

LORILLARD'S COMMENTS TO FDA ON THE TPSAC REPORT ON MENTHOL CIGARETTES

EXECUTIVE SUMMARY

TPSAC was charged with evaluating the available data on menthol in cigarettes in an objective, comprehensive, and scientifically rigorous manner. Lorillard believes that the TPSAC report on the public health impact of menthol cigarettes falls short of fulfilling this charge. Overall, Lorillard has serious concerns about the rigor and reliability of the TPSAC report.¹ Further, Lorillard strongly disagrees with the conclusions and recommendations of the report. The vast majority of the summary conclusions in each chapter and the “Conclusions and Recommendations” in Chapter 8 are not supported by the scientific data. This submission outlines some of the most serious flaws in the TPSAC report. This submission, however, is not intended to be an exhaustive or comprehensive statement of all the errors and omissions in the report. Finally, given the fundamental flaws throughout the TPSAC report, Lorillard does not believe that the conclusions and recommendations therein can be relied on in FDA’s consideration or regulation of menthol cigarettes under the Family Smoking Prevention and Tobacco Control Act (FSPTCA).

This submission focuses on three major areas of concern regarding the TPSAC report: 1) the lack of transparency and methodological flaws in the evaluation of the data, 2) numerous errors in the analysis of data, and 3) the inappropriate use of a novel, untested standard to categorize the strength of evidence to base its conclusions.

The submission is organized in the following manner to illustrate these concerns:

- I. TPSAC’s methods are neither transparent nor evidence based:
 - A. The literature review is neither comprehensive nor systematic
 - B. The process for drawing conclusions is neither clear nor scientifically rigorous
 - C. Criteria for judging study quality are not clearly defined
 - D. Coverage of different topics is unbalanced and not logical
 - E. Weight given to unpublished papers is inconsistent

- II. TPSAC’s data analysis has significant flaws:
 - A. Conclusions are internally inconsistent
 - B. Important conclusions are made without adequate supporting data
 - C. Results of some studies are misinterpreted
 - D. Some conclusions rely heavily on document analysis articles and decades-old industry documents that do not meet requisite scientific data quality standards
 - E. Statistical results are misstated
 - F. Unadjusted baseline data and adjusted outcome data are treated equally

¹ All references to the “TPSAC report” or the “report” are to the “Annotated Version of the Report” posted to the FDA website and available at www.fda.gov.

- G. Findings are selectively cited to support conclusions
- H. Causal criteria are inappropriately used before an association has been demonstrated
- I. Omissions and inconsistencies are evident throughout the report

III. TPSAC's use of an "Equipoise" Standard is not scientifically appropriate:

- A. The "Equipoise" standard used by TPSAC is inappropriate for assessing weight of evidence on menthol cigarette smoking
- B. The application of the "Equipoise" standard is unclear

Despite its description in Chapter 2, TPSAC's methods are neither transparent nor evidence-based. It is not clear how and why certain studies were given substantial weight, while others were ignored. In some cases, worthy and highly relevant, peer-reviewed research receives only cursory consideration or is omitted entirely. Of the studies that were included, TPSAC's process for drawing conclusions is also unclear. There are instances in which large human studies are acknowledged by TPSAC but given less weight than smaller laboratory studies. Also, in some circumstances in which TPSAC describes the evidence as "mixed," the vast majority of the studies find no differences between menthol and nonmenthol smokers. TPSAC's methods in reaching its conclusions cannot be replicated and many conclusions are not scientifically justified.

- For example, it is not clear how TPSAC can conclude that the evidence regarding the relationship between menthol cigarettes and smoking cessation among White smokers is mixed (p147). An evaluation of all available data, with greatest weight given to the most methodologically strong studies (peer-reviewed prospective and cross-sectional studies that assess long-term cessation of at least 6 months) clearly leads to the conclusion that there is no relationship between menthol smoking and reduced cessation among Whites. Even given the description in the TPSAC report (p133), most of the studies show either no difference in cessation between menthol and nonmenthol smokers (13 studies) or that menthol smokers had higher prevalence of cessation (2 studies). Although an additional 12 studies are cited in the report as providing evidence of reduced cessation among menthol vs. nonmenthol smokers, only two of those studies (one of which is not peer reviewed) actually reported reduced cessation among White menthol smokers compared to White nonmenthol smokers. A conclusion that the data are "mixed" does not accurately reflect the weight of the available evidence.

The analysis in the TPSAC report is often flawed. In a number of instances, the report incorrectly interprets study results. The TPSAC report also represents some study findings as being statistically significant (i.e. a result "tends to be higher" or "was higher") when researchers reported no statistically significant differences. The report often mixes unadjusted baseline data and adjusted outcome data, inappropriately drawing conclusions from the unadjusted baseline measures which are merely descriptive data such as study subjects' characteristics in convenience samples of populations. The TPSAC report sometimes draws some important conclusions in the absence of adequate data. In at least one case, the report relies on a single unpublished study, which has significant weaknesses, to draw major and impactful conclusions.

- For example, several conclusions in the TPSAC report are internally inconsistent. The conclusion in Chapter 8 that "[t]he evidence is sufficient to conclude that a relationship

is more likely than not that the availability of menthol cigarettes increase the likelihood of addiction and the degree of addiction in youth smokers (Above Equipoise)” (p216) is not supported by the evidence presented in Chapter 6 which stated “[t]o date, one unpublished secondary analysis has addressed this issue in a sample of adolescent students who were assessed in different regions of the U.S. This study suggests that menthol cigarettes are associated with increased transition of greater or established smoking and dependence” (p149). The existence of a single, unpublished study which “suggests” a possible association between menthol cigarettes and increased likelihood of dependence is not sufficient to support a conclusion that the evidence is “Above Equipoise.”

The example set forth above also shows that TPSAC’s adoption and application of a novel, untested hierarchy for categorizing the strength of evidence, based loosely on the concept of “equipoise,” to describe the strength of evidence is an inappropriate standard upon which to base regulatory action. TPSAC’s approach falls short of the objective scientific rigor required to draw conclusions regarding any impact of the use of menthol in cigarettes on the public health.

Presented below are several examples that are representative of Lorillard’s concerns. There are many additional flaws throughout the TPSAC report and these examples do not comprise an exhaustive and comprehensive listing of all such weaknesses in the TPSAC evaluation process. Given the magnitude and extent of the errors in the TPSAC report, Lorillard does not believe that FDA can reasonably rely on the TPSAC report in making any regulatory decision regarding the use of menthol in cigarettes.

I. TPSAC’S METHODS ARE NEITHER TRANSPARENT NOR EVIDENCE-BASED

The TPSAC report states that its core principles in evaluating the data on menthol cigarettes were that “the fact finding, evidence gathering and synthesis, and deliberations about the evidence are conducted in a transparent manner” and “the recommendations of the TPSAC are evidence-based” (p6). However, there is ample evidence that TPSAC did not adhere to either of these principles. Despite the discussion of methodology in Chapter 2 of the TPSAC report, it is not clear how TPSAC chose the literature upon which it relied or its rationale for excluding other pertinent literature; how TPSAC weighted the studies it did consider; or how TPSAC drew conclusions based on its selection from the total body of literature. Good science dictates that an investigator should define a hypothesis, specify inclusion/exclusion criteria based on quality characteristics that are specific to the issue under study, assemble the relevant information, and finally assess in an objective manner whether or not the hypothesis was supported. These criteria apply equally to experimental studies, as well as review of scientific literature. TPSAC fails to do this at every step of the process. Specific examples of TPSAC’s methodological flaws are provided below.

