The scope of FDA's proposed tobacco product standard setting a maximum level of nicotine in tobacco products should be expanded to include all nicotine delivery products that are not authorized by the FDA Center for Drug Evaluation and Research for cessation, including, but not limited to, e-cigarettes and nicotine pouches

Docket No. FDA-2024-N-5471
for "Tobacco Product Standard for Nicotine Yield of Cigarettes
and Certain Other Combusted Tobacco Products."

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September 13, 2025

The FDA should expand the scope of the proposed tobacco product standard for nicotine yield to include all nicotine delivery products that are not authorized by the FDA Center for Drug Evaluation and Research (CDER) for cessation, including, but not limited to, e-cigarettes and nicotine pouches. By excluding these products, the proposed standard is likely to drive not only current smokers, but also current non-smokers, including youth, young adults, and former smokers, to initiate using highly addictive newer nicotine delivery products and promote dual use, which could increase harm beyond just smoking.

FDA specifically requested comment on excluding non-combusted products from the proposed rule (page 5101):

> FDA is not including noncombusted tobacco products, such as ENDS (which include e-cigarettes) and smokeless tobacco products, in the scope of this proposed product standard. FDA's approach in proposing this product standard for cigarettes and certain other combusted tobacco products seeks to protect public health by reducing combusted tobacco product use (and therefore reducing exposure to harmful toxicants created through combustion) while potentially less harmful, noncombusted tobacco products remain available for people who do not quit all tobacco-product use. As such, at this time, FDA is focusing this proposed rule on nicotine levels in cigarettes and certain other combusted products because combusted tobacco products are responsible for the majority of death and disease due to tobacco use. Importantly, this action would also help to prevent people who experiment with cigarettes and cigars (mainly youth) from moving beyond experimentation, developing an addiction to nicotine, and progressing to regular use of combusted tobacco products as a result of that addiction. We request comments, data, and research regarding the proposed scope of this rule.

The Family Smoking Prevention and Tobacco Control Act section 907 requires the FDA to determine that proposed tobacco product standards are "appropriate for the protection of the public health." This involves weighing the potential harms of nicotine-naïve non-users initiating the use of the product and/or current users changing their usage in ways that cause increased harm, against any potential benefits of current users completely stopping smoking. ***In its proposed rule, FDA did not adequately consider the likelihood that non-users, especially nicotine-naïve youth and young adults, will be driven to using newer nicotine delivery products, including e-cigarettes and nicotine pouches, start consuming high levels of nicotine, and thus become addicted to nicotine products which can create substantial health harms that they otherwise would have not been exposed to, or that initiation with these newer nicotine delivery products will lead to subsequent smoking or dual use.***

E-cigarettes should be included in the nicotine product standard

As of 2024, e-cigarettes were the most popular tobacco product among youth in the US, with 3,870,000 (14.0 %) middle and high school students using e-cigarettes.[1] E-cigarettes are available in hundreds of flavors attractive to children[2],[3],[4] and are available in nicotine levels as high as a pack of cigarettes in a single pod,[5] making them extremely addictive.[6],[7] A study of national sales data found that between January 2017 and March 2022, the monthly average nicotine strength of disposable e-cigarettes increased substantially and has exceeded prefilled pods since May 2020. E-cigarettes with menthol flavor and youth-appealing flavors, like fruit, also had sharp increases in monthly average nicotine strength.[8] Both the nicotine concentration and size of e-cigarette vaping devices increased, while prices fell between 2017 and 2022,

[1] Jamal A, Park-Lee E, Birdsey J, et al. Tobacco Product Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:917–924. DOI: http://dx.doi.org/10.15585/mmwr.mm7341a2

[2] Zhu S, Sun JY, Bonnevie E*, et al*. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco Control* 2014;**23:**iii3-iii9.

[3] Ali FR, Seidenberg AB, Crane E, Seaman E, Tynan MA, Marynak K. E-cigarette Unit Sales by Product and Flavor Type, and Top-Selling Brands, United States, 2020–2022. MMWR Morb Mortal Wkly Rep 2023;72:672–677. DOI: http://dx.doi.org/10.15585/mmwr.mm7225a1

[4] Monitoring E-Cigarette Trends in the United States: Urgent Action Needed to Protect Kids from Flavored E-Cigarettes. CDC Foundation, November 21, 2024. https://tobaccomonitoring.org/wp-content/uploads/2024/11/2024MonitoringE-CigaretteTrendsUS-1.pdf.

[5] Prochaska JJ, Vogel EA, Benowitz N. Nicotine delivery and cigarette equivalents from vaping a JUULpod. Tob Control. 2022 Aug;31(e1):e88-e93. doi: 10.1136/tobaccocontrol-2020-056367. Epub 2021 Mar 24. PMID: 33762429; PMCID: PMC8460696.

[6] Cho YJ, Mehta T, Hinton A, et al. E-Cigarette Nicotine Delivery Among Young Adults by Nicotine Form, Concentration, and Flavor: A Crossover Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(8):e2426702. doi:10.1001/jamanetworkopen.2024.26702.

