Center for the Assessment of Tobacco Regulations [CAsToR] TCORS 3.0

September 5, 2025

Center for the Assessment of Tobacco Regulations (CAsToR)
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To: U.S Food and Drug Administration (FDA) Center for Tobacco Products

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

To Whom It May Concern:

The Center for the Assessment of Tobacco Regulations (CAsToR), a research partnership between the University of Michigan, Georgetown University, and Rutgers University, submits this comment in response to the United States Food and Drug Administration (FDA, or the Agency) proposed Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products (Proposed Rule, hereafter referred to 'a nicotine product standard'). CAsToR research provides estimates of the public health effects of a tobacco product standard for very low nicotine content cigarettes (VLNC), as well as evidence of the potential impacts of the FDA's proposed rule on specific populations.

Throughout this statement, the term 'nicotine product standard' refers to a product regulation that limits the level of nicotine in cigarettes and certain combusted tobacco products to a maximum of 0.70 mg of nicotine per gram of tobacco, in alignment with the text of the proposed rule.

CAsToR research supports the immediate implementation of a nicotine product standard to maximize public health benefits to the population.

CAsToR modeling research shows that a nicotine product standard would avert millions of premature deaths.

CAsToR simulation modeling analyses have projected that a nicotine product standard would lead to major reductions in premature mortality, consistent with the FDA's own modeling analyses described in the proposed rule. A recent US population microsimulation modeling study estimated that if a nicotine product standard is implemented by 2027, smoking prevalence would be expected to decrease to <1% by 2040, with 1.7 million (1.3 to 1.7) premature deaths averted through 2100. This reduction translates to 74.7 million life-years gained (LYG) for the US population.[1]

In another study, CAsToR investigators used a macro-simulation model to compare cumulative mortality and life-years saved from 2025-2100 between two nicotine reduction scenarios starting in 2025: immediate and gradual (over 10 years) nicotine reduction to non-addictive levels (consistent with the proposed standard). The results indicated that an immediate reduction enacted in 2025 could avert between 1.2 and 2.3 million premature deaths, corresponding to 19.1 to 39.5 million life-years saved by 2100. In comparison, a gradual nicotine reduction policy would prevent 0.5 to 1.3 million premature deaths and save 7.2 to 20 million life-years over 2025-2100.[2]

While these studies highlight the health gains associated with a future nicotine product standard, a separate CAsToR modeling study has quantified the costs to human life if a nicotine standard is delayed.

CAsToR investigators' research demonstrates that earlier implementation of a nicotine product standard could have averted millions more premature deaths related to cigarette smoking. Cigarette manufacturers have had the technical feasibility to create and market very-low nicotine cigarettes (VLNC) for decades. CAsToR researchers estimated the public health benefits had the cigarette industry implemented a nicotine reduction standard in 1965, 1975, or 1985, starting when companies first had the technical capability to do so. The model projected the effect of a nicotine product standard on smoking attributable deaths (SADs) and life-years lost (LYLs). A standard implemented in 1985 could have averted 16.3 million SADs and 211.5 million LYLs from 1985 to 2084. If implemented ten years earlier in 1975, the total would increase to 18.9 million SADs and 245.4 million LYLs from 1975 to 2074. Yet another decade sooner could have averted 21 million SADs and 272 million LYLs from 1965 to 2064.[3]

Taken together, our work emphasizes the need for immediate action on the proposed rule. Any delays to the implementation of a nicotine product standard would come at great cost to the American people.

Public Health Impacts of a Nicotine Product Standard

A nicotine product standard will directly benefit people with mental health conditions who smoke.

People with mental health conditions have much higher rates of cigarette smoking compared to the general population, driven in part by the bidirectional relationship between smoking and mental health, where smoking increases risk for poor mental health, and poor mental health increases risk for smoking.[4] In recent years, among Americans who continue to smoke, a rising proportion have psychiatric comorbidities. A nicotine standard will drastically reduce smoking in this population, addressing long-standing FDA goals to reduce smoking-related disparities for people with mental health conditions.

Tobacco manufacturers have claimed that the Nicotine Product Standard will harm those with mental health conditions.[5] Existing evidence demonstrates otherwise. Scientific research has debunked widespread misperceptions that smoking cessation harms mental health. A Cochrane systematic review[6] of 106 studies found that smoking cessation does not lead to worse mental health symptoms, and may even improve mental health symptoms.[7] Studies using Mendelian

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[1] Skolnick, Sarah, Andrew Brouwer, Charlene Cheng, and Jamie Tam. 2025. "Health, Equity, and Economic Impacts of a Nicotine Product Standard in the United States for People With and Without Major Depression." *medRxiv*. https://doi.org/10.1101/2025.07.10.25331302.