A. The Literature Review is neither Comprehensive nor Systematic

TPSAC says it made an effort to identify all relevant evidence on menthol in cigarettes. However, there is clear evidence that TPSAC’s review is neither comprehensive nor systematic.

- TPSAC omitted readily available peer-reviewed, published papers. Specifically:

- Relevant studies based on nationally representative survey data (e.g., Mendiondo et al. 2010) were not included.
- Two case-control epidemiology studies of lung cancer that provided quantitative estimates of risk associated with menthol versus nonmenthol smoking were also omitted (Stellman et al. 2003, Etzel et al. 2008).
- The important disease-related findings of a major and very recent cohort study of Blot et al. 2011 were mentioned in only a cursory manner.
- Relevant studies on biomarkers (Ahijevych and Wewers 1994, Gan et al. 2008, Strasser et al. 2011 and Xia et al. 2010) were not included.
- The discussion in Chapter 3 on menthol desensitization omits several relevant studies, including Foster et al. 1993, Green and McAuliffe 2000, Lee et al. 2007, and Zanotto et al. 2008.

In some cases, a more complete analysis would have led to different conclusions. For example, in the discussion of menthol desensitization and interaction with nicotine, inclusion of the omitted studies would have shown that, overall, the results are inconsistent, with some showing increased sensitivity and others showing decreased sensitivity.

- An attempt to replicate the TPSAC analysis using the same search methodology set forth in Chapter 4 (Patterns of Menthol Cigarette Smoking) yielded different results than those reported by TPSAC. This method returned sources that TPSAC failed to cite in Chapter 4 (e.g., Fernander et al. 2010) and also failed to return sources cited in that Chapter (e.g., Rock et al. 2010, Hersey et al. 2010).
- Nationally representative surveys are an important source of data on demographics, but it is generally recognized that, due to different questions and methods, the different surveys provide somewhat different estimates of smoking prevalence, and thus it is important to consider all of these estimates and inherent shortcomings of each. TPSAC emphasized certain surveys (e.g., NSDUH, NYTS) over others (NHANES and NHIS). NSDUH provides higher estimates of menthol use than other national surveys, particularly for the NSDUH surveys conducted subsequent to the revision of the menthol question in the survey instrument in 2004 to one that was less definitive in identifying respondents as primarily menthol cigarette smokers (*See* Altria submission for July 2010 TPSAC meeting (beginning p105)).

B. The Process for Drawing Conclusions is neither Clear nor Scientifically Rigorous

TPSAC's process for evaluating the available literature and drawing conclusions is neither clear nor scientifically rigorous. Good science dictates that an investigator should define a hypothesis, specify inclusion/exclusion criteria based on quality characteristics that are specific to the issue under study, assemble the relevant information, and finally assess in an objective manner whether or not the hypothesis was supported. These criteria apply to both experimental studies, as well as review of

scientific literature. TPSAC fails to adhere to these fundamental principles and practices at every step of the process.

For example, it is unclear how TPSAC can conclude that the evidence regarding the relationship between menthol cigarettes and smoking cessation among White smokers is mixed (p147). An evaluation of all data, with greatest weight given to the most methodologically strong studies (peer-reviewed prospective and cross-sectional studies that assess long-term cessation of at least 6 months), clearly leads to the conclusion that there is no relationship between menthol smoking and reduced cessation among Whites.

Even by TPSAC's description (p133), most of the studies show either no difference in cessation between menthol and nonmenthol smokers (13 studies) or that menthol smokers had a better outcome (2 studies). TPSAC cites an additional 12 studies as providing evidence of reduced cessation among menthol vs. nonmenthol smokers (beginning p133). However, careful examination of these 12 studies reveals that:

- Four studies show reduced cessation outcomes only for non-Whites (Gundersen et al. 2009, Stahre et al. 2010, Gandhi et al. 2009, King et al. unpublished); among Whites in these studies, cessation was similar for menthol and nonmenthol smokers.
- A fifth study (Levy et al. 2011) examined races separately, but only reported reduced cessation among African American menthol smokers who had quit in the past 5 years.
- Three studies did not present results by race (Foulds et al. 2006, Pletcher et al. 2006) or had too few White menthol smokers to draw conclusions with confidence (Reitzel et al. unpublished(c)).
- Two studies only examined Black subjects (Okuyemi et al. 2003, Okuyemi et al. 2007) and thus provide no data on Whites.

In fact, only two studies actually reported reduced cessation among White menthol smokers compared to White nonmenthol smokers, one of which has not been peer-reviewed: Trinidad et al. 2010, Delnevo et al. (unpublished). Given the large body of evidence on cessation (which includes at least 15 studies cited by TPSAC as showing no reduced cessation among menthol smokers compared to nonmenthol smokers), a conclusion that the data are "mixed" does not accurately reflect the weight of available evidence. Furthermore, a simplistic counting of studies does not take into account the most important methodological features and study strengths/limitations. As mentioned above, when looking at the most scientifically reliable studies (peer-reviewed prospective and cross-sectional studies that assess long-term cessation of at least 6 months), the vast majority of studies find no significant difference in cessation between White menthol and nonmenthol smokers.

Similarly, it is unclear how TPSAC can conclude that there is sufficient evidence based on national surveys to show that non-white smokers, particularly African American, of menthol cigarettes compared to nonmenthol cigarettes experience more difficulty with cessation (p150). There is no scientific reason to limit the studies upon which the TPSAC reports bases its conclusion to studies examining data from self-reported national surveys, because data are available from

methodologically sound prospective studies (Blot et al 2011, Hyland et al 2002, and Muscat et al 2002). When all studies that present data by race cited by TPSAC are considered, the data show:

- About half of the studies that present data on smoking cessation by race found no difference between African American menthol and nonmenthol smokers (Cubbin et al. 2010, Hyland et al. 2002, Muscat et al. 2002, Blot et al. 2011, Hyland and Rivard unpublished, Cropsey et al. 2009, Harris et al. 2004, Reitzel et al. unpublished (a), Reitzel et al. unpublished (b), Reitzel et al. (c)) or that African American menthol smokers were more likely to report successful cessation than nonmenthol smokers (Hyland and Kasza unpublished).
- About half of the studies reported reduced cessation among African Americans who smoked menthol cigarettes compared to nonmenthol smokers (Gundersen et al. 2009, Stahre et al. 2010, Trinidad et al. 2010, Delnevo et al. unpublished, Levy et al. 2011, Gandhi et al. 2009, Okuyemi et al. 2003, Okuyemi et al. 2007, King et al. unpublished).

Note that the studies that found reduced cessation among African American menthol smokers are a combination of cessation clinic studies and surveys without rigorous definitions of cessation, including two that have not undergone peer-review. Given the large body of evidence on cessation, this does not constitute “sufficient” evidence to draw a conclusion that non-White menthol smokers have reduced cessation success.

