External Letter Peer Review of FDA's *Methodological Approach to Modeling the Potential Impact of a Nicotine Tobacco Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S.*

Final Summary Report

May 9, 2023

Contract No. 75F40122F19004

Prepared for:
U.S. Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Ave.
Silver Spring, MD 20993

Prepared by:
ICF
1902 Reston Metro Plaza
Reston, VA 20190

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1. Introduction

The U.S. Food and Drug Administration (FDA), Center for Tobacco Products (CTP) developed a document, entitled "Methodological Approach to Modeling the Potential Impact of a Nicotine Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S.," that outlines the methodology and framework of a computational model aimed to quantify the potential public health impact of a nicotine product standard for cigarettes and other combusted tobacco products in the United States. This effort is in accordance with FDA's authority under section 907 of the Federal Food, Drug, & Cosmetic Act (FD&C Act) (Pub. L. 111-31) which authorizes FDA to issue tobacco product standards that are appropriate for the protection of the public health, including provisions that would require the reduction or elimination of a constituent (including a smoke constituent), or harmful component of tobacco products and provisions respecting the construction, components, ingredients, additives, constituents (including smoke constituents), and properties of the tobacco product (section 907(a)(3), (a)(4)(A)(ii), and (a)(4)(B)(i) of the FD&C Act).

ICF, an independent FDA contractor, coordinated an external letter peer review of FDA's draft document. For this peer review, four external scientific experts were screened for conflict of interest (COI) and selected by ICF to evaluate the document and provide written comments on the scientific support for FDA's conclusions, as well as any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, outcomes not discussed, or recommendations of any additional publicly available information.

This report documents the peer review and provides all reviewer comments. Section II of this report lists the charge questions given to the reviewers regarding the objective of the peer review and specific advice sought through the peer review. Section III provides a table containing the individual (anonymized) peer reviewers' comments.

1.1. Peer Reviewers

Below are the names and affiliates of the peer reviewers:

David Levy, PhD
Georgetown Lombardi Comprehensive Cancer Center
Georgetown University

Rafael Meza Rodriguez, PhD
BC Cancer Research Centre (Vancouver, British Columbia)

David Mendez, PhD, MS
School of Public Health
University of Michigan

Andrea Villanti, PhD, MPH
Center for Tobacco Studies
Rutgers University

2. Charge to Reviewers

FDA has developed a population health projection model using inputs derived from available empirical evidence and expert opinion to estimate the impact of changes in tobacco product initiation, cessation, switching, and dual use on tobacco use prevalence, morbidity, and mortality in the United States in response to a potential tobacco product standard that establishes a maximum nicotine level in cigarettes and certain other combusted tobacco products. The completed document, entitled "Methodological Approach to Modeling the Potential Impact of a Nicotine Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S.," presents the methodology and framework of this computational model.

2.1. Charge Questions

1. Is the modeling framework and methodological approach of the population health model appropriate? If not, please explain.
2. Are the data inputs and assumptions of the baseline scenario appropriate and reasonable? If not, please specify alternatives and provide details regarding the source of that data.
3. Are the data inputs and assumptions of the policy scenario appropriate and reasonable? If not, please specify alternatives and provide details regarding the source of that data.
4. Is the approach to incorporate uncertainty through the sensitivity analyses detailed in the document appropriate? If not, please provide details on alternative approaches.
5. Other comments, suggestions, or recommendations for improving the report.

3. Reviewer Comments

In the following sections, the individual comments from the external peer reviewers are organized according to the sequence of the charge questions, i.e., general impressions followed by Questions 1 through 5. Comments from all four reviewers, anonymized as Reviewers A through D, are itemized and listed under each charge question.

3.1. General Impressions

Comment ID	Reviewer	Comment
A1	Reviewer A	The draft "Methodological Approach to Modeling the Potential Impact of a Nicotine Product Standard on Tobacco Use, Morbidity, and Mortality in the U.S." provides a clear description of the framework, methods, data inputs, and sensitivity analyses conducted to quantify the public health impact of a nicotine product standard for cigarettes and certain other combusted tobacco products. The rationale for base case estimates, policy scenario, and ranges used in sensitivity analyses are appropriate and justified; where possible, comparisons across different models are presented, highlighting consistency of findings from this model with different modeling parameters and assumptions. It updates and extends prior models published by FDA (Vugrin 2015, Apelberg 2018) to estimate the impact of the policy on mortality from secondhand smoke exposure, smoking-related perinatal conditions, smoking-related fires, and the use of non-premium cigars and pipe tobacco. Additional analyses address the potential impact of illicit trade on public health outcomes, highlighting the robustness of policy effects on smoking cessation, tobacco-attributable deaths avoided, and life-years gained.
A2	Reviewer A	The text, tables, figures, and appendices convey the inputs and assumptions of each aspect of the simulation modeling approach, as well as the median results and range (5th – 95th percentile) of findings for each outcome. This level of clarity and transparency ensures the rigor and reproducibility of these analyses and aligns with guidelines for Modeling Good Research Practices. FDA's interpretations of estimates throughout the report follow directly from the data presented, as do the conclusions. Findings from this model support that a nicotine product standard would be expected to result in significant reductions in smoking prevalence, premature death from tobacco, and improved health-related quality of life. This model builds on two peer-reviewed, published studies using this population health model to estimate the potential impact of a nicotine product standard for cigarettes and certain other combusted tobacco products, accounting for updated input parameters and assumptions based on the changing tobacco and nicotine marketplace. Together, rigor, transparency, coherence, and model validation strengthen confidence in conclusions derived from this model.
D3	Reviewer D	I have read and studied this report in detail. I reviewed the model's constructs, as well as the published models used as references. I carefully examined the appendices containing technical details of the study and parameters used to populate the model.

