PEER REVIEW SUMMARY REPORT

External Peer Review of the FDA Scientific Evaluation of the Possible Health Effects of Menthol versus Nonmenthol Cigarettes

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I. INTRODUCTION

Menthol is widely used in consumer and medicinal products and has long been used in cigarettes, often as a flavor-characterizing additive. In medical products, menthol is regulated as a drug with restrictions on allowable doses and use; however, there are no product standards for menthol when used in cigarettes.

Approximately one-fourth of all cigarettes sold in the United States are menthol. More than 80% of adult smokers in the U.S. start to smoke before age 18. Thus, youth and young adulthood appears to be a critical age-span for initiation of cigarette smoking and it has been postulated that menthol cigarettes may have an impact on initiation rates that differ from nonmenthol cigarettes. Further, the impact of menthol cigarettes on dependence, cessation, and health risks has been the topic of scientific inquiry and intense debate.

The Family Smoking Prevention and Tobacco Control Act (Section 907 (e)) requires the FDA's Tobacco Products Scientific Advisory Committee (TPSAC) to submit a report and recommendation to the Secretary of Health and Human Services (HHS) on the impact of the use of menthol in cigarettes on the public health – including use among children, African Americans, Hispanics, and other racial/ethnic minorities – by March 23, 2011. In March, 2010, TPSAC began its process of reviewing the available evidence as well as soliciting and receiving valuable input from many people, including researchers, tobacco industry representatives, consultants to the tobacco industry, representatives of the public health sector, and others. On July 21, 2011, TPSAC voted on its final report and recommendations on menthol, which contained the recommendation that "removal of menthol cigarettes from the marketplace would benefit public health in the United States." In addition, the non-voting industry representatives of TPSAC submitted a separate document reflecting the industry perspective. That document acknowledged the inherent risks of all tobacco products, including those that are menthol, and raised the possibility of countervailing effects, including potential risks of contraband menthol products, should a ban be imposed.

Independently, FDA has undertaken a thorough review of the available science concerning menthol cigarettes. To accomplish this task, FDA weighed the collective body of evidence for the impact of the use of menthol in cigarettes on public health. One of the first considerations in weighing the value of a particular study was the relevance of the information to the consumption of menthol cigarettes in the United States. Consideration was given to findings that were replicated in different studies, especially different types of studies. FDA also considered the source of information, type of study, and quality of study methods and data. In drawing conclusions, more consideration was given to peer-reviewed studies, studies in humans, and studies that were appropriately powered and designed. In this process, FDA evaluated the peer reviewed literature, industry and other submissions to TPSAC, as well as performed or commissioned additional analyses in an attempt to fill in and inform some of the gaps in the literature.

The purpose of this document is to provide the comments of an external peer review panel on the FDA "Scientific Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes".

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II. CHARGE TO REVIEWERS

Please provide written responses to the following questions:

Charge Questions:

I. Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

II. For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

III. For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

IV. Are you aware of additional publicly available information which should have been included? If so, please specify.

V. Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

III. OVERVIEW OF CONCERNS

GENERAL IMPRESSIONS

In general, the reviewers agreed that the majority of the document was well written, clear, and thorough. Some reviewers felt that, in some sections the conclusions were overstated and not always convincing. Other reviewers suggested revising the organization of the document, and more specifically, revising the document so that it reads as if written by a single author.

RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

Most reviewers felt that, in general, the report was well written, provided good summaries, and followed a logical structure. Specific suggestions included adding an introductory sentence to the Executive Summary that states the goals of the science sections and a summary of the conclusions that were shown in each section. Reviewers also felt that consistent language should be used throughout the sections when describing the overall findings or conclusions to make comparisons between the sections easier. It was noted by one reviewer that sections provided early in the report note industry-related documents, whereas later sections do not. This should be consistent throughout the document, because there may be bias of findings in some studies due to conflict of interest. This information would likely be useful information for readers.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

A number of reviewers noted that the format for study descriptions varied and should be kept consistent. It was suggested that all sections should provide the same format and level of detail for study descriptions, study limitations, sample sizes, and results. One reviewer stated that the "Patterns of Use" section provided a good template for presenting study descriptions and that study limitations should be presented as shown in the "Dependence" section. Other reviewers commented that providing some explanation of what the study findings mean before describing them in technical detail would serve to better explain the findings to non-technical readers. Specific sentence revisions were provided for the following sections: Toxicology and Chemistry, Physiology, and Patterns of Use, and are shown in detail in the individual reviewer comments. One reviewer commented that some overview of a possible hypothesis on the impact of mentholation on health effects should be included and noted that the Executive Summary was possibly the most appropriate place.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

Reviewers noted that in some sections the conclusions were difficult to understand and needed more details. They commented that some studies show mixed findings, while others have reversed findings. Some studies may be weighted differently because they are large-scale, have follow-up studies, or are nationally representative; however these studies also have limitations. Some reviewers recommended that the authors specify the criteria used to weight the evidence that led to their conclusions. Reviewers provided specific objections and/or suggestions for changes and enhancements to conclusions presented in select sections: Physiology, Biomarkers, Marketing and Consumer Perceptions, Initiation of Smoking, and Smoking Cessation. These comments were generally based on

the conclusions not being supported by the data provided in the sections or by the authors over stating them. One reviewer also noted that the conclusion on cessation shown in the Executive Summary is not consistent with what is provided in the Cessation section of the document.

4) Are you aware of additional publicly available information that should have been included? If so, please specify.

Several reviewers provided additional literature citations to be considered for inclusion in the document. See Reviewer #1, page 9; Reviewer #2, page 16; and Reviewer #6, page 48 for specific citations.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

One reviewer suggested that some minor stylistic differences between sections should be addressed to improve the readability of the document and ensure consistent presentation of evidence. Specifically, the "Physiology" and "Biomarkers" sections use imprecise adjectives to quantify the available evidence. In the "Physiology" section, the conclusion could include a statement that summarizes any noticeable differences between industry-sponsored studies and independent (academic) studies.

Another reviewer noted in the "Patterns of Use" section, the term "brand" is consistently used to indicate "menthol or nonmenthol" and seemed to be inaccurate and that menthol vs. nonmenthol should instead be identified as "type of cigarette product." This reviewer also noted that in the "Cessation" section, the conclusion should be reorganized as follows: first a summary of the reviews; then key insights/interpretations; finally, the determination statements based on the weight-of-evidence.

In addition, it was suggested by one reviewer that more research is needed, particularly in the context of the combustion products of menthol (with or without the presence of tobacco combustion products) and for the effects on the two primary subclasses of Chronic Obstructive Pulmonary Disease (COPD). Another reviewer recommended that additional data on the effect of menthol on cessation be included in the document.

IV. INDIVIDUAL REVIEWER COMMENTS

REVIEWER #1

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol versus Nonmenthol Cigarettes

Reviewer #1

I. GENERAL IMPRESSIONS

Overall, the report is well written and concisely and accurately summarizes existing evidence for each of the broad categories. The write-up of existing evidence in each section uses consistent language and presents the information in a similar manner, which helps with the overall flow of the document. Additionally the final conclusions drawn by the authors are accurate based on the weight of the evidence presented in this document. However, there are a few revisions that could be addressed by the authors to help improve the overall document. First, some sections provide better descriptions of the studies they are reviewing, the limitations of the studies, and how the results are related to the other studies being reviewed for a particular area. It would be helpful for the readers of this report if the sections could be more consistent in how they present the results of reviewing the existing evidence for each category (specific examples of this suggestion are provided below as part of my responses to the charge questions). Second, some of the sections may need to regroup the review of studies to eliminate some redundancy. For example, the Initiation section reviews a number of studies using NYTS data. It may make more sense to write a description of the NYTS survey first and then group all related studies under that description with some brief information provided regarding sample sizes and overall study objective. Finally, I also think that the conclusions drawn at the end of some of the sections may be worded too strongly based on the weight of the evidence, or more detail may need to be provided in the concluding paragraphs. For example, in the section on Dependence non-menthol smokers appear to smoke more cpd than menthol smokers, yet the weight of the evidence supports the conclusion that dependence is likely associated with menthol in cigarettes based on "questions concerning this measure and FTND to the current smoking situation in adult smokers." The authors need to better summarize, in the conclusion and the body of this section, the reasons why these are not the most appropriate variables to use to measure dependence. It would also be useful to include citations to support this claim, if they exist, or why they are still so widely used in this field if they are no longer reliable indicators of dependence. There are explanations provided in the body of the Dependence section, but there are no citations nor any mention of comparisons made to studies conducted pre- and post-implementation of smoke free air policies. At the very least, it would be useful to provide evidence of how smoking behavior has changed due to the increasing prevalence of smoke free air policies.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

Comment: Overall the report is well written and follows a logical structure. The reviews of the literature are concise and nicely sum up the findings as they relate to menthol cigarettes. The sections also use consistent language to describe overall findings, which helps tie together the individual sections of the report. There are variations in the level of detail included about the studies being reviewed across sections. It would be useful to try and make this more consistent. I have listed my primary suggestions for improving the summaries of articles in my response to Charge Question #2 below.

The conclusions drawn from the literature reviews in the section I reviewed included:

- It is difficult to determine the strength of the relationship between marketing and consumer perceptions and its impact on behavior due to the limitations in study designs included in this literature review.
- The available data leads to the conclusion that advertising is a strong driver of brand preference among adolescents, perhaps more than the presence of menthol.
- The evidence is not sufficient to support a conclusion that perception of harm is associated with menthol in cigarettes or the use of menthol cigarettes.
- The weight of evidence supports the conclusion that brand preference among adolescents and the African American community is likely associated with the marketing of menthol cigarettes.

However, only the final bullet point is reported in the executive summary. I think it would be helpful to include all conclusions drawn in each section in the executive summary.

I think, where possible, it would be useful to provide in an overall summary the connections between some of these sections. For example the evidence shows that the use of menthol in cigarettes increases smoking initiation. There is also evidence that targeted marketing of menthol cigarettes is associated with more adolescents smoking menthol brands. Obviously, someone reading the full document can make these connections, but it would also help to better tie together the sections by adding these kinds of summaries at the end of the document.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

Comment: I reviewed the Marketing and Consumer Perceptions section. Overall the section was well written and nicely summarized all cited literature. I just have a couple of suggestions to improve upon this section. First, the study descriptions were mixed. Some provided sample sizes while others did not. It would be useful to provide consistent study descriptions for the entire section. The Patterns of Use section actually provides a nice example with each description of a study mentioning the source of the data, whether it was cross sectional or longitudinal, the study sample size, a brief description of the sample, and the main objective of the study. Second, the section could have better outlined the study limitations. The section on dependence did this nicely by ending each study description with limitations and comparisons or reason why it cannot be compared to other studies.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

Comment: I reviewed the section on Marketing and Consumer Perceptions. I think there is a field of tobacco marketing research that is lacking from this section. It is mentioned in the conclusion, but no review of the literature is provided for any existing evidence on the effect of point-of-sale marketing strategies on smoking behavior. Given that this accounts for a significant percentage of current tobacco marketing expenditures. It is certainly an important to examine its impact on smoking behavior in general and differences between menthol and non-menthol smoking and advertising. If a literature review was conducted and insufficient evidence was found, then this should be incorporated into the report. I also think the conclusion written about insufficient evidence to support that the use of menthol cigarettes is associated with perceptions of harm is written too strongly given that only 3 articles are included in the literature review. Given the

limited evidence I also don't think it's appropriate to state that "consumer perceptions in relation to menthol vary across age, race, gender, and education level." It could be written to show there is limited evidence or something along those lines.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

Comment: The citations provided below are specific to the section I reviewed:

Marketing and Consumer Perceptions

J. Rising and L. Alexander. Marketing of menthol cigarettes and consumer perceptions. Tobacco Induced Diseases (2011); 9 (Suppl 1):S2.

OY Lee and SA Glantz. Menthol: putting the pieces together. Tobacco Control (2011); 20 (Suppl 2):ii1-7.

Klausner K. Menthol cigarettes and smoking initiation: a tobacco industry perspective. Tobacco Control (2011); 20 (Suppl 2): ii12-19.

Seidenberg AB, Caughey RW, Rees VW, Connolly GN. Storefront cigarette advertising differs by community demographic profile. American Journal of Health Promotion. (2010); 24(6): e26–e31

Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP. Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods. Nicotine and Tobacco Research (2011). epub ahead of print.

Henriksen L, Schleicher NC, Feighery EC, Fortmann SP. A longitudinal study of exposure to retail cigarette advertising and smoking initiation. Pediatrics (2010); 126(2):232-8.

Shadel WG, Tharp-Taylor S, Fryer CS. How does exposure to cigarette advertising contribute to smoking in adolescents? The role of the developing self-concept and identification with advertising models. Addictive Behaviors (2009); 34(11):932-7.

Ruel E, Mani N, Sandoval A, Terry-McElrath Y, Slater S, Tworek C, Chaloupka F. After the Master Settlement Agreement: Trends in the American Retail Environment. Health Promotion Practice (2004); S5(3): 99S-110S.

Slater SJ, Chaloupka FJ, Wakefield M, Johnston LD, O'Malley PM. The Impact of Retail Cigarette Marketing Practices on Youth Smoking Uptake. Archives of Pediatrics and Adolescent Medicine (2007); 161(5): 440-445.

Cigarette Advertising and Smoking Perceptions

Jameison P, Romer D (2001). "What do young people think they know about the risks of smoking?" In: P. Slovic P (ed.). Smoking: risk, perception, and policy. Thousand Oaks, CA: Sage Publications, 51-63.

Pechmann C and Knight S (2002). An experimental investigation of the joint effects of advertising and peers on adolescents' beliefs and intentions about cigarette consumption. Journal of Consumer Research. 29: 5-19.

Romer D, Jameison P (2001). "Advertising, Smoker Imagery, and the Diffusion of Smoking Behavior." In: P. Slovic P (ed.). Smoking: risk, perception, and policy. Thousand Oaks, CA: Sage Publications, 127-187.

Shore TH, Tashchian A, Adams JS (2000). Development and Validation of a Scale Measuring Attitudes Toward Smoking. Journal of Social Psychology; 140: 615-623.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

Comment: I have included all my comments in other sections of this document.

III. SPECIFIC OBSERVATIONS

Page	Line	Comment
36	1580-81	The report states that "econometric studies report teens' brand preference is three times more sensitive to effects of cigarette ads than adults". However it does not contain a literature review of variation in advertising across community SES and demographic characteristics. There is some evidence (e.g. Seidenberg et al. 2011) suggesting that cigarette advertising in low income, minority communities is more prominent and more likely to promote menthol cigarettes.
37	1582	"Top three most heavily advertised brands" when the cited articles were published in the 1990s these brands were Marlboro, Camel and Newport. It would be useful to cite more recent data showing brand preferences and advertising shares. If MTF still includes the question on brand preference it would be possible to look at more recent information, at least for adolescents.
37	1596-97	"O'Connor (2005) found Newport's popularity declines dramatically after age 26." Is this at a similar rate across all racial/ethnic groups? Is it possible to determine this if it was not included in the original article?
37	1597-99	"Newport is overwhelmingly preferred by African Americans, with 41% of African American adults and 75% of African American youth reporting preference for Newport cigarettes."-- Is there less of a decline in African American youth switching to non-menthol cigarette brands as they move into adulthood than white/Hispanic youth?
37	1602-05	"Additionally, there is evidence to suggest regional differences, with more teens reporting a preference for Newport in the Northeast than in the West (CDC, 1994; Johnston et al., 1999). CDC (1994) suggests regional preferences for Newport combined with a decrease in overall advertisement expenditures by Newport suggests this brand may rely more heavily on a regional marketing strategy than a national strategy." Given the dates of the research cited here, this may not be true anymore, Ruel et al. 2004 found significant increases in the price of Newport cigarettes from 1999-2002 coupled with a decline in cigarette promotions from 2001-2002.

Page	Line	Comment
37	1619	What about including the effects of point-of-sale cigarette advertising on youth smoking? (e.g. Slater et al. 2007 found an increase in the pervasiveness of point-of-sale advertising increased the likelihood that adolescents would experiment or initiate smoking, with younger youth being more influenced by increased levels of advertising.
39	1699	Could add here the Seidenberg et al. citation listed above.
40	1748	I would add to the document that White et al. controlled for household income in their models (which was insignificant). Is it that menthol smokers take advantage of price promotions more often, or are they targeted more often with promotions? This is unclear from the way the promotional questions are reported in the study.
40	1760	The Rising and Alexander review article should be added to the Consumer Perceptions section.
41	Section on Consumer Risk Perceptions	I think this section needs more of an introduction about how advertising can affect perceptions to better integrate this section with the marketing evidence.
42	1811-1813	You state, "It is difficult to determine the strength of the relationship between marketing and consumer perceptions and its impact on behavior due to the limitations in study designs included in this literature review." However the three articles cited on consumer perceptions don't actually examine the affect of marketing on perceptions. See Lee and Glantz 2011 for a better example of this. There is also existing literature that examines the impact of tobacco advertising on smoking risk perceptions, which may help improve this section (citations listed above).
42	1827-29	You state, "In addition, it is likely that the standard marketing mix approach of price, promotion, product, and place has been used to drive menthol cigarette preference among the urban African American community." I don't think you provide enough evidence in the review to support this comment. You need to add a review of the associations between point-of-sale marketing and smoking behavior to the paper.
42		You state, "The evidence is not sufficient to support a conclusion that perception of harm is associated with menthol in cigarettes or the use of menthol cigarettes." The language in the ensuing discussion should be changed slightly. This section was based on the findings of only 3 studies, yet the research is described as "some studies". There really doesn't appear to have been enough research conducted to draw any definitive conclusions to use words like "some" and "while others"

REVIEWER #2

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #2

I. GENERAL IMPRESSIONS

The report is a comprehensive review of the potential impact of menthol in cigarettes on public health. The broad categories for review—i.e., toxicology and chemistry, physiology, biomarkers, epidemiology, marketing, initiation, dependence, and cessation—seem properly selected. Reviews of the studies for each of the categories are also very thorough. There are, however, a few points that I would like to suggest for improving the report. Some of these points are detailed in the relevant sections under Part II below.

