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THINK BEFORE YOU BAN: THE AWKWARD CASE OF E-CIGARETTE FLAVORS

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CONTENTS

INTRODUCTION

On March 20, 2018, the Food and Drug Administration (FDA) announced a consultation on proposed rule-making about the use of flavors in tobacco products.[1] The FDA's initiative is driven by a perceived problem: namely, that flavors make tobacco products attractive to young people and thus increase initiation and consumption, which causes harm. But the FDA also recognizes that non-combustible products can provide benefits by reducing smoking. For example, with respect to flavors in non-combustible products, Commissioner Scott Gottlieb, has acknowledged:

> It's possible for flavors to do both harm and good. The troubling reality is that e-cigarettes are the most commonly used tobacco product among middle and high school students, and flavors are identified as one of the top three reasons for use [...] At the same time, we're aware that certain flavors may help currently addicted adult smokers switch to potentially less harmful forms of nicotine-containing tobacco products.[2]

In light of this apparent double-edged sword, the agency is seeking feedback to inform its rule-making initiative. Accordingly, the present study focuses on the flaws in the FDA's framing of the problem. It then sets out the challenges the FDA will face to show that any proposed rule directed at flavors in non-combustible tobacco/nicotine products is "appropriate for the protection of public health," as required by the Tobacco Control Act. On the contrary, the unintended consequences that arise from ill-conceived rule-making designed to reduce the attractiveness of alternatives to smoking have their own harmful impacts—on both young people and adults.

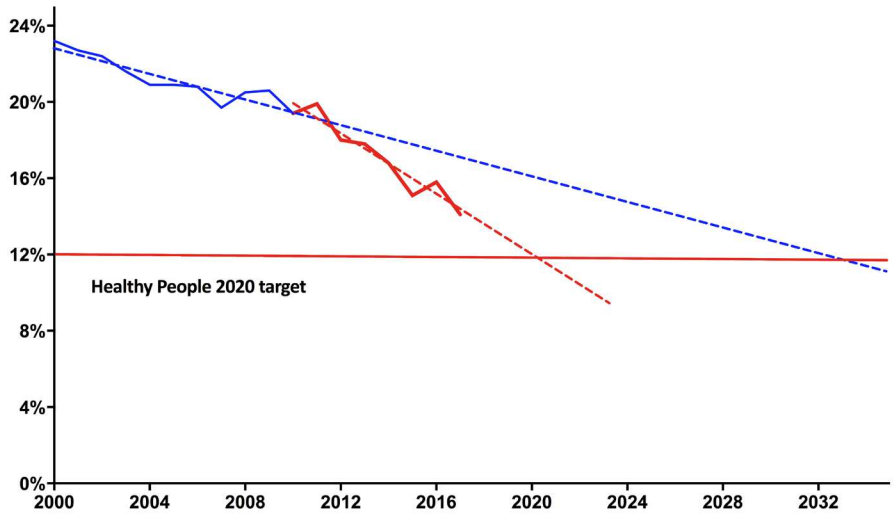
This is because to the extent that flavors contribute to the appeal that causes smokers or potential smokers to switch to vaping instead, the flavors themselves actually provide a public health *benefit*. Accordingly, the FDA does a disservice to the possibility of efficacious rulemaking when it frames the flavor issue as a trade-off between adult benefits and adolescent harms.

On the contrary, it is more likely than not that vaping is net beneficial to youth, as regular youth vaping is highly concentrated in current, former and potential smokers. Thus, where vaping displaces smoking there is a large benefit to smokers. And indeed, even where vaping displaces abstinence, there is only a small detriment to vapers—and this is true among both adolescents and adults.

1. Food and Drug Administration, Regulation of Flavors in Tobacco Products, U.S. Dept. of Health and Human Services, Docket No. FDA-2017-N-6565, March 21, 2018. https://www.gpo.gov/fdsys/pkg/FR-2018-03-21/pdf/2018-05655.pdf.

2. "Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors — including menthol — in tobacco products," Statement from FDA Commissioner," U.S. Food and Drug Administration, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601690.htm.

FIGURE I: TREND IN U.S. ADULT SMOKING PREVALENCE: PRE-2010 VS. POST-2010



SOURCE: National Health Interview Survey, 2017

NOTE: Solid blue line indicates actual prevalence of smoking from 2000-2010, with the linear trend line (dotted). Solid red line indicates the actual prevalence of smoking from 2010-2017, with linear trend line (dotted). The chart demonstrates where the trends would intercept the Healthy People Target.

SITUATION REPORT

Adults

In 2010, the federal government set an objective to reduce adult cigarette smoking to less than 12 percent by 2020.[3] The purpose of the objective was to "reduce illness, disability, and death related to tobacco use and secondhand smoke exposure," which is a clearly expressed harm reduction mandate.[4] In the most recent presentation of its major review of e-cigarettes, the National Academies of Science confirmed that e-cigarette use is likely to prove much less harmful than smoking, noting that: "While e-cigarettes are not without health risks, they are likely to be far less harmful than combustible tobacco cigarettes." [5] This conclusion aligns with the carefully expressed assessment of relative risk made by the Royal College of Physicians of London:

> Although it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products and may well be substantially lower than this figure.[6]

Further, on the basis of the trend in the present decade, which is a substantial improvement on the last one, the 2020 Healthy People target is proceeding well and is on track to be met.[7]

However, the present decade also corresponds to the rise of vaping in the United States, which by 2016 had reached 3.2% of adults or 8 million Americans.[8] Although we cannot know exactly to what extent the uptake of vaping by adults has *caused* the sharp improvement in the rate of decline shown in the chart, four recently published studies that use large, national-U.S. datasets suggest that e-cigarettes are associated

3. Office of Disease Prevention and Health Promotion, "Healthy People 2020," U.S. Department of Health and Human Services, 2010. https://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use. Hereinafter referred to as "Healthy People target."

