

V. PEER REVIEW COMMENT TABLE: This document addresses the reviewer comments in a narrative, rather than tabular, form. FDA responses are *italicized*.

I. GENERAL IMPRESSIONS

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.

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.

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”.

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.

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.

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 Assessments” 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.

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.

COMMENT

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.

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.

FDA RESPONSE: We have revised the document to try to address the comments of the reviewers. Sections were rewritten and reformatted to try to improve consistency between sections and to make sure the conclusions in the body of the document are worded the same as the conclusions in the executive summary. We have used the inclusion of sponsorship of papers in the references as a means of allowing the reader to make their own assessment of possible bias by the authors. This has been corrected to indicate that this study was sponsored by Altria.

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.”

FDA RESPONSE: The purpose of this evaluation was to determine whether there are independent associations between menthol in cigarettes and various outcomes of interest. In doing so, we evaluated the weight of evidence, taking into account potential threats to validity, such as bias or confounding, and whether the findings were generalizable to the U.S. population The evaluations were not an attempt to establish causality.

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.

FDA RESPONSE: We believe that this concern/comment about causality is not as issue for the current assessment, since the conclusions are associations, not causal inferences.

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.

FDA RESPONSE: Tables giving annotated bibliographic information are now included in each chapter.

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 ___.”

FDA RESPONSE: We appreciate the comment about the order of an association between an exposure and an outcome. The order of the association has been revised to indicate that “menthol cigarettes use is associated with an outcome X”.

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.

FDA RESPONSE: We appreciate this comment. We have attempted to increase the use of plain language and reduce technical jargon to make this document accessible to a wider audience.

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?).

FDA RESPONSE: These are, indeed, two different efforts that used a similar conclusion structure). The TPSAC report was submitted in March of 2011. The scientific assessment was submitted for peer review in July of 2011. Both processes ran in parallel for several months, however they were independent of each other. The current assessment was carried out separately from the TPSAC report. We

have attempted to address this comment by explicitly stating that FDA conducted an independent review.

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 phrase “harmful chemicals” introduced. So in the Executive Summary, it is not clear that “Chemistry” is referring to “Harmful Chemistry.”

FDA RESPONSE: Chemistry is being kept general (not “harmful chemistry) because it is more inclusive. However this has been clarified as “Smoke Chemistry and Toxicology”.

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.

FDA RESPONSE: We appreciate the reviewer’s concern and have carefully considered this sentence. We believe that sentence should remain as is.

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?

FDA RESPONSE: FDA strongly disagrees with the reviewer’s comment that we “cherry picked” findings. This conclusion was based primarily on menthol’s cooling effects. The lack of effect on topography or chemical metabolism doesn’t alter this evidence of physiological action.

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?

FDA RESPONSE: This information has been added.

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

FDA RESPONSE: This information has been added.

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?

FDA Response: We appreciate the reviewer’s comment and regret any confusion this may have caused. We presented demographic comparisons between menthol and non-menthols smokers (based on Table 1, Alexander 2000). For example, menthol smokers were more likely to be females versus males (55.1% vs. 44.9%) (100% total); whereas nonmenthol smokers were more likely to be males vs. females (56.6% vs. 43.4%) (100% total). In other words, menthol smokers were more likely to be females compared with nonmenthol smokers (55.1% vs. 43.4%). After calculation using the data shown in Table 1, we found that among smokers, African Americans were more likely to use menthol cigarettes than other races combined (72.5% vs. 20.8%), a finding which is consistent with other studies and our Executive Summary. In addition, we found among smokers, women were more likely to use menthol cigarettes than men (30% vs. 20.7%). The text was revised accordingly to clarify the data directly presented in the article (page 29).

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.

FDA Response: We appreciate the reviewer’s comments. The text was revised accordingly to focus on menthol cigarette use information by race/ethnicity. The information that was not related to menthol cigarette use was deleted from the document (pages 30 and 32).

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.

FDA RESPONSE: No response.

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?

FDA RESPONSE: We appreciate this suggestion. A comparison by race/ethnicity is now provided, however percentages of youth who usually smoke a nonmentholated brand of cigarettes, or those who reported no usual brand were not provided in the primary article.

Dependence

Very, very well-written and convincing.

FDA RESPONSE: No response.