First, to make a scientific assessment, this report evaluated previous studies to determine the significant associations of menthol in cigarettes with different types of impacts. These associations are classified "associated," "likely associated," "likely not associated," "not associated," and "evidence not sufficient to support a conclusion of an association." But sometimes, the way each of the report's sections reaches its conclusion about these five associations is neither clear nor convincing. One reason is that the studies relevant to the corresponding category have mixed results. Thus, it would be beneficial to provide more specific criteria or rationales for how the evidence is weighted to conclude in one way over the other.

Second, most of the reviews of the studies are clear, informative, and accurate. In some cases, though, presentation of the study findings could be further clarified to produce the following results: make the reports less technical; suggest what the findings mean to menthol cigarettes or their impact; and provide more information on what the reports (e.g., on statistical findings, study limitations) mean.

Third, although each section follows the same basic format and organizational scheme, some of them deviate and should be made more consistent with the others. I detailed this point below, but to be short, introduction and conclusion of some sections are much clearer than the others. Some of the limitations acknowledged for the reviewed studies are too frequently repeated, with the effect that they interrupt the argument structure.

Other than these points, I believe that the report provides important and useful information for understanding scientific evidence on menthol cigarettes and its implications for policy and regulations.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

Comment:

Overall, the report is clearly written and follows a logical structure and layout. It attempts to maintain a consistent format: each section starts with the topic it deals with, indicates the purpose/objective of the section, and mentions the types of studies it will subsequently review. Then, each section ends with a summary of the reviews and a conclusion based on the weight of evidence. Some of the sections, though, could be made more consistent. For example, the

introduction to section "D. Patterns of Use" needs to duplicate the format and order of topics used in the other introductions: importance of the topic covered in the section, purpose of the section, and overview of the types of studies reviewed in the section.

Also, while the early sections specifically note "industry reviews of menthol" or industry-sponsored studies (e.g., Sections A and B), the later sections do not specify the industry-sponsored studies. Because there may be some bias of the findings due to the conflict of interest, readers might find it useful to know which studies are industry-sponsored. For example, on p. 22, Wang et al.'s study (2010) was introduced without the information that it is an industry source, whereas it was identified as such in the earlier sections.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

Comment:

Most of the study descriptions are adequate, but in some places they could have been a bit less technical. It might be better to insert some lay explanations of what the study findings mean before describing them in technical detail. For example:

On p. 15, in the 2nd paragraph from the bottom:

"Orani et al. (1991) found that, in guinea pigs, cooling of the larynx and application of l-menthol to the laryngeal lumen reduced ventilation, and application of menthol to the nasal cavity markedly enhanced the ventilatory inhibition."

Perhaps add one sentence to explain in lay terms what the finding means.

On p. 16, line 4:

"Topical anesthesia of the nasal cavity with 2% lidocaine abolished these responses."

Again, it may be more meaningful to insert an explanation of what this finding means, similar to the sentence that appears in the last line of the same page—i.e., "These studies suggest that the presence of menthol might increase exposure of carcinogens and nicotine, which in turn might increase the risk of cancer and dependence."

Some of the reports on the study findings could be further clarified. For example,

On p. 70, line 4 of the 3rd paragraph:

"Although the CPS-TUS is a good, nationally representative dataset, there are serious flaws with this study. There were very weak definitions of ever and former smokers."

It is not clear what the study's serious flaws are and why the definitions of ever and former smokers are weak.

On p. 77, lines 4-7 in the 4th column:

"This time, investigators found a non-statistically significant trend towards reduced risk (p=0.08) among male menthol smokers (<10 yrs) vs male never smokers [OR (95% CI): 0.50 (0.23-1.07)], but showed no trend toward increased risk for >10 yr menthol smokers."

I think this sentence meant to say "marginally significant" instead of "non-statistically significant." Otherwise, the sentence does not seem logical.

On p. 78, 3 lines up from the bottom of the first column:

"Since the authors did not report odds ratio to the nearest hundredth makes it difficult to determine how close this result was to statistical significance."

This sentence is too technical; the meaning of "odds ratio to the nearest hundredth" needs to be explained, as well as the consequence of not reporting it.

For one further point, I understand that the authors tried to address the limitations of the various studies reviewed in this report. However, too often they repeat mentioning the same kinds of limitations (e.g., on cross-sectional and self-reported studies), and those repetitions interrupt the report's logical flow. These repetitions become more obvious in the later sections. Here are just a few examples:

p. 47
" But, similar to other cross-sectional studies, self-reported data were used and menthol status was ascertained at the time of survey with no follow up."

"As with other cross-sectional studies, there is reliance on self-report for classification of menthol use and lack of follow up."

p.48
"As with other cross-sectional surveys, this survey relied on self-report, ascertained menthol use at the time of the survey, and lacked follow up."

p.68
"Self-reported menthol status may be subject to recall bias and misclassification."

pp.70-71
"In all studies available for evaluation, menthol use/preference was based solely on self-report. Although this could be associated with misclassification, self-report is the standard of this research field and not considered detrimental to the study results."

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

Comment:

While most of the conclusions on either "likely associated" or "not likely associated" make sense, some do not. Studies reviewed in each section show some mixed findings because some of them support the conclusion while others do not. Some studies have reversed findings. At the same time, some studies may be more rigorous than others because they are either large-scale, have follow-up studies, or are nationally representative. But even such rigorous studies have weaknesses/limitations. For this reason, it is important that the authors specify which criteria they

used to weigh the evidence that leads to the conclusion of either "likely" or "not likely" associated with menthol in cigarettes. If readers do not know the specific criteria, they might not agree with the conclusion provided in each of the sections.

For example, the sections on "biomarkers," "initiation," "dependence," and "cessation" review studies that show mixed findings. But the conclusion for biomarkers was "likely not associated with menthol in cigarettes," while the other sections conclude "likely association." Again, if the report does not specify clear rationales for what studies are weighted more, shouldn't some mixed findings lead to a scientific determination of "not sufficient to support a conclusion"? In this sense, Section E (marketing and consumer perception) seems to have a reasonable determination because it concludes, "the evidence is not sufficient to support a conclusion that consumer perceptions of harm are associated with the use of menthol cigarettes" (p.42).

What therefore need to be provided are clearer and more convincing rationales for such conclusions. To do so, the writers could carry out two revisions: (1) clearly indicate what was weighted (e.g., Were nationally representative studies weighted more than regional studies? Were longitudinal studies weighted more than cross-sectional studies? Or were the judgments simply based on counting whether more or fewer studies support the conclusion?); (2) provide a table that summarizes all the studies reviewed. In such a table, rows could indicate each of the studies, and columns could include sample, findings (support, not support), control variables, DVs, method, etc. If readers are given such a table, it would make it easier for them to see which studies did or did not support the conclusion. Otherwise, they would have to not only read the entire section but also picture such a table in their heads.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

Comment:

Section E, on marketing and consumer perception, reviews many studies on brand preferences, receptivity to advertising, marketing strategies (particularly for youth and minorities), and consumer perceptions. Although not directly related to menthol cigarettes, a few important studies that touch upon these topics are missing in the report. To cite just a few examples:

On susceptibility/receptivity to tobacco advertising and marketing:

Altman, D. G.., Levine. D. W., Coeytaux, R., Slade, J., & Jaffe, R. (1996). Tobacco promotion and susceptibility to tobacco use among adolescents aged 12 through 17 years in a nationally representative sample. American Journal of Public Health, 86(11), 1590-1593.

DiFranza, J. R., Wellman, R. J. Sargent, J. D., Weitzman, M., Hipple, B. J., & Winickoff, J. P. (2006). Tobacco promotion and the initiation of tobacco use: Assessing the evidence for causality. Pediatrics, 117(6), e1237-e1248.

Gilpin, E. A., Pierce, J. P., & Rosbrook, B. (1997). Are adolescents receptive to current sales promotion practices of the tobacco industry? Preventive Medicine, 26(1), 14-21.

On perception and regulatory implications about "light" cigarettes:

Canova, D., Myers, M. L., Smith, D. E., & Slade, J. (2001). Changing the future of tobacco marketing by understanding the mistakes of the past: Lessons from "Lights." Tobacco Control, 10(1), 43-44.

Gilpin, E. A., Emery, S., White, M. M., & Pierce, J. P. (2002). Does tobacco industry marketing of "light" cigarettes give smokers a rational for postponing quitting? Nicotine & Tobacco Research, 4 (Supplement 2), 147-155.

Kropp, R. Y., & Halpern-Felsher, B. L. (2004). Adolescents' beliefs about the risks involved in smoking "light" cigarettes. Pediatrics, 114(4), 445-451.

On tobacco marketing and claims in advertising that target youths:

Krugman, D. M., Morrison, M., & Sung, Y. (2006). Cigarette advertising in popular youth and adult magazines: A ten-year perspective. Journal of Public Policy & Marketing, 25(2), 197-211.

Krugman, D. M., Quinn, W. H., Sung, Y., & Morrison, M. (2005). Understanding the role of cigarette promotion and youth smoking in a changing marketing environment. Journal of Health Communication, 10(3), 261-278.

Paek HJ, Reid LN, Choi H, Jeong HJ. Promoting health (implicitly)? A longitudinal content analysis of implicit health information in cigarette advertising, 1954-2003. J Health Commun. 2010 Oct;15(7):769-87.

Paek HJ, Reid LN, Jeong HJ, Choi H. Five Decades of Promotion Techniques in Cigarette Advertising: A Longitudinal Content Analysis. Health Marketing Quarterly. 2012 (in press).

Pierce, J. P., Choi, W. S., Gilpin, E. A., Farkas, A. J., & Berry, C. C. (1998). Tobacco industry promotion of cigarettes and adolescent smoking. Journal of the American Medical Association, 279(7), 511-515.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

Comment:

In Section B, physiology, the conclusion could include a statement that summarizes any noticeable differences between industry-sponsored studies and independent (academic) studies.

In Section D, patterns of use, the term “brand” is consistently used to indicate “menthol, nonmenthol” (2 lines up from the bottom on p. 28). This use of the term seems inaccurate. According to the American Marketing Association, “brand” typically refers to a particular “name, term, design, symbol, or any other feature that identifies one seller’s product or service that can be differentiated from those of other sellers.” Thus, menthol vs. nonmenthol should not be “brand” but rather “type of cigarette product.” It may be okay to say “brand” when referring to a specific menthol product—e.g., “exclusive brand (Newport or Kool)” (p.31). But other than that, all the labels of “brand” in Section D should be changed to “type.”

In Section H, cessation, the conclusion should be reorganized as follows: first, provide a summary of the reviews; then, state key insights/interpretations of the reviews; and finally, provide the determination statements based on the weight of evidence. These three important pieces of information were buried among redundant mentions of study limitations.

III. SPECIFIC OBSERVATIONS

Several line-specific comments have been made in the narrative comments preceding this section.

Page	Line	Comment
4	4th from the bottom	"…increased dependence is likely associated with menthol in cigarettes." Remove "increased"?
6	4th -8th	"Among those studies reviewed, it was consistent that African American menthol smokers were consistently less likely to successfully stop smoking than African American nonmenthol smokers. From the available studies, the weight of evidence supports the conclusion that success in smoking cessation is likely associated with menthol in cigarettes, especially among African American menthol smokers." These two sentences seem contradictory. The second sentence is misleading because it sounds as if African American menthol smokers are more likely to be successful in smoking cessation than the other ethnic groups.
8	3rd from the bottom	"A total of six articles were evaluated which were applicable to this question." Delete the redundant "were."
17	2nd para	"It was reported that menthol cigarette smoking inhibits the metabolism of nicotine through 1) slower oxidative metabolism to cotinine and 2) appeared to slow glucuronide conjugation." Revise this sentence to make items 1) and 2) stylistically parallel.
17	4th para	"For example, one study suggested that menthol has an antitumor property. In addition, a few in vitro studies and a small clinical study suggested that menthol might have a role on exposure and metabolism of nicotine and TSNAs." These two sentences need citations.
25	2nd para from the bottom	"Controlling for age; sex; race/ethnicity; and the length, frequency, and level of smoking; descriptive and regression analysis found that menthol vs. nonmenthol cigarette use was not significantly associated with salivary cotinine level models that included CPD smoked." This sentence needs to be revised; it is not punctuationally correct.
46	The last two lines from the first paragraph	"Rather, the current assessment includes differences in prevalence rates, age of first cigarette, progression to regular smoking, and industry documents research." This sentence lacks parallel construction: "industry documents research"

Page	Line	Comment
		should be changed so that it matches the other topics mentioned in the list.
46	The last three lines from the bottom	"That study addressed the serious issue of misclassification of the kind of cigarettes smoked, but as with other cross-sectional surveys, the data were self-reported and represent a "snapshot" with no follow-up." This sentence needs clarification. Which study--Hersey et al. (2006) or Rock et al. (2010)? What kind of serious issue of misclassification?
47	5th line from the bottom in the 2nd para	"…used three menthol smoking status definitions to model the relationship between menthol cigarette use…" Please specify the three menthol smoking status definitions.
47	1st line in the 3rd para	" Rock et al. (2010…." Need a close parenthesis ")"
48		"Although there were more menthol smokers (n=407) than nonmenthol smokers (n=73), there was sufficient power to make this comparison." It is not clear whether this sentence refers to "power analysis" or to a "statistically significant difference." If the latter is the case, please say so.
55	3rd line from the bottom in the 2nd para	"While the data seems generalizable to most smokers, …" the data **seem** (plural)
57	2nd para	"A total of five peer-reviewed publications, and a non-peer-reviewed secondary data analysis were evaluated for this section." Please double check the number of publications reviewed. Based on my calculation, a total of **eight** studies were reviewed.
58	9th line from the bottom	"less that 10 cpd were more likely to be…" less **than**…
60	The last three lines in the 3rd para	"…youth who reported initiation in the final wave were included in an expanded analysis in order to increase sample size, even though these smokers are not followed for smoking progression or menthol use change over time." Font size is smaller than the surrounding text.
61	1st and 2nd paragraph	1 h, 1hr, 1 hour, 1h … Need to be consistent
65	2nd para	"A total of ten peer-reviewed articles were reviewed for this section, including three population or community-based studies, and eight clinically-based studies." Check the number of articles. If 8 + 3 studies were reviewed, the total should be eleven, not ten.
69	The last 2 lines in the 2nd para	"More importantly, the utility of the findings of this study are limited due to significant scientific flaws."

Page	Line	Comment
		It is not clear what findings are significantly flawed.
70	3rd para	Levy et al. (2011) is reviewed but not cited in the reference list.

REVIEWER #3

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #3

I. GENERAL IMPRESSIONS

The report appears to be very complete and comprehensive in terms of the issues addressed and the extensive reviews of the peer reviewed literature. The additional non-peer reviewed analyses seem well-conducted and make important contributions to the report, helping to yield more definitive conclusions in some cases. The writing is well-organized and stylistically clear. Nevertheless, the report would benefit from some revisions. In terms of structure, some refinement of the "scientific determination" categories is recommended to make causal attributions more explicit. It would help to identify specific studies whose designs are strong enough to support causal attributions. It also would help to add a one- page tabular "scorecard" for each section indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause of each impact. The conclusions arrived at in most of the sections appear justifiable based on the literature reviews. Recommended is consideration of modified conclusions for several sections. The "physiology" section seems to need some additional conclusions and the two sections "marketing and consumer preference" and "initiation of smoking" should probably conclude less certainty about causal relationships.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

The report is well-organized and clearly written, in the sense of being understandable. But there are three issues of requiring clarification or elaboration.

First, the categories for "scientific determination" appear to be ambiguous in one important respect (p. 4). In commonly used scientific parlance, the term "association" is usually synonymous with "correlation," simply denoting statistical co-variation between variables. However, the entire intent of the report is to determine whether menthol causes negative or positive health conditions, which would then be considered the "effects" or "consequences" of menthol. A scientific truism is that "correlation is not causation." (To determine whether menthol causes specified negative or positive health conditions requires information that goes beyond showing the existence of a correlation [association] between menthol in cigarettes and a public health-related condition –more on that below). In order for the scientific determination categories to be clearly aligned with the intent of the report, I suggest their language be changed as follows:

The weight of evidence supports the conclusion that menthol in cigarettes is a cause of x.
The weight of evidence supports the conclusion that menthol in cigarettes is likely a cause of x.
Etc.

X may have multiple causes, so that it why the term would be "a cause."

Second, studies differ in their ability to support causal inferences. The main problematic sections in this regard are marketing and consumer perceptions, initiation, dependence and cessation. The report seems to recognize this, in that some studies are singled out for more attention than others. Studies with greater ability to support causal inferences are those with experimental or quasi-

experimental designs and/or studies which can rule out potential (and plausible) confounding variables through statistical control. Generally it would help if the report were more explicit about why some studies should be given more weight due to their ability to rule out alternative explanations for the causal inference under examination - "menthol in cigarettes is a cause of x." The main alternative explanations would be that the association (correlation) observed between menthol presence/use and x is spurious (i.e., due to a third variable- a confounder – causing both the presence/use of menthol and x) or that there is a causal connection, but the reverse of that hypothesized (i.e., x causes menthol presence/use). It would help to more specifically identify studies whose designs are strong enough to support causal attributions in the sections listed above.

