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June 29, 2010

Lawrence Deyton, M.S.P.H., M.D.  
Director, Center for Tobacco Products  
Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, MD 20850-3229

Re: Lorillard Submission In Regard to FDA-CTP Staff Briefings and Preparation  
of a White Paper on Menthol Science

Dear Dr. Deyton:

On behalf of Lorillard, I attended the first meetings of the Tobacco Products Scientific Advisory Committee on March 30-31, 2010. Lorillard is concerned that the format and content of these meetings was not consistent with a fair and impartial process and several of the presentations fell far short of our expectation of a totally inclusive and objective review of the literature with respect to the current state of menthol science. Additionally, the written submissions provided to FDA in advance of the meetings by Lorillard and others on or before the specified deadline of March 22, 2010 are still not publicly available at the TPSAC web site at this writing. The process transparency and engagement of the regulated industry that Commissioner Hamburg and others have stated as fundamental themes of the FDA-CTP regulatory process going forward may only be achieved if and when the regulated industry is provided access to all appropriate pre- and post-meeting materials in a timely manner.

Lorillard recognizes both the time constraints and volume of information that must be considered by the TPSAC in evaluating the state of the scientific evidence on the use of menthol in cigarettes. We appreciate the challenge the FDA-CTP faced to assemble a staff quickly and identify scientists to make the initial review presentations to the committee. However, most of the issues related to menthol in cigarettes require competent analysis by scientists with years of expertise. The large volume of published studies in several topic disciplines requires adequate time to thoroughly review and understand the strengths and limitations of the underlying data and statistical models used. Lorillard is concerned that the schedule is driving the evaluation process rather than a complete critical analysis of the scientific evidence. This is not acceptable in a process grounded in the principles of sound science to which the FDA-CTP has committed to adhere. The committee was clearly impacted by the information and conclusions presented as evidenced

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in their follow-up discussions. The fact that, in several instances, the information and conclusions presented were incomplete and/or inaccurate has tainted the process and the committee. Lorillard urges the FDA-CTP to take specific action to acknowledge the limitations of these initial presentations and ensure that a thorough and objective review be provided in the upcoming staff White Paper.

Several presentations made to the TPSAC contained slides in which “tobacco industry-funded studies” were identified with an asterisk and red font color. In contrast, referenced studies that were conducted or sponsored by tobacco control organizations, some of which were not peer-reviewed or contained no primary scientific data, received no such designation. The highlighting of certain peer-reviewed, published scientific papers as “tobacco industry-funded studies” is inappropriate and compromises the objective science base of the TPSAC process. The potential of this manner of presentation to instill bias into what should be an objective assessment is unacceptable by any reasonable standard and should be deleted from all subsequent presentations, summaries and white papers. Going forward, the TPSAC will find that some of the most significant and advanced analyses and laboratory assessments of tobacco products have been conducted by tobacco industry interests or performed by these interests at independent extramural laboratories. This body of work must be considered in a balanced manner alongside similar work from non-industry investigators.

In addition, certain presentations made at the March 2010 Meetings included selective, detailed representations of only those studies, or portions of certain studies, that have suggested a potential effect of menthol. These presentations made only passing mention of worthy studies that have not found menthol to be associated with meaningful adverse effects, or omitted them entirely. In some instances, the presentations delivered to the TPSAC included interpretations that were contradictory to those of the authors of the cited published papers. This kind of presentation is scientifically inappropriate and does not constitute an accurate summarization of the state of current knowledge on menthol in cigarettes. Future TPSAC presentations by FDA-CTP staff must adhere to the scientific principles of objectivity and inclusiveness that are essential element of the regulatory process going forward.

In particular, the presentations of Allison C. Hoffman, Ph.D. were the most egregiously lacking in objectivity and thoroughness. Dr. Hoffman presented three Powerpoint slide presentations. The presentation entitled “Possible Health Effects of Cigarette Mentholation,” ostensibly on the published scientific literature regarding the potential health effects of menthol, was particularly selective and presented an inaccurate representation of this literature to the TPSAC. She was particularly comfortable deviating from the conclusions presented in the papers she reviewed and offering her own speculative theories and assertions that have origins in advocacy rhetoric that are not supported by scientific data. For example, Dr. Hoffman’s Slide #30, “Tobacco-Related Diseases” states that menthol has not been shown to alter smokers’ likelihood of developing “[s]everal kinds of cancer, including lung and non-lung smoking related cancer” or “[c]ardiovascular disease or coronary heart disease”. The slide goes on to state “[b]ut, may not be so straightforward...”[emphasis added]. To describe the compelling epidemiology evidence as less than straightforward is an inaccurate characterization of the state of science regarding menthol cigarettes and disease risks.

Further, Dr. Hoffman has a history of activity in a closed advocacy forum on the subject of menthol cigarettes. Dr. Hoffman, detailed to the FDA-CTP from N.I.D.A., is listed among the organizers of the 2009 Second Menthol Conference, a closed advocacy forum funded and attended by tobacco litigation interests, anti-menthol activist groups, tobacco control organizations, academics, and government employees. This meeting was not open to the public or to scientists who may hold different scientific opinions regarding menthol. Dr. Hoffman's recent history of active participation in the organization of this event constitutes a clear conflict of interest that in my opinion should unequivocally preclude her from participation in the preparation of what is intended to be an objective summary review and distillation of all of the available scientific information on the possible health effects of menthol in cigarettes. Other presentations also suffered from selective analysis and omissions, although none to the extent of Dr. Hoffman's.

Accompanying this letter is a copy of Lorillard's submission (submitted to FDA under separate cover) containing an overview of Lorillard's positions on the state of science with respect to the use of menthol in cigarettes. Lorillard's submission also contains specific comments regarding several of the presentations made at the March 2010 Meetings. Lorillard's submission is intended to assist the FDA-CTP and TPSAC in fulfilling their respective obligations to develop sound, science-based regulatory processes and advisory opinions in regard to tobacco products.

Lorillard remains ready to assist the FDA-CTP in meeting its charge to develop informative, inclusive and defensible science-based briefing papers to inform future TPSAC discussions.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "William R. True". The signature is fluid and cursive, written in a professional style.