4. The target is not pre-occupied with nicotine *per se* but rather disease outcomes that arise from its use.

5. "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/reports/2018/public-health-consequences-of-e-cigarettes.aspx.

6. Tobacco Advisory Group, "Nicotine without smoke: tobacco harm reduction," Royal College of Physicians, 2016. p. 87. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0.

7. National Center for Health Statistics, "Prevalence of current cigarette smoking among adults aged 18 and over: United States, 1997–September 2017," *National Health Interview Survey*, 1997–2017, Figure 8.1, 2018. https://www.cdc.gov/nchs/nhis/releases/released201803.htm#8.

8. Centers for Disease Control and Prevention, "Percentage of Adults Who Ever Used an E-cigarette and Percentage Who Currently Use E-cigarettes, by Age Group — National Health Interview Survey, United States, 2016" *Morbidity and Mortality Weekly Report* 66:892 (2017). http://dx.doi.org/10.15585/mmwr.mm6633a6.

with smoking cessation.[9] Equally, claims that e-cigarettes may somehow increase smoking by reducing smoking cessation have been carefully analyzed and dismissed; an independent review team ultimately concluded that e-cigarettes are used to reduce smoking and harms not to increase them.[10] In fact, the situation regarding adult vaping is highly positive. Smoking is falling at a rapid rate and smokers are turning to vaping as a common means to quit. Thus far, no significant health effects or harms have been found, and the appeal of these products is opening a smoking cessation strategy to many smokers who would not otherwise wish to quit with other Nicotine Replacement Therapies (NRTs), pharmacotherapy or counseling.

Adolescents

There has been much concern about the rise in youth vaping. However, some care is required to properly understand what is happening with youth nicotine use. And, particularly with respect to rule-making about flavors, four characteristics of youth e-cigarette use are relevant:

Most youth vaping is occasional or experimental use.[11] In 2014, the National Youth Tobacco Survey found that almost half (45%) of those counted as vaping were doing it an average one to two days per month and 74 percent vaped less than ten days per month. Less than 10 percent of those vaping were doing it daily.[12]

Youth vaping, and especially regular vaping, is highly concentrated among those who smoke or have smoked. In the 2015 National Youth Tobacco Survey, past-30-day-e-cigarette use was reported by 54.5 percent of current smokers, 26.5 percent of former smokers and only 4.6 percent of never smokers.[13] A similar review of the same dataset found that less than 0.1 percent of never smokers used e-cigarettes on ten or more days in the past month.[14]

Most youth vaping is self-reported to be without nicotine. According to an analysis based on findings from the *Monitoring the Future* survey: "Among students who had ever used a vaporiser, 65–66% last used 'just flavoring' [...] Nicotine use came in a distant second, at about 20% in 12th grade."[15] While it is possible that there is misreporting because young people do not always know what it is in the products, it is likely that much adolescent vaping behavior falls outside the definition of "tobacco use." If this is the case, it is inappropriately included in tobacco-use statistics and falls outside the jurisdiction of the Tobacco Control Act and the Food and Drug Administration.

There has been a continuing rapid decline in teenage smoking. The most problematic behavior—combustible cigarette use—is declining and it is possible that youth vaping has played a role in this. Between 2011 and 2016, according to the National Youth Tobacco Survey report, "a nonlinear decrease occurred in current use of any combustible tobacco product (21.8% to 13.8%)."[16] This demonstrates that although the problem of youth vaping is frequently portrayed in eye-catching headline statistics, it is actually smaller than it first appears. This is because much vaping is occasional and without nicotine. It is also more complicated than it first appears because use, and especially regular use, is concentrated among smokers or former smokers where it may actually be substituting for smoking or *helping young people to quit*, as it appears to do for adults.

Despite such facts, Dr. Scott Gottlieb has proclaimed that: "No child should use any tobacco products, including e-cigarettes."[17] However, in effect, such a stance absolves the FDA of any interest in, or responsibility for, what happens to

9. See, e.g., Shu-Hong Zhu et al., "E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys," *British Medical Journal* (2017) p. 358. http://www.bmj.com/content/358/bmj.j3262; Daniel P Giovenco et al., "Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers," *Addiction Behavior* 76: (2018) pp. 129–34. http://www.sciencedirect.com/science/article/pii/S0306460317302915; Su Hyun Park et al., "Characteristics of Adults Who Switched From Cigarette Smoking to E-cigarettes," *American Journal of Preventative Medicine* 53:5 (2017) pp. 652–60. https://www.ajpmonline.org/article/S0749-3797(17)30363-X/fulltext; David T. Levy et al., "The Relationship of E-Cigarette Use to Cigarette Quit Attempts and Cessation: Insights From a Large, Nationally Representative U.S. Survey," *Nicotine and Tobacco Research* (2017). https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntx166/4096490?redirectedFrom=fulltext.

