

FDA's Response to External Peer Review on The Scientific Assessment of the Impact of Menthol in Cigarettes, April 6, 2022

I. INTRODUCTION

As part of FDA's ongoing effort to review the science on menthol in cigarettes, FDA has completed two scientific assessment documents. The first, entitled "Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980-2021," covers the peer-reviewed, publicly available literature spanning the period from 1980 to April 30, 2021, and focuses on the impact of menthol cigarettes on outcomes related to addiction, including progression to regular use, dependence, and cessation. The second, entitled "Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes," is comprised of three distinct evaluations: section 1 describes the results of a reproducible, transparent, and documented review of the scientific literature evaluating the impact of flavored tobacco sales restrictions or bans on tobacco use behaviors, sales of tobacco products, and unintended consequences; section 2 describes the scientific evidence relevant to consumers' product choices and intended use behaviors in response to a hypothetical menthol cigarette ban; and section 3 summarizes and evaluates modeling studies that quantify the effects of a menthol cigarette ban to inform an assessment of the potential behavioral responses to a menthol product standard. Both scientific assessment documents were included in this external peer review.

Versar, Inc., an independent contractor, coordinated an external letter peer review of these two scientific assessment documents on the impact of menthol in cigarettes. The peer review was conducted for FDA's Center for Tobacco Products. For this peer review, four experts were selected by Versar, Inc. to evaluate and provide written comments on the scientific support for FDA's conclusions in the scientific assessment documents, additional publicly available information that should have been included in the assessments, and any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

In Section II of this peer review response report, we list the charge questions given to the reviewers regarding the objective of the peer review and specific advice sought through the peer review. In Section III of this report, we provide a table containing the individual (anonymized) peer reviewers' comments along with FDA's responses to those comments, including either a description of any changes made to the scientific assessment documents in response to peer reviewer comments or an explanation of our decision to not make suggested changes.

Based on this external peer review, the scientific assessment documents were updated where appropriate and subsequently finalized. The final versions can be found at <https://www.fda.gov/science-research/peer-review-scientific-information-and-assessments/completed-peer-reviews>.

Below are the names and affiliations of the peer reviewers:

Cristine Delnevo, PhD, MPH

Rutgers University

Rachel Denlinger, PhD

Wake Forest University

Geoffrey T. Fong, PhD, FRSC, FCAHS

University of Waterloo

Andrea Villanti, PhD, MPH

University of Vermont

II. CHARGE TO REVIEWERS

Charge Questions (answered separately for each scientific assessment document):

1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.
2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.
3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

III. FDA RESPONSES TO INDIVIDUAL REVIEWER COMMENTS

In the following sections, FDA's responses to individual comments from the reviewers are organized according to the sequence of the charge questions, i.e., general impressions followed by questions 1 through 3. Comments from all four reviewers were itemized and listed under each charge question.

Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p>The <i>Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980-2021</i> is a well-written, comprehensive review of the literature. One major strength of the document is that it is reproducible and transparent, which will enable updating as additional research becomes available in the future. The weight of evidence approach is an appropriate review methodology for the intended goals of the review and the details of the weight of evidence approach are explained in great detail. Additionally, the weight of evidence figures included at the end of each section are very helpful for interpreting the conclusions, especially when topics had dozens of studies to review or the literature was mixed findings. The study inclusion/exclusion criteria are explicitly stated and have an accompanying figure describing the article selection process. However, some additional information explaining why these criteria were implemented could improve the overall quality of the review. For example, justification is needed for why only studies conducted in the US were considered eligible. Overall, the conclusions reported in this review are sound and supported by the literature. However, I recommend downgrading the conclusion regarding menthol in cigarettes and youth dependence due to the heterogeneity of study findings (additional details listed in charge question 1).</p>	<p>We thank the reviewer for this comment. Comments related to justification for criteria and downgrading conclusions regarding menthol in cigarettes and youth dependence are addressed in Reviewer #1 responses to Charge Question 1.</p>
Reviewer #2	<p>This report summarizes a tremendous volume of data and has sufficient detail to support transparency. The approach for the review is sound and logical given the stated goals of the report. The conclusions drawn across the key content areas are reasonable and scientifically supported given the available evidence. That said, there are a few areas that warrant attention.</p>	<p>We thank the reviewer for this comment. Responses to areas warranting attention are provided for the respective comments.</p>
Reviewer #2	<p>First and foremost, I did not find the rationale for <i>not</i> updating <i>all</i> topic areas through to 2021 convincing. If the focus of this report was to focus on areas where menthol was shown to have the greatest impact on public health (i.e.,</p>	<p>We have updated the review to cover topic areas for dependence in adults and smoking topography through 2021. Conclusions remain</p>

I. General Impressions		
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	<p>sensory effects, progression to regular use, dependence in youth, and cessation) – then perhaps the report should just be limited to these areas – and the older reviews on dependence and topography could be referenced. This would also improve the readability of the report as the dependence in adult section is extremely long. Alternatively, update the review for dependence in adults and smoking topography through to 2021.</p>	<p>unchanged for these areas. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.</p>
Reviewer #2	<p>Second, some additional details regarding methods seem warranted (see below). In particular, it was not clear to me as a reviewer exactly how research articles that addressed multiple topic areas were “scored” with respect to strength. Was the score (Strong or Moderate) based on the article or the methodological details for each analysis?</p>	<p>The score was based on the methodological details for each separate analysis. The rationale for this approach was because individual articles could contain analyses for multiple topic areas. Therefore, the same article could have a different score for a different topic (e.g., dependence vs. cessation).</p>
Reviewer #2	<p>Third, it is noted that there were “analyses with overlap between populations, which could reflect duplicate findings” but the report does not explain if and how this was attended to.</p>	<p>Within the conclusion sections for each topic, we have included discussion of whether there was overlap between populations, whether any findings potentially reflected duplicate findings, and how it was addressed. We also note that we considered all analyses to be distinct unless otherwise indicated.</p>
Reviewer #3	<p>The “Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021” is a well-conceived and executed systematic review of the literature on the role of menthol in cigarettes on smoking initiation and progression to regular use; sensory effects and their impact on smoking experiences; nicotine dependence; smoking topography; and smoking cessation. The consistency of the search strategy over time, clear eligibility criteria, and use of three independent reviewers ensure a rigorous review</p>	<p>We thank the reviewer for this comment.</p>

I. General Impressions		
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	<p>process likely to capture all relevant literature. The “weight of evidence” approach is appropriate, given the range of study designs and outcomes included in the review. A particular strength of this review is the application of the “weight of the evidence” approach in identifying strong, moderate and weak studies and documenting how each was categorized and used in the summative evaluations for each research question. The graphs presented for each question aid in synthesizing the body of literature, leading to the conclusions in the text.</p>	
Reviewer #3	<p>The Background and Rationale to the review provided important insight into the sensory and biological functions of menthol in cigarettes, as well as the background of FDA’s work on this topic, both independently and through its Tobacco Products Scientific Advisory Committee. The Background sections for each research question are accurate and clearly written, as are the brief descriptions of each analysis included in the section, and the overall conclusions. The systematic approach to categorizing, describing, and evaluating each study in the review is evident in each section of the report. The summative evaluations derive from a standardized weighting of the data presented; the graphs and tables in each section provide clear results of these procedures. Together, these methods highlight the rigor and transparency of the review process and the conclusions presented.</p>	We thank the reviewer for this comment.
Reviewer #4	<p>The scientific review of the many studies on the effects of menthol in cigarettes on tobacco addiction was well-organized. The introduction and background of key sections of the review provided important context for the evidence review that followed, and consequently, the review offered important information to understand the mechanisms for the impact of menthol on initiation/progression, greater dependence, and lowered rates of cessation success: sensory effects and smoking topography. As a result, the review</p>	We thank the reviewer for this comment.

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	<p>resulted in addressing not only <i>whether</i> menthol was associated with the effects but <i>how</i> and <i>why</i> those effects were obtained.</p> <p>As presented below in the section-by-section comments, the many studies reviewed were described accurately as were the findings of the analyses of those studies.</p> <p>The review presented the conclusions drawn in the strength-of-evidence review in each of the sections were scientifically justified and appropriate.</p> <p>FDA's evidence review concludes that menthol in cigarettes is associated with effects on sensory effects, progression to regular smoking, dependence, and cessation, both among smokers in the general population, and among African American smokers. These effects of menthol, taken as a whole, lead to the general conclusion that menthol in cigarettes has a negative impact on public health. This evidence offers a sound foundation for considering measures to address the negative impact of menthol in cigarettes on public health.</p>	

II. Response to Charge Questions

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.

REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p><u>Age of Initiation Conclusion</u> – The review’s conclusion (menthol in cigarettes is not associated with an earlier age of smoking initiation) is supported based on the literature reviewed and the weight of evidence analysis. Only 2 articles categorized as strong were included in the analysis and both reported no effect. The remaining articles included in the analysis were categorized as moderate with 1 reporting a positive effect, 14 reporting no effect, and 3 reporting a negative effect. Thus, no association is the appropriate conclusion for age of initiation.</p>	We thank the reviewer for this comment.
Reviewer #1	<p><u>Sensory Effects</u> –The review’s conclusion (the sensory effects of menthol are associated with positive smoking experiences among menthol cigarette smokers) is supported based on the literature reviewed and the weight of evidence analysis. All studies reported in this section, including clinical and non-clinic studies, met the review criteria and were appropriate for analysis. Of the 23 strong/moderate articles included in the review, 18 found that sensory effects of menthol contributed to positive subjective experiences, while 5 found no differences in sensory experiences between menthol and non-menthol smokers. Thus, menthol is associated with positive smoking experiences.</p>	We thank the reviewer for this comment.

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Reviewer #1	<u>Progression to Regular Use</u> – The review’s conclusion (menthol in cigarettes is associated with progression to regular cigarette smoking among youth and young adults) is supported based on the literature reviewed and weight of evidence analysis. Although the analysis only included six studies, four were categorized as strong, tier 1 studies and two were categorized as strong, tier 2 studies. Five studies included nationally representative samples. All studies supported the conclusion that menthol smoking facilitates progression to regular smoking among youth and young adults.	We thank the reviewer for this comment.
Reviewer #1	<u>Dependence (Adults)</u> – The review’s conclusion (the evidence is not sufficient to support conclusions of an association of menthol in cigarettes with dependence among adults) is supported based on the literature reviewed and the weight of evidence analysis. Although this topic had the most number of studies (n=197), the majority (n=110) found no significant differences in dependence between adult menthol and non-menthol smokers. Given that inconsistency of findings across numerous studies, the conclusion that an association cannot be determined is appropriate.	We thank the reviewer for this comment.
Reviewer #1	<u>Dependence (Youth)</u> – The review’s conclusion (menthol in cigarettes is associated with greater dependence among youth) should be shifted down one category in the NavGuide systematic review methodology. This would result in the following conclusion: menthol in cigarettes is likely associated with greater dependence among youth . I acknowledge that multiple strong studies, including nationally representative data, are included in this weight of evidence analysis; but, the evidence was split between studies reporting a positive association (n=12) and no effect (n=12). However, the positive association did have more studies categorized as strong (n=8) compared to no effect (n=1). There were also three studies that found a negative association. Since the study results are mixed, albeit skewed towards a positive association,	We respectfully disagree that conclusions on menthol cigarettes and youth dependence should be downgraded. We note that there were 19 articles on youth dependence with 29 analyses, i.e., some articles contained more than one dependence outcome or evaluated more than one youth sample and were counted as separate analyses within the same article. Although some analyses did not find a relationship between menthol cigarettes and dependence in youth, the limitations of these analyses resulted in their

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	I would recommend changing the conclusion by adding the qualifier “ likely ” to address any potential ambiguity.	lower weight in the totality of evidence, such that a positive association has been established through multiple well-designed, well-conducted studies where chance, bias, and confounding can be ruled out with reasonable confidence. For example, when considering the human nationally representative analyses, we note that nine of the analyses that either did not find an effect of menthol or found a negative effect on youth dependence were from two articles that evaluated dependence measures in youth from the 1999-2019 NHANES and 2003, 2006/7 TUS-CPS samples. However, no sample sizes were reported for any population in the study and the study included participants aged 18-19 years in the youth category, who could legally purchase and openly use tobacco at the time of the survey; thus, this age group has patterns of tobacco use and accessibility that differs from 12-17 year olds (i.e., the majority age group used for other nationally representative surveys of youth and tobacco dependence). These factors likely confound the results. Alternatively, six strong and one moderate nationally representative analyses from independent articles that analyzed surveys designed to collect data on youth tobacco use (i.e., NYTS, PATH) support that youth who smoke menthol cigarettes are more dependent than

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		youth who smoke non-menthol cigarettes. Four of the strong analyses are recent findings, identified in the 2019-2021 update. In support of this association, in Section XV. Summary of Evidence, we also highlight a mechanism by which menthol enhances the addictive effects of nicotine in the brain. Given that youth are particularly susceptible to nicotine addiction due to ongoing brain development, the combined effects of menthol and nicotine in the youth brain indicate a mechanism that supports the behavioral findings of greater dependence from the strongest nationally representative studies on youth dependence. Therefore, we maintain the conclusion that menthol in cigarettes is associated with greater dependence among youth.
Reviewer #1	<u>Topography</u> – The review’s conclusion (the evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with altered smoking topography) is supported based on the literature reviewed and the weight of evidence analysis. Eleven articles were reviewed in this section and overall reported mixed findings. Five studies reported no effect, three reported positive associations and three reported negative association. Thus, insufficient evidence to support an association is the appropriate conclusion.	We thank the reviewer for this comment.
Reviewer #1	<u>Cessation (General Population)</u> – The review’s conclusion (menthol in cigarettes is likely associated with decreased cessation success among the general population) is supported by the literature reviewed and the weight of	We thank the reviewer for this comment and agree that the Okuyemi et al. 2003 and Harris et al. 2004 studies represent duplicative findings. As

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	<p>evidence analysis. The evidence was mixed with 20 positive associations (13 tier 1 studies; 7 tier 2 studies) and 15 no effect studies (8 tier 1 studies; 7 tier 2 studies). However, the results skewed towards a positive association based on the greater number of strong studies versus moderate studies in the positive direction. No studies reported a negative association (menthol smokers had increased cessation success compared to non-menthol smokers), which further strengthens the evidence towards a likely positive association of decreased cessation success for menthol smoking.</p> <p>Note: The Harris et al., 2004 study reported in this section is a secondary analysis of Okuyemi et al., 2003 (an efficacy trial of bupropion). It is unclear if/why Harris et al., 2004 is included in the weight of evidence analysis since it seems both manuscripts report cessation outcomes by menthol status.</p>	<p>such, we have removed the Harris et al. 2004 study from the weight of evidence for cessation. The conclusions for cessation remain unchanged.</p>
Reviewer #1	<p><u>Cessation (African American Population)</u> – The review’s conclusion (menthol in cigarettes is associated with decreased cessation success among African Americans*) is supported by the literature reviewed and the weight of evidence analysis. Twelve studies reported positive associations and all were categorized as strong studies. Eight studies reported no effect and zero reported a negative association. Based on the greater number of strong versus moderate studies reported for the positive association, the conclusion of decreased cessation among African American persons is appropriate. These findings are consistent with two meta-analyses (Sanders et al., 2017; Smith et al., 2020) that were not included in the weight of evidence analysis.</p> <p>*Suggestion: Include ‘persons’ or ‘individuals’ after African Americans.</p>	<p>We thank the reviewer for this comment and for suggesting the inclusion of ‘persons’ or ‘individuals’ after ‘African American’ and other racial/ethnic groups.’ We have updated the review to incorporate this language throughout.</p>
Reviewer #2	<p>Based on the weight of evidence- the conclusions drawn across the key content areas are reasonable and scientifically supported given the available evidence.</p>	<p>We thank the reviewer for this comment.</p>

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
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Reviewer #3	In each section of the report, the conclusions were scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	Yes, the conclusions of the evidence review in each section were scientifically supported given the available evidence. I have provided specific comments in section III Specific Observations for each section. There were no sections in this evidence review for which the conclusions were not supported.	We thank the reviewer for this comment.

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p>Three additional manuscripts report baseline smoking characteristics (e.g., dependence, cigarettes per day, biomarkers of nicotine exposure) between menthol and non-menthol smokers enrolled in cigarette nicotine reduction studies.</p> <ul style="list-style-type: none"> • Davis DR, Miller ME, Streck JM, et al. Response to Reduced Nicotine Content in Vulnerable Populations: Effect of Menthol Status. Tob Regul Sci. 2019;5(2):135-142. doi:10.18001/TRS.5.2.5 • Denlinger-Apte RL, Cassidy RN, Colby SM, Sokolovsky AW, Tidey JW. Effects of Cigarette Nicotine Content and Menthol Preference on Perceived Health Risks, Subjective Ratings, and Carbon Monoxide Exposure Among Adolescent Smokers. Nicotine Tob Res. 2019;21(Suppl 1):S56-S62. doi:10.1093/ntr/ntz127 • Denlinger-Apte RL, Kotlyar M, Koopmeiners JS, et al. Effects of Very Low Nicotine Content Cigarettes on Smoking Behavior and Biomarkers 	We thank the reviewer for suggesting these articles. A more detailed response is provided immediately below.

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	of Exposure in Menthol and Non-menthol Smokers. Nicotine Tob Res. 2019;21(Suppl 1):S63-S72. doi:10.1093/ntr/ntz160	
Reviewer #1	<p>Given that several other studies and trials reporting baseline characteristics of menthol and non-menthol smokers were included in the review, it seems reasonable to include these as well. They may be relevant to include in Section XIV. Strength of Evidence: Dependence. In the Davis et al. 2019 manuscript, there were no observed differences in cigarettes per day or dependence as assessed by the FTCD between menthol and non-menthol smokers; however, the sample was comprised of people with opioid dependence, affective disorders and low socioeconomic status. There was a non-significant trend towards older age of first cigarette among menthol smokers. In the Denlinger-Apte, Kotlyar et al., 2019 manuscript, menthol smokers reported smoking fewer cigarettes per day, had lower TNEs and CO relative to non-menthol smokers at baseline. However, no differences in dependence as assessed by the FTCD were observed between menthol and non-menthol smokers. In Denlinger-Apte, Cassidy et al., 2019 manuscript, daily adolescent menthol smokers had higher dependence as assessed by the mFTQ and non-significant trend towards smoking more cigarettes per day (p=0.06) at baseline compared to daily adolescent non-menthol smokers. This study may also be appropriate to include in Section XII. Strength of Evidence: Sensory Effects as it reports outcomes by menthol status for the Cigarette Evaluation Scale. Specifically, menthol, normal nicotine content Spectrum cigarettes had lower craving reduction compared to non-menthol normal nicotine content Spectrum cigarettes (p=0.04); no other differences were observed for the other subscales.</p>	<p>We have updated the adult dependence section of the review to include studies published from 2019 through April 30, 2021. These articles were identified in the search for dependence in adults. Study summaries have been included in the dependence section and incorporated into the weight of evidence for dependence. With the addition of these analyses, conclusions remain unchanged: the evidence is not sufficient to support conclusions of an association of menthol in cigarettes with dependence among adults. We also thank the reviewer for highlighting the Denlinger-Apte, Cassidy et al., 2019 manuscript, which focuses on adolescents, and should have been included in the weight of evidence for youth dependence and sensory effects. With the addition of these analyses, the weight of evidence continues to support that menthol in cigarettes is associated with greater dependence in youth and that the sensory effects of menthol are associated with positive subjective smoking experiences among menthol cigarette smokers.</p>
Reviewer #1	<p>One topography study by Gunawan & Juliano (2020) is included in Section XIV. Strength of Evidence: Dependence but not in Section XV. Strength of</p>	<p>We note that the referenced article was included in the Sensory Effects section and is now included</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
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	Evidence: Topography. In this study, menthol smoking status was not associated with increased smoke exposure so it seems like an important study to include in the review.	in the sections for Topography and Dependence, with the addition of 2019-2021 analyses covering these topic areas.
Reviewer #2	I am not aware of any additional publicly available information that should have been included given the search parameters. I am unclear however why the search was limited to only studies occurring the US. The rationale for this should be included.	Studies were limited to the US to account for potential differences in cigarette design across countries, ¹ differences in the prevalence and patterns of menthol use, ² and non-US tobacco regulatory policies (e.g., menthol cigarette restrictions, cigarette packaging bans) ³ that may influence menthol cigarette use. We have included this rationale as footnotes under Section VI. Study Selection.
Reviewer #3	I did not identify other publicly available information that should have been included in the review based on the Research Questions and the dates of inclusion. There are, however, studies published after April 2021 addressing the role of menthol cigarettes in smoking cessation and changes in smoking behavior that would likely be captured in a future review. Two of these are listed below: <ul style="list-style-type: none"> Leas EC, Benmarhnia T, Strong DR, Pierce JP. Effects of menthol use and transitions in use on short-term and long-term cessation from 	We thank the reviewer for this comment and for noting two additional articles that would likely be captured in future reviews of the literature.

¹ O'Connor RJ, Hammond D, McNeill A, et al (2008) How do different cigarette design features influence the standard tar yields of popular cigarette brands sold in different countries? *Tobacco Control*;17:i1-i5.

² Giovino GA, Sidney S, Gfroerer JC, et al (2004). Epidemiology of menthol cigarette use. *Nicotine & Tobacco Research*, 6 Suppl 1, S67–S81. <https://doi-org.fda.idm.oclc.org/10.1080/14622203710001649696>

³ Erinoso O, Clegg Smith K, Iacobelli M, et al. (2021) Global review of tobacco product flavour policies. *Tobacco Control*;30:373-379.