[7] Falarowski, C., Pieper, E., Rabenstein, A. *et al.* Disposable e-cigarettes and their nicotine delivery, usage pattern, and subjective effects in occasionally smoking adults. *Sci Rep* **15**, 16270 (2025). https://doi.org/10.1038/s41598-025-97491-5

[8] Xu Wang, Ramesh Ghimire, Sundar S Shrestha, Mateusz Borowiecki, Sherry Emery, Katrina F Trivers, Trends in Nicotine Strength in Electronic Cigarettes Sold in the United States by Flavor, Product Type, and Manufacturer, 2017–2022, *Nicotine & Tobacco Research*, Volume 25, Issue 7, July 2023, Pages 1355–1360, https://doi.org/10.1093/ntr/ntad033

facilitating increasing nicotine consumption.[9],[10] A new study published in 2025 of the national Monitoring the Future data found in 2024, most US youths with past-30-day vaping reported using e-cigarettes with very high nicotine concentrations or not knowing the concentration. The study found dose-response associations of nicotine concentration with frequent, chronic vaping and poly-tobacco use, and youths who vaped ultrahigh (≥6%) vs very high (5%) nicotine e-cigarettes had incrementally increased risk of using various nicotine products and frequent, chronic vaping patterns.[11]

Providing e-cigarettes to smokers in the real world creates more dual users than smokers who "completely switch" from cigarettes to e-cigarettes.[12] Dual use is associated with higher risks than just smoking.[13] Consistent with earlier RCTs conducted in a clinical environment, this study found a statistically significant increase in the odds of no longer smoking cigarettes among the people randomized to receive free e-cigarettes compared to the people randomized to receive no product: OR 1.8 (95% confidence interval 1.0-2.2). In absolute terms, at 6 months, 14% of the smokers given free e-cigarettes had stopped smoking cigarettes compared to 8% of the control group.[14] Thus, for every 100 people given free e-cigarettes, 6 more stopped smoking cigarettes than would have quit anyway, thanks to the e-cigarettes. However, as shown in all the earlier studies, these "stoppers" included "switchers" who stopped smoking cigarettes but were consuming e-cigarettes and "quitters" who had stopped smoking cigarettes without continuing to consume nicotine from e-cigarettes. Considering *any* nicotine use, there was no significant difference in having quit (stopped using nicotine: 8% of e-cig group vs 6% of control group; p=0.510).

The results for dual use were even more important. At 6 months, 45% of the people who received e-cigarettes were dual users compared to just 11% of the control group (OR 6.8, 95% CI 4.2-10.9, p<0.001). In other words, ***for every person who stopped smoking cigarettes (including switchers who continued using e-cigarettes and quitters who did not smoke cigarettes or use e-cigarettes) in the group that had been provided e-cigarettes, 2.7 smokers became dual users. This compares with 1.8 in the control group. This difference is even more pronounced for***

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[9] Diaz MC, Silver NA, Bertrand A*, et al*. Bigger, stronger and cheaper: growth in e-cigarette market driven by disposable devices with more e-liquid, higher nicotine concentration and declining prices. *Tobacco Control* 2025;**34:**65-70.

[10] Monitoring E-Cigarette Trends in the United States: Urgent Action Needed to Protect Kids from Flavored E-Cigarettes. CDC Foundation, November 21, 2024. https://tobaccomonitoring.org/wp-content/uploads/2024/11/2024MonitoringE-CigaretteTrendsUS-1.pdf.

[11] Cho J, Miech RA, Harlow AF, et al. Nicotine Concentration of E-Cigarettes Used by Youths. *JAMA Netw Open.* 2025;8(3):e252215. doi:10.1001/jamanetworkopen.2025.2215

[12] Hanewinkel R, Glantz SA. Clinical trial shows that giving smokers free e-cigarettes creates more dual users than switchers or quitters. EClinicalMedicine. 2024 Feb 1;68:102452. doi: 10.1016/j.eclinm.2024.102452. PMID: 38333538; PMCID: PMC10850401.

[13] Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid. 2024 Mar;3(3):EVIDoa2300229. doi: 10.1056/EVIDoa2300229. Epub 2024 Feb 27. PMID: 38411454; PMCID: PMC11562742.

[14] Carpenter MJ, Wahlquist AE, Dahne J, Gray KM, Cummings KM, Warren G, Wagener TL, Goniewicz ML, Smith TT. Effect of unguided e-cigarette provision on uptake, use, and smoking cessation among adults who smoke in the USA: a naturalistic, randomised, controlled clinical trial. EClinicalMedicine. 2023 Aug 15;63:102142. doi: 10.1016/j.eclinm.2023.102142. PMID: 37753443; PMCID: PMC10518503.

quitters (stopped smoking and stopped e-cigs): For every quitter in the e-cigarette group, there were 5.7 dual users, compared to 1.8 in the control group.

Therefore, the FDA's approach designed to move conventional cigarette smokers to e-cigarettes is flawed and will not protect public health, because cigarette smokers who end up becoming dual users with e-cigarettes will be exposed to more harm than if they smoked cigarettes alone.

Nicotine pouches

Nicotine pouch use has exploded in the US.[15,16] The 2024 National Youth Tobacco Survey (NYTS) found that an estimated 840,000 (3.5%) of US middle and high school students had ever used nicotine pouches, up from an estimated 580,000 (2.3%) in just the year prior.[17] [18] Among US 9th-12th grade high school students, the prevalence of past-30-day use of nicotine pouches increased by 40% in just one year, from 1.5% (1.0–2.1) in 2023 to 2.4% (2.0–2.9) in 2024. The 2024 prevalence estimates reported in NYTS likely underestimate the actual prevalence rate today among US youth, particularly among older high school students.