3.2. Response to Charge Questions

3.2.1. Charge Question 1

Is the modeling framework and methodological approach of the population health model appropriate? If not, please explain.

Comment ID	Reviewer	Comment
A4	Reviewer A	The modeling framework and methodological approach of the population health model derive from a peer-reviewed multi-state dynamic model that incorporates underlying population changes and projects the impact of changes in tobacco use initiation, cessation, switching, and dual use on tobacco use prevalence, morbidity, and mortality in the U.S. Specification of the population covered by the model and the data sources used to estimate population changes accounting for births, migration, and deaths are clearly presented. This modeling approach addresses transitions in use of two products (i.e., cigarettes and non-combusted tobacco products), which maps to the most likely product transitions following a nicotine product standard on cigarettes and certain other combusted products. While it sacrifices detail on specific product transitions (e.g., cigarette to smokeless tobacco) resulting from policy change, it allows for more robust estimation of key tobacco product use transitions (e.g., combusted tobacco to non-combusted tobacco) and their resulting effect on prevalence and health outcomes as they relate to the FDA's public health standard.
B5	Reviewer B	The modeling framework and approach are adequate. This is a comprehensive model of tobacco use behavior and its health consequences in the U.S. The analysis is thorough, the model and assumptions are clearly described, and the policy scenario impacts are well justified. Overall, this is an outstanding analysis, and I commend the authors for describing the model and analysis so clearly and thoroughly.
C6	Reviewer C	The primary analysis involves a simulation model that examines the impact of a nicotine standard on cigarette and noncombustible use and related attributable mortality and is later used to gauge the impact on premature mortality of non-premium cigar use, and perinatal and second-hand smoke health issues. The methodological framework for the basic cigarette-centered baseline model is appropriate. While I am critical of some aspects of the methodology, the results derived from the modeling as they apply to cigarette and noncombustible use are generally well supported.

Is the modeling framework and methodological approach of the population health model appropriate? If not, please explain.		
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C7	Reviewer C	The model applies a standard Markov process approach. This approach implies that future states depend on the immediate past time state and not previous time states. That assumption raises potential complications. The instability and measurement problems that modelers today face in a highly complex, dynamic nicotine product environment requires added attention to the unstable use patterns in the last 5 years of the use of combustible (smoking prevalence rates of youth and young adults dramatically dropped) and noncombustible (e-cigarettes dramatically increased and then fell) products, and potential impact of changing regulatory policies especially as they are applied to non-combustibles. As described below, a more structured approach to sensitivity analysis would improve the model presentation. Uncertainty about the appropriate measures of prevalence and stability of transitions is a central problem in modeling nicotine product use in the current environment and needs to be more clearly recognized.
C8	Reviewer C	While the main analysis was well-conducted, I found the extensions to the basic cigarette-oriented approach, such as to non-premium cigars, as second-hand smoke, perinatal and fire impacts problematic. It was unclear how the use of noncombustibles was treated. These extensions are analyzed separately from the model, raising questions on their validity (see discussion below).
C9	Reviewer C	In reviewing the report, my major concern is that I found the parts of the presentation confusing. I found the discussion in the Methods section particularly confusing. Up front, it can be made clearer that the baseline model directly applies only to transitions to and from cigarette and noncombustible (with emphasis on e-cigarette) use and does not incorporate non-premium cigar, heated tobacco product or oral nicotine pouch use. In the beginning of the Methodology section, it would help to include a diagram that shows the impact of a potential nicotine product standard on cigarette and noncombustible use, which in turn affects related morbidity and mortality. I would suggest emphasizing the central role of cigarette use and more generally their health risks relative to noncombustible health risks, which underlies the support for a nicotine product standard. On first reading, I was baffled by the Conceptual Framework diagram in the second section of the Methodology section, both because the diagram is very complex and because it was not immediately clear why each box had two states (e.g., Never, Never). The two states should be defined, presumably combustible (or cigarettes only?) vs. noncombustible use.

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		In light of all of the arrows, it may be preferable to either simplify the diagram or provide more explanation (perhaps best kept in the Appendices as currently also provided).
D10	Reviewer D	The model described in the report is a linear, dynamic, compartmental model, where individuals are classified by age, gender, combusted tobacco use status (including current, never, and former smokers, the latter further identified by years-since-quit), and non-combusted tobacco use status. Appropriate differential all-cause mortality is applied to the compartments of the model. The constructs of the model are conceptually and technically sound and are fully presented in the appendices and references. The framework and model presented in the report are appropriate for the study's goals.
D11	Reviewer D	My only minor criticism about this model's framework, as well as that of most tobacco-related models in the literature, is the treatment of initiation and cessation parameters as exogenous variables. Such treatment was appropriate when the population's smoking initiation and cessation rates were slowly changing. During the last decade, we have seen initiation rates plummeting and cessation rates rising at an accelerating pace. It is more than likely that non-linear diffusion effects, endogenous to the processes of initiation and cessation, are at play in determining the trend on these parameters. In this study, this lack of modeling detail is handled by an extensive sensitivity analysis of the initiation and cessation rates. For the purposes of the study, this is appropriate, although future efforts should attempt to incorporate those non-linear effects within the model's constructs.
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3.2.2. Charge Question 2

Are the data inputs and assumptions of the baseline scenario appropriate and reasonable? If not, please specify alternatives and provide details regarding the source of that data.