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	<p>cigarettes among US smokers. Tob Control. 2021. PubMed PMID: 34230056.</p> <ul style="list-style-type: none"> • Davis DR, Parker MA, Delnevo CD, Villanti AC. Examining Menthol Preference as a Correlate of Change in Cigarette Smoking Behavior over a One-Year Period. Int J Environ Res Public Health. 2021;18(20). PubMed PMID: 34682624. PubMed Central PMCID: PMC8535481. 	
Reviewer #3	<p>There is also a paper that may be relevant for the background and rationale, documenting the nicotine levels in 100 brands of U.S. cigarettes. This research was funded by the 22nd Century Group and reports nicotine levels in cigarettes marketed as menthol and non-menthol. The citation is listed below:</p> <ul style="list-style-type: none"> • Carmines, E., & Gillman, I. G. (2019). Comparison of the Yield of Very Low Nicotine Content Cigarettes to the Top 100 United States Brand Styles. Beiträge zur Tabakforschung International/Contributions to Tobacco Research, 28(6), 253-266. https://doi.org/doi:10.2478/cttr-2019-0005. 	<p>We thank the reviewer for this comment. Given the primary focus of the referenced research is the nicotine content and yield of very low nicotine content cigarettes, we did not identify information that would provide additional background and rationale for this menthol review.</p>
	<p>This more recent study adds to the body of evidence on menthol and cessation, and is consistent with the conclusions of the review on the effects of menthol on decreasing cessation success:</p> <p>Leas EC, Benmarhnia T, Strong DR, et al. Effects of menthol use and transitions in use on short-term and long-term cessation from cigarettes among US smokers. Tob Control. Published Online First: 6 July 2021. doi: 10.1136/tobaccocontrol-2021-056596.</p> <p>A study of US adult smokers (pooled sample of two cohorts participating in PATH study: n=3590, 2013-2016; n=2169, 2014-2017) found that switching from menthol to non-menthol cigarettes (vs maintaining menthol use) significantly increased both short-term (30+ day) and long-term (12 month) smoking cessation, while switching from</p>	<p>We thank the reviewer for this comment. We note that the Leas 2021 article was published after the April 2021 search cutoff for this document and would likely be captured in future reviews of the literature.</p>

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	non-menthol to menthol cigarettes (vs maintaining non-menthol use) significantly decreased cessation success.	
Reviewer #4	<p>There are other experimental studies in which menthol smokers are switched to non-menthol cigarettes. Such studies provide evidence on the potential impact of a menthol cigarette ban on smoking behavior, and would possibly be a bridge between the studies on addiction in this evidence review and the evidence on the potential impact of prohibiting menthol as a characterizing flavor in cigarettes. These two U.S. studies described below could be included in this evidence review or in the other evidence review:</p> <p>Bold KW, Jatlow P, Fucito LM, et al. Evaluating the effect of switching to non-menthol cigarettes among current menthol smokers: an empirical study of a potential ban of characterising menthol flavour in cigarettes. <i>Tob Control</i> 2020;29:624–30.doi:10.1136/tobaccocontrol-2019-055154pmid:http://www.ncbi.nlm.nih.gov/pubmed/31685586</p> <p>Within-subject trial where current menthol smokers (n=29) in Connecticut were switched to non-menthol cigarettes for two-week period to model a potential menthol cigarette ban. After switching to matched-brand non-menthol cigarettes, menthol smokers used fewer non-menthol cigarettes per day relative to menthol cigarettes (mean decrease=2.2 cigarettes, SD=3.2, p<0.001), had lower nicotine dependence (reduced by >18%, p<0.001), greater increases in motivation and confidence in quitting (motivation: mean increase=2.1, SD=2.8, p<0.001; confidence: mean increase=1.3, SD=3.3, p=0.04). Preliminary analyses found that Black smokers had greater reductions in cigarettes per day (mean decrease=3.5 cigarettes, SD=2.8) vs non-Black smokers (mean decrease=0.2, SD=2.6). When asked what they</p>	<p>We agree that the suggested articles provide evidence supporting the potential impact of a menthol cigarette ban on smoking behavior. While these studies were identified in our menthol search, they were determined to be out of scope for this review, given our specific focus on addiction and not evaluation or assessment of potential consequences of a menthol ban. We note that in these studies, some menthol smokers were switched to non-menthol cigarettes and the cessation outcomes were evaluated between menthol smokers and menthol smokers who were artificially switched to non-menthol cigarettes. However, such an analysis does not appropriately address whether menthol affects cessation success.</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>would do if menthol cigarettes were no longer available at the end of the study, smokers reported they were significantly more likely to quit smoking (M=6.5 out of 10, SD=3.0) than to continue smoking the non-menthol cigarettes they tried (M=4.1 out of 10, SD=2.6), $t(28)=2.52$, $p=0.02$, Cohen's $d=0.47$.</p> <p>Kotlyar M, Shanley R, Dufresne SR et al. Effects of smoking behavior of switching menthol smokers to non-menthol cigarettes. NTR 2021;11:1921-1921. https://doi.org/10.1093/ntr/ntab090</p> <p>Study conducted in Minnesota where African American menthol smokers who were interested in quitting were randomized to continue smoking menthol (n=60) or switch to non-menthol cigarettes (n=62) for a four-week period prior to a quit attempt. Menthol smokers who switched to non-menthol cigarettes smoked fewer cigarettes per day (mean ratio: 0.86; 95% confidence interval [CI]: 0.76, 0.98; $p = .02$), reported lower withdrawal symptom severity (mean difference -1.29; 95% CI: -2.6 to -0.01; $p = .05$) and higher perceived effectiveness of their skills for quitting smoking (mean difference 0.56; 95% CI: 0.02-1.10; $p = .05$), compared to menthol smokers who continued using menthol cigarettes. The authors note that the decrease in smoking was modest, and that biomarkers of exposure were similar for those who switched to non-menthol and those who continued using menthol.</p>	

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	Justification for the inclusion/exclusion criteria for identifying relevant studies is needed. For the searching and identifying articles criteria, why was 1980 selected as the first year for inclusion and why were only studies conducted in the US included? For study inclusion/exclusion criteria, why were studies on intentions to quit or number of quit attempts excluded from the review, when other proxy measures of dependence (like CPD and TNE) were included?	Cigarette design and smoke composition have changed since 1950. We selected 1980 as the cut-off year for inclusion to minimize the potential for differences in cigarette design, other than menthol, that may have influenced study findings (e.g., changes in filter tips). ⁴ Similarly, studies were limited to the US to account for potential differences in cigarette design across countries, ⁵ differences in the prevalence and patterns of menthol use, ⁶ and non-US tobacco regulatory policies (e.g., menthol cigarette restrictions, cigarette packaging bans) ⁷ that may influence menthol cigarette use. We have included this rationale as footnotes under Section VI. Study Selection. Regarding studies on quit intentions and attempts, these outcomes and analyses were not included because they are not direct indicators of cessation success, whereas CPD and TNE were included as indices of dependence/abuse liability.

⁴ Dietrich Hoffmann, Ilse Hoffmann (1997) The changing cigarette, 1950-1995, Journal of Toxicology and Environmental Health Part A, 50:4, 307-364, DOI: 10.1080/009841097160393

⁵ O'Connor RJ, Hammond D, McNeill A, et al (2008) How do different cigarette design features influence the standard tar yields of popular cigarette brands sold in different countries? Tobacco Control;17:i1-i5.

⁶ Giovino GA, Sidney S, Gfroerer JC, et al (2004). Epidemiology of menthol cigarette use. Nicotine & Tobacco Research, 6 Suppl 1, S67–S81. <https://doi-org.fda.idm.oclc.org/10.1080/14622203710001649696>

⁷ Erinoso O, Clegg Smith K, Iacobelli M, et al. (2021) Global review of tobacco product flavour policies. Tobacco Control;30:373-379.

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	Additional explanation is needed for why recent publications (2019-2021) were not included in reviews for age of initiation, dependence in adults, and smoking topography. If the FDA was monitoring the literature routinely and read additional articles sufficiently to conclude “the evidence remained consistent for these topic areas” (page 16, paragraph 3), then why not incorporate the studies into the formal weight of evidence analysis and have a completely up to date review?	We have updated the review to cover topic areas for dependence in adults and smoking topography through 2021. Conclusions remain unchanged for these areas. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.
Reviewer #1	In Appendix E, is there a reason the numerical score is not included and just the categorical score of strong or moderate is reported? Additionally, as I was reading each study description within the main text I thought including the tier and score at the end in parenthesis would help the reader to better conceptualize the weight of evidence analysis and interpret the figures.	We thank the reviewer for this suggestion. We updated the article headings to include the study and included the strength of each study in parenthesis at the end of each study description to improve comprehension. In Appendix E, we used the strong, moderate, or weak (not included) categorization because this provided sufficient information for the weight of evidence ranking and to limit the appearance of criticism of the studies.
Reviewer #1	I have several comments related to the overall presentation and formatting of the document. First, I would recommend alphabetizing the study descriptions in each section by order of the first author’s last name. In most sections, this was attempted but some articles were out of order. I found sections that started each paragraph with the Author’s Last Name and Date were easier to read and keep the content organized compared to sections that wrote each paragraph more in a narrative form (i.e., did not start with Author and Date). Given the length of the document, small revisions to enhance readability are helpful. Second, in some sections, the length of the study descriptions were quite long (upwards of ½ page or more) while in other sections the study	We alphabetized the study descriptions in each section as suggested by the reviewer. Regarding the length of the study descriptions, we note that study descriptions were generally shorter in cases where the outcome was not the primary focus of the study or when the study had been previously described in the section. However, for clarity, we have added additional detail to various study summaries throughout the document and other edits to enhance readability. We also reported p-

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
	descriptions could be as short as 1-2 sentences. As I was reading, I questioned whether the inconsistency in length could unconsciously imply that some studies are more important than others. For the studies with longer descriptions, it could be beneficial to streamline the information presented while for studies with shorter descriptions it might be beneficial to expand the content reported. Third, statistics and p-values were reported inconsistently throughout the document. In some study descriptions, the p-value and/or the actual statistic were included, others not.	values and statistics throughout for significant findings; p-values were not included for null findings unless there was a trend toward significance.
Reviewer #1	One important limitation briefly noted was publication bias. The sections that reported inconsistent results and thus an association could not be determined could be disproportionately impacted by publication bias. It seems plausible that other studies and/or analyses found no significant differences between menthol and non-menthol smokers but were not published due to journal biases against publishing null results. As such, I think publication bias requires slightly more discussion as a review limitation than one sentence.	We thank the reviewer for this suggestion and for noting the effect publication bias may have had on inconsistent results reported in the literature. We have included additional discussion and citations on publication bias to the limitations section.
Reviewer #1	One final comment is to incorporate people-first language into the review document, especially when referring to different racial groups (e.g., African American persons rather than African Americans).	We thank the reviewer for this comment. We have updated the review to incorporate 'persons' or 'individuals' when referring to African American individuals and other racial/ethnic groups throughout.
Reviewer #2	It was not clear to me as a reviewer exactly how research articles that may have addressed multiple topic areas were handled. Was the score (i.e., strong, moderate, or weak) based on the article or the methodological details for each analysis? This is a particular area of concern for the two Curtin et al., research papers (scored as "Moderate") which used multiple datasets to examine multiple outcomes. In particular, I was struck on page 54 where the authors of	Each score was based on the methodological details for each analysis. The rationale for this approach was to address articles that contained multiple topic areas (e.g., dependence vs. cessation). Therefore, an analysis that addressed two topic areas has two independent scores: one

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
	the report note “... given the cross-sectional nature of the study, it is unclear how the assessment of odds of being a daily vs. nondaily smoker could be classified as progression without a baseline reference point of initial use.” This seems to be a considerable weakness for the outcome of focus but the Curtin et al., paper is scored as “moderate.”	for each topic area. We have explicitly stated this in section “VIII: Weight of Evidence” for clarity. We also note that the referenced Curtin paper was evaluated as a smoking frequency (dependence) outcome rather than progression, given the noted limitation to the progression definition.
Reviewer #2	The sample sizes and characteristic column in the appendix table should clearly and explicitly note the data sources if they are large public access datasets like NSDUH, NYTS, TUS-CPS etc. to facilitate identification of studies examining similar outcomes.	We have included data sources in the appropriate columns in Appendix E.
Reviewer #2	The report on page 14 notes that “analyses with overlap between populations, which could reflect duplicate findings” was attended to, but not <i>how</i> it was attended to.	Within the conclusion sections for each topic, we have included discussion of whether there was any overlap between populations, whether any of the findings potentially reflected duplicate findings, and how this was addressed. We also note that we considered all analyses to be distinct unless otherwise indicated.
Reviewer #2	On page 110 it states “Because several studies performed analyses using the same sample population (i.e., data set, survey), some publications may present repetitive or duplicative results. Although we note data source and sample populations, we considered all analyses to be distinct.” It would be useful to explain to the reader more clearly what the limitations of this approach might be. Does it conflate any findings? Does it yield conflicting findings? Some consideration of this seems warranted.	We acknowledge that this approach has the potential to conflate findings or yield conflicting findings. However, given different statistical methods or variable definitions of outcomes, we think that each analysis adds value to the evidence base and FDA is transparent about the identified analyses that may be duplicative. We

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
		included additional language in the limitations section to address this issue.
Reviewer #3	One methodological concern with the review methods is the lack of assessment of “other bias” as a potential risk of bias, as outlined in Cochrane Review Methods. This could reflect the funding source of the study or a departure from standard measures (e.g., age groups, heaviness of smoking index – HSI) that could produce bias in analysis or reporting of study measures. Inclusion of “other bias” would affect the overall scoring of each analysis.	Within the scoring sheets (Appendix C), we have incorporated risk of bias criteria (Appendix B) to assess several potential risk of bias areas, including sampling and selection bias, recall bias, response bias, attrition bias, and considerations for assessments that departed from standard measures (i.e., threats to construct validity and using measures that have not been validated). We acknowledge that funding bias was not incorporated as a consideration in scoring the studies and have included this as a limitation in the “Limitations” section of the document.
Reviewer #3	Analyses related to initiation focus on age of first cigarette among current cigarette smokers, but the review currently misses the broader context of menthol use related to initiation: the higher prevalence of menthol cigarette use among youth and young adults compared to older adults. Epidemiological studies document a strong age gradient in use, with the youngest cigarette smokers most likely to use menthol cigarettes. These data are essential to evaluating the impact of menthol cigarettes on public health and are not presented in the current review. Additionally, it is not clear why several studies that reported “age at initiation” as part of baseline data were excluded, when a number of included studies did not report “age at initiation” as a primary outcome, but did so in the description of their study sample.	We agree that epidemiological studies of menthol prevalence are important for understanding the impacts of menthol on public health. However, the scope of this RTD is menthol’s impact on addiction, and therefore did not include studies that focused on the prevalence of menthol use. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
Reviewer #3	<p>Other recommendations include:</p> <ul style="list-style-type: none"> • Providing detail on the age groups used in each analysis – Adults? Young adults? Youth? Findings from these studies may differ depending on the age at which participants are surveyed. 	We have provided additional details on age groups in the section summaries
Reviewer #3	<ul style="list-style-type: none"> • Providing subheadings of strong, moderate and quantitative/qualitative when describing individual studies under a specified topic. Another option is to note these categories in parentheses (e.g., (Quantitative, Strong)) to be able to track how the articles appear in the figures. 	We have clarified the analyses' strength rating following its summary throughout the document.
Reviewer #3	<ul style="list-style-type: none"> • Spelling out comparison groups in all descriptions of analyses (e.g., higher odds of outcome compared with [reference group]). 	We have stated the comparison groups in all descriptions of analyses throughout the document.
Reviewer #3	<ul style="list-style-type: none"> • Considering inclusion of 2019-2021 data on age of initiation, dependence in adults, and smoking topography. It is unclear why these studies were excluded from the full review, but their findings noted at a high level. It would be preferable to have everything presented consistently in this single document. 	We have updated the review to cover topic areas for dependence in adults and smoking topography through 2021. Conclusions remain unchanged for these areas. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.
Reviewer #4	<p>My specific comments on methodology, strength of data, limitations are provided in section III Specific Observations. In general, there were no concerns about the methodological quality of the review. This was a strong evidence review that resulted in important conclusions that were scientifically supported.</p>	<p>We thank the reviewer for this comment. Responses to specific comments on methodology, strength of data, and limitations are provided in Section III.</p>

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	5	Acronyms List	The following are missing: PND, ANOVA, ANCOVA	We have included these acronyms in the list.
Reviewer #1	5	Acronyms List	RRR: Relative risk ratio needs to be separated from prior acronym	We separated RRR: Relative risk ratio from the prior acronym.
Reviewer #1	7	2	“thus promoting cigarette smoking” – Is promoting the best word or perhaps facilitating/enabling would be more appropriate?	We have updated this word to “facilitating.”
Reviewer #1	10	1	How frequently was a fourth independent reviewer required for the full text screening? I would include this information in the paragraph.	There were no instances that required resolution by a fourth independent reviewer. We have included this information in the review.
Reviewer #1	14	2	‘A qualitative professional assessment...’ – What do the authors mean by ‘professional’ in this context? Was this completed by a separate qualitative research professional?	The reference to “professional” is intended to reflect that article assessments were conducted by subject matter experts in fields relevant to the topic areas and articles included in the review. We have removed the word “professional” and revised the language to clarify “subject matter experts.”
Reviewer #1	19	N/A	Summary of Analyses on Age at First Use – I would recommend re-ordering the studies so they are in alphabetical order based on the first author. Most articles seem to be in order but a few are not.	We thank the reviewer for this suggestion. We have updated the document throughout so that the studies are listed in alphabetical order by the last name of the first author in each section.
Reviewer #1	20	N/A	“Curtin et al. (2014a) analyzed data from TUS-CPS (2003, 2006/7). They found that menthol smoking was associated with a statistically older mean <i>age of regular smoking</i> by approximately 2.5 months for past month (p	We thank the reviewer for this comment. Based on issues raised by reviewers about the age of

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			< 0.0001), regular (p < 0.0001), and daily smokers (p < 0.0001) compared to non-menthol smokers.” – I think this study is listed in the wrong subsection. Currently, it is under the <i>‘Ten analyses found no relationship between menthol and age of regular use’</i> but since the results show older mean age I think it belongs in <i>‘One analysis found that menthol use is associated with an older age of regular use.’</i>	initiation topic, this section has been removed from the document.
Reviewer #1	20	N/A	<i>‘One analysis found that menthol use is associated with an older age of regular use.’</i> needs to be revised to say <i>‘Two analyses’</i> if the above study is moved to this subsection.	We thank the reviewer for this comment. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.
Reviewer #1	29	3	The first sentence for Perkins et al., 2018 has inconsistent spacing/formatting. In the second sentence, the ellipsis seems out of place/unnecessary.	We corrected the formatting in this section and removed the ellipsis from the second sentence.
Reviewer #1	34	2	There are three typographical errors in Villanti et al., 2019. In sentence three, nonflavored should be non-flavored. In sentence three, the word ‘use’ is missing after “past 12-month and past 30-day cigarette”. In sentence four, it should be ‘adjusted prevalence ratio’ not “adjusted prevalence ration”.	We thank the reviewer for this comment. We have updated the review to correct these typographical errors as suggested.
Reviewer #1	39	N/A	Scales of Nicotine Dependence – Consider reviewing this section and alphabetizing the study order based on author’s last name.	We thank the reviewer for this suggestion. We have updated the document throughout so that the studies are listed in alphabetical order by the last name of the first author in each section.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	39	4	Curtin et al., 2014 – The study citation is at the end of the paragraph rather than the beginning like other listed studies. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	41	5	Miller et al., 1994 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	42	2	Muscat et al., 2009 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	42	4	Okuyemi et al., 2007 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	42	6	Rojewski et al., 2014 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	43	5	Ahijevych & Parsley, 1999 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	45	2	Sentence 5 – I did not understand what was meant by “30 non-overlapping estimates”	This statement is in reference to the results as presented in the cited study. Per the publication, where multiple papers were based on the same source data, the paper that utilized the largest percentage of the data was generally selected. “Non-overlapping” is assumed to reference

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
				studies included in the meta-analysis that did not contain overlapping data.
Reviewer #1	45	3	Curtin et al., 2014 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	45	4	Hyland et al., 2002 – The study citation is at the end of the paragraph rather than the beginning. Consider revising for consistency and readability.	We adjusted the citation so it is at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	46	1	Ahijevych et al., 2002 – Avoid using the word Caucasian. It has a racist legacy. Instead use White persons or European American persons (depending on which is appropriate).	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	47	4	Blot et al., 2011 – This is the only study in this Cigarettes per Day (CPD) section to report the actual number of cigarettes smoked per day by menthol and non-menthol status. It seems odd to include it here but not in the other studies. Either delete the CPD data here or consider adding CPD data to each study in this section.	We have removed the CPD-specific information from this summary.
Reviewer #1	47	5	Brinkman et al., 2012 – I am not sure why this study is included in this section. It is examining differences in exposure to particles when smoking menthol and non-menthol cigarettes. The conclusion that participants smoked fewer menthol CPD seems irrelevant since they	We agree that the study’s primary outcome does not focus on CPD, but we note that the study is included in the CPD section because the outcome is presented in the study. Study weaknesses related to the possible confounding effect given

