

Final Summary Report

External Letter Peer Review of FDA's

Scientific Assessment of the Impact of Menthol in Cigarettes

March 29, 2022

Contract No. HHSF223201700015B
BPA No. 18

Prepared for:

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

Peer Reviewers:

Cristine Delnevo, PhD, MPH
Rachel Denlinger, PhD
Geoffrey T. Fong, PhD, FRSC, FCAHS
Andrea Villanti, PhD, MPH

Prepared by:



Versar, Inc.
6850 Versar Center
Springfield, VA 22151

Table of Contents

I. INTRODUCTION.....	1
II. CHARGE TO REVIEWERS	2
III. INDIVIDUAL REVIEWER COMMENTS.....	3
A. Reviewer #1	4
B. Reviewer #2.....	19
C. Reviewer #3.....	25
D. Reviewer #4	35
IV. PEER REVIEWER COMMENT TABLES	65
Report 1.....	66
I. General Impressions	66
II. Response to Charge Questions	68
III. Specific Observations on Report 1	78
Report 2.....	100
I. General Impressions	100
II. Response to Charge Questions.....	103
III. Specific Observations on Report 2	116

I. INTRODUCTION

Versar, Inc. (Versar), an independent Food and Drug Administration (FDA) contractor, coordinated an external letter peer review of FDA’s scientific assessment of the impact of menthol in cigarettes. The peer review was conducted for FDA’s Center for Tobacco Products.

The Tobacco Control Act, enacted on June 22, 2009, amended the Federal Food, Drug, & Cosmetic Act (FD&C Act) and provided FDA with the authority to regulate tobacco products (Pub. L. 111-31). Among other provisions, the Tobacco Control Act established a “Special Rule for Cigarettes” that bans characterizing flavors in cigarettes, other than menthol. The special rule makes clear that it does not limit the authority of the Secretary of HHS to take action on menthol or any other artificial or natural flavor, herb, or spice not specified in the special rule (section 907(a)(1)(A) of the FD&C Act).

In general, FDA may pursue product standards related to reducing the appeal, toxicity, or addictiveness of tobacco products. Specifically, section 907 of the FD&C Act authorizes FDA to issue tobacco product standards that are appropriate for the protection of the public health, including provisions that would require the reduction or elimination of a constituent (including a smoke constituent), or harmful component of tobacco products and provisions respecting the construction, components, ingredients, additives, constituents (including smoke constituents), and properties of the tobacco product (section 907(a)(3), (a)(4)(A)(ii), and (a)(4)(B)(i) of the FD&C Act).

In accordance with its statutory authority, FDA completed a scientific assessment evaluating the impact of menthol in cigarettes.

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

FDA has completed two scientific assessment documents evaluating the impact of menthol in cigarettes: a “Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980-2021” (Report 1) and a “Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes” (Report 2).

Charge Questions (to be answered separately for each document)

Please provide written responses to the following questions:

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. INDIVIDUAL REVIEWER COMMENTS

A. Reviewer #1

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #1

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

I. GENERAL IMPRESSIONS

The *Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980-2021* 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).

II. RESPONSE TO CHARGE QUESTIONS

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.

Age of Initiation Conclusion – 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.

Sensory Effects –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.

Progression to Regular Use – 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.

Dependence (Adults) – 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.

Dependence (Youth) – 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, I would recommend changing the conclusion by adding the qualifier “**likely**” to address any potential ambiguity.

Topography – 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.

Cessation (General Population) – 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 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.

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.

Cessation (African American Population) – 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.

*Suggestion: Include ‘persons’ or ‘individuals’ after African Americans.

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.

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.

- 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 of Exposure in Menthol and Non-menthol Smokers. *Nicotine Tob Res.* 2019;21(Suppl 1):S63-S72. doi:10.1093/ntr/ntz160

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.

One topography study by Gunawan & Juliano (2020) is included in **Section XIV. Strength of Evidence: Dependence** but not in **Section XV. Strength of 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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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?

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?

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.

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 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.

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.

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).

III. Specific Observations on *Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021*

Page	Paragraph	Comment
5	Acronyms List	The following are missing: PND, ANOVA, ANCOVA
5	Acronyms List	RRR: Relative risk ratio needs to be separated from prior acronym
7	2	“thus promoting cigarette smoking” – Is promoting the best word or perhaps facilitating/enabling would be more appropriate?
10	1	How frequently was a fourth independent reviewer required for the full text screening? I would include this information in the paragraph.
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?
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.
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 ($p < 0.0001$), 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>
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 ‘Two analyses’ if the above study is moved to this subsection.
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.
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”.
39	N/A	Scales of Nicotine Dependence – Consider reviewing this section and alphabetizing the study order based on author’s last name.
39	4	Curtin et al., 2014 – The study citation is at the end of the

Page	Paragraph	Comment
		paragraph rather than the beginning like other listed studies. Consider revising for consistency and readability.
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.
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.
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.
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.
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.
45	2	Sentence 5 – I did not understand what was meant by “30 non-overlapping estimates”
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.
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.
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).
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.
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 were mostly non-menthol smokers and the study purpose was not a behavioral assessment of differences in smoking.
48	6	Hyland et al., 2002 – Missing p-value and limited information presented about the study design.
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

Page	Paragraph	Comment
		smokers?
49	7	Gan et al., 2016 – should it be fewer pack-years (rather than smaller pack-years)?
50	3	
51	2	Fagan et al., 2016 – Very little information presented about the study design
51	3	Faseru et al., 2011 – Very little information presented about the study design
52	10	Ahijevych et al., 2018 – Write out hour instead of abbreviating it ‘hr’
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.
56	2	Perkins et al., 2018 – Inconsistent spacing for the first sentence.
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.
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?
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”.
60	3	Ross et al., 2016 – Did menthol smoking status predict higher or lower TNE?
61	N/A	<i>Twenty-five analyses found no significant effect of menthol on nicotine exposure</i> – 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.
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?
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?
64	5	Ross et al., 2017 – What do the percentages in parentheses reference?
71	3	Azagba et al., 2020 – Missing parenthesis in the last adjusted odds ratio reported in the paragraph.