Comment ID	Reviewer	Comment
A12	Reviewer A	Baseline scenario inputs and assumptions are clearly documented and use recent data from the U.S. Census, other national sources, and published studies. These are appropriate and reasonable.
B13	Reviewer B	In general, the assumptions are reasonable. However, I have some suggestions for your consideration: Smoking projections. The model projections in the baseline scenario (figure 3) agree with the current smoking prevalence trends. However, this is unclear from the model validation presented in the supplement as these show an old version of the model and NHIS data only through 2012 (figure C2 and Table C1). Could these figures be updated to show the performance of the current version of the model relative to more recent data?
B14	Reviewer B	On a related note, the model uses CISNET initiation and cessation parameters based on data through 2018. While the model seems to be doing a reasonable job with more recent trends and starts with an adult prevalence of around 12% in 2021, I wonder if there might be updated CISNET data to inform the model, as there have been considerable changes in smoking initiation and cessation in the past few years. I do not think this is essential, and I am satisfied with the model as presented, as the projected smoking in the baseline scenario seems reasonable, reaching 6% after 2070. But I wonder how using more updated rates might affect the model projections.
B15	Reviewer B	Switching between cigarettes and non-combusted products. These are based on Brouwer et al. for the baseline scenario. However, as described in the report, these are based on earlier PATH surveys. Sensitivity analyses were conducted assuming 50% and 100% higher switching rates versus the baseline. Brouwer et al. recently updated their analysis estimating switching rates based on more recent PATH surveys (https://www.medrxiv.org/content/10.1101/2022.12.15.22283292v1). It would be helpful to assess if the assumption of 50% or 100% versus the baseline agrees with the estimates from this new analysis of Brouwer et al. If so, should one of the higher switching rates scenarios become the baseline scenario?

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B16	Reviewer B	The assumption of 80% of cigar mortality coming from non-premium cigars is likely an overestimation of the risk of premium cigars, since premium cigar users tend not to smoke cigarettes and not to use cigars frequently. A 90% from non-premium vs 10% from premium break might be more realistic.
B17	Reviewer B	Decrease in mortality by the Lee-Carter method. This is a reasonable approach as it is a validated demography methodology. However, I was surprised by the huge impact on infant and childhood mortality. For example, by 2100, it is projected that infant mortality will be only 10% of that in 2021 (scaling factor 0.111). This is very optimistic. This likely has a limited impact as the bigger decreases in mortality are seen for young ages, so these are unlikely to impact the projections of smoking-related mortality. However, one additional sensitivity analysis could keep the mortality rates constant after a given year (e.g., 2060) to assess the impact of the optimistic decreases in mortality from the Lee-Carter approach.
C18	Reviewer C	Initial population. The model is initialized with population and smoking prevalence for the year 2020. The year 2020 is a logical choice, since it is largely pre-covid pandemic and thus avoids some of the data problems and issues related to product use measures. It would be useful to provide additional references for this choice, especially regarding potential impacts of covid and survey issues. I would recommend that the report present the specific prevalence measures used to initialize exclusive cigarette, exclusive combustible, and dual use in the model in the initial population section. Currently, some of that information is provided in the transitions section, but, as described below, the discussion is often unclear as it relates to each of the categories of use. In particular, it is important to stress the importance of measuring regular use for the purpose of public health analyses, and specifically defending a measure of relatively stable dual use patterns (in terms of extent of use of both cigarettes and noncombustibles), which is admittedly a difficult task. Instead, the first paragraph launches into a discussion of how the previous model accurately incorporates projections of smoking prevalence over time, which is more directly relevant to the section on transitions. The discussion in the first sections may be less confusing by first discussing initial population measures along with population transitions (births, migration, and deaths) and then separately discuss combustible and noncombustible measures and transitions.

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C19	Reviewer C	Product Transitions: It would be helpful to begin this section by summarizing the transition parameters needed, i.e., initiation and cessation rates for exclusive combustible, dual combustible, and exclusive noncombustible rates, and switching rates between combustibles and noncombustibles. The set of assumptions made with regard to transitions could then be explicitly set out in a table. I found that it was unclear what assumptions were being made regarding transition rates from exclusive cigarette and dual use and whether any distinctions are made within noncombustible categories (e.g., distinguishing smokeless tobacco from e-cigarette use).
C20	Reviewer C	Cigarettes: It would be helpful to discuss the age-period-cohort analysis in more detail. The use of the two-year cessation rates is appropriate, as this methodology has now been widely used and has been shown by the CISNET group to capture relevant trends. However, this simplification will not pick up the gradual reduction in relative risks beyond two years of quitting smoking (which cumulates over time). The following statement is unclear, "Under these assumptions, model projections in the baseline scenario closely match estimates of population size, mortality, and smoking prevalence for the U.S. produced by other federal agencies.", i.e., over what time period and which federal agencies (why even mentioned?). In addition to mentioning validation in the previous FDA nicotine standard analysis, I would suggest citing recent CISNET publications regarding validation and use of the two-year cessation rates. While the measure of cessation is discussed, the measurement of smoking initiation is not discussed.
C21	Reviewer C	A discussion of how the NHIS age-period-cohort analysis incorporates cohort and period over time and thus implicitly incorporates recent changes in trend would be helpful. In particular, the use of NHIS data through 2018 in the age-period-cohort analysis raises concern; the large drop in the initiation rates of recent cohorts and the general increase in cessation rates may incorporate the replacement of cigarette with noncombustible use, and thus have implications for the measurement of switching rates (see discussion below). My concerns arise because the period 2013-2021 includes dramatic shifts in smoking and e-cigarette patterns. In particular, more attention is warranted regarding the unstable nicotine product use and transition patterns from 2013-2021, especially those observed between 2017 and 2022.
C22	Reviewer C	Non combustibles: In general, I found the application of transitions to initial levels of combustible and noncombustible use unclear and assumptions regarding those transitions were not made