10. See, e.g., Andrea C. Villanti et al., "How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor," *Addiction* 113:3 (2017), pp. 391-404. http://onlinelibrary.wiley.com/doi/10.1111/add.14020/abstract.

11. This is captured by the standard measure of prevalence (use of a product at least once in the last 30 days).

12. Linda J. Neff et al., "Table 35: Frequency of Tobacco Use Among Middle and High School Students--United States, 2014," *Morbidity and Mortality Weekly Report* 64 (2015), pp. 1061–65. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6438a1.htm.

13. Konstantinos E. Farsalinos et al., "Frequency of Use and Smoking Status of U.S. Adolescent E-Cigarette Users in 2015," *American Journal of Preventive Medicine* 54:6 (2018) pp. 814–20. https://www.ajpmonline.org/article/S0749-3797(18)31626-X/fulltext.

14. Lauren K. Collins et al., "Frequency of youth e-cigarette, tobacco, and poly-use in the United States, 2015: Update to Villanti et al., Frequency of youth e-cigarette and tobacco use patterns in the United States: Measurement precision is critical to inform public health," *Nicotine and Tobacco Research* 19:10 (2017), pp. 1253–54. https://academic.oup.com/ntr/article/19/10/1253/3748287.

15. Richard Miech et al., "What are kids vaping? Results from a national survey of US adolescents," *Tobacco Control* 26:4 (2017), pp. 386–91. http://tobaccocontrol.bmj.com/content/26/4/386.

16. Ahmed Jamal et al., "Tobacco Use Among Middle and High School Students - United States, 2011-2016" *Morbidity and Mortality Weekly Report* 66:23 (2017) pp. 597–603. https://www.cdc.gov/mmwr/volumes/66/wr/mm6623a1.htm.

17. "Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth [...]" https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601690.htm.

young people who do use nicotine products.[18] At no point in its framing narrative does the FDA acknowledge that vaping may provide a beneficial harm reduction effect to young people, which greatly complicates the assessment of the costs and benefits of flavor regulation.

Gateway Effects

There have been persistent attempts to identify a "gateway effect," by which e-cigarette use *causes* a transition to cigarette smoking that would not otherwise have happened. It is, however, difficult to imagine a method that could establish this causal relationship. The same individual characteristics, and family and social circumstances that incline young people to smoke also incline them to vape, so studies find strong *associations* between vaping and smoking; an effect known as "common liability."[19]

The difficulty is to know whether the smoking associated with vaping would have occurred anyway. It is impossible to completely correct for these confounding variables to isolate any effect of the e-cigarette use itself and therefore it is impossible to know whether any observed effect is residual, uncorrected, confounding or an observed gateway effect.[20] Indeed, a recent literature review on relevant studies concluded that: "While research exists to support either side of the argument, we conclude, currently, that youth use of e-cigarettes is unlikely to increase the ranks of future cigarette smokers." [21] Further, in its extensive e-cigarette review, The National Academies of Science noted that longitudinal studies showed individual-level associations between smoking and vaping, but these were contradicted by population-level data:

> Overall, the population-based data broadly show opposing trends in e-cigarette and cigarette use prevalence across time among U.S. youth in recent years and thus do not provide confirmatory evidence of the epidemiologic person-level positive associations of vaping and smoking. [22]

It is also possible that uncorrected confounding may be masking "exit" gateway effects; that is, cases where e-cigarette use actually reduces *or* prohibits smoking that would otherwise have happened. Put simply, neither the transition from smoking to vaping or vaping initiation that may displace smoking has attracted much research interest thus far.

The bottom line, however, is that when the FDA considers a population health test for its rulemaking, it should consider the full range of pathways in nicotine use, including those that are beneficial because they displace smoking and other pathways current adolescents may later take as adults.

CATEGORIZATION CONSIDERATIONS

Many consider that the inclusion of e-cigarettes as tobacco products is misleading and inappropriate. However, currently, e-cigarettes are positioned to be defined as "tobacco products" given the Tobacco Control Act's definition of the same as:

> any product made or derived from tobacco that is intended for human consumption, including any component, part, accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product).[23]

Within this framework, there are three main categories: combustible products, smokeless tobacco products, and tobacco products – often called "other tobacco products," which is used as a catch-all category for nicotine-derived products. Because they cannot be classified as either a cigarette or as a smokeless tobacco product due to the lack of tobacco, by default, e-cigarettes are categorized as a general "tobacco product."

However, there is justification to consider approaches to regulations of flavors based on whether or not there is combustion. Flavored, non-combustible products offer a harm reduction pathway to smokers (or users who would otherwise smoke), and the appeal of such products may thereby create a benefit. No such benefit applies in the case of combustibles – and thus a completely different approach is required to analyze their public health impacts and to define appropriate policy. Put simply, given the pronounced variation in risk and the opportunity for non-combustibles to

18. Mitch Zeller, "An Update on FDA's Comprehensive Plan on Tobacco and Nicotine," E-cigarette Summit, April 30, 2018. https://vimeo.com/album/5155140/video/268310418.