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 made more interpretable if a standard were selected and everything changed to the same direction (easy to make consistent by simply taking the reciprocals).

FDA Response: We appreciate the review's comments. In order to minimize potential errors that could result from data transformation, we prefer to cite the estimates that were reported in the literature.

Disease Risk

A very well-written and clear discussion.

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

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.

FDA Response: We appreciate the comments, Gundersen et al. in the "Pattern of Use" section was deleted.

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.

FDA Response: We appreciate the comments. We tried to find a balance between being repetitive and providing the reader as much information in the specific section as needed.

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.

COMMENT

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.

FDA RESPONSE: FDA has revised much of the format of the report to try to improve consistency between sections.

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 1-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.

FDA RESPONSE: FDA has added language to address this concern.

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.”

FDA RESPONSE: FDA has added language to address this concern, however we have not used the suggested language.

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.

FDA RESPONSE: Clarification is now provided (e.g., data transformations, calculation of prevalence differences)

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.

FDA RESPONSE: Since the trend failed to reach significance, the language has been modified.

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.

FDA RESPONSE: An explanatory sentence has been added.

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.”

FDA RESPONSE: We understand that there is redundancy. In this case, we thought that it would best to retain this since some people will not read the entire chapter and will instead look at individual sections or studies. When discussing the limitations of specific studies that are referred to multiple times, we have provided those limitations in a single paragraph to try to reduce duplication.

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.

FDA RESPONSE: No response.

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.

FDA RESPONSE: No response.

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.

FDA RESPONSE: No response.

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.

FDA Response: We appreciate the reviewer’s comment. We agree that sociodemographic variables may not be defined as an “impact x” for menthol associated behavioral and/or health outcomes, but these variables could modify the associations between menthol cigarette use and various behavioral and/or health outcomes. The main objective of section “Pattern of Use” is to provide descriptive epidemiologic information on the pattern of menthol cigarette use among subgroups categorized by variables such as sex and race/ethnicity. The results will help inform us whether certain subgroups are more likely to be affected by menthol cigarettes, and help us develop a basis for targeted intervention if needed.

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).

FDA RESPONSE: The purpose of this chapter was to review literature specifically related to the marketing of menthol cigarettes as well as consumer perceptions of menthol cigarettes. The introduction and conclusion sections of the chapter have been revised to better reflect this objective and the related conclusions.

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.

FDA RESPONSE: Because the literature reviewed in this section was not specific menthol, this section was revised significantly. A brief review of the advertising receptivity literature was included in the marketing strategies subsection to acknowledge the relevant literature and provide additional background, rather than to define or critique the construct itself. As noted, researchers have defined the construct of ad receptivity and have developed several scales for measuring this construct; limitations were noted. Conclusions made in the Marketing and Consumer Perceptions section were based on the totality of the science reviewed.

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.”

FDA RESPONSE: Although “first smoking experience” and “progression to smoking” are distinct behaviors, we are including them as different measurements of “Initiation of smoking”. The conclusion on this broader topic is based on the studies of different measurements. “First smoking experience” is, therefore, part of “initiation of smoking”. We believe these concepts are clearly defined in the text of the document.

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).

FDA RESPONSE: No response.

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.

FDA Response: Each section now contains a table summarizing the studies. We also agree that some studies provide stronger evidence for an association than others. In our report, we took into account the ability of different study design for an association by presenting data according to study design.

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.

FDA Response: No response.

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.

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: These were suggested by the study authors. This has been clarified.

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.

FDA RESPONSE: There were no data on menthol being burned by itself, however the section on in vitro toxicity of menthol tobacco includes information on pyrolysis of menthol in the form of a complex smoke mixture. Since the effects listed are "possible effects", we do not believe this to be an overstatement.

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.

FDA RESPONSE: The suggested article does not add anything new regarding the testing outcomes, therefore FDA is not adding this.

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.

FDA RESPONSE: This refers to all and is a general statement. This is not referencing anything specific in this assessment.

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.)

FDA RESPONSE: FDA agrees that IL-6 is multifunctional and has effects on the immune system. However, no studies were found that investigated the impact of menthol, IL-6 and immune response. The Sidell article (1991) says that the study says that menthol inhibited cell growth of a cancer cell line and also down-regulated IL-6 receptors. In general, if something causes inhibition of cell growth, it has anti-proliferative effects.