A third example comes from TPSAC’s discussion of menthol and tobacco-specific nitrosamines in both Chapter 3 (p23) and Chapter 7 (p199). In Chapter 3, TPSAC incorrectly states that Ritchie et al. 1997 “hypothesized that menthol inhibits NNAL glucuronidation” (p23). TPSAC misrepresents the findings and hypothesis advanced by Ritchie et al. 1997. These authors hypothesized and indeed concluded from their metabolite analyses and an accompanying laboratory experiment that intrinsic pharmacogenetic differences appear to account for race-associated differences in NNAL metabolite ratios. The alternate theory that menthol preference may account for such differences was explicitly rejected by the authors: “... it is unlikely that these differences can be attributed to use of mentholated cigarettes ...” and “... it is unlikely that the dissimilarities are due to racial differences in preference for mentholated cigarettes...” In Chapter 7, TPSAC states that: “Larger studies have generally not found independent effects of menthol cigarette smoking on exposure biomarkers. However, the findings of the study by Muscat et al. suggest that menthol may impair detoxification of NNAL, which is a pulmonary carcinogen” (p199). While TPSAC acknowledges that numerous large studies were consistent in their lack of findings of any menthol effect on NNK metabolism, it then highlights the Muscat study, a single report of a reanalysis of urine samples, originally discussed by Ritchie et al. 1997, as showing a race- but not menthol-associated difference in NNAL metabolite ratios. The extreme and nonphysiological substrate concentrations (hundreds to millions-fold in excess of those that might be found in human smokers’ systems) and the homogenized liver *in vitro* incubation conditions employed in a small accompanying experiment reported by Muscat et al. 2009 do not constitute sound evidence for the biological plausibility of the authors’ speculation, never independently confirmed, that menthol may affect NNK metabolism *in vivo*. The notion that differences in urinary NNAL metabolite ratios are related to lung cancer risk is in any event speculative, and a considerable weight of epidemiological evidence does not support the hypothesis that menthol affects smokers’ metabolism of NNAL in any meaningful way.

A more appropriate, transparent and scientifically defensible approach to assigning more weights to some studies and less to other entails the clear specification of the most important study quality characteristics, followed by an objective assessment of each topic (initiation, cessation, dependence, health risks), with assignment of the greatest weight to those studies that are the strongest methodologically.

C. Criteria for Judging Study Quality are not Clearly Defined

For most topics, TPSAC provided no discussion of quality criteria. Consequently, TPSAC does not appear to distinguish powerful from less powerful studies on the basis of methodology or definition of outcome. For example, TPSAC does not discuss the complex process of smoking cessation and how cessation should be defined. A single statement (p145) defines “appropriate criteria for cessation” as “not smoking even a puff on a cigarette;” however, note that no duration requirement is specified for length of abstinence. Such a definition is inadequate to capture the difficult smoking cessation experience and process that leads many smokers to achieve eventual and persistent long-term cessation that may ultimately be confirmed through measurement of biomarkers such as carboxyhemoglobin. Consequently, most of the studies that TPSAC cites as evidence that menthol smokers have reduced cessation than nonmenthol smokers do not have rigorous definitions of cessation. For example, Okuyemi et al. 2003, Okuyemi et al. 2007 defined cessation as no smoking in past 7 days; Gundersen et al. 2009 defined cessation as now smoking “not at all.” A more rigorous approach, used in other analyses, defines cessation as long-term abstinence (i.e., being abstinent from smoking for at least 6 months) as a better means to characterize a genuine, long-term change in smoking status as opposed to a transient condition.

In some sections of the report (e.g., cessation) TPSAC’s approach appears biased, organizing the data by study results (whether menthol smokers had reduced cessation than nonmenthol smokers) rather than by study design or methodological quality.

Finally, it was noted that TPSAC appears to give equal or greater weight to unpublished studies than to those that are peer-reviewed and published studies.

D. Coverage of Different Topics is Unbalanced and Not Logical

TPSAC’s mandate is to evaluate the public health impact of menthol in cigarettes, which includes such major topics as smoking prevalence, smoking initiation and cessation, addiction and dependence, and disease risks. Given this mandate, TPSAC’s coverage of the different topics is unbalanced and not logical. For example, in Chapter 7 (disease risks), TPSAC gives a very brief, selective and superficial discussion of the available epidemiology data, which constitute the most important evidence regarding the effect of menthol cigarettes on disease risks. Epidemiologic outcomes reflect *all* aspects of smoking behavior, including smoking topography, exposure intensity/biomarkers, toxicology, age of initiation, and age/effect of cessation. Importantly, these studies are overwhelmingly consistent in finding no excess risk of disease associated with menthol cigarettes as compared to nonmenthol cigarettes. Oddly, much more discussion is devoted to other parts of this chapter (smoking topography, biomarkers), which are at most intermediate steps in the examination of disease risks that are the culmination of individuals’ and populations’ smoking experiences. The body of available literature on smoking topography and exposure biomarkers is in any event quite consistent in indicating that menthol does not meaningfully affect smoking behavior or resulting exposures in a manner that increases disease risks.

In some places, TPSAC appears biased in its coverage of topics. For example in the section of Chapter 6 on addiction and dependence, there is a detailed table (Table 5, p174-175) describing the studies of addiction/dependence in adolescents (where TPSAC concludes there is an association with menthol). However, there is no comparable table for studies of adults, even though there are substantially more studies. Note that TPSAC does not find menthol to be associated with increased dependence among adults, suggesting that TPSAC may be emphasizing findings averse to menthol while neglecting those that indicate otherwise.

E. Weight Given to Unpublished Papers is Inconsistent

It is not common for decision-making bodies to rely on data that have not undergone peer review and have not been published. Despite this, TPSAC indicated that it considered both unpublished FDA white papers and unpublished tobacco industry documents. However, TPSAC is inconsistent in considering unpublished materials. TPSAC failed to cite three unpublished studies on lung diseases (including the Lee meta-analysis on lung cancer, Hyland and Kasza, Stellman and Neugut), but cited many unpublished studies in other sections of the report dealing with initiation and cessation behaviors (e.g., Nonnemaker, Giovino). Perhaps the clearest example of this inconsistency is with respect to the unpublished analyses of several large surveys by Curtin. These are *not* cited in TPSAC's section on smoking cessation (Chapter 6), although this work is cited in other parts of the report, including the sections of Chapter 6 on initiation and dependence (pp102,103,109,113,122,124,132).

Furthermore, TPSAC makes no distinction (in terms of weight in decision-making) between published and unpublished studies. In fact, TPSAC provides much more attention to some unpublished studies (e.g., Nonnemaker et al. 2010, pp120-121) than to some peer-reviewed, published studies. In several sections of the discussion of addiction and dependence in Chapter 6 (cigarettes per day, time to first cigarette, and dependence among adolescents), approximately one-third of the studies cited by TPSAC are unpublished.

II. TPSAC'S DATA ANALYSIS HAS SIGNIFICANT FLAWS

TPSAC makes numerous errors in its evaluation of data, including misinterpreting statistics and results, drawing conclusions based on inadequate data, and mixing baseline descriptive data with adjusted outcome data. Specific examples of these analytical errors are set forth below.