19. See, e.g., Michael M. Vanyukov et al., "Common liability to addiction and 'gateway hypothesis': theoretical, empirical and evolutionary perspective," *Drug and Alcohol Dependence* 123:Suppl 1 (2012), pp. S3-17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3600369; Jean-Francois Etter, "Gateway effects and electronic cigarettes," Addiction (2017). https://www.ncbi.nlm.nih.gov/pubmed/28786147.

20. Carl V. Phillips, "Gateway Effects: Why the Cited Evidence Does Not Support Their Existence for Low-Risk Tobacco Products (and What Evidence Would)," *International Journal of Environmental Research and Public Health* 12 (2015), pp. 5439–64. http://www.mdpi.com/1660-4601/12/5/5439.

21. Lynn T. Kozlowski et al., "Adolescents and e-cigarettes: Objects of concern may appear larger than they are," *Drug and Alcohol Dependence* 174 (2017), pp. 209–14. http://www.sciencedirect.com/science/article/pii/S0376871617300236?showall%3Dtrue%26via%3Dihub.

22. "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/reports/2018/public-health-consequences-of-e-cigarettes.aspx.

23. Family Smoking Prevention and Tobacco Control Act, P.L. 111-31 S101 (a)(rr)(1). https://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf

substantially reduce health risks to people who would otherwise smoke, combustible and non-combustible flavored products should never be lumped together in policy considerations,

QUESTIONS SURROUNDING FLAVORS

At one level, it is obvious that flavors play a role in the use of all vaping products, so it is necessary to define what exactly constitutes a "flavor." Currently, the regulatory framework for flavored cigarettes only excludes characterizing flavors with the exception of menthol. Using a strict definition, "flavor" could be any artificial chemical added to an Electronic Nicotine Delivery System (ENDS) that activates our sensory systems. This raises the question of whether flavor restrictions aimed at ENDS would include those that are not regulated in combustible cigarettes? After all, "unflavored" cigarettes are not *flavorless*, but taste of the thousands of chemicals in tobacco smoke. Thus, every orally consumed tobacco/nicotine product is flavored in one way or another. For this reason, to eliminate flavor, which is an essential component of vaping products, would amount to their prohibition. Such action would run counter to the FDA's new nicotine strategy, which stresses the importance of the availability of low-risk nicotine products as alternatives to combustible cigarettes. It follows, then, that the question is how to identify a subset of flavors, with well-described selection criteria, that present concerns above and beyond simply making vaping products viable.

As Commissioner Gottlieb has stated, he has: "real concerns about kids' use of e-cigarettes [...] especially those products marketed with obviously kid-appealing flavors." [24] But what exactly constitutes such a flavor? Much advocacy focuses on names, such as "Gummy Bear," for example, because some of these trademarked products are thought to be marketed primarily to children. However, whether or not the use of such names constitutes trademark infringement is a matter for private litigation. It does not, however, constitute a regulatory justification.

This is particularly true given that such attempts at childlike branding very likely do not even appeal to the adolescent population at risk. In fact, it may be just as likely that adolescents are concerned with reinforcing their adult identity and thus prefer flavors or branding that reflect adult values.

How, then, should appeal of such flavors be characterized? One option to identify youth-attracting flavors would be to focus on those that have the greatest proportion of sales to younger people. However, unless preferences are uniform across all age bands, there will always be a category that has higher youth uptake. How pronounced should the bias toward youth sales be before the flavor or category becomes a matter of concern? It is likely that adults would use more tobacco flavor, as most adult vapers will be current or former smokers. To account for this, it must be considered how any youth-adult biases in flavor preferences should be assessed (aside from tobacco flavor) and how disproportional youth appeal/use must be to adult appeal/use before a flavor should be considered a concern.

Behavioral Considerations

If flavors are playing a role in changing behavior, it is necessary to both define a harmful risk behavior and consider the possible trade-offs with other objectives, such as adult smoking cessation. We might define adolescent use as harmful but need to consider that regulating reduced-risk products with a zero-tolerance mindset could negatively impact several types of e-cigarette users. And, this group would include adolescents that would otherwise use combustible cigarettes. As previously discussed, data suggests much adolescent e-cigarette use is experimental and occasional and, as such, poses minimal risk. Furthermore, regular e-cigarette use is strongly concentrated in smokers.[25]

While there might be flavors that are more or less attractive to youth, it requires an additional step to show that these flavors exert such a powerful attraction that they cause additional use of a product where there would otherwise be none. But the decision to try vaping could be made for several reasons other than interest in flavor options (e.g., curiosity of a novel product, trying something other than smoking or social bonding). For this reason, the choice of flavor could be a secondary or even lower consideration.