Page	Paragraph	Comment
77	2	Inconsistent citation format for Wackowski & Delnevo 2007.
77	3	Space needed between “1980-2021 supports”
79	Table 3	Should the <i>Note</i> be displayed under the table?
81	1	Watson et al., 2017 – Avoid use of Caucasian.
82	2	Jarvik et al., 1994 – Avoid use of ‘substance abuse’ terminology. Revise to ‘substance use disorder’
83	1	McCarthy et al., 1995 – Avoid use of Caucasian.
83	2	Miller et al., 1994 – Space needed between “of \geq 15”
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.
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.
84	3	Ahijevych et al., 1996 – Avoid use of Caucasian.
84	Header	Potential typographical error: “One cross-sectional analysis suggests that menthol increases in smoking topography.” I think ‘in’ could be removed from the subsection header.
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.
90	3	Reitzel et al., 2013 – non-Hispanic Blacks should be revised to non-Hispanic Black persons or something similar.
92	1	Delnevo et al., 2011 – Mexicans and Hispanics should be revised to Mexican persons and Hispanic persons or something similar.
92	3	Levy et al., 2011 – Blacks should be revised to Black persons or something similar.
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.
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.
94	1	Avoid use of Caucasian
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)?
102	2	Should sentence two be revised to say “...found a positive effect

Page	Paragraph	Comment
		of menthol on reduced cessation success...”?
102	2	Should sentence two be revised to say “a positive association with menthol and reduced cessation.”?
105	2	Inconsistent formatting for Smith et al., 2020 citation
106	5	Dependence – possible typographical error in sentence one “...an association between menthol <i>and</i> cigarettes and dependence among adults”
108	6	Cessation – typographical errors in sentence one (unnecessary period after general) and sentence two (“...studies of among smokers...”).
109	1	Space needed between “n=18,78.3%”
109	2	Inconsistent formatting for Smith et al., 2020 citation and unnecessary double parentheses at the end of the paragraph.
140	Reference Table	Cubbin et al., 2010 – avoid use of Caucasian
142	Reference Table	Inconsistent formatting for Smith et al., 2014 citation
143	Reference Table	Watson et al., 2017 – avoid use of Caucasian
144	Reference Table	Inconsistent formatting for Cohn & D’Silva, 2019; Cohn et al, 2019 and Cohn et al., 2020 citations
144	Reference Table	Cohn et al., 2019 – formatting issue for text listed in the outcome measures cell
148	Reference Table	Inconsistent formatting for Wang et al., 2014 citation
150	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation
154	Reference Table	Brinkman et al., 2012 – avoid use of Caucasian
167	Reference Table	Inconsistent formatting for Smith et al., 2014 citation
168	Reference Table	Inconsistent formatting for Wang et al., 2010 citation
170	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation
173	Reference Table	Inconsistent formatting for Wackowski & Delnevo 2007 citation
174	Reference Table	Inconsistent formatting for Wang et al., 2014 citation
185	Reference Table	Inconsistent formatting for Smith et al., 2020 citation

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #1

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

I. GENERAL IMPRESSIONS

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

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. 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.

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).

II. RESPONSE TO CHARGE QUESTIONS

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.

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

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.

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 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 (Gyudish et al., 2020), than the first paragraph stating the conclusion.

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.

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.

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 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.

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.

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?

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 *most* 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...”.

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 overstated. Alternatively, if the majority is accurate, then more details are needed in this section to support this conclusion.

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?

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.

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.

Section 3: Modeling the public health effects of a menthol cigarette ban in the United States

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.

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.

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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.

One minor suggestion is to include an abbreviations list at the beginning of the review document.

III. Specific Observations on Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes

Page	Paragraph	Comment
11	2	Rossheim et al., 2017 – There is an extra parenthesis in the second sentence.
12	3	Yang et al., 2020 – Is the study conclusion that the flavor ban resulted in substitution of regular cigarettes?
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).
16	5	Summary and Conclusions – Sentence 2 requires clarification regarding what the authors mean by “Some menthol smokers

Page	Paragraph	Comment
		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?
18	4	In the first sentence, hyphenate “4 week” and possibly capitalize “information” since it is part of a corporation name.
20	6	In the sixth sentence, add a comma after ban (i.e., “...clove cigarette ban, unit sales...”)
22	1	There is an extra parenthesis in the third sentence.
22	1	I think ‘cigarettes’ is missing from the sentence “...California policy that included menthol and ENDS...”
22	2	In the last sentence, add a comma after authorities (i.e., “...according to local authorities, there were only...”)
23	1	Possible typographical error in the second sentence: “Trend in unit sales <u>in</u> observed in the proximal...”
24	4	Typographical error in the final sentence: delete the extra ‘i’
31	Reference list	Zheng et al., 2017 has inconsistent formatting relative to the other citations.
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.”
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> both demonstrated significant increases of <u>5%</u> (p=0.003) and <u>4%</u> (p=0.030), respectively.” In this sentence, three products are listed but only two % increases are reported.
45	2	Stoklosa 2019 – Typographical error in the second to last sentence: “...period from 2014 <u>o</u> 2018...”
62	2	Denlinger-Apte et al., 2021 – Typographical error: noncigarette should be non-cigarette
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.
69	2	Reviewer initials are listed in parentheses. Is this necessary? If so, the other two sections do not include review initials.

B. Reviewer #2

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #2

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

I. GENERAL IMPRESSIONS

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.

First and foremost, I did not find the rationale for *not* updating *all* 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., 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.