Third, and this pertains to all the sections, the study-by-study descriptions are essential, but when it's time to arrive at a conclusion, it is difficult for the reader to integrate the results for comparison with the report's conclusions. What would help is a one- page tabular "scorecard" for each section indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause of each impact. Since the results of the studies are often mixed, it becomes a matter of judgment as to what percentage of the reviewed studies must provide evidence to justify a determination of "likely associated" and what percentage must provide evidence to justify a determination of "associated." Now it's understood that these determinations are not made solely based on numbers, but the numbers are clearly a major part of the determinations and should be better and more conveniently summarized. Since some studies provide "stronger" causal evidence than others, due to their superior design, that certainly can be taken into account in drawing conclusions. But if some studies are given more weight, that should be explicitly stated and the reason should be given.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

Tobacco Toxicology and Chemistry

The section is well-organized in that different toxicological effects and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses that aid interpretability. The discussion of the studies is clear and objective.

Physiology

The section is well-organized in that different physiological effects and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses that aid interpretability. The discussion of the studies is clear and objective.

Biomarkers

The section is well-organized in that different biomarkers of exposure and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses (e.g., controlling for possible confounders) that aid interpretability. The discussion of the studies is clear and objective.

Patterns of Smoking

I would recommend naming this section "sociodemographic patterns of smoking." A more explicit rationale for the inclusion of this section is needed, since it does not quite fit into the scientific determination paradigm above. That is, the sociodemographic variables cannot be defined as an "impact x!" The rationale for including this section is that, if menthol in cigarettes is found to be harmful, then it can be useful to know what groups are most likely to smoke menthol, for instance in order to target interventions to reduce menthol cigarette smoking. Otherwise, the section is well-organized in that the different surveys are reviewed separately. The surveys were adequately summarized in terms of their research designs, findings, limitations and statistical analyses (e.g., controlling for possible confounders) that aid interpretability. The discussion of the surveys is clear and objective.

Marketing and Consumer Perceptions

This section needs a better rationale for its inclusion. In brief, what is being defined as "x" in terms of the scientific determination paradigm? In one conclusion, the "impact" x relevant to this section appears to be "brand preference" and the putative causal variable appears to be "marketing of menthol cigarettes." In the other conclusion, the impact x appears to be "use of menthol cigarettes" and the putative causal variable appears to be "consumer perceptions of harm."

The report needs to note that smoking menthol cigarettes is only a relevant "impact" if menthol in cigarettes is shown to be harmful, which is the issue under examination in most of the other parts of the report. While smoking is already known to be harmful, the question is whether smoking menthol cigarettes increases such harm from smoking.

Since the product under examination is menthol, this section of the report should derive a conclusion pertaining to "brand preference for menthol cigarettes," not just "brand preference." If there is no reference to menthol in a conclusion, it does not seem relevant to the report. But in that case, would the two impacts really be the same impact – and could these two aspects of the literature review be combined to draw a conclusion about the impact of marketing on "use of menthol cigarettes"- since "brand preference for menthol cigarettes" would just be a proxy measure for menthol smoking (i.e., if they prefer and buy the menthol brand, they smoke it).

There is a problem in how "receptivity to advertising" may be defined in some of the studies. The report says this might include "brand preference." (p. 37, 4th paragraph). But "brand preference" is also an impact variable in this section. This could lead to tautological results ('circular reasoning"). The report should ensure that conclusions in this section are not partially based on this fallacy.

"Receptivity to advertising," although a term that appears in the literature, is a misleading term. It would be better to term this concept "exposure to and/or engagement in advertising." Since "receptivity" can be interpreted as synonymous with "susceptibility." My thesaurus gives "receptiveness" as a synonym for susceptibility. Yet in some of the advertising research literature, the two terms are distinct; it's confusing.

Initiation of Smoking

The above term includes two distinct behaviors (impacts) – termed in the report "first smoking experience" and "progression to regular smoking." It would be clearer if the report drew separate conclusion about these two distinct impacts. I also think that the lay public would interpret "initiation of smoking" as referring only to "first smoking experience."

Tobacco Dependence

The section is well-organized in that each measure of dependence is reviewed separately. The studies were adequately summarized in terms of their research designs, findings and statistical analyses that aid interpretability (e.g., control variables).

Smoking Cessation

For this section and perhaps for all sections, it would help to present a 1 page tabular scorecard indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause of the impact, in this case smoking cessation. Since the results of the studies are mixed, it becomes a matter of judgment as to what percentage of the reviewed studies must provide evidence to justify a determination of "likely associated" and what percent must provide evidence to justify a determination of "associated." Now it's understood that these determinations are not made solely based on numbers, but the numbers are clearly major part of the determination and should be better and more conveniently summarized. Since some studies provide "stronger" causal evidence than others, that can be taken into account in drawing a conclusion.

Disease Risk Relative to Non-mentholated Cigarettes

The section is well-organized in that each category of disease is reviewed separately. The studies were adequately summarized in terms of their research designs, findings and statistical analyses that aid interpretability (e.g., control variables). The discussion of the studies is objective.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

Tobacco Toxicology and Chemistry

The conclusion seems to objectively reflect the data.

Physiology

The report states:
"Overall, the evidence is sufficient to conclude that, by acting primarily through receptors on sensory nerves, menthol is likely associated with reduced nicotine irritation." (p. 18). However, there was only one paper that I could see which directly addressed that issue (Dessirier, 2001). The conclusion might be framed too narrowly here. The Executive Summary states: "There are some in vivo and in vitro studies that show menthol has cooling, desensitizing, and proanalgesic effects….From the available studies, the weight of evidence supports the conclusion that changes in physiology are likely associated with menthol in cigarettes." (P. 4). This seems to accurately summarize the research – a variety of physiological effects are reported. However, the conclusion that: "Menthol acts primarily through receptors on sensory nerves" (p. 4) seems inaccurate, as additional loci or sites of action were reported. For instance, "The data suggested that smoking menthol cigarettes may lead to inhibition of nicotine metabolism" (p .16, 5th paragraph) and "significantly increased the tissue reservoir formation in porcine esophageal mucosa" (p. 16, 6th paragraph). I think the conclusions need to be rewritten for this section to take the full range of findings into account.

What is missing from the research base on physiology is any consideration of differences by age or by race, especially African American vs. White. This is because there are strong age and racial differences in menthol cigarette preferences, but these are largely unexplained thus far. It would fill in some "missing gaps" to know whether there objective differences in physiologic reactions to menthol or menthol cigarettes by age or race.

Biomarkers

The conclusion seems to objectively reflect the data.
The additional secondary analyses adjusting for possible confounders performed by FDA and RTI were useful in leading to a reasonably definitive conclusion. These analyses might be further refined by conducting a statistical sensitivity analysis. For instance, the report states: "The observed statistically significant differences in biomarkers of exposure (unadjusted data) between menthol and nonmenthol smokers may be due to differences in demographic or smoking behavior characteristics between menthol and nonmenthol smokers." (p. 24, 2nd paragraph). It might be possible to identify which of the control variables contributed to eliminating the differences observed in the unadjusted analysis, and which did not.

Patterns of Smoking

The conclusions seem to objectively reflect the data.

Marketing and Consumer Perceptions

This section was difficult to evaluate because the questions driving the section were not explicitly articulated at the start of the section. There seem to be three scientific determinations ("conclusions") at the end of the section, but only one is stated using the term "weight of evidence." And only 2 of the 3 conclusions appear in the Executive Summary ("perception of harm" appears to be omitted). The main conclusion is: "From the available studies, the weight of evidence supports the conclusion that brand preference among adolescents and the African American community is associated with the marketing of menthol cigarettes." I think is this intended to state, marketing strategies are a cause of brand preference. However, it appears that pre-existing preference for menthol among these groups is a given, and that an alternative explanation of the correlation would be that advertising is being targeted to the known preferences of the groups - adolescents and African Americans (AAs) tend to like menthol cigarettes and so the advertising to them emphasizes menthol brands. There is much advertising of this type generally and it makes sense. (Of course it is unknown why AAs tend to prefer menthol, but its doubtful companies and advertisers decided to create such a preference uniquely among AAs and that they would have the means to do so.) There may be some studies that enable the direction of causality to be disentagled, but merely having longitudinal data is not a panacea for this. For instance, it may be the advertising emphasizing menthol at time 1 is associated with greater menthol brand preference at time 2 – but one also has to examine whether brand preference at time 1 is associated with advertising emphasizing menthol at time 2. That is, disentangling causal direction is this way may require some very careful and sophisticated analysis – are there longitudinal studies which have done that? As presented, I am doubtful that the weight of the evidence supports the conclusion above.

Initiation of smoking

In terms of "first smoking experience," this reviewer agrees that the research cited (p. 48) is not sufficient to support a conclusion that availability of menthol cigarettes is associated with earlier

first smoking experiences. (Incidentally, I only saw 3 studies reviewed, not 4.). That is, the report concluded: "There is no indication that menthol smokers experience cigarette smoking any earlier or later than nonmenthol smokers"(p. 51, third paragraph).

But at the end of the conclusion section, a different conclusion seems to be reached, based on inferences from a different type of data - epidemiological studies: "…. the weight of evidence supports the conclusion that the initiation of cigarette smoking is likely associated with menthol in cigarettes" (p. 52, first paragraph).

This reviewer does not agree with the report's interpretation of the epidemiological smoking prevalence studies to support such a conclusion about initiation. These studies show that "younger, newer smokers prefer menthol at levels far above that of the general population; a finding that is generally consistent across racial/ethnic groups." (p. 52). These data would support a role for menthol in initiation if younger, newer smokers would be less likely to progress to regular smoking if menthol cigarettes were unavailable. However, a preference for a certain type of cigarette does not necessarily imply that the person would not smoke at all or even smoke less. At one time consumers preferred tail fins on cars, but had tail fins not been available, that does not imply that fewer cars would have been sold or that consumers would have driven them less. It is probably true that beef eaters prefer steak, but it's doubtful that the unavailability of steak would result in fewer people taking up beef eating or that they would eat less beef. Of course the consequences of any behavior could be made sufficiently noxious or expensive that people would avoid it, but there does not seem to be sufficient evidence that unavailability of menthol cigarettes, which are definitely preferred by certain subgroups if available, would reduce the rate of first smoking experience or progression to regular smoking (or more exactly, that the availability of menthol cigarettes increases those rates over what the rates would be without their availability).

In term of "progression to regular smoking as the impact," the studies that should carry the most weight in terms of making causal inferences are the longitudinal studies, although as I remark elsewhere it also depends on the specifics of the design and how appropriately such data are analyzed. Regarding these studies, I agree with the report that "data regarding age of onset of regular smoking are mixed." (p. 51).

Tobacco Dependence

My only suggestion here would be for the report to consider the possibility that degree of dependence might affect choice of menthol or not. For instance, someone who needs to smoke a lot (or gets to that point) may prefer or switch to menthol because of the "soothing" effect that it has for some people. The conclusion would be stronger if there were testimonial data on why people choose menthol or switch to menthol. The report says it does not review the "switching" data because it is difficult to interpret for understanding initiation (p. 46), but qualitative data on this to see if relates to increased dependence might shed additional light. The conclusion would also be stronger if there were any theory or data on the mechanism of action that results in menthol increasing the probability of tobacco dependence. The conclusion would also be stronger if the results for different measures of dependence were not somewhat mixed. But nonetheless, it appears reasonable to draw the "likely association" conclusion as the report did. More – and improved! - research on this key issue is definitely needed, however.

Smoking Cessation

There seems to be a typo in the conclusions, e.g., the sentence "From the available studies, the weight of evidence supports the conclusion that increased dependence is likely associated with

menthol in cigarettes, especially among African American menthol smokers." (p.71, my italics). Shouldn't that say, "success in smoking cessation?"

The report seems to imply that studies that adjust for dependence factors (an over adjustment for the purpose of this section) should be considered as providing "evidence" for menthol reducing rate of cessation. What the probable over adjustment has done is make the result uninterpretable, since we do not know whether menthol would be associated with cessation without that adjustment for dependence. Since so many studies need to be excluded from consideration due to this probable over adjustment, and since the result of the others are mixed, the most conservative conclusion seems to be, based on a count of studies alone, that the evidence does not support a conclusion of an association (a causal link between menthol and success in cessation).

However, I do think the reanalysis done by the FDA of the CPS-TUS dataset is useful and it does show an association. Note that the OR for whites and AAs is similar – I assume the AA association is not significant due to the smaller sample size for the AAs. Thus it can be difficult to interpret racial difference statistics based on statistical significance alone - I would give more weight to the effect sizes when doing subgroup comparisons. Ask the question – would this effect size be "significant" if the sample size were the same as for the other subgroup?

If we add the CPS-TUS result above, there may be barely enough evidence to justify concluding that there is a likely association between cessation and specifically AA menthol vs. non-menthol smokers.

Disease Risk Relative to Non-mentholated Cigarettes.

The conclusion seems to objectively reflect the data. Again, I would suggest a 1-page table that lists each study and indicates the scientific determination of causation for that study – does it support an association or not?

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

Not aware of any.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

I think I've addressed everything.

III. SPECIFIC OBSERVATIONS

Page	Line	Comment
None provided.		

REVIEWER #4

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #4

I. GENERAL IMPRESSIONS

Overall, the position is very well written and clear, and conclusions are reasonable given the data. The one global issue is that the correlated relationship between dependence, cessation and disease risk has not been well thought out. Specifically, it will be important to decide if the question is of the independent impact of menthol on each of these outcomes, or whether pathways between these outcomes can be considered. That is, if menthol increases dependence, then it will naturally be associated with cessation. Likewise, it is reasonable to assume that if menthol is associated both dependence and cessation, then it will be related to disease risk. The work takes the position that adjustment for dependence may be considered as "over adjustment" in the assessment of cessation, implying that the pathway of action should be incorporated in the consideration (i.e., the reason for lower cessation rates is greater dependence). However, it then considers disease risk only among current smokers, in essence "conditioning out" the potential for both increased dependence and cessation to have an impact on disease risk, since disease prevention from stopping is not considered (how can a product that is associated with both dependence and cessation not be related to disease risk?). This does not seem consistent, and careful consideration needs to be made in this important decision.

While the writing and presentation of the position is generally strong, the exception is the section on "Patterns of Use," which is presented in a very confusing and disorganized manner. This section needs a bit of attention.

Other concerns and comments are relatively minor.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

I. Executive Summary

The categories for the evidence (from "supports …" to "is not sufficient to support…") is great and thoughtful. However, although a matter of personal taste, the statement does not reflect the appropriate direction of causation. That is, saying "___ is associated with menthol" seems to suggest the outcome is causing the use of menthol. Wouldn't it be clearer to say "menthol is associated with ___."

It may be important to remember that the Summary will be read by more non-technical readers, and as such it could be better received if it "helped" these readers understand the goals of the science sections with an introductory sentence that provides the goals. This was well-done for "Cessation" where the first sentence was "This review analyzed studies addressing the questions of whether or not menthol smokers were differentially successful in smoking cessation." For the non-scientific reader, a similar brief and clear statement of goal for each of the other sections would strengthen the summary and help the understanding of the findings.

I was confused between the charge to the FDA TPSAC committee described in paragraph 3, and the "Independent" review described in paragraph 4. Are these the same effort (I think not) or are

they different efforts led by different people? What is the time (dates) for the independent review, and how does this relate to the timing of the TPSAC efforts (could the TPSAC efforts and this independent effort influence each other?).

Although a minor issue, "Chemistry" is never really defined in the discussion of "Toxicology and Chemistry" in the Executive Summary. Of course menthol is associated with the chemistry … it now has menthol (a chemical) in the cigarette. Only when one gets to the detailed section is the phase "harmful chemicals" introduced. So in the Executive Summary, it is not clear that "Chemistry" is referring to "Harmful Chemistry."

II. Science Reviews

A. Toxicology and Chemistry

The sentence "This … the reported differences are relative differences to other constituents and do not necessary reflect overall changes to the amount of harmful smoke constitutes delivered per cigarette" is confusing to me. This seems in conflict with the previous and subsequent sentences in the paragraph, so I must not understand the logic that leads to the statement.

The summary is fair and balanced, and does a great job of explaining that high levels of menthol could be harmful, but at the levels in cigarettes is not an issue.

B. Physiology

The definition of smoking topography is clear (first sentence in that section).

While there are several sections, the conclusion seems to "cherry pick" findings. For example, the section on Smoking Topography seems to not suggest much of an association, so would it be fair to add a statement that menthol is not related smoking topography to the conclusions?

C. Biomarkers

The subsection on CO needs to be made more consistent, either offering sample size on all studies (the preferred) or not offering on any. How large were the studies by Clark and Heck?

I am sure that it is a minor oversight, but a "Conclusions" title to the final paragraph would help the reader.

D. Patterns of Use

The paragraph discussing the important study of Alexander (first paragraph of the "Tobacco Use Supplement to the CPS") needs to be re-written. It is not clear to what the percentages refer. For example, the meaning is not at all clear of "… a higher percentage of African American (30.2% versus 4.4%) … among menthol cigarette smokers compared with non-menthol cigarettes." Does that mean that 30.2% of AAs are menthol cigarette smokers (seems to be in conflict with the statement in the Executive Summary that the majority of black cigarette smokers use menthol cigarettes? Similar concerns exist for the second paragraph. In this paragraph is what is being said is that among smoking women 58.0% use menthol and 47.3% use non-menthol (for a total of 105.3%??). If this is women versus men, then this should be rewritten something similar to "among smokers, women were more likely to use menthol cigarettes than men (58.0% versus 47.3%)…"

In the third paragraph, 24.6% use menthol cigarettes and 70.9% use nonmenthol cigarettes, raising the question what the other 4.5% use. Since the point of the section is on the

magnitude of use differences, should this paragraph also provide the magnitude of the "female, African American, younger (18-24) …" differences?