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.

FDA RESPONSE: The effects of menthol on Ca²⁺ are different in different tissues and species that explained the above question. We also added more context in the text to make it clearer for readers.

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.

FDA RESPONSE: We re-organized and kept the paragraph with the biomarker section.

I suggest reorganizing the subsections in the Physiology section to combine 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.”

FDA RESPONSE: This section has been re-organized, as suggested.

Biomarkers

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

FDA RESPONSE: We understand there is redundancy. We believe that this redundancy benefits those who will be reading only selected chapters.

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.”

FDA RESPONSE: We understand there is redundancy. We believe that this redundancy benefits those who will be reading only selected chapters. For the Clark (1996 study), there was no mention of adjustment for gender. In all cases, all adjustments (as stated by the study authors) were included.

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.

FDA RESPONSE: Research gaps are beyond the scope of this assessment; the focus is on the existing science.

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.

FDA RESPONSE: FDA intends to summarize the key conclusions on the available scientific evidence in the Executive summary. The proposing of hypotheses is a different issue.

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. 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.

FDA RESPONSE: Tables with annotated bibliographic information are now included in all chapters.

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.

COMMENT

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.

FDA RESPONSE: The purpose of this chapter was to review literature specifically related to the marketing of menthol cigarettes. While we did not include general literature on the effect of point of sale strategies on smoking behavior, we did include findings from several studies that examined point of sale strategies specific to menthol cigarettes.

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.

FDA RESPONSE: This conclusion was made because of the limited number of studies available. "Not sufficient evidence" refers to the limited data available. To better articulate this, we have revised the conclusion to read "Given the limited data reviewed and mixed results, at this time the weight of evidence is not sufficient to support a conclusion that consumer perceptions of harm are associated with the use of menthol cigarettes."

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.

FDA RESPONSE: This statement was removed.

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).

FDA RESPONSE: Mixed results do not necessarily mean that there was insufficient evidence. Rather, each section weighed studies according to their particular strengths. For example, in the biomarkers section, although some small laboratory studies suggested some differences, there were no differences found by large, well-controlled studies. Therefore, it was concluded that there was likely no association between menthol and levels of exposure as measured by biomarkers. Using marketing as an example, there was so little information on menthol that the conclusion is that there is insufficient information to make any association.. FDA has added more detailed rationales to each section to help explain which studies were most convincing for us to draw the conclusions that are stated in the document.

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.

FDA RESPONSE: FDA has added more detailed explanations for each of the conclusions and has added tables of the cited references for each section.

Tobacco toxicology and chemistry

The conclusion seems to objectively reflect the data.

FDA RESPONSE: No response.

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.

FDA RESPONSE: FDA has updated the relevant sentences, although not exactly as suggested, as we want to state key points in the executive summary.

Biomarkers

The conclusion seems to objectively reflect the data.

FDA RESPONSE: No response.

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.

FDA Response: Our view is that racial differences in cotinine levels are almost certainly the cause of the finding of differences between the unadjusted and adjusted regressions' significance levels.

Patterns of Smoking

The conclusions seem to objectively reflect the data.

FDA RESPONSE: No response.

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).

FDA RESPONSE: We have clarified the purpose of the chapter in the introduction.

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 in 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.

FDA RESPONSE: The conclusion has been revised to better highlight the two primary conclusions of this chapter related to the marketing of menthol cigarettes and consumer perceptions of menthol cigarettes. The purpose of this evaluation was to determine independent associations between menthol in cigarettes and various outcomes of interest.

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)

FDA RESPONSE: The lack of association with first smoking experience or progression to regular smoking do not alter this evidence for an association between menthol and initiation of smoking. As discussed in the evaluation, both are directly affected by race/ethnicity as well as ethnic background. The chapter conclusion was therefore based primarily on the prevalence data.

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).

FDA RESPONSE: As discussed in the evaluation, while we agree that there could be a cohort effect, we believe that this is unlikely due to the consistency of findings across datasets gathered from different years, with younger, newer smokers preferring menthol at levels far above that of the general population, suggesting that as smokers grow older, menthol preferences change. There may be various reasons for the associations observed. The purpose of this assessment was not to assess all the potential pathways. In the document we have provided a more detailed explanation of how we arrived at the conclusions based on the available studies.