William R. True, Ph.D.  
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cc: Cristi Stark, M.S., Acting Designated Federal Official Office of Science, CTP  
Karen Templeton-Somers, Ph.D. OS/CTP, David L. Ashley, Ph.D., Director, Office of  
Science

**To The  
Tobacco Products Scientific Advisory Committee**

**Submission of  
Lorillard Tobacco Company  
in Regard to FDA-CTP Staff Briefings  
And Preparation of a White Paper**

**On**

**The Science  
Relating to Menthol Cigarettes**

**Submitted  
June 29, 2010**

Available for Public Disclosure Without Redaction

## INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act, signed into law by the President on June 22, 2009, established the Tobacco Products Scientific Advisory Committee (“TPSAC”). FDA announced the creation of the TPSAC on August 26, 2009 (Final Rule (Aug. 26, 2009)). The Final Rule states: “The committee reviews and evaluates safety, dependence, and health issues relating to tobacco products and provides appropriate advice, information, and recommendations to the Commissioner.” Among the topics on which the committee will submit reports and recommendations is “[t]he impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, Hispanics and other racial and ethnic minorities.”

On March 1, 2010, FDA announced the voting members of the Committee, as well as the first meetings of the Committee on March 30-31, 2010 (Press Release (Mar. 1, 2010)). During the first meetings (March 2010 Meetings), the FDA staff stated that a white paper on the science related to menthol in cigarettes (White Paper) was being prepared. Lorillard Tobacco Company submits these comments to accompany the White Paper for consideration by the TPSAC.

Lorillard believes that a single scientific standard must apply to the performance, publication and subsequent consideration of all available research data. A similar standard must apply to the summarization of scientific literature meant to guide the TPSAC in its contribution to the development of FDA policy in matters of science. That single standard is objectivity in considering scientific information, inclusion of all available information on a given topic, and consideration of the full spectrum of worthy interpretations of existing data. The statutory charge requires the TPSAC to render objectively-formed advisory opinions that are founded in sound science, and Lorillard fully supports an open and objective TPSAC process.

In this submission, Lorillard presents information that demonstrates that menthol in cigarettes has no meaningful effect on public health. This conclusion is evidenced by a substantial weight of published scientific data. Lorillard provides this submission, in part, to clarify portions of several presentations made at the March 2010 Meetings. Some presentations failed to include important available published scientific studies on menthol in cigarettes and made only passing mention of, or entirely omitted worthy studies that have not found menthol to be associated with meaningful adverse health effects. In some instances, the presentations delivered to the TPSAC included interpretations that were contradictory to those of the authors of the cited published papers.

## SUMMARY

An overwhelming body of epidemiology findings indicates that chronic smoking-related disease risks are unrelated to cigarette mentholation. These findings are powerfully supported by and consistent with available chemistry, toxicology and biomarkers data that indicates that menthol and nonmenthol cigarettes do not differ in terms of public health impacts.

Levels of biomarkers of exposure, which are quantitative measures of smokers' systemic exposures that reflect the combined influences of all aspects of smoking behavior, are not elevated among menthol smokers. Biomarkers findings to date are consistent with similar smoking behaviors and inhalation intensities between menthol and nonmenthol cigarette smokers.

Both the epidemiology and biomarkers results are consistent with equivalent smoking cessation by menthol and nonmenthol cigarette smokers in the general population.

Major surveys of cigarette brand preferences among adolescent and adult smokers show that the top three largest-selling brands are the same across all age categories of both occasional and regular smokers. African-American adolescent smokers report a higher preference for menthol cigarettes than do White adolescent smokers, and yet those African-American adolescents have, for many years, reported a much lower rate of smoking than their White counterparts. This and other information indicates that menthol does not facilitate smoking among youth. In fact, a state-by state comparison of youth smoking rates and menthol cigarette sales shows a modest but statistically-significant inverse correlation. Menthol is clearly not a causal factor in youth smoking initiation.

The smoke chemistry of menthol and nonmenthol cigarettes is not meaningfully different in terms of the concentrations of substances that are broadly suggested to be involved in the etiology of smoking-related diseases. The smoke of menthol cigarettes is no more toxic in a variety of laboratory toxicology studies (Heck (2010)) and does not elevate putative biomarkers of harm that are presently under development and validation for application in comparative risk evaluations among cigarettes (Hatsukami *et al.* (2007); Frost-Pineda *et al.* (2010)).

At the March 2010, Meetings, the following presentations were made to the TPSAC:

- Use of Menthol Cigarettes by Demographic Groups, by R. S. Caraballo, Ph.D., M.P.H. (Caraballo Demographic Groups)
- Menthol Sensory Properties and Possible Effects on Topography, by D. Lawrence, Ph.D., M.P.H. (Lawrence Topography)
- Perceptions and Marketing of Mentholated Cigarettes, by Josh Rising, M.D., M.P.H. (Rising Perceptions and Marketing)
- Menthol and Initiation of Smoking, by Josh Rising, M.D., M.P.H. (Rising Initiation)

- Menthol's Potential Effect on Nicotine Dependence, by Allison C. Hoffman, Ph.D. (Hoffman Nicotine Dependence)
- Menthol and Smoking Cessation Behavior, by Allison C. Hoffman, Ph.D. (Hoffman Cessation)
- Possible Health Effect of Cigarette Mentholation, by Allison C. Hoffman, Ph.D. (Hoffman Health Effects)

Specific comments on these FDA staff briefing presentations to the TPSAC are offered below.

## **I. EPIDEMIOLOGY STUDIES ARE STRONG AND CONSISTENT IN FINDING THAT MENTHOL IN CIGARETTES DOES NOT INCREASE DISEASE RISK**

### **A. Epidemiology Studies Overview**

The extensive body of published epidemiology studies that have compared the disease risk between menthol and nonmenthol smokers establishes that menthol smokers are at no greater risk of developing smoking related diseases than nonmenthol smokers.