[2] Thuy T.T. Le and David Mendez. "The Impact on US Mortality of Reducing Nicotine in Cigarettes to Non-addictive Levels Gradually versus Instantaneously." [in preparation] Currently available at https://drive.google.com/drive/folders/125f4bAKeJQBqCiiQFJHtTP766x9_-l7T?usp=sharing.

[3] Levy, David T., K. Michael Cummings, Bryan W. Heckman, Yameng Li, Zhe Yuan, Tracy T. Smith, and Rafael Meza. "The Public Health Gains Had Cigarette Companies Chosen to Sell Very Low Nicotine Cigarettes." *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco* 23, no. 3 (February 16, 2021): 438–46. https://doi.org/10.1093/ntr/ntaa128.

[4] Fluharty, Meg, Amy E. Taylor, Meryem Grabski, and Marcus R. Munafò. 2017. "The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review." *Nicotine & Tobacco Research* 19 (1): 3–13. https://doi.org/10.1093/ntr/ntw140.

[5] Murillo, Jose Luis. Public Comment from Altria on Advance Notice of Proposed Rulemaking on Tobacco Product Standard for Nicotine Level of Certain Tobacco Products (Docket No. FDA-2017-N-6189). Comment ID: FDA-2017-N-6189-7074. Published online June 16, 2018. Accessed May 26, 2025. https://www.regulations.gov/comment/FDA-2017-N-6189-7074; Ogden, Michael W. Public Comment from RAI Services Company on Proposed Rule 'Tobacco Product Standard for Nicotine Level of Combusted Cigarettes' (Docket No. FDA-2017-N-6189). Comment ID: FDA-2017-N-6189-6710. Published online June 13, 2018. Accessed May 26, 2025. https://www.regulations.gov/comment/FDA-2017-N-6189-6710.

[6] Taylor, Gemma MJ, Nicola Lindson, Amanda Farley, Andrea Leinberger-Jabari, Katherine Sawyer, Rebecca te Water Naudé, Annika Theodoulou, Naomi King, Chloe Burke, and Paul Aveyard. 2021. "Smoking Cessation for Improving Mental Health." *Cochrane Database of Systematic Reviews*. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013522.pub2/full.

[7] Wu, Angela Difeng, Min Gao, Paul Aveyard, and Gemma Taylor. 2023. "Smoking Cessation and Changes in Anxiety and Depression in Adults With and Without Psychiatric Disorders." *JAMA Network Open* 6 (5): e2316111. https://doi.org/10.1001/jamanetworkopen.2023.16111.

randomization methods–which leverage genetic randomization to make causal inferences–have demonstrated that smoking causes major depressive disorder.[8] Because smoking harms mental health, it follows that a nicotine product standard to reduce population smoking may well have mental health benefits.

Research led by CAsToR investigators further supports this claim. They conducted a simulation modeling analysis to evaluate the potential impact of a nicotine product standard on people with and without major depression. This model includes cigarette and e-cigarette use, and it explicitly accounts for the bidirectional and causal relationship between smoking and major depression.[9] If implemented in 2027, a nicotine product standard would result in 8.5 million fewer cases of depression by 2100, and ~200,000 premature deaths averted among people with major depression.

A nicotine product standard will improve maternal and infant health outcomes.

Smoking during pregnancy markedly increases adverse outcomes, including infant death: infants born to mothers who smoke face more than three times the risk of death compared with infants of non-smokers.[10] Smoking also increases the risks of miscarriage, placental abruption, and placenta previa.[11] These placental complications routinely incur approximately $17,000–$43,000 per case, and infant deaths are associated with median hospital costs of roughly $77,000.

A nicotine product standard would deliver immediate, measurable benefits for reproductive and infant health while averting costly, traumatic events for families and the healthcare system. CAsToR investigators developed the Smoking, E-Cigarette Use, and Pregnancy (SEP) microsimulation model to project maternal and infant outcomes in the U.S. population. If a nicotine standard takes effect in 2027, the model estimates ~63,000 infant deaths prevented by