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		explicit. To derive initiation rates for noncombustibles, smoking initiation rates are scaled, implying that age and gender patterns for the initiation and cessation of combustible use follows those of cigarettes. This assumption should be clearly stated. The application of scalers transitions is applied to exclusive combustible as well as dual use is not clear. In the model, combustible smoking cessation rates are applied as cessation rates for noncombustibles. This decision is based on a comparison of quit ratios for smokeless and cigarette users (how are dual users treated), but has unclear applicability to e-cigarettes users. Why not use the quit rates provided through the Brouwer article (used to determine switch rates, see below) or cessation rates estimated from PATH (or possibly the ratio of transition to no use by smokers as compared to e-cigarette users)? The application of smoking initiation rates to noncombustible rates is not justified. While it is difficult to determine noncombustible transition patterns, it would be useful to conduct analysis of use rates at early ages using PATH survey to consider initiation patterns with respect to e-cigarettes.
C23	Reviewer C	As mentioned above, the relationship of transitions to exclusive and noncombustible use to measures of initial exclusive is unclear. The use of a 20 of the last 30 days for regular youth use is acceptable, although arguably it is too restrictive especially at younger ages (although some sensitivity analysis is later conducted). While the study uses NYTS, potentially better measures can be obtained from PATH, where they specifically ask about "fairly regular" use and distinctions can also be made regarding number of days in the past month. A range of estimates in terms of days used can then be applied for sensitivity analysis. A recent paper by Brouwer (NTR 2022) considers the role of prevalence definitions (e.g., number of days) in gauging transitions.
C24	Reviewer C	Regarding switching rates, the use of transitions developed by Brouwer (TC, 2022) is a good choice. Note, however, that the Brouwer transitions are over a 1-year period, unlike smoking cessation which is over a 2-year period. It appears from the discussion that switching rates from Brouwer were applied to exclusive cigarette use, but Brouwer also considers switching from dual use and the application of these two measures is not specified. While the report mentions potential instability in switching rates and provides a sensitivity analysis, more attention is needed here. I would suggest also examining PATH data, especially regarding recent transitions from waves 4 to 5 (over nearly a two-year period). A paper by Brower, available on Medriv,

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		considers the stability of transitions using data from PATH 2017-2019 compared to wave 2015-2017. Another potential problem is that the use of NHIS through 2018 in the age-period cohort analysis may incorporate some of the switching from cigarettes to other products as reflected in the period and cohort effects on cessation rates in recent years, thus raising concerns regarding double counting of the switching process. Another concern is that increases in switching rates may have occurred since 2019, especially in regard to young adults in recent years (e.g., NHIS survey results show major declines in age 18-24 smoking prevalence from 2013 up through 2021).
C25	Reviewer C	Mortality rates: The measures of never-smoker mortality rates were well developed. Although it would be useful to control for smokeless tobacco use, it would be impractical to conduct that analysis as suggested in the report. For smoker mortality rates, updated data were used relative to the earlier FTC nicotine reduction analysis, and a hazard rate analysis was appropriately applied. It would be useful to present and reference this hazard rate analysis in the supplementary material. A comparison of the results to the previous FTC analysis and to other studies would also be helpful in evaluating the results.
C26	Reviewer C	I found the analysis of noncombustible and dual use mortality rates more problematic. Regarding smokeless tobacco mortality rates, the studies reviewed (2005 and 2008) are outdated, as patterns of exclusive and dual smokeless use changed considerably beginning in 2002 (with cigarette companies buying up the smokeless tobacco companies in 2006 and 2009). The associated risks of smokeless tobacco have also likely declined with the use of oral nicotine pouches, snus and other more recent forms of smokeless tobacco. The applicability of smokeless tobacco relative risks to e-cigarettes is particularly questionable, given the wide variety of types of smokeless products at the time of the 2005 and 2008 studies and the introduction of presumably safer forms since those studies. I would recommend surveying the e-cigarette literature. The England Public Health Service has recently published an extensive analysis and update of their analysis of e-cigarette (and heated tobacco product) risks, and in my view is the most rigorous attempt to date. I would suggest using their estimates but conducting extensive sensitivity analysis especially at higher relative risk estimates. The assumption regarding the risk to dual users (same as exclusive smokers) is conservative, and sensitivity analysis should be conducted at lower levels of risks. In my view, the basis for increased risk of dual use is weak;

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		stronger evidence is available for lower risks among dual users than exclusive smokers, as found in biomarker studies, smokeless tobacco studies that consider dual use, and simply that lower rates of cigarette use suggest reduced lung cancer and COPD risks, especially for those who initiate into dual use at a younger age (as opposed to those that transition into dual use from exclusive cigarette use).
D27	Reviewer D	Yes, for the most part. The assumption of frozen initiation and cessation rates can be challenged since those population parameters have been trending for some time (see my remarks on question 1). A more realistic baseline, with an increasing cessation rate and a decreasing initiation rate, would result in a smaller policy effect.
D28	Reviewer D	The initiation, cessation, and transition rates are obtained exogenously. Transitions among combustible, non-combustible, and dual product use are published estimates by Brower et al. (2022) based on analysis of PATH data. A question could be raised whether those transition parameters are stable, although they are the best available information on the subject.
D29	Reviewer D	Initiation rates are taken to be CISNET estimates. I have a certain concern about these figures, but I am not sure whether my misgiving is totally justified. According to Table D6, about 19% of a cohort would initiate smoking between the ages 9 and 30, which seems very high since the 2018 prevalence for 18–24-year-olds was only 7.8%, according to NHIS data. This apparent discrepancy could be driven by the specific definition of smoking initiation used in this study. Nevertheless, I recommend that the report's authors double-check the initiation rate figures.
D30	Reviewer D	All input data are properly referenced and/or shown in the appendix.