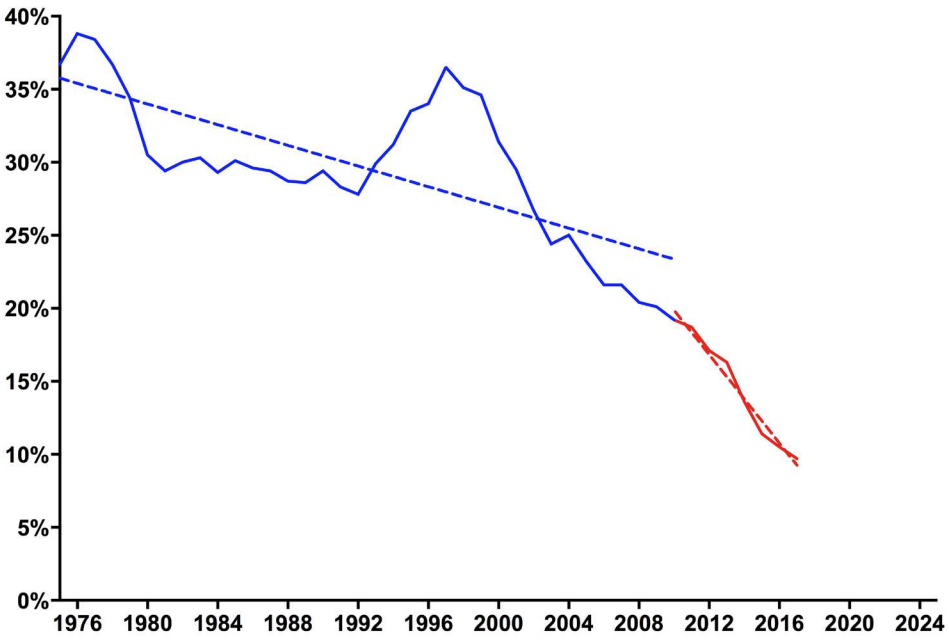
On this account, at least one survey suggests that flavors exert negligible attraction on adolescent non-smokers or e-cigarette users.[26] When nonsmoking teens were asked to rate their interest in using e-cigarettes on a scale of 0-10 and were offered a list of flavors, they reported minimal interest, reaching an average interest score of only 0.41 out of 10. Current adult smokers showed a significantly higher interest in flavor options, with the highest interest level being among those who had tried e-cigarettes.

24. Scott Gottlieb, "Remarks by Commissioner of Food and Drug Administration—Protecting American Families: Comprehensive Approach to Nicotine and Tobacco" U.S. Food and Drug Administration, July 28, 2017. https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm.

25. See, e.g., Andrea C. Villanti et al., "Frequency of youth e-cigarette and tobacco use patterns in the U.S.: Measurement precision is critical to inform public health," *Nicotine and Tobacco Research* 19:11 (November 2017). https://academic.oup.com/ntr/article-abstract/doi/10.1093/ntr/ntw388/2738979/Frequency-of-Youth-E-Cigarette-and-Tobacco-Use.

26. Saul Shiffman et al., "The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes," *Nicotine and Tobacco Research* 17:10 (October 2015), pp. 1255-62. http://www.ncbi.nlm.nih.gov/pubmed/25566782.

FIGURE 2: TREND IN US YOUTH CIGARETTE SMOKING PREVALENCE (12TH GRADE – PAST 30-DAY USE)



SOURCE: Chart created by Clive Bates using data found in Richard Miech et al., "Data Tables: Trends in Prevalence of Use of Cigarettes in Grades 8, 10, and 12," Monitoring the Future: National Adolescent Drug Trends in 2017, December 2017. http://monitoringthefuture.org/data/17data.html.

NOTE: Solid blue line indicates actual prevalence of smoking from 1975-2010, with the linear trend line (dotted). Solid red line indicates the actual prevalence of smoking from 2010-2017, with linear trend line (dotted).

However, a widely cited 2015 analysis of the Population Assessment of Tobacco and Health (PATH) Study data found—perhaps unsurprisingly—that when asked their reasons for using e-cigarettes, 81 percent of adolescent respondents answered positively to "(It) comes in flavors I like," for each tobacco/nicotine product. [27] But an affirmative answer to that question is hardly useful. After all, who would use a product with a flavor they *did not* like? Moreover, the question does not identify specific flavors of concern, so it is merely referring to an integral feature of the product, without which the product would have no appeal. This makes it particularly problematic that this study is frequently cited as justification for intervening to restrict flavors to protect youth.[28]

Interestingly, yet perhaps less cited from the same study is that 79 percent of respondents also affirmatively answered that: "(They) might be less harmful to me than cigarettes."[29] This indicates that in the absence of such an option, they might otherwise use combustible cigarettes.

With respect to whether adolescent uptake of e-cigarettes caused by flavors would be harmful or beneficial to health, if it is assumed that: (1) it is possible to identify flavors that are attractive to adolescents and (2) to show that these flavors change behavior (i.e., increase regular nicotine use or cause initiation), it is then necessary to establish (3) whether the change in behavior is harmful or beneficial. After all, if the behavior change prompted by an appealing flavor diverts a minor from smoking to vaping, we should consider this a benefit.

A reanalysis[30] of the PATH data showed that harm-reduction (to self and others) motivation was also a reason cited for using e-cigarettes by 88 percent of the young people surveyed.[31] Moreover, there was significant overlap in the youth who cited the availability of flavors as a motive for e-cigarette use and also cited harm reduction. The authors, therefore, conclude that: "Teens commonly endorse multiple reasons for using e-cigarettes, rendering the analysis of motives complex."[32] It is quite possible to conclude from this data

27. Bridget K. Ambrose et al., "Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014," *Journal of the American Medical Association* 314:17 (2015), pp. 1871-73. http://jamanetwork.com/journals/jama/fullarticle/2464690.