[8] Burke, Chloe, Gemma Taylor, Tom P. Freeman, et al. 2025. “Disentangling the Effects of Nicotine versus Non-Nicotine Constituents of Tobacco Smoke on Major Depressive Disorder: A Multivariable Mendelian Randomisation Study.” *Addiction* 120 (6): 1240–52. https://doi.org/10.1111/add.70001; Burke, Chloe, Tom P. Freeman, Hannah Sallis, Robyn E. Wootton, and Gemma MJ Taylor. 2024. “Examining the Independent Roles of Cannabis Use and Tobacco Use in Depression Risk: A Multivariable Mendelian Randomisation Study.” Preprint, *medRxiv*, July 17. https://doi.org/10.1101/2024.07.17.24310564.
[9] Skolnick, Sarah, Andrew Brouwer, Charlene Cheng, and Jamie Tam. 2025. “Health, Equity, and Economic Impacts of a Nicotine Product Standard in the United States for People With and Without Major Depression.” *medRxiv*. https://doi.org/10.1101/2025.07.10.25331302.
[10] Sun, Jiahong, Xue Liu, Min Zhao, Costan G. Magnussen, and Bo Xi. 2023. “Dose-Response Association between Maternal Smoking during Pregnancy and the Risk of Infant Death: A Nationwide, Population-Based, Retrospective Cohort Study.” *EClinicalMedicine.* https://doi.org/10.1016/j.eclinm.2023.101858.
[11] Pineles, Beth L., Edward Park, and Jonathan M. Samet. 2014. “Systematic Review and Meta-Analysis of Miscarriage and Maternal Exposure to Tobacco Smoke During Pregnancy.” *American Journal of Epidemiology*. https://doi.org/10.1093/aje/kwt334.

2100 and ~$4.9 billion in direct healthcare savings from avoided pregnancy-related morbidity. By reducing the addictiveness of smoking among females of reproductive age, the standard would cut nicotine addiction before and during pregnancy, improving pregnancy outcomes. Along with CAsToR's broader modeling of impacts on mortality which shows substantial near-term population health gains, these findings support finalizing the standard.

Multiple strands of evidence refute claims about 'compensatory' smoking.

Previous debates have included arguments that a nicotine reduction standard could lead to 'compensatory' smoking, i.e., someone smoking more than they would have otherwise in an attempt to self-titrate their nicotine content.

Evidence does not support this argument for two reasons. First, trials have already demonstrated that compensatory smoking is unlikely.[12] Second, diversification in the tobacco and nicotine product market has substantially changed the context. In particular, compensatory smoking is highly unlikely because many lower-risk alternative nicotine delivery system substitutes are already available on the market.

Randomized Controlled Trials have demonstrated that, in people who smoke, moving to alternative nicotine delivery systems, including traditional nicotine replacement products (available over the counter and by prescription in the US) and electronic cigarettes with nicotine (available as consumer products; FDA has authorized marketing of these products on the basis of being appropriate for the protection of public health) can help people quit smoking and reduce exposure to harmful substances. There is no evidence from these trials that nicotine

[12] Benowitz, Neal L, Eric C Donny, Kathryn C Edwards, Dorothy K Hatsukami, and Tracy T Smith. 2019. "The Role of Compensation in Nicotine Reduction." *Nicotine & Tobacco Research* 21 (Supplement_1): S16–18. https://doi.org/10.1093/ntr/ntz120; Smith, Tracy T., Joseph S. Koopmeiners, Dorothy K. Hatsukami, Katelyn M. Tessier, Neal L. Benowitz, Sharon E. Murphy, Andrew A. Strasser, et al. 2020. "Mouth-Level Nicotine Intake Estimates from Discarded Filter Butts to Examine Compensatory Smoking in Low Nicotine Cigarettes." *Cancer Epidemiology, Biomarkers & Prevention* 29 (3): 643–49. https://doi.org/10.1158/1055-9965.EPI-19-0905; Smith, Tracy T., Joseph S. Koopmeiners, Cassidy M. White, Rachel L. Denlinger-Apte, Lauren R. Pacek, Victor R. De Jesus, Lanqing Wang, et al. 2020. "The Impact of Exclusive Use of Very Low Nicotine Cigarettes on Compensatory Smoking: An Inpatient Crossover Clinical Trial." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research,* Cosponsored by the American Society of Preventive Oncology 29 (4): 880–86. https://doi.org/10.1158/1055-9965.EPI-19-0963; Tidey, Jennifer W., Rachel N. Cassidy, and Mollie E. Miller. 2016. "Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without Nicotine Replacement, in Smokers With Schizophrenia and Controls." *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco* 18 (9): 1807–12. https://doi.org/10.1093/ntr/ntw089; Tidey, Jennifer W., Damaris J. Rohsenow, Gary B. Kaplan, Robert M. Swift, and Christopher G. Ahnallen. 2013. "Separate and Combined Effects of Very Low Nicotine Cigarettes and Nicotine Replacement in Smokers with Schizophrenia and Controls." *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco* 15 (1): 121–29. https://doi.org/10.1093/ntr/nts098.

replacement therapies or e-cigarettes with nicotine cause serious harms in the short to medium term when used for this purpose.[13]

A nicotine product standard will lead to significant increases in worker productivity and consumer spending due to the life-years gained.