3.2.3. Charge Question 3

Are the data inputs and assumptions of the policy scenario appropriate and reasonable? If not, please specify alternatives and provide details regarding the source of that data.

Comment ID	Reviewer	Comment
A31	Reviewer A	This model updates estimates for the impact of the proposed standard on behavioral transitions in tobacco use (e.g., initiation, cessation, product switching) from a 2018 Expert Elicitation. FDA investigators describe reviewing clinical data from trials of very low nicotine content cigarettes and justify the use of the expert elicitation estimates, as they better reflect real-world conditions rather than an idealized research setting. This approach is appropriate and reasonable.
B32	Reviewer B	The policy scenario assumptions are reasonable and based on the best available information. I appreciated the careful description and justification of the policy impact assumptions, the description of the results of the expert-elicitation, and the comparison with the available empirical data.
C33	Reviewer C	The introductory paragraph of the Product Standard Scenario Data Inputs and Assumptions section clearly summarizes the relevant transitions under a nicotine product standard. The transitions under a nicotine standard are based on an expert elicitation (EE) conducted in 2018, following a similar procedure used for the original 2015 EE minus one participant. Like the 2015 EE, the 2018 EE follows well-established practices. However, the early date of the EE, 2018, limits the ability to incorporate the abundance of more recent studies of nicotine reduction policies, and knowledge about the dramatic changes in combustible and noncombustible use patterns and transitions since 2018, especially in terms of prevalence (the referenced Jamal study is outdated) and initiation.
C34	Reviewer C	With the above caveats, the description of the EE process (particularly in an Appendix) and the results of the EE were well presented. However, there was limited discussion of how the estimates were actually applied. The median measure and incorporation of uncertainty is discussed in the next (uncertainty and sensitivity) section, but I found that discussion to be cursory. There appears to be bimodal distributions for some of the transition parameters. Was there any consideration of this variation? There was reference to application of the EE analysis in an Appendix, but I could not find information on the choice of median and uncertainty measures. Information about how measures are applied and the rationale for the choice of the median and

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		variation measure in the first section of the Product Standard section would clarify later discussion of the uncertainty and sensitivity analysis.
C35	Reviewer C	Following the discussion of the EE process and results, the report discusses and correctly dismisses premium cigars as playing a significant role. The focus on e-cigarettes by the experts is also indicated, confirming the importance of the abovementioned issues regarding the measures, transitions and risks involving e-cigarettes.
C36	Reviewer C	In addition to the nicotine standard transition analysis based on the EE process, the report includes an analysis based on clinical studies (p. 17-18), "In addition to applying the experts' estimates of cigarette smoking cessation, we also examined a scenario in which the impact of the proposed product standard on smoking cessation is derived from clinical studies of VLNC cigarette use." While I find the results from the cited studies generally convincing that compensation is minimal, the cited studies are not the most up to date. The report later presents results of a broader public health analysis using the clinical studies (p. 24). I found that discussion confusing and incomplete, and, therefore, a diversion from the main analysis. I would recommend either expanding that analysis (perhaps in an Appendix) or omitting the analysis. It is unclear how that analysis complements the more comprehensive analysis using EE results.
C37	Reviewer C	In the discussion of regulatory impacts, I would recommend including potential compliance problems (i.e., the ability to obtain illicit non-reduced nicotine cigarettes), and not delaying this discussion until the next section. That issue will be important to some tobacco control researchers and advocates.
C38	Reviewer C	The Outcome Metric section at the end of the regulatory analysis section was brief and provides the reader with minimal discussion of the outcomes themselves and how the public health analysis is conducted. I would suggest a paragraph describing each of the health outcomes in more detail and their relevance to public health, with a second paragraph describing cumulation of these outcomes over time. A third paragraph would then consider how public health impacts are derived, i.e., the difference in each of health outcomes related to all nicotine product use between the baseline and nicotine standard scenarios. I expect that most readers will need this background. This discussion should probably be a separate section from the regulatory analysis.

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Comment ID	**Reviewer**	**Comment**
C39	Reviewer C	In results section, the discussion of the impact of reduced secondhand smoke exposure, smoking-related perinatal conditions, smoking-related fires, and use of non-premium cigars and pipe tobacco should provide more information about how their impacts are measured in the original studies. In applying these estimates to the impact of a reduced nicotine standard, none of these studies, to my knowledge, incorporate substitution to noncombustible use. Consistent with the nicotine standard analysis, the impact on noncombustible use would need to be considered. Please clarify and state any implicit assumptions (e.g., no fire deaths caused by e-cigarettes) regarding those analyses.
D40	Reviewer D	Yes, in general. The weakest aspect of the analysis is the use of expert elicitation to estimate the effects of a nicotine product standard policy. of the effects of the policy. I understand there is no "real world" empirical data to draw from, and expert elicitation might be the best course of action, but this weakness must always be weighted heavily when discussing the analysis results' implications. I am somewhat concerned that the experts estimated different policy effects in 2018 from the 2015 analysis. I am also concerned about the wide differences among the experts in estimating certain parameters. I understand this approach might be the best way to proceed, but sometimes, the best might not be good enough. Having expressed my misgivings about estimating the policy effects on initiation, cessation, and transition rates, I would like to note that the expert elicitation process is clearly documented in the report and appears to be well executed, except, possibly, on one step.
D41	Reviewer D	The experts were asked to provide their best estimate of the "true value of the parameter" and the 5th, 25th, 75th, and 95th percentiles of their estimates. Later, in the appendix, it is explained that the "true value" asked would be assigned to the median of the uncertainty distribution. I think this works on a unimodal symmetric distribution where the mode and the median coincide. For skewed distributions, for instance, most individuals would report the mode (the most likely parameter value) as the "true value of the parameter." In fact, in many settings, it is customary to ask experts for the "lowest possible value," "the most likely value," and the "highest possible value." To carry on the uncertainty analysis using Monte Carlo simulation, those three values serve as parameters of a triangular uncertainty distribution from which to sample. I find it unlikely that the experts had a clear idea of the location of the 50th percentile in all cases and could have