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?

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.

II. RESPONSE TO CHARGE QUESTIONS

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.

Based on the weight of evidence- the conclusions drawn across the key content areas are reasonable and scientifically supported given the available evidence.

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.

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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 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.”

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.

The report on page 14 notes that “analyses with overlap between populations, which could reflect duplicate findings” was attended to, but not *how* it was attended to.

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.

III. Specific Observations on *Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021*

Page	Paragraph	Comment
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.
13	1st P	Again, the issue of “clinical” and “non-clinical” comes up. It’s confusing and inconsistent.
14	Middle of page	Document states “Based on interrater agreement, the resulting ranges were determined to be sufficient for weighing independent articles: Strong: 0.75-1.00 Moderate: 0.56-0.74 Weak: 0.00-0.55 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.

Page	Paragraph	Comment
53	5th	Soulakova and Danczak uses CPS TUS data; this should be explicit.
170		Header seems to be missing at the top of this table - which presumably is focused on adolescents.

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #2

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

I. GENERAL IMPRESSIONS

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.

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.

II. RESPONSE TO CHARGE QUESTIONS

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.

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 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.

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 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.

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.

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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.

III. Specific Observations on Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes

Page	Paragraph	Comment
		None provided

C. Reviewer #3

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #3

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

I. GENERAL IMPRESSIONS

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 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.

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.

II. RESPONSE TO CHARGE QUESTIONS

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.

In each section of the report, the conclusions were scientifically supported given the available evidence.

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.

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:

- Leas EC, Benmarhnia T, Strong DR, Pierce JP. Effects of menthol use and transitions in use on short-term and long-term cessation from cigarettes among US smokers. *Tob Control*. 2021. PubMed PMID: 34230056.
- 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.

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:

- 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>.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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.

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.

Other recommendations include:

- 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.
- 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.
- Spelling out comparison groups in all descriptions of analyses (e.g., higher odds of

outcome compared with [reference group]).

- 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.

III. Specific Observations on *Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021*

Page	Paragraph	Comment
18	2 (Background)	Please clarify if analyses of different populations (youth, adults) were scored separately.
35	4 (Conclusions)	Villanti et al 2020 citation should be Villanti et al. 2019.
38	1	Please spell out biomarkers of exposure (BOE) in this first instance in this section.
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.”
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).
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).
40	2	In Allen and Unger analyses, recommend using “correlated with” rather than “predictive of” given the cross-sectional nature of the study.
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.
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).
40	4	Curtin et al NHANES analyses should be separate paragraph from NSDUH analyses to aid counting analyses across each section.
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.
46	4	Curtin et al TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.
47	2	Spell out “hour” at the end of Ahijevych 2018 paragraph.
47	4	Create new paragraph for Brinkman et al. 2012 findings.

Page	Paragraph	Comment
47	5	Curtin et al NHIS and TUS-CPS analyses should be separate paragraphs from NHANES analyses to aid counting analyses across each section.
50	7	Curtin et al NSDUH analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.
54	3/Sentence	Underline “nicotine administration” in “One analysis suggested...” sentence.
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.”
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.
56	1/Sentence	Add “given the same nicotine content” to the end of “One analysis found no effect of menthol on cigarette choice.” This study examined interaction between menthol and nicotine content.
57	3	Confirm “α4α6*” vs. “α4α6&” at the end of the paragraph.
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.
59	4	Please spell out mouth-level exposure (MLE) at first instance in this section.
60	3	Delete “with” in sentence that begins “Although these data appear to contradict with...”
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.
69	1	Villanti et al. 2020 - Specify comparison group in last sentence. “...no significant bivariate relationships between first menthol cigarette compared with first non-menthol cigarette and subsequent nicotine dependence...”
69	3	Curtin et al. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.
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

Page	Paragraph	Comment
		where individual analyses within the same dataset are treated as separate entries.
70	2	Cohn et al. (2019) – Please specify comparison group in the last sentence.
70	4	Curtin et al. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.
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.
84	2	Pickworth et al. (2002) – Please verify “racial” versus “ethnic” differences in the last sentence. This study appears to report on race.
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?
97	3	Delnevo et al. (2016) – Please confirm “NYAHS” vs. “NYAH” in the study description.

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #3

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

I. GENERAL IMPRESSIONS

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.

II. RESPONSE TO CHARGE QUESTIONS

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.

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.

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.

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

Section 1

- 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.

Section 2

- 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 sizes and timeframe of data collection to better understand how they inform the research question in the “current market.”
- 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.
- 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.

Section 3

- 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.

III. Specific Observations on *Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes*

Page	Paragraph	Comment
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.” 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.
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...”
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).
10	3	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.
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.
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.

Page	Paragraph	Comment
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.
12	2	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.
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.
14	4	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.
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.
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.
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).

D. Reviewer #4

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #4

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

I. GENERAL IMPRESSIONS

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 resulted in addressing not only *whether* menthol was associated with the effects but *how* and *why* those effects were obtained.

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.

The review presented the conclusions drawn in the strength-of-evidence review in each of the sections were scientifically justified and appropriate.

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.

II. RESPONSE TO CHARGE QUESTIONS

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.

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.

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.

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:

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.

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 non-menthol to menthol cigarettes (vs maintaining non-menthol use) significantly decreased cessation success.

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:

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. *Tob Control* 2020;29:624–30. doi:10.1136/tobaccocontrol-2019-055154 pmid:<http://www.ncbi.nlm.nih.gov/pubmed/31685586>

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 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.

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>

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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.