Chronic disease epidemiology provides the foundation for all of the Surgeon General's conclusions on disease causation associated with smoking (SGR 2004). Most importantly, epidemiological studies integrate the combined impact of composition and design of cigarettes, the age of smoking initiation, smoking cessation (including both continued smoking and quitting), and smoking intensity and behaviors on public health. Stratton *et al.* (2001) stated: "Most of what is known about harmful tobacco products has resulted from epidemiology. ... [E]pidemiological studies can provide the most definitive data about tobacco harm." The recognition of epidemiology as the most powerful tool to provide definitive information about risks to public health by the Surgeon General and the National Academies of Science, Institute of Medicine, is particularly relevant to the evaluation of any health effects of menthol in cigarettes.

Menthol is unique among cigarette flavoring ingredients in that numerous epidemiological studies have investigated whether menthol smokers are at a greater risk for developing smoking-related diseases than are nonmenthol smokers.

The epidemiological evidence provides a compelling basis to conclude that the risks for developing cancers and other smoking-related diseases are not increased for menthol cigarette smokers as compared to nonmenthol cigarette smokers. To date, thirteen epidemiological studies comparing smoking-related disease outcomes between menthol versus non-menthol cigarette smokers have been published (Hebert & Kabat (1988); Hebert & Kabat (1989); Kabat & Hebert (1991); Kabat & Hebert (1994); Sidney, *et al.* (1995); Friedman, *et al.* (1998); Carpenter, *et al.* (1999); Brooks, *et al.* (2003); Stellman, *et al.* (2003); Jockel, *et al.* (2004), Pletcher, *et al.* (2006); Murray, *et al.* (2007); Etzel, *et al.* (2008)) The disease outcomes evaluated include smoking-related cancers such as those of the lung, esophagus, oropharynx, upper aerodigestive tracts, pancreas, kidney, urinary

tract and uterine cervix as well as coronary calcification, pulmonary function decline and mortality from coronary heart disease, cardiovascular disease, lung cancer and all causes.

Twelve of the thirteen studies reported no significant differences between menthol versus non-menthol smokers for any of the health outcomes evaluated. The overwhelming findings of these studies demonstrate that menthol in cigarettes plays no role in the inherent disease risks of smoking

- *“We analyzed existing data from a case-control study of esophageal cancer and found no menthol effect.”* (Hebert and Kabat (1988))
- *“Our results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer.”* (Hebert and Kabat (1989))
- *“Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types or lung cancer in this study. In contrast, the number of cigarettes smoked per day and duration of smoking were strong risk factors.”* \*Kabat and Hebert (1991))
- *“These results indicate that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer.”* (Kabat and Hebert (1994))
- *“Risk was not increased among persons who currently smoked mentholated compared with plain cigarettes for all of the non-lung smoking related cancers combined or for most sites studied.”* (Friedman, et al. (1998))
- *“Our results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes. Our data do not support the hypothesis that the increased risk of lung cancer among African Americans is due to the increased prevalence of menthol smoking.”* (Carpenter, et al. (1999))
- *“In summary, our results do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer more than does smoking nonmenthol cigarettes”.* (Brooks, et al. (2003))
- *“While black smokers in our study were more likely to choose menthol than non-menthol brands (Table 2), our data provide no evidence that menthol cigarettes per se produce greater lung cancer risk than do non-menthol brands (Table 4).”* (Stellman, et al. (2003))
- *“The present study gives no indication for an additional risk [of lung cancer] of ever smoking menthol cigarettes if total amount of smoking is taken into account”.* (Jockel, et al. (2004))
- *“Mentholation of cigarettes does not seem to explain disparities in ischemic heart disease and obstructive pulmonary disease between African Americans and European Americans in the United States....”* (Pletcher, et al. (2006))
- *“In sum, we found no indication in these data that mentholation of cigarettes is a property that contributes to the well-known harms from smoking.”* The authors also mentioned a manuscript in preparation that may report findings that *“... menthol cigarettes are indeed protective against cancer (manuscript in preparation).”* (Murray, et al. (2007))
- *“...[W]e observed no significant [excess] risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes (OR range, 0.69–0.99) and our*

*data suggested a possible protective effect of mentholated cigarettes for current smokers.” (Etzel, et al. (2008))*

Only one of the studies reported a statistically elevated risk [relative risk (RR) 1.45; 95%CI: 1.03-2.02] for lung cancer among men who smoked menthol cigarettes compared with men who smoked non-menthol cigarettes (Sidney, *et al.* (1995)). No significant menthol-related increase in risk, however, was found among women in this study. The same investigators conducted a follow-up investigation using the same study population to determine if increases related to smoking menthol cigarettes in other smoking-related cancers were observed (Friedman, *et al.* (1998)). No increases in risk for smoking menthol cigarettes were found for the other smoking-related cancers studied. The authors of this later study noted that “...[T]he association of mentholation with lung cancer in this study population may be merely a chance finding, particularly as it was absent in women and has not been replicated elsewhere.” (Friedman *et al.* (1998)).

Given that the overwhelming weight of the epidemiology evidence specifically addressing the risk of smoking menthol cigarettes shows no difference between the disease risks of smoking menthol cigarettes and nonmenthol cigarettes, claims that the results of the epidemiology are equivocal or mixed are scientifically invalid.

**B. Presentation to TPSAC on Possible Health Effects of Cigarette Mentholation, by Allison C. Hoffman, Ph.D.**

Lorillard offers these specific comments on the Hoffman Health Effects presentation:

1. **Hoffman Health Effects Slide #14, Cell Membrane Permeability (continued):** The slide discusses the work of Azzi, *et al.* (2006) that employed an isolated pig esophageal segment to study potential interactive effects of ethanol and menthol on tissue permeation by B[a]P and NNK. The authors’ stated intent was to explore potential bases for the claim that smoking and drinking may act synergistically to increase esophageal cancer risk.