Are the data inputs and assumptions of the policy scenario appropriate and reasonable? If not, please specify alternatives and provide details regarding the source of that data.		
Comment ID	**Reviewer**	**Comment**
		reported the mode. However, I do not think this issue significantly affects the results of the uncertainty analysis.

3.2.4. Charge Question 4

Is the approach to incorporate uncertainty through the sensitivity analyses detailed in the document appropriate? If not, please provide details on alternative approaches.

Comment ID	Reviewer	Comment
A42	Reviewer A	A range of sensitivity analyses are described and conducted to understand the robustness of model findings accounting for uncertainty of model parameters. Of particular relevance, the use of Monte Carlo simulation for the product standard scenario estimates (i.e., behavioral responses to a nicotine product standard) resulted in 7,000 simulations which were aggregated to produce distribution percentiles and inform the median, 5th percentile and 95th percentile findings. This method captures the range of potential responses to the policy and ensures that estimates reflect the median response across this range. Novel sensitivity analyses documented the potential impact of an illicit market on the public health impacts of a nicotine product standard for cigarettes and certain other combusted products. These approaches are appropriate and well-described.
B43	Reviewer B	Yes, I appreciate the care and effort to assess the impact of the model assumptions on the results via extensive sensitivity analyses. I found it valuable to include the alternative policy scenario based on the limited trial/empirical data. While all sensitivity analyses are helpful and reasonable, I have some questions about a couple of assumptions.
B44	Reviewer B	Sensitivity analysis of dual use relative risks. In the baseline analysis it was assumed that the mortality risks of dual use were equivalent to those of exclusive smoking. In a sensitivity analysis, it was assumed that the mortality risks of dual use were higher than those of exclusive smoking. While I agree with the baseline scenario, I wonder if a sensitivity analysis assuming lower risk from dual versus exclusive cigarette smoking should also be considered, given the lack of data on the risks of dual use, as mentioned to justify the baseline scenario.
B45	Reviewer B	Why does the sensitivity analysis of non-combustible use prevalence among youth assume increasing trends since these are currently decreasing? It seems contradictory to the data presented. I am referring to this assumption: *"According to results from the NYTS, frequent e-cigarette use defined as use at least 20 days in the past 30 days among middle school and high school students ages 9-17 rose from 2.9% in 2018 to 5.3% in 2019, then declined to 3.9% in 2020 (see Cullen et al., 2018, Wang et al., 2019, and Wang et al., 2020 for additional results). Given previous trends, in a sensitivity analysis we also projected prevalence for exclusive cigarette*

Is the approach to incorporate uncertainty through the sensitivity analyses detailed in the document appropriate? If not, please provide details on alternative approaches.		
Comment ID	**Reviewer**	**Comment**
		smoking, exclusive non-combusted use, and dual use for the period 2021-2030 from NYTS data, assuming that exclusive non-combusted use and dual use would increase by 25% during the period 2021-2030 (see Appendix D, Table D2).” Is the assumption that the decreases since 2019 are sort of a reversion to the mean and that non-combustible product use will now increase? While plausible, I believe this might also do not agree with the NYTS 2021 and 2022 data. In any case, I do agree with the value of doing a sensitivity analysis with increasing non-combusted use prevalence. But perhaps it should not be justified with the current trends which do not agree with it.
C46	Reviewer C	The analysis applies a Monte-Carlo simulation process, an appropriate state-of-art technique, subject to underlying assumptions, to develop confidence intervals for the nicotine standard scenario. Sensitivity analyses are then applied to very specific parameters. While the analysis focuses on those parameters that the authors found most problematic, it does not consider parameters that can be also argued problematic (see above discussion). For example, in recent years, the dramatic drop in smoking initiation and increase in smoking cessation merit attention both in terms of whether those changes will be maintained, increase, or decrease. A more systematic approach would involve examining the credible ranges in all transition parameters in the base case and the nicotine standard scenario. As suggested above, other areas for sensitivity analysis include lower risks of noncombustibles, lower risks from dual use, and the smoking and noncombustible initiation and cessation parameters.
C47	Reviewer C	The report focuses on sensitivity to individual parameters to draw conclusion about the robustness of results, whereas the robustness depends more broadly on the multiple variation of parameters, particularly those most central to the analysis. That point should be recognized in the sensitivity analysis section and how application of some of the more serious areas of parameter uncertainty combined might affect the analysis.
D48	Reviewer D	The report describes thorough uncertainty and sensitivity analyses. The uncertainty analysis was carried out via Monte Carlo simulation, sampling from the parameter distributions specified by the expert panel. While the overall analysis is sound, it neglects to consider the correlation between parameters estimated by the same individual. It is likely that, when asked to provide ranges for parameters, the expert panelists thought about different scenarios that affect multiple

Is the approach to incorporate uncertainty through the sensitivity analyses detailed in the document appropriate? If not, please provide details on alternative approaches.		
Comment ID	**Reviewer**	**Comment**
		parameters simultaneously. For example, when asked to provide a lower limit for the effects of a nicotine reduction policy on smoking cessation, experts thought about a scenario that would carry a small policy effect on smoking initiation. As described in the report, it appears that the uncertainty distributions belonging to a particular expert were sampled independently, which likely lowers the uncertainty range of the outputs. The added sampling correlation to the simulation exercise might not make a significant difference, but it should be checked in case it does since the assumption of independence is likely reducing the output variance artificially.