III. Specific Observations on *Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021*

Page	Paragraph	Comment
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>
9-12		<p>The research questions and procedures to address those research questions are all reasonable and appropriate. The screening process yielded 154 articles for this review.</p>
6-7		<p>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.</p>
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</p>

Page	Paragraph	Comment
		is based on NavGuide systematic review methodology, which is appropriate and reasonable.
16-17		The procedures described here are reasonable and appropriate.
18-24		<p>This is an additional area of evidence review that was not included in the past reviews of FDA and TPSAC.</p> <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>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.</p>
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.
31-32		The conclusion that the sensory effects of menthol are associated with positive subjective smoking experiences among menthol cigarette smokers is scientifically supported.
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

Page	Paragraph	Comment
		Study, the American Legacy Longitudinal Tobacco Use Reduction Study, and the National Youth Adult Health Survey.
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.
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.
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.
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.
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.
53-56		The studies measuring night waking to smoke, individual item assessments of dependence, craving, smoking 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.
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.
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.
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.
66-67		These seven analyses from animal studies are described accurately and summarized appropriately. The five analyses on nicotine exposure and

Page	Paragraph	Comment
		the two analyses on nicotine pharmacokinetics also support the conclusion that menthol has no significant effect on nicotine exposure and nicotine pharmacokinetics.
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>
69-70		These analyses are described accurately and summarized appropriately. The 9 analyses do not show an overall relationship between menthol and dependence as measured by time to first cigarette and cigarettes per day.
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.
72-73		The analyses are described accurately and summarized appropriately.
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.
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."
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 conclusion that "menthol in cigarettes is associated with greater dependence among youth."

Page	Paragraph	Comment																																			
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>																																			
87-88		<p>The introduction provides study-specific criteria for evaluating weight of evidence. The criteria for weighting the studies are reasonable and appropriate.</p>																																			
88		<p>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:</p> <p style="padding-left: 40px;">“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> <table border="1" data-bbox="509 1415 1398 1782"> <thead> <tr> <th colspan="5" data-bbox="509 1415 1398 1503">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 data-bbox="509 1503 850 1556">Level of Intention to Quit at Wave 1</th> <th data-bbox="850 1503 987 1556">USA</th> <th data-bbox="987 1503 1123 1556">Canada</th> <th data-bbox="1123 1503 1260 1556">UK</th> <th data-bbox="1260 1503 1398 1556">Australia</th> </tr> </thead> <tbody> <tr> <td data-bbox="509 1556 850 1602">Those with no intention to quit</td> <td data-bbox="850 1556 987 1602">4</td> <td data-bbox="987 1556 1123 1602">3</td> <td data-bbox="1123 1556 1260 1602">4</td> <td data-bbox="1260 1556 1398 1602">3</td> </tr> <tr> <td data-bbox="509 1602 850 1648">Intention to quit beyond 6 months</td> <td data-bbox="850 1602 987 1648">6</td> <td data-bbox="987 1602 1123 1648">8</td> <td data-bbox="1123 1602 1260 1648">7</td> <td data-bbox="1260 1602 1398 1648">7</td> </tr> <tr> <td data-bbox="509 1648 850 1694">Intention to quit within 6 months</td> <td data-bbox="850 1648 987 1694">10</td> <td data-bbox="987 1648 1123 1694">15</td> <td data-bbox="1123 1648 1260 1694">15</td> <td data-bbox="1260 1648 1398 1694">13</td> </tr> <tr> <td data-bbox="509 1694 850 1740">Intention to quit within 1 month</td> <td data-bbox="850 1694 987 1740">21</td> <td data-bbox="987 1694 1123 1740">18</td> <td data-bbox="1123 1694 1260 1740">22</td> <td data-bbox="1260 1694 1398 1740">12</td> </tr> <tr> <td data-bbox="509 1740 850 1782">Adjusted Odds Ratio: <1M vs. no intention</td> <td data-bbox="850 1740 987 1782">7.52</td> <td data-bbox="987 1740 1123 1782">3.79</td> <td data-bbox="1123 1740 1260 1782">5.69</td> <td data-bbox="1260 1740 1398 1782">3.16</td> </tr> </tbody> </table> <p data-bbox="509 1793 1398 1873">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>	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
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																																	

Page	Paragraph	Comment
		<p>There is a substantial prospective association between intentions to quit and quitting.</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 to quit outcome may have been present, which could have been used to project impact on quitting in the future.</p>
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>
88-94		The 13 longitudinal analyses, 6 cross-sectional analyses, and the 2 meta-analyses finding a relationship between menthol and decreased cessation success are all accurately described and properly summarized.
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.
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.
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.
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

Page	Paragraph	Comment
		among the general population. This conclusion is scientifically supported and justified from the strength-of-evidence review.
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.
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 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.
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.
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.
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.
106		The conclusion that menthol in cigarettes is associated with progression to regular smoking among youth and young adults is scientifically supported given the available evidence.
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

Page	Paragraph	Comment
		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.
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.
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.
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.
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.
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.
110		The limitations of this evidence review are well noted and reasonable.
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.

Scientific Support Document(s) for Potential Tobacco Product Standards: Menthol Cigarettes

Reviewer #4

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

I. GENERAL IMPRESSIONS

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?

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.

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.

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 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.

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.

From my own examination of the evidence, and in evaluating FDA's evidence review, I concur with that conclusion.

II. RESPONSE TO CHARGE QUESTIONS

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.

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.

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.

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., 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).

Section1

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.

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 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.

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.

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% 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.

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. *Tob Control* 2021;30:492-497.

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.

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: 10.1177/0193841X211051873. PMID: 34693773.

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.

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/>.

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 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.

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%).

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.

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.

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:

$$18,3289,597 \text{ menthol smokers in the U.S.} \times 7.3\% \text{ additional quitting} = \\ 1,337,988 \text{ additional smokers who would quit. (95\% CI: } 384,901\text{-}2,291,075\text{).}$$

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):

$$8,368,816 \text{ African American menthol smokers} \times 7.3\% \text{ additional quitting} = \\ 610,924 \text{ additional African American smokers who would quit. (95\% CI: } 154,070\text{-}1,191,575\text{).}$$

The presentation also made the following points about the Chung-Hall et al. ITC evaluation study:

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.