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			were mostly non-menthol smokers and the study purpose was not a behavioral assessment of differences in smoking.	that the majority of smokers were non-menthol smokers are noted in the review and were considered in the study score.
Reviewer #1	48	6	Hyland et al., 2002 – Missing p-value and limited information presented about the study design.	P-values were not reported for these results. We have revised the language in this summary remove the term “significantly,” as this term was not used in the publication for these results.
Reviewer #1	48	7	Jain et al., 2014 – Very little information is presented about the study design. Did the analyses adjust for any covariates when reporting differences in CPD between menthol and non-menthol smokers?	We have included additional details of the study within the text. Analysis reported for CPD were unadjusted.
Reviewer #1	49	7	Gan et al., 2016 – should it be fewer pack-years (rather than smaller pack-years)?	We have updated the language to state “fewer pack-years.”
Reviewer #1	51	2	Fagan et al., 2016 – Very little information presented about the study design	We have included additional details of the study within the text.
Reviewer #1	51	3	Faseru et al., 2011 – Very little information presented about the study design	We have included additional details of the study within the text.
Reviewer #1	52	10	Ahijevych et al., 2018 – Write out hour instead of abbreviating it ‘hr’	We have updated “hr” to “hour.”
Reviewer #1	53	2	Gubner et al., 2018 – This study reported the statistic (t-test) and the p-value while most other studies in this section just include the p-value. Consider deleting this statistic for this study or revising all studies to include the statistic.	We removed the t-test statistic from the text for consistency.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	56	2	Perkins et al., 2018 – Inconsistent spacing for the first sentence.	We have adjusted the spacing in this sentence for consistency.
Reviewer #1	57	4	Henderson et al., 2017 – “Menthol also selectively enhanced $\alpha 4\alpha 6^*$ nAChR upregulation...” I am tagging this to confirm the correct subtype is reported since other subtypes are very similar ($\alpha 4\beta 2$ or $\alpha 4\alpha 6\beta 2$). Also, in the last sentence ‘ $\alpha 4\alpha 6\&$ ’ the subtype includes an ampersand. I am tagging this to confirm it is correct.	We confirm that the correct subtype ($\alpha 4\alpha 6^*$) is reported. We also corrected the ampersand, which was a typographical error.
Reviewer #1	59	6	Fagan et al., 2016 – This study description needs to be revised for clarity. I believe it should be Native Hawaiian rather than Hawaiian. If the study is among Native Hawaiian persons (with a sample size of 186) why are results reported for White menthol smokers?	We revised the language to clarify that the study was conducted among smokers in Hawaii.
Reviewer #1	60	2	Jones et al., 2013 – This study description needs to be revised for clarity. Is there a statistic or p-value to include? Also, in sentence two “...the effect was lost...” could be revised to say “no longer significant”.	We revised the study description to include the odds ratio and confidence intervals and adjusted the language to read “no longer significant.”
Reviewer #1	60	3	Ross et al., 2016 – Did menthol smoking status predict higher or lower TNE?	We adjusted the language to clarify “higher” TNE.
Reviewer #1	61	N/A	<u>Twenty-five analyses found no significant effect of menthol on nicotine exposure</u> – Studies in this subcategory inconsistently report null results. Some studies include p-values and others do not. Consider revising each study to include p-values for consistency.	We have removed p-values throughout the document when reporting null results, unless there was a trend toward significance.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	63	8	Marchand et al., 2017 – The study reports no menthol effect; however, the study describes multiple tobacco products. Is the no menthol effect exclusive to cigarettes or all tobacco products?	We re-reviewed the referenced study and agree the study does not describe effects specific to menthol cigarettes (as opposed to multiple tobacco products). We excluded this study from the review.
Reviewer #1	64	4	Fagan et al., 2016 – I think it should be Native Hawaiian not Hawaiian. Also, why was race included in the model if it is a study of Native Hawaiian persons?	We revised the language to clarify that the study was conducted among smokers in Hawaii.
Reviewer #1	64	5	Ross et al., 2017 – What do the percentages in parentheses reference?	We clarified for this reference that the percentages represent the percentages of menthol smokers who were slow nicotine metabolizers compared to fast nicotine metabolizers.
Reviewer #1	71	3	Azagba et al., 2020 – Missing parenthesis in the last adjusted odds ratio reported in the paragraph.	We added a parenthesis to the last adjusted odds ratio in the paragraph.
Reviewer #1	77	2	Inconsistent citation format for Wackowski & Delnevo 2007.	We have corrected the formatting for this citation.
Reviewer #1	77	3	Space needed between “1980-2021supports”	We have adjusted the spacing for consistency.
Reviewer #1	79	Table 3	Should the <i>Note</i> be displayed under the table?	We adjusted the formatting so the <i>Note</i> is now displayed under the table.
Reviewer #1	81	1	Watson et al., 2017 – Avoid use of Caucasian.	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
				not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	82	2	Jarvik et al., 1994 – Avoid use of ‘substance abuse’ terminology. Revise to ‘substance use disorder’	We have revised the language in this section to avoid use of ‘substance abuse’ terminology.
Reviewer #1	83	1	McCarthy et al., 1995 – Avoid use of Caucasian.	We thank the reviewer for raising this issue. We have revised the language according to the article.
Reviewer #1	83	2	Miller et al., 1994 – Space needed between “of _≥ 15”	We have included a space in the identified location.
Reviewer #1	83	3	Jarvik et al., 1994 – Sometimes the authors refer to previous sections when reporting different outcomes for the same study. Other times the entire study design is repeated. Consider revising for consistency throughout the document.	We have revised the document throughout for consistency when reporting different outcomes for the same study.
Reviewer #1	84	2	Pickworth et al., 2002 – The last sentence of the paragraph says “Ethnic differences...may have impacted the study results.” The study reports outcomes among African American persons, which is a race not an ethnicity. Additionally, African American persons are overrepresented as menthol smokers due in part to tobacco industry marketing influences so this sentence feels a little problematic.	We thank the reviewer for this comment. We have revised the sentence to simply note that “the overrepresentation of African American smokers in the menthol group may have impacted the study results.”

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	84	3	Ahijevych et al., 1996 – Avoid use of Caucasian.	We thank the reviewer for raising this issue. We have revised the language according to the article.
Reviewer #1	84	Header	Potential typographical error: “One cross-sectional analysis suggests that menthol increases <u>in</u> smoking topography.” I think ‘in’ could be removed from the subsection header.	We thank the reviewer for this comment. We have updated the review to correct these typographical errors as suggested.
Reviewer #1	89	2	Harris et al., 2004 – This study is a secondary analysis of Okuyemi et al., 2003. However, it is unclear how the two publications differ based on the study description provided. Both report cessation outcomes. Additional information clarifying how the manuscripts are distinct would be beneficial.	We have included additional details to differentiate the referenced studies.
Reviewer #1	90	3	Reitzel et al., 2013 – non-Hispanic Blacks should be revised to non-Hispanic Black persons or something similar.	We thank the reviewer for this comment and updated the review to incorporate this language throughout.
Reviewer #1	92	1	Delnevo et al., 2011 – Mexicans and Hispanics should be revised to Mexican persons and Hispanic persons or something similar.	We thank the reviewer for this comment and updated the review to incorporate this language throughout.
Reviewer #1	92	3	Levy et al., 2011 –Blacks should be revised to Black persons or something similar.	We thank the reviewer for this comment and updated the review to incorporate this language throughout.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	93	1	Stahre et al., 2010 – Whites, Asian Americans, American Indian/Alaskan Native, and Hispanics should all be revised to have persons or something similar after them.	We thank the reviewer for this comment and updated the review to incorporate this language throughout.
Reviewer #1	93	2	Sulsky et al., 2014 – Is the sample size in sentence two for the non-menthol smokers (n = 7,665,552) correct? It seems low relative to menthol smokers n = 30,112,430.	We thank the reviewer for catching this error. We have updated the sentence to note that the unweighted sample sizes were not reported.
Reviewer #1	94	1	Avoid use of Caucasian	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	101	Figure 8	Does the positive effect of menthol in the figure mean menthol smokers have reduced cessation success compared to non-menthol smokers? So a positive effect (yes there is an association) for a negative outcome (reduced cessation)?	Yes, the “positive” effect refers to studies which found that menthol smokers had a negative outcome (i.e., reduced cessation success) compared to non-menthol smokers.
Reviewer #1	102	2	Should sentence two be revised to say “...found a positive effect of menthol on reduced cessation success...”?	We thank the reviewer for the comment and have updated the language.
Reviewer #1	102	2	Should sentence two be revised to say “a positive association with menthol and reduced cessation.”?	We thank the reviewer for the comment and have updated the language.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	105	2	Inconsistent formatting for Smith et al., 2020 citation	We adjusted the citation to be at the beginning of the paragraph, consistent with the other summaries.
Reviewer #1	106	5	Dependence – possible typographical error in sentence one “...an association between menthol <i>and</i> cigarettes and dependence among adults”	We deleted the additional “and” in this sentence, so it now reads “...an association between menthol cigarettes and dependence among adults.”
Reviewer #1	108	6	Cessation – typographical errors in sentence one (unnecessary period after general) and sentence two (“...studies of among smokers...”).	We deleted the unnecessary period after “general” in sentence one and “of” in sentence two.
Reviewer #1	109	1	Space needed between “n=18,78.3%”	We added a space in this sentence.
Reviewer #1	109	2	Inconsistent formatting for Smith et al., 2020 citation and unnecessary double parentheses at the end of the paragraph.	We have corrected the formatting for this citation and removed the extra parenthesis.
Reviewer #1	140	Reference Table	Cubbin et al., 2010 – avoid use of Caucasian	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	142	Reference Table	Inconsistent formatting for Smith et al., 2014 citation	We have corrected the formatting for this citation.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	143	Reference Table	Watson et al., 2017 – avoid use of Caucasian	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	144	Reference Table	Inconsistent formatting for Cohn & D’Silva, 2019; Cohn et al, 2019 and Cohn et al., 2020 citations	We have corrected the formatting for this citation.
Reviewer #1	144	Reference Table	Cohn et al., 2019 – formatting issue for text listed in the outcome measures cell	We have corrected the formatting for this citation.
Reviewer #1	148	Reference Table	Inconsistent formatting for Wang et al., 2014 citation	We have corrected the formatting for this citation.
Reviewer #1	150	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation	We have corrected the formatting for this citation.
Reviewer #1	154	Reference Table	Brinkman et al., 2012 – avoid use of Caucasian	We thank the reviewer for raising this issue. We have added a statement in “Section X: Study Summaries,” stating that FDA is aware of the racist origins of the term “Caucasian” and does not endorse the term; the term is only used in the review when that particular language was used by the study authors.
Reviewer #1	167	Reference Table	Inconsistent formatting for Smith et al., 2014 citation	We have corrected the formatting for this citation.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #1	168	Reference Table	Inconsistent formatting for Wang et al., 2010 citation	We have corrected the formatting for this citation.
Reviewer #1	170	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation	We have corrected the formatting for this citation.
Reviewer #1	173	Reference Table	Inconsistent formatting for Wackowski & Delnevo 2007 citation	We have corrected the formatting for this citation.
Reviewer #1	174	Reference Table	Inconsistent formatting for Wang et al., 2014 citation	We have corrected the formatting for this citation.
Reviewer #1	185	Reference Table	Inconsistent formatting for Smith et al., 2020 citation	We have corrected the formatting for this citation.
Reviewer #2	10		It states "Clinical studies that directly measure and compare use of menthol cigarettes (or other combusted tobacco products) to use of non-menthol cigarettes/products" but this "clinical" language is inconsistent with the rest of the report – which focused on longitudinal and cross sectional human studies and lab studies. It further goes on at the bottom of the page to define clinical studies and makes no mention how cross sectional were included - many of which are not clinical in nature.	We revised to clarify "human studies" or "studies in humans."
Reviewer #2	13	1st P	Again, the issue of "clinical" and "non-clinical" comes up. It's confusing and inconsistent.	We revised to clarify "human studies" or "studies in humans."
Reviewer #2	14	Middle of page	Document states "Based on interrater agreement, the resulting ranges were determined to be	We clarified that the ranges presented are for the analysis scores. We also included additional

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REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			<p>sufficient for weighing independent articles: Strong: 0.75-1.00 Moderate: 0.56-0.74 Weak: 0.00-0.55</p> <p>It is not clear whether these are scores for the inter-rater agreement or the scores themselves. Some clarity here is needed. This writeup is confusing. Presumably, the authors mean the study score. If this is the case, some details on the inter-rater agreement would be useful.</p>	<p>details of the process for determining consistency between reviewers for scoring articles based on the assigned scoring criteria.</p>
Reviewer #2	53	5th	Soulakova and Danczak uses CPS TUS data; this should be explicit.	We have updated this text to explicitly state use of TUS-CPS data in this study.
Reviewer #2	170		Header seems to be missing at the top of this table - which presumably is focused on adolescents.	A break is included in the table to separate the adolescent and adult dependence studies. Due to the table formatting, the adolescent header does not appear at the top of the table.
Reviewer #3	18	2 (Background)	Please clarify if analyses of different populations (youth, adults) were scored separately.	We note that this comment is in reference to the age of initiation background section. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.
Reviewer #3	35	4 (Conclusions)	Villanti et al 2020 citation should be Villanti et al. 2019.	We have updated this citation.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #3	38	1	Please spell out biomarkers of exposure (BOE) in this first instance in this section.	We have spelled out BOE at first mention under "XI. Study Selection." As a result, we retain the acronym 'BOE' on p. 38 for consistency.
Reviewer #3	38	4	Please use this text in the Background of earlier sections where there are multiple outcomes assessed: "each outcome was counted as a separate analysis."	With the deletion of the "Age of Initiation" section, the Dependence section is the first section where there were multiple outcomes within the same paper, counted as separate analyses; this language is incorporated in that section.
Reviewer #3	39	1	In an earlier section, each dataset used by Curtin et al. is counted as a separate analysis. Recommend being consistent in each section; this paragraph should relate only to NSDUH (i.e., delete the lead-in sentence about the datasets used).	We have deleted the lead-in sentence from the Curtin et al. study summary. We also separated each summary of the different surveys within the Curtin et al. study to clarify that each assessment was counted as a separate analysis.
Reviewer #3	39	1	Curtin et al. analyses report HSI category distributions inconsistent with the definition of HSI by Heatherton et al. (0-1 low, 2-4 mod, 5-6 high).	We thank the reviewer for this comment and acknowledge that various studies may have used different distributions and cut-offs for measures of dependence (e.g., HSI, TTFC, CPD). This may have contributed to inconsistency in findings across studies. We also note that limitations associated with departures from standard measures were considered as part of the scoring assessment.
Reviewer #3	40	2	In Allen and Unger analyses, recommend using "correlated with" rather than "predictive of" given the cross-sectional nature of the study.	We revised the language in this study summary to state "correlated with."

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REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #3	40	3	Benowitz 2010 paper reports on difference “between menthol and regular cigarette smokers.” Please clarify if this is non-menthol regular cigarette smokers or simply, non-menthol cigarette smokers.	We clarified that the language in the paper uses “regular cigarettes” and “regular smokers” to reference non-menthol cigarettes and smokers, respectively. We added text to the summary to clarify this language.
Reviewer #3	40	4	Curtin et al. analyses report HSI category distributions inconsistent with the definition of HSI by Heatherton et al. (0-1 low, 2-4 mod, 5-6 high).	We thank the reviewer for this comment and acknowledge that various studies may have used different distributions and cut-offs for measures of dependence (e.g., HSI, TTFC, CPD). This may have contributed to inconsistency in findings across studies. We also note that limitations associated with departures from standard measures were considered as part of the scoring assessment.
Reviewer #3	40	4	Curtin et al NHANES analyses should be separate paragraph from NSDUH analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.
Reviewer #3	46	3	Benowitz 2010 paper reports on difference “between menthol and regular cigarette smokers.” Please clarify if this is non-menthol regular cigarette smokers or simply, non-menthol cigarette smokers.	We clarified that the language in the paper uses “regular cigarettes” and “regular smokers” to reference non-menthol cigarettes and smokers, respectively. We added text to the summary to clarify this language.
Reviewer #3	46	4	Curtin et al TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #3	47	2	Spell out "hour" at the end of Ahijevych 2018 paragraph.	We revised to spell out "hour" in the Ahijevych 2018 study summary.
Reviewer #3	47	4	Create new paragraph for Brinkman et al. 2012 findings.	We have separated the Brinkman et al. 2012 findings into a new paragraph.
Reviewer #3	47	5	Curtin et al NHIS and TUS-CPS analyses should be separate paragraphs from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.
Reviewer #3	50	7	Curtin et al NSDUH analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.
Reviewer #3	54	3/Sentence	Underline "nicotine administration" in "One analysis suggested..." sentence.	We have adjusted so that "nicotine administration" is also underlined in the heading.
Reviewer #3	54	4	Revise wording of Curtin et al. findings from TUS-CPS: "non-menthol smokers had lower odds of being daily vs. non-daily smokers compared to menthol smokers."	We thank the reviewer for this comment. We have revised the wording in the Curtin et al. finding as indicated by the reviewer.
Reviewer #3	55	5	Delete "In the analysis of data from four nationally-representative surveys" from the beginning of the Curtin et al. paragraph. Create separate paragraph for NHIS analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have deleted the lead-in sentence and separated analyses to aid in counting within sections.
Reviewer #3	56	1/Sentence	Add "given the same nicotine content" to the end of "One analysis found no effect of menthol on cigarette	We thank the reviewer for this suggestion. Rather than add this distinction to the heading, we have clarified in the summary that the study examined

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			choice." This study examined interaction between menthol and nicotine content.	the interaction between menthol and nicotine content.
Reviewer #3	57	3	Confirm "α4α6*" vs. "α4α6&" at the end of the paragraph.	We have corrected the typographical error and revised the section to read "α4α6*."
Reviewer #3	59	3	Benowitz 2004 – Specify comparison group in text: "White menthol smokers had lower nicotine exposures when smoking menthol cigarettes." Add "than non-menthol cigarettes" if appropriate.	We have updated this reference to specify the comparison group, i.e., "non-menthol cigarettes."
Reviewer #3	59	4	Please spell out mouth-level exposure (MLE) at first instance in this section.	We note that 'MLE' is spelled out at first mention on p. 38. As a result, we retained the acronym 'MLE' in this section for consistency.
Reviewer #3	60	3	Delete "with" in sentence that begins "Although these data appear to contradict with..."	We have removed "with" from the referenced sentence.
Reviewer #3	68	3	Curtin et al. analyses report HSI category distributions inconsistent with the definition of HSI by Heatherton et al. (0-1 low, 2-4 mod, 5-6 high). Create new paragraph for TUS-CPS analyses to aid counting analyses across each section.	We thank the reviewer for this comment and acknowledge that various studies may have used different distributions and cut-offs for measures of dependence (e.g., HSI, TTFC, CPD). This may have contributed to inconsistency in findings across studies. We also separated analyses to aid in counting within sections.
Reviewer #3	69	1	Villanti et al. 2020 - Specify comparison group in last sentence. "...no significant bivariate relationships between first menthol cigarette <u>compared with first non-</u>	We thank the reviewer for providing this clarification and added the comparison group to the last sentence.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			<u>menthol cigarette</u> and subsequent nicotine dependence..."	
Reviewer #3	69	3	Curtin et al. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.
Reviewer #3	69	4	Curtin et al. TUS-CPS analyses show both longer TTFC and no difference in TTFC, depending on how the youth subgroup is defined (past-month, daily, regular cigarette smokers). This should be noted explicitly, as it is the only place in the report where individual analyses within the same dataset are treated as separate entries.	We thank the reviewer for highlighting this analysis. We have added a statement explicitly noting this finding.
Reviewer #3	70	2	Cohn et al. (2019) – Please specify comparison group in the last sentence.	We adjusted the sentence for clarity so it better reflects the comparison group (i.e., past 30-day non-menthol smokers).
Reviewer #3	70	4	Curtin et al. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.
Reviewer #3	71	4	Curtin et al. (2014) – Please delete the first sentence re: the various surveys and focus on the datasets and years used in the analyses presented. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	We thank the reviewer for this suggestion and have separated analyses to aid in counting within sections.