Analysis of Monitoring the Future data for 10th and 12th graders showed that between 2023 to 2024, exclusive nicotine pouch and dual use of pouches plus e-cigarettes increased significantly. Between 2023 and 2024, the prevalence of nicotine pouch use among 10th and 12th graders roughly doubled for lifetime use (2.3% to 4.0%), past-12-month use (1.7% to 3.2%), and past-30-day use (0.8% to 1.8%), with the prevalence of past-30-day use among 12th graders rising in just one year from 1.4% to 3.4%. Older students were a higher risk of using nicotine pouches. The adjusted risk ratios for nicotine pouch use were significantly higher for 12th graders compared to 10th graders: lifetime 1.48 (95% CI 1.07, 2.04), past 12 months 1.60 (95% CI 1.14, 2.23), and past 30 days 1.65 (1.11, 2.44). The analysis showed that rural students are at particularly high risk of starting to use nicotine pouches. ***The prevalence of nicotine pouch use among students living in rural areas increased rapidly in just one year to high levels across all measures: lifetime 7.5% to 11.2%, past 12 months 7.2% to 9.7%, and past 30 days 4.4% to 7.7%.*** Among students living in rural areas, compared to students living in urban areas, the adjusted risk ratios were significantly higher for all measures: lifetime: 2.26 (95% CI 1.34, 3.80), past 12 months: 2.52 (95% CI 1.19, 4.26), and past 30 days: 3.01 (95% CI 1.70, 5.33). The study also showed that students who aimed to achieve a lower level of education were at higher risk of using nicotine pouches. ***Among students who did not plan to attend a 4-year college, the***

[15] Han D, Harlow AF, Miech RA, et al. Nicotine Pouch and E-Cigarette Use and Co-Use Among US Youths in 2023 and 2024. *JAMA Netw Open.* 2025;8(4):e256739. doi:10.1001/jamanetworkopen.2025.6739.
[16] Nicotine Pouch Data Briefs, April, 2025. CDC Foundation. https://tobaccomonitoring.org/wp-content/uploads/2025/08/Nicotine-Pouch-Brief-4.20.2025.pdf
[17] : Birdsey J, Cornelius M, Jamal A, et al. Tobacco Product Use Among U.S. Middle and High School Students — National Youth Tobacco Survey, 2023. MMWR Morb Mortal Wkly Rep 2023;72:1173–1182. DOI: http://dx.doi.org/10.15585/mmwr.mm7244a1
[18] Jamal A, Park-Lee E, Birdsey J, et al. Tobacco Product Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:917–924. DOI: http://dx.doi.org/10.15585/mmwr.mm7341a2

prevalence of nicotine pouch use increased rapidly for all measures: lifetime 5.4% to 8.0%, past 12 months 3.9% to 6.9%, past 30 days: 2.5% to 3.9%.[19]

Children and teens are particularly susceptible to initiating use of nicotine pouches because these products are easy to hide. Nicotine pouches are made with many enticing fruity and minty/mentholated flavors, making them especially attractive to youth. Of particular concern, nicotine pouches are available in nicotine levels as high as 47.5 mg/pouch, with nicotine delivery comparable to other tobacco products, making them extremely addictive.[20] [21]

In 2023, Belgium banned the sale of nicotine pouches based on concerns of youth uptake of nicotine pouches, followed in 2025 by the Netherlands and the State of South Australia.

Adolescents using low-nicotine cigarettes are likely to seek alternative nicotine sources, so including other nicotine products in the FDA standard is important.[22]

Conclusion

The proposed product standard that would establish a maximum nicotine level of 0.7 mg/g in conventional cigarettes and certain other combustible tobacco products, but set no limit on the nicotine levels newer nicotine delivery products that are not authorized by the FDA Center for Drug Evaluation and Research (CDER) for cessation, including, but not limited to, e-cigarettes and nicotine pouches level will likely increase demand for these highly addictive youth-appealing products. FDA accepts this likelihood on the *assumption* that there will be a reduction in overall public harm. ***As discussed above, there is direct evidence contradicting this assumption for e-cigarettes, and as discussed in our comment on FDA's proposal to exempt heated tobacco products (HTPs) from the proposed standard[23] (and appended to this comment by reference), there is direct evidence that this assumption is not correct for HTPs.***

The likelihood of increased youth and young adult initiation and promotion of relapse to smoking among adults is particularly concerning. ***A product standard that reduces the nicotine***

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[19] Han D, Harlow AF, Miech RA, et al. Nicotine Pouch and E-Cigarette Use and Co-Use Among US Youths in 2023 and 2024. JAMA Netw Open. 2025;8(4):e256739. doi:10.1001/jamanetworkopen.2025.6739.

[20] Felicione NJ, Ozga JE, Eversole A, Hart JL, Tackett A, Hrywna M, Halquist M, Stanton CA. Oral Nicotine Pouches: Rising Popularity and State of the Science. Public Health Rep. 2025 Apr 28:333549251313668. doi: 10.1177/00333549251313668. Epub ahead of print. PMID: 40293136; PMCID: PMC12037535.