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.

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.

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>

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.

This study provides some initial support of a positive impact of the May 2020 menthol cigarette ban, mandated under the EU Tobacco Products Directive.

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 whether these results are reliable with respect to the impact of the menthol cigarette ban on illicit sales.

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. *Nicotine Tob Res*; in press. Published on-line September 15, 2021. <https://doi.org/10.1093/ntr/ntab188>.

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.

Section 3

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. *J Urban Health* (2021). <https://doi.org/10.1007/s11524-021-00581-8>

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 be greater among females (particularly Black females) vs males and other racial/ethnic subgroups.

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.

3. Provide any additional comments, such as methodological concerns, objectivity and strength of the data, limitations, or outcomes not discussed.

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.

III. Specific Observations on *Review of Studies Assessing the Potential Impact of Prohibiting Menthol as a Characterizing Flavor in Cigarettes*

Page	Paragraph	Comment
4	1	<p>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 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>
4	2	<p>The three electronic databases searched—PubMed, Web of Science, and Embase—are the three leading databases for research on biomedical science and public health.</p>
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 market that are relevant to the aggregate measures of sales and illicit sales.</p>
5-6		<p>Information Sources and Search Strategy: The search strings used are reasonable.</p>
6-7		<p>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.</p>
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</p>

Page	Paragraph	Comment
		<p>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 future menthol cigarette ban than studies that evaluate a ban on other flavors.</p>
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>
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 (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</p>

Page	Paragraph	Comment
		<p>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>
12		<p>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.</p>
12		<p>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.</p>
12		<p>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 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</p>

Page	Paragraph	Comment
		<p>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 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 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.</p>
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,</p>

Page	Paragraph	Comment
		<p>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>
13		<p>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.</p>
13-15		<p>There are two aspects of the Canadian menthol cigarette ban that make it closely analogous to the U.S. situation.</p> <p>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 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>
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>

Page	Paragraph	Comment
		<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><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.</i> (IARC Handbook, 2008, page 40).</p> <p>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.</p>
13-15		<p>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.</p>
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 been a misclassification of</p>

Page	Paragraph	Comment
		<p>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>
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>
15		<p>The Guydish 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 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.</p>
15-16		<p>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.</p>
16		<p>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.</p>
16-17		<p>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 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>

Page	Paragraph	Comment
		<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>
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>
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>
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 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</p>

Page	Paragraph	Comment
		<p>“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>
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>
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>
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 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>

Page	Paragraph	Comment
26		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.
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>
26-27		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 (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.
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.
27		The other comments in this Limitation section are also sound.
50-51		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.

Page	Paragraph	Comment
		<p>This concern about external validity may be even greater for the studies of self-reported behavioral intentions in 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.</p>
51-52		<p>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.</p>
52-53		<p>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).</p>
53-54		<p>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 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.</p>
54		<p>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.</p>
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</p>

Page	Paragraph	Comment
		the marketing and sales of such products) to initiate use among young people, in an overall assessment of the impact of a menthol cigarette ban in the U.S.
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>
68		The Study Eligibility Criteria are reasonable, as were the procedures employed for the search strategy, data extraction, and analysis.
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 rates 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).
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.

Page	Paragraph	Comment
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.
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.
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>
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 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.

IV. PEER REVIEWER COMMENT TABLES

Menthol Cigarettes
Report 1
Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980–2021

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
Reviewer #1	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).	
Reviewer #2	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.	
Reviewer #2	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., 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.	
Reviewer #2	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	

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	were “scored” with respect to strength. Was the score (Strong or Moderate) based on the article or the methodological details for each analysis?	
Reviewer #2	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.	
Reviewer #3	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 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.	
Reviewer #3	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.	
Reviewer #4	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	

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	<p>and smoking topography. As a result, the review 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. <i>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.</i>		
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>	
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</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
	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.	
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.	
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.	
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, I would recommend changing the conclusion by adding the qualifier “ likely ” to address any potential ambiguity.	
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	

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
	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.	
Reviewer #1	<p><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 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>	
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>	
Reviewer #2	Based on the weight of evidence- the conclusions drawn across the key content areas are reasonable and scientifically supported given the available evidence.	
Reviewer #3	In each section of the report, the conclusions were scientifically supported given the available evidence.	

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 #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.	

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. <i>Tob Regul Sci.</i> 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. <i>Nicotine Tob Res.</i> 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 of Exposure in Menthol and Non-menthol Smokers. <i>Nicotine Tob Res.</i> 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.</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
	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.	
Reviewer #1	One topography study by Gunawan & Juliano (2020) is included in Section XIV. Strength of Evidence: Dependence but not in Section XV. Strength of 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.	
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.	
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 cigarettes among US smokers. Tob Control. 2021. PubMed PMID: 34230056. • 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	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	

CHARGE QUESTION 2. <i>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.</i>		
REVIEWER	COMMENT	RESPONSE
	<p>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. <i>Beiträge zur Tabakforschung International/Contributions to Tobacco Research</i>, 28(6), 253-266. https://doi.org/doi:10.2478/cttr-2019-0005. 	
	<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. <i>Tob Control</i>. 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 non-menthol to menthol cigarettes (vs maintaining non-menthol use) significantly decreased cessation success.</p>	
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-2019-055154 pmid:http://www.ncbi.nlm.nih.gov/pubmed/31685586</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>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 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?	
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?	
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.	
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 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.	