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REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #3	84	2	Pickworth et al. (2002) – Please verify “racial” versus “ethnic” differences in the last sentence. This study appears to report on race.	We thank the reviewer for this comment. We have revised the sentence to note that “the overrepresentation of African American smokers in the menthol group may have impacted the study results.”
Reviewer #3	91	1	Smith et al. (2014) – Please describe the outcome assessed in the sentence that includes “showed a significant effect of menthol smoking among females and African Americans.” Significant effect of menthol smoking on lower cessation?	We thank the reviewer for this comment and have appropriately clarified the relationship.
Reviewer #3	97	3	Delnevo et al. (2016) – Please confirm “NYAHS” vs. “NYAH” in the study description.	We have confirmed that “NYAHS” is the proper acronym to use.
Reviewer #4	7-8		<p>The Background and Rationale sets the stage nicely for this review, which represents a reproducible transparent document, which was not entirely the case in the past reviews by FDA and TPSAC.</p> <p>Further, this review examined two possible mediating processes in assessing the possible impact of menthol on initiation/progression, greater dependence, and lowered rates of cessation success: sensory effects and smoking topography. Finally, there was an additional examination of age of initiation.</p> <p>The resulting review thus covers a more comprehensive set of research areas relevant to assessing the effects of menthol in cigarettes on tobacco addiction.</p>	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #4	9-12		The research questions and procedures to address those research questions are all reasonable and appropriate. The screening process yielded 154 articles for this review.	We thank the reviewer for this comment.
Reviewer #4	6-7		Article Selection: The procedures used to exclude articles were reasonable, leading to the reduction from 230 unique records to 25 studies included in the review.	We thank the reviewer for this comment.
Reviewer #4	13-15		<p>The approach employed in this review is reasonable, given the broad range of clinical and nonclinical evidence and the diversity of research methods across the 154 articles. It employs key elements of Cochrane, or adapted from Cochrane (e.g., Cochrane Risk of Bias Tool).</p> <p>The use of scoring for categorizing studies into strong, moderate, and weak follow known procedures that are all reasonable. The decision to only include those studies with strong and moderate analyses is also reasonable.</p> <p>Summarizing the evidence on each research question with reference to the five statements about the overall quality and strength of the evidence is based on NavGuide systematic review methodology, which is appropriate and reasonable.</p>	We thank the reviewer for this comment.
Reviewer #4	16-17		The procedures described here are reasonable and appropriate.	We thank the reviewer for this comment.
Reviewer #4	18-24		This is an additional area of evidence review that was not included in the past reviews of FDA and TPSAC.	This comment raises important limitations regarding conclusions that can be drawn from the <i>Age of Initiation</i> section. Because available

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			<p>Unfortunately, as the review states on page 18 (last paragraph): “The reviewed studies do not ask participants whether they initiated smoking with menthol or non-menthol cigarettes; thus not having information on the first smoked cigarette limits some understanding regarding the influence of menthol on early cigarette smoking trajectories (i.e., experimentation)...”</p> <p>I would say that not having this critical information makes it impossible to address the question of whether menthol is associated with age of initiation. The temporality of the two variables—age of initiation and smokers’ reports that they are smoking menthol cigarettes—runs opposite to what would be required to establish causality.</p> <p>Going even further, I would suggest that it is difficult to establish a reasonable causal mechanism for how menthol would actually have an influence on age of initiation. The possible effects of menthol on sensory experiences (e.g., reduction of harshness), and on other aspects of cigarette smoking—topography, dependence, etc.—are all based on the experience of smoking menthol cigarettes. But by definition, the age of initiation cannot be affected by these possible effects of menthol since they are not present prior to initiation.</p> <p>To be sure, the impact of menthol could be experienced in “early cigarette smoking trajectories”, but not what this section on Age of Initiation is intended to focus on.</p>	<p>studies did not collect response data on the cigarette type being used at the ages of first or regular use, we agree that it is not possible to establish a causal mechanism for how menthol would influence age of initiation and use transitions. Menthol’s effects on sensory experiences and other aspects of smoking are covered more directly in other sections of this review. While epidemiological data on use prevalence across age groups is informative, it does not address the intended research question and is out of scope for this review.</p> <p>Therefore, we have removed the Age of Initiation section and conclusions from this review because, as the reviewer notes, the question was not able to be addressed by the available evidence, from both a conceptual and empirical basis.</p>

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			Thus, the conclusion on menthol and age of initiation (pp. 21-22) that there is no association is inapposite, since this research question was not addressable from both a conceptual and an empirical basis.	
Reviewer #4	25-31		Each of the studies in this section are summarized appropriately. The human research studies are generally consistent with those of the animal studies, all of which conclude that menthol intake was associated with increased nicotine consumption.	We thank the reviewer for this comment.
Reviewer #4	31-32		The conclusion that the sensory effects of menthol are associated with positive subjective smoking experiences among menthol cigarette smokers is scientifically supported.	We thank the reviewer for this comment.
Reviewer #4	33-35		Each of the four longitudinal and two cross-sectional studies are summarized appropriately. The studies in this domain are notable for their very high quality: Each of the six studies were conducted from one of three large nationally representative surveys in the U.S.: The PATH Study, the American Legacy Longitudinal Tobacco Use Reduction Study, and the National Youth Adult Health Survey.	We thank the reviewer for this comment.
Reviewer #4	35-36		The findings from all six studies support the conclusion that menthol in cigarettes is associated with progression to regular cigarette smoking among youth and young adults. This conclusion is scientifically supported.	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #4	37-38		The introduction and background summarize the ways in which nicotine dependence and abuse liability have been conceptualized and measured in the many human studies and animal studies reviewed in this section. This section is appropriate and reasonable in setting the stage for the evidence review that follows.	We thank the reviewer for this comment.
Reviewer #4	39-43		The 31 studies of menthol and dependence as measured by scales of nicotine dependence are described accurately and summarized appropriately. The body of evidence here does not support a conclusion that menthol is associated with greater dependence in adults.	We thank the reviewer for this comment.
Reviewer #4	43-47		The 27 studies and 1 meta-analysis on the relation between menthol cigarette smoking and time to first cigarette are described accurately and summarized appropriately. The studies in this section plus the Sanders et al. (2017) meta-analysis of 15 studies support the conclusion that menthol cigarette smoking is associated with an earlier time to first cigarette, which is indicative of greater dependence.	We thank the reviewer for this comment.
Reviewer #4	47-53		The 53 studies reviewed in this section are described accurately and summarized appropriately. These studies support the conclusion that menthol cigarette smokers smoke fewer cigarettes per day than do non-menthol smokers.	We thank the reviewer for this comment.
Reviewer #4	53-56		The studies measuring night waking to smoke, individual item assessments of dependence, craving, smoking	We thank the reviewer for this comment and agree with this summary.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			frequency, and one study assessing the effect of menthol on cigarette choice are described accurately and summarized appropriately. The analyses on night waking to smoke, individual item assessments of dependence tend to suggest that menthol is associated with greater dependence, but the analyses on craving, smoking frequency, and behavioral choice do not support that same conclusion.	
Reviewer #4	56-58		These animal studies are described accurately and summarized appropriately. They support the conclusion that menthol enhances the behavioral effects of nicotine in adult animal models of abuse liability.	We thank the reviewer for this comment.
Reviewer #4	59-64		The 40 analyses on nicotine exposure are described accurately and summarized appropriately. They tend to support the conclusion that menthol increases nicotine exposure.	We thank the reviewer for this comment.
Reviewer #4	64-65		The 13 analyses on nicotine pharmacokinetics are described accurately and summarized appropriately. These studies tend to support the conclusion that menthol has no significant effect on nicotine pharmacokinetics although four analyses found that menthol attenuates nicotine pharmacokinetics.	We thank the reviewer for this comment.
Reviewer #4	66-67		These seven analyses from animal studies are described accurately and summarized appropriately. The five analyses on nicotine exposure and the two analyses on nicotine pharmacokinetics also support the conclusion	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			that menthol has no significant effect on nicotine exposure and nicotine pharmacokinetics.	
Reviewer #4	67-69		<p>The 8 analyses of menthol and dependence as measured by scales of nicotine dependence are described accurately and summarized appropriately. I agree with the comments on study weaknesses in some, but not all, of the analyses that found no significant difference between adolescent menthol and non-menthol cigarette smokers. The Villanti et al (2020) study, however, is a high-quality longitudinal analysis of the first four waves of the PATH Study, and did not find a significant relationship between first menthol cigarette and subsequent nicotine dependence in youth. But it should be noted that whether a young person's very first cigarette was menthol or not should not be considered a robust predictor of whether menthol is related to subsequently higher nicotine dependence. This same study showed in longitudinal analyses that first use of a menthol cigarette was associated with greater past 12-month use of cigarettes at the subsequent wave.</p> <p>In general, these analyses did support the conclusion that menthol in cigarettes is associated with nicotine dependence in adolescents as measured by scales of nicotine dependence.</p>	We thank the reviewer for this comment and agree with the high-quality longitudinal analysis and strengths of the overall article. We note that articles with multiple outcomes were scored separately and the discussion in this section is specific to the limitations of the youth dependence analysis in the study.
Reviewer #4	69-70		These analyses are described accurately and summarized appropriately. The 9 analyses do not show an overall relationship between menthol and dependence as	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			measured by time to first cigarette and cigarettes per day.	
Reviewer #4	70-72		The 6 analyses are described accurately and summarized appropriately. Four analyses support the conclusion that adolescent menthol cigarette smokers exhibit stronger signs of dependence than non-menthol smokers, and two analyses from the Curtin et al. NHANES and TUS-CPS study do not show this.	We thank the reviewer for this comment.
Reviewer #4	72-73		The analyses are described accurately and summarized appropriately.	We thank the reviewer for this comment.
Reviewer #4	73-74		The procedures used to classify the studies with respect to strength in the weight-of-evidence approach are sound. It was also appropriate to evaluate the studies in adults separately from the evaluation of studies in adolescents.	We thank the reviewer for this comment.
Reviewer #4	75-76		The weight of evidence analysis conducted on the 197 analyses across the 94 articles reviewed, presented in Figure 5, do support the conclusion that “the evidence is not sufficient to support conclusions of an association of menthol in cigarettes with dependence among adults.”	We thank the reviewer for this comment.
Reviewer #4	77-79		There were considerably fewer studies/analyses available for examining the association of menthol in cigarettes with dependence. But the weight of evidence analysis conducted on the 27 analyses across the 18 articles reviewed, presented in Figure 6, provide support for the	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			conclusion that “menthol in cigarettes is associated with greater dependence among youth.”	
Reviewer #4	80-86		<p>The background section provides a good short foundation for the relevance and appropriateness of topography studies in assessing the association of menthol in cigarettes with dependence and potentially exposure to harmful constituents in tobacco smoke.</p> <p>The studies in this section are described accurately and summarized appropriately.</p> <p>The conclusion drawn from the weight-of-evidence analysis of the few studies that have been conducted on topography is that “the evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with altered smoking topography.” This conclusion is justified from the weight-of-evidence analysis that is presented in Figure 7 on page 86.</p>	We thank the reviewer for this comment.
Reviewer #4	87-88		The introduction provides study-specific criteria for evaluating weight of evidence. The criteria for weighting the studies are reasonable and appropriate.	We thank the reviewer for this comment.
Reviewer #4	88		The review did not include quit attempts or quit intentions. I think it is reasonable that the focus of the review is on behavioral outcomes (cessation) rather than these precursors to behavior. However, I think that it is important to point out that the statement:	We thank the reviewer for their comment. We have revised this language to state that we did not include data on quit attempts or quit intentions because they are not direct measures of cessation success.

III. Specific Observations

REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE																																			
			<p>“The literature is mixed as to whether these indices are positively or negatively associated with cessation success”</p> <p>is not correct. There is sound evidence that quit intentions are associated with future quit attempts and with quit success.</p> <p>From the ITC cohort data across United States, Canada, United Kingdom, and Australia, here are the data on the association between quit intentions at a Wave 1 (2002) and quitting (point-prevalence) at the Wave 2 (2003):</p> <p>There is a substantial prospective association between intentions to quit and quitting.</p> <table border="1" data-bbox="653 889 1310 1166"> <thead> <tr> <th colspan="5">Percentage of smokers in the ITC Four Country Survey at Wave 1 (2002) who reported having quit smoking at Wave 2 (2003) in the United States, Canada, United Kingdom, and Australia by levels of intention to quit at Wave 1</th> </tr> <tr> <th>Level of Intention to Quit at Wave 1</th> <th>USA</th> <th>Canada</th> <th>UK</th> <th>Australia</th> </tr> </thead> <tbody> <tr> <td>Those with no intention to quit</td> <td>4</td> <td>3</td> <td>4</td> <td>3</td> </tr> <tr> <td>Intention to quit beyond 6 months</td> <td>6</td> <td>8</td> <td>7</td> <td>7</td> </tr> <tr> <td>Intention to quit within 6 months</td> <td>10</td> <td>15</td> <td>15</td> <td>13</td> </tr> <tr> <td>Intention to quit within 1 month</td> <td>21</td> <td>18</td> <td>22</td> <td>12</td> </tr> <tr> <td>Adjusted Odds Ratio: <1M vs. no intention</td> <td>7.52</td> <td>3.79</td> <td>5.69</td> <td>3.16</td> </tr> </tbody> </table> <p>Source: Hyland A, Borland R, Li Q, Yong H-H, McNeill A, Fong GT, O’Connor RJ, Cummings KM. Individual- level predictors of cessation behaviours among participants in the International Tobacco Control (ITC) Four Country Survey. <i>Tobacco Control</i> 2006; 15(Suppl III): iii83-iii94.</p> <p>So although it was reasonable in this review to focus on behavior as the outcome, there may have been additional studies involving menthol cigarettes where the intention</p>	Percentage of smokers in the ITC Four Country Survey at Wave 1 (2002) who reported having quit smoking at Wave 2 (2003) in the United States, Canada, United Kingdom, and Australia by levels of intention to quit at Wave 1					Level of Intention to Quit at Wave 1	USA	Canada	UK	Australia	Those with no intention to quit	4	3	4	3	Intention to quit beyond 6 months	6	8	7	7	Intention to quit within 6 months	10	15	15	13	Intention to quit within 1 month	21	18	22	12	Adjusted Odds Ratio: <1M vs. no intention	7.52	3.79	5.69	3.16	
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III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			to quit outcome may have been present, which could have been used to project impact on quitting in the future.	
Reviewer #4	88	2	<p>It was important to recognize that the self-reports of cessation outcomes are subject to recall bias. (Berg CJ, An LC, Kirch M, Guo H, Thomas JL, Patten CA, et al. Failure to report attempts to quit smoking. <i>Addictive Behaviors</i>. 2010;35:900–904. doi:10.1016/j.addbeh.2010.06.009; Borland R, Partos TR, Yong HH, Cummings KM, Hyland A. How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control Four Country cohort survey. <i>Addiction</i>. 2012;107:673–682. doi:10.1111/j.1360-0443.2011.03685.x.)</p> <p>In this evidence review, without access to the actual data sets from which analyses might be conducted to more rigorously examine (and possibly control for) these recall biases, it was reasonable to rank the cross-sectional studies as lower than the longitudinal analyses. However, it should be noted that this ranking would have been established even without knowing that cross-sectional studies would be particularly subject to recall bias, so I am not sure whether there was any additional downgrading of the cross-sectional studies.</p>	We thank the reviewer for this comment and note that recall bias was a consideration in the scoring for all analyses. Any additional downgrading of cross-sectional cessation studies was study-dependent and based on cessation-specific criteria noted in the scoring sheets in Appendix C.
Reviewer #4	88-94		The 13 longitudinal analyses, 6 cross-sectional analyses, and the 2 meta-analyses finding a relationship between	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			menthol and decreased cessation success are all accurately described and properly summarized.	
Reviewer #4	94-98		The 13 longitudinal analyses, 5 cross-sectional analyses, and the 2 meta-analyses finding a relationship between menthol and decreased cessation success are all accurately described and properly summarized.	We thank the reviewer for this comment.
Reviewer #4	94-98		It is important to note that none of the 40 analyses across the 39 studies reviewed found that menthol was associated with an <i>increased</i> probability of cessation success.	We thank the reviewer for this comment. However, we identified three sub-analyses where menthol smoking was associated with increased cessation success. Because none of the studies identified this relationship in the same sub-population, we did not include these studies in the weight of evidence.
Reviewer #4	99		The procedures used to conduct the weight of evidence review in this category of studies were all reasonable and appropriate. The decision to divide the review into general population and African Americans specifically was sound, reflecting the importance of understanding the impact of menthol among African Americans, where prevalence of menthol cigarettes is much higher than in the general population.	We thank the reviewer for this comment.
Reviewer #4	100-102		The strength-of-evidence review for the studies of the general population was conducted appropriately. The studies reviewed provide strong evidence to support FDA's conclusion that menthol in cigarettes is likely associated with decreased cessation success among the	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			general population. This conclusion is scientifically supported and justified from the strength-of-evidence review.	
Reviewer #4	100-102		It should be noted that 13 longitudinal studies conducted with general population samples that found an association between menthol smoking and decreased cessation success examined short-term quitting (range: 3-7 weeks across studies), which was typically higher among menthol smokers vs non-menthol smokers. There were generally no significant differences for long-term quitting (range: 6 months to 5 years across studies, with a few exceptions) among menthol smokers vs non-menthol smokers. This suggests that menthol smokers may have reduced success for long-term quitting, which could be due to higher likelihood of relapse back to smoking over time in jurisdictions where menthol cigarettes are available, despite initial quit success.	We thank the reviewer for this comment and for highlighting this point.
Reviewer #4	100-102		Longitudinal studies that found association between menthol smoking and decreased cessation success do not examine outcomes by menthol smoking status (daily vs non-daily menthol smokers), with exception of Mills et al. (2020). Analyses that separate daily and non-daily menthol smokers are needed to determine whether menthol has different effects on smoking cessation across these two user groups. It is possible that studies that have reported no effects of menthol on smoking cessation may reflect differences among smokers who	We thank the reviewer for this comment and agree, that the Mills et al. (2020) study highlights an area of heterogeneity that likely contributes to differences in study conclusions on cessation success between menthol and non-menthol smokers.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			use menthol cigarettes on a daily vs non-daily basis, and that menthol has a greater impact on cessation outcomes among those who smoke menthol cigarettes regularly.	
Reviewer #4	103-105		The strength-of-evidence review of studies among African American smokers was conducted appropriately. Figure 9 summarizes the findings of the review, which is consistent with the conclusion reach about the general population: "menthol in cigarettes is associated with decreased cessation success among African Americans." Again, this conclusion is scientifically supported and justified from the strength-of-evidence review.	We thank the reviewer for this comment.
Reviewer #4	106		The conclusion that menthol in cigarettes is not associated with an earlier age of smoking initiation is scientifically supported given the available evidence. Note comments provided above that examining whether menthol in cigarettes is associated with age of smoking initiation may not be appropriate given the improbable hypothesis that the properties of menthol would affect age of initiation.	We thank the reviewer for this comment. Based on issues raised by reviewers about the age of initiation topic, this section has been removed from the document.
Reviewer #4	106		The conclusion that the sensory effects of menthol in cigarettes contributes to positive smoking experiences among menthol smokers is scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	106		The conclusion that menthol in cigarettes is associated with progression to regular smoking among youth and	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
			young adults is scientifically supported given the available evidence.	
Reviewer #4	106-107		The studies relating to the association between menthol and dependence are varied and complex. The organization of the review was designed in accordance with that complexity. The conclusion that the strength of evidence is not sufficient to support conclusions of an association between menthol and cigarettes and dependence among adults is scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	107		The analyses of the evidence on youth led to a different conclusion: the weight of the evidence from the strongest nationally representative studies on youth supports [the conclusion] that menthol is associated with increased dependence among youth. This conclusion is scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	108		The conclusion that the evidence is not sufficient to support a conclusion of an association between menthol in cigarettes and altered smoking topography is scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	108-109		The review of the evidence in this important set of studies was guided by the observation from the meta-analyses that there was high heterogeneity of the studies. As discussed above, it was important to consider the studies in this domain by the general population and among African Americans.	We thank the reviewer for this comment.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	COMMENT	RESPONSE
Reviewer #4	108		The conclusion that the weight of evidence supports [the conclusion] that menthol in cigarettes is likely associated with reduced cessation success in both the general population and among African American smokers is scientifically supported given the available evidence.	We thank the reviewer for this comment.
Reviewer #4	109		The summary of the studies of how menthol enhances the effects of nicotine in the brain provides important information for <i>why</i> menthol smokers have greater difficulty quitting.	We thank the reviewer for this comment.
Reviewer #4	110		The limitations of this evidence review are well noted and reasonable.	We thank the reviewer for this comment.
Reviewer #4	110- 111		The summary of conclusions on menthol in cigarettes, presented in Table 6, is scientifically supported, and the further brief discussion provides important context for this evidence review, which provides the foundation to inform potential future regulatory activities related to menthol in cigarettes.	We thank the reviewer for this comment.

Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p>The <i>Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes</i> is a well-written and comprehensive review of the literature. The study inclusion/exclusion criteria are straightforward for each section and benefit from the addition of figures depicting the article selection process. Organizing the document into three separate topics is useful to the reader. However, the structure and formatting differed across sections, which affected the readability of the document. In Section 1, each topic has an opening paragraph identifying the studies, separate paragraphs for each study explaining relevant findings, and then a final paragraph with the summary/conclusions statements and study limitations. For me, this organizational structure was easier for processing the research content and conclusions. In Section 2, the first paragraph of each topic reports the overall conclusions and then the following paragraphs providing the supporting evidence. Honestly, I found this paragraph flow challenging for processing the content and conclusions. Also, the readability of Section 2 could be improved by including subheadings for each topic similar to the structure of Section 1.</p>	<p>We have included subheadings for each topic in Section 2 congruent with Section 1. We have reorganized Section 2 so that there is an opening paragraph identifying the studies, bulleted findings from each study relevant to the topic, and summary and conclusion statements at the end of each subsection.</p>
Reviewer #1	<p>Additionally, in Section 2, the decision to exclude studies published prior to 2016 makes logical sense given the rapidly evolving tobacco marketplace. However, this resulted in only ten studies meeting the inclusion criteria (and two are international studies with minimal relevance to the current review). A scoping review of a menthol cigarette ban (Cadham et al., 2020), one of the ten studies meeting eligibility criteria for the current review, reports behavioral intentions data for several studies published prior to 2016. Another approach would be to eliminate the ‘published prior to 2016’ exclusion criterion and report all studies with behavioral intentions data for a menthol cigarette ban.</p>	<p>We have removed the timeframe criteria in our literature search to include articles published prior to 2016, resulting in five additional studies reviewed. In addition, we added three other studies to the review due to expanded inclusion criteria that included qualitative studies and international studies, and one additional study that was published in 2021 after our original literature search. We have noted in the</p>

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	Then, consistent with the other studies included in the current review, acknowledge the study limitations, such as differences in tobacco product availability at the time of publication.	limitations section that differences in tobacco product availability at the time of data collection limit our ability to draw conclusions across studies.
Reviewer #1	Overall, the conclusions reported in this review are sound and supported by the literature. However, two conclusions in Section 1 would benefit from adding qualifiers to soften the language (outlined below in charge question 1).	We thank the reviewer for this comment. We have updated the language in the conclusions regarding illicit sales and user modification in Section 1.
Reviewer #2	This report summarizes a limited volume of data regarding the potential impact of prohibiting menthol as a characterizing flavor in cigarettes. Characterizing flavor is not defined. The report summarized three areas: policy evaluation evidence on the impact of flavored tobacco sales restrictions or bans; consumers’ product choices and intended use behaviors if menthol cigarettes became unavailable; and modeling the public health effects of a menthol cigarette ban in the US. A summary table of the conclusions in each section would facilitate the readability of the document. Generally speaking, the conclusions appear scientifically supported – but the conclusions don’t rely on any framework to assess the strength of the evidence. A framework would have aided tremendously in this regard. This is especially problematic in policy evaluation section as noted below.	<p>We thank the reviewer for this comment. We have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of studies reviewed in Section 1 and Section 2. A table summarizing the conclusions and the strength of evidence for each conclusion has been added to Section 1 and Section 2. In addition, a table describing characteristics and findings of each study included in Section 1 and Section 2 grouped by outcome of interest and with an assessment of each study’s key strengths and limitations has been added to Section 1 and 2.</p> <p>Section 3 now includes a table summarizing each of the 3 models included in the review; however, due to the limited amount of available literature, no assessment framework was applied.</p>

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
Reviewer #2	<p>With respect to the policy evaluation, the report indicates that the authors of the RTD literature review considered the internal and external validity of each study. To do so, the authors of the RTD indicate that they considered things like the study population, study design (e.g., pre-post, control group..), sample size and data analysis. Yet while this was considered, the qualitative assessment of these important factors is not explicitly reported. Indeed, the report would have benefited from a more critical analysis of the strengths of the research in each area. The lack of a framework to assess the strength of the studies especially diminished the policy evaluation literature review given the greater number of research questions considered and articles reviewed.</p>	<p>We appreciate the reviewer’s comment and have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To address this comment, we added three new tables and additional text within Section 1. The first table provides a summary of flavored tobacco sales restriction policies of included evaluation studies. The second table describes characteristics (e.g., study design, sample characteristics) and findings of each study included in Section 1 grouped by outcome of interest and with an assessment of each study’s key strengths and limitations. The review team followed the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to characterize the weight of the evidence for each conclusion. In addition to considering the strengths and limitations of each study, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. This assessment is reported in a third table and is discussed within the Summary and Conclusions section for each outcome in</p>

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
		Section 1. Additional details on the review team’s approach have been added to the Methods section.
Reviewer #3	The “Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes” includes three reviews of the literature on: 1) evaluations of flavored tobacco sales restrictions or bans; 2) studies assessing discrete choice experiments or behavioral intentions in response to a hypothetical menthol ban; and 3) studies modeling the potential impact of a menthol cigarette ban on health outcomes. For each section, the search strategies are clearly outlined, as are the eligibility criteria. Sections 1 and 3 describe use of two independent reviewers to ensure reliability of the application of eligibility criteria across titles, abstracts, and full text articles. Section 2 does not provide the same methodological detail, nor the flowchart of included studies or description of independent reviewers. Study designs, sample sizes, and years of data collection for some studies are missing in each section, limiting the ability to draw inferences on the strength or relevance of the evidence to the research questions posed. Summaries from these sections of the report generally reflect a narrative review rather than a systematic review, without an assessment of risk of bias or evaluation of the strength of the various studies. As a result, the qualitative synthesis of the included studies leading to conclusions in each section lack transparency. Some description of the evaluation of the evidence in each section or subsection would provide greater insight into the strength of the existing evidence and the conclusions drawn from them. Additionally, there is an opportunity in these sections to provide context regarding the consistency (or inconsistency) of effects across study designs and populations, which would strengthen the conclusions drawn.	We thank the reviewer for this comment. We have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of studies reviewed in Section 1 and Section 2. In addition to considering the strengths and limitations of each study, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. A table summarizing the conclusions and the strength of evidence for each conclusion has been added to Section 1 and Section 2. In addition, a table describing characteristics (e.g., study design, sample size, years of data collection, key findings) and findings of each study included in Section 1 and Section 2 grouped by outcome of interest and with an assessment of each study’s key strengths and limitations has been added to Section 1 and 2.