The slide properly itemizes some of the limitations of the experimental approach. While not discussing epidemiology in this slide, the slide goes on to state, inaccurately, that “[e]pidemiological studies are inconclusive” in regard to the relative esophageal cancer risks for menthol and nonmenthol cigarettes. This point is discussed further in comments below on menthol cigarette epidemiology. Briefly, Hebert and Kabat (1988) stated in a published letter report that “[w]e analyzed existing data from a case-control study of esophageal cancer and found no menthol effect.” These same authors performed a subsequent, more detailed analysis of their findings (Hebert and Kabat (1989)) and concluded that “[o]ur results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer.” These two papers appear to be the

only reports to date that have specifically addressed esophageal cancer risk, but the authors' own conclusions indicate that the state of knowledge in this area is not accurately represented as "inconclusive" as it was in Dr. Hoffman's slide #14. In addition, Friedman *et al.* (1998) concluded that the risk of developing cancers of the upper aerodigestive tract for menthol smokers was not increased over that risk for nonmenthol smokers. The conclusions stated in the Hebert and Kabat and Friedman papers are clear and completely inconsistent with a characterization that the state of knowledge in this area is inconclusive.

2. **Hoffman Health Effects Slide #15, Cytotoxicity or Reduced Cell Proliferation:** The numerous toxicology studies on both menthol as an individual compound and cigarette smoke from menthol cigarettes were summarized in Heck (2010). In paragraph 3.9.4 *Conclusions regarding menthol cigarette toxicology*, Heck (2010) noted "[a]n extensive and reassuring weight of *in vitro* and experimental animal investigation indicates that menthol does not pose a toxic or carcinogenic hazard..." and "[t]he presence of menthol at realistic and exaggerated levels in experimental test cigarettes has not been found to introduce novel manifestations of toxicity to the smoke or smoke condensate, nor does it increase the inherent toxicity of the smoke..."  
The characterization of menthol as "[t]oxic in *in vitro* biologic model systems" in the presentation is scientifically unsupportable.
3. **Hoffman Health Effects Slide #17, Respiration:** The slide states that "...[a]n early tobacco industry study reported that mentholation of cigarettes appeared to exert an adverse effect on respiratory function." This statement is referenced to a discussion of internal industry documents published by Wayne and Connolly (2004), which states that "...[a]n early Philip Morris study of Paxton cigarettes found that "menthol seemed to exhibit an adverse effect on the respiratory function" (Carpenter (1964))." The cited source document, a two paragraph memorandum dated February 10, 1964, contains no additional information to allow an appraisal of what the author of the 46 year-old internal memorandum was referring to. This sort of citation is arguably out of scope for the March 30, 2010 TPSAC theme of reviewing published scientific literature and has no place in a slide summary representing itself to be an objective summary of available peer-reviewed studies on a given scientific topic. Further, the presentation on this respiratory function topic neglects to mention the peer-reviewed cohort study of Murray *et al.* (2007) which reported no differences in respiratory function decline between smokers of menthol and nonmenthol cigarettes. The omitted Murray paper, developed from the Lung Health Study cohort with a 15-year

follow-up, is clearly and powerfully in scope and on-topic as a human study of respiratory function. These authors stated that “[w]e conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking.”

4. **Hoffman Health Effects Slide #21, Cardiovascular Function (continued):** This entire slide is devoted to the reports of Ciftci *et al.* (2008a,b; 2009). The 2009 paper is not listed among the references. These Turkish studies were performed with unidentified cigarettes of unknown composition and menthol content that were presumably obtained from the Turkish marketplace. How these cigarettes may compare to those in the US marketplace is not discussed in the reports and, therefore, extrapolating the results to U.S. menthol cigarettes is inappropriate.

Further, the slide fails to note that several studies have reported no effect of menthol in cigarettes on cardiovascular function (Nil and Battig (1989); Caskey *et al.* (1993); Miller *et al.* (1994); McCarthy *et al.* (1995) and Pickworth *et al.* (2002). Pletcher *et al.* (2006) concluded that menthol in cigarettes did not increase the risk of atherosclerosis. Murray *et al.* (2007) reported that, in the Lung Health Study, there was no indication that menthol in cigarettes increased risks of coronary heart disease or cardiovascular disease. Based on these findings, the reported observations of Ciftci *et al.* seem to be not only irrelevant to the cigarettes in the US marketplace, but also at odds with the weight of available scientific literature on menthol and cardiovascular risks.

5. **Hoffman Health Effects Slide #23, Allergic Reactions and Inflammation:** The cited 1951 and 2003 papers are representative of scattered case reports of unusual allergic responses attributed to menthol cigarettes, possibly akin to those that have appeared periodically in association with the topical use of other menthol-containing consumer products. Rare individuals manifest hypersensitivity reactions to a variety of flavorings and functional food and consumer product ingredients. Menthol is not notable in this regard, as has been repeatedly reported in expert panel evaluations around the world. The rare individual who may find that menthol exerts untoward reactions may simply choose alternative products without characterizing levels of menthol. To present studies of only four individuals as meaningful to menthol smokers, generally, is improper. As with the Ciftci papers discussed above at Hoffman Health Effects Slide #21, it is inappropriate for the presentation to include these reports, but fail to include so many other more relevant publications.

6. **Hoffman Health Effects Slide #30, Tobacco-Related Diseases (cont.):** The slide states that menthol has not been shown to alter smokers' likelihood of developing "[s]everal kinds of cancer, including lung and non-lung smoking related cancer" or "[c]ardiovascular disease or coronary heart disease". The slide goes on to state "[b]ut, may not be so straightforward..." To describe this compelling evidence as less than straightforward is an inaccurate characterization of the state of science regarding menthol cigarettes and disease risks.

7. **Hoffman Health Effects Slides #31 and 32, Tobacco-Related Diseases (cont.):** Slide #31 states that Carpenter *et al.* (1999) "suggested an increased risk for male menthol smokers and lung cancer...not statistically significant". This is an inaccurate representation of that study's conclusion that "... the results from this study suggest little or no increase in lung cancer risk associated with mentholated cigarette smoking compared to non-mentholated smoking."

Slide #31 also mentions the sole epidemiology study which found a slightly increased risk of lung cancer for male menthol smokers only (Sidney *et al.* (1995)). The slides, however, fail to disclose fact that one of the study's co-authors later stated "*...the association of mentholation with lung cancer in this study population may be merely a chance finding, particularly as it was absent in women and has not been replicated elsewhere.*" (Friedman *et al.* (1998)).