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	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.	
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).	
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 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.”	
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.	
Reviewer #2	The report on page 14 notes that “analyses with overlap between populations, which could reflect duplicate findings” was attended to, but not <u>how</u> it was attended to.	
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.	
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	

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
	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.	
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.	
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. 	
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. 	
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]). 	
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. 	
Reviewer #4	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.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	5	Acronyms List	The following are missing: PND, ANOVA, ANCOVA	
Reviewer #1	5	Acronyms List	RRR: Relative risk ratio needs to be separated from prior acronym	
Reviewer #1	7	2	“thus promoting cigarette smoking” – Is promoting the best word or perhaps facilitating/enabling would be more appropriate?	
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.	
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?	
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.	
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 ($p < 0.0001$), 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>	
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 ‘Two analyses’ if the above study is moved to this subsection.	
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.	
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	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			cigarette”. In sentence four, it should be ‘adjusted prevalence ratio’ not “adjusted prevalence ration”.	
Reviewer #1	39	N/A	Scales of Nicotine Dependence – Consider reviewing this section and alphabetizing the study order based on author’s last name.	
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.	
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.	
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.	
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.	
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.	
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.	
Reviewer #1	45	2	Sentence 5 – I did not understand what was meant by “30 non-overlapping estimates”	
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.	
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.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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).	
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.	
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 were mostly non-menthol smokers and the study purpose was not a behavioral assessment of differences in smoking.	
Reviewer #1	48	6	Hyland et al., 2002 – Missing p-value and limited information presented about the study design.	
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?	
Reviewer #1	49	7	Gan et al., 2016 – should it be fewer pack-years (rather than smaller pack-years)?	
Reviewer #1	51	2	Fagan et al., 2016 – Very little information presented about the study design	
Reviewer #1	51	3	Faseru et al., 2011 – Very little information presented about the study design	
Reviewer #1	52	10	Ahijevych et al., 2018 – Write out hour instead of abbreviating it ‘hr’	
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.	
Reviewer #1	56	2	Perkins et al., 2018 – Inconsistent spacing for the first sentence.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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?	
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”.	
Reviewer #1	60	3	Ross et al., 2016 – Did menthol smoking status predict higher or lower 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.	
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?	
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?	
Reviewer #1	64	5	Ross et al., 2017 – What do the percentages in parentheses reference?	
Reviewer #1	71	3	Azagba et al., 2020 – Missing parenthesis in the last adjusted odds ratio reported in the paragraph.	
Reviewer #1	77	2	Inconsistent citation format for Wackowski & Delnevo 2007.	
Reviewer #1	77	3	Space needed between “1980-2021supports”	
Reviewer #1	79	Table 3	Should the <i>Note</i> be displayed under the table?	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	81	1	Watson et al., 2017 – Avoid use of Caucasian.	
Reviewer #1	82	2	Jarvik et al., 1994 – Avoid use of ‘substance abuse’ terminology. Revise to ‘substance use disorder’	
Reviewer #1	83	1	McCarthy et al., 1995 – Avoid use of Caucasian.	
Reviewer #1	83	2	Miller et al., 1994 – Space needed between “of _≥ 15”	
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.	
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.	
Reviewer #1	84	3	Ahijevych et al., 1996 – Avoid use of Caucasian.	
Reviewer #1	84	Header	Potential typographical error: “One cross-sectional analysis suggests that menthol increases in smoking topography.” I think ‘in’ could be removed from the subsection header.	
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.	
Reviewer #1	90	3	Reitzel et al., 2013 – non-Hispanic Blacks should be revised to non-Hispanic Black persons or something similar.	
Reviewer #1	92	1	Delnevo et al., 2011 – Mexicans and Hispanics should be revised to Mexican persons and Hispanic persons or something similar.	
Reviewer #1	92	3	Levy et al., 2011 –Blacks should be revised to Black persons or something similar.	