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).

FDA RESPONSE: The purpose of this evaluation was to determine independent associations between menthol in cigarettes and various outcomes of interest.. In the document we have provided a more detailed explanation of how we arrived at the conclusions based on the available studies.

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.

FDA RESPONSE: Although testimonial-style information is available, FDA relied on research studies that addressed the questions of interest.

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?”

FDA RESPONSE: We agree and this has been modified.

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).

FDA RESPONSE: We agree that caution should be used when interpreting studies that may have “over adjusted”. Our intention was merely to note that increased dependence may be on the pathway between menthol use and cessation. If so, adjusting for dependence would be inappropriate and would be expected to dilute the association observed. Even with this concern, many of the studies found independent associations between menthol use and cessation. This caution was included in our weighing of the evidence and our conclusions regarding an association between menthol and 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.

FDA RESPONSE: We agree that the FDA reanalysis of the CPS-TUS dataset is useful. This was included in our weighing of the evidence and our conclusions regarding an association between menthol in cigarettes and cessation.

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?

FDA RESPONSE: The purpose of this evaluation was to determine independent associations between menthol and various outcomes of interest. Tables with annotated bibliographic information are now included in each chapter.

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).

FDA RESPONSE: We are not drawing causal conclusions. We are evaluating potential associations between menthol cigarette use and various outcomes such as dependence, cessation and disease outcomes. . The overall effect of menthol cigarettes use on disease risk could be mediated by multiple intermediate factors. Dependence could be such a factor. However, to date, an association between menthol use and increased disease risk has not been observed.

Science Reviews

Toxicology and Chemistry

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

FDA RESPONSE: No response.

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.

FDA RESPONSE: We appreciate the reviewer's comment. We now use the more neutral "experience".

Biomarkers

Fair and balanced conclusion.

FDA RESPONSE: No response.

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.

FDA RESPONSE: We appreciate the reviewer's comment. We would like to clarify that addressing limitations is not an apology. Rather, it is intended to provide a scientific assessment of the study. It also suggests the need and future direction of research, such as validation of data collection methodologies..

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.

FDA RESPONSE: FDA RESPONSE: The purpose of this evaluation was to determine independent associations between menthol in cigarettes and various outcomes of interest.

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.

FDA RESPONSE: FDA RESPONSE: Our view is that a cohort effect is unlikely and, furthermore, cannot be documented with existing data. Repeated cross sectional survey data produces prevalence rates that do not suggest a cohort effect but it remains a possibility until a set of cohorts is followed over time We have included statements reflecting the possibility that a cohort effect exists.

Dependence

Very well presented and fair. The evidence appears overwhelming.

FDA RESPONSE: No response.

Cessation

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

FDA RESPONSE: We agree that cessation may have dependence as a possible mediating factor, and have included this in our discussion of potential issues of studies that adjusted for levels of dependence.

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.

FDA RESPONSE: We agree that multiple exposure/risk factors contribute to disease causation. The effect of menthol cigarette use on disease risk may be influenced by dependence and/or cessation, however there may be other factors that have a much stronger influence. Therefore, any influence of dependence and/or cessation on disease risk may not be significant.

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.

FDA RESEPONSE: We address the reviewer’s comments regarding tobacco industry documents in the next section, as we believe this is the “key evidence” to which the reviewer is referring. We provided more details in the conclusion sections in order to better explain our rationale for drawing the conclusions that we did.

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.

FDA RESPONSE: Industry research studies that addressed the questions of interest were included in the report. We used other industry data to provide context, as appropriate. We provided more details in the conclusion sections in order to better explain our rationale for drawing the conclusions that we did.

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.

FDA RESPONSE: These conclusions may, in fact, be related. The language of the cessation conclusion has been clarified, as it is a decreased likelihood of cessation success that is associated with menthol use.

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.

FDA RESPONSE: The discrepancy was corrected.

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.

FDA RESPONSE: We agree.

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.

FDA RESPONSE: No response.

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

COMMENT

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

FDA RESPONSE: This is a review that is not being included because the current assessment relies primarily on original sources/publications.

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

FDA RESPONSE: This was published after the search for literature was completed and is now included.

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

FDA RESPONSE: This was published after the search for literature was completed and is now included.