28. "The Flavor Trap: How Tobacco Companies Are Luring Kids with Candy-Flavored E-Cigarettes and Cigars," Campaign for Tobacco Free Kids and others, 2017. https://www.tobaccofreekids.org/microsites/flavortrap.

29. Ambrose et al. http://jamanetwork.com/journals/jama/fullarticle/2464690.

30. Saul Shiffman et al., "PATH Data: Harm Reduction is Teens' Top Reason for Using e-cigarettes," Society for Research on Nicotine and Tobacco Annual Conference, 2017. https://www.clivebates.com/documents/ShiffmanFlavorsPosterSRNT2017.pdf.

31. Ambrose et al., pp. 1871-73. http://jamanetwork.com/journals/jama/fullarticle/2464690.

32. Shiffman et al. https://www.clivebates.com/documents/ShiffmanFlavorsPosterSRNT2017.pdf.

that palatable or even enjoyable e-cigarette flavors assist with realizing the primary motivation to reduce harm or quit smoking. In other words, that flavors actually contribute to a health *benefit* in youth.

There is also the plausible hypothesis that, whatever the motivation, teenage vaping has played a contributory role in the rapid decline in teenage smoking witnessed in the United States since 2010.[33]

The chart below, based on University of Michigan *Monitoring the Future* data shows the rate of decline since 2010 is four times greater than compared to the long run trend (1975-2010).

This suggests that the enhanced appeal of e-cigarette products may be supporting the displacement of cigarette initiation or consumption with e-cigarette use, which is a much lower risk behavior. Before flavors are denounced as increasing teenage e-cigarette use, it is important to have a sense of what would have happened in the absence of e-cigarettes. Would young vapers simply have smoked? That e-cigarettes can substitute for smoking among youth is supported by convergent results of independent analyses, which show that regulations limiting access to e-cigarettes *increase* youth smoking.[34]

Finally, it is important that the beneficial impacts of flavored, non-combustible products for adults are recognized before any FDA rule is made that might potentially undermine them. A 2017 assessment suggests, for example, that e-cigarettes are likely having a positive (i.e. downward) effect on adult smoking prevalence via an increased smoking cessation rate.[35] Due to the presence of e-cigarettes, it concluded that the substantial increase in e-cigarette use among U.S. adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level.[36] These findings need to be weighed carefully in regulatory policy-making regarding e-cigarettes and in planning tobacco control interventions.

We already know that adults make extensive use of non-tobacco flavors, including fruit and candy, even though these may be considered childish, or even "kid-appealing." One study found that 68 percent of American adult e-cigarette users had used non-tobacco flavors in the past 30 days.[37] Of these, 45 percent had used fruit, 44 percent menthol or mint, and 26 percent candy, chocolate or other sweet flavor.[38] Other evidence suggests that the availability of non-tobacco flavors helps some adult smokers transition completely away from smoking and to the much safer practice vaping. [39] As above, it is likely that benefits to people already smoking, or at high risk of smoking, would greatly outweigh risk from additional uptake of vaping.

Toxicity considerations

Chemicals used to give e-liquids their flavors are usually derived from food flavors, and with the significant exception of tobacco flavor are "generally regarded as safe" (GRAS), although this designation is intended for oral routes of ingestion rather than through inhalation. This has prompted investigation into what chemicals may be designated a risk when added to e-liquids.[40] The direct risk of flavorings or the class of chemical present in e-liquid should be considered but should be managed through technical standards, as required.

Accordingly, when evaluating the toxicity of flavors or any other chemical constituents present in e-liquid the following principles should apply:

Toxicity should be considered within a broader harm reduction framework. *In vitro* models of exposure show that flavoring chemicals can adversely affect cell viability, metabolic activity and inflammatory responses, but that is when compared to the control environment of air. Any exposures should be assessed alongside comparable exposures arising from cigarette smoking.

33. See, e.g., Richard A Miech et al., "Table 2: Trends in Prevalence of Use of Cigarettes in Grades 8, 10, and 12," *Monitoring the Future: national survey results on drug use*, 1975-2016, 2016. http://www.monitoringthefuture.org/data/16data.html; Jamal A, Gentzke A, et al. "Tobacco Use Among Middle and High School Students - United States, 2011-2016," Morbidity and Mortality Weekly Report 66:23 (2017), pp. 597–603. https://www.cdc.gov/mmwr/volumes/66/wr/mm6623a1.htm.

34. See, e.g., Abigail S. Friedman, "How does Electronic Cigarette Access affect Adolescent Smoking? *Journal of Health Economics* 44 (December 2015), pp. 300-08. http://www.ncbi.nlm.nih.gov/pubmed/?term=26583343; and Michael F. Pesko et al., "The influence of electronic cigarette age purchasing restrictions on adolescent tobacco and marijuana use," Preventative Medicine 87 (2016), pp. 207-12. http://www.ncbi.nlm.nih.gov/pubmed/26971853.