III. Specific Observations on Report 1				
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.	
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.	
Reviewer #1	94	1	Avoid use of Caucasian	
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)?	
Reviewer #1	102	2	Should sentence two be revised to say “...found a positive effect of menthol on reduced cessation success...”?	
Reviewer #1	102	2	Should sentence two be revised to say “a positive association with menthol and reduced cessation.”?	
Reviewer #1	105	2	Inconsistent formatting for Smith et al., 2020 citation	
Reviewer #1	106	5	Dependence – possible typographical error in sentence one “...an association between menthol <i>and</i> 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...”).	
Reviewer #1	109	1	Space needed between “n=18,78.3%”	
Reviewer #1	109	2	Inconsistent formatting for Smith et al., 2020 citation and unnecessary double parentheses at the end of the paragraph.	
Reviewer #1	140	Reference Table	Cubbin et al., 2010 – avoid use of Caucasian	
Reviewer #1	142	Reference Table	Inconsistent formatting for Smith et al., 2014 citation	
Reviewer #1	143	Reference Table	Watson et al., 2017 – avoid use of Caucasian	
Reviewer #1	144	Reference Table	Inconsistent formatting for Cohn & D’Silva, 2019; Cohn et al, 2019 and Cohn et al., 2020 citations	
Reviewer #1	144	Reference Table	Cohn et al., 2019 – formatting issue for text listed in the outcome measures cell	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	148	Reference Table	Inconsistent formatting for Wang et al., 2014 citation	
Reviewer #1	150	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation	
Reviewer #1	154	Reference Table	Brinkman et al., 2012 – avoid use of Caucasian	
Reviewer #1	167	Reference Table	Inconsistent formatting for Smith et al., 2014 citation	
Reviewer #1	168	Reference Table	Inconsistent formatting for Wang et al., 2010 citation	
Reviewer #1	170	Reference Table	Inconsistent formatting for Cohn et al., 2019 citation	
Reviewer #1	173	Reference Table	Inconsistent formatting for Wackowski & Delnevo 2007 citation	
Reviewer #1	174	Reference Table	Inconsistent formatting for Wang et al., 2014 citation	
Reviewer #1	185	Reference Table	Inconsistent formatting for Smith et al., 2020 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.	
Reviewer #2	13	1st P	Again, the issue of “clinical” and “non-clinical” comes up. It’s confusing and inconsistent.	
Reviewer #2	14	Middle of page	Document states “Based on interrater agreement, the resulting ranges were determined to be sufficient for weighing independent articles: Strong: 0.75-1.00 Moderate: 0.56-0.74 Weak: 0.00-0.55 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.	
Reviewer #2	53	5th	Soulakova and Danczak uses CPS TUS data; this should be explicit.	
Reviewer #2	170		Header seems to be missing at the top of this table - which presumably is focused on adolescents.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #3	18	2 (Background)	Please clarify if analyses of different populations (youth, adults) were scored separately.	
Reviewer #3	35	4 (Conclusions)	Villanti et al 2020 citation should be Villanti et al. 2019.	
Reviewer #3	38	1	Please spell out biomarkers of exposure (BOE) in this first instance in this section.	
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.”	
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).	
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).	
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.	
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.	
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).	
Reviewer #3	40	4	Curtin et al NHANES analyses should be separate paragraph from NSDUH analyses to aid counting analyses across each section.	
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.	
Reviewer #3	46	4	Curtin et al TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #3	47	2	Spell out “hour” at the end of Ahijevych 2018 paragraph.	
Reviewer #3	47	4	Create new paragraph for Brinkman et al. 2012 findings.	
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.	
Reviewer #3	50	7	Curtin et al NSDUH analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	
Reviewer #3	54	3/Sentence	Underline “nicotine administration” in “One analysis suggested...” sentence.	
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.”	
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.	
Reviewer #3	56	1/Sentence	Add “given the same nicotine content” to the end of “One analysis found no effect of menthol on cigarette choice.” This study examined interaction between menthol and nicotine content.	
Reviewer #3	57	3	Confirm “α4α6*” vs. “α4α6&” at the end of the paragraph.	
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.	
Reviewer #3	59	4	Please spell out mouth-level exposure (MLE) at first instance in this section.	
Reviewer #3	60	3	Delete “with” in sentence that begins “Although these data appear to contradict with...”	
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).	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			Create new paragraph for TUS-CPS analyses to aid counting analyses across each section.	
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-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.	
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.	
Reviewer #3	70	2	Cohn et al. (2019) – Please specify comparison group in the last sentence.	
Reviewer #3	70	4	Curtin et al. TUS-CPS analyses should be separate paragraph from NHANES analyses to aid counting analyses across each section.	
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.	
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.	
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?	
Reviewer #3	97	3	Delnevo et al. (2016) – Please confirm “NYAHS” vs. “NYAH” in the study description.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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>	
Reviewer #4	9-12		<p>The research questions and procedures to address those research questions are all reasonable and appropriate. The screening process yielded 154 articles for this review.</p>	
Reviewer #4	6-7		<p>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.</p>	
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</p>	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			evidence is based on NavGuide systematic review methodology, which is appropriate and reasonable.	
Reviewer #4	16-17		The procedures described here are reasonable and appropriate.	
Reviewer #4	18-24		<p>This is an additional area of evidence review that was not included in the past reviews of FDA and TPSAC.</p> <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>	

III. Specific Observations on Report 1				
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.	
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.	
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.	
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.	
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.	
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.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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.	
Reviewer #4	53-56		The studies measuring night waking to smoke, individual item assessments of dependence, craving, smoking 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.	
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.	
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.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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 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>	
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 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	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			non-menthol smokers, and two analyses from the Curtin et al. NHANES and TUS-CPS study do not show this.	
Reviewer #4	72-73		The analyses are described accurately and summarized appropriately.	
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.	
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.”	
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 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</p>	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			conclusion is justified from the weight-of-evidence analysis that is presented in Figure 7 on page 86.	
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.	
Reviewer #4	88		<p>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:</p> <p style="padding-left: 40px;">“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>	

III. Specific Observations on Report 1																																			
REVIEWER	Page	Paragraph/ Line	Comment		RESPONSE																														
			<p style="text-align: center;">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</p> <table border="1"> <thead> <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>There is a substantial prospective association between intentions to quit and quitting.</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 to quit outcome may have been present, which could have been used to project impact on quitting in the future.</p>		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	
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																															
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>																																

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	
Reviewer #4	88-94		The 13 longitudinal analyses, 6 cross-sectional analyses, and the 2 meta-analyses finding a relationship between 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.	
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.	
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.	
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 general population . This conclusion is scientifically supported and justified from the strength-of-evidence review.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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 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.	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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.	
Reviewer #4	106		The conclusion that menthol in cigarettes is associated with progression to regular smoking among youth and 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.	
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.	
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.	
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	

III. Specific Observations on Report 1				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			consider the studies in this domain by the general population and among African Americans.	
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.	
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.	
Reviewer #4	110		The limitations of this evidence review are well noted and reasonable.	
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.	

Report 2

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

I. General Impressions

REVIEWER	COMMENT	RESPONSE
Reviewer #1	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.	
Reviewer #1	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. 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.	
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).	
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	

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	<p>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>	
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>	
Reviewer #3	<p>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</p>	

I. General Impressions		
REVIEWER	COMMENT	RESPONSE
	sections to provide context regarding the consistency (or inconsistency) of effects across study designs and populations, which would strengthen the conclusions drawn.	
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?	
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.	
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.	
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 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>	

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>	
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 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.</p>	
Reviewer #1	<p>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.</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	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.	
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 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.	
Reviewer #1	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.	
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?	
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...”.	