A. Conclusions are Internally Inconsistent

TPSAC draws conclusions in the Evidence Synthesis at the end of each of its subject-matter Chapters 3 through 7, and then reiterates these conclusions using Equipoise categories in the final Chapter 8. While the conclusions in these two parts of the TPSAC report are generally consistent, there are instances in which this is not true. As one example, it is unclear how TPSAC reached its Equipoise conclusion regarding addiction in young people:

- Question: Does the availability of menthol cigarettes increase the likelihood of becoming addicted?

Conclusion in Chapter 6 (p149): “To date, one unpublished secondary analysis has addressed this issue in a sample of adolescent students who were assessed in different regions in the U.S. This study strongly suggests that menthol cigarettes are associated with increased transition to greater or established smoking and dependence.”

Equipoise conclusion in Chapter 8 (p216): “The evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes increases the likelihood of addiction and the degree of addiction in youth smokers. (Above Equipoise)”

The Equipoise conclusion in Chapter 8 is not supported by the evidence presented in Chapter 6. It is unclear how “one unpublished secondary analysis” that “suggests” a relationship between menthol cigarettes and increased likelihood of dependence could be considered sufficient evidence to draw a conclusion.

B. Important Conclusions are Made Without Adequate Supporting Data

One significant conclusion of the TPSAC report is that “menthol cigarettes are associated with increased transition to greater or established smoking and dependence” (p149). However, this conclusion is not justified, given the available data. There is limited information on the transition from experimentation to established smoking, and there are currently no published studies that examine type of cigarette (menthol vs. nonmenthol) used by experimenting smokers to initiate established smoking. In the absence of such information, the conclusion in the report is based largely on a single unpublished study (Nonnemaker et al.), which it calls “persuasive” (p121). This study has not been peer-reviewed and is unpublished; furthermore, the TPSAC report acknowledges the limitations of the study (including a population that is not representative of the entire youth population, significant drop-out, and small numbers of subjects in certain groups; p121), so it is not responsible to draw a firm conclusion based on this or any other single study.

The analysis and conclusions in the TPSAC report regarding the so-called “indirect” and “implicit” health messages in Chapter 5 – “Do Consumers Perceive Menthol Cigarette as Safer or Less Harmful than Nonmenthol Cigarettes” are critically flawed, not supported by the scientific literature, and fundamentally at odds with other findings in the TPSAC report. The report contains vague and misleading terminology which suggests that there is reason to be concerned about “implicit” health claims in menthol marketing.

- In the introductory paragraph of this section of the report, two articles (Hammond and Parkinson 2009, Hammond et al. 2009) are cited for the proposition that certain “branding elements about taste and sensory experience may contribute to beliefs that some cigarettes are less harmful than others” (p82). These studies have no relevance in assessing (a) whether menthol marketing contains implicit health messages, or (b) whether menthol cigarettes are perceived as less harmful to health. Although the TPSAC report correctly discloses that neither study involved menthol cigarettes or menthol marketing, the report incorrectly suggests that these studies are relevant in assessing whether menthol taste descriptors and menthol packaging constitute implicit health claims. Both studies focus exclusively on product descriptors and other indicia of reduced tar yields. Smokers clearly understand that tar and nicotine are bad for their health; smokers have been told this by the public health community and many others for more than 50 years. Beginning by at least 1957 and

continuing for the next 40 years, smokers were told by the public health community that they could reduce the health risks of smoking by switching to reduced/lower tar cigarettes. In sharp contrast, smokers have never been told by the public health community that menthol cigarettes are less hazardous than nonmenthol cigarettes. These studies make it clear that, to the extent smokers have an understanding that a lighter tasting cigarette might be less hazardous, the basis of such understanding is that smokers know that lighter tasting cigarettes have less tar than full flavor cigarettes; thus, the perception of reduced risk is based on the perception of reduced tar. In short, none of the findings in these studies are transferable to the menthol context.

- The TPSAC report correctly concludes that the vast majority of smokers do not attribute any “explicit” reduced health risks to menthol cigarettes (p87). This conclusion is based on several recent studies which directly and explicitly ask smokers whether they perceive menthol cigarettes to be less hazardous to health. These studies consistently conclude that smokers understand that menthol cigarettes are not less likely to cause cancer or other serious disease. The report attempts to draw a distinction between smoker perceptions re: “implicit” versus “explicit” health protection (p88). This distinction is meaningless in describing smoker beliefs regarding the health hazards of menthol cigarettes. It simply is not logical to acknowledge that the overwhelming majority of smokers state an explicit opinion that menthol cigarettes are not less hazardous, yet on the other hand assert an opposite and conflicting conclusion based on so-called “implicit” perception of health protection.
- The report cites five articles (Pollay and Dewhirst 2002, Wakefield, et al. 2002, DiFranza et al. 2002, Hammond and Parkinson 2009, and Paek, et al. 2010) for the proposition that various taste and sensory descriptors (e.g., cooling, smoothness, reduced tar, mildness) are interpreted by smokers “to imply reduced harm” (p85). The implicit message in the report is that these studies show that menthol marketing activities communicate “implied” health messages. The cited articles provide no basis for this assertion.
 - Hammond and Parkinson 2009 has nothing to do with menthol cigarettes or menthol marketing. The focus of this article is product descriptors and taste/sensory descriptors of low/reduced tar cigarettes, which some smokers interpret as suggesting reduced risk. The article states that some smokers have the perception that a milder tasting cigarette may be less harmful, but it is clear that such perception is based on the understanding that milder taste goes hand-in-hand with reduced tar. The perception regarding reduced harm is based solely on lower tar, and has nothing to do with menthol.
 - Paek 2010 makes no effort to determine whether, in fact, smokers interpret various marketing terms or ad imagery as implying health benefits or reduced risk. Instead, this article simply asserts, without any independent analysis, that various terms such as “mild,” “smooth,” and various low tar descriptors communicate an implied health message. The substantive analysis in this article merely purports to quantify the frequency of so-called implied health messages from 1954-2003. Again, the article does not attempt to measure the extent to which smokers, in fact, receive an implied health message from menthol marketing. Indeed, the authors explicitly acknowledge that mere ad content analysis does not provide evidence regarding the effects of

cigarette advertising, but merely provides an empirical basis for “speculating” about the possible effects that cigarette ads have on consumers. (*See Paek at 783.*)