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
		<p>We have provided further methodological detail in Section 2, including a flow chart of inclusion coding methodology</p> <p>Section 3 now includes a table summarizing each of the 3 models included in the review; however, due to the limited amount of available literature, no assessment framework was applied.</p>
Reviewer #4	The literature review of studies prepared by FDA is well-organized. The three sections of the review each focus on important questions that need to be addressed in assessing the potential impact of a menthol ban: What is known about the possible impact of a menthol cigarette ban? What might menthol cigarette smokers do in response to a ban on their preferred product? And what are the possible future impacts of a menthol cigarette ban for key public health indicators?	We thank the reviewer for this comment.
Reviewer #4	The review of the studies in each of the three areas was well-designed and used appropriate methodology in selecting the initial pool of studies, and then conducting further review to reduce the initial set of studies to obtain the final set of 25 studies.	We thank the reviewer for this comment.
Reviewer #4	The FDA engaged in a narrative review of the studies. Given the heterogeneity across studies in the policies evaluated (e.g., in Section 1: flavor bans other than menthol vs. menthol bans); location of the study (community-level, state-level, and Federal level in the U.S.; provinces in Canada), it was not appropriate to attempt any kind of quantitative review, such as meta-analysis.	We appreciate the reviewer's comment and agree.
Reviewer #4	The studies were summarized accurately, the presentation of each study and the summary and conclusions drawn at the end of each section were clear and captured well the studies that had been reviewed. The conclusions drawn were	We thank the reviewer for this comment

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	scientifically sound and supported, although I did note some minor differences at times between FDA's conclusions and my own in emphasis and strength of conclusions. These are described below.	
Reviewer #4	<p>In all, FDA's evidence review is a well-conducted and concise examination of the research relevant to the possible impact of a menthol cigarette ban in the United States. That review concluded that there would be likely strong public health benefit from a menthol cigarette ban in the United States, both in the short term, with an expected significant increase in quitting, and in the medium- and long-term, with an expected substantial decrease in deaths averted and a corresponding increase in life-years gained.</p> <p>From my own examination of the evidence, and in evaluating FDA's evidence review, I concur with that conclusion.</p>	We thank the reviewer for this comment.

II. Response to Charge Questions

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.

REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p>Section 1: Summary of the Policy Evaluation Evidence on the Impact of Flavored Tobacco Sales Restrictions or Bans: A Reproducible, Transparent, Documented (RTD) Literature Review</p> <p>Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on Tobacco Use Behaviors of Young People – The conclusion that flavored tobacco product sales restrictions or bans reduces tobacco use among young people is supported by the literature reported in this review. Although a few studies reported increases in certain types of tobacco product use after flavor restrictions, the evidence points towards reductions in overall tobacco consumption after flavor bans. Further, most studies included in this section reported on local municipality flavor restrictions, which are likely to have the smallest impact on behavior due to ease of access to products from other nearby localities without restrictions. Despite this regulatory challenge, the studies of local municipalities still reported decreases in overall flavored tobacco use among young people.</p>	We appreciate the reviewer’s comment and agree with the reviewer’s conclusions.
Reviewer #1	<p>Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on Tobacco Use Behaviors of Adults – While I agree with the stated conclusions in this section (increased quitting/quit attempts; switching to non-menthol cigarettes/other tobacco products), as written, it is a relatively weak conclusion section. The paragraph is two sentences long, which is surprising since the section is comprised of several studies reporting on the federal menthol ban in Canada. Given these studies provide strong evidence regarding</p>	We appreciate the reviewer’s comment. We have added additional language summarizing the evidence supporting the conclusions.

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
	the benefits of federal and provincial menthol cigarette bans, consider bolstering the conclusions by briefly restating the supporting evidence. The second paragraph provides more detail about the study that did not support the conclusion (Guydish et al., 2020), than the first paragraph stating the conclusion.	
Reviewer #1	Additionally, the public health implications for people who smoke menthol cigarettes switching to non-menthol cigarettes or other flavored combusted products (e.g., no benefit) are likely different from people who smoke menthol cigarettes switching exclusively to flavored e-cigarettes or other non-combusted products (e.g., possible harm reduction benefit). The authors may want to acknowledge the potential outcomes when switching to different products.	We appreciate the reviewer’s comment. The conclusion has been updated to acknowledge the potential outcomes when switching to different products.
Reviewer #1	Finally, I would briefly acknowledge potential differences between the Canadian menthol cigarette ban and a potential US menthol cigarette ban (e.g., different demographic characteristics of people who smoke menthol cigarettes) and how differences could affect tobacco use behavior.	We appreciate the reviewer’s comment. We agree with the reviewer that there are differences in the demographics of menthol cigarette use and sales of menthol cigarettes between Canada and the US. In the Limitations section, we acknowledge potential differences in demographic compositions and tobacco use behaviors between Canada and the US and potential impact on interpretation of findings for the US context.
Reviewer #1	Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on Sales of Tobacco Products – The conclusion that sales of overall tobacco and specific tobacco products declined following flavored tobacco product sales restrictions or bans is supported by the literature reported in this	We appreciate the reviewer’s comment and agree with the reviewer’s conclusions.

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
	<p>review. Although increases in sales were observed in some studies for tobacco products not subject to the restriction or ban, such increases did not offset the overall declines, which is encouraging. Additionally, the initial evidence of concept-flavor sales increasing after flavored tobacco regulations or bans is supported by several, but not all, studies.</p>	
Reviewer #1	<p>Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on Illicit, Cross-Border, or Online Sales of Tobacco Products – The conclusion that illicit/cross-border/online sales may slightly increase after flavored tobacco product restrictions or bans is generally supported by the reviewed literature. However, given that seven out of nine studies reported increased illicit/cross-border/online sales, I would consider eliminating the word “slightly” from the conclusion sentence. One suggestion would be to acknowledge that although there may be increases in illicit/cross-border/online sales following flavored tobacco restrictions or bans, these increases do not offset the overall reductions in flavored tobacco purchasing. Further, a federal ban for menthol cigarettes and/or flavored tobacco products would likely minimize some of the cross-border purchasing observed in the studies examining local or provincial flavor restrictions.</p>	<p>We thank the reviewer for this comment. In response to another peer reviewer comment, we have updated this section in the document to report study findings on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively). We have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. In addition to considering the strengths and limitations of each study, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. Regarding illicit sales, we conclude that the impact of a flavored tobacco product sales restriction or ban on the illicit market is not significant.</p>

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	One additional thought I had when reviewing the Canadian studies is to what extent were people purchasing menthol cigarettes from First Nations reserves prior to the federal or provincial flavor restrictions?	We agree this is an interesting question and are not aware of estimates of purchases from First Nations reserves prior to federal or provincial flavor restrictions in the current literature. To address the reviewer’s comment, language in this section of the document only uses “increase” to describe changes when pre and post policy data are available.
Reviewer #1	Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on User Modification of Tobacco Products – The conclusion that most tobacco users do not modify their products in response to a menthol cigarette policy is slightly overstated based on the available evidence. Only two studies reported on modification behaviors, so it feels premature to conclude that <i>most</i> tobacco users will not modify their products after implementation of flavored tobacco restrictions or bans. I would recommend including qualifying language within the conclusion sentence, such as “...most tobacco users likely do not modify their product use...”.	We appreciate the reviewer’s comment and agree that there is limited evidence of reports of increased user modification of tobacco products after a flavored tobacco sales restriction. We have updated the language in the Summary and Conclusion to state that there is limited evidence of reports of increased user modification of tobacco products after a flavored tobacco sales restriction.
Reviewer #1	Section 2: Consumers’ Product Choices and Intended Use Behaviors If Menthol Cigarettes Became Unavailable Behavioral Intentions in Response to Hypothetical Menthol Cigarette Bans – The conclusion that “the majority of menthol smokers state they would try to quit tobacco products in the event of a menthol ban” does not necessarily follow from the evidence stated in this section. The scoping review reports quitting intentions ranging from 24-64% (Cadham et al., 2020) and Rose et al., 2019 reported less than half of young adult menthol smokers intended to quit. While I agree that many people who smoke menthol cigarettes have intentions to quit if menthol cigarettes are banned, as written, “the majority” feels slightly	We have changed the language so that it states “a plurality” of menthol smokers state that they would try to quit tobacco use following a menthol ban.

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
	overstated. Alternatively, if the majority is accurate, then more details are needed in this section to support this conclusion.	
Reviewer #1	The conclusion paragraph only reports quit intentions rather than all behavioral intentions (e.g., switching, dual use); but, one of the subsequent paragraphs discusses anticipated increases in ENDS use among people who use menthol cigarettes and ENDS. Is this paragraph in the appropriate section or should conclusions about dual use be added to the conclusion paragraph?	The behavioral intentions section includes evidence of intent to switch to non-menthol cigarettes, intent to switch to menthol e-cigarettes, and intent to switch to some other tobacco product in response to a menthol ban. We summarize all behavioral intentions in the summary and conclusion paragraph of the behavioral intent section.
Reviewer #1	Behavioral Economics Studies examining U.S. Adults’ Product Choices – The conclusion that “menthol flavor appears to influence menthol smokers’ product choices; however, smokers prefer cigarettes compared to ENDS, and some menthol smokers select non-menthol combusted tobacco products as substitutes for menthol cigarettes” is supported by the literature reported in this review. However, I would suggest separating the section in to two subsections, Discrete Choice Experiments (DCEs) and Experimental Tobacco Marketplace (ETM) study, and then separate conclusions based on study design. The DCEs indicate that cigarettes are preferred over ENDS but in the ETM study menthol/mint ENDS were the primary substitution products for menthol cigarettes. DCEs provide important information about preference when two products are presented against each other. However, DCE do not necessarily provide information about product selection under conditions restricting menthol cigarette access, like the ETM study. Thus, separating the sections may be helpful for understanding their implications with respect to a menthol cigarette ban.	We now separately discuss the findings from discrete choice experiments and experimental marketplace studies. We also provide separate conclusions based on study design.

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	<p>Discrete Choice Experiments with Samples of Adolescents in Mexico & Guatemala –Despite these two studies meeting inclusion criteria, they do not seem to contribute meaningful information regarding menthol cigarette and/or flavored tobacco product regulations in the US. Is it necessary to include them in the review? The conclusion that youth had lower interest in trying menthol cigarettes does not feel relevant in the context of a marketplace that sells cigarettes in a variety of flavors.</p>	<p>For transparency, we retain these studies in the review rather than change the inclusion criteria post-review. However, as suggested, we do not use findings from these studies to draw overall conclusions about US population behavioral intentions.</p>
Reviewer #1	<p>Section 3: Modeling the public health effects of a menthol cigarette ban in the United States</p> <p>The conclusion “that population health models simulating menthol ban policies support and are consistent with a strong public health benefit” is supported by the literature reviewed. Although both models have assumptions and limitations, they have significant methodological strengths and contribute vital information about the public health impact of menthol cigarette smoking and banning menthol cigarettes. Levy et al., in press estimated approximately 650,000 premature deaths averted with a menthol cigarette and cigar ban while Le and Mendez, 2021 estimated 378,000 premature deaths were attributable to menthol cigarette smoking.</p>	<p>We thank the reviewer for this comment.</p>
Reviewer #2	<p>Generally speaking, the conclusions appear scientifically supported. However, no framework is used to assess the strength of the evidence and this would have aided tremendously in this regard. For example, in some sub-areas of focus for the policy evaluation, there are several studies but the strength of some of the studies - in the eyes of this reviewer – I would qualitatively characterize as weak or moderate (e.g., impact of flavored tobacco sales restrictions on young people). Whereas in other sub-areas of focus there are few studies, but I consider some of these studies stronger (e.g., impact on</p>	<p>We appreciate the reviewer’s comment and have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To address this comment, we added three new tables and additional text within Section 1. The first table provides a summary of flavored tobacco sales</p>

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
	sales), and in others there is very little research (e.g., user modifications) but the data are derived from an actual menthol ban – not a simulation, and therefore meaningful. In summary, it is difficult to weigh the strength of the evidence.	restriction policies of included evaluation studies. The second table describes characteristics (e.g., study design, sample characteristics) and findings of each study included in Section 1 grouped by outcome of interest and with an assessment of each study’s key strengths and limitations. The review team followed the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to characterize the weight of the evidence for each conclusion. In addition to considering the strengths and limitations of each study, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. This assessment is reported in a third table and is discussed within the Summary and Conclusions section for each outcome in Section 1. Additional details on the review team’s approach have been added to the Methods section.
Reviewer #2	Of note, I found the Courtemanche et al., 2017 paper problematic. This paper analyzed national YTS pre and post the 2009 flavored cigarette ban. At the time the TCA was signed the cigarette marketplace was largely unflavored (with the	We appreciate the reviewer’s comment. We have updated the language in the document regarding the conclusions drawn from this study and have

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.

REVIEWER	COMMENT	RESPONSE
	<p>exception of menthol). On its face, that a flavored cigarette ban would produce that dramatic a shift in youth tobacco use is questionable. Moreover, not addressed either in Courtemanche et al., 2017 or this RTD was the fact that the cigarette flavor ban in 2009 coincided with an increase in the federal excise tax for cigarettes (39 cents to \$1.01 cents per pack) and youth are known to be price sensitive.</p>	<p>included additional details from Courtemanche et al. (2017) study regarding covariates that were adjusted for in their analyses. We have also added language in the RTD stating that the US federal ban on flavored cigarettes coincided with an increase in the federal excise tax for cigarettes, which may have contributed to the decrease in cigarette use and any tobacco use.</p>

CHARGE QUESTION 1. For each section that you reviewed, were the conclusions scientifically supported given the available evidence? If not, provide specific examples as to where conclusions are not supported.		
REVIEWER	COMMENT	RESPONSE
Reviewer #3	In Section 1, conclusions regarding the impact of a flavored tobacco products sales restriction or ban on illicit, cross-border, or online sales were not scientifically supported by the available evidence. The conclusions appear to be based on several self-report surveys with limited sample sizes, to the exclusion of the multi-year studies conducted using more objective measures (e.g., cigarette seizures, sales) across larger geographic areas. Within the latter studies addressing cigarette seizures and sales, there is also variation in the population covered by the study, ranging from approximately 20 million in the New York City metropolitan area to 1 million in Nova Scotia and Rhode Island (200,000 in Providence, RI). The two studies conducted over several years in larger geographic areas (New York City, Nova Scotia) show no effect of flavored tobacco sales restrictions or bans on cigarette seizures (Nova Scotia) or increases in cross-border sales (New York City metropolitan area); the study conducted across a state in which one city had a flavor restriction show increases in sales in other counties in the state (Rhode Island). Throughout this section, there is an opportunity to evaluate the data with respect to generalizability for the broader U.S. in the context that any federal action will cover all states and localities equally and not be limited to a single city within a state, nor a single state within the country.	We thank the reviewer for this comment. In response to another peer reviewer comment, we have updated this section in the document to report study findings on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively). We have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. In addition to considering the strengths and limitations of each study, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. We have also added a discussion on the generalizability for the broader U.S. in the Limitations section of this section of the report.
Reviewer #4	Yes, the conclusions were scientifically supported given the available evidence. I have provided specific comments throughout section III Specific Observations by page in order for those comments to be presented in their proper context.	We thank the reviewer for this comment. We have provided responses to specific comments in Section III.

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	I am not aware of additional studies or publicly available information that should be included in the review for Sections 1 or 3. Other applicable publications for Section 2 exist but they do not meet enrollment criteria due to publication dates prior to 2016.	We have removed the timeframe criteria in the Section 2 literature search to include articles published prior to 2016. This resulted in an additional five studies reviewed. In addition, we added three other studies to the review due to expanded inclusion criteria that included qualitative studies and international studies, and one additional study that was published in 2021 after our original literature search.
Reviewer #2	I suggest expanding the time frame for the potential behavioral responses to a menthol cigarette product standard. The rationale to limit the date range (2016-2021) to capture only studies that provided response options most likely to reflect the types of options available in the current tobacco marketplace is not well justified as e-cigarettes and other forms of non-combustible tobacco (e.g., snus) were available prior to 2016. Additionally, a behavioral response could include cessation, and the time frame in this regard is less of an issue.	We have removed the timeframe criteria in our literature search to include articles published prior to 2016. This resulted in an additional five studies included. In addition, we added three other studies to the review due to expanded inclusion criteria that included qualitative studies and international studies, and one additional study that was published in 2021 after our original literature search.
Reviewer #3	The 2011 TPSAC report on "Menthol Cigarettes and Public Health" includes modeling conducted by David Mendez (Appendix A) that does not appear to be included in Section 3 of this report.	The modeling work conducted by Mendez in the 2011 TPSAC report is largely superseded by the 2021 study by Le and Mendez which used a similar model and was published in a peer-reviewed journal
Reviewer #4	Yes, I have provided additional publicly available information that would be appropriate to include. Some of this additional information consists of recent studies and follow-up analyses that have been made publicly available (e.g.,	We appreciate the reviewer for sharing information regarding recent publications and presentations that may be relevant. We have