Slides #31 and #32 inaccurately represent the available body of published menthol cigarette epidemiology findings, with selective "cherry-picking" of only the few published odds ratios, hazard ratios or relative risks from some studies that have trended above 1.0, all but one of which (See Sidney *et al.* (1995) discussed, above) were not statistically significant. This markedly incorrect representation of extant data ignores many more such main and sub-group comparisons found in the very same mentioned papers that clearly show that menthol and nonmenthol cigarettes are statistically indistinguishable in terms of risk. There are, in fact, an equal or greater number of such comparisons in these same papers that show by the very same methods that menthol cigarettes convey a reduced disease risk.

The tobacco industry's non-voting TPSAC member's clarifying question to Dr. Hoffman in regard to the omission from her presentation any discussion of the latest available case-control study comparing lung cancer occurrence among African-American smokers of menthol and nonmenthol cigarettes (Etzel *et al.*, 2008) is a matter of record in the meeting transcript. This paper, published in an

official journal of the American Association for Cancer Research, was included on page 92 of the NCI menthol bibliography and it was also provided to FDA and the TPSAC as an appendix to written comments submitted by the Lorillard on March 23, 2010. Dr. Hoffman's response to the TPSAC member's question on the omitted 2008 Etzel paper was telling. Dr. Hoffman obviously was familiar with the paper, so its exclusion from the presentation to TPSAC does not appear to have been unintentional. This excluded paper's conclusion that "...[o]ur data suggests a protective effect for mentholated cigarettes for current smokers..." appears to have been inconveniently at odds with the biased conclusion regarding menthol that Dr. Hoffman seemed to be presenting to the TPSAC members. Dr. Hoffman mentioned that the Etzel paper would be included in the white paper, although this was the first and only mention that a white paper was being developed.

In addition, the official transcript of the March 2010 Meetings, as posted on the FDA website, contained a serious transcription error as well as a number of minor errors. On page 269, lines 8-10, of the official transcript of the March 2010 Meetings, the transcript read: "DR. HECK: The paper also concluded that menthol isn't near as protective, in their words, relative to nonmenthol cigarettes." The correct transcription is "**DR. HECK: The paper concluded that menthol is near protective, in their words, relative to nonmenthol cigarettes**[emphasis added]." FDA was notified of the major transcription error that served to represent the speaker's statement to be the opposite of that intended on May 25, 2010.

8. **Hoffman Health Effects Slide #34, Discussion:** Neither of the papers cited on this slide (Rabinoff *et al.* (2007); Garten *et al.* (2003)) contain any primary scientific data to support their authors' speculations regarding menthol and other ingredients. These papers recite previously-reported speculations about menthol and do not meaningfully add new knowledge on the topic. These references are not worthy elements of a summary of published scientific studies that is intended to brief a Scientific Advisory Committee.

## II. MENTHOL IN CIGARETTES HAS NO MEANINGFUL EFFECT ON BIOMARKERS OF CIGARETTE SMOKE CONSTITUENT EXPOSURE

### A. Biomarkers Studies Overview

Biomarker studies integrate and reflect the impact of all the diverse elements of complex human smoking behaviors, including cigarettes smoked per day, puffing intensity (puff

number, volume, interval and duration), percent of cigarette smoked and filter ventilation hole blocking, if any.

A substantial body of published work comparing biomarkers of exposure to several smoke compounds in smokers of menthol and non-menthol cigarettes shows that menthol in cigarettes does not increase exposure of smokers to smoke constituents, including some constituents that are believed to cause disease. The majority of published studies have reported that measured biomarkers of exposure are similar (*i.e.*, do not differ to a statistically-significant degree) between smokers of menthol and nonmenthol cigarettes (Richie *et al.* (1997); Rosenblatt *et al.* (1998); Patterson *et al.* (2003); Benowitz *et al.* (2004); Moolchan *et al.* (2006); Muscat *et al.* (2009); Heck (2009); Wang *et al.* (2010)).

**B. Presentation to TPSAC on Possible Health Effects of Cigarette Mentholation, by Allison C. Hoffman, Ph.D.**

Lorillard offers these additional specific comments on the Hoffman Health Effects presentation:

1. **Hoffman Health Effects Slide #8, Carbon Monoxide (continued):** Neither of the published papers cited on this slide (Ahijevych *et al.* (1996); Rabinoff *et al.* (2007)) contains any primary data that substantiates the speculations offered here that menthol may affect physiologic variables, that menthol deliveries in smoke may be reduced by pyrolysis, or that menthol may interact with other chemicals present in smoke. FDA should focus on published primary literature or balanced reviews of that literature that represent the spectrum of available primary scientific information.
2. **Hoffman Health Effects Slide #9, Tobacco-Specific Nitrosamines:** FDA is referred to the written comments submitted by Lorillard on March 22, 2010 (pages 18–21 and Appendix F) for discussion of the different findings of the two papers from Muscat and coworkers (Richie *et al.* (1997); Muscat *et al.* (2009)) and the limitations of the latter paper's experimental design in regard to the reported microsomal incubation. Briefly, that experiment comprised a single, 2-hour incubation with menthol concentrations greatly in excess of physiological concentrations that may plausibly be attained from smoking cigarettes, and NNK concentrations approximately 5 million-fold in excess of reported smoker plasma levels. Any single experiment performed under such physiologically irrelevant conditions, and still unconfirmed by any other independent laboratory, is a fragile and inadequate scientific basis for a summary statement to the TPSAC that menthol may affect NNK or NNAL metabolism and excretion.

3. **Hoffman Health Effects Slide #10, Does Menthol Inhibit Metabolism of NNAL in Smokers?:** This slide inaccurately communicates to the audience that the findings of Heck (2009) and of Muscat *et al.* (2009) are at odds in terms of reported effects of menthol on NNAL glucuronidation. In fact, the human smoker biomarkers report of Heck (2009) was not intended to analyze and did not discuss the NNAL:NNAL-glucuronide metabolite ratio.

The papers of Heck (2009) and Muscat *et al.* (2009) are entirely in agreement in finding that menthol and nonmenthol cigarette smokers do not exhibit substantive differences in total NNK metabolite excretion.