- Wakefield et al. 2002 is based solely on an analysis of tobacco industry documents and focuses on cigarette package design. The article states that green packs merely suggest menthol taste. Nothing in the article suggests that smokers perceive menthol cigarettes or menthol marketing to imply reduced harm. It should also be noted that the select few menthol-related tobacco industry documents cited in the article are each dated in the 1970s, more than 30 years ago, and thus are not relevant in assessing contemporary smoker perceptions about menthol cigarettes.
- DiFranza et al, 2002 also focuses exclusively on analyzing tobacco industry documents. The article has very little discussion regarding menthol cigarettes in general. There is no indication that smokers perceive menthol cigarettes as less harmful, and there is no suggestion that menthol marketing communicates an implied health message.
- Pollay and Dewhirst 2002 contains a very limited discussion to the effect that menthol cigarettes were perceived as less harmful during the 1950s; the article contains no discussion which purports to address whether smokers presently view menthol cigarettes as less hazardous. Moreover, the article repeatedly makes the point that, to the extent smokers view some cigarettes as less hazardous, such perceptions are based on reduced tar, not menthol.
- The TPSAC report correctly states that the data analyzed for the Bansal 2004 article reflects that the smokers who participated in the study “disagreed that menthol cigarettes were less harmful than regular cigarettes.” The report fails to acknowledge, however, that even higher levels of disagreement were registered on the specific question of whether “menthol cigarettes are safer than regular cigarettes.” The data analyzed in the Bansal article also reflect moderate agreement that menthol cigarettes are “smoother on your throat” and “easier on your chest.” The fact that these same data show strong disagreement that menthol cigarettes are safer than regular cigarettes demonstrates that taste/sensory perceptions do not constitute implicit health messages.
- The TPSAC report acknowledges that smokers are “acutely aware of the harms of smoking” and that “it is increasingly unlikely that consumers would identify any cigarettes as offering explicit health benefits” (p85). Nonetheless, the report goes on to state that “some studies reveal consumer perceptions that some cigarettes are safer than others,” citing articles by Hammond and Parkinson 2009 and Hammond et al. 2010. Given the context of this discussion, it is important to clarify whether either of these studies has any application to menthol cigarettes. In fact, neither study contains any discussion or analysis regarding menthol cigarettes or menthol marketing. There is no discussion or analysis in either article indicating that smokers perceive menthol cigarettes as less hazardous. The discussion in these articles focuses on the extent to which smoker perceptions regarding reduced tar result in perceptions regarding reduced risk.

C. Results of Some Studies are Misinterpreted

The TPSAC report cites a number of studies as evidence of reduced cessation among menthol smokers compared to nonmenthol smokers; however, correct interpretation of the results does not support this conclusion. Specific errors are described below:

- Foulds et al. 2006 (p142): This is an evaluation of a treatment clinic in which abstinence was assessed at 4 weeks and 6 months. The TPSAC report interprets this as a study that shows that nonmenthol smokers were more likely than menthol smokers to be abstinent, citing a “trend toward significant menthol effects, $p=0.053$.” This is an incorrect interpretation. In fact, a p value of 0.053 indicates that the results at 4 weeks were not significant (meaning chance cannot be excluded as an explanation for the finding). More importantly, cigarette type was not associated with abstinence at 26 weeks. The longer term results are the most important ones, as some people manage abstinence for brief periods but do not quit permanently.
- Pletcher et al. 2006 (p141) analyzed data from the CARDIA cohort study and assessed cessation over 15 years of follow-up. The report cites this study as one that showed reduced cessation among menthol smokers, noting a statistically significant increase in risk of relapse in menthol smokers compared to nonmenthol smokers, with similar results among African Americans and Whites. However, this study had 5 measures to assess cessation, and there were no significant associations between menthol smoking and 4 of these measures (not currently smoking; recent quit attempts; cessation if recent quit attempt; and sustained cessation, defined as no current smoking in the past 2 CARDIA exams, which were 2 to 5 years apart). The only significant association was with documented relapse, i.e., smoking at one follow-up visit after self-reported quitting at a prior visit (OR=1.89, 95% CI:1.17-3.05). Smokers at the baseline visit may have had a number of reasons to report not smoking at any single one of their follow-up contacts other than a decision to permanently quit smoking. Based on this single finding, the authors concluded that “... menthol cigarettes may be harder to quit smoking, but uncertainty about this point remains, in part because of the difficulty and large sample sizes required to tease apart the effects of ethnicity and menthol preference, which are highly correlated.” It is clear that the majority of measures of cessation in this study showed no difference, and the fact that “effects of ethnicity” are evident in a number of different cessation studies confirms the likelihood that uncorrected mediating or confounding factors associated with ethnicity or demographics are major determinants of cessation outcomes rather than menthol preference.
- Okuyemi et al. 2007 (p143): This publication describes a randomized clinical trial of smoking cessation (defined as 7-day abstinence) among African American light smokers (≤ 10 cigarettes/day). The TPSAC report states that at 26 weeks, abstinence rates were significantly lower for menthol smokers than nonmenthol smokers (11.2% vs. 18.8%, $p=0.015$). However, these percentages are not adjusted, even though there were significant differences between menthol and nonmenthol smokers in potentially confounding factors, including age and duration of smoking in years. Other analyses that considered relevant mediating factors and confounders did not show a significant difference in cessation success

for menthol compared with nonmenthol cigarette smokers. For example, adjusted logistic regression models stratified by age group (aged <50 and ≥50 years) did not indicate that menthol versus nonmenthol status was significantly associated with abstinence.

- Okuyemi et al. 2003 (p143): This is a randomized clinical trial of bupropion for smoking cessation among African Americans. Among subjects who received bupropion, abstinence at 6 weeks was significantly higher among nonmenthol smokers than menthol smokers (the same was not true for subjects who received placebo). However, that difference had disappeared by the terminal 6-month evaluation (p=0.21). Furthermore, abstinence rates did not differ by menthol status among those who received placebo, suggesting that menthol added to cigarettes does not influence spontaneous cessation (not aided by pharmaceuticals). It is unclear why the TPSAC report considers this as evidence that menthol smokers have reduced cessation outcomes.

D. Some Conclusions Rely Heavily on Document Analysis Articles and Decades-Old Industry Documents that do not Meet Requisite Scientific Data Quality Standards

The TPSAC report places too much emphasis on papers which purport to analyze industry documents (Kreslake NTR 2008, Klausner (in press)², and Wayne and Connolly 2004) to support the conclusions about the public health impact of menthol on smoking initiation.

- The report devotes significant space to summarizing industry document review papers and fully accepting those papers' analyses and conclusions at face value without examination or analysis of the underlying documents on which the review papers are based. TPSAC and the underlying papers' authors draw broad conclusions regarding the industry's knowledge of menthol's effects on smoking initiation and attribute industry-wide action based on a very limited and selective review of documents.
- The three document review papers cited in the TPSAC report section on smoking initiation offer analysis (pp115-116) of a very limited number of industry documents. For example, Klausner (in press) provided search terms and based on those terms identified 252,823 documents - a voluminous document set. The total number of industry documents cited in the three documents review papers totaled only 171 documents or .068 percent of all menthol related documents initially identified by Klausner. Klausner (in press) reported on 46 industry documents. Kreslake NTR 2008 reported on 58 industry documents and Wayne and Connolly 2004 reported on 67 industry documents. The majority of the documents reported on were dated in the 1970s and 1980s, decades ago.
- Drawing conclusions about six major corporations (Lorillard, Philip Morris, R.J. Reynolds, American Tobacco, Brown & Williamson and British American Tobacco) over a 50-60 year period based on less than one tenth of one percent of the available, potentially relevant documents is clearly insufficient to support the conclusions in these review papers. No information was reported regarding the context of the reviewed documents. These

² It is unclear which version of the Klausner article is cited in the TPSAC report. TPSAC received an unpublished Klausner paper as part of its briefing materials. The Klausner article was not published until May 2011, after the TPSAC report was issued. The paper from Klausner included in the briefing materials differs substantially from the published Klausner article.

document-review analyses are not objective, reproducible science; rather such reviews are primarily strings of quotes, often taken out of context, to support the authors' conclusions about how the industry's actions or knowledge should be construed.

