰⁴ Tackett AP, Lechner WV, Meier E, Grant DM, Driskill LM, Tahirkheli NN, Wagener TL. Biochemically verified

¹⁰⁴ Tackett AP, Lechner WV, Meier E, Grant DM, Driskill LM, Tahirkheli NN, Wagener TL. Biochemically verified smoking cessation and vaping beliefs among vape store customers. Addiction. 2015 May;110(5):868-74. doi: 10.1111/add.12878

effect of flavors on adult cigarette cessation. Chen¹⁰⁵ found that young adults (age 18-34) in Waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study who used ecigarette flavors (sweet and fruity or tobacco and menthol/mint) were more likely to have reduced or stopped smoking cigarettes. In particular, e-cigarette users with one (AOR = 2.5, p < 0.001) and multiple nontobacco or menthol flavors (AOR = 3.0, p < 0.001) were more likely to have reduced or quit smoking over the past year compared to non-e-cigarette users. (It is not clear how "smoking reduction" was defined.) While the longitudinal nature of this study is a strength, the failure to distinguish between reduction of number of cigarettes smoked and smoking cessation is a serious limitation.

Smith et al.¹⁰⁶ reported results of a nationally representative, telephone-based survey completed in 2012 by 1443 US adult tobacco users asked about use of 9 tobacco products: cigarettes, e-cigarettes, cigars, cigarillos, little filtered cigars, pipes, hookah, smokeless tobacco and snus. They found that first use of a flavored tobacco product was associated with current flavored tobacco use and polytobacco use. Users of flavored non-cigarette products were less likely to have made a cigarette quit attempt than those who did not use flavored non-cigarette products (OR 0.45 95% CI 0.30-0.67), and were more likely to be current cigarette smokers (OR 1.55, 95% CI 1.08-2.22) than people who used non-flavored tobacco products (including cigarettes). Thus, this cross-sectional study shows that *the presence of flavors was associated with less cigarette cessation.*

Conclusion

¹⁰⁵ Chen J. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation-A Large National Study among Young Adult Smokers. Subst Use Misuse. 2018 Apr 6:1-15. doi: 10.1080/10826084.2018.1455704. [Epub ahead of print]

¹⁰⁶ Smith DM, Bansal-Travers M, Huang J, Barker D, Hyland AJ, Chaloupka F. Association between use of flavoured tobacco products and quit behaviours: findings from a cross-sectional survey of US adult tobacco users. Tob Control. 2016 Nov;25(Suppl 2):ii73-ii80. doi: 10.1136/tobaccocontrol-2016-053313. Epub 2016 Oct 5.

Taken together, the scientific evidence clearly shows that flavored tobacco products, including menthol, fruit, and candy-flavored products, attract adolescents and young adults to initiate and continue using tobacco. Further, menthol and other flavors disproportionately attract certain populations to smoke, including African Americans and those from the LGBTQ+ community. The basis for these conclusions comes from numerous cross-sectional and longitudinal studies focusing on combustible cigarettes, smokeless tobacco, cigars, and ecigarettes showing that youth are attracted to flavored tobacco products, more susceptible to initiating and using tobacco, and more likely to actually use tobacco with flavors. Conversely, youth are significantly less likely to use tobacco if unflavored. Further, there is clear evidence from human and animal studies that the flavorants used in tobacco is responsible for health consequences, including health effects observed in and outside of the respiratory system. In contrast, there is very little and inconsistent evidence that flavored tobacco helps adults quit combustible cigarettes. The published data generally show that adults are not attracted to flavors, and that those who attempt to quit cigarette use via e-cigarettes or other flavored products are less likely to quit.

These findings clearly show that the original May 2016 draft of the Deeming Rule indicating that tobacco manufacturers must receive a marketing order from the FDA in order to market flavored tobacco products and that such approval would only be granted IF the marketing of the flavored tobacco product would benefit public health should be reinstated and enforced. Prohibiting the use of flavors in all tobacco products, including menthol, will likely reduce adolescent and young adult tobacco use, reduce impediments to successful adult cessation attempts, and overall benefit public health.

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In the event that a manufacturer can provide compelling evidence that use of a specific flavor in a specific product helps adult smokers quit without attracting youth, the manufacturer could apply to the FDA for permission to market this product and the FDA could approve the application because it would be good for public health.