CAsToR research also shows substantial benefits to worker productivity under a nicotine product standard. Dramatically reducing smoking across the population through the standard will increase life expectancy and improve overall quality of life; with fewer people living with chronic diseases caused by smoking, workers will be able to contribute to the labor market for longer. Modeling research estimates that if a nicotine product standard is implemented by 2027 as proposed, this will increase overall productivity by $266 billion USD through 2100.[14] The increased life years gained across the population will also lead to an additional $1.2 trillion in consumer spending, further boosting the economy. Any potential economic costs associated with a nicotine product standard will be offset by these large-scale benefits.

Projected health and economic gains from the standard outweigh illicit trade concerns.

Tobacco manufacturers have claimed that a nicotine product standard could undermine public health by creating an illicit market for normal nicotine combustible tobacco products, citing the size of the current illicit market today.[15] However, current estimates of the US illicit trade market

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[13] Lindson, Nicola, Ailsa R. Butler, Hayden McRobbie, Chris Bullen, Peter Hajek, Angela Difeng Wu, Rachna Begh, et al. 2025. "Electronic Cigarettes for Smoking Cessation." *Cochrane Database of Systematic Reviews*, January. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub9/full; Hartmann-Boyce, Jamie, Samantha C. Chepkin, Weiyu Ye, Chris Bullen, and Tim Lancaster. 2018. "Nicotine Replacement Therapy versus Control for Smoking Cessation." *Cochrane Database of Systematic Reviews*, May. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000146.pub5/full; Lindson, Nicola, Annika Theodoulou, José M. Ordóñez-Mena, Thomas R. Fanshawe, Alex J. Sutton, Jonathan Livingstone-Banks, Anisa Hajizadeh, et al. 2023. "Pharmacological and Electronic Cigarette Interventions for Smoking Cessation in Adults: Component Network Meta-analyses." *Cochrane Database of Systematic Reviews*, September. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015226.pub2/full.

[14] Skolnick, Sarah, Andrew Brouwer, Charlene Cheng, and Jamie Tam. 2025. "Health, Equity, and Economic Impacts of a Nicotine Product Standard in the United States for People With and Without Major Depression." *medRxiv*. https://doi.org/10.1101/2025.07.10.25331302.

[15] Murillo, Jose Luis. Public Comment from Altria on Advance Notice of Proposed Rulemaking on Tobacco Product Standard for Nicotine Level of Certain Tobacco Products (Docket No. FDA-2017-N-6189). Comment ID: FDA-2017-N-6189-7074. Published online June 16, 2018. Accessed May 26, 2025. https://www.regulations.gov/comment/FDA-2017-N-6189-7074; Ogden, Michael W. Public Comment from RAI Services Company on Proposed Rule 'Tobacco Product Standard for Nicotine Level of Combusted Cigarettes' (Docket No. FDA-2017-N-6189). Comment ID: FDA-2017-N-6189-6710. Published online June 13, 2018. Accessed May 26, 2025. https://www.regulations.gov/comment/FDA-2017-N-6189-6710.

are based on evasion of state cigarette taxes.[16] This type of tax evasion across state borders is largely irrelevant when considering a nicotine standard implemented at the federal level. In addition, as the FDA continues to authorize the marketing of non-combustible tobacco products, such as e-cigarettes, many viable and legal substitute products are widely available to consumers who wish to continue using nicotine following the standard.

Even if an illicit market for normal nicotine cigarettes forms, it would only dampen the potential benefits of the standard; if illicit trade reduces the number of people who would quit smoking in response to the standard, this affects only the magnitude of health and economic gains, but not the direction of change. As the FDA notes in their previous concept paper,[17] study participants randomized to receive very low nicotine cigarettes (VLNCs) had easy access to normal nicotine cigarettes on the market. Even in contexts where non-compliance with VLNC randomized clinical trials was common, this did not change study conclusions that VLNCs increased quitting and reduced smoking magnitude in those who continued to smoke. Complete elimination of illicit trade may not be possible, but the negative impact of such trade on society pales in comparison to the enormous toll of smoking on American health: 480,000 deaths due to tobacco each year.

Recommendation

The evidence discussed above strongly supports the implementation of a nicotine product standard. FDA must fulfill its mission to protect the American people from the dangers of combustible tobacco use and finalize the nicotine product standard without delay.

Signed,

Center for the Assessment of Tobacco Regulations (CAsToR) TCORS 3.0

[16] Reuter, Peter, and Malay Majmundar, eds. 2015. *Understanding the U.S. Illicit Tobacco Market: Characteristics, Policy Context, and Lessons from International Experiences*. With the National Research Council. The National Academies Press. http://link.springer.com/10.1007/s12117-016-9290-3.
[17] Griffiths, Christopher. 2018. *Illicit Trade in Tobacco Products after Implementation of an FDA Product Standard*. FDA. https://www.fda.gov/files/tobacco%20products/published/Illicit-Trade-in-Tobacco-Products-After-Implementation-of-an-FDA-Product-Standard.pdf.