Conclusions in the TPSAC report also rely on out-of-date tobacco industry documents which are not informative in assessing present-day smoker perception regarding the relative health risks of menthol versus non-menthol cigarettes. Neither the TPSAC report, nor any of the articles cited therein have any evidence of recent tobacco industry documents which suggest that smokers perceive menthol cigarettes to be less hazardous. Moreover, TPSAC selectively reports on document excerpts and provides incomplete quotes and summaries of literature reporting on industry documents in a way that is misleading.

- The discussion and analysis of Giovino et al. 2004 is incomplete and misleading (p83). Only a very small portion of this article addresses whether smokers perceive menthol cigarettes as less hazardous. Indeed, the article refers to only a few tobacco industry documents which purport to indicate that menthol cigarettes are perceived as being better for health; all cited documents are over 30 years old and do not reflect current smoker beliefs. More importantly, TPSAC, in its discussion of Giovino 2004, fails to acknowledge explicit statements in the article that more recent data show that only a very small percentage of smokers perceives any relative health advantage from menthol cigarettes.
- The discussion of Anderson (in press)³ is inaccurate and misleading (pp84). First, the TPSAC report incorrectly states that Anderson analyzed tobacco industry documents on consumer perception of menthol cigarettes “up to the mid 1990s.” In this regard, TPSAC cites a “1997” RJR document, while the Anderson article clearly states that the RJR document is dated 1977, not 1997. Moreover, the report fails to acknowledge that the American Tobacco focus group study is from 1969, over 40 years old. Second, and of greater concern, the report mischaracterizes the RJR document, quoting it for the proposition that “health concern was perhaps the primary motive in switching to menthol in the first place” (p84). The report, however, ignores language from the Anderson article which clarifies that the RJR document dealt with an analysis regarding the potential for share growth among “high filtration” menthol cigarettes, not just menthol cigarettes in general. A review of the entire RJR document reflects that statements concerning smoker perception as to “health protection” were based primarily on reduced tar, not just menthol. Indeed, both the TPSAC report and Anderson fail to acknowledge relevant information on the last page of the RJR document, which sets out a list (in descending order of significance) of the top 50 product benefits/attributes desired by menthol smokers. Notably, the benefit/attribute described as “Is least harmful to my health” ranked next to last, 49th out of 50.”
- The discussion of Klausner (in press) suffers from similar flaws. The Klausner article is cited as yet another example of an analysis of tobacco industry documents which allegedly show that menthol cigarettes are perceived as less harmful to health (p84). TPSAC fails to acknowledge that none of the pertinent tobacco industry documents discussed by Klausner

³ It is unclear which version of the Anderson article is cited by TPSAC. TPSAC received an unpublished Anderson paper as part of its briefing materials. The Anderson article was not published until May 2011, after the TPSAC report was issued. The paper from Anderson included in the briefing materials differs substantially from the published Anderson article.

were prepared during the last 25 years. Moreover, the TPSAC report provides a misleading characterization of a BAT consumer research study discussed by Klausner. Aside from the fact that the BAT study did not pertain to the United States market, both the report and Klausner fail to note that the BAT document also included statements which directly contradict the assertion that menthol cigarettes are perceived as less hazardous.

- The TPSAC report contains a fairly detailed discussion of the Kreslake NTR 2008 article. In particular, the report states: “Kreslake, et al. conclude that smokers who may otherwise quit because of the perceived harshness and health effects of higher tar cigarettes, seek out menthol cigarettes for their ‘substitute sensation’ as they move to what they perceive as a lower tar cigarette with its associated implicit health reassurance” (p84). TPSAC suggests that Kreslake indicates that the availability of menthol cigarettes has a negative impact on smoking cessation. Notably, this issue was not analyzed in Kreslake, but instead appears to rest on an isolated comment from a single participant in a focus group study conducted in the mid 1970s (*See* Kreslake at 711-712). More importantly, Kreslake contains no analysis of tobacco industry documents which purport to indicate that menthol cigarettes are perceived as less harmful. The reference in the TPSAC report regarding smoker perception of implied “health reassurance” is based on lower tar, not menthol (p84).

E. Statistical Results are Misstated

In a number of instances, the TPSAC report refers to study findings as being statistically significant when they are not. For example:

- Foulds et al. 2006 (p142): As described above, this is an evaluation of a treatment clinic in which abstinence was assessed at 4 weeks and 6 months. TPSAC interprets this as a study that shows that nonmenthol smokers were more likely than menthol smokers to be abstinent, citing a “trend toward significant menthol effects, $p=0.053$.” In fact, a p value of 0.053 indicates that the results at 4 weeks were not significant (meaning chance cannot be excluded as an explanation for the finding).
- The TPSAC report cites Muscat et al. 2009 as a paper that shows a shorter time to first cigarettes (TTFC) among menthol vs. nonmenthol smokers (OR=2.1; 95% CI: 96-3.8) (p127). In fact, the statistical analyses presented in this paper included no significant menthol vs. nonmenthol differences for FTND scores, daily cigarettes, heavy smoking and TTFC.

In other cases, the TPSAC report suggests that there are differences without providing statistics. For example:

- In its discussion of switching between menthol and nonmenthol cigarettes (pp113-115), TPSAC concludes that there is “some evidence to suggest that more menthol smokers switch to nonmenthol cigarettes within certain populations of smokers” (p115). A more appropriate analysis would consider the strengths and weaknesses of those studies, and find the evidence to be mixed and inconclusive.

- In arguing that the increasing trend in menthol use among youth is also true for novice smokers, the TPSAC report cites a single analysis (by RTI) with no statistical information. TPSAC reports data that show that the percentage of Marlboro menthol smokers increased more among novice than experienced smokers; however, no statistics are provided (p107).
- In its description of Ahijevych et al. 1996 (p197), the report states that plasma cotinine *tended* to be higher in menthol smokers than nonmenthol smokers, even though analysis showed these differences were not statistically significant.

F. Unadjusted Baseline Data and Adjusted Outcome Data are Treated Equally

In discussing various measures of dependence in Chapter 6, the TPSAC report contains an important error by confusing unadjusted baseline data⁴ with adjusted outcome data. Several measures of dependence were evaluated, including cigarettes per day (CPD), time to first cigarette (TTFC), and Fagerström test of nicotine dependence (FTND). Specifically, TPSAC failed to distinguish between those publications in which CPD (or TTFC or FTND) was an outcome variable (adjusted for relevant covariates) and those in which CPD (or TTFC or FTND) was merely reported as a baseline variable (not adjusted). It is inappropriate to draw conclusions from unadjusted baseline measures of CPD (or TTFC or FTND), because these are merely descriptive data. Menthol smoking is associated with numerous characteristics and one must do a multivariate analysis to determine which associations are independent and which are due to confounding by other variables. No analysis of the possible contributing factors was reported in the report.

G. Findings are Selectively Cited to Support Conclusions

In its discussion of addiction and dependence, the TPSAC report selectively sets forth findings that support its conclusion about adolescent menthol smokers, and ignores findings that do not support that conclusion.