The slide states correctly in regard to the Heck (2009) study that it included smokers only of “light” cigarettes, but incorrectly that these were “...(defined by the author as 7-15 mg “tar”).” Heck had in fact sourced the paper’s description of the “light” cigarette category in reference #27 [Kozlowski LT, O’Connor RJ, Sweeney CT. Cigarette design. In: *Risks associated with smoking cigarettes with low machine-measured tar and nicotine yields*. NCI Smoking and Tobacco Control Monograph No 13. Bethesda: 2001]. The subjects in the Heck study smoked cigarettes ranging from 8.5 – 9.8 mg “tar” as determined by the standard Cambridge filter-machine smoking method.

4. **Hoffman Health Effects Slide #36, Summary:** The statement “The data on biomarkers (CO and tobacco-specific nitrosamines) are inconclusive” distorts the state of knowledge on the most meaningfully measurable biomarkers in the largest and most recent investigations. Several published biomarkers studies, including the largest ever conducted, are quite consistent in showing that smoke exposure biomarkers are similar in smokers of menthol and nonmenthol cigarettes (Heck (2009); Muscat *et al.* (2009); Wang *et al.* 2010)). The conclusion of Benowitz *et al.* (2004) is consistent with this literature in reporting that “...[o]ur data do not support the hypothesis that mentholated cigarette smoking results in a greater absorption of tobacco smoke toxins.”

### III. MENTHOL DOES NOT INHIBIT SMOKING CESSATION SUCCESS AMONG THE GENERAL POPULATION OF SMOKERS

#### A. Cessation Studies Overview

Evaluations of spontaneous smoking cessation in several of the largest and most representative population surveys have indicated no significant differences in cessation rates between smokers of menthol and nonmenthol cigarette brands (Hyland *et al.* (2002); Li *et al.* (2005); Muscat *et al.* (2002); NHANES (2005-2006, 2007-2008); Murray *et al.* (2007)). Notably, these large population surveys include the large COMMIT cohort (13,268

subjects), as well as the substantial NHANES data set for young smokers (age 12-19 years; 10,343 subjects), a substantial disease case-control study of 19,545 subjects (Muscat *et al.* (2002)), and 5,883 middle-aged participants in the Lung Health Study (Murray *et al.* (2007)).

The findings relating to continuation or cessation of smoking in these large studies are worthy of particular consideration for several reasons. First, they collate the incidence of spontaneous quitting that accounts for the great majority of successful quitting, as opposed to clinically-aided cessation (Chapman (2008); Chapman and MacKenzie (2010)). Secondly, these large national and regional studies include a spectrum of subjects who are unquestionably more representative of the general population of smokers in the United States, than are smoking cessation clinical populations that are known to differ in several important respects from the general population (Etter *et al.* (2009)). Further, the interpretation of results from all of the cessation clinic studies reported to date is compromised by the fact that the enrolled populations received various pharmacotherapy and counseling treatment regimes, the efficacy of which was the primary objective of the studies rather than any effect of cigarette mentholation. Still more uncertainty arises from concern about the potential of penalized imputation (the presumption that subjects failing to complete the cessation study interval must have resumed smoking) to constrain attempts to use clinical smoking cessation studies to inform hypotheses about menthol that the studies were not appropriately designed to address (Nelson *et al.*, 2009).

Several analyses developed from smoking cessation clinical populations have reported a number of subject characteristics that are statistically associated with reduced cessation success under experimental cessation therapy protocols that include various combinations of pharmacotherapy (nicotine replacement medications, Chantix, Zyban) and counseling/coaching sessions (Okuyemi *et al.* (2004); Foulds *et al.* (2006); Bover *et al.* (2008); Gandhi *et al.* (2009)). Not a single one of the available, published reports on stop-smoking clinical outcomes, however, has directly assessed menthol as an independent variable; *i.e.*, has compellingly tested cigarette mentholation as a potential “cause” of smoking cessation outcome.

Further, cross sectional, retrospective analyses of self-reported information can provide only limited insight into cultural, socioeconomic and cultural mediating factors that may influence the outcome of a reported attempt to quit smoking. A considerable body of literature indicates that African-American and Hispanic smokers generally achieve less success in quitting smoking relative to Whites when subjected to identical, multifaceted cessation clinic therapies. Pharmacogenetic, metabolic and related constitutional differences among racial and ethnic groups have been proposed and investigated as a basis for race-associated difference in both biomarker levels and cessation outcomes (Perez-Stable *et al.* (1998); Moolchan *et al.* (2006); Ho *et al.* (2009)). These factors apply to the smoking of cigarettes, generally, and are not restricted to menthol or nonmenthol cigarettes. Such pharmacogenetic differences provide a far more plausible and soundly based scientific explanation for race-associated differences in smoking behaviors, biomarkers and disease incidence, than does the presence of menthol in cigarettes.

Cessation of both menthol and nonmenthol cigarette smoking can be difficult for many smokers and success in quitting typically requires persistence and a serious commitment to achieve that goal. The influence of daily stresses, employment status, social and family stability and related socioeconomic factors can be profound, both in a pharmacotherapy-aided clinical setting and in the general population. Human smoking behavior is manifested as a complex interplay of individual subjects' constitutional, demographic, situational and social elements that are far too complex to be represented by a single subject or product characteristic.

As discussed above, the overwhelming majority of epidemiological investigations of the potential of menthol to affect population risks for cancer have shown no elevated risk of disease (reviewed by Werley *et al.* (2007); Heck (2010); Etzel *et al.* (2007)). Every smoking cessation program, whether State, Federal or community-based, is intended to reduce the incidence of chronic smoking-related diseases because quitting smoking, even for persons with a considerable history of smoking, is unquestionably the most effective way to reduce disease risk (Jemal *et al.* (2009)). Because disease risks are positively correlated with smoking intensity and duration (*e.g.*, pack-years and similar metrics), if menthol impaired smoking cessation, the disease risk for smokers of menthol cigarettes would be expected to be markedly higher than that of nonmenthol smokers. It simply is not.