[21] Mallock-Ohnesorg N, Rabenstein A, Stoll Y, Gertzen M, Rieder B, Malke S, Burgmann N, Laux P, Pieper E, Schulz T, Franzen K, Luch A, Rüther T. Small pouches, but high nicotine doses-nicotine delivery and acute effects after use of tobacco-free nicotine pouches. Front Pharmacol. 2024 May 22;15:1392027. doi: 10.3389/fphar.2024.1392027. PMID: 38841367; PMCID: PMC11150668.

[22] Cassidy RN, Tidey JW, Jackson KM, Cioe PA, Murphy SE, Krishnan-Sarin S, Hatsukami D, Colby SM. The Impact of Reducing Nicotine Content on Adolescent Cigarette Smoking and Nicotine Exposure: Results From a Randomized Controlled Trial. Nicotine Tob Res. 2023 Apr 6;25(5):918-927. doi: 10.1093/ntr/ntac279. PMID: 36482794; PMCID: PMC10077938.

[23] Ling P, Glantz SA, Lempert L. Apollonio DE, Vijayaraghavan M. Pravosud V, Benowitz N, Max W, Bialous S, Silver LD, Leutwyler H, Hall S, Mock J, Tsoh J, Halpern-Felsher B, Yerger V, Springer M, Chaffee BW. FDA's proposed tobacco product standard setting a maximum level of nicotine in tobacco products will help prevent youth from becoming addicted to conventional cigarettes, help adult smokers quit, and will reduce tobacco-related diseases and deaths, Docket No. FDA-2024-N-5471 for "Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products." September 13, 2025.

level in these newer nicotine delivery products that are not authorized by the FDA CDER for cessation will help deter tobacco companies from using the loophole to expand consumers' use of nicotine products and deter cessation.

The FDA should not exclude newer nicotine delivery products that are not authorized by the FDA CDER for cessation, including e-cigarettes and nicotine pouches, from maximum nicotine level standards. The FDA should, instead, establish maximum levels of nicotine for newer nicotine delivery products that are at parity with the maximum levels of nicotine the FDA establishes for conventional cigarettes.

If, at some point in the future, there is compelling evidence that allowing higher levels of nicotine in e-cigarettes, nicotine pouches, and other newer nicotine delivery products that are not authorized by the FDA CDER for cessation will not result in youth use and is appropriate for the protection of public health, the FDA could consider amending the standard.

FDA's proposed tobacco product standard setting a maximum level of nicotine in tobacco products will help prevent youth from becoming addicted to conventional cigarettes, help adult smokers quit, and will reduce tobacco-related diseases and deaths

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and Certain Other Combusted Tobacco Products."

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1. We enthusiastically support FDA's proposed tobacco product standard that would regulate nicotine yield by establishing a maximum nicotine level in tobacco products.

We enthusiastically support the FDA's proposed rule setting the maximum level of nicotine in conventional cigarettes and other combusted tobacco products at 0.7 mg/g in a single step. This rule would reduce nicotine in combustible tobacco products to non-addictive levels, advancing a policy first proposed in July 2017 during the first Trump Administration[1] and endorsed by scientists, medical experts, and public health advocates since the implementation of the Family Smoking Prevention and Tobacco Control Act (TCA) in 2009.

2. FDA's proposed standard would protect public health by limiting the addictiveness of toxic tobacco products.

The Family Smoking Prevention and Tobacco Control Act section 907 gives the FDA the authority to implement a tobacco product standard that reduces nicotine to non-addictive levels if the proposed regulation meets the standard that it is "appropriate for the protection of the public health." To meet this standard, the FDA must demonstrate the risks and benefits to the entire population, including the likelihood that non-users, particularly youth, will start using tobacco products, and that current users will change their behavior—whether by

[1] Protecting American Families: Comprehensive Approach to Nicotine and Tobacco, Remarks by Scott Gottlieb, MD, Commission, Food and Drug Administration, July 28, 2017. Available: https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017

stopping, reducing, or increasing their usage of tobacco products in ways that may cause greater harm. Additionally, to set a standard requiring the reduction of a constituent (such as nicotine), the FDA must demonstrate that the proposed standard will reduce or eliminate the risk of illness or injury.

In the preamble to its proposed rule, FDA appropriately documents the significant body of scientific evidence demonstrating that reducing the maximum level of nicotine to 0.7 mg of nicotine per gram of total tobacco would protect public health by making it more likely that non-users, including youth, and former users will not initiate tobacco use and that current users will quit. As the FDA explains, regardless of whether the nicotine itself is toxic, it is the nicotine in tobacco products that creates and sustains addiction, and tobacco products have been deliberately designed by tobacco companies to control nicotine delivery in a way that creates and sustains addiction. By setting a maximum level of nicotine permitted in tobacco products, the proposed standard would limit the addictiveness of tobacco products, which are themselves toxic and responsible for 490,000 smoking-attributable deaths each year.[2] FDA clearly met its statutory burden of demonstrating that the proposed standard is appropriate for the protection of the public health.