Much of this entire section does not really focus on the effect of menthol. For example, only one sentence of the entire (long) first paragraph describing the NYTS focus on menthol, with the remainder focusing on racial/ethnic differences that are not the focus of this report. Other examples of lack of focus abound, for example description of the study of Gundersen for the NHIS seems to focus on whether menthol cigarette use is related to being a former smoker, and the connection of this to the overall goals of this section is not clear.

E. Marketing and Consumer Perceptions

While the section is challenging based on the nature of the data, and while I believe the conclusion overstated (see comments below), it is well-written and very well presented.

F. Initiation

For the differences in preference rates, it is not clear how the study from Appleyard adds to the argument, could a comparison for the 42% menthol use be provided?

G. Dependence

Very, very well-written and convincing.

H. Cessation

I was somewhat confused, particularly in the cross-sectional section, of whether risk ratios (odds ratio, prevalence ratios, etc.) were for successful cessation or failure to stop. I think these are reported in both ways, and the section could be making more interpretable if a standard were selected and everything changed to the same direction (easy to make consistent by simply taking the reciprocals).

I. Disease Risk

A very well-written and clear discussion.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

I. Executive Summary

It is going to be important to think through how to handle the fact that "dependence," "cessation," and "disease risk" are likely to be very correlated outcomes. The statement that there may be "over adjustment" for dependence in the cessation section requires serious thought. Is the question whether cessation is affected independent of dependence, or is the question whether the cessation is affected through a pathway of dependence. It seems for "disease risk" the authors have made the distinction that the question is whether it is an independent effect, for how else can a harmful agent that is causes more dependence and is more difficult to stop not be associated with an increased disease risk? Surely if the writers should consider over adjustment as an "excuse" for cessation to not be more difficult to stop, but not use dependence and cessation issues as non-excuse for not greater disease risk? This appears to be as bias in the cessation section. Also, do the authors really want to conclude (without explanation) that something that makes people more dependent on smoking and more difficult to quit smoking is not associated with greater disease risk?

II. Science Reviews

A. Toxicology and Chemistry

As noted above, I thought the data were clearly and fairly presented.

B. Physiology

For the study by Ahijevych & Parsley, were there other aspects of smoking topography that were considered and found to not be associated with menthol. Could the finding with puff volume be a spurious finding arising from testing a large number of potential outcomes (only one of which is significant by chance alone).

C. Biomarkers

I was somewhat underwhelmed by the arguments in the CO study section. The sample size of many of these studies is tiny, increasing the possibility of unpublished negative studies. More importantly, equating these tiny studies with the over 3000 people in the TES seems to be inappropriate. I am personally a great deal more influenced by the finding of the TES (only because of the sample size) than these minor studies.

The finding of Clark on Biomarker Exposure to Nicotine seems to focus on racial differences rather than nicotine. As pointed out elsewhere, AAs may be more likely to be menthol smokers, but this is a leap of faith in equating racial differences as menthol differences. This extends to the entire second paragraph of the section (starting with "A few papers described .."). I would suggest that there are many reasons why AAs may have higher markers of nicotine, and I would suggest the entire paragraph should be removed.

D. Patterns of Use

While the presentation is confusing, I feel that it is unbiased (particularly given what is apparently simply overwhelming evidence that menthol affects pattern of use.

E. Marketing and Consumer Perceptions

The data, to the extent they exist, are fairly presented.

F. Initiation

The argument for Differences in Preference rates seems to focus on the observation that younger people tend to be more likely to be menthol users (this case is made very well); however, it is not clear that this could not be due to a "cohort effect." That is, younger people could prefer menthol for some other reason, and if followed longitudinally will continue to prefer menthol as they age – without having any association with initiation. As such, some caution needs to be expressed that higher use in young/new smokers may not be evidence of menthol being associated with higher initiation, but could also represent a simple cohort effect. Similar concerns exist for the other sections.

G. Dependence

Very, very well-written and convincing.

H. Cessation

As noted in the discussion of the Executive Summary, the section is confusing because a lack of clarity regarding the question addressed. Specifically, is the question that of menthol's effect on cessation independent of dependence, or is dependence part of the pathway through which it may be acting. To me, the former is more interesting, but if one considers the different studies, some adjust for dependence and some do not. Importantly, the statement

that the adjustment for dependence may be over-adjustment may present problem for the next section, where disease risk is likely affected by both dependence and cessation, but here it seems that the independent effect is considered.

I. Disease Risk

Much of this contrasts the disease risk for current smokers, and clearly suggests that menthol is not associated with disease risk. Because this entire arguments condition on current use (associations in current users are almost exclusively considered), the impact of dependence and cessation has been obscured. It is not clear whether this is a good or bad strategy; however, if menthol use is associated with both dependence and cessation, one would assume that it has to be associated with disease risk. Do the authors wish to conclude that menthol is related to both dependence and cessation, but that it is not related to disease risk?

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

I. Executive Summary

As noted above, I am concerned that the approach to handle the relationship between "dependence," "cessation," and "disease risk" has not well considered. Is the question a matter of cessation independent of dependence, and also disease risk independent of both dependence and cessation? I am concerned that for cessation it appears to take the position that cessation is there because of a greater dependence (i.e., not worrying about independence of effects), but concludes that menthol is not associated with great disease risk despite previously concluding that it is associated with both dependence and cessation (i.e., now apparently considering the independent effect).

II. Science Reviews

A. Toxicology and Chemistry

As noted above, I thought the data were clearly and fairly presented.

B. Physiology

The statement "Smokers enjoy the cooling sensation of menthol and cigarettes and menthol is perceived as reducing the irritation and harshness of smoking" is made. Although this seems obvious, I am not sure that it is supported by the (largely chemical/physiological) data that is presented. Shouldn't this conclusion be moved to the section on "Marketing and Consumer Perceptions"? It seems that statements of "enjoyment" and the reasons for enjoyment would require marketing research and opinion data, which I do not think is presented.

C. Biomarkers

Fair and balanced conclusion.

D. Patterns of Use

The conclusions are appropriate, but very poorly presented. Over half of the conclusion apologizes for the nature of the (self-reported) data. These apologies take away much of the impact of what is clearly some of the strongest evidence for any of these sections on science reviews.

E. Marketing and Consumer Perceptions

Without doubt, this is the most challenging section. I feel that the authors did a great job documenting that companies target marketing of menthol cigarettes to special groups.

However, the conclusion that this marketing is likely responsible for the brand preference may be a bit of an overstatement. The causation of this association is more problematic than in any other section. For example, it is more clear that young smokers tend to use menthol cigarettes (perhaps because of reduced harshness when "learning" to smoke). It would then be natural for the tobacco companies to advertise to this group to have them select their specific menthol cigarette relative to other company's products. That is, it is not the menthol that is related, but the other aspects of the company's brand of menthol. A similar argument could be made to the targeted marketing that is clearly made to AAs. As such, I am not convinced of this conclusion.

F. Initiation

This is a difficult section that is well-written. It clearly makes the case that younger newer smokers are more likely menthol users. The conclusion discussed the limitations of data being self-reported (which I see as only a minor limitation), but fails to acknowledge that this could be a cohort effect. For example, for some other reason it could be that young people are attracted to menthol brands, and it is not the menthol that makes it easier to for initiation. I am comfortable with the conclusion that initiation is still "likely" associated with initiation; however, acknowledging this possibility would be fairer.

G. Dependence

Very well presented and fair. The evidence appears overwhelming.

H. Cessation

Please see the concerns on from Question #3 above (regarding independent effect versus pathway effect).

I. Disease risk

I do think the conclusions of the impact of current smoking are reasonable, however, again if menthol use is associated with both dependence and cessation, one would assume that it has to be associated with disease risk.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

I. Executive Summary: Not applicable.
II. Science Reviews
Toxicology and Chemistry: none known.
Physiology: none known.
Biomarkers: none known.
Patterns of Use: none known.
Marketing and Consumer Perceptions: none known.
Initiation: none known.
Dependence: none known.
Cessation: none known.
Disease Risk: none known.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

None needed.

I. SPECIFIC OBSERVATIONS

Page	Line	Comment
None provided.		

REVIEWER #5

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #5

I. GENERAL IMPRESSIONS

The report reflects a thorough assessment of the public health effects of menthol as a cigarette additive. These effects include those related to the physical properties of smoke from menthol cigarettes (toxicology and chemistry); physiological consequences associated with smoking menthol cigarettes (cellular processes, biomarkers, dependence, and disease); and behavioral outcomes (patterns of use, marketing, initiation, and cessation).

In general, the report is laudable for its careful consideration of relevant peer-reviewed research and its inclusion of other relevant evidence, including studies conducted by the tobacco industry. This evidence is presented in a clear and concise manner. The report's conclusions are firmly rooted in the evidence and stated in appropriately probabilistic language (e.g., "is associated with," "is likely associated with," "is likely not associated with").

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

Comment: The report is clearly written and follows a logical structure and layout.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

Comment: In general, the study descriptions were adequate and tended to effectively note specific limitations. In nearly all cases, the study descriptions noted samples sizes and representativeness relative to the general U.S. population, key aspects of study methods, test statistics for menthol-related study findings, and significant limitations.

The only instance I observed where a study's findings were not characterized appropriately relates to a non-peer reviewed analysis by Muscat reported on page 76. The report indicates that a "marginally statistically significant lower risk of lung cancer among current menthol smokers" was found, but the p-value was less than .05, indicating a "significantly lower risk" at the conventional level of statistical significance, which appears to have been used throughout the remainder of the report.

Also, the discussion of Squier et al. (2010), which runs from the bottom of page 16 to the top of page 17, includes possible implications of the study's findings. Since most of these implications do not appear to be supported by the other studies noted throughout the report (e.g. there is no evidence to suggest that smoking menthol cigarettes leads to increased cancer risk as compared against nonmenthol cigarettes), it does not seem appropriate to include them.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

Comment: The report's conclusions pertaining to toxicology and chemistry, physiology, biomarkers, patterns of use, marketing and consumer perceptions, dependence, and disease risk appear to be appropriate based on the application of any reasonable weighting to the available evidence. However, the report's conclusion pertaining to initiation is not as firmly rooted in the evidence as its other findings. Importantly, this appears to be due to the lack of consideration given to key evidence. In other words, the conclusion appears to be appropriate, but it requires the discussion of additional evidence. In addition, the report offers inconsistent conclusions about the influence of menthol on cessation; importantly, this inconsistency can be easily addressed via a minor revision to the main text.

With respect to initiation, the report's conclusion that "the initiation of cigarette smoking is likely associated with menthol in cigarettes" appears to be based primarily on the observation of differential preferences for menthol as compared against nonmenthol cigarettes for middle and high school students, especially African-Americans. However, as noted in the previous section on marketing and consumer perceptions, this differential usage pattern can be explained by differential targeting – i.e., menthol cigarettes are marketed more heavily toward young adult and African-American segments. Therefore, an important question is: does targeting fully explain the differential usage pattern or is there something about the presence of menthol per se that leads to disproportionate use by first-time smokers? The best answer to this question would examine whether differences in ad spending fully account for the market share of menthol cigarettes. If so, then the initiation of cigarette smoking would be likely associated with the message, rather than the menthol. To my knowledge, the data needed to provide the best answer to this question are not available in the public domain. Therefore, we are left to consider the second best answer to this question, which involves examining what is known about consumer preferences for menthol cigarettes. According to Yerger (2011), Kreslake (2008a), and other studies cited by these articles, tobacco industry documents show that many menthol smokers specifically seek the sensation of menthol without the harshness of tobacco smoke and the irritating qualities of nicotine. Therefore, to the extent that available evidence links middle and high school students to a similar preference profile, the conclusion that "the initiation of cigarette smoking is likely associated with menthol in cigarettes" is warranted.

With respect to cessation, the conclusion in the executive summary "success in smoking cessation is likely associated with menthol in cigarettes, especially among African American menthol smokers" (p. 6) is not consistent with the conclusion in the main document text "increased dependence is likely associated with menthol in cigarettes, especially among African American menthol smokers" (p.71). Given that the pertinent section of the main text discusses cessation, the former conclusion seems more appropriate.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

Comment: I am not aware of any additional information in the public domain which should have been included.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

Comment: There are some minor stylistic differences between sections that should be addressed to ensure consistent presentation of the available evidence. Specifically, the sections pertaining to "Physiology" and "Biomarkers" use imprecise adjectives to quantify the available evidence (e.g.,

"a few studies," "some studies," "several articles"). The other sections, which specify the precise number of articles and enumerate additional non-peered reviewed analyses, should be emulated.

III. SPECIFIC OBSERVATIONS

Page	Line	Comment
8	12	Awkward listing
10	21	Typo: "Theses"
11	13	Use of term "American style" may be confusing, as this is the only reference in the document.
15	19-25	More details about what tobacco industry documents show about the preference profiles of menthol smokers would add to the weight of evidence.
17	21	Not sure what "(-)-menthol" refers to. Is this a typo?
18	7-9	Statement about what smokers enjoy is not well supported by the review of evidence. (see comment about page 15 above).
31	14	Period missing at the end of the paragraph.
58	35	Check the number of CPD reported for menthol smokers; the magnitude of the difference suggests that there may be a typo.
60	29-31	Inconsistent font size.
70	11	Word missing between "as" and "who"
76	15	The text refers to a data analysis as being "provided in the Appendix." However, the report does not appear to include an appendix, making this statement highly misleading.

REVIEWER #6

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #6

I. GENERAL IMPRESSIONS

Overall, the document is well written and clear. It addresses most of the key elements of the role of mentholated cigarettes in health effects and I did not find any overt inaccuracies. It seems that a little more effort in highlighting the inconsistencies and contradictions in the literature, especially those leading to conclusions of "x is (not) likely" rather than "is" associated with menthol would improve the document. There are some significant overlaps among the discussions of the various epidemiological factors, as well as redundancies addressed more specifically in the sections below.

That said, the document reads as if written by a separate author for each section, with little attempt at integration beyond the repeated comments about the potential for the self-reporting of mentholated cigarette use to be associated with misclassification, and that bias in such reporting is constant over time.

The separation of the "Industry Assessment" or "Industry Reviews" for some sections (Toxicology and Chemistry, Physiology, Initiation) was useful, but calls into question whether some of the information reported in the other sections was tobacco industry-generated results, and not set apart in a similar way: there are certainly references in some sections that are tagged as having authors associated with the industry. Noting the funding sources and author affiliations in the reference lists was a novel and helpful addition.

One conclusion, for the Marketing and Consumer Perception section, differs between the Executive summary where it is stated that "brand preference . . IS associated with the marketing," and the conclusion in that section, where it is stated that "brand preference . . is LIKELY associated with the marketing." This needs to be resolved.

In addition, there is some new information that was not included: Tobacco Control, Vol 20, Suppl. 2 was specifically focused on menthol cigarettes.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

The report is quite clear and in general well written. The structure is generally logical, although there are some redundancies and some information is provided in an inappropriate section. For instance, one section, page 32 paragraph beginning "Gundersen et al. . . ." in the Patterns of Use section would be more appropriate in the Cessation section. There is also considerable overlap between the Marketing and Consumer Perceptions section and the Initiation and Cessation sections, and the metabolic effects of menthol on nicotine metabolism are covered in both the Physiology and Biomarkers sections. Some of this may be unavoidable, but the document would appear better integrated if a decision to include the data as primarily in one section with a reference to that section in the other relevant sections.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

My review focused on the sections on Toxicology and Chemistry, Physiology, and Biomarkers.

Toxicology and Chemistry

The paragraph on smoke chemistry indicates few effects on the composition of smoke as a function of menthol, although it indicates evidence for the production of PAH's from burning menthol. It may be worth pointing out that the studies reported in the next section, indicating that menthol was not itself active in any of the mutagenesis assays, did not address the pyrolysis products. The next paragraph summarizing the Rabinoff 2007 article, may overstate the results of that article, since the "complex interaction with nicotine" was just an unreferenced line in a table. Finally, there is one recent article that should be cited, although it does not provide any novel insights at least it used more modern techniques to evaluate the smoke constituents: Gordon et al., Chem Res. Toxicol 2011.

Related to the comment above on pyrolysis products is that the first paragraph of the next section (middle of pg. 9) on antiproliferative effects, states that "as has already been stated, menthol smoke condensate from burned tobacco is genotoxic," but this statement is not referenced, and it was not obvious to which previous citation this statement refers. Importantly, it is not clear whether that article actually compared smoke condensates from menthol and non-menthol cigarettes. (It appears possible that the article/articles are actually referenced later, in the first full paragraph on page 10, in the in vitro toxicity section). The subsequent statement, that "it should not be assumed that a compound that had anti-proliferative effects in a tumor cell line or even a transfected animal model would definitely have oncolytic effects in humans" is certainly true, but it is unclear to what "transfected animal model" the statement refers.

Also in this section, the reference to the Sidell article (1991) indicating a down regulation of IL-6 receptors in a myeloma cell line is interesting, but the relationship to proliferative activity is unclear. Instead, this has potential ramifications for immune/inflammatory responses, processes not otherwise addressed in the document, but of possible importance (e.g., Juergens et al., 1998: Eur. J Med. Res. 6;3 :539-45; and Marcuzzi et al., 2010, Int. Immunopharmacol 10:639-42.)

Physiology

There seem to be some inconsistencies between the reports of menthol via the TRPM8 receptor in this section versus the Toxicology and Chemistry section. Specifically, in the Toxicology and Chemistry section, menthol is reported to act as an agonist to this receptor, activating Ca influx, while in the physiology section, it is reported to inhibit MCh and K+ induced Ca influx (paragraph 3 under Physiology), and later in Mechanisms of Menthol Action as an antagonist of DHP Ca2+ channels, and possibly even as a direct agonist for opioid receptors (Analgesic Effects section). If the suppression of Ca influx was (or might have been) due to desensitization, this should be clarified. Alternatively, the TRPM8 receptor was unknown at the time of the Sidell article, and the possibility of crosstalk among these receptors could account for the observations.