**B. Presentation to TPSAC on Menthol and Smoking Cessation Behavior, by Allison C. Hoffman, Ph.D.**

Lorillard offers these additional specific comments on the Hoffman Cessation presentation:

1. **Hoffman Cessation Slide #7, Adults (cont.):** Dr. Hoffman notes the report of Okuyemi *et al.* (2003) from a clinical smoking cessation trial of bupropion (Zyban) in 265 Black smokers. Smokers of menthol cigarettes reported a significantly poorer response to bupropion than did smokers of nonmenthol cigarettes, as assessed by 6-week smoking abstinence. Notably, the 270 Black smokers comprising the placebo control group exhibited no difference in smoking cessation success for menthol and nonmenthol cigarettes, consistent with the similar FTND scores reported for these smoker groups in the discussed study. The presentation included selective mention of only the intermediate 6-week study time point and neglected to discuss other study findings, including the key observation that at the terminal 6-month follow up there was no statistically significant difference in smoking cessation success between menthol and nonmenthol cigarette smokers (Okuyemi *et al.* (2003)).

The placebo control group in the Okuyemi study reflects the experience of smokers in other studies of spontaneous cessation unassisted by pharmacotherapy (Hyland *et al.* (2002); Muscat *et al.*

(2002); Okuyemi *et al.* (2004)) in showing that menthol cigarettes are no more difficult to quit than are nonmenthol cigarettes. Spontaneous quitting overwhelmingly represents the most common and successful cessation strategy among smokers (Chapman (2008); Chapman and MacKenzie (2010)) and provides the most meaningful perspective on the potential of menthol to affect cessation success. The observation by Okuyemi *et al.* (2003) that a clinical subject population of Black smokers of menthol cigarettes apparently had a lower response to bupropion in an intermediate term (6 weeks) assessment, and further that this intermediate finding did not predict long-term (6 months) smoking abstinence may be of some interest to clinicians who employ this pharmacotherapy, but this observation does not inform the typical smoker quitting experience.

2. **Hoffman Cessation Slide #9, Adults (cont.):** This slide presented a graphical summary of cessation outcome findings reported by Okuyemi *et al.* (2007). Other findings not presented included the authors' observation that the menthol smokers participating in the study expressed significantly lower confidence in their ability to quit, which the authors discussed as a potent, previously-reported predictor of cessation success that may have accounted for the higher smoking relapse rate for the menthol cigarette smoking subjects. The Okuyemi paper also reported similar, statistically indistinguishable levels of expired CO and serum cotinine between menthol and nonmenthol cigarette smokers, consistent with other biomarkers and epidemiology studies that indicate that exposures and effects of smoking these cigarette types are similar. This finding was not mentioned in the exposure biomarkers presentation and should be discussed appropriately in that section of the data summary under preparation by FDA staff.
3. **Hoffman Cessation Slide #15, Menthol and Cessation in Youth:** Dr. Hoffman reported on some conclusions in Hersey *et al.* (2006), but neglected to point out that, although the authors suggested that menthol cigarettes "may be a starter product for youth," they cautioned that "... these analyses were conducted with cross-sectional data, and association does not necessarily imply causality. The evidence discussed in this article would be strengthened by longitudinal data. Although the study indicates that menthol cigarettes may be a starter product, this is not necessarily the same as being a gateway product in terms of facilitating subsequent use. Although that possibility is consistent with these data, the issue of whether menthol serves as a gateway product will require a longitudinal study."

#### IV. MENTHOL DOES NOT MEANINGFULLY AFFECT SMOKING INITIATION BY ADOLESCENTS OR ADULTS

##### A. Smoking Initiation Studies Overview

The majority of smoking adolescents aged 12-17, as well as young adults aged 18-25, and adult smokers aged 26 and older, all continue to report a preference for non-menthol cigarette brands (NSDUH (2009)). Brand preferences vary year-to-year. Overall, approximately 25-30% of cigarettes purchased in the United States are menthol brands, while the majority (about 70-75%) comprises nonmenthol brands. While the actual number of menthol cigarettes sold in the U.S., like all cigarettes, is declining, the overall menthol cigarette market share has remained relatively stable, trending modestly upward in recent years. Characterization of this modest increase in menthol cigarette market share as a substantial expansion of menthol cigarette popularity is not accurate.

African-American adolescents identifying themselves as smokers (including both recent initiates reporting smoking histories of less than 12 months duration, as well as those reporting smoking for over 12 months) represent a substantially smaller percentage of the adolescent population than do adolescents of European-American identity (NSDUH (2007)). African-American youth have reported themselves to be smoking at about half the rate reported by European-American youth for many years now. The notion that African-American youth are particularly responsive to menthol cigarette advertising or are initiating smoking at an exceptionally high rate is simply not borne out by the NSDUH survey findings (NSDUH (2007)). African-American smokers who reported themselves to have smoked within the last month and who were identified as presumptive recent smoking initiates were in fact *less* likely to have reported a preference for menthol cigarettes than their longer-term smoking counterparts (73.9% vs. 82.8%, respectively)(NSDUH( 2009)).

A state-by-state comparison of the popularity of menthol cigarettes (expressed as menthol share-of-market and youth smoking incidence (Campaign for Tobacco Free Kids (2007)) is highly informative (*See*, 2007 Menthol Share of Market v. 2007 Youth Smoking Rate by State; attached as Appendix H to Lorillard's Briefing Regarding the Science Relating to Menthol Cigarettes, March 30-31, 2010, submitted to the FDA on March 22, 2010). A poor correlation between the magnitude of the state-by-state popularity of mentholated cigarettes in the marketplace and youth smoking incidence is readily apparent. Notably, menthol market share is *inversely* related to youth smoking among all 50 states to a statistically significant degree. These data indicate that youth smoking rates are generally lower in states with higher menthol market share.

A variety of observational/cross-sectional survey data is also available to inform speculation concerning menthol cigarette brand preferences and attitudes of persons who report histories of only a few years of smoking. The recent smoking initiates described in most surveys are primarily adolescents who have not yet attained the age to legally buy cigarettes. These persons typically obtain their first, initiating cigarette from friends, family members or other irregular sources (Colvin and Mermelstein (2010)). These

adolescents who cannot purchase cigarettes legally also might be anticipated to obtain cigarettes and report brand preferences irregularly. The brand or style of cigarettes reported by younger smokers may bear no fixed or predictable relationship to a future preferred brand that may be legally purchased.