The UCSF TCORS submitted a comment to the Advance Notice of Proposed Rulemaking (ANPRM) related to a tobacco product standard for nicotine level in July 2018[3] in which we detailed the scientific evidence supporting a reduction in nicotine levels. We attach and incorporate that comment by reference.

3. FDA's proposed standard would help to prevent youth from initiating with and becoming addicted to tobacco products.

Reducing the nicotine yield in tobacco products to minimally or non-addictive levels will prevent youth from becoming addicted. The FDA's own population health model estimates that by the year 2100, the proposed rule would prevent 48 million youth and young adults in the US from starting to smoke, and would lead to approximately 19.5 million people quitting smoking within five years of implementation, thereby averting 1.8 million tobacco-related deaths by 2060, and 4.3 million deaths by the end of the century.[4]

A randomized controlled trial studying the effects of reduced nicotine cigarettes in adolescent smokers found that very low nicotine cigarette use resulted in fewer cigarettes

[2] U.S. Department of Health and Human Services. Eliminating Tobacco-Related Disease and Death: Addressing Disparities—A Report of the Surgeon General: Executive Summary. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2024.
[3] Glantz SA, Benowitz N, Chaffee B, Gotts J, Halpern-Felsher B, Jacob P, Ling PM, Max W, Moazed F, Springer M, St.Helen G, Vogel E, Lempert L. Tobacco Product Standard for Nicotine Level: The FDA Should Set a Nicotine Level to be Achieved in a Single Step for All Combusted Tobacco Products. Docket No. FDA-2017-N-6189. July 12, 2018.
[4] Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products, 90 FR 5032 (January 16, 2025).

smoked per day and was associated with lower levels of craving, suggesting that the proposed reduced standard may result in reduced smoking in adolescent smokers.[5]

4. FDA's proposed standard would help to reduce smoking and protect the health of a wide range of individuals and populations.

Reducing nicotine in conventional cigarettes and other combustible tobacco products to minimally addictive or nonaddictive levels is likely to reduce smoking across a wide range of individuals and populations who are disproportionately impacted by tobacco use,[2,6] including among low-income populations and those with mental health conditions and substance abuse disorders.[7,8,9,10,11]

5. Substantial scientific evidence supports the FDA's proposed nicotine limit of 0.7 mg/g.

Scientific evidence supports the FDA's proposed approach to setting a maximum nicotine content level of 0.7 mg of nicotine per gram of total tobacco because it would reduce nicotine dependence and increase quit attempts and cessation without increasing craving, withdrawal, or compensatory smoking.[7 8 9 10]

6. FDA's proposed immediate reduction approach is supported by significant scientific evidence.

Scientific evidence supports the FDA's proposed immediate nicotine reduction approach to reach the proposed maximum nicotine level, rather than a gradual reduction or stepped-down approach. [4 12 13]

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[5] Cassidy RN, Tidey JW, Jackson KM, Cioe PA, Murphy SE, Krishnan-Sarin S, Hatsukami D, Colby SM. The Impact of Reducing Nicotine Content on Adolescent Cigarette Smoking and Nicotine Exposure: Results From a Randomized Controlled Trial. Nicotine Tob Res. 2023 Apr 6;25(5):918-927. doi: 10.1093/ntr/ntac279. PMID: 36482794; PMCID: PMC10077938.

[6] Tidey JW, Snell LM, Colby SM, Cassidy RN, Denlinger-Apte RL. Effects of very low nicotine content cigarettes on smoking across vulnerable populations. Preventive medicine. 2022 Dec 1;165:107099.

[7] Donny EC, White CM. A review of the evidence on cigarettes with reduced addictiveness potential, *Int J Drug Policy*. 2022;99:103436.

[8] Foulds J, et al. The effects of reduced nicotine content cigarettes on biomarkers of nicotine and toxicant exposure, smoking behavior and psychiatric symptoms in smokers with mood or anxiety disorders: a double-blind randomized trial. *PLoS One*. 2022;1711):e0275522.

[9] Meier E., et al. Immediate switching to reduced nicotine cigarettes in a US-based sample: the impact on cannabis use and related variables at 20 weeks. *Nicotine Tob Res*. 2023;25(5):867-874.

[10] Gaalema DE, et al. Potential effects of nicotine content in cigarettes on use of other substances. *Prev Med*. 2022;165(pt B):107290.

[11] Peters EN, et al., Effect of very low nicotine content cigarettes on alcohol drinking and smoking among adult smokers who are at-risk alcohol drinkers. *Exp Clin Psychopharmacol*. 2023;31(3):733-744.

[12] Li Q, Chen X, Li X, Gorowska M, Li Z, Li Y. The Effects of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Smoking Behavior: An Ecological Momentary Assessment Study. Front Psychiatry. 2022 May 11;13:884605. doi: 10.3389/fpsyt.2022.884605. PMID: 35633808; PMCID: PMC9130591.

[13] EM, Luo X, Jensen J, al'Absi M, Cinciripini PM, Robinson JD, Drobes DJ, McClernon J, Strasser AA, Strayer LG, Vandrey R, Benowitz NL, Donny EC, Hatsukami DK. Smoking abstinence and cessation-related outcomes one

7. FDA should not exempt Heated Tobacco Products (HTPs)

FDA has specifically requested "comments, data, and research regarding the proposal to exclude noncombusted cigarettes (such as HTPs that are cigarettes) from the scope of this proposed rule, including any data that could justify otherwise."[14] The available evidence does not support the exclusion of HTPs. In fact, as detailed below, the available evidence requires that HTPs be included in the rule.