35. Shu-Hong Zhu et al., p. 3262. http://www.bmj.com/content/358/bmj.j3262.

36. Ibid.

37. Michele G. Bonhomme et al., "Flavoured non-cigarette tobacco product use among US adults: 2013-2014," *Tobacco Control* 25:Suppl 2 (2016), pp. ii4-ii13. http://tobaccocontrol.bmj.com/content/25/Suppl_2/ii4.

38. Ibid.

39. Konstantinos E. Farsalinos et al., "Impact of flavour variability on electronic cigarette use experience: an internet survey," *International Journal of Environmental Research and Public Health* 10:12 (2013), pp. 7272–82. http://www.mdpi.com/1660-4601/10/12/7272/htm.

40. See, e.g., Zachary T. Bitzer et al., "Effect of flavoring chemicals on free radical formation in electronic cigarette aerosols," *Free Radical Biology and Medicine* 120 (2018), pp. 72-79. https://www.sciencedirect.com/science/article/pii/S0891584917310997; Noel J. Leigh et al., "Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS)," *Tobacco Control* 25:Suppl 2 (2016), pp. ii81-ii87. http://tobaccocontrol.bmj.com/content/25/Suppl_2/ii81; Thivanka Muthumalage et al., "Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine," *Frontiers in Physiology* 8 (2017), p. 1130. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5768608; Skylar Klager et al., "Flavoring Chemicals and Aldehydes in E-Cigarette Emissions," *Environmental Science and Technology* 51:18 (2017), pp. 10806–13. https://pubs.acs.org/doi/abs/10.1021/acs.est.7b02205; Joseph G. Allen et al., "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes," *Environmental Health Perspective* 124:6 (2015), pp. 733-39. https://ehp.niehs.nih.gov/15-10185.

Normal principles of toxicology should apply. The presence of a hazardous agent is not sufficient to justify concern, it must be present at levels that create a material risk. Equipment should be operated in conditions used by human vapers and not in conditions in which the liquid is overheated, for example.

Where human exposures are simulated (for example in mouse studies), these should be realistic proxies and overconfident interpolation from an animal to human impact avoided. An observed effect (for example cell death) in an *in vitro* study may not translate easily to a disease risk.

It is the ethical responsibility of manufacturers to take reasonable measures to make their product as safe as it can be given current technology and toxicology studies. However, limiting constituents that create a flavor profile may be losing sight of the bigger picture and thus may drive people back to a product that is much more harmful.

THE THREAT OF UNINTENDED CONSEQUENCES

As suggested, there may be multiple ways in which an FDA rulemaking initiative designed to make non-combustible products unattractive to youth could cause additional net harm, and thus fail the public health test required by the Tobacco Control Act. The most prevalent are as follows:

- Adult smokers could be deterred from switching to vaping.
- Adult vapers could relapse to smoking if their preferred flavors are no longer available.
- Adolescent vapers could lose interest in vaping and smoke instead.
- Adolescents might no longer use vaping to quit smoking.
- Adolescents who are inclined to smoke or vape could initiate with smoking instead of vaping.
- Adolescents who smoke now may become less likely to switch to vaping as adults.
- Adolescents or adults could turn to DIY flavor-making and start marketing unauthorized products.
- An illicit trade in flavored e-liquids or flavor agents could develop.
- Vaping businesses may be put out of business or otherwise economically harmed, thereby reducing the diversity and competition that drives innovation.
- The FDA's own strategy to reduce nicotine in cigarettes could be undermined because the agency has also made the most promising alternative to smoking (vaping) less appealing.

Though not an exhaustive list, it illustrates the complexity involved in intervening to reduce the appeal of a product that functions as a low-risk alternative to smoking. Therefore, a successful intervention would require crossing the following evidential hurdles:

- That a significant number of young people who have never used nicotine would take up vaping and then (for a material harm to occur) go on to smoke;
- That the cause of this uptake is an e-cigarette flavor or class of flavors (either the flavor itself or the descriptor);
- That these flavors can be identified, classified and an intervention designed to ban them;
- That the intervention does not impede harm-reduction behavior among adults;
- That the intervention does not impede harm reduction behavior among adolescents;
- That the intervention does not trigger different risk behaviors in the target population.

Such a complex set of cumulative evidential hurdles render rulemaking impossible with respect to the behavioral consequences that arise from the appeal of flavors in non-combustible tobacco and nicotine products. This is because these products have the possibility of a harm-reduction effect *at any age*, and product appeal is integral to securing this benefit. Accordingly, any intervention should be confined to toxicological concerns and individual health risks that arise from flavors or other e-liquid ingredients.