The Industry Assessment of Menthol Effects subsection appears primarily to reflect the effect on COHb, NNAL, and nicotine metabolism, and might be better kept with the Biomarkers section in which they are also described.

I suggest reorganizing the subsections in the Physiology section to combine the into subsections on "Sensory Effects" (paragraph one of the Physiology subsection, and the Cooling Effects

section), "Receptor-Mediated Mechanisms" incorporating the second and third paragraphs of the Physiology section, the Analgesic Effects subsection, and the Mechanisms of Menthol Action, followed by the Menthol and TSNAs subsection (possibly renamed to "Metabolic Effects"), then the Effects of Menthol on Smoking Topography subsection and the Industry Assessment of Menthol Effects section.

Lastly in this main section, I suggest changing the last sentence from ". . .menthol is likely associated with reduced nicotine irritation" to ". . .menthol is likely associated with reduced irritation from smoke constituents."

Biomarkers
As mentioned above, there is some redundancy between this section and the Physiology section.

There is also considerable redundancy between the sections on Biomarkers of Exposure to CO and Biomarkers of Exposure to Nicotine. I suggest combining these two sections into "Biomarkers of Cigarette Smoke Exposure," which would eliminate the need to cite the Ahijevych, Clark, and Williams studies twice. In both of these sections, the description of the Clark (1996) study states that the comparisons between White and African American smokers were adjusted for race. Should this be after correction for gender, since it is not possible to detect a racial difference after "adjusting for race"? Similarly, in the first full paragraph on page 23, the effects of cotinine as a function of menthol/nonmenthol cigarette use are said to be "adjusted for . . . menthol/nonmenthol use."

One additional comment in the section on Disease Risk: I was surprised not to see more information on the impact of menthol on the risk for COPD (emphysema and chronic bronchitis). However, I did search for this type of information and it does not appear there is anything reported. If that's true, I think it would be appropriate to call these out specifically as areas for which data does not currently support or refute effects of menthol.

Two additional final points.

First: I think it might be helpful to include some overview of the possible hypotheses regarding the potential impact of mentholation on health effects, possibly in the Executive Summary. In my view, these include the following:

1. Menthol or its combustion products could have adverse effects (toxicity or addiction potential) independent of other tobacco-associated chemicals.
2. Menthol could have additional independent effects such as anti-inflammatory properties or anti-proliferative properties.
3. Menthol, by reducing the irritation factor, could lead to increased cigarette consumption (including initiation) and therefore increase risk.
4. Menthol, by altering metabolism of nicotine, could prolong the physiological effects of a single cigarette, reducing cravings and therefore reducing smoking and the associated health risks.
5. Menthol could alter metabolism of other smoke-associated chemicals, either increasing or decreasing their half-lives and thus affecting their toxic effects.

Second, there are several sections for which a summary TABLE would be helpful, particularly those for which there seemed to be evidence both for and against differences.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

In the three sections on which I focused, the conclusions were appropriate. Although I didn't review the other sections in as much detail, the conclusions also seemed appropriate, except for the Marketing and Consumer Perception section where there is a discrepancy between the conclusion reported in the executive summary and the actual conclusions paragraph in the section.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

A recent issue of Tobacco Control (Vol. 20, suppl. 2) was focused on mentholated cigarettes. Although many of the articles appear to be reviews, and therefore contain much of the same information as the current document, there are some additional new data that should be incorporated.

One new article is also available related to the chemistry of smoke from menthol and nonmenthol cigarettes: Gordon et al., Chem Res. Toxicol 2011 Sep 19. [Epub ahead of print] Effect of Cigarette Menthol Content on Mainstream Smoke Emissions.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

Although it's almost become a cliché, it is clear more research is needed. This is particularly true in the context of the combustion products of menthol (with or without the presence of tobacco combustion products) and for the effects on the two primary subclasses of COPD.

III. SPECIFIC OBSERVATIONS

Page	Line	Comment
4	21	Suggest changing "menthol impacted the appearance" to menthol impacted the presence"
4	5th from last	"smoking menthol cigarette" should be "smoking menthol cigarettes"
6	26	Delete comma in phrase "as menthol smokers, show greater signs of nicotine dependence"
7	abbreviations	There are many abbreviations used in the document that do not appear on this list: COHb, COMMIT, FDA, HHS, MCh, NE (nicotine equivalents), NTP, RTI, SENCAR. FEV1 should include "in one second" in the definition. 4-ABP actually isn't defined.
16	26	Constitutes should be constituents
24	Add'l Evidence paragraph, line 10	Hyphens needed in cigarette-adjusted and creatinine-adjusted
60	Last lines in 3rd paragraph	Font is smaller for part of the sentence beginning "In addition, youth who reported"
		There are two places where there are duplicated periods at the end of sentences. p. 7 second line; P 52, middle of the page.

REVIEWER #7

Peer Review Comments on the FDA Evaluation of the Possible Health Effects of Menthol Versus Nonmenthol Cigarettes

Reviewer #7

I. GENERAL IMPRESSIONS

My overall impression of the information provided is very positive. The report is clearly balanced and it follows accurately from the papers cited and provided. The writing style is also very clear. I was impressed that articles both agreeing and disagreeing with the FDA position were provided. The issues were addressed from all relevant perspectives from basic biochemistry and toxicology to clinical and behavioral issues and even to advertising. Thus I found this to be a thorough and un-biased review and very convincing.

I appreciated the reliance on peer-reviewed journals and on primary data when possible. The use of statistics seems quite reasonable and accurate in my non-statistician opinion.

II. RESPONSE TO CHARGE QUESTIONS

1) Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.

The report is clearly written and logically presented. It gives adequate balance to all possibilities and draws opinions with the basis of these opinions clearly stated.

2) For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.

I was particularly concerned with data on subjective effects of menthol on the smoker's perceptions and ease of beginning smoking. Based on my own observations on the conditioned aspects of addiction, I was alert for the discussion of conditioned cues and learning. I found that my area of research was well covered. There were discussions of smoking initiation, treatment methods, relapse issues and clinical outcome studies.

Although effects on lung physiology and function and on biomarkers associated with smoking were given adequate attention, significant effects of menthol on these measures were not found.

The findings of a predilection for menthol among African American youth was consistent and importance as it also translates into increased difficulty in successfully quitting.

3) For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.

The review was divided into specific categories that could be evaluated by the existing peer reviewed literature. I was convinced that the disease burden for smokers of menthol cigarettes was not significantly increased compared to other smokers. Where the review was most persuasive in my opinion was the evidence for menthol in facilitating the initiation of smoking and the difficulty in quitting. The data were most persuasive for minority groups, particularly African Americans. Based on the literature and on the data from smokers in treatment, it may be that the menthol contributes to a complex conditioning stimulus that becomes linked to nicotine

reinforcement. Certainly ease of initiating is another factor that has been cited and addressed in some of the studies that I reviewed. It would be helpful to add this theoretical mechanism (conditioned stimulus) to the discussion because it could explain why.

Thus my own opinion of the risks associated with menthol found in some brands of cigarettes is that the practice of including menthol produces a significant hazard. This is most clearly evident from studies of adolescents and minorities.

4) Are you aware of additional publicly available information which should have been included? If so, please specify.

To my knowledge, the overall review was comprehensive and inclusive.

5) Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).

As a therapist involved for many years in the treatment and study of smokers, I would like to see more data on the effect of menthol on quitting. An obvious problem is that there are so many variables that influence success rate of treatment that it is very difficult to isolate any one class. The rate of sustained abstinence in former smokers is low, even with the best available medicines and behavioral treatments. Thus any element such as menthol that may reduce the success rate of quitting is important and should be emphasized in the report.

The information on ease of starting smoking is very important because most smokers begin as adolescents and there is growing clinical data indicating that young people can become dependent very rapidly as compared to adults. If menthol eases the irritation experienced by new smokers, this could be an important factor in increasing the proportion that become dependent. Some of the papers reporting rates of nicotine dependence in teenage smokers after as little as one month of tobacco exposure could be added as this could be an important consequence of the menthol effect on the conditioned cue of cigarettes.

Based on the data reviewed and my own interpretation of the findings, I support the conclusion that menthol is an added risk factor to cigarettes because it affects the addicting properties of cigarettes. It is also a potential factor in increasing the difficulty of quitting and increasing the likelihood of relapse.

III. SPECIFIC OBSERVATIONS

Page	Line	Comment
6	16	Since pack years has been shown to be associated with disease burden and menthol smokers tend to smoke more, this apparent inconsistency should be noted and addressed.
31	9	"Among African American students, smokers in middle school (87.5%) and in high school (86.8%) smoked predominantly menthol cigarettes. " I recommend adding a comment about the consistency of the data showing a predilection for menthol cigarettes among African American adolescents. As this would correlate with their poor treatment response.
32	2nd to last paragraph	While the conclusion is obvious, the point about fewer "former" menthol smokers supports the notion that menthol makes smokers more difficult to treat and less likely to achieve abstinence.

Page	Line	Comment
34	Last paragraph	Apparently no treatment outcome data are available, but I think the fact that menthol may increase the addictive property of cigarettes should at least be alluded to. The conclusion could be made stronger by pointing out the fact that nicotine dependence has in general a poor treatment outcome rate and that menthol may play an important role in lack of treatment success.

V. PEER REVIEWER COMMENT TABLE

I. GENERAL IMPRESSIONS		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	Overall well written. Sections should be more consistent in the way that reviewed documents are presented in regards to description of the study, limitations, and how the results are related to other studies. Some sections should revise the grouping of studies to eliminate redundancy. Some conclusions may be overstated and need revision based on the evidence presented or require additional citations.	
Reviewer #2	Categories are well selected and reviews are thorough. Some sections conclusions about the five types of associations of menthol in cigarettes (associated, likely associated, etc.) are not always clear or convincing. More specific criteria or rationales for how evidence is weighted would be beneficial. Some reviewed papers could be better explained to make the reports less technical, suggest what the findings mean in regards to menthol in cigarettes, and provide more information on what the reports mean. Finally, some sections deviate from the organizational scheme and should be made more consistent with the others.	
Reviewer #3	The report is clear and comprehensive, well-organized and stylistically clear. Some refinement in the "scientific determination" categories is needed. A "scorecard" for each section indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause for each impact would be helpful. Conclusions should be revised or modified for several sections, specifically "physiology", "marketing and consumer preference" and "initiation of smoking".	
Reviewer #4	Overall the report is well written and clear with reasonable conclusions. The correlated relationship between dependence, cessation and disease risk has not been well thought out, it would be important to decide if the question is independent impact of menthol or whether pathways between outcomes can be considered. "Patterns of Use" section is presented in a confusing and disorganized manner, this needs revised.	
Reviewer #5	The report reflects a thorough assessment of the public health effects of menthol as a cigarette additive. The report is laudable for its careful consideration of relevant peer-reviewed research and its inclusion of other relevant evidence.	
Reviewer #6	Overall the document is well written and clear. Inconsistencies and contradictions in the literature should be highlighted more. There are overlaps among discussions of various epidemiological factors as well as redundancies. Each section reads as if written by a different author. There is a potential that some sections did not separate out "Industry Reviews" and "Industry Assesments" as was done in some sections, this should be consistent. Noting funding sources and author affiliations in the reference list was helpful. In the "Marketing and Consumer Perception" section it is stated that "brand preference… IS associated with the marketing" then later "brand preference… IS LIKELY associated with the marketing", this needs to be resolved. Tobacco Control, Vol 20, Suppl. 2 should be included as a reference as it focused on menthol cigarettes.	
Reviewer #7	The report is clearly balanced and it follows accurately from the papers cited and provided. The issues were addressed from all relevant perspectives from basic biochemistry and toxicology to clinical and behavioral issues and even to advertising.	

II. RESPONSE TO CHARGE QUESTIONS		
CHARGE QUESTION 1: Is the report clearly written and does it follow a logical structure and layout? If not, the reviewer should provide suggestions for how to improve the document.		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	There are variations in the level of detail included about the studies being reviewed across sections. It would be helpful to include all conclusions drawn in each section in the executive summary. It would be useful to provide in an overall summary the connections between some of these sections. For example the evidence shows that the use of menthol in cigarettes increases smoking initiation. There is also evidence that targeted marketing of menthol cigarettes is associated with more adolescents smoking menthol brands. Obviously, someone reading the full document can make these connections, but it would also help to better tie together the sections by adding these kinds of summaries at the end of the document.	
Reviewer #2	Overall, the report is clearly written and follows a logical structure and layout. It attempts to maintain a consistent format. Then, each section ends with a summary of the reviews and a conclusion based on the weight of evidence. Some of the sections, though, could be made more consistent. For example, the introduction to section "D. Patterns of Use" needs to duplicate the format and order of topics used in the other introductions: importance of the topic covered in the section, purpose of the section, and overview of the types of studies reviewed in the section. Also, while the early sections specifically note "industry reviews of menthol" or industry-sponsored studies (e.g., Sections A and B), the later sections do not specify the industry-sponsored studies. Because there may be some bias of the findings due to the conflict of interest, readers might find it useful to know which studies are industry-sponsored. For example, on p. 22, Wang et al.'s study (2010) was introduced without the information that it is an industry source, whereas it was identified as such in the earlier sections.	
Reviewer #3	The report is well-organized and clearly written, in the sense of being understandable. But there are three issues of requiring clarification or elaboration. First, the categories for "scientific determination" appear to be ambiguous in one important respect (p. 4). In commonly used scientific parlance, the term "association" is usually synonymous with "correlation," simply denoting statistical co-variation between variables. However, the entire intent of the report is to determine whether menthol causes negative or positive health conditions, which would then be considered the "effects" or "consequences" of menthol. A scientific truism is that "correlation is not causation." (To determine whether menthol causes specified negative or positive health conditions requires information that goes beyond showing the existence of a correlation [association] between menthol in cigarettes and a public health-related condition –more on that below). In order for the scientific determination categories to be clearly aligned with the intent of the report, I suggest their language be changed as follows: • The weight of evidence supports the conclusion that menthol in cigarettes is a cause of x. • The weight of evidence supports the conclusion that menthol in cigarettes is likely a cause of x. • Etc.	

	• X may have multiple causes, so that it why the term would be "a cause." Second, studies differ in their ability to support causal inferences. The main problematic sections in this regard are marketing and consumer perceptions, initiation, dependence and cessation. The report seems to recognize this, in that some studies are singled out for more attention than others. Studies with greater ability to support causal inferences are those with experimental or quasi-experimental designs and/or studies which can rule out potential (and plausible) confounding variables through statistical control. Generally it would help if the report were more explicit about why some studies should be given more weight due to their ability to rule out alternative explanations for the causal inference under examination - "menthol in cigarettes is a cause of x." The main alternative explanations would be that the association (correlation) observed between menthol presence/use and x is spurious (i.e., due to a third variable- a confounder – causing both the presence/use of menthol and x) or that there is a causal connection, but the reverse of that hypothesized (i.e., x causes menthol presence/use). It would help to more specifically identify studies whose designs are strong enough to support causal attributions in the sections listed above. Third, and this pertains to all the sections, the study-by-study descriptions are essential, but when it's time to arrive at a conclusion, it is difficult for the reader to integrate the results for comparison with the report's conclusions. What would help is a one- page tabular "scorecard" for each section indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause of each impact. Since the results of the studies are often mixed, it becomes a matter of judgment as to what percentage of the reviewed studies must provide evidence to justify a determination of "likely associated" and what percentage must provide evidence to justify a determination of "associated." Now it's understood that these determinations are not made solely based on numbers, but the numbers are clearly a major part of the determinations and should be better and more conveniently summarized. Since some studies provide "stronger" causal evidence than others, due to their superior design, that certainly can be taken into account in drawing conclusions. But if some studies are given more weight, that should be explicitly stated and the reason should be given.	
Reviewer #4	**Executive Summary** The categories for the evidence (from "supports …" to "is not sufficient to support…") is great and thoughtful. However, although a matter of personal taste, the statement does not reflect the appropriate direction of causation. That is, saying " ___is associated with menthol" seems to suggest the outcome is causing the use of menthol. Wouldn't it be clearer to say "menthol is associated with ___." It may be important to remember that the Summary will be read by more non-technical readers, and as such it could be better received if it "helped" these readers understand the goals of the science sections with an introductory sentence that provides the goals. This was well-done for "Cessation" where the first sentence was "This review analyzed studies addressing the questions of whether or not menthol smokers were differentially successful in smoking cessation." For the non-scientific reader, a similar brief and clear statement of goal for each of the other sections would strengthen the summary and help the understanding of the findings.	