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

FDA RESPONSE: This was published after the search for literature was completed and is now included.

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.

FDA RESPONSE: This was published after the search for literature was completed and is now included.

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.

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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.

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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.

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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.

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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.

FDA RESPONSE: This is a book chapter (review) that is not being included because the current assessment relies primarily on original sources/publications.

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.

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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.

FDA RESPONSE: This is a book chapter (review) that is not being included because the current assessment relies primarily on original sources/publications.

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

FDA RESPONSE: This article does not compare menthol and non-menthol so it is not included.

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 rationale 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.

FDA RESPONSE: This assessment relies on articles that directly compare menthol and non-menthol. Since these suggestions do not do this, they are not included in the assessment.

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.

FDA RESPONSE: Reviews are generally not included as the current assessment relies primarily on original sources/publications, however the recommendations of specific articles are appreciated.

Gordon et al., Chem Res. Toxicol 2011 Sep 19. [Epub ahead of print] Effect of Cigarette Menthol Content on Mainstream Smoke Emissions.

FDA RESPONSE: This was published after the search for literature was completed. This was not included as this doesn't provide any new information. Although a specific design feature (Camel Crush) resulted in greater VOC levels, there was no effect of menthol in other cigarettes.

CHARGE QUESTION 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.

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

FDA RESPONSE: All studies were evaluated using the same approach. Funding is noted in the tables and the bibliographies.

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.”

FDA Response: We appreciate the comments and agree with the reviewer about the distinction between “type” and “brand” of cigarettes. However, we intended to cite what was reported in the individual articles without making any changes. For example, in Fagan et al (2010), the author assessed the “usual cigarette brand” by asking respondent: ‘Is your usual brand menthol or non-menthol?’ In addition, the author presented the demographic comparisons between menthol and nonmenthol smokers in their published table (Table 1 in their article) and the

title of the table was labeled as “Socio-demographic characteristics of daily smokers by usual cigarette brand”. The text was revised accordingly.

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.

FDA RESPONSE: We appreciate the suggestion and have added summary text to the beginning of the conclusion.

I think I’ve addressed everything.

FDA RESPONSE: No response.

None needed.

FDA RESPONSE: No response.

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.

FDA RESPONSE: This has been clarified.

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.

FDA RESPONSE: Research gaps are beyond the scope of this assessment; the focus is on the existing science.

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.

FDA RESPONSE: There may be various reasons for the association. The purpose of this assessment was not to evaluate possible pathways.

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.

FDA RESPONSE: We agree this is a complicated issue and there could be many mediating factors.

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.

FDA RESPONSE: A review of variations in the advertising of menthol across community SES and demographic characteristics is covered in the Marketing Strategies sub-section within the Marketing and Consumer Perceptions section.

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.

FDA RESPONSE: Citations have been updated

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?

FDA RESPONSE: Data was analyzed from the 2010 National Survey on Drug Use and Health (NSDUH) to answer this question. Findings were included in the chapter.

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?

FDA RESPONSE: Please see Initiation chapter for more information on youth smoking behaviors.

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.

FDA RESPONSE: More recent data were included in the chapter along with other additional information and revisions that address this 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.

FDA RESPONSE: The purpose of this chapter was to review literature specifically related to the marketing of menthol cigarettes. While we did not include the Slater et al (2007) reference, we did include findings from Henriksen et al (2011) related to youth and menthol advertising promotions.

39 1699 Could add here the Seidenberg et al. citation listed above.

FDA RESPONSE: The citation was added.

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.

FDA RESPONSE: FDA has included the household income control and have clarified the survey questions analyzed by the authors of this study.

40 1760 The Rising and Alexander review article should be added to the Consumer Perceptions section.

FDA RESPONSE: This is a review article. The current assessment focuses on primary sources.

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.

FDA RESPONSE: The introduction to this chapter was revised to clarify the objectives of the chapter.

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).

FDA RESPONSE: The citation was included in the chapter and the conclusions around consumer perception were clarified. The objective of this chapter was to describe trends in marketing as well as consumer perceptions related to menthol cigarettes. This chapter does not attempt to describe the effect of marketing menthol cigarettes on consumer perceptions.

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.

FDA RESPONSE: A review of additional point-of-sale marketing literature was included in this chapter.