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>journal articles and presentations). I provide full citations for each of these studies/presentations below. Of particular note are follow up analyses of the evaluation of the Canadian menthol cigarette ban, which pool the data from the two cohort evaluation studies. The resulting pooled analysis of the Ontario Menthol Ban Study and the ITC Canada Survey constitutes the most complete results of the impact of the Canadian menthol cigarette ban to date, and the effect sizes from that pooled analyses allow for an estimate of the impact of a menthol cigarette ban in the U.S. on additional quitting, if the impact of a U.S. menthol cigarette ban were equivalent to that of the Canadian ban. The estimate from the pooled analysis is that the U.S. menthol cigarette ban could lead to an additional 1,337,988 smokers (95% CI: 384,901-2,291,075) who would quit, of whom 381,272 additional quitters would be African American smokers (95% CI: 109,681-652,863).</p>	<p>added the Zatoński et al. (2020), Chaiton et al. (2021), and Kock et al. (2021) studies to the review. We will continue to monitor the literature for peer review publication of the pooled analysis of the Ontario Menthol Ban Study and ITC Canada Survey.</p>
Reviewer #4	<p><u>Section 1</u></p> <p>1. Zatoński M, Herbec A, Zatoński WA, et al. Cessation behaviours among smokers of menthol and flavoured cigarettes following the implementation of the EU Tobacco Products Directive: Findings from the EUREST-PLUS ITC Europe Surveys. Eur J Pub Health. 2020;30(Suppl 3): iii34-iii37. doi: 10.1093/eurpub/ckaa050.</p> <p>This two-wave cohort study evaluated the impact of the European Tobacco Products Directive (TPD) ban on characterizing flavors in cigarettes other than menthol (2016). The longitudinal data analysis of the EUREST-PLUS International Tobacco Control (ITC) Project Europe Surveys (n = 16 534; Wave 1 in 2016 and Wave 2 in 2018) and non-menthol flavored cigarette use (by 1.32%; P < 0.001), following the 2016 TPD. documenting the impact of the ban on cigarette flavors (excepting menthol). The study also found a significant but small decrease in the weighted prevalence of menthol (by 0.94%; P = 0.041), which was not banned</p>	<p>We have added the Zatoński et al. (2020) study to the review.</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>until May 2020, after this study’s Wave 2 survey. The decrease in menthol at post-ban is interesting given the findings of the Rossheim et al. evaluation of the US Federal ban on non-menthol flavored cigarettes, which found a short-term increase in menthol cigarettes, followed by a decrease. It should be noted that the Rossheim et al. study used quarterly data, it was possible in that study to examine the fine-grained time trajectory of the impact of the non-menthol flavor ban. This level of specificity was not present in this single-post ban measurement, and thus it was not clear whether the 6 EU countries had experienced the same initial increase in menthol. In this study, the majority of smokers who smoked flavored cigarettes before the ban switched to unflavored tobacco. Cigarette consumption declined between waves, but there was no statistically significant difference in decrease between flavored and unflavored tobacco smokers on smoking and cessation behaviors between the waves.</p>	
Reviewer #4	<p><u>Section 1</u></p> <p>2. Chaiton M, Schwartz R, Kundu A, et al. Analysis of wholesale cigarette sales in Canada after menthol cigarette bans. JAMA Netw Open. 2021;4(11):e2133673. doi:10.1001/jamanetworkopen.2021.33673.</p> <p>Evaluated change in cigarette sales associated with the implementation of menthol cigarette bans across ten Canadian provinces between 2010 and 2018. Menthol cigarette bans led to significant reduction in menthol cigarette sales and total cigarette sales. There was a gradual increase in menthol cigarette sales in all ten provinces from 2013 (before bans) until menthol cigarette ban was implemented (series of provincial bans beginning in May 2015, with federal ban in October 2017). After menthol cigarette bans, menthol cigarette sales decreased to zero in all provinces, with an overall -4.6% change from cigarettes sales in the same month in the previous year. There was no significant trend in overall cigarette sales before menthol cigarettes bans (0.001%; 95% CI, -0.002%</p>	<p>We have added the Chaiton et al. (2021) study to the review.</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	to 0.004%; P = .48). There was a nonsignificant decline in trend after the bans (-0.06%; 95% CI, -0.21% to 0.09%; P = .39). The postestimation test of the combined effect size of the ban on the magnitude (-4.6%; 95% CI, -8.2% to -1.0%) and trend (-0.06%; 95% CI, -0.21% to 0.09%) was significant (P = .02). The authors note that the study did not include data for contraband cigarette sales.	
Reviewer #4	<p><u>Section 1</u></p> <p>3. D'Silva J, Moze J, Kingsbury JH, et al. Local sales restrictions significantly reduce the availability of menthol tobacco: findings from four Minnesota cities. <i>Tob Control</i> 2021;30:492-497.</p> <p>Quasi-experimental study examined changes in the availability and marketing of menthol tobacco products after the implementation of restrictions on the sale of these products to adult-only tobacco shops and liquor stores in four Minnesota, US cities (Minneapolis, St. Paul, Duluth, and Falcon Heights), and in six comparison cities (Mankato, Winona, Brooklyn Park, Maplewood, Burnsville, and Fridley) without menthol restrictions. Findings showed high compliance across all four cities with menthol sales restrictions (Minneapolis, 84.4%; Duluth, 97.5%; and St. Paul and Falcon Heights, 100.0%). In comparison city stores, menthol tobacco was available in 96.0% of exempted tobacco shops and liquor stores (vs 6.0% in intervention city stores) at post-policy.</p>	<p>This study focuses on retail availability. Studies that reported on outcomes in response to a policy other than behavior, legal sales of tobacco products, illicit sales of tobacco products, or user modification of tobacco products were excluded from the review (e.g., retailer inventory of tobacco products, retailer compliance with a policy, legal challenges to implementation of a policy, public opinion on a policy). Given this, we did not add this study to the RTD review. However, in response to this reviewer's comment, we have added a discussion of the compliance and enforcement, including a brief summary of studies (including D'Silva et al. 2021) assessing retailer compliance and availability of flavored tobacco products after a flavored tobacco sales restriction, in the Limitations section for context.</p>
Reviewer #4	<p><u>Section 1</u></p>	<p>This study focuses on retail availability. Studies that reported on outcomes in response to a policy other than behavior, legal sales of tobacco</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>4. Andersen-Rodgers E, Zhang X, Vuong TD, et al. Are California's local flavored tobacco sales restrictions effective in reducing the retail availability of flavored tobacco products? A multicomponent evaluation. Eval Rev. Published online 25 October 2021. doi: 10.1177/0193841X2111051873. PMID: 34693773.</p> <p>Evaluation of California’s local restrictions on flavored tobacco sales on retail availability of these products in jurisdictions with and without an ordinance (conducted between April 2015 and January 2019). Flavored tobacco availability was significantly lower in ordinance jurisdictions than in matched jurisdictions: menthol cigarettes (40.6% vs 95.0%), cigarillos/cigar wraps with explicit flavor descriptors (56.4% vs 85.0%), and vaping products with explicit flavor descriptors (6.1% vs 56.9%). The study did not examine the effect of flavor restrictions on consumer behavior, and tobacco use prevalence.</p>	<p>products, illicit sales of tobacco products, or user modification of tobacco products were excluded from the review (e.g., retailer inventory of tobacco products, retailer compliance with a policy, legal challenges to implementation of a policy, public opinion on a policy). Given this, we did not add this study to the RTD review.</p> <p>However, in response to this reviewer’s comment, we have added a discussion of the compliance and enforcement, including a brief summary of studies (including Andersen-Rodgers et al. 2021) assessing retailer compliance and availability of flavored tobacco products after a flavored tobacco sales restriction, in the Limitations section for context.</p>
Reviewer #4	<p><u>Section 1</u></p> <p>5. Fong GT. The impact of Canada’s menthol cigarette Ban on quitting among menthol smokers: Findings from a new pooled analysis of ITC Canada Survey and Ontario Menthol Ban Study data. Presentation given at the European Network for Smoking and Tobacco Prevention (ENSP) Side Event During the 9th Session of the Conference of the Parties of the WHO Framework Convention on Tobacco Control, 9 November 2021. Publicly available from: http://ensp.network/4559-2/.</p> <p>This pooled analysis combined data from the two cohort studies that evaluated the menthol cigarette ban in Canada: the Ontario Menthol Ban Study, consisting of 1,084 smokers in the province of Ontario, and the ITC Canada Survey, consisting of 1,236 smokers across seven provinces including Ontario. The two</p>	<p>We appreciate the reviewer for informing us of this presentation. The finding that pre-ban menthol smokers were significantly more likely to have quit at post-ban compared to non-menthol smokers is consistent with findings reported in Section 1. We will continue to monitor the literature for peer review publication of these findings.</p> <p>In addition, the finding of low-level use of illicit menthol cigarettes is consistent with the findings in Section 1 of the report. We agree the finding that the percentage of pre-ban menthol smokers</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>studies were conducted at nearly the same time at both pre-ban (ITC Survey: July-November 2016; Ontario Menthol Survey: September-December 2016) and post-ban (ITC Survey: February-July 2018; Ontario Menthol Survey: January-August 2018). Both studies also used comparable measures of menthol smoking and non-menthol smoking, and of quitting.</p> <p>The main findings were that pre-ban menthol smokers were significantly more likely to have quit at post-ban compared to non-menthol smokers. For daily smokers, 21.2% of menthol smokers had quit vs. 13.2% of non-menthol smokers, a difference of 8.0% (p=0.005; 95% Confidence Interval: 2.4-13.7%). For all smokers (daily and non-daily), 22.3% of menthol smokers had quit vs. 15.0% of non-menthol smokers, a difference of 7.3% (p=0.006; 95% CI: 2.1-12.5%).</p> <p>These effect sizes combine all individual-level data known on the impact of Canada’s menthol cigarette ban across provinces covering 83% of the Canadian population.</p> <p>Relevant to Section 3 of this review (“Modeling the Public Health Effects of a Menthol Cigarette Ban in the United States”), the presentation presented calculations from the pooled analysis of the 7.3% additional quitting of menthol smokers to estimate the number of additional quitters in the U.S. and the E.U. if the menthol cigarette ban were to have the same effect as observed in Canada.</p> <p>For the U.S., the number of menthol smokers in the U.S. (where prevalence of menthol smoking is much higher—nearly eight times higher than it was in Canada), was estimated from the 2019 National Survey on Drug Use and Health (NSDUH). The estimated number of additional smokers who would quit in the U.S. (again assuming the same effect size as observed in Canada) was:</p>	<p>who purchased cigarettes from illegal sources post-ban didn’t differ from non-menthol smokers aligns with the Stoklosa 2019 finding. We will continue to monitor the literature for peer review publication of these findings for future inclusion in this report.</p> <p>We also agree that Canadian findings are consistent with the modeling of the US population described in Section 3 of the report. We will continue to monitor the literature for peer review publication of these findings.</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	<p>18,3289,597 menthol smokers in the U.S. x 7.3% additional quitting = 1,337,988 additional smokers who would quit. (95% CI: 384,901-2,291,075).</p> <p>From NSDUH, the number of African American menthol smokers was obtained, and the same estimation of additional quitters was calculated (again assuming the same effect size as observed in Canada):</p> <p>8,368,816 African American menthol smokers x 7.3% additional quitting = 610,924 additional African American smokers who would quit. (95% CI: 154,070-1,191,575).</p> <p>The presentation also made the following points about the Chung-Hall et al. ITC evaluation study:</p> <p>The overall level of menthol smokers still smoking menthols as reported by respondents was fairly low (19.5%). This was reported in the original Tobacco Control article.</p> <p>But in follow-up analyses conducted after the Tobacco Control article: the ITC survey also asked smokers to report on the brand they were smoking, which allowed for an assessment of whether those who reported smoking menthols were really still smoking menthols. Many of them were not. After removing incorrect reporting of post-ban menthol cigarettes, fewer than 10% of menthol smokers (13 of 138) were smoking illicit menthol cigarettes.</p> <p>The percentage of pre-ban menthol smokers who purchased cigarettes from known illegal sources (First Nations reserves) after the ban did not differ from non-menthol smokers (12.2% vs. 9.0%) (n.s.). This lack of increase in illicit purchasing replicates the Stoklosa (2019) finding in Nova Scotia.</p>	

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
Reviewer #4	<p><u>Section 1</u></p> <p>6. Kock L, Shahab L, Bogdanovica I, Brown J. The profile of menthol cigarette smokers in the months following the removal of these products from the market: a cross-sectional population survey in England. Tob Control; in press. Published on-line November 17, 2021. http://dx.doi.org/10.1136/tobaccocontrol-2021-057005</p> <p>Cross-sectional population survey of current smokers (18+) (n=2,681) in England conducted between July 2020 and June 2021, after May 2020 EU TPD menthol cigarette ban. Between July 2020 and June 2021, 15.7% (95%CI 14.5–17.1) of smokers reported smoking menthol cigarettes. The fitted non-linear trend supported no initial change followed by a possible reduction across April-June 2021. The authors note that because the survey question used to measure flavored cigarette smoking also covered tobacco accessories (menthol flavored capsules, filter tips, cards or flavored rolling papers) that were exempt from the menthol ban, prevalence of post-ban menthol smoking could reflect use of these compliant products. The study was not able to infer whether pre-policy menthol smokers transitioned to use of menthol flavored accessories due to lack of data on prevalence of only menthol flavor accessory use before the ban.</p> <p>This study provides some initial support of a positive impact of the May 2020 menthol cigarette ban, mandated under the EU Tobacco Products Directive.</p> <p>This study also presents results showing a significant decline in illicit sales from 30.1% in the last 6 months of 2020 to 17.5% in the first 6 months of 2021. However, given the possible impact of the COVID-19 pandemic, it is not clear</p>	<p>We have added the Kock et al. (2021) study to the review.</p>

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	whether these results are reliable with respect to the impact of the menthol cigarette ban on illicit sales.	
Reviewer #4	<p><u>Section 1</u></p> <p>7. Rogers T, Brown EM, Siegel-Reamer L, et al. A comprehensive qualitative review of studies evaluating the impact of local US laws restricting the sale of flavored and menthol tobacco products. <i>Nicotine Tob Res</i>; in press. Published on-line September 15, 2021. https://doi.org/10.1093/ntr/ntab188.</p> <p>This US-only qualitative review of local US laws on flavored and menthol tobacco products overlaps with the FDA evidence review and it would thus be important to review to identify conclusions in the Rogers et al. review that are consistent or inconsistent with this FDA review.</p>	Since relevant studies cited in the Rogers et al. (2021) review are already reviewed in Section 1, this paper was not included in the RTD review.
Reviewer #4	<p><u>Section 3</u></p> <p>1. Li, Y., Sisti, J., Flórez, K.R. et al. Assessing the Health and Economic Impact of a Potential Menthol Cigarette Ban in New York City: a Modeling Study. <i>J Urban Health</i> (2021). https://doi.org/10.1007/s11524-021-00581-8</p> <p>This modeling study estimated the long-term impact of a menthol cigarette ban on CVD risk among adult smokers in New York City (NYC). The model projected that without a menthol cigarette ban, there could be 57,232 (95% CI: 51,967–62,497) myocardial infarction (MI) cases and 52,195 (95% CI: 47,446–56,945) stroke cases per 1 million adult smokers in NYC over a 20-year period. If a menthol cigarette ban was implemented, an estimated 2,862 MI cases (5% reduction) and 1,983 stroke cases (3.8% reduction) per 1 million adults could be averted, with an average of \$1.62 billion in healthcare costs saved among all adult smokers over 20 years. Reductions in adverse CVD outcomes would likely</p>	This paper does not meet the inclusion criteria because it is limited to New York City only and does not address all-cause deaths averted or all-cause life-years lost averted as an outcome.

CHARGE QUESTION 2. Are you aware of additional publicly available information that should have been included? If so, please specify what that information is and discuss its relevance to the scientific assessment.		
REVIEWER	COMMENT	RESPONSE
	be greater among females (particularly Black females) vs males and other racial/ethnic subgroups.	
Reviewer #4	<p><u>Section 3</u></p> <p>2. Brouwer AF, Jeon J, Cook SF, et al. The impact of menthol cigarette flavor in the U.S.: cigarette and ENDS transitions by sociodemographic group. Am J Prev Med. 2021:S0749-3797(21)00442-6. doi: 10.1016/j.amepre.2021.08.007. Multistate transition model based on longitudinal data from the PATH Study (sample of 23,232 adults from Waves 1-4, 2013-2017) was used to estimate transitions in tobacco use (menthol and non-menthol smoking, ENDS use, and dual use), and the impact of menthol cigarette flavorings on tobacco product use transitions over time. Findings showed that Non-Hispanic Blacks (NHBs) who smoked menthol cigarettes discontinued smoking at a 60% lower rate vs NHBs who smoked non-menthol cigarettes, but there was no difference in discontinuation rates by menthol flavoring for Non-Hispanic Whites (NHWs). There was no significant difference by menthol flavoring for any of the transitions among Hispanics. Across sociodemographic groups other than NHWs, menthol smoking (vs non-menthol smoking) was not significantly associated with initiation or discontinuation of ENDS products. Initiation of menthol smoking was higher among young adults vs older adults, but there were no differences in initiation of non-menthol smoking between age groups. The authors highlight the implications of these findings for the potential impact of menthol ban on combustible products in the US: 1) menthol ban could lead to substantial smoking cessation among NHBs who would otherwise not quit, 2) menthol ban may reduce smoking initiation among young adults. Females (particularly Black females) vs males and other racial/ethnic subgroups.</p>	Although a highly relevant paper, this study does not meet the inclusion criteria for this literature review, as it does not forecast behavioral transitions under a menthol ban, and does not simulate deaths averted and life-years gained under such a scenario.

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	The article summaries for Section 2 (see Appendix B) are written as outlines rather than in narrative format like in Section 1 (see Appendix A). I have no preference for outline vs narrative but it should be consistent across sections.	We have written the Section 2 article summaries in narrative format for consistency with Section 1.
Reviewer #1	One minor suggestion is to include an abbreviations list at the beginning of the review document.	Section 1, Section 2, and Section 3 now include a list of abbreviations used in each section. The list of abbreviations appears after the Table of Contents for each section.
Reviewer #2	The utility of this document in its current form is limited given the absence of a framework to assess the strength of evidence. The organization of the report could also be improved via the use of summary tables.	<p>We thank the reviewer for this comment. We have adapted the level of evidence framework used in NASEM's 2018 Public Health Consequences of E-Cigarettes report to assess the strength of studies reviewed in Section 1 and Section 2. A table summarizing the conclusions and the strength of evidence for each conclusion has been added to Section 1 and Section 2. In addition, a table describing characteristics (e.g., study design, sample size, years of data collection, key findings), of each study included in Section 1 and Section 2 grouped by outcome of interest and with an assessment of each study's key strengths and limitations has been added to Section 1 and 2.</p> <p>Section 3 now includes a table summarizing the models included in the review.</p>

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
Reviewer #3	<p><u>Section 1</u></p> <ul style="list-style-type: none"> Collapsing illicit, cross-border, and online sales is problematic. Some of these studies address illicit cigarettes (Stoklosa 2019), some address cross-border sales (Rogers 2017, 2020) and some address purchasing behaviors (Guydish 2020; Yang 2020; Soule 2019; Chaiton 2018, 2020; Chung-Hall 2021). The studies on purchasing behaviors reflect self-reported behavior in small samples of menthol cigarette users. Three of these studies report purchasing menthol cigarettes on First Nations reserves without explanation of whether or how the menthol cigarette ban applied to First Nations reserves. Earlier in this section, the Delnevo & Hrywna (2015) paper is described as it relates to sales of flavored cigars (clove) in response to the flavored cigarette ban, but not as it relates to changes in tobacco company behavior to exploit a policy loophole. Together, these data speak to the potential impact of loopholes on the effectiveness of the regulation and identify outcomes to track, but not all these behaviors are illegal (e.g., purchasing). The Background and Conclusions for this section do not address tobacco industry behavior related to illicit trade, nor the tools available through the 2009 Family Smoking Prevention and Tobacco Control Act to combat illicit trade or to minimize loopholes through regulation itself. 	<p>We thank the reviewer for this comment. In response to this comment, we have updated this section in the document to report study findings on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively). We have adapted the level of evidence framework used in NASEM's 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented and characterize the strength of evidence for illicit sales, cross-border sales, and online sales separately. We included purchases from First Nations reserves as cross-border sales and clarified that First Nations reserves were generally exempted from the sales restriction. Tobacco industry behavior in response to flavored sales restrictions is outside the scope of the research questions addressed by this document.</p>
Reviewer #3	<p><u>Section 2</u></p> <ul style="list-style-type: none"> The Behavioral Intentions literature includes a review and three empirical studies, though it is not clear which of the three empirical studies are included in the review. I recommend including the relevant empirical studies from the Cadham et al. (2020) review, rather than the review itself, and presenting the range of estimates across the empirical studies assessed. Additionally, these studies need more detail on sample 	<p>We now review all articles included in the Cadham et al. (2020) review that met our inclusion criteria. We cite the Cadham review but did not consider it when drawing conclusions across studies.</p>

CHARGE QUESTION 3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.		
REVIEWER	COMMENT	RESPONSE
	sizes and timeframe of data collection to better understand how they inform the research question in the “current market.”	We have added a summarizing table that includes information on sample size and timeframe of data collection.
Reviewer #3	<ul style="list-style-type: none"> It is unclear why the detail on the Denlinger-Apte et al. (2021) findings are presented in the Conclusions paragraph for Behavioral Economics studies, not later in the section. This study included n = 40 menthol smokers compared to the other studies reported in this section that included over 1,000 adult smokers. 	Details on the Denlinger-Apte findings are now presented in the experimental tobacco marketplace subsection. While we recognize the small number of participants in the Denlinger-Apte study is a limitation, the study findings are strengthened by the field assessment where participants were given the products they purchased during one of their shopping trips.
Reviewer #3	<ul style="list-style-type: none"> In both the Behavioral Intentions and Behavioral Economics sections, a table presenting study design, sample size, time/years of data collection, and results would be helpful to synthesize the range of findings and consistency of results across studies. 	We have added a table that summarizes study design, sample, data source, key findings, and key strengths/limitations
Reviewer #3	<p><u>Section 3</u></p> <ul style="list-style-type: none"> A table presenting results across the three studies showing how the estimates are similar/different across different models with different assumptions/parameters would be particularly helpful. These estimates are consistent with each other in terms of the order of magnitude of the impact of a menthol ban on deaths averted (hundreds of thousands), despite using different timeframes, models, and assumptions. More qualitative and quantitative synthesis in the text, rather than detail on each model, will provide greater support for the conclusions. 	We have created a table (Appendix C) of results describing and comparing the studies in Section 3.

CHARGE QUESTION 3. <i>Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.</i>		
REVIEWER	COMMENT	RESPONSE
Reviewer #4	My specific comments on methodology, strength of data, and limitations are provided in Section III. Specific Observations. In general, there were no concerns about the methodology of the review. The studies reviewed varied in the strength of their research design and methods and also in their applicability/generalizability to a possible menthol cigarette ban in the U.S.	We thank the reviewer for this comment. We have responded to specific comments in Section III.

III. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	11	2	Rosshiem et al., 2017 – There is an extra parenthesis in the second sentence.	We have deleted the extra parenthesis in the second sentence.
Reviewer #1	12	3	Yang et al., 2020 – Is the study conclusion that the flavor ban resulted in substitution of regular cigarettes?	The finding of increased cigarette use prevalence among 18- to 24- year-olds in Yang et al. (2020) was not statistically significant at alpha level 0.05. We have deleted sentences referring to this finding in the review.
Reviewer #1	14	2	Chaiton et al., 2020 – Consider revising the second sentence in this paragraph because the structure as written is difficult to follow (i.e., what the percentages reference and what the comparison is).	We have updated the language discussing findings from Chaiton et al. (2020) to improve readability.
Reviewer #1	16	5	Summary and Conclusions – Sentence 2 requires clarification regarding what the authors mean by “Some menthol smokers may quit completely...” Does this mean quit only cigarettes or quit all tobacco products? Further, the sentence as written is repetitive. “...while others may switch to <u>other tobacco products</u> such as non-menthol cigarettes and <u>other tobacco products</u> .” Should this be other flavored tobacco products?	This sentence has been revised for clarity. We have clarified that “quit completely” refers to cigarettes. Additionally, “other tobacco products” has been revised to say, “flavored tobacco products.”
Reviewer #1	18	4	In the first sentence, hyphenate “4 week” and possibly capitalize “information” since it is part of a corporation name.	We have hyphenated “4 week” and capitalized “information.”
Reviewer #1	20	6	In the sixth sentence, add a comma after ban (i.e., “...clove cigarette ban, unit sales...”)	We have added a comma after the ban (i.e., “... clove cigarette ban, unit sales...”).