HTPs such as IQOS, which Philip Morris International's own scientists describe as "an electrically heated cigarette smoking system" produce harmful emissions composed of a wide range of chemicals.[15] [16] Although HTPs are promoted by the tobacco companies as being safer because they emit lower concentrations of *some* harmful substances on the FDA's outdated list of Harmful and Potentially Harmful Constituents (HPHC) than conventional cigarettes, HTPs in fact release many other toxic and potentially harmful compounds that are not on the HPHC list at much higher levels than conventional cigarettes.[17]

The current HPHC list was released by the FDA 13 years ago, in 2012. This list contains 93 compounds, mostly carcinogens in conventional cigarette smoke. The FDA proposed updating the HPHC list in 2019 by adding 19 compounds to the list[18] that go beyond carcinogens and reflect important toxins in new products, such as propylene glycol, which is in at least some HTPs. As summarized in a public comment the UCSF TCORS submitted at the time,[19] these additions were well-justified. The FDA should not be using the existing HPHC as a de facto product standard for assessing HTPs.

An August 2025 literature review of 55 current research studies on the health impacts of HTPs found significant effects of HTP use on the cardiovascular system, respiratory diseases,

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month after an immediate versus gradual reduction in nicotine content of cigarettes. Prev Med. 2022 Dec;165(Pt B):107175. doi: 10.1016/j.ypmed.2022.107175. Epub 2022 Jul 20. PMID: 35870575; PMCID: PMC10676511.

[14] Proposed rule, page 5101.

[15] Schorp MK, Tricker AR, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 1: Non-clinical and clinical insights. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S1-S10. doi:10.1016/j.yrtph.2012.08.008

[16] Zenzen V, Diekmann J, Gerstenberg B, Weber S, Wittke S, Schorp MK. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S11-S34. doi:10.1016/j.yrtph.2012.08.004

[17] St.Helen G, Jacob P III, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. TobControl. 2018;27(Suppl1):s30–s36.

[18] Food and Drug Administration. Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions. Posted by the Food and Drug Administration on Aug 5, 2019. https://www.regulations.gov/document/FDA-2012-N-0143-0002.

[19] Lempert LK, St.Helen G, Gotts J, Kozlovich S, Springer M, Halpern-Felsher B, Glantz SA. In addition to the 19 constituents FDA proposes to add to the list of Harmful and Potentially Harmful Constituents, FDA should also add compounds that may be carcinogenic or cause pulmonary or cardiovascular harms when inhaled, especially oils and chemicals and chemical classes found in e-cigarette flavorants, and FDA should use as additional criteria California's Proposition 65 list of carcinogens and reproductive toxicants and the California Air Resources Board's list of Toxicant Air Contaminants. FDA Docket No. FDA-2012-N-0143. October 2, 2019. Regulations.gov tracking number 1k3-9cij-8wgr.

and the reproductive system.[20] Studies on the cardiovascular system found smoking HTPs increased blood pressure, heart rate, platelet clot formations, and an enhanced inflammatory response, often followed by endothelial dysfunction. The studies showed a correlation between HTP smoking and negative effects on lung physiology, human bronchial epithelial cells, acute eosinophilic pneumonia, allergies, and asthma. HTP smoking during pregnancy was associated with health effects on the fetus, newborn, and mothers.

An April 2025 systematic review of available data on the effects of HTP smoking on biomarkers of potential harm and adverse events did not provide a clear indication of the benefits of smoking HTPs compared with smoking conventional cigarettes, even though most of the 40 interventional clinical trials included were industry-affiliated and at high risk of bias.[21]

Of particular concern, studies show that most HTP smokers are dual users. For example, in Italy, where the IQOS HTP has been available since 2014, a May 2025 comprehensive systematic review found that HTPs are especially popular among youth, and more than two-thirds of HTP users are dual users smoking both HTPs and conventional cigarettes.[22]

In Japan, a national survey conducted by the Ministry of Health, Labour, and Welfare showed that dual smoking of conventional cigarettes and HTPs has become a significant problem. In 2023, male among smokers of conventional cigarettes and HTPs ages 20-29, 23.3% reported dual use.[23]

We know that the use of multiple tobacco products does not reduce and may increase harm. An analysis of National Health Interview Survey data linked to the National Death Index compared "exclusive cigarette users," "dual users of cigarettes and cigars/pipes," "dual users of cigarettes and smokeless tobacco," and "poly-users who used cigarettes, cigars/pipes, and smokeless tobacco" and found that smokers of conventional cigarettes who additionally used other tobacco products smoked as many if not more conventional cigarettes per day than exclusive conventional cigarette smokers, and smokers of conventional cigarettes who additionally used other tobacco products had mortality risks that were as high as and sometimes higher than those of exclusive smokers of conventional cigarettes.[24] An analysis of data from 2,679 adult participants from Wave 5 of the Population Assessment on Tobacco and Health Study, including individuals reporting current exclusive smoking of conventional cigarettes (n = 1,913), exclusive e-cigarette use (n = 316), and dual use (n =