	I was confused between the charge to the FDA TPSAC committee described in paragraph 3, and the "Independent" review described in paragraph 4. Are these the same effort (I think not) or are they different efforts led by different people? What is the time (dates) for the independent review, and how does this relate to the timing of the TPSAC efforts (could the TPSAC efforts and this independent effort influence each other?). Although a minor issue, "Chemistry" is never really defined in the discussion of "Toxicology and Chemistry" in the Executive Summary. Of course menthol is associated with the chemistry … it now has menthol (a chemical) in the cigarette. Only when one gets to the detailed section is the phase "harmful chemicals" introduced. So in the Executive Summary, it is not clear that "Chemistry" is referring to "Harmful Chemistry." **Science Reviews** **Toxicology and Chemistry** The sentence "This … the reported differences are relative differences to other constituents and do not necessary reflect overall changes to the amount of harmful smoke constitutes delivered per cigarette" is confusing to me. This seems in conflict with the previous and subsequent sentences in the paragraph, so I must not understand the logic that leads to the statement.The summary is fair and balanced, and does a great job of explaining that high levels of menthol could be harmful, but at the levels in cigarettes is not an issue. **Physiology** The definition of smoking topography is clear (first sentence in that section). While there are several sections, the conclusion seems to "cherry pick" findings. For example, the section on Smoking Topography seems to not suggest much of an association, so would it be fair to add a statement that menthol is not related smoking topography to the conclusions? **Biomarkers** The subsection on CO needs to be made more consistent, either offering sample size on all studies (the preferred) or not offering on any. How large were the studies by Clark and Heck? I am sure that it is a minor oversight, but a "Conclusions" title to the final paragraph would help the reader. **Patterns of Use** The paragraph discussing the important study of Alexander (first paragraph of the "Tobacco Use Supplement to the CPS") needs to be re-written. It is not clear to what the percentages refer. For example, the meaning is not at all clear of "… a higher percentage of African American (30.2% versus 4.4%) … among menthol cigarette smokers compared with non-menthol cigarettes." Does that mean that 30.2% of AAs are menthol	

	cigarette smokers (seems to be in conflict with the statement in the Executive Summary that the majority of black cigarette smokers use menthol cigarettes? Similar concerns exist for the second paragraph. In this paragraph is what is being said is that among smoking women 58.0% use menthol and 47.3% use non-menthol (for a total of 105.3%??). If this is women versus men, then this should be rewritten something similar to "among smokers, women were more likely to use menthol cigarettes than men (58.0% versus 47.3%)…" In the third paragraph, 24.6% use menthol cigarettes and 70.9% use nonmenthol cigarettes, raising the question what the other 4.5% use. Since the point of the section is on the magnitude of use differences, should this paragraph also provide the magnitude of the "female, African American, younger (18-24) …" differences? Much of this entire section does not really focus on the effect of menthol. For example, only one sentence of the entire (long) first paragraph describing the NYTS focus on menthol, with the remainder focusing on racial/ethnic differences that are not the focus of this report. Other examples of lack of focus abound, for example description of the study of Gundersen for the NHIS seems to focus on whether menthol cigarette use is related to being a former smoker, and the connection of this to the overall goals of this section is not clear. **Marketing and Consumer Perceptions** While the section is challenging based on the nature of the data, and while I believe the conclusion overstated (see comments below), it is well-written and very well presented. **Initiation** For the differences in preference rates, it is not clear how the study from Appleyard adds to the argument, could a comparison for the 42% menthol use be provided? **Dependence** Very, very well-written and convincing. **Cessation** I was somewhat confused, particularly in the cross-sectional section, of whether risk ratios (odds ratio, prevalence ratios, etc.) were for successful cessation or failure to stop. I think these are reported in both ways, and the section could be making more interpretable if a standard were selected and everything changed to the same direction (easy to make consistent by simply taking the reciprocals).	

	Disease Risk A very well-written and clear discussion.	
Reviewer #5	The report is clearly written and follows a logical structure and layout.	
Reviewer #6	The report is quite clear and in general well written. The structure is generally logical, although there are some redundancies and some information is provided in an inappropriate section. For instance, one section, page 32 paragraph beginning "Gundersen et al. . . ." in the Patterns of Use section would be more appropriate in the Cessation section. There is also considerable overlap between the Marketing and Consumer Perceptions section and the Initiation and Cessation sections, and the metabolic effects of menthol on nicotine metabolism are covered in both the Physiology and Biomarkers sections. Some of this may be unavoidable, but the document would appear better integrated if a decision to include the data as primarily in one section with a reference to that section in the other relevant sections.	
Reviewer #7	The report is clearly written and logically presented. It gives adequate balance to all possibilities and draws opinions with the basis of these opinions clearly stated.	
CHARGE QUESTION 2: For each section that you reviewed, were the study descriptions adequate and the evaluations and conclusions unbiased (including limitations, assumptions, etc)? Please be as specific as possible with your rationale.		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	First, the study descriptions were mixed. Some provided sample sizes while others did not. It would be useful to provide consistent study descriptions for the entire section. The Patterns of Use section actually provides a nice example with each description of a study mentioning the source of the data, whether it was cross sectional or longitudinal, the study sample size, a brief description of the sample, and the main objective of the study. Second, the section could have better outlined the study limitations. The section on dependence did this nicely by ending each study description with limitations and comparisons or reason why it cannot be compared to other studies.	
Reviewer #2	It might be better to insert some lay explanations of what the study findings mean before describing them in technical detail. For example: On p. 15, in the 2nd paragraph from the bottom: "Orani et al. (1991) found that, in guinea pigs, cooling of the larynx and application of l-menthol to the laryngeal lumen reduced ventilation, and application of menthol to the nasal cavity markedly enhanced the ventilatory inhibition." Perhaps add one sentence to explain in lay terms what the finding means. On p. 16, line 4: "Topical anesthesia of the nasal cavity with 2% lidocaine abolished these responses." Again, it may be more meaningful to insert an explanation of what this finding means, similar to the sentence that appears in the last line of the same page—i.e., "These studies suggest that the presence of menthol might	

	increase exposure of carcinogens and nicotine, which in turn might increase the risk of cancer and dependence." Some of the reports on the study findings could be further clarified. For example, On p. 70, line 4 of the 3rd paragraph: "Although the CPS-TUS is a good, nationally representative dataset, there are serious flaws with this study. There were very weak definitions of ever and former smokers." It is not clear what the study's serious flaws are and why the definitions of ever and former smokers are weak. On p. 77, lines 4-7 in the 4th column: "This time, investigators found a non-statistically significant trend towards reduced risk (p=0.08) among male menthol smokers (<10 yrs) vs male never smokers [OR (95% CI): 0.50 (0.23-1.07)], but showed no trend toward increased risk for >10 yr menthol smokers." I think this sentence meant to say "marginally significant" instead of "non-statistically significant." Otherwise, the sentence does not seem logical. On p. 78, 3 lines up from the bottom of the first column: "Since the authors did not report odds ratio to the nearest hundredth makes it difficult to determine how close this result was to statistical significance." This sentence is too technical; the meaning of "odds ratio to the nearest hundredth" needs to be explained, as well as the consequence of not reporting it. For one further point, I understand that the authors tried to address the limitations of the various studies reviewed in this report. However, too often they repeat mentioning the same kinds of limitations (e.g., on cross-sectional and self-reported studies), and those repetitions interrupt the report's logical flow. These repetitions become more obvious in the later sections. Here are just a few examples: p. 47 " But, similar to other cross-sectional studies, self-reported data was used and menthol status was ascertained at the time of survey with no follow up." "As with other cross-sectional studies, there is reliance on self-report for classification of menthol use and lack of follow up." p.48 "As with other cross-sectional surveys, this survey relied on self-report, ascertained menthol use at the time of the survey, and lacked follow up."	

	p.68 "Self-reported menthol status may be subject to recall bias and misclassification." pp.70-71 "In all studies available for evaluation, menthol use/preference was based solely on self-report. Although this could be associated with misclassification, self-report is the standard of this research field and not considered detrimental to the study results."	
Reviewer #3	**Tobacco Toxicology and Chemistry** The section is well-organized in that different toxicological effects and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses that aid interpretability. The discussion of the studies is clear and objective. **Physiology** The section is well-organized in that different physiological effects and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses that aid interpretability. The discussion of the studies is clear and objective. **Biomarkers** The section is well-organized in that different biomarkers of exposure and types of studies are reviewed separately. The studies were adequately summarized in terms of their research designs, findings, limitations and statistical analyses (e.g., controlling for possible confounders) that aid interpretability. The discussion of the studies is clear and objective. **Patterns of Smoking** I would recommend naming this section "sociodemographic patterns of smoking." A more explicit rationale for the inclusion of this section is needed, since it does not quite fit into the scientific determination paradigm above. That is, the sociodemographic variables cannot be defined as an "impact x!" The rationale for including this section is that, if menthol in cigarettes is found to be harmful, then it can be useful to know what groups are most likely to smoke menthol, for instance in order to target interventions to reduce menthol cigarette smoking. Otherwise, the section is well-organized in that the different surveys are reviewed separately. The surveys were adequately summarized in terms of their research designs, findings, limitations and statistical analyses (e.g., controlling for possible confounders) that aid interpretability. The discussion of the surveys is clear and objective. **Marketing and Consumer Perceptions** This section needs a better rationale for its inclusion. In brief, what is being defined as "x" in terms of the	

	scientific determination paradigm? In one conclusion, the "impact" x relevant to this section appears to be "brand preference" and the putative causal variable appears to be "marketing of menthol cigarettes." In the other conclusion, the impact x appears to be "use of menthol cigarettes" and the putative causal variable appears to be "consumer perceptions of harm." The report needs to note that smoking menthol cigarettes is only a relevant "impact" if menthol in cigarettes is shown to be harmful, which is the issue under examination in most of the other parts of the report. While smoking is already known to be harmful, the question is whether smoking menthol cigarettes increases such harm from smoking. Since the product under examination is menthol, this section of the report should derive a conclusion pertaining to "brand preference for menthol cigarettes," not just "brand preference." If there is no reference to menthol in a conclusion, it does not seem relevant to the report. But in that case, would the two impacts really be the same impact – and could these two aspects of the literature review be combined to draw a conclusion about the impact of marketing on "use of menthol cigarettes"- since "brand preference for menthol cigarettes" would just be a proxy measure for menthol smoking (i.e., if they prefer and buy the menthol brand, they smoke it). There is a problem in how "receptivity to advertising" may be defined in some of the studies. The report says this might include "brand preference." (p. 37, 4th paragraph). But "brand preference" is also an impact variable in this section. This could lead to tautological results ('circular reasoning"). The report should ensure that conclusions in this section are not partially based on this fallacy. "Receptivity to advertising," although a term that appears in the literature, is a misleading term. It would be better to term this concept "exposure to and/or engagement in advertising." Since "receptivity" can be interpreted as synonymous with "susceptibility." My thesaurus gives "receptiveness" as a synonym for susceptibility. Yet in some of the advertising research literature, the two terms are distinct; it's confusing. **Initiation of Smoking** The above term includes two distinct behaviors (impacts) – termed in the report "first smoking experience" and "progression to regular smoking." It would be clearer if the report drew separate conclusion about these two distinct impacts. I also think that the lay public would interpret "initiation of smoking" as referring only to "first smoking experience." **Tobacco Dependence** The section is well-organized in that each measure of dependence is reviewed separately. The studies were adequately summarized in terms of their research designs, findings and statistical analyses that aid interpretability (e.g., control variables).	

	Smoking Cessation For this section and perhaps for all sections, it would help to present a 1 page tabular scorecard indicating which individual studies support or do not support the menthol vs. no menthol condition as a cause of the impact, in this case smoking cessation. Since the results of the studies are mixed, it becomes a matter of judgment as to what percentage of the reviewed studies must provide evidence to justify a determination of "likely associated" and what percent must provide evidence to justify a determination of "associated." Now it's understood that these determinations are not made solely based on numbers, but the numbers are clearly major part of the determination and should be better and more conveniently summarized. Since some studies provide "stronger" causal evidence than others, that can be taken into account in drawing a conclusion. **Disease Risk Relative to Non-mentholated Cigarettes** The section is well-organized in that each category of disease is reviewed separately. The studies were adequately summarized in terms of their research designs, findings and statistical analyses that aid interpretability (e.g., control variables). The discussion of the studies is objective.	
Reviewer #4		
Reviewer #5	The only instance I observed where a study's findings were not characterized appropriately relates to a non-peer reviewed analysis by Muscat reported on page 76. The report indicates that a "marginally statistically significant lower risk of lung cancer among current menthol smokers" was found, but the p-value was less than .05, indicating a "significantly lower risk" at the conventional level of statistical significance, which appears to have been used throughout the remainder of the report. Also, the discussion of Squier et al. (2010), which runs from the bottom of page 16 to the top of page 17, includes possible implications of the study's findings. Since most of these implications do not appear to be supported by the other studies noted throughout the report (e.g. there is no evidence to suggest that smoking menthol cigarettes leads to increased cancer risk as compared against nonmenthol cigarettes), it does not seem appropriate to include them.	
Reviewer #6	**Toxicology and Chemistry** The paragraph on smoke chemistry indicates few effects on the composition of smoke as a function of menthol, although it indicates evidence for the production of PAH's from burning menthol. It may be worth pointing out that the studies reported in the next section, indicating that menthol was not itself active in any of the mutagenesis assays, did not address the pyrolysis products. The next paragraph summarizing the Rabinoff 2007 article, may overstate the results of that article, since the "complex interaction with nicotine" was just an unreferenced line in a table. Finally, there is one recent article that should be cited, although it does not provide any novel insights at least it used more modern techniques to evaluate the smoke	

	constituents: Gordon et al., Chem Res. Toxicol 2011. Related to the comment above on pyrolysis products is that the first paragraph of the next section (middle of pg. 9) on antiproliferative effects, states that "as has already been stated, menthol smoke condensate from burned tobacco is genotoxic," but this statement is not referenced, and it was not obvious to which previous citation this statement refers. Importantly, it is not clear whether that article actually compared smoke condensates from menthol and non-menthol cigarettes. (It appears possible that the article/articles are actually referenced later, in the first full paragraph on page 10, in the in vitro toxicity section). The subsequent statement, that "it should not be assumed that a compound that had anti-proliferative effects in a tumor cell line or even a transfected animal model would definitely have oncolytic effects in humans" is certainly true, but it is unclear to what "transfected animal model" the statement refers. Also in this section, the reference to the Sidell article (1991) indicating a down regulation of IL-6 receptors in a myeloma cell line is interesting, but the relationship to proliferative activity is unclear. Instead, this has potential ramifications for immune/inflammatory responses, processes not otherwise addressed in the document, but of possible importance (e.g., Juergens et al., 1998: Eur. J Med. Res. 6;3 :539-45; and Marcuzzi et al., 2010, Int. Immunopharmacol 10:639-42.) **Physiology** There seem to be some inconsistencies between the reports of menthol via the TRPM8 receptor in this section versus the Toxicology and Chemistry section. Specifically, in the Toxicology and Chemistry section, menthol is reported to act as an agonist to this receptor, activating Ca influx, while in the physiology section, it is reported to inhibit MCh and K+ induced Ca influx (paragraph 3 under Physiology), and later in Mechanisms of Menthol Action as an antagonist of DHP Ca2+ channels, and possibly even as a direct agonist for opioid receptors (Analgesic Effects section). If the suppression of Ca influx was (or might have been) due to desensitization, this should be clarified. Alternatively, the TRPM8 receptor was unknown at the time of the Sidell article, and the possibility of crosstalk among these receptors could account for the observations. The Industry Assessment of Menthol Effects subsection appears primarily to reflect the effect on COHb, NNAL, and nicotine metabolism, and might be better kept with the Biomarkers section in which they are also described. I suggest reorganizing the subsections in the Physiology section to combine the into subsections on "Sensory Effects" (paragraph one of the Physiology subsection, and the Cooling Effects section), "Receptor-Mediated Mechanisms" incorporating the second and third paragraphs of the Physiology section, the Analgesic Effects subsection, and the Mechanisms of Menthol Action, followed by the Menthol and TSNAs subsection (possibly renamed to "Metabolic Effects"), then the Effects of Menthol on Smoking Topography subsection and the Industry Assessment of Menthol Effects section.	