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	22	1	There is an extra parenthesis in the third sentence.	We have deleted the extra parenthesis.
Reviewer #1	22	1	I think 'cigarettes' is missing from the sentence "...California policy that included menthol and ENDS..."	The sentence is accurate as written. The San Francisco, California policy restricted sale of all flavored (including menthol) tobacco products (including ENDS).
Reviewer #1	22	2	In the last sentence, add a comma after authorities (i.e., "...according to local authorities, there were only...")	We have added a comma after "authorities."
Reviewer #1	23	1	Possible typographical error in the second sentence: "Trend in unit sales <u>in</u> observed in the proximal..."	We have edited the sentence: "Trends in unit sales observed in the proximal..."
Reviewer #1	24	4	Typographical error in the final sentence: delete the extra 'i'	We have deleted the extra 'i'.
Reviewer #1	31	Reference list	Zheng et al., 2017 has inconsistent formatting relative to the other citations.	We have updated the formatting of the Zheng et al. 2017 reference.
Reviewer #1	36	2	Chaiton et al., 2021 – Typographical error in sentence 6: nonmenthol should be non-menthol. Additionally, I think a word might be missing from this sentence: "It was not clear if the convenience sample was targeted to provide more information on specific group relevant to the research question."	We have updated "nonmenthol" to "non-menthol" and have revised the flagged sentence for clarity: "This study used a supplemental convenience sample; it was not clear if the convenience sample was used to provide more information on specific groups relevant to the research question."
Reviewer #1	38	3	Farley & Johns, 2016 – "However, the changes in non-flavored product-specific sales for <u>cigars</u> and <u>pipe</u> and <u>RYO</u> <u>both</u> demonstrated significant increases of <u>5%</u> (p=0.003)	In Farley & Johns (2016), pipe and RYO were collapsed as one tobacco product group; therefore, only two percentages are reported (one for cigars, and one for pipe and RYO). We

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			and 4% (p=0.030), respectively.” In this sentence, three products are listed but only two % increases are reported.	have clarified the presentation of findings in the text: “However, the changes in non-flavored product-specific sales for 1) cigars and 2) pipe/RYO both demonstrated significant increases of 5% (p=0.003) and 4% (p=0.030), respectively.”
Reviewer #1	45	2	Stoklosa 2019 – Typographical error in the second to last sentence: “...period from 2014 <u>o</u> 2018...”	We have corrected this typographical error.
Reviewer #1	62	2	Denlinger-Apte et al., 2021 – Typographical error: noncigarette should be non-cigarette	We have hyphenated all instances of the term “non-cigarette” in Section 2.
Reviewer #1	63	1	Denlinger-Apte et al., 2021 – “When menthol LCCs were available, the most frequently purchased <u>non-menthol cigarette products</u> were...” Consider revising the underlined words to say “alternative products”. As written, the sentence is a little confusing.	We have revised the phrase “non-menthol cigarette products” to “alternative products” in the summary of Denlinger-Apte findings.
Reviewer #1	69	2	Reviewer initials are listed in parentheses. Is this necessary? If so, the other two sections do not include review initials.	Reviewer initials have been removed from Section 3.
Reviewer #2			None provided.	---
Reviewer #3	8	4	Some of the studies described in the “Summary of Studies on the Impact of Flavored Tobacco Sales Restrictions or Bans on Tobacco Use Behaviors of Young People” are described as “cross-sectional pre-and post-policy” design, while others are simply “pre- and post-policy designs.”	In response to this comment, we have clarified the study designs described in this section. All of the studies described in this section used data collected from cross-sectional surveys.

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			Please clarify the differences between these designs (e.g., repeated cross-sectional surveys pre- and post-policy implementation versus longitudinal studies of the same individuals pre- and post-policy implementation).	
	9	2/Subheading	Recommend deleting “Subject and/or Not Subject to Sales Restriction” in the subheading. This added text creates confusion about what is presented in the studies, which address changes in any tobacco use, any flavored tobacco use, or use of specific tobacco products.	We have deleted “Subject and/or Not Subject to Sales Restriction” for the subheading regarding evidence of decreases in use of tobacco products by young people.
Reviewer #3	9	2	Farley and Johns (2016) - Recommend using “proportion” rather than “percent” in describing the study: “...found that the PROPORTION of youth who reported ever using flavored tobacco products declined 4 percentage points...”	This statement presented findings that were not statistically significant at the 0.05 level. Since we focus on reporting primary findings significant at the 0.05 level in the RTD, we have deleted the sentence.
Reviewer #3	10	2	Pearlman et al. (2019) – Recommend revising the language about findings spanning the 2017 active enforcement of the policy; the “(3 years post-policy)” and “(5 years post-policy)” language is confusing. These findings focus on the change before and after enforcement, not implementation. Check the consistency of formatting for 95% CIs in this section (e.g., 11.4 to 15.1 vs 11.4-15.1).	We have deleted the language regarding “3 years post-policy” and “5 years post-policy” and revised clarifying that the findings from 2016 to 2018 represent changes after enforcement. We have updated formatting for 95% CIs in Section 1 to make the formatting consistent throughout (95% CI XX – XX).
Reviewer #3	10	3	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	We have added sample sizes when discussing findings from Yang et al. (2020).

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Reviewer #3	11	1	Courtemanche et al. (2017) – Please specify the years of data collection included in this study (i.e., NYTS 1999 – 2013) and how pre-ban and post-ban were defined in these analyses.	We have added information on years of data included in the analysis and how pre-ban and post-ban were defined in the Courtemanche et al. (2017) analysis.
Reviewer #3	11	2	Rosshiem et al. (2017) – Please specify the years of data collection included in this study and how pre-ban and post-ban were defined in these analyses.	We have added information on years of data included in the analysis and how pre-ban and post-ban were defined in the Rosshiem et al. analysis.
Reviewer #3	11	3/Subheading	Recommend deleting “Subject and/or Not Subject to Sales Restriction” in the subheading. This added text creates confusion about what is presented in the studies.	We have deleted “Subject and/or Not Subject to Sales Restriction” from the subheading regarding evidence of increases in use of tobacco products by young people.
Reviewer #3	12	2	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	We have added sample size information when discussing findings from Yang et al. (2020). The reference to Yang et al. (2020) findings on page 12, paragraph 2 was deleted in response to another peer reviewer comment.
Reviewer #3	13	1/ Summary	Recommend providing detail here on the number of studies that found increases, compared to the number that found decreases to support the conclusion.	In the Summary and Conclusion sections, we now report the number of studies supporting each conclusion.
Reviewer #3	14	4	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	We have added sample size information when discussing findings from Yang et al. (2020).

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #3	16	4/ Summary	Recommend providing detail here on the number of studies that found increases and the strength of the evidence, compared to the number that found other outcomes to support the conclusion.	In the Summary and Conclusion sections, we now report the number of studies supporting each conclusion.
Reviewer #3	25	2/ Summary	See notes above re: concerns with grouping illicit, cross-border, and/or online sales together, as well as conclusions drawn from the data presented.	We have updated this section in the document to report study findings and overall conclusions on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively).
Reviewer #3	25	5	Chaiton et al. (2020) – Please provide the sample size for this study, as well as the numbers reporting modification of their products (in addition to the percentages).	We have added information on sample size, when available, in addition to the percentages when reporting findings from Chaiton et al. (2020) on modification. Chaiton et al. (2020) did not report sample size information for the percent of baseline daily menthol smokers using flavor additives in 2016, 2017, 2018, and 2019.
Reviewer #4	4	1	The questions listed in the Purpose are appropriate and capture the breadth of the important outcomes/consequences of a potential prohibition of menthol, covering the studies of both individual-level outcomes—behavior of young people and adults—and the aggregate outcome of sales. The last two research questions focus on the possible consequences that would weaken the impact of a menthol prohibition. Again, these questions cover an individual-level outcome—user	We thank the reviewer for the comment and agree that the research questions capture the important outcomes of potential menthol product standard.

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			<p>modification of tobacco products—and an aggregate outcome of illicit sales.</p> <p>Together, the evidence review is structured to assess the potential net impact—costs as well as benefits—of a ban on menthol as a characterizing flavor in cigarettes to reduce the death and disease from tobacco use.</p>	
Reviewer #4	4	2	The three electronic databases searched—PubMed, Web of Science, and Embase—are the three leading databases for research on biomedical science and public health.	We thank the reviewer for this comment.
Reviewer #4	4		<p>The Eligibility Criteria are reasonable, requiring peer reviewed published or in-press journal articles, conference proceedings, and book chapters where full text is available.</p> <p>Very few jurisdictions have banned menthol, and while evaluation studies of those menthol bans are most applicable to a possible FDA menthol cigarette ban, and should thus be accorded greater weight and consideration, evaluation studies of bans on other flavours are also relevant and are properly included in this review.</p> <p>The evidence on the impact of non-menthol flavor bans will provide insights on the possible impact of a future menthol ban to the extent that non-menthol and menthol flavors are similar in their effects on users (e.g., addiction, appeal, etc., covered in the other FDA review, <i>Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021</i>) and in the characteristics of the cigarette</p>	We thank the reviewer for this comment. We have added language in the “Methods” stating that studies evaluating policies restricting the sale of menthol cigarettes were considered to have higher external validity than studies evaluating non-menthol cigarette policy restrictions in the RTD review.

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			market that are relevant to the aggregate measures of sales and illicit sales.	
Reviewer #4	5-6		Information Sources and Search Strategy: The search strings used are reasonable.	We thank the reviewer for this comment.
Reviewer #4	6-7		Article Selection: The procedures used to exclude articles were reasonable, leading to the reduction from 230 unique records to 25 studies included in the review.	We thank the reviewer for this comment.
Reviewer #4	7-8		<p>FDA cites the IARC Handbook of Cancer Prevention (2008), <i>Methods for Evaluating the Impact of Tobacco Control Policies</i>, as a key source for assessing the internal and external validity of studies. The brief description of some of the design features of studies that increase internal validity and those that increase external validity are reasonable, although the last sentence doesn't quite capture the use of external validity that applies to the issues at hand.</p> <p>Studies employing probability-based sampling do "have higher external validity", when the sample is meant to generalize to the population from which it was drawn. But in addition to that kind of external validity, there is another kind of external validity that is relevant here: the extent to which the findings of a study could be generalized to making inferences about the possible impact of a ban on menthol as a characterizing flavour in the United States. For example, studies that evaluate a menthol cigarette ban would, ceteris paribus, be more applicable to a possible</p>	We have clarified the sentence regarding assessment of external validity of studies.

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			future menthol cigarette ban than studies that evaluate a ban on other flavors.	
Reviewer #4	8-13		<p>These studies examine the impact of the 2009 Federal flavored cigarette ban (excluding menthol) and specific flavor bans at the state-level, county-level, and community-level among young people. These include evaluation studies of New York City’s 2010 flavor ban (excepting menthol), counties in Massachusetts (2011-17), Lowell, MA (2016), Providence, RI (2013), and San Francisco, CA (2018, including menthol).</p> <p>The studies are summarized appropriately, and describe the basic findings, showing that in those jurisdictions where flavored tobacco products (excepting menthol) were banned, smoking among youth and young people in particular was significantly reduced.</p> <p>These studies are well-conducted, with strong designs (although the Yang et al. San Francisco study employed a retrospective design, which is not as strong as a true pre-post study).</p>	We appreciate the reviewer’s comment.
Reviewer #4	11-12		<p>Comments on specific studies in this section.</p> <p>The Rossheim et al. (2020) study, analyzing NSDUH data from 2002-17, found that after the 2009 Federal flavored cigarette ban (excepting menthol), after an initial increase in the first quarter after the ban among adolescents and young adults, cigarette smoking declined significantly</p>	We appreciate the comments on the Rossheim and Courtemanche studies. These comments align with the discussion in Section 1.

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			<p>(change in both slope and total effect), with a strong age gradient: the greatest reduction in cigarette smoking was observed among adolescents, followed by young adults, and then adults. There was no effect of the ban on cigarette smoking among older adults. This study, and others, suggest that the impact of flavor bans may be strongest among youth and young adults.</p> <p>The Rossheim et al. (2020) study also found evidence for initial substitution—there was an initial significant increase in menthol cigarettes in the first quarter post-ban, but then a significant decrease in menthol cigarettes after that first quarter. Of note, this significant decrease in menthols was greatest among youth (12-17 years) and young adults (18-25) after the initial increase. This suggests that a flavor ban (excepting menthol) may have led these smokers to substitute to menthol—the only flavor that was available—but this initial attempt was quickly not maintained, and menthol prevalence declined quickly afterwards.</p> <p>The study by Courtemanche et al. (2017) evaluated the 2009 Federal ban in an analysis of NYTS data from 1999-2013. They also found an overall association between the flavored cigarette ban and the probability of being a cigarette smoker. Courtemanche et al. also found evidence supporting substitution, not only to menthol cigarettes, but also to other tobacco products where flavors were not restricted: cigars and pipes.</p>	

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #4	12		These studies and others highlight the importance of applying bans to not only the target product class (cigarettes) but also other products where flavors like menthol would otherwise be available as substitutes for cigarette smokers. This is particularly important for potential substitutes that are combustible tobacco products—cigars, small cigars/cigarillos.	We agree and thank the reviewer for this comment.
Reviewer #4	12		As mentioned earlier, studies that evaluate a menthol cigarette ban are of greatest applicability to a possible future U.S. ban on menthol cigarettes. There are two studies in the U.S. that evaluated the July 2018 San Francisco ban of all flavored tobacco products (cigarettes, e-cigarettes), which included menthol.	In the Methods section, we have added text indicating that the degree to which evaluation study findings can be generalized to making inferences about the possible impact of a ban on menthol cigarettes in the US was evaluated and that studies evaluating policies restricting the sale of menthol cigarettes were considered to have higher external validity than studies evaluating policies restricting the sale of other flavored tobacco products. In Appendix D Table, we include “policy includes a menthol cigarette restriction” as a study strength for studies evaluating the flavored tobacco sales restrictions including menthol in San Francisco and Canada.
Reviewer #4	12		Yang et al. (2020) examined the impact of the San Francisco ban in a retrospective study of a convenience sample of 18-34 year ever tobacco users in San Francisco. In November 2018, these respondents were asked for their tobacco use	Thank you for the comment. In our discussion of findings from Friedman (2021), we have added text describing a methodological mistake recently reported by Liu et al. (2022) that the

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>before and after the ban. Although prevalence of overall flavored tobacco use decreased only slightly, cigarette smoking increased among 25-34 year olds, although not significantly.</p> <p>Friedman (2021) in an analysis of YRBSS high school survey data, comparing San Francisco to other school districts, found that 30-day smoking increased significantly in San Francisco, both pre-post within San Francisco, and compared to the other districts.</p> <p>Why would cigarette smoking increase after a ban of menthol and all flavors in tobacco products? This would seem, initially, to be contrary to the studies evaluating the 2009 Federal ban on flavored cigarettes (excepting menthol), which found cigarette smoking to decrease.</p> <p>The explanation may be that in San Francisco, the ban was applied to all tobacco products, which included the most dominant tobacco product—e-cigarettes. Cigarettes and e-cigarettes are substitutes, and since the vast majority of vapers, especially youth and young adults vape non-tobacco flavored e-cigarettes, a ban on flavors on e-cigarettes would be potentially more significant in reducing the attractiveness and appeal of e-cigarettes than it would be on cigarettes. Consequently, substitution from flavored e-cigarettes to unflavored cigarettes might have been more</p>	<p>2019 YRBS was conducted in Fall 2018 prior to when the flavor policy was enforced in April 2019 indicating that the Friedman (2021) analysis was a pre-only rather than pre/post as reported by Friedman (2021). Given this, findings from Friedman (2021) do not reflect the impact of San Francisco’s flavored tobacco sales restriction on cigarette use.</p>

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			<p>likely than substitution from flavored cigarettes to unflavored e-cigarettes.</p> <p>That transition, from e-cigarettes to cigarettes and vice versa, is not the only transition of course, as the earlier studies evaluating the 2009 Federal flavor ban has shown. Both e-cigarette users and cigarette users could have quit using either of these products. What we see in the Friedman data is the net result of these transition patterns across all products, including quitting.</p> <p>Given the past studies of a significant decrease in cigarette smoking after a cigarette flavor ban, then one possible interpretation of the Friedman study and the Yang et al. study showing an increase in cigarette smoking is that it reflects a transition from e-cigarette users to cigarettes that was substantially greater than the increased quitting of menthol cigarette smokers, leading to a net increase in cigarette smoking.</p> <p>Neither the Yang et al. study nor the Friedman study had a design that was capable of assessing transitions, so this possible interpretation could not be assessed.</p> <p>However, the impact of the San Francisco ban on all flavored tobacco products, including e-cigarettes, and the complexity of the findings of those evaluation studies points to the need to carefully assess how substitutability of cigarettes with other tobacco products will affect the</p>	

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			impact of a menthol cigarette ban—the extent to which menthol smokers will quit or transition to other combustible products (e.g., cigars, cigarillos) or non-combustible products (e.g., e-cigarettes), and to assess the net public health benefit of transitions from cigarettes to those other products.	
Reviewer #4	12		<p>The complexities of the San Francisco flavor ban on cigarettes, other combustible products, and e-cigarettes leads to difficulties in interpreting the findings since observed impact on prevalence of each of those product classes is the net impact of restrictions of each class and the restrictions of the other classes, with possible substitution.</p> <p>For example, the observed impact on cigarette prevalence is the net result of both the impact of the restriction on flavored cigarettes, but also the impact of the restriction on flavors of the other tobacco products (notably e-cigarettes, which has the highest prevalence, especially among youth and young adults) and the possible impact on vapers transitioning to cigarettes. It is thus difficult to assess from the San Francisco flavor ban what the impact of a ban on menthol cigarettes alone or the impact of a ban on menthol cigarettes and other combustible tobacco products given this confounding effect of the simultaneous ban on flavored e-cigarettes.</p>	<p>Thank you for the comment. In our discussion of findings from Friedman (2021), we have added text describing a methodological mistake recently reported by Liu et al. (2022) that the 2019 YRBS was conducted in Fall 2018 prior to when the flavor policy was enforced in April 2019 indicating that the Friedman (2021) analysis was a pre-only rather than pre/post as reported by Friedman (2021). Given this, findings from Friedman (2021) do not reflect the impact of San Francisco’s flavored tobacco sales restriction on cigarette use.</p>

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REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #4	13		The Summary and Conclusion are appropriate given the studies reviewed: that expanding the Federal ban on flavored cigarettes to include menthol is likely to lead to lower use of tobacco products by young people. Using a flavored product standard would be more powerful than the retailer-only level restrictions/bans that have been applied at the local level.	Thank you for the comment. We agree that national policies or regulations that cover the US as a whole would increase the impact of flavored tobacco restrictions on tobacco use among young people by reducing the extent of available and accessible restricted tobacco products in nearby jurisdictions where they are not restricted. In addition, a flavored tobacco product standard would apply to tobacco product manufacturers and retailers and be accompanied with strong enforcement at the federal level, unlike local flavored tobacco product sales restrictions that apply only to retailers. We have added this to the Limitations section.
Reviewer #4	13-15		There are two aspects of the Canadian menthol cigarette ban that make it closely analogous to the U.S. situation. The first aspect is the history of the menthol ban in Canada. Between May 2015 and October 2017, seven Canadian provinces implemented a ban on menthol cigarettes. In October 2017, the Federal government then implemented a ban on menthol cigarettes that applied to the remaining three provinces. Prior to these menthol bans, Canada had banned all other flavors in cigarettes. Thus, the menthol cigarette ban in Canada, adding menthol to the already existing ban on other flavors, constituted the same incremental ban as would be the case in a possible future	Thank you for your comment. We agree that these two aspects of the Canadian menthol cigarette ban make it closely analogous to the US situation. We have added language in the Limitations highlighting this.