REQUIREMENTS OF THE FDA BEFORE RULEMAKING

Whether flavored, reduced-risk products can encourage people to move away from combustible cigarettes – or never start them in the first place – will depend on their availability and appropriate regulation. Since its first issue, the Family Smoking Prevention and Tobacco Control Act prohibits characterizing flavors of cigarettes with the exception of tobacco and menthol flavors.[41] However, these flavor bans currently do not extend to products other than combustible cigarettes, such as cigars, cigarillos, or non-combustible products like smokeless tobacco Electronic Nicotine Delivery Systems. Over the last ten years, the increased prevalence of ENDS use in the United States has prompted the FDA to

41. Family Smoking Prevention and Tobacco Control Act, P.L. 111-31 S907 (a)(1)(A). https://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf.

issue an advanced notice of proposed rulemaking to reexamine "how flavors attract youth to initiate tobacco product use and about whether and how certain flavors may help adult cigarette smokers reduce cigarette use and switch to potentially less harmful products."[42]

For now, it is unclear how the FDA could design interventions that only address harms without compromising the likely benefits. However, several important points are worthy of further discussion if the FDA is to shape reasonable regulations around flavored tobacco products:

- The disposition of harms and benefits attributable to flavors must be known;
- How flavor-related intervention would modify smoking and vaping behavior, as well as the patterns of harm and benefit must be assessed;
- And finally, the FDA would need to be confident that its intervention would reduce rather than increase harm.

What's more, this is exactly the sort of assessment, analysis and modeling for the protection of public health that the agency demands of companies applying to market new tobacco products or make modified-risk claims for products.

The rule-making procedure available to the FDA is governed by section 907 of the Tobacco Control Act. This requires that the Health Secretary is satisfied that the rule is "appropriate for the protection of public health" and has applied the following criteria:

> [T]he Secretary shall consider scientific evidence concerning the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard; the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products. [43]

Therefore, the FDA is required to assess all the possible consequences – both beneficial and adverse – of making rules on flavors. Accordingly, the burden of proof rests with the agency to show that it has made this assessment and has appropriately demonstrated that any rule is appropriate for the protection of public health.

Given the complex landscape of multiple behavioral pathways how will it be possible to assess unintended harmful consequences of a policy designed to reduce the appeal of e-cigarettes? In fact, that question should be applied to several FDA interventions, including the Real Cost campaign, which will now target e-cigarettes[44] or the regulatory burdens created by the deeming rule.[45] Regrettably, the 2016 U.S. Surgeon General's report on youth and e-cigarettes[46] did not engage with the complexities set out above, and therefore cannot provide helpful scientific orientation to policymakers.

Although there is some research that does inform a definition of the problem, we know of none that provides evidence on the likely behavioral response to an intervention designed to limit appeal. It certainly cannot be assumed that all youth who identify a preference for a vaping flavor will stop vaping, so any effect of intervention would be attenuated by switching to different flavors that are not prohibited. If the prohibition was broadly defined, then it is possible the behavioral response would be to use other tobacco products – including those at are more harmful – or to source preferred products via international internet purchasing

CONCLUSION

Harm reduction greatly complicates rulemaking on flavors. While there may be a case to prohibit flavors in some combustible tobacco products where it can be shown they promote smoking initiation or a pathway to regular use in young people, that case is not examined here. And, the equivalent case certainly cannot be made to regulate non-combustible products because they are much-lower-risk and can act as substitutes for smoking, as an alternative to initiating tobacco use with cigarettes or as a means of quitting. Where vaping displaces smoking, there is a benefit to health and this can apply to both adults and adolescents.

Regulators' interventions are prone to unintended consequences. Even if problem flavors or descriptors could be identified and classified, there are further challenges to determine the effect of an intervention such as a prohibition.

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42. Regulation of Flavors in Tobacco Products. https://www.gpo.gov/fdsys/pkg/FR-2018-03-21/pdf/2018-05655.pdf.

43. "Tobacco Product Standards," Federal Food, Drug, and Cosmetic Act, Sec. 907, 2009. http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm263053.htm.

See also, "Tobacco product standards: determinations," Sec. 907(a)(3). https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm263053.htm.

44. U.S. Food and Drug Administration, "FDA to expand public education campaign to focus on prevention of youth e-cigarette use," Press Release, Aug. 8 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm570501.htm.

45. For a description of unintended consequence and limited benefits of the deeming rule, see: "Brief of *amici curiae* of Clive Bates and fifteen others in support of plaintiffs' motion for summary judgement," U.S. District Court for the District of Columbia, Civ. No. 1:16-cv-0878-ABJ, Aug. 5 2016. http://www.clivebates.com/documents/AmicusTHR.pdf.

46. Office of Smoking and Health, "E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General" U.S. Department of Health and Human Services, December 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf.

Young people prone to risk-seeking behavior may react in ways other than simply complying with a ban and stopping vaping. They may use different flavors, take up smoking or adopt other risk behaviors. The intervention could thus be harmful in two ways: first, it could stop beneficial harm reduction from happening and; second, it could trigger behaviors that are riskier than the vaping it seeks to prevent. There is almost no existing evidence that provides insights into the behavioral response to possible FDA interventions, and the FDA itself has provided none.

In non-combustible tobacco and nicotine products, flavor regulation should therefore be confined to toxicity and safety. However, even this approach is fraught with potential unintended consequences. If a flavor is banned because of a trivial toxicological risk, there is a countervailing consequence of lost attractiveness and with that, potentially reduced switching and increased relapse to smoking. The FDA must hold itself to a high standard of evaluation and analysis. Therefore, in bringing forward draft rules (or deciding not to), the agency must correctly frame its analysis and justification, taking account of all possible benefits and harms, including those harms any rule might induce.

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