- For example, the report states that Hersey et al. 2006 found that adolescent menthol smokers were 45% more likely to score above the median on the Nicotine Dependence Scale for adolescents than nonmenthol smokers (p130). However, TPSAC fails to acknowledge contradictory findings from that same study: menthol smokers were significantly less likely to report smoking on ≥ 20 of the last 30 days or to smoke ≥ 6 cigarettes per day. Thus, the findings of this study with respect to dependence among adolescent menthol smokers are mixed, not conclusive.
- The TPSAC report notes that Curtin et al. (unpublished) found that adolescent menthol smokers from the NYTS were significantly more likely to be overrepresented in higher versus lower cigarette use categories compared to nonmenthol smokers (p132). However, the report fails to acknowledge contradictory findings from Curtin's analyses of other survey data: that there were no significant differences in cigarettes per day between adolescent menthol versus nonmenthol smokers in the NHANES or NSDUH data sets.

⁴ Unadjusted baseline data (such as type of cigarette smoked, number of cigarettes smoked per day or time to first cigarette) merely describe the subjects at study entry. Many of these characteristics are correlated and, therefore, no conclusions can be drawn about any single characteristic until it has been examined as an outcome variable that has been adjusted for relevant confounders.

In the analysis of smoking cessation, Table 7 in Chapter 6 of the report presents findings of longitudinal cohort and clinical trial studies of smoking cessation. Appended to this table is an entire page of data on smoking cessation by cigarette type from the Delnevo et al. (unpublished) secondary analysis of the TUS/CPS survey (p187). Other (published) secondary analyses of data from the TUS/CPS are not included in this table (Alexander et al. 2010, Fagan et al. 2007, Fagan et al. 2010, Levy et al. 2011, Trinidad et al. 2010). It is unclear why one unpublished secondary analysis based on survey data is included in this table, although it is one of only two survey analyses that finds that Whites who smoke menthol cigarettes have lower rates of cessation than Whites who smoke nonmenthol cigarettes.

While devoting an entire page to the Delnevo unpublished analysis, TPSAC omits the Blot et al. 2011 study from Table 7, although it is discussed in the text (pp136,146). This large prospective study showed that, among Blacks, the prevalence of having quit smoking was similar for menthol and nonmenthol smokers; among whites, menthol users were statistically significantly more likely to have quit than nonmenthol smokers. Although the Blot study was embargoed until the afternoon that the TPSAC report was due to FDA, TPSAC had access to some version of this study as evidenced by the discussion of the study findings in the report (pp136,146). Curiously, several studies that were not published until after March 23, 2011, are included in Table 7. This study should have been included also, as it is an important addition to the literature on menthol smoking and cessation.

H. Causal Criteria are Inappropriately used before an Association has been Demonstrated

Early in Chapter 3, the TPSAC report raises questions regarding the biological plausibility that menthol increases the addictiveness of cigarette smoking, and suggestions of biological plausibility are raised repeatedly in other sections of the report. For example, in discussing smoking behavior, the report states “Also, by reducing the harshness of smoke, it is biologically plausible that menthol would facilitate deeper and prolonged inhalation of tobacco smoke, resulting in greater smoke intake per cigarette” (p26). It appears that biological plausibility is raised to strengthen the notion that there are associations between menthol smoking and various outcomes. Neither Bradford Hill 1965, nor The Surgeon General 1964 and 2004, intended any of the causal criteria to be used in this manner. According to the Surgeon General, the idea of biological plausibility is “that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms...” Both are careful to assert that biological plausibility is used as a “check” only after an association has been established. It cannot be used to establish the association.

I. Omissions and Inconsistencies are Evident Throughout the Report

The TPSAC report contains numerous omissions and inconsistencies. Some of the discussions are very difficult to follow. Examples of such discrepancies include:

- In the discussion regarding smoking cessation in Chapter 6, it is unclear how many studies TPSAC considered. Page 133 has conflicting statements, indicating that there were either 25 or 27 studies ($13 + 2 + 12 = 27$); Tables 6 and 7 list 25 studies (pp176-186).

- TPSAC’s discussion of dependence cites some studies as showing BOTH that menthol smokers smoke fewer CPD than nonmenthol smokers, AND as showing no difference in CPD between menthol and nonmenthol smokers (e.g., Fu et al. 2008, Hyland et al. 2002, p123).
- The term “novice” smokers is sometimes defined as smokers who have smoked less than 1 year (p41); smokers who have smoked less than 100 cigarettes in their lifetime, despite that some smokers may have smoked the 100 cigarettes over a period of several years (pp104,107,111,112,148,149), and is sometimes undefined (pp24,110,189). In addition, the heading in Table 3 (pp169-172) refers to “novice” smokers, while the studies cited in that table use different definitions of that term. The term “recent” smokers is also used (pp110,112).
- It is often difficult to determine which studies are being cited in the TPSAC report. For example, on pages 64,65,66,67,68,70,72,74,77,84 and 93, a study by Anderson is cited as “Anderson, in press.” Page 74 of the report cites “Anderson et al. (in press) and page 64 cites “Anderson 2010.” No citation for a study by Anderson is given in the chapter reference list. A study by S.J. Anderson titled “Marketing of menthol cigarettes and consumer perceptions: a review of tobacco industry documents” was published May 1, 2011 in Tobacco Control, 20(Supp. 2) ii20-ii28. An unpublished “white paper” titled “Menthol Marketing and Consumer Perceptions” from Anderson was also provided to TPSAC in briefing materials for the October 7, 2010 meeting. There are several differences between the Anderson “white paper” and the later publication. For example, the published Anderson article omits the listing of limitations that are present in the “white paper”.
- The TPSAC report fails to include the results of the most recent National Cancer Institute summary (NCI 2010) of smoking trends which reports that age of smoking initiation is rising, reflecting a decline in underage smoking. Sales of both menthol and nonmenthol cigarettes are continuing to decline, with sales volume of menthol brands showing a modestly less precipitous decline. It is misleading to equate the relative current popularity of one cigarette or another with an expansion of smoking prevalence in the face of a stable general decline in smoking.

III. TPSAC’S USE OF AN “EQUIPOISE” STANDARD IS NOT SCIENTIFICALLY APPROPRIATE

Chapter 2 of the TPSAC report states that “TPSAC provides its summary statements on the strength of evidence in a uniform fashion, offering a classification intended to be useful for decision making.” TPSAC used a “hierarchical classification for the strength of evidence providing its summary judgments:

- The evidence is sufficient to conclude that a relationship is more likely than not.
- The evidence is sufficient to conclude that a relationship is at least as likely as not.
- The evidence is insufficient to conclude that a relationship is more likely than not.
- There is insufficient evidence to determine whether a relationship exists.”

TPSAC stated that this hierarchy “was based around the concept of ‘equipoise.’”

A. The “Equipoise” Standard Used by TPSAC is Inappropriate for Assessing Weight of Evidence on Menthol Cigarette Smoking

Even if no other errors existed, the TPSAC report is fundamentally flawed as a result of TPSAC’s adoption and application of an entirely novel hierarchy for categorizing the strength of evidence, based loosely on the concept of “equipoise.” TPSAC’s use of this untested method of describing the strength of evidence is an inappropriate standard upon which to base regulatory action, and falls short of the objective scientific rigor required to draw conclusions regarding any impact of the use of menthol in cigarettes on public health.