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			<p>US ban on menthol cigarettes, where menthol would be added to the already existing 2009 flavor ban.</p> <p>Second, the Canadian menthol ban was not accompanied by restrictions on flavors on e-cigarettes, which as discussed earlier, led to difficulties in interpreting the results of the San Francisco flavor ban on all tobacco products. Evaluation studies of the Canadian menthol ban thus provide cleaner, less confounded estimates of the impact of a possible menthol cigarette ban in the U.S. unconfounded by aspects of the San Francisco flavor ban other than the menthol cigarette ban.</p> <p>If a future U.S. ban on menthol cigarettes would not be accompanied by similar flavor restrictions on e-cigarettes, then that would be a second similarity between Canada and the U.S. that would enhance the applicability and generalizability of the Canadian experiences to that of the U.S.</p>	
Reviewer #4	13-15		<p>It is important to note that both the Ontario Menthol Ban Study (Chaiton et al.) and the ITC Canadian Survey (Chung-Hall et al.) were both cohort studies, which, unlike the other studies in this section, allows for a detailed assessment of how individual menthol cigarette smokers responded to the menthol cigarette ban. That individual-level analysis is not possible in repeat cross-sectional studies.</p>	<p>We appreciate the reviewer's comment and agree. As mentioned in a previous response, we have adapted the level of evidence framework used in NASEM's 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To assess strengths and limitations of each study, we considered the study design, study population, setting, data collection, and</p>

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			<p>Further, both Canadian studies had very high internal validity in that it was possible to compare rates of quit attempts and quitting among menthol smokers to those of non-menthol smokers. This constitutes a quasi-experimental design in which one group of smokers—the menthol smokers—was subjected to a ban (the “treatment group”), whereas the other group—the non-menthol smokers—was not (the “no-treatment group”).</p> <p>The IARC Handbook, <i>Methods for Evaluating Tobacco Control Policies</i>, which is used here as a key source guiding the evaluation of the studies, discusses the importance of the similarity between the treatment group and the no-treatment group. Specifically, to the extent that the policy treatment group and the non-policy no-treatment group are similar to each other the evaluation study will have greater internal validity:</p> <p style="padding-left: 40px;"><i>The internal validity of the quasi-experimental design, although generally greater than the single group pre-post design, is dependent on the extent to which the non-policy group is similar to the policy group (e.g., similar levels of economic development, tobacco use prevalence). The greater the similarity, the more reasonable the comparison will be. (IARC Handbook, 2008, page 40).</i></p>	<p>threats to internal and external validity. In addition to the strengths and limitations, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. Studies with stronger designs (including temporality and specificity) and higher external validity were given greater weight.</p>

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			The key potential public health impact of a possible menthol cigarette ban is whether such a ban might lead to an increase in quitting. Of all studies reviewed in this section, the Canadian studies are the most specifically relevant to addressing that important question.	
Reviewer #4	13-15		Both Canadian studies found that quit attempts and quitting among menthol smokers was significantly higher than among non-menthol smokers, which can be taken as estimates of the increased attempts and quitting attributed to the menthol ban.	We appreciate the reviewer’s comment and agree. We have made this point in the summary and conclusion write up of this section.
Reviewer #4	14	3	<p>In the description of the Chung-Hall et al. study, the last sentence reads:</p> <p><i>“An important limitation is the fact that the post-policy survey relied on self-reported cigarette brand last purchased to determine menthol vs. non-menthol smoker status, which could have resulted in misclassification.”</i></p> <p>Although this sentence is a bit unclear, it is not an accurate statement: self-reported cigarette brand last purchased was NOT used to determine whether a respondent was still smoking. Instead, the question asking a respondent to report on his/her brand was to determine whether those still smoking were smoking a menthol cigarette brand or a non-menthol cigarette brand. To be sure, there could have</p>	<p>We appreciate the reviewer’s comment. The authors report “we used smokers’ self-reports of cigarette brand they last purchased to measure post-ban menthol smoking status, which may lead to potential misclassification at follow-up” as a limitation in their Discussion. However, in the Methods section, the authors state “At Wave 2, respondents were asked to identify the flavour of their usual cigarette brand or the brand they last purchased.” Since it is unclear how the authors determined menthol status at follow-</p>

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			<p>been a misclassification of whether the brand smoked was a menthol or non-menthol brand, but this would NOT be indicative of a misclassification in whether the respondent was smoking or not.</p> <p>The determination of smoking status was made at the start of the survey, using key questions used by the ITC Project in the four main countries (US, Canada, England/UK, and Australia) over 13 surveys since 2002. So the question about brand smoked is not relevant to the findings on the impact of the menthol ban on quitting. This statement needs to be corrected.</p>	<p>up, we have deleted this limitation from the RTD.</p>
Reviewer #4	14		<p>It should further be noted that the Chung-Hall et al. evaluation study also found that those menthol smokers who had quit before the menthol ban were significantly more likely to report being quit (12.7%) than those non-menthol smokers who had quit before the menthol ban (5.2%), $p < 0.05$. That suggests that in addition to the Canadian menthol ban’s impact on increasing quit attempts and quitting, that it also had a beneficial impact on reducing relapse back to smoking. This important finding was not mentioned in the review.</p>	<p>We appreciate the reviewer’s comment and agree. We have added language to the discussion on “Evidence of Increased Quit Attempts and Quitting by Smokers After a Menthol Cigarette Sales Restriction” highlighting this finding.</p>
Reviewer #4	15		<p>The Gydish et al. (2020) study of the impact of the San Francisco ban among adult clients in residential treatment facilities for substance abuse did not find any increased quitting behaviors. There are weaknesses in the design and the complexities of San Francisco flavor ban on all tobacco</p>	<p>We appreciate the reviewer’s comment and agree. We have added additional language in the summary and conclusions regarding the strength of evidence.</p>

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			products make it difficult to draw clear conclusions that are applicable to assessing the possible impact of a proposed menthol cigarette ban in the absence of a flavor ban on e-cigarettes.	
Reviewer #4	15-16		In all studies reviewed, there were some adult menthol cigarette smokers who switched to non-menthol cigarettes. Both the Chaiton et al. and the Chung-Hall et al. studies showed that the majority of pre-ban menthol smokers switched to non-menthol cigarettes. This is not surprising given the very high addictiveness of cigarettes. I am surprised that the rate of switching to non-menthol cigarettes was not higher than the 59% reported in the Chung-Hall et al. study.	We appreciate the reviewer's comment and agree. We have added language to the summary and conclusion section stating that a majority of adult menthol cigarette smokers switched to non-menthol cigarettes.
Reviewer #4	16		The Ontario Menthol Ban Study (Chaiton et al.) found that menthol smokers switched to other tobacco products, which given the substitutability of those other products, is also not surprising. Of particular note is that baseline menthol smokers were more likely to use flavored cigar products after the policy relative to non-menthol smokers. This suggests the importance of considering extending the ban on menthol beyond cigarettes to other combustibles such as small cigars and cigarillos.	We appreciate the reviewer's comment and agree with the reviewer's point.
Reviewer #4	16-17		A stronger conclusion could be made here, based on the similarity between the Canadian menthol ban and a possible future U.S menthol ban: both would represent the same incremental regulation of adding menthol to an	We appreciate the reviewer's comment and agree. As mentioned in a previous response, we have adapted the level of evidence framework used in NASEM's 2018 Public Health

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			<p>already existing ban on other flavors in cigarettes; and if FDA were to not also ban menthol in e-cigarettes concurrent with a menthol cigarette ban, that would constitute a second similarity.</p> <p>Further, the Canadian menthol ban evaluation studies have important strengths in the cohort design and the quasi-experimental comparison between menthol smokers and non-menthol smokers, with added strength from the similarity of the two groups. In contrast, the Friedman quasi-experimental study compared San Francisco to other locations in the U.S., and the differences between San Francisco and other locations are considerably greater on multiple dimensions than the menthol smokers vs. non-menthol smokers in the Canadian study.</p> <p>Although the possibility that a menthol cigarette ban might have a weaker impact on those with substance use disorder, for whom nicotine dependence tends to be higher, there should be caution in generalizing from the Guydish et al. study of the flavor ban in San Francisco to the possible impact of a menthol cigarette ban among residential treatment populations, due to the complexities of the San Francisco ban, which have been discussed above. A further examination of the impact of menthol cigarette bans on these high-prevalence, highly dependent, vulnerable populations is warranted.</p>	<p>Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To assess strengths and limitations of each study, we considered the study design, study population, setting, data collection, and threats to internal and external validity. In addition to the strengths and limitations, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. As such, we have updated our conclusions.</p>

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Reviewer #4	17		<p>A wide variety of studies were examined involving bans on different kinds of flavored tobacco products and different locations, including two studies of the Ontario ban of menthol cigarettes and one study of the Canadian federal menthol cigarette ban.</p> <p>The comment about the strengths of evaluation studies based on sales data is well-taken. However, given that such studies rely on sales in legal retail outlets, the studies here should conceptually, if not actually, be combined with studies on illicit sales, to obtain a more complete assessment of the impact of a flavor ban on sales of tobacco products.</p>	<p>We appreciate the reviewer's comment and agree that findings from research questions 3 and 4 complement each other. We chose to frame these as separate research questions. While both questions focus on sales of tobacco products, question 3 is focused on studies that use scanner data (legal sales). Question 4 focuses on studies that use self-report purchasing of illicit tobacco products and illicit cigarette seizure data. Since these are different outcomes, we report them separately.</p>
Reviewer #4	18-20		<p>The studies presented in this section are accurately summarized, showing significant reduction in sales of tobacco products that were restricted, but also reductions in sales of tobacco products overall, showing that switching to other tobacco products post-restriction was not complete.</p>	<p>We thank the reviewer for this comment.</p>
Reviewer #4	20		<p>The findings from studies of sales data on unaffected products mirror those in the previous section. For example, after the Ontario menthol cigarette ban, there was an increase in sales of non-menthol cigarettes. It should be noted that the reported percentage increase in sales of non-menthol cigarettes was lower (0.4%) in Ontario than the market share of menthol cigarettes before the ban (about 5%). Although this gap may have been partially</p>	<p>We appreciate the reviewer's comment and agree. We have explicitly stated in the conclusions that the percentage increase in sales of non-menthol cigarettes was lower in Ontario than the market share of menthol cigarettes before the ban.</p>

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			<p>explained by illicit purchasing of menthols, or other flavored products, but there does seem to be a significant effect on overall sales.</p> <p>The Delnevo and Hrywna (2015) study provides nice specificity in its analysis of sales in the clove tobacco market before and after the 2009 U.S. flavored cigarette ban (excluding menthol). Their conclusion that “failing to extend the cigarette flavor ban to cigars created an opportunity for new products to replace flavored cigarettes” is sound, reflecting the general conclusion that could be drawn about a possible future ban on menthol cigarettes.</p>	
Reviewer #4	21		<p>The studies in this section generally come to the same conclusion: that bans on flavored tobacco products lead to a significant decrease in sales of the restricted/banned products, and some increase in sales of non-restricted products, with the increase in the latter being lower than the decrease in the former, leading to an overall net decrease in tobacco product sales. The Summary and Conclusion are scientifically supported.</p>	We thank the reviewer for this comment.
Reviewer #4	23-25		<p>The studies in this section are mixed with respect to whether there was an increase in illicit or cross-border sales of restricted tobacco products after a flavored tobacco sales restriction/ban.</p>	We have updated this section in the document to report study findings on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively). Also as mentioned in a previous response, we have adapted the level of evidence framework used in NASEM's

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				2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To assess strengths and limitations of each study, we considered the study design, study population, setting, data collection, and threats to internal and external validity. In addition to the strengths and limitations, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. As such, we have updated conclusions.
Reviewer #4	25		<p>The Summary and Conclusion states that there may be a slight increase in illicit, cross-border, and/or online sales following a menthol flavor ban.</p> <p>Although there was some evidence from local community studies in the U.S. supporting this conclusion, it should be noted that the experience of the Canadian menthol cigarette ban was that there was no significant increase in illicit trade—in both the Stoklosa (2019) study of Nova Scotia and the ITC evaluation study across seven Canadian provinces covering 83% of the Canadian population (see Fong, 2021, listed on page 13 as an additional publicly</p>	<p>We have updated this section in the document to report study findings on 1) illicit sales, 2) cross-border sales, and 3) online sales separately (vs. collectively). Also as mentioned in a previous response, we have adapted the level of evidence framework used in NASEM’s 2018 Public Health Consequences of E-Cigarettes report to assess the strength of policy evaluation studies presented. To assess strengths and limitations of each study, we considered the study design, study population,</p>

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			<p>available study, in which pre-ban menthol smokers who were still smoking at the post-ban wave were no more likely to purchase cigarettes from First Nations reserves, the most extensive source for illicit cigarettes in Canada, than were pre-ban non-menthol smokers who were still smoking at the post-ban wave (12.2% vs, 9.0%, n.s.).</p> <p>FDA’s comment that a national flavor restriction would reduce the ease with which restricted products could be obtained is reasonable, pointing both to the challenge of the current local/state-specific restrictions/bans and to the benefits of those same restrictions/bans if implemented at the national level.</p> <p>But this conclusion that a national flavor restriction would make it less likely that illicit sales would increase should then lead to much greater weight being accorded to the Canadian studies, which showed no significant increase in illicit sales after the menthol cigarette ban. Consequently, the Summary and Conclusion that there might be a slight increase in illicit, cross-border, and/or online sales following a menthol flavor ban is not supported by the evidence reviewed.</p>	<p>setting, data collection, and threats to internal and external validity. In addition to the strengths and limitations, when evaluating the strength of the body of evidence, we also considered factors such as consistency of findings across studies, directionality of study findings, magnitude of the observed effects, and the extent to which findings have been replicated in other studies of different study designs and populations. We appreciate the reviewer for informing us of the Fong 2021 presentation and will continue to monitor the literature for peer review publication of these findings.</p>
Reviewer #4	26		<p>Minor correction in the last line of the description of the Chaiton, Schwartz, Cohen, et al. (2020) paper: the study was not conducted “nationally” but rather only in the province of Ontario.</p>	<p>We have revised this sentence for clarity.</p>

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Reviewer #4	26		<p>The Summary and Conclusion is scientifically supported. There is some evidence of user modification following the Ontario menthol cigarette ban in the form of adding menthol to cigarettes using flavor cards, oils, or papers. But the prevalence of this user modification was fairly low.</p> <p>It is unclear whether this observed user modification was just an initial reaction to the menthol cigarette ban, or whether it would be sustained over time. It may have been similar to the significant initial increase in menthol cigarettes observed in the Rossheim et al. study of the 2009 Federal flavored cigarette ban (excepting menthol), suggesting a desire to seek a suitable substitute of the banned cigarette flavors for menthol—the only flavor that was available. As noted earlier, the initial increase in menthol cigarettes was not maintained beyond the first quarter post-ban, and menthol prevalence declined quickly afterwards. A number of factors would be expected to be associated with user modification, including added cost, the sensory acceptability of adding menthol through these mechanisms (notably, since menthol has a strong sensory effect, whether the delivery of menthol through flavor cards or other external methods can attain the level and consistency of menthol flavor that is acceptable to menthol cigarette smokers).</p>	<p>We added language to the conclusion indicating that given the limited studies on user modification, it is unclear whether observed user modification of tobacco products was an initial reaction to the menthol cigarette sales restriction and the extent that user modification would be sustained over time.</p>
Reviewer #4	26-27		<p>The Limitations section is a good description of the limitations of the RTD. It includes an important comment of the inability of sales data to fully capture the purchasing</p>	<p>We thank the reviewer for this comment.</p>

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			(and indirectly the use) of tobacco products, both those affected by restrictions/bans and those not affected directly by those restrictions/bans but which might be affected by their status as possible substitutes for the restricted products. Nielsen data, for example, are well-known to be limited given their in-store scanning methods being limited to broader retail outlets, leaving out specialty stores such as vape shops, online sales, or smaller retailers.	
Reviewer #4	27		The discussion of the importance of the comparability of the policies being evaluated to a possible implementation of a menthol cigarette ban in the U.S. is consistent with my comments on the external validity of studies above.	We thank the reviewer for this comment.
Reviewer #4	27		The other comments in this Limitation section are also sound.	We thank the reviewer for this comment.
Reviewer #4	50-51		<p>The research questions listed in the Purpose are appropriate. Discrete choice experiments and experimental tobacco marketplace studies have been shown to provide unique insights into possible effects of future policies and regulations. The experimental methodology provides strong internal validity, but the external validity, that is, the extent to which the conditions of the experimental or discrete choice studies capture the real-world conditions of an actual policy/regulation, is often a source of concern.</p> <p>This concern about external validity may be even greater for the studies of self-reported behavioral intentions in</p>	We have noted the limitations provided by the reviewer and others inherent to each type of study in the limitations section.

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			scenarios with hypothetical menthol cigarette sales restrictions, bans, or product standards. With such studies, there are concerns about the extent to which respondents comprehend the hypothetical restriction/ban and its implications, and also their ability to envision the impact of those hypothetical measures on their future behavior.	
Reviewer #4	51-52		The Eligibility Criteria are reasonable, and whereas the previous section on the behavioral impact of actual restrictions/bans expanded the scope of such literature searches beyond menthol bans to flavor bans (excepting menthol), the literature search here stayed within those studies that examined restrictions/bans on menthol.	No response needed.
Reviewer #4	52-53		The description of the three studies on hypothetical menthol cigarette bans are appropriate, as are the conclusions drawn in summarizing the studies. Indeed, the pattern of results of these studies are consistent with the pattern of results found in the evaluation studies presented in Section 1, notably in the Cadham et al. (2020) finding that a higher percentage of young adults would quit following a menthol cigarette ban compared to adults. This was found in the evaluation of the 2009 non-menthol flavor ban by Rossheim et al. (2020).	We thank the reviewer for noting the appropriateness of studies on hypothetical menthol cigarette and bans and the consistency of findings across Sections 1 and 2.
Reviewer #4	53-54		The descriptions of the behavioral economic studies in the U.S. are appropriate, and these studies provide some interesting findings regarding the substitution strength of other tobacco products that are of the same flavor as their	We appreciate the reviewer's comment. We agree that behavioral economic studies help assess the possible impact of a menthol

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			own (banned) flavor vs. other non-banned flavors. These studies are valuable in assessing the possible impact of a menthol cigarette ban on switching to other products (e.g., e-cigarettes) and the implications if menthol is also banned in ENDS.	cigarette ban under scenarios where different tobacco products are available.
Reviewer #4	54		I agree with the decision not to review the discrete choice experiments in Mexico and Guatemala. In reference to the criteria for applicability and potential for generalizing from a study to a possible future ban of menthol cigarettes in the U.S., these studies are less capable of providing important insights into a future menthol cigarette ban in the U.S.	We appreciate the reviewer's agreement that the Barrientos-Gutierrez et al. and Monzón et al. articles are less able to provide insight into the actions of US menthol cigarette smokers in response to a menthol ban.
Reviewer #4	50		<p>Executive Summary: the conclusions based on the literature review of studies in this section are scientifically supported.</p> <p>From these studies, menthol smokers who do not quit in response to a menthol cigarette ban are likely to switch to non-menthol cigarettes, and some of these smokers may dual use with menthol ENDS. The Executive Summary also appropriately raises the importance of the presence or absence of other tobacco products around the time of the menthol cigarette ban and after the ban.</p> <p>In addition, it is appropriate to assess the harmfulness of those other products, their potential to act as effective substitutes for menthol smokers, their addictiveness and potential (both product based and in the marketing and sales of such products) to initiate use among young people,</p>	We appreciate the reviewer's comment that the conclusions in Section 2 are scientifically supported and agree that menthol smokers who do not quit in response to a menthol cigarette ban will switch to non-menthol cigarettes or use other tobacco products.

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			in an overall assessment of the impact of a menthol cigarette ban in the U.S.	
Reviewer #4	68		<p>The studies in this section use simulation modeling to quantify the effects of a menthol cigarette ban. Such studies are valuable because they translate effect sizes, which are presented in units that are difficult to translate into tangible population-level impact. Odds ratios are obscure to laypeople, and even percentages as effect sizes are not readily understandable in their implications for population-level change.</p> <p>These simulation modeling studies translate these effect sizes into important public health indicators, for example deaths averted and life-years gained. By comparing a status quo model to different policy scenario models, the differences in the outcomes, projected over many years, produce estimates of these important public health outcomes.</p> <p>The research question that guided the evidence review in this section captures the importance of the outcomes of these studies: "What are the quantitative effects (e.g., deaths averted and life-years gained) of a potential menthol cigarette ban in the U.S.?"</p>	We thank the reviewer for this comment.
Reviewer #4	68		The Study Eligibility Criteria are reasonable, as were the procedures employed for the search strategy, data extraction, and analysis.	We thank the reviewer for this comment.

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Reviewer #4	69-71		The Levy et al. (2021) simulation study, using the Smoking and Vaping Model (SAVM) to simulate the benefit of a menthol cigarette ban in the U.S. during 2021-2060 is well-described. This study used NHIS historical data, with data from PATH Study on smoking and ENDS use, including raters of initiation, cessation, and switching among menthol smokers and non-menthol smokers. For the critically important effect sizes, Levy et al conducted an expert elicitation, which provided estimates for key behaviors such as menthol to non-menthol switching, cigarettes to ENDS or smokeless tobacco product switching, and impact on youth and young adults (e.g., initiation rates).	We thank the reviewer for this comment.
Reviewer #4	70-71		The resulting estimates from the SAVM simulation, comparing the Status Quo Scenario to the Menthol Ban Scenario are dramatic. Overall smoking prevalence is estimated to be reduced by 14.7% in 2026 and 15.1% by 2060, with the increase in non-menthol smoking (from substitution: 47.4% by 2026 and 58.0% by 2060) being more than offset by the near total elimination in menthol smoking (reductions of 92.5% by 2026 and 96.5% by 2060), and in the US, where menthol share is very high, that greater impact on menthol smoking pays off. In all, the estimates of the model are that by 2060, 654,000 premature deaths and 11.3M life years lost would be averted by a U.S. menthol cigarette ban. Sensitivity analyses had only a minor impact on the projected gains of a menthol cigarette ban.	We thank the reviewer for this comment and agree with this assessment.

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Reviewer #4	71		The Le and Mendez (2021) study also offers historical estimates of how menthol cigarettes from 1980 to 2018 caused the deaths of 378,000 premature deaths, 3M life years lost, and 10.1M new smokers.	We thank the reviewer for this comment.
Reviewer #4	71-72		The Levy et al. (2011) study—the initial simulation modeling of the impact of a menthol cigarette ban—generated estimates that are similar to those of the more recent simulation studies.	We thank the reviewer for this comment.
Reviewer #4	68, 72		<p>Executive Summary (p. 68): the conclusions based on the literature review of studies in this section are scientifically supported.</p> <p>The Discussion and Conclusion section mentions the absence of important other factors in the modeling studies that would affect the realized impact of a menthol cigarette ban in the U.S., including industry reactions to the menthol ban. That would be an important consideration for future simulation modeling studies.</p> <p>The conclusion that “population health models simulating menthol ban policies support and are consistent with a strong public health benefit.” is appropriate given the findings of these important simulation modeling studies.</p>	We thank the reviewer for this comment.
Reviewer #4	70		I note that the SAVM modeling relied on expert elicitation to estimate various key parameters of behavioral impact of a future menthol cigarette ban. The evaluation studies of the Canadian menthol ban, which as described above are	We agree that new data from other countries with recent menthol bans will be able to provide additional refinement to estimations of product transitions in simulation studies.

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			<p>similar in key respects to a possible future U.S. menthol cigarette ban, have yielded initial estimates of effect sizes. As the evaluation of the Canadian menthol ban continue to play out (the ITC Project’s Canada Survey has already collected data from 2020, two years after the first follow-up in 2018, reported in the Chung-Hall et al. (2021) article; those data have not yet been published, and there will be another cohort survey wave conducted in 2022), it may be the case that some of the effect sizes based on estimates of experts can be replaced by effect sizes derived from the actual behavioral impact of the Canadian menthol cigarette ban.</p>	<p>However, the regulatory climate and small size of the Canadian menthol cigarette market may make it challenging to completely substitute those estimates for US-focused elicited estimates.</p>