3.2.5. Charge Question 5

Other comments, suggestions, or recommendations for improving the report.		
Comment ID	**Reviewer**	**Comment**
A49	Reviewer A	Page 4, paragraph 1 – Scope of the analysis: Context for inclusion of roll-your-own tobacco, non-premium cigars, and pipe tobacco in the product standard should be introduced early in this document. Recommend including the following sentence from Table I1 as the second sentence in this paragraph: "Roll-your-own tobacco, non-premium cigars, and pipe tobacco are the combusted products that people who smoke cigarettes would be most likely to switch to in order to sustain addiction."
A50	Reviewer A	Page 6, paragraph 1 – Births and Net International Migration: Text from Table 1 should be included in this paragraph to understand why 2014-2018 NHIS data were used to estimate tobacco product use in recent immigrants to the U.S., as follows: "We opted for not pooling 2018 and earlier data with 2019 and later data due to significant changes introduced in 2019 to NHIS data collection."
A51	Reviewer A	Page 15, paragraph 3 – Incorporation of Uncertainty and Sensitivity Analyses: Please clarify how the relative mortality risk for non-combusted product use from Henley et al 2005 (i.e., 1.1 and 1.3) was used in sensitivity analyses presented in the in-text equations.
A52	Reviewer A	Page 22, paragraph – Description of the assumptions for estimating the mortality impact on new outcomes from this model (e.g., secondhand smoke exposure, smoking-related perinatal conditions, smoking-related fires, use of non-premium cigars and pipe tobacco) derive from existing estimates of the ratio of these deaths to primary smoking-attributable deaths. There is a comment related to the likelihood that deaths from smoking-related perinatal conditions would have immediate rather than lagged effects and are thus, underestimated. Recommend clarifying the lag between exposure and outcome for the analyses of these new outcomes and whether they are consistent with the three-year lag used in the general model and Apelberg 2018.
A53	Reviewer A	Page 28, paragraph 2 – Conclusion: Please reword "This document provides documentation…" Recommend "This document outlines…" I suggest including the median estimated impacts on cigarette smoking prevalence, premature deaths from tobacco, and QALYs in the final sentence of this paragraph.

Other comments, suggestions, or recommendations for improving the report.		
Comment ID	**Reviewer**	**Comment**
B54	Reviewer B	Table 3 and Figure J3. One suggestion is to add more explanation about the life-years and QALYs behavior in Table 3 and Figure J3. At first, I was confused by the results showing that QALYs were higher than the cumulative life-years gained in the first few decades after policy implementation. This is likely because QALYs are a function of morbidity, with former smokers assumed to have a higher quality of life even if not living longer than current smokers. In contrast, life years gained are calculated exclusively by increases in population counts (reasonable approach). Assuming this is indeed correct, it would help the reader if a couple of sentences could be added explaining these patterns.
B55	Reviewer B	Could the authors please clarify why this assumption is needed: "*We used the estimated HRs in the baseline scenario, while in the product standard scenario, we capped HRs for former smokers at the levels for current smokers of the same sex and age group because increased smoking cessation in this scenario would be due to the policy rather than the cessation of smoking due to existing illness (Apelberg et al., 2018)*"? The exposure stopped regardless of the reason. Does this mean HRs for former smokers are as high as those for current smokers in the policy scenario?
B56	Reviewer B	Table 1. "Examine the impact of lower (RR=1.1) and higher (RR=1.3) non-combusted tobacco product risk." It would be helpful to give the range in terms of the percentage of excess risk of exclusive smoking (7 to 20%) as this is how it is presented in the preceding text.
B57	Reviewer B	Section 4. "We then calculated the ratio of non-premium cigar to cigarette-attributable deaths, 1.7%, and applied that value to the projections of avoided tobacco-attributable deaths under the main policy (Table 3)." It might be helpful to explain where the 1.7% comes from ((0.8*9,246/437,400))
B58	Reviewer B	Table A1. Description of Baseline Input Parameters and Data Sources Used in the Analysis: Description of Baseline Input Parameters and Data Sources Used in the Analysis; Tobacco use Status parameter. It would be helpful to list the product use definitions used for each survey (NHIS, NYTS).
B59	Reviewer B	Table A1. Immigrant smoking prevalence by sex: Not pooling of 2018 and 2019 NHIS data (described in Table A1, Immigrant smoking prevalence by sex). This is reasonable, but analysis by