TPSAC’s novel categorization hierarchy has not been used in any context other than the TPSAC report. Equipoise has historically been used in two contexts: (1) to provide an ethical basis for conducting medical research involving treatments of patients in clinical trials (Friedman 1987) and (2) to evaluate veterans’ eligibility for certain benefits for service-related injuries or conditions (Institute of Medicine 2008). Friedman described theoretical equipoise in the clinical context as the point “when, overall, the evidence on behalf of two alternative treatment regimes is exactly balanced.” He also indicated that theoretical equipoise “is disturbed when the clinician has, in Shafer’s words, what ‘might be labeled as bias or a hunch,’ a preference of a ‘merely intuitive nature.’” In using the concept of equipoise to determine whether veterans were eligible for benefits based on their exposure to Agent Orange, the Institute of Medicine stated “[w]e created the category of Equipoise and Above to capture the spirit of presumption: the tie goes to the veteran....”

Given the subjective nature of determining when “equipoise” exists in the clinical context and the presumption in favor of the existence of “equipoise” in the veterans’ benefits context, the application of the concept of “equipoise” cannot be translated appropriately to a scientifically rigorous evaluation of a relationship between menthol cigarette smoking and a particular health effect. Whether a cause-and-effect relationship exists for given associations among menthol cigarette preference and disproportionate consequences to the health of individual smokers or to the public health when compared to nonmenthol cigarette preference must be objectively evaluated based on a full and balanced consideration of data that are contrary to the hypothesis, as well as data that support the hypothesis.

The concept of “equipoise” might be useful in comparing and weighting results from two clinical studies of similar size and quality which have opposing findings. It is particularly inappropriate, however, to invoke the concept of “equipoise” as a conceptual point of exact balance between two bodies of scientific evidence when the body of available science is as heterogeneous as it is for menthol in cigarettes. Diverse and abundant data from laboratory experimentation and analysis, human biomarkers evaluations, epidemiological studies and surveys of self-reported human behaviors cannot reasonably be represented as being in a state of “exact balance” or imbalance, as these bodies of data are by nature too disparate and diverse to be weighed against one another. Rather, the entire body of disparate information on menthol in cigarettes must be considered together as a whole, with appropriate emphasis given to well-performed, rigorous studies reporting measurable and quantifiable outcomes when such studies are available. The strongest scientific evaluations of menthol in cigarettes are indeed very consistent in their findings that menthol and nonmenthol cigarettes convey similar risks to the smoker and similarly impact the public health at any level of use.

Using a standard based on “equipoise” allows TPSAC to draw conclusions that relationships between menthol cigarette smoking and various health effects exist based on a paucity of very weak data.

Further, TPSAC did not use the equipoise categories previously developed by the Institute of Medicine, but created its own categories which are completely untested and have not been used in any context previously. TPSAC eliminated the IOM category in which the evidence suggests no relationship exists between menthol cigarette smoking and the health outcome being examined. Even if the “equipoise” standard used by TPSAC began on a level playing field, TPSAC’s failure to include the “no relationship” category undercuts its analysis of menthol. Importantly, a very substantial body of diverse and powerful data falls clearly into the “no relationship” category which was improperly excluded by TPSAC’s interpretation of “equipoise.”

This flaw is of most concern in TPSAC’s conclusions regarding smoking initiation in Chapters 6 and 8. In Chapter 6 (pp109-110), the TPSAC report states “[t]he evidence strongly suggests a higher prevalence of menthol cigarette use among adolescent smokers compared to adult smokers, except among African Americans... The results also show that a higher proportion of younger adolescent smokers tend to smoke and prefer menthol cigarettes compared to older adolescent smokers... It is unclear whether greater proportions of younger adolescents initiate and experiment with cigarette smoking with menthol cigarettes compared with older adolescents.” The report also states in Chapter 6 (p113) that “[t]he preponderance of evidence shows that menthol cigarette smokers do not report an earlier age of initiation of cigarette use (age of onset of first cigarette or regular smoking (emphasis added)). However, the one study that examined an adolescent sample observed an earlier age of first smoking a whole cigarette among menthol vs. non-menthol smokers.” The cited study is unpublished. Despite these statements, in Chapter 8 (p216), TPSAC concludes that “[t]he evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes increases experimentation and regular smoking (Above Equipoise).” This example demonstrates how little evidence was required by TPSAC to tip the balance in favor of concluding that the evidence was “Above Equipoise.”

Objectivity and consideration of all the evidence, both for and against the existence of a purported causal relationship, are hallmarks of required regulatory science principles. These requirements are not met under the standard adopted by TPSAC. A significant example of the inadequacy of the “equipoise” standard as represented by TPSAC to objectively assess any public health consequences of menthol in cigarettes is the fact that findings of some epidemiological investigations and analyses that suggest modest to statistically significant reduced risks for lung cancer (e.g. Etzel et al. 2008, Blot et al. 2011, Lee 2011) are assigned no weight whatsoever in the TPSAC analysis.

B. The Application of the “Equipoise” Standard is Unclear

Throughout the TPSAC report, TPSAC’s unproven hierarchical categorizations lack the methodological rigor necessary to determine how its causal conclusions were made. Unlike the criteria used by the Surgeon General, IARC, EPA and others to determine the existence or the strength of causal relationships, the application of TPSAC’s adopted categories is unclear. TPSAC’s approach lacks specific common assessment criteria to be followed in evaluating the evidence. TPSAC stated that “[b]ecause of the variable nature of the evidence considered from chapter to chapter, TPSAC did not propose specific criteria that would be applied uniformly.” The evidence

available on the subject of menthol in cigarettes is indeed varying and diverse, but the strength of such diversity cannot be meaningfully represented by the loose and subjective process that was applied by TPSAC.

The absence of uniform, specified criteria severely limits conclusions that can be drawn from TPSAC's approach. TPSAC's lack of a methodical evaluation of the evidence and a consistent, explicit statement of its justification for weighting of diverse evidence does not permit an independent reproduction of the process that resulted in TPSAC's conclusions. Further, TPSAC often fails to state its conclusions in a way so that the conclusions clearly fall into one of its proposed categories thereby adding additional uncertainty in regard to the bases for those conclusions.

CONCLUSION

Lorillard continues to believe that FDA regulation of tobacco should be driven by a comprehensive, objective and rigorous assessment of the scientific data. Lorillard, respectfully, does not believe that the TPSAC report on the use of menthol in cigarettes meets this standard. Given the fundamental flaws throughout the TPSAC report (examples of which have been discussed above), the TPSAC report fails to meet the standards of quality, inclusiveness, comprehensiveness and scientific rigor that were communicated in the FDA charge to the committee. These standards are similar or identical to those required for other evaluations of diverse scientific information for the purposes of promoting sound regulatory science and informed policy decision-making in all areas of FDA and other agencies' purview. These standards apply to both experimental research, as well as reviews of scientific literature.

The low quality and numerous errors and omissions of the TPSAC report are unacceptable. Lorillard does not believe that the TPSAC report meets the necessary standard upon which FDA can rely in any regulation of the use of menthol in cigarettes. Further, Lorillard does not believe that the TPSAC report and the recommendations therein have any place in FDA's consideration or regulation of menthol cigarettes under the FSPTCA.

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