[20] Znyk M, Kaleta D. The Health Effects of Heated Tobacco Product Use—A Narrative Review. In Healthcare 2025 Aug 18 (Vol. 13, No. 16, p. 2042). MDPI.
[21] Braznell S, Dance S, Hartmann-Boyce J, Gilmore A. Impact of heated tobacco products on biomarkers of potential harm and adverse events: a systematic review and meta-analysis. Tobacco Control. 2025 Apr 30.
[22] Scala M, Dallera G, Gorini G, Achille J, Havermans A, Neto C, Odone A, Smits L, Zambon A, Lugo A, Gallus S. Patterns of use of heated tobacco products: a comprehensive systematic review. Journal of Epidemiology. 2025 May 5;35(5):213-21.
[23] Japan Ministry of Health, Labour and Welfare (2024) Summary of the National Health and Nutrition Survey Results, page 21. https://www.mhlw.go.jp/content/10900000/001338334.pdf
[24] Kelvin Choi, Maki Inoue-Choi, Timothy S McNeel, Neal D Freedman, Mortality Risks Associated With Dual– and Poly–Tobacco-Product Use in the United States, *American Journal of Epidemiology*, Volume 191, Issue 3, March 2022, Pages 397–401, https://doi.org/10.1093/aje/kwz143

450) found that dual users had higher levels of toxicant exposure than smoking conventional cigarettes alone.[25] A study of HTP smokers and dual users in Hong Kong found that dual users of conventional cigarettes and HTPs smoked fewer conventional cigarettes per day than exclusive smokers of conventional cigarettes, but consumed more tobacco in total.[26] Dual- or poly-use of other tobacco products concurrently with smoking conventional cigarettes is more dangerous than smoking conventional cigarettes alone.[27] [28] [29]

Although HTP smoking is currently not as high among middle and high school students in the US as e-cigarette use, youth trends can change quickly and unexpectedly, as happened with the 2018 youth vaping epidemic driven by JUUL, especially when the tobacco industry adjusts its focus and targets its marketing and promotions towards young people. In any case, the 2024 National Youth Tobacco Survey (NYTS)[30] found that a higher percentage of middle and high school students reported smoking HTPs (1.6%) compared to smoking pipe tobacco (1.5%), yet HTPs are excluded from the scope of the proposed regulation, while pipe tobacco is included.

IQOS HTPs are currently available in the US in two menthol flavors, which may make them more attractive to current menthol smokers who would otherwise quit smoking conventional cigarettes with reduced nicotine levels. Flavored HTP-specific cigarettes produced by Philip Morris International (PMI), British American Tobacco, and Japan Tobacco International for other markets like Japan can be purchased easily by US consumers through the internet, including IQOS-specific Shine Pearl cigarettes that PMI describes as "a bursting flavor with rich and fruity aroma" that have flavor capsules embedded in the filter.

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[25] Zheng Xue, Eva Orr-Souza, Nigar Nargis, Minal Patel, Tyler Nighbor, Nicotine and Toxicant Exposure among Individuals using both Combustible Cigarettes and E-cigarettes Based on Level of Product Use, *Nicotine & Tobacco Research*, Volume 27, Issue 9, September 2025, Pages 1591–1599, https://doi.org/10.1093/ntr/ntaf053

[26] Zhang X, Sun Y, Cheung YTD*, et al*. Cigarettes, heated tobacco products and dual use: exhaled carbon monoxide, saliva cotinine and total tobacco consumed by Hong Kong tobacco users. *Tobacco Control* 2024;**33:**457-463.

[27] Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid. 2024 Mar;3(3):EVIDoa2300229. doi: 10.1056/EVIDoa2300229. Epub 2024 Feb 27. PMID: 38411454; PMCID: PMC11562742.

[28] Pisinger C, Rasmussen SKB. The Health Effects of Real-World Dual Use of Electronic and Conventional Cigarettes versus the Health Effects of Exclusive Smoking of Conventional Cigarettes: A Systematic Review. Int J Environ Res Public Health. 2022 Oct 21;19(20):13687. doi: 10.3390/ijerph192013687. PMID: 36294263; PMCID: PMC9603628.

[29] Coleman SRM, Piper ME, Byron MJ, Bold KW. Dual Use of Combustible Cigarettes and E-cigarettes: a Narrative Review of Current Evidence. Curr Addict Rep. 2022 Dec;9(4):353-362. doi: 10.1007/s40429-022-00448-1. Epub 2022 Oct 17. PMID: 36467719; PMCID: PMC9718538.

[30] Jamal A, Park-Lee E, Birdsey J, et al. Tobacco Product Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:917–924. DOI: http://dx.doi.org/10.15585/mmwr.mm7341a2

Moreover, HTP smoking does not help smokers of conventional cigarettes quit beyond short-term quitting, and HTP smoking does not prevent former smokers of conventional cigarettes from relapsing.[31] [32]

The FDA should not be making policy based on unproven assumptions about smoking HTPs being less harmful than smoking conventional cigarettes, especially when the available reliable scientific evidence is not consistent with those assumptions.