	Lastly in this main section, I suggest changing the last sentence from ". . .menthol is likely associated with reduced nicotine irritation" to ". . .menthol is likely associated with reduced irritation from smoke constituents." **Biomarkers** As mentioned above, there is some redundancy between this section and the Physiology section. There is also considerable redundancy between the sections on Biomarkers of Exposure to CO and Biomarkers of Exposure to Nicotine. I suggest combining these two sections into "Biomarkers of Cigarette Smoke Exposure," which would eliminate the need to cite the Ahijevych, Clark, and Williams studies twice. In both of these sections, the description of the Clark (1996) study states that the comparisons between White and African American smokers were adjusted for race. Should this be after correction for gender, since it is not possible to detect a racial difference after "adjusting for race"? Similarly, in the first full paragraph on page 23, the effects of cotinine as a function of menthol/nonmenthol cigarette use are said to be "adjusted for . . . menthol/nonmenthol use." One additional comment in the section on Disease Risk: I was surprised not to see more information on the impact of menthol on the risk for COPD (emphysema and chronic bronchitis). However, I did search for this type of information and it does not appear there is anything reported. If that's true, I think it would be appropriate to call these out specifically as areas for which data does not currently support or refute effects of menthol. Two additional final points. First: I think it might be helpful to include some overview of the possible hypotheses regarding the potential impact of mentholation on health effects, possibly in the Executive Summary. In my view, these include the following: 1. Menthol or its combustion products could have adverse effects (toxicity or addiction potential) independent of other tobacco-associated chemicals. 2. Menthol could have additional independent effects such as anti-inflammatory properties or anti-proliferative properties. 3. Menthol, by reducing the irritation factor, could lead to increased cigarette consumption (including initiation) and therefore increase risk. 4. Menthol, by altering metabolism of nicotine, could prolong the physiological effects of a single cigarette, reducing cravings and therefore reducing smoking and the associated health risks. 5. Menthol could alter metabolism of other smoke-associated chemicals, either increasing or decreasing their half-lives and thus affecting their toxic effects. Second, there are several sections for which a summary TABLE would be helpful, particularly those for	

	which there seemed to be evidence both for and against differences.	
Reviewer #7	I was particularly concerned with data on subjective effects of menthol on the smoker's perceptions and ease of beginning smoking. Based on my own observations on the conditioned aspects of addiction, I was alert for the discussion of conditioned cues and learning. I found that my area of research was well covered. There were discussions of smoking initiation, treatment methods, relapse issues and clinical outcome studies. Although effects on lung physiology and function and on biomarkers associated with smoking were given adequate attention, significant effects of menthol on these measures were not found.	
CHARGE QUESTION 3: For each section that you reviewed, were the conclusions appropriate given the available evidence? Please be as specific as possible as to why or why not.		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	**Marketing and Consumer Perceptions** I think there is a field of tobacco marketing research that is lacking from this section. It is mentioned in the conclusion, but no review of the literature is provided for any existing evidence on the effect of point-of-sale marketing strategies on smoking behavior. Given that this accounts for a significant percentage of current tobacco marketing expenditures. It is certainly an important to examine its impact on smoking behavior in general and differences between menthol and non-menthol smoking and advertising. If a literature review was conducted and insufficient evidence was found, then this should be incorporated into the report. I also think the conclusion written about insufficient evidence to support that the use of menthol cigarettes is associated with perceptions of harm is written too strongly given that only 3 articles are included in the literature review. Given the limited evidence I also don't think it's appropriate to state that "consumer perceptions in relation to menthol vary across age, race, gender, and education level." It could be written to show there is limited evidence or something along those lines.	
Reviewer #2	While most of the conclusions on either "likely associated" or "not likely associated" make sense, some do not. Studies reviewed in each section show some mixed findings because some of them support the conclusion while others do not. Some studies have reversed findings. At the same time, some studies may be more rigorous than others because they are either large-scale, have follow-up studies, or are nationally representative. But even such rigorous studies have weaknesses/limitations. For this reason, it is important that the authors specify which criteria they used to weigh the evidence that leads to the conclusion of either "likely" or "not likely" associated with menthol in cigarettes. If readers do not know the specific criteria, they might not agree with the conclusion provided in each of the sections. For example, the sections on "biomarkers," "initiation," "dependence," and "cessation" review studies that show mixed findings. But the conclusion for biomarkers was "likely not associated with menthol in cigarettes," while the other sections conclude "likely association." Again, if the report does not specify clear rationales for what studies are weighted more, shouldn't some mixed findings lead to a scientific determination of "not sufficient to support a conclusion"? In this sense, Section E (marketing and consumer	

	perception) seems to have a reasonable determination because it concludes, "the evidence is not sufficient to support a conclusion that consumer perceptions of harm are associated with the use of menthol cigarettes" (p.42). What therefore need to be provided are clearer and more convincing rationales for such conclusions. To do so, the writers could carry out two revisions: (1) clearly indicate what was weighted (e.g., Were nationally representative studies weighted more than regional studies? Were longitudinal studies weighted more than cross-sectional studies? Or were the judgments simply based on counting whether more or fewer studies support the conclusion?); (2) provide a table that summarizes all the studies reviewed. In such a table, rows could indicate each of the studies, and columns could include sample, findings (support, not support), control variables, DVs, method, etc. If readers are given such a table, it would make it easier for them to see which studies did or did not support the conclusion. Otherwise, they would have to not only read the entire section but also picture such a table in their heads.	
Reviewer #3	**Tobacco toxicology and chemistry** The conclusion seems to objectively reflect the data. **Physiology** The report states: "Overall, the evidence is sufficient to conclude that, by acting primarily through receptors on sensory nerves, menthol is likely associated with reduced nicotine irritation." (p. 18). However, there was only one paper that I could see which directly addressed that issue (Dessirier, 2001). The conclusion might be framed too narrowly here. The Executive Summary states: "There are some in vivo and in vitro studies that show menthol has cooling, desensitizing, and proanalgesic effects….From the available studies, the weight of evidence supports the conclusion that changes in physiology are likely associated with menthol in cigarettes." (P. 4). This seems to accurately summarize the research – a variety of physiological effects are reported. However, the conclusion that: "Menthol acts primarily through receptors on sensory nerves" (p. 4) seems inaccurate, as additional loci or sites of action were reported. For instance, "The data suggested that smoking menthol cigarettes may lead to inhibition of nicotine metabolism" (p .16, 5th paragraph) and "significantly increased the tissue reservoir formation in porcine esophageal mucosa" (p. 16, 6th paragraph). I think the conclusions need to be rewritten for this section to take the full range of findings into account. What is missing from the research base on physiology is any consideration of differences by age or by race, especially African American vs. White. This is because there are strong age and racial differences in menthol cigarette preferences, but these are largely unexplained thus far. It would fill in some "missing gaps" to know whether there objective differences in physiologic reactions to menthol or menthol cigarettes by age or race.	

	Biomarkers The conclusion seems to objectively reflect the data. The additional secondary analyses adjusting for possible confounders performed by FDA and RTI were useful in leading to a reasonably definitive conclusion. These analyses might be further refined by conducting a statistical sensitivity analysis. For instance, the report states: "The observed statistically significant differences in biomarkers of exposure (unadjusted data) between menthol and nonmenthol smokers may be due to differences in demographic or smoking behavior characteristics between menthol and nonmenthol smokers." (p. 24, 2nd paragraph). It might be possible to identify which of the control variables contributed to eliminating the differences observed in the unadjusted analysis, and which did not. **Patterns of Smoking** The conclusions seem to objectively reflect the data. **Marketing and Consumer Perceptions** This section was difficult to evaluate because the questions driving the section were not explicitly articulated at the start of the section. There seem to be three scientific determinations ("conclusions") at the end of the section, but only one is stated using the term "weight of evidence." And only 2 of the 3 conclusions appear in the Executive Summary ("perception of harm" appears to be omitted). The main conclusion is: "From the available studies, the weight of evidence supports the conclusion that brand preference among adolescents and the African American community is associated with the marketing of menthol cigarettes." I think is this intended to state, marketing strategies are a cause of brand preference. However, it appears that pre-existing preference for menthol among these groups is a given, and that an alternative explanation of the correlation would be that advertising is being targeted to the known preferences of the groups - adolescents and African Americans (AAs) tend to like menthol cigarettes and so the advertising to them emphasizes menthol brands. There is much advertising of this type generally and it makes sense. (Of course it is unknown why AAs tend to prefer menthol, but its doubtful companies and advertisers decided to create such a preference uniquely among AAs and that they would have the means to do so.) There may be some studies that enable the direction of causality to be disentagled, but merely having longitudinal data is not a panacea for this. For instance, it may be the advertising emphasizing menthol at time 1 is associated with greater menthol brand preference at time 2 – but one also has to examine whether brand preference at time 1 is associated with advertising emphasizing menthol at time 2. That is, disentangling causal direction is this way may require some very careful and sophisticated analysis – are there longitudinal studies which have done that? As presented, I am doubtful that the weight of the evidence supports the conclusion above. **Initiation of Smoking** In terms of "first smoking experience," this reviewer agrees that the research cited (p. 48) is not sufficient to	

	support a conclusion that availability of menthol cigarettes is associated with earlier first smoking experiences. (Incidentally, I only saw 3 studies reviewed, not 4.). That is, the report concluded: "There is no indication that menthol smokers experience cigarette smoking any earlier or later than nonmenthol smokers"(p. 51, third paragraph). But at the end of the conclusion section, a different conclusion seems to be reached, based on inferences from a different type of data - epidemiological studies: "…. the weight of evidence supports the conclusion that the initiation of cigarette smoking is likely associated with menthol in cigarettes" (p. 52, first paragraph) This reviewer does not agree with the report's interpretation of the epidemiological smoking prevalence studies to support such a conclusion about initiation. These studies show that "younger, newer smokers prefer menthol at levels far above that of the general population; a finding that is generally consistent across racial/ethnic groups." (p. 52). These data would support a role for menthol in initiation if younger, newer smokers would be less likely to progress to regular smoking if menthol cigarettes were unavailable. However, a preference for a certain type of cigarette does not necessarily imply that the person would not smoke at all or even smoke less. At one time consumers preferred tail fins on cars, but had tail fins not been available, that does not imply that fewer cars would have been sold or that consumers would have driven them less. It is probably true that beef eaters prefer steak, but it's doubtful that the unavailability of steak would result in fewer people taking up beef eating or that they would eat less beef. Of course the consequences of any behavior could be made sufficiently noxious or expensive that people would avoid it, but there does not seem to be sufficient evidence that unavailability of menthol cigarettes, which are definitely preferred by certain subgroups if available, would reduce the rate of first smoking experience or progression to regular smoking (or more exactly, that the availability of menthol cigarettes increases those rates over what the rates would be without their availability). In term of "progression to regular smoking as the impact," the studies that should carry the most weight in terms of making causal inferences are the longitudinal studies, although as I remark elsewhere it also depends on the specifics of the design and how appropriately such data are analyzed. Regarding these studies, I agree with the report that "data regarding age of onset of regular smoking are mixed." (p. 51). **Tobacco Dependence** My only suggestion here would be for the report to consider the possibility that degree of dependence might affect choice of menthol or not. For instance, someone who needs to smoke a lot (or gets to that point) may prefer or switch to menthol because of the "soothing" effect that it has for some people. The conclusion would be stronger if there were testimonial data on why people choose menthol or switch to menthol. The report says it does not review the "switching" data because it is difficult to interpret for understanding initiation (p. 46), but qualitative data on this to see if relates to increased dependence might shed additional	

	light. The conclusion would also be stronger if there were any theory or data on the mechanism of action that results in menthol increasing the probability of tobacco dependence. The conclusion would also be stronger if the results for different measures of dependence were not somewhat mixed. But nonetheless, it appears reasonable to draw the "likely association" conclusion as the report did. More – and improved! - research on this key issue is definitely needed, however. **Smoking Cessation** There seems to be a typo in the conclusions, e.g., the sentence "From the available studies, the weight of evidence supports the conclusion that increased dependence is likely associated with menthol in cigarettes, especially among African American menthol smokers." (p.71, my italics). Shouldn't that say, "success in smoking cessation?" The report seems to imply that studies that adjust for dependence factors (an over adjustment for the purpose of this section) should be considered as providing "evidence" for menthol reducing rate of cessation. What the probable over adjustment has done is make the result uninterpretable, since we do not know whether menthol would be associated with cessation without that adjustment for dependence. Since so many studies need to be excluded from consideration due to this probable over adjustment, and since the result of the others are mixed, the most conservative conclusion seems to be, based on a count of studies alone, that the evidence does not support a conclusion of an association (a causal link between menthol and success in cessation). However, I do think the reanalysis done by the FDA of the CPS-TUS dataset is useful and it does show an association. Note that the OR for whites and AAs is similar – I assume the AA association is not significant due to the smaller sample size for the AAs. Thus it can be difficult to interpret racial difference statistics based on statistical significance alone - I would give more weight to the effect sizes when doing subgroup comparisons. Ask the question – would this effect size be "significant" if the sample size were the same as for the other subgroup? If we add the CPS-TUS result above, there may be barely enough evidence to justify concluding that there is a likely association between cessation and specifically AA menthol vs. non-menthol smokers. **Disease risk relative to non-mentholated cigarettes.** The conclusion seems to objectively reflect the data. Again, I would suggest a 1-page table that lists each study and indicates the scientific determination of causation for that study – does it support an association or not?	
Reviewer #4	**Executive Summary** As noted above, I am concerned that the approach to handle the relationship between "dependence,"	

	"cessation," and "disease risk" has not well considered. Is the question a matter of cessation independent of dependence, and also disease risk independent of both dependence and cessation? I am concerned that for cessation it appears to take the position that cessation is there because of a greater dependence (i.e., not worrying about independence of effects), but concludes that menthol is not associated with great disease risk despite previously concluding that it is associated with both dependence and cessation (i.e., now apparently considering the independent effect). **Science Reviews** **Toxicology and Chemistry** As noted above, I thought the data were clearly and fairly presented. **Physiology** The statement "Smokers enjoy the cooling sensation of menthol and cigarettes and menthol is perceived as reducing the irritation and harshness of smoking" is made. Although this seems obvious, I am not sure that it is supported by the (largely chemical/physiological) data that is presented. Shouldn't this conclusion be moved to the section on "Marketing and Consumer Perceptions"? It seems that statements of "enjoyment" and the reasons for enjoyment would require marketing research and opinion data, which I do not think is presented. **Biomarkers** Fair and balanced conclusion. **Patterns of use** The conclusions are appropriate, but very poorly presented. Over half of the conclusion apologizes for the nature of the (self-reported) data. These apologies take away much of the impact of what is clearly some of the strongest evidence for any of these sections on science reviews. **Marketing and Consumer Perceptions** Without doubt, this is the most challenging section. I feel that the authors did a great job documenting that companies target marketing of menthol cigarettes to special groups. However, the conclusion that this marketing is likely responsible for the brand preference may be a bit of an overstatement. The causation of this association is more problematic than in any other section. For example, it is more clear that young smokers tend to use menthol cigarettes (perhaps because of reduced harshness when "learning" to smoke). It would then be natural for the tobacco companies to advertise to this group to have them select their specific menthol cigarette relative to other company's products. That is, it is not the menthol that is related, but the other aspects of the company's brand of menthol. A similar argument could be made to the targeted	

	marketing that is clearly made to AAs. As such, I am not convinced of this conclusion. **Initiation** This is a difficult section that is well-written. It clearly makes the case that younger newer smokers are more likely menthol users. The conclusion discussed the limitations of data being self-reported (which I see as only a minor limitation), but fails to acknowledge that this could be a cohort effect. For example, for some other reason it could be that young people are attracted to menthol brands, and it is not the menthol that makes it easier to for initiation. I am comfortable with the conclusion that initiation is still "likely" associated with initiation; however, acknowledging this possibility would be fairer. **Dependence** Very well presented and fair. The evidence appears overwhelming. **Cessation** Please see the concerns on from Question #3 above (regarding independent effect versus pathway effect). **Disease risk** I do think the conclusions of the impact of current smoking are reasonable, however, again if menthol use is associated with both dependence and cessation, one would assume that it has to be associated with disease risk.	
Reviewer #5	The report's conclusion pertaining to initiation is not as firmly rooted in the evidence as its other findings. Importantly, this appears to be due to the lack of consideration given to key evidence. In other words, the conclusion appears to be appropriate, but it requires the discussion of additional evidence. In addition, the report offers inconsistent conclusions about the influence of menthol on cessation; importantly, this inconsistency can be easily addressed via a minor revision to the main text. With respect to initiation, the report's conclusion that "the initiation of cigarette smoking is likely associated with menthol in cigarettes" appears to be based primarily on the observation of differential preferences for menthol as compared against nonmenthol cigarettes for middle and high school students, especially African-Americans. However, as noted in the previous section on marketing and consumer perceptions, this differential usage pattern can be explained by differential targeting – i.e., menthol cigarettes are marketed more heavily toward young adult and African-American segments. Therefore, an important question is: does targeting fully explain the differential usage pattern or is there something about the presence of menthol per se that leads to disproportionate use by first-time smokers? The best answer to this question would examine whether differences in ad spending fully account for the market share of menthol cigarettes. If so, then the initiation of cigarette smoking would be likely associated with the message, rather than the menthol. To my knowledge, the data needed to provide the best answer to this question are not available in the public domain.	

	Therefore, we are left to consider the second best answer to this question, which involves examining what is known about consumer preferences for menthol cigarettes. According to Yerger (2011), Kreslake (2008a), and other studies cited by these articles, tobacco industry documents show that many menthol smokers specifically seek the sensation of menthol without the harshness of tobacco smoke and the irritating qualities of nicotine. Therefore, to the extent that available evidence links middle and high school students to a similar preference profile, the conclusion that "the initiation of cigarette smoking is likely associated with menthol in cigarettes" is warranted. With respect to cessation, the conclusion in the executive summary "success in smoking cessation is likely associated with menthol in cigarettes, especially among African American menthol smokers" (p. 6) is not consistent with the conclusion in the main document text "increased dependence is likely associated with menthol in cigarettes, especially among African American menthol smokers" (p.71). Given that the pertinent section of the main text discusses cessation, the former conclusion seems more appropriate.	
Reviewer #6	In the three sections on which I focused, the conclusions were appropriate. Although I didn't review the other sections in as much detail, the conclusions also seemed appropriate, except for the Marketing and Consumer Perception section where there is a discrepancy between the conclusion reported in the executive summary and the actual conclusions paragraph in the section.	
Reviewer #7	The review was divided into specific categories that could be evaluated by the existing peer reviewed literature. I was convinced that the disease burden for smokers of menthol cigarettes was not significantly increased compared to other smokers. Where the review was most persuasive in my opinion was the evidence for menthol in facilitating the initiation of smoking and the difficulty in quitting. The data were most persuasive for minority groups, particularly African Americans. Based on the literature and on the data from smokers in treatment, it may be that the menthol contributes to a complex conditioning stimulus that becomes linked to nicotine reinforcement. Certainly ease of initiating is another factor that has been cited and addressed in some of the studies that I reviewed. Thus, my own opinion of the risks associated with menthol found in some brands of cigarettes is that the practice of including menthol produces a significant hazard. This is most clearly evident from studies of adolescents and minorities.	
CHARGE QUESTION 4: Are you aware of additional publicly available information which should have been included? If so, please specify.		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	**Marketing and Consumer Perceptions** J. Rising and L. Alexander. Marketing of menthol cigarettes and consumer perceptions. Tobacco Induced Diseases (2011); 9 (Suppl 1):S2.	

OY Lee and SA Glantz. Menthol: putting the pieces together. Tobacco Control (2011); 20 (Suppl 2):ii1-7.

Klausner K. Menthol cigarettes and smoking initiation: a tobacco industry perspective. Tobacco Control (2011); 20 (Suppl 2): ii12-19.