Other comments, suggestions, or recommendations for improving the report.		
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		the CDC of the impact of the redesign in smoking and e-cig prevalence suggest limited impact: https://www.cdc.gov/nchs/data/nhis/earlyrelease/EReval202009-508.pdf
B60	Reviewer B	Appendix. Projected Tobacco Use Prevalence to Compute Non-Combusted Product Initiation for Sensitivity Analysis: Change "4.58% / 1.42%" to "4.58% / 1.42% = 3.23%" so it is clear where the scaling factors in table D4 come from? Similar for other examples presented.
C61	Reviewer C	The Introduction would benefit from setting out a framework in terms of combustibles vs. noncombustibles. From the outset, it is important to clarify what that distinction means and why it is important. The definition of combustibles would benefit from early discussion. While most readers will be aware of the role of cigarettes and roll-your-own and non-premium cigars are recognized (end of the last paragraph of the Introduction), the role of little cigars/cigarillos in particular merits earlier discussion in terms of their importance as a substitute for cigarettes. References should be provided. Less clear is the role of pipe tobacco. The point also needs to be made that the health risk of combustibles is well-defined by a large literature and central to the public health implications of the analysis, while the risk of noncombustibles is less well-defined but likely far less than for combustibles. The definition of non-combustibles also benefits from a discussion up front. In particular, the definition of smokeless products would benefit from clarification, e.g., especially the role of (modern) oral nicotine pouches and perhaps nicotine lozenges. The role of substitution of noncombustible for combustible use merits early discussion. Discussion of recent studies by Donny, Hatsukami et al. will help readers understand the thrust of the analysis and the potential role of noncombustibles. With this discussion up-front, I expect that the discussion in the methodology section will become clearer and more comprehensible. In the Introduction, please also define what is meant by "scalar methodology."
C62	Reviewer C	In the Health Impact from Main Analysis section, it would be useful to provide a description of projected baseline trends in cigarette (a relatively large initial reduction with slowing decline) and dual use (increases slightly and flattens) for context in later discussing trends with a nicotine standard. Only exclusive combustible trends are described. The report provides a graph on overall nicotine use, which in my view is unneeded and may be misleading given the problems in defining what is meant overall nicotine use and that the analysis does not include oral nicotine pouches. I expect that the provision of that figure may detract from the more relevant results on exclusive cigarette, exclusive noncombustible and dual use. The rest of the section and the

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		section on mortality impact were well presented (although the cumulative measures should probably be explained to avoid confusion, i.e., attributable deaths each year presumably decline).
C63	Reviewer C	In the Conclusion section, the first two paragraphs provide a nice summary of the report. It would also be helpful to add a paragraph here which compares the results to the earlier 2018 paper (based on the 2015 EE) analysis. I also recommend a paragraph on any additional insights from the literature on nicotine reductions since 2018 that support or contradict the results from the 2018 EE.
C64	Reviewer C	Limitations: 1) More limited data are available for non-combusted tobacco products. It is stated, "Where possible, we conducted sensitivity analyses to examine the impact of these assumptions on the reductions in morbidity and mortality." Definitely more is possible and is suggested as discussed above.
C65	Reviewer C	Limitations: 2) Inability to capture the wide variety of tobacco product use. "It was also not possible" could be better stated, "we were not able" (anything is possible). The discussion is otherwise well-presented.
C66	Reviewer C	Limitations: 3) Application of model-derived attributable mortality projections as the basis for projecting avoided mortality due to use of other combusted products (i.e., non-premium cigars and pipe tobacco). The discussion is on point, but, as discussed above, it is not clear how that analysis incorporates transitions to noncombustible products.
C67	Reviewer C	Limitations: 4) Morbidity from non-combusted tobacco product use was not assessed. Point well taken.
C68	Reviewer C	Limitations: 5) Other future population-level policies could impact the inputs and assumptions of the model (e.g., changes in tobacco use behaviors, prevalence rates, as well as changes in the tobacco market). This is an important point, especially in light of recent FDA regulatory policies. More broadly, the analysis depends on the implementation and enforcement of recent and newly implemented policies toward combustibles and noncombustibles. Another important and related limitation is that the results depend on how the nicotine reduction standard is implemented (gradual vs all at once) as well as policies to enforce a nicotine standard (e.g., limiting noncompliance through illegal markets).

Other comments, suggestions, or recommendations for improving the report.		
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C69	Reviewer C	Limitations: 6) Any attempt to model the impact of future actions on behavior over the long-term will be inherently uncertain. Drop the phrase "Any attempt to." The report then states that "the expert elicitation was completed in 2018 and was based on the state of the science on VLNC cigarettes available at that time. Findings from more recent studies could impact expert opinion." As discussed above, I would recommend discussing that literature, given the large growth in literature in the past 4 years (including a recent review article by Donny et al.)
C70	Reviewer C	Limitations: 7) The "analysis was not able to capture all possible sources of uncertainty." That point is obvious, but more important is to point out some of the areas that might further be considered.
C71	Reviewer C	Another limitation not mentioned is that the report does not distinguish smokers by SES or mental health issues, both in terms of projections in the baseline scenario and potential impacts under the nicotine standard.
C72	Reviewer C	Other Public Health Impacts: The statement, "The overall public health benefits are likely to be even greater than those quantified, since our analysis does not account for the full range of impacts that smoking has on public health in the U.S." is too overstated given that there are reasons that risks may be overestimated. Instead, I would suggest stating that the analysis is conservative in that it does not incorporate some additional public health benefits that would likely arise from a nicotine standard. In addition to the failure to incorporate some quality-of-life factors, other benefits from secondhand smoke reduction, reduced fires, and benefits from reducing the number of cigarettes smoked, another benefit from a public health perspective and more generally a health equity standpoint is the potential impacts on health disparities by reducing the relatively high smoking rates for those of low SES and those with mental health issues. The report ends after the section on Other Public health Impacts. A concluding paragraph is suggested to emphasize the main results of the report.
D73	Reviewer D	Overall, this study represents a solid scientific effort to evaluate the likely impact of a nicotine standard policy on tobacco products. The modeling approach is sound, as it is the

Other comments, suggestions, or recommendations for improving the report.		
Comment ID	**Reviewer**	**Comment**
		implementation of the model. The strength of the study lies in its transparency and reproducibility, as well as the extensive uncertainty and sensitivity analyses carried out to evaluate the range of the potential impact of the policy on public health measures. My main concern in the analysis is the overreliance on expert elicitation to estimate the effect of a nicotine standard policy on the model's parameters. There should be an attempt to formally incorporate into the analysis the empirical results from clinical studies.