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”

FDA RESPONSE: Revisions were made to clarify the quantity of the literature reviewed.

4 4th from the bottom “...increased dependence is likely associated with menthol in cigarettes.” Remove “increased”?

FDA RESPONSE: The factors considered suggest that there is increased dependence and are not yes/no assessments (e.g., more night wakings, more craving).

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.

FDA RESPONSE: This has been clarified. The effect is lower cessation success.

8 3rd from the bottom “A total of six articles were evaluated which were applicable to this question.” Delete the redundant “were.”

FDA RESPONSE: This has been clarified.

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.

FDA RESPONSE: This has been clarified.

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.

FDA RESPONSE: These have been added.

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.

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been modified.

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?

FDA RESPONSE: This has been clarified.

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.

FDA RESPONSE: This has been clarified.

47 1st line in the 3rd para“ Rock et al. (2010....”

Need a close parenthesis “)”

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been clarified.

55 3rd line from the bottom in the 2nd para “While the data seems generalizable to most smokers, ...”

The data seem (plural)

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been corrected.

58 9th line from the bottom “less that 10 CPD were more likely to be...”
less than...

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been corrected.

61 1st and 2nd paragraph 1 h, 1hr, 1 hour, 1h ...
need to be consistent

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: This has been clarified.

70 3rd para Levy et al. (2011) is reviewed but not cited in the reference list.

FDA RESPONSE: This has been corrected.

8 12 Awkward listing

FDA RESPONSE: We are not sure what this comment refers to.

10 21 Typo: “Theses”

FDA RESPONSE: This has been corrected.

11 13 Use of term “American style” may be confusing, as this is the only reference in the document.

- FDA RESPONSE: This was specified by the article’s authors, as this research was done outside the United States.*
- 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.
FDA RESPONSE: F Industry research studies that addressed the questions of interest were included in the report. We used other industry data to provide context, as appropriate.
- 17 21 Not sure what “(-)-menthol” refers to. Is this a typo?
FDA RESPONSE: This was used by the study authors but has been modified to be consistent with the rest of the assessment.
- 18 7-9 Statement about what smokers enjoy is not well supported by the review of evidence. (see comment about page 15 above).
FDA RESPONSE: This has been clarified.
- 31 14 Period missing at the end of the paragraph.
FDA RESPONSE: This has been corrected.
- 58 35 Check the number of CPD reported for menthol smokers; the magnitude of the difference suggests that there may be a typo.
FDA RESPONSE: This has been corrected.
- 60 29-31 Inconsistent font size.
FDA RESPONSE: This has been corrected.
- 70 11 Word missing between “as” and “who”
FDA RESPONSE: This has been corrected.
- 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.
FDA RESPONSE: This has been corrected.
- 4 21 Suggest changing “menthol impacted the appearance” to menthol impacted the presence”
FDA RESPONSE: This has been corrected.
- 4 5th from last “smoking menthol cigarette” should be “smoking menthol cigarettes”
FDA RESPONSE: This has been corrected.
- 6 26 Delete comma in phrase “as menthol smokers, show greater signs of nicotine dependence”
FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: All except SENCAR have been added. SENCAR is the actual name of the assay.

FEV1 should include “in one second” in the definition.

FDA RESPONSE: This has been corrected.

4-ABP actually isn't defined.

FDA RESPONSE: This was defined in the text “red blood cell 4-aminobiphenyl (4-ABP)...” and is the abbreviation for the type of hemoglobin adduct .

16 26 Constitutes should be constituents

FDA RESPONSE: This has been corrected.

24 Add'l Evidence paragraph, line 10 Hyphens needed in cigarette-adjusted and creatinine-adjusted

FDA RESPONSE: This has been corrected.

60 Last lines in 3rd paragraph Font is smaller for part of the sentence beginning “In addition, youth who reported”

FDA RESPONSE: This has been corrected.

There are two places where there are duplicated periods at the end of sentences. p. 7 second line; P 52, middle of the page.

FDA RESPONSE: This has been corrected.

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.

FDA RESPONSE: According to the Dependence chapter, menthol smokers actually tend to smoke either fewer cigarettes per day or the same number of cpd as compared to nonmenthol smokers. But may smoke more years due to decreased quitting success..