8. FDA should not exempt waterpipe tobacco.

The FDA requested comment on its proposal to exclude waterpipe (Draft rule, page 5101). FDA justifies this decision as follows:

> FDA considered including waterpipe tobacco products within the scope of this proposed product standard; however, the Agency has determined that waterpipe tobacco involves profoundly different use behaviors than combusted cigarettes, which makes it an unlikely substitute for cigarettes. We therefore do not propose including waterpipe tobacco products within the scope of this proposed rule.
>
> Data on frequency of use differentiates waterpipe tobacco from cigarettes. For instance, according to the 2024 NYTS, 0.7 percent of middle and high school students (or approximately 190,000 students) reported using waterpipe tobacco within the previous 30 days, compared with estimates for previous 30-day cigarette use (1.4 percent; 380,000 students) and cigar use (1.2 percent; 330000 students) (Ref. 3). However, waterpipe tobacco is significantly less likely to be smoked daily. In fact, given the relative infrequency of waterpipe use, it is often reported in terms of monthly versus less than monthly use, rather than daily versus non-daily. Data from Waves 1 (2013–2014) and 2 (2014–2015) of the PATH Study indicated that, among adults who used waterpipes in the past year, 77.1 percent reported less than monthly use at Wave 1; by Wave 2, 44.9 percent of these adults continued using waterpipe less than monthly, while 6.4 percent progressed to monthly or more frequent use (Ref. 643). For comparison, 59.1 percent of adults in the 2018 NHIS who smoke cigarettes report daily use (Ref. 644). Wave 3 (2015–2016) PATH Study data also indicate the infrequency of daily waterpipe use: 0.1 percent of youth, 0.3 percent of young adults, and 0 percent of adults 25 and older reported daily waterpipe use (Ref. 645). Comparatively, analysis from Wave 3 of the PATH study found that 0.6 percent of youth, 11.4 percent of young adults, and 15.3 percent of adults older than 25 reported daily cigarette smoking (Ref. 646).
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> FDA acknowledges that the health consequences of waterpipe usage are far from innocuous. People who use waterpipes are exposed to many of the same toxicants as people who smoke cigarettes, and due to the extended duration of each waterpipe session (*i.e.,* approximately 1 hour), waterpipe use may lead to higher toxicant exposure per session than toxicant exposure from one cigarette (Refs. 647 and 648). Thus, people who use waterpipes are likely subject to many of the same severe negative health effects as people who smoke cigarettes (Ref. 649).
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> However, FDA does not anticipate significant migration to waterpipe usage under the proposed product standard. Waterpipes as currently marketed are generally large and require time consuming preparation, leading to an approximate waterpipe smoking session of 1 hour (Ref. 650).

[31] Odani S, Tsuno K, Agaku IT, Tabuchi T. Heated tobacco products do not help smokers quit or prevent relapse: a longitudinal study in Japan. Tobacco Control. 2024 Jul 1;33(4):472-80.

[32] Kim SH, Lee JA, Cho HJ. Association between heated tobacco product use and quitting combustible cigarette smoking among Korean adults. Nicotine and Tobacco Research. 2025 Feb 8:ntaf030.

> The limited accessibility and mobility of waterpipes as generally currently used contribute to their predominant intermittent usage patterns (Ref. 650). FDA assesses that these aspects of waterpipe design would similarly substantially limit their utility as a substitute for cigarettes and other combusted tobacco products that would be subject the proposed product standard, especially as compared to the portability and ease of use of many HTP, ENDS, and other noncombusted tobacco products that are currently legally marketed and not subject to the proposed product standard.

FDA's argument that because of different behaviors associated with waterpipe use, it would be an "unlikely substitute for cigarettes" is not compelling. Hookah lounges are proliferating in the US and are especially popular with young adults, with many jurisdictions that otherwise prohibit smoking in commercial establishments allowing smoking at hookah cafes.

The FDA does not address dual use or how the existence of waterpipes that deliver high levels of nicotine could affect cessation of conventional cigarette smoking or relapse.

Waterpipe tobacco is almost always fruit- or candy-flavored, which would make it an attractive alternative to tobacco-flavored, very low-nicotine cigarettes under the proposed rule. Flavored waterpipe is even available in jurisdictions where other flavored tobacco products are prohibited.[33]

The FDA should not be making policy based on unproven assumptions about smoking waterpipe tobacco being less harmful than smoking conventional cigarettes, especially when the available reliable scientific evidence is not consistent with those assumptions.

9. Conclusion

We strongly support the FDA's proposed standard setting the maximum level of nicotine in cigarettes and other combusted tobacco products at 0.7 mg/g in a single step. FDA's proposed rule limiting nicotine levels to minimally- or non-addictive levels is an important step that will significantly reduce cigarette smoking and initiation and increase cessation, thereby reducing smoking-related death and disease***. The FDA should not exclude HTPs and waterpipe tobacco from maximum nicotine level standards. The FDA should, instead, establish maximum levels of nicotine for HTPs and waterpipe tobacco that are at parity with the maximum levels of nicotine the FDA establishes for conventional cigarettes.***

If, at some point in the future, evidence emerges that allowing higher levels of nicotine in HTPs and/or waterpipe tobacco would not result in youth use and be appropriate for the protection of public health, the FDA could amend the standard.

[33] California Health and Safety Code - HSC § 104559.5.