The hypothesis that menthol in cigarettes may facilitate smoking initiation or serve as a “*starter product for youth*” (Hersey *et al.* (2006)) has arisen from simple surveys of brand use among youth (typically 12-17 years old). Such survey instruments typically ask respondents to identify a cigarette brand or style most recently smoked or most frequently smoked rather than the identity of the cigarette smoked in the respondents’ first smoking experience (*i.e.*, at smoking initiation). It is important to distinguish a true smoking initiation event (*i.e.*, a previously non-smoking individual’s first experience in smoking all or a portion of a first cigarette) from a conscious purchasing decision or a distinct reported preference for a given brand, even if that preference is reported for early years of smoking (*e.g.*, ages 12-17).

Most important, not a single one of the major U.S. survey instruments to date, including NHANES, NSDUH, TUS-CPS, NYTS, use questions that explicitly ask respondents about the brands or menthol/nonmenthol brand style of the respondents’ first smoked cigarette. Rather, the major survey instruments ask a variety of brand preference information for most recent (generally last 30 days) smoking experience or brand/style usually smoked. Responses to the menthol question are subject to misinterpretation because respondents could answer “Yes” to the menthol question even if the respondents smoked only one menthol cigarette during the past 30 days, while the cigarettes smoked “*most often*” were nonmenthol.

**B. Presentation to TPSAC on Menthol and Initiation of Smoking, by Josh Rising, M.D., M.P.H.**

Lorillard offers these specific comments on the Rising Initiation presentation:

Dr. Rising asserted that “menthol cigarettes are more widely used by beginner youth smokers than by established youth smokers” (Slide 22). This assertion is based on data from the 2002 NYTS (Slide 8) and the 2004-2008 data from NSDUH (Slide 9). For the reason discussed below regarding our critique of the presentation by Dr. Caraballo, the NSDUH data regarding youth menthol smoking rates is flawed and unreliable. The presentation does not mention any of the significant limitations that plague the NSDUH data on this issue. With regard to the NYTS data, two points deserve noting. First, the presentation does not address the more recent data which shows a significant (greater than 10%) decline in overall youth menthol smoking rates from 2002 to 2006. Second, there are inconsistencies and contradictions in the data which materially undermine the reliability of the NYTS data on this issue.

The very real distinction between reported youth smoking incidence/brand preference survey data and the markedly fewer youth who continue beyond youthful experimentation

to become smokers (true initiators) was very recently referred to by Dr. Deyton in his 2010 New England Journal of Medicine *Perspective*: "...Each day, roughly 3900 Americans 12 to 17 years of age start smoking cigarettes; 1000 of them become regular users." If, in fact, only about one in four self-reported youthful smokers are true smoking initiators, then surveys such as NSDUH (2009) in all likelihood grossly overestimate the acquisition of smoking, even as youth smoking rates are at or near an all-time historical low.

Dr. Deyton's distinction between true initiation of long-term smoking by approximately 25% of adolescents who may report themselves to have recently smoked a cigarette in survey studies demonstrates the fragility of assertions that one cigarette type or another may meaningfully differ in its likelihood to lead to chronic smoking. As Hersey *et al.* (2006) cautioned, such conclusions require longitudinal studies which have not been pursued and reported to date. Other research (DiFranza (2004)) is not consistent with the assertion that a youthful first-smoking experience with a menthol cigarette is more likely to lead to continued smoking (true smoking initiation) than is a nonmenthol cigarette experience. In the absence of scientific data to substantiate the hypothesis that menthol in cigarettes is causally related to chronic smoking into adulthood, speculation based on brand preference surveys of smokers of any age is entirely insufficient to support a sound science-based conclusion in regard to any causal association between menthol and the likelihood of chronic smoking initiation. This may particularly be true for initiation by persons under the legal age because cigarettes smoked are more likely to be those to which youth have access, rather than a true brand preference. In addition, underage mixed smoking of both menthol and nonmenthol cigarettes is likely and cannot be accounted for by the survey questions asked. Consideration of such survey findings as a basis for any TPSAC advisory opinions is without precedent and does not meet any reasonable standard of sound science in support of such opinions.

Additional, nationwide evidence that smoking experimentation with menthol cigarettes by adolescents is no more likely to lead to chronic smoking than is similar experimentation with nonmenthol cigarettes is seen in data on state-by-state youth smoking rates compiled by the Center for Tobacco-Free Kids (CTFK). A comparison of these data for the most recent year available (2007) with menthol cigarettes' sales volumes as reported by Management Science Associates, Inc. (MSAI) for this same year reveals that there is absolutely no positive relationship between the popularity of menthol cigarettes and youth smoking. In fact, a modest, but statistically significant *inverse* relationship exists between menthol cigarette sales and youth smoking for all 50 States. The state-specific menthol share-of-market values captures the availability of cigarettes that may be illegally sold to adolescents at retail as well as those cigarettes that may be acquired from their older friends or family members who legally purchase cigarettes.

C. **Presentation to TPSAC on Menthol and Demographics, by Ralph S. Caraballo, Ph.D., M.P.H.**

Lorillard offers these specific comments on the Caraballo Demographics presentation:

Although Dr. Caraballo's presentation was essentially accurate, the limitation of this presentation to the data developed using the National Survey on Drug Use and Health (NSDUH) is scientifically inappropriate to draw definitive conclusions regarding menthol cigarette use. The NSDUH data are simply not sufficient to reach a reliable conclusion that youth are disproportionately smoking menthol cigarettes. The NSDUH question regarding menthol use (whether the cigarettes they smoked during the last 30 days were menthol) is fundamentally flawed and thus not a reliable basis on which to identify youth menthol smokers. It is uncontroverted that beginning smokers routinely experiment with various cigarette brands and types, and they get their cigarettes from a variety of sources without having developed a brand/category preference. Thus, it is not at all surprising that many beginning smokers would have smoked at least one or a few menthol cigarettes during a 30 day period. The survey design creates the likely scenario that youth smokers