Seidenberg AB, Caughey RW, Rees VW, Connolly GN. Storefront cigarette advertising differs by community demographic profile. American Journal of Health Promotion. (2010) ; 24(6): e26–e31

Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP. Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods. Nicotine and Tobacco Research (2011). epub ahead of print.

Henriksen L, Schleicher NC, Feighery EC, Fortmann SP. A longitudinal study of exposure to retail cigarette advertising and smoking initiation. Pediatrics (2010);126(2):232-8.

Shadel WG, Tharp-Taylor S, Fryer CS. How does exposure to cigarette advertising contribute to smoking in adolescents? The role of the developing self-concept and identification with advertising models. Addictive Behaviors (2009);34(11):932-7.

Ruel E, Mani N, Sandoval A, Terry-McElrath Y, Slater S, Tworek C, Chaloupka F. After the Master Settlement Agreement: Trends in the American Retail Environment. Health Promotion Practice (2004); S5(3): 99S-110S.

Slater SJ, Chaloupka FJ, Wakefield M, Johnston LD, O'Malley PM. The Impact of Retail Cigarette Marketing Practices on Youth Smoking Uptake. Archives of Pediatrics and Adolescent Medicine (2007); 161(5): 440-445.

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Jameison P, Romer D (2001). "What do young people think they know about the risks of smoking?" In: P. Slovic P (ed.). Smoking: risk, perception, and policy. Thousand Oaks, CA: Sage Publications, 51-63.

Pechmann C and Knight S (2002). An experimental investigation of the joint effects of advertising and peers on adolescents' beliefs and intentions about cigarette consumption. Journal of Consumer Research. 29: 5-19.

	Romer D, Jameison P (2001). "Advertising, Smoker Imagery, and the Diffusion of Smoking Behavior." In: P. Slovic P (ed.). Smoking: risk, perception, and policy. Thousand Oaks, CA: Sage Publications, 127-187. Shore TH, Tashchian A, Adams JS (2000). Development and Validation of a Scale Measuring Attitudes Toward Smoking. Journal of Social Psychology; 140: 615-623.	
Reviewer #2	Section E, on marketing and consumer perception, reviews many studies on brand preferences, receptivity to advertising, marketing strategies (particularly for youth and minorities), and consumer perceptions. Although not directly related to menthol cigarettes, a few important studies that touch upon these topics are missing in the report. To cite just a few examples: **On susceptibility/receptivity to tobacco advertising and marketing** Altman, D. G.., Levine. D. W., Coeytaux, R., Slade, J., & Jaffe, R. (1996). Tobacco promotion and susceptibility to tobacco use among adolescents aged 12 through 17 years in a nationally representative sample. American Journal of Public Health, 86(11), 1590-1593. DiFranza, J. R., Wellman, R. J. Sargent, J. D., Weitzman, M., Hipple, B. J., & Winickoff, J. P. (2006). Tobacco promotion and the initiation of tobacco use: Assessing the evidence for causality. Pediatrics, 117(6), e1237-e1248. Gilpin, E. A., Pierce, J. P., & Rosbrook, B. (1997). Are adolescents receptive to current sales promotion practices of the tobacco industry? Preventive Medicine, 26(1), 14-21. **On perception and regulatory implications about "light" cigarettes:** Canova, D., Myers, M. L., Smith, D. E., & Slade, J. (2001). Changing the future of tobacco marketing by understanding the mistakes of the past: Lessons from "Lights." Tobacco Control, 10(1), 43-44. Gilpin, E. A., Emery, S., White, M. M., & Pierce, J. P. (2002). Does tobacco industry marketing of "light" cigarettes give smokers a rational for postponing quitting? Nicotine & Tobacco Research, 4 (Supplement 2), 147-155. Kropp, R. Y., & Halpern-Felsher, B. L. (2004). Adolescents' beliefs about the risks involved in smoking "light" cigarettes. Pediatrics, 114(4), 445-451.	

	On tobacco marketing and claims in advertising that target youths: Krugman, D. M., Morrison, M., & Sung, Y. (2006). Cigarette advertising in popular youth and adult magazines: A ten-year perspective. Journal of Public Policy & Marketing, 25(2), 197-211. Krugman, D. M., Quinn, W. H., Sung, Y., & Morrison, M. (2005). Understanding the role of cigarette promotion and youth smoking in a changing marketing environment. Journal of Health Communication, 10(3), 261-278. Paek HJ, Reid LN, Choi H, Jeong HJ. Promoting health (implicitly)? A longitudinal content analysis of implicit health information in cigarette advertising, 1954-2003. J Health Commun. 2010 Oct;15(7):769-87. Paek HJ, Reid LN, Jeong HJ, Choi H. Five Decades of Promotion Techniques in Cigarette Advertising: A Longitudinal Content Analysis. Health Marketing Quarterly. 2012 (in press). Pierce, J. P., Choi, W. S., Gilpin, E. A., Farkas, A. J., & Berry, C. C. (1998). Tobacco industry promotion of cigarettes and adolescent smoking. Journal of the American Medical Association, 279(7), 511-515.	
Reviewer #3	Not aware of any.	
Reviewer #4	**Executive Summary**: Not applicable. **Science Reviews** Toxicology and Chemistry: none known. Physiology: none known. Biomarkers: none known. Patterns of use: none known. Marketing and Consumer Perceptions: none known. Initiation: none known. Dependence: none known. Cessation: none known. Disease risk: none known.	
Reviewer #5	I am not aware of any additional information in the public domain which should have been included.	
Reviewer #6	A recent issue of Tobacco Control (Vol. 20, suppl. 2) was focused on mentholated cigarettes. Although many of the articles appear to be reviews, and therefore contain much of the same information as the current document, there are some additional new data that should be incorporated. One new article is also available related to the chemistry of smoke from menthol and nonmenthol cigarettes:	

	Gordon et al., Chem Res. Toxicol 2011 Sep 19. [Epub ahead of print] Effect of Cigarette Menthol Content on Mainstream Smoke Emissions.	
Reviewer #7	To my knowledge, the overall review was comprehensive and inclusive.	
CHARGE QUESTION 5: Provide any additional comments including editorial suggestions, not addressed in the previous points (1-4).		
NAME	**COMMENT**	**RESPONSE**
Reviewer #1	I have included all my comments in other sections of this document.	
Reviewer #2	In Section B, Physiology, the conclusion could include a statement that summarizes any noticeable differences between industry-sponsored studies and independent (academic) studies. In Section D, Patterns of Use, the term "brand" is consistently used to indicate "menthol, nonmenthol" (2 lines up from the bottom on p. 28). This use of the term seems inaccurate. According to the American Marketing Association, "brand" typically refers to a particular "name, term, design, symbol, or any other feature that identifies one seller's product or service that can be differentiated from those of other sellers." Thus, menthol vs. nonmenthol should not be "brand" but rather "type of cigarette product." It may be okay to say "brand" when referring to a specific menthol product—e.g., "exclusive brand (Newport or Kool)" (p.31). But other than that, all the labels of "brand" in Section D should be changed to "type." In Section H, Cessation, the conclusion should be reorganized as follows: first, provide a summary of the reviews; then, state key insights/interpretations of the reviews; and finally, provide the determination statements based on the weight of evidence. These three important pieces of information were buried among redundant mentions of study limitations.	
Reviewer #3	I think I've addressed everything.	
Reviewer #4	None needed.	
Reviewer #5	There are some minor stylistic differences between sections that should be addressed to ensure consistent presentation of the available evidence. Specifically, the sections pertaining to "Physiology" and "Biomarkers" use imprecise adjectives to quantify the available evidence (e.g., "a few studies," "some studies," "several articles"). The other sections, which specify the precise number of articles and enumerate additional non-peered reviewed analyses, should be emulated.	
Reviewer #6	Although it's almost become a cliché, it is clear more research is needed. This is particularly true in the context of the combustion products of menthol (with or without the presence of tobacco combustion products) and for the effects on the two primary subclasses of COPD.	
Reviewer	As a therapist involved for many years in the treatment and study of smokers, I would like to see more data	

#7	on the effect of menthol on quitting. An obvious problem is that there are so many variables that influence success rate of treatment that it is very difficult to isolate any one class. The information on ease of starting smoking is very important because most begin as adolescents and there is growing clinical data indicating that young people can become dependent very rapidly as compared to adults. If menthol eases the irritation experienced by new smokers, this could be an important factor in increasing the proportion that become dependent.			
III. SPECIFIC OBSERVATIONS				
NAME	**PAGE**	**LINE**	**COMMENT**	**RESPONSE**
Reviewer #1	36	1580-81	The report states that "econometric studies report teens' brand preference is three times more sensitive to effects of cigarette ads than adults" . However it does not contain a literature review of variation in advertising across community SES and demographic characteristics. There is some evidence (e.g. Seidenberg et al. 2011) suggesting that cigarette advertising in low income, minority communities is more prominent and more likely to promote menthol cigarettes.	
	37	1582	"Top three most heavily advertised brands" when the cited articles were published in the 1990s these brands were Marlboro, Camel and Newport. It would be useful to cite more recent data showing brand preferences and advertising shares. If MTF still includes the question on brand preference it would be possible to look at more recent information, at least for adolescents.	
	37	1596-97	"O'Connor (2005) found Newport's popularity declines dramatically after age 26." Is this at a similar rate across all racial/ethnic groups? Is it possible to determine this if it was not included in the original article?	
	37	1597-99	"Newport is overwhelmingly preferred by African Americans, with 41% of African American adults and 75% of African American youth reporting preference for Newport cigarettes."-- Is there less of a decline in African American youth switching to non-menthol cigarette brands as they move into adulthood than white/Hispanic youth?	
	37	1602-05	"Additionally, there is evidence to suggest regional differences, with more teens reporting a preference for Newport in the Northeast than in the West (CDC, 1994; Johnston et al., 1999). CDC (1994) suggests regional preferences for Newport combined with a decrease in overall advertisement expenditures by Newport suggests this brand may rely more heavily on a regional marketing strategy than a national strategy." Given the dates of the research cited here, this may not be true anymore, Ruel et al. 2004 found significant increases in the price of Newport cigarettes from 1999-2002	

			coupled with a decline in cigarette promotions from 2001-2002.		
	37	1619	What about including the effects of point-of-sale cigarette advertising on youth smoking? (e.g. Slater et al. 2007 found an increase in the pervasiveness of point-of-sale advertising increased the likelihood that adolescents would experiment or initiate smoking, with younger youth being more influenced by increased levels of advertising.		
	39	1699	Could add here the Seidenberg et al. citation listed above.		
	40	1748	I would add to the document that White et al. controlled for household income in their models (which was insignificant). Is it that menthol smokers take advantage of price promotions more often, or are they targeted more often with promotions? This is unclear from the way the promotional questions are reported in the study.		
	40	1760	The Rising and Alexander review article should be added to the Consumer Perceptions section.		
	41	Section on Consumer Risk Perceptions	I think this section needs more of an introduction about how advertising can affect perceptions to better integrate this section with the marketing evidence.		
	42	1811-1813	You state, “It is difficult to determine the strength of the relationship between marketing and consumer perceptions and its impact on behavior due to the limitations in study designs included in this literature review.” However the three articles cited on consumer perceptions don’t actually examine the affect of marketing on perceptions. See Lee and Glantz (2011) for a better example of this. There is also existing literature that examines the impact of tobacco advertising on smoking risk perceptions, which may help improve this section (citations listed above).		
	42	1827-29	You state, “In addition, it is likely that the standard marketing mix approach of price, promotion, product, and place has been used to drive menthol cigarette preference among the urban African American community.” I don’t think you provide enough evidence in the review to support this comment. You need to add a review of the associations between point-of-sale marketing and smoking behavior to the paper.		
	42		You state, “The evidence is not sufficient to support a conclusion that perception of harm is associated with menthol in cigarettes or the use of menthol cigarettes.” The language in the ensuing discussion should be changed slightly. This section was based on the findings of only 3 studies, yet		

			the research is described as "some studies". There really doesn't appear to have been enough research conducted to draw any definitive conclusions to use words like "some" and "while others"		
Reviewer #2					
	4	4th from the bottom	"…increased dependence is likely associated with menthol in cigarettes." Remove "increased"?		
	6	4th -8th	"Among those studies reviewed, it was consistent that African American menthol smokers were consistently less likely to successfully stop smoking than African American nonmenthol smokers. From the available studies, the weight of evidence supports the conclusion that success in smoking cessation is likely associated with menthol in cigarettes, especially among African American menthol smokers." These two sentences seem contradictory. The second sentence is misleading because it sounds as if African American menthol smokers are more likely to be successful in smoking cessation than the other ethnic groups.		
	8	3rd from the bottom	"A total of six articles were evaluated which were applicable to this question." Delete the redundant "were."		
	17	2nd para	"It was reported that menthol cigarette smoking inhibits the metabolism of nicotine through 1) slower oxidative metabolism to cotinine and 2) appeared to slow glucuronide conjugation." Revise this sentence to make items 1) and 2) stylistically parallel.		
	17	4th para	"For example, one study suggested that menthol has an antitumor property. In addition, a few in vitro studies and a small clinical study suggested that menthol might have a role on exposure and metabolism of nicotine and TSNAs." These two sentences needs citations.		
	25	2nd para from the bottom	"Controlling for age; sex; race/ethnicity; and the length, frequency, and level of smoking; descriptive and regression analysis found that menthol vs. nonmenthol cigarette use was not significantly associated with salivary		

			cotinine level models that included CPD smoked." This sentence needs to be revised; it is not punctuationally correct.		
	46	The last two lines from the first paragraph	"Rather, the current assessment includes differences in prevalence rates, age of first cigarette, progression to regular smoking, and industry documents research." This sentence lacks parallel construction: "industry documents research" should be changed so that it matches the other topics mentioned in the list.		
	46	The last three lines from the bottom	"That study addressed the serious issue of misclassification of the kind of cigarettes smoked, but as with other cross-sectional surveys, the data were self-reported and represent a "snapshot" with no follow-up." This sentence needs clarification. Which study--Hersey et al. (2006) or Rock et al. (2010)? What kind of serious issue of misclassification?		
	47	5th line from the bottom in the 2nd para	"…used three menthol smoking status definitions to model the relationship between menthol cigarette use…" Please specify the three menthol smoking status definitions.		
	47	1st line in the 3rd para	" Rock et al. (2010…." Need a close parenthesis ")"		
	48		"Although there were more menthol smokers (n=407) than nonmenthol smokers (n=73), there was sufficient power to make this comparison." It is not clear whether this sentence refers to "power analysis" or to a "statistically significant difference." If the latter is the case, please say so.		
	55	3rd line from the bottom in the 2nd para	"While the data seems generalizable to most smokers, …" The data **seem** (plural)		
	57	2nd para	"A total of five peer-reviewed publications, and a non-peer-reviewed secondary data analysis were evaluated for this section." Please double check the number of publications reviewed. Based on my		

			calculation, a total of **eight** studies were reviewed.		
	58	9th line from the bottom	"less that 10 CPD were more likely to be…" less **than**…		
	60	The last three lines in the 3rd para	"…youth who reported initiation in the final wave were included in an expanded analysis in order to increase sample size, even though these smokers are not followed for smoking progression or menthol use change over time." Font size is smaller than the surrounding text.		
	61	1st and 2nd paragraph	1 h, 1hr, 1 hour, 1h … need to be consistent		
	65	2nd para	"A total of ten peer-reviewed articles were reviewed for this section, including three population or community-based studies, and eight clinically-based studies." check the number of articles. If 8 + 3 studies were reviewed, the total should be eleven, not ten.		
	69	The last 2 lines in the 2nd para	"More importantly, the utility of the findings of this study are limited due to significant scientific flaws." It is not clear what findings are significantly flawed.		
	70	3rd para	Levy et al. (2011) is reviewed but not cited in the reference list.		
Reviewer #3	None provided.				
Reviewer #4	None provided.				
Reviewer #5	8	12	Awkward listing		
	10	21	Typo: "Theses"		
	11	13	Use of term "American style" may be confusing, as this is the only reference in		

			the document.	
	15	19-25	More details about what tobacco industry documents show about the preference profiles of menthol smokers would add to the weight of evidence.	
	17	21	Not sure what "(-)-menthol" refers to. Is this a typo?	
	18	7-9	Statement about what smokers enjoy is not well supported by the review of evidence. (see comment about page 15 above).	
	31	14	Period missing at the end of the paragraph.	
	58	35	Check the number of CPD reported for menthol smokers; the magnitude of the difference suggests that there may be a typo.	
	60	29-31	Inconsistent font size.	
	70	11	Word missing between "as" and "who"	
	76	15	The text refers to a data analysis as being "provided in the Appendix." However, the report does not appear to include an appendix, making this statement highly misleading.	
Reviewer #6	4	21	Suggest changing "menthol impacted the appearance" to menthol impacted the presence"	
	4	5th from last	"smoking menthol cigarette" should be "smoking menthol cigarettes"	
	6	26	Delete comma in phrase "as menthol smokers, show greater signs of nicotine dependence"	
	7	abbreviations	There are many abbreviations used in the document that do not appear on this list: COHb, COMMIT, FDA, HHS, MCh, NE (nicotine equivalents), NTP, RTI, SENCAR. FEV1 should include "in one second" in the definition. 4-ABP actually isn't defined.	
	16	26	Constitutes should be constituents	
	24	Add'l Evidence paragraph, line 10	Hyphens needed in cigarette-adjusted and creatinine-adjusted	
	60	Last lines in 3rd paragraph	Font is smaller for part of the sentence beginning "In addition, youth who reported"	
			There are two places where there are duplicated periods at the end of sentences. p. 7 second line; P 52, middle of the page.	

Reviewer #7	6	16	Since pack years has been shown to be associated with disease burden and menthol smokers tend to smoke more, this apparent inconsistency should be noted and addressed.		