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 2: Consumers’ Product Choices and Intended Use Behaviors If Menthol Cigarettes Became Unavailable</p> <p>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 overstated. Alternatively, if the majority is accurate, then more details are needed in this section to support this conclusion.</p>	
Reviewer #1	<p>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?</p>	
Reviewer #1	<p>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.</p>	
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</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
	menthol cigarettes does not feel relevant in the context of a marketplace that sells cigarettes in a variety of flavors.	
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>	
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 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.</p>	
Reviewer #2	<p>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 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>	

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	<p>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).</p> <p>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.</p>	
Reviewer #4	<p>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.</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 #1	<p>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.</p>	
Reviewer #2	<p>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</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
	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.	
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.	
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., 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).	
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 until May 2020, after this study’s Wave 2 survey. The decrease in menthol at post-ban is interesting given the</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
	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.	
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% 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.</p>	
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. Tob Control 2021;30:492-497.</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>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>	
Reviewer #4	<p><u>Section 1</u> 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: 10.1177/0193841X211051873. PMID: 34693773. 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>	
Reviewer #4	<p><u>Section 1</u> 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/. 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 studies were conducted at nearly the same time at both pre-</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>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%). 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>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>	

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>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>	
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</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>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 whether these results are reliable with respect to the impact of the menthol cigarette ban on illicit sales.</p>	
Reviewer #4	<p><u>Section 1</u> 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. 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>	
Reviewer #4	<p><u>Section 3</u> 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 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 be greater among females (particularly Black females) vs males and other racial/ethnic subgroups.</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>Section 3</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.</p> <p>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>	

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.	
Reviewer #1	One minor suggestion is to include an abbreviations list at the beginning of the review document.	
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.	

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. 	
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 sizes and timeframe of data collection to better understand how they inform the research question in the “current market.” 	
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. 	

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	<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. 	
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. 	
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.	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #1	11	2	Rossheim et al., 2017 – There is an 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?	
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).	
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.	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			“...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?	
Reviewer #1	18	4	In the first sentence, hyphenate “4 week” and possibly capitalize “information” since it is part of a corporation name.	
Reviewer #1	20	6	In the sixth sentence, add a comma after ban (i.e., “...clove cigarette ban, unit sales...”)	
Reviewer #1	22	1	There is an extra parenthesis in the third sentence.	
Reviewer #1	22	1	I think ‘cigarettes’ is missing from the sentence “...California policy that included menthol and ENDS...”	
Reviewer #1	22	2	In the last sentence, add a comma after authorities (i.e., “...according to local authorities, there were only...”)	
Reviewer #1	23	1	Possible typographical error in the second sentence: “Trend in unit sales in observed in the proximal...”	
Reviewer #1	24	4	Typographical error in the final sentence: delete the extra ‘i’	
Reviewer #1	31	Reference list	Zheng et al., 2017 has inconsistent formatting relative to the other citations.	
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.”	
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> both demonstrated significant increases of <u>5%</u> (p=0.003) and <u>4%</u> (p=0.030), respectively.” In this sentence, three products are listed but only two % increases are reported.	
Reviewer #1	45	2	Stoklosa 2019 – Typographical error in the second to last sentence: “...period from 2014 o 2018...”	
Reviewer #1	62	2	Denlinger-Apte et al., 2021 – Typographical error: noncigarette should be non-cigarette	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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 #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.” 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.	
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...”	
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.	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			Check the consistency of formatting for 95% CIs in this section (e.g., 11.4 to 15.1 vs 11.4-15.1).	
Reviewer #3	10	3	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	
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.	
Reviewer #3	11	2	Rosshem 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.	
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.	
Reviewer #3	12	2	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	
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.	
Reviewer #3	14	4	Yang et al. (2020) – Please provide the sample sizes for this study wherever it is presented.	
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.	
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.	
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).	
Reviewer #4	4	1	The questions listed in the Purpose are appropriate and capture the breadth of the important outcomes/consequences of a potential	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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 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.	
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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			cigarette 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.	
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.	
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, <i>ceteris paribus</i>, be more applicable to a possible future menthol cigarette ban than studies that evaluate a ban on other flavors.</p>	
Reviewer #4	8-13		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,	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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>	
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 (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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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>	
Reviewer #4	12		<p>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.</p>	
Reviewer #4	12		<p>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.</p>	
Reviewer #4	12		<p>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 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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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 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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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 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.</p>	
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>	

III. Specific Observations on Report 2				
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.	
Reviewer #4	13-15		<p>There are two aspects of the Canadian menthol cigarette ban that make it closely analogous to the U.S. situation.</p> <p>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 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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			the applicability and generalizability of the Canadian experiences to that of the U.S.	
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>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><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</i></p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p><i>reasonable the comparison will be.</i> (IARC Handbook, 2008, page 40).</p> <p>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.</p>	
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.	
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 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</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	
Reviewer #4	14		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.	
Reviewer #4	15		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 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.	
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	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	
Reviewer #4	16-17		<p>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 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>	
Reviewer #4	17		A wide variety of studies were examined involving bans on different kinds of flavored tobacco products and different locations, including	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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>	
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>	
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 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>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #4	21		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.	
Reviewer #4	23-25		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.	
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 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>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	
Reviewer #4	26		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.	
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>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #4	26-27		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 (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.	
Reviewer #4	27		The other comments in this Limitation section are also sound.	
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 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.</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	
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).	
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 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.	
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.	
Reviewer #4	50		Executive Summary: the conclusions based on the literature review of studies in this section are scientifically supported. From these studies, menthol smokers who do not quit in response to a menthol cigarette ban are likely to switch to non-menthol cigarettes,	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>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, in an overall assessment of the impact of a menthol cigarette ban in the U.S.</p>	
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>	
Reviewer #4	68		<p>The Study Eligibility Criteria are reasonable, as were the procedures employed for the search strategy, data extraction, and analysis.</p>	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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).	
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.	
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.	
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.	

III. Specific Observations on Report 2				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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>	
Reviewer #4	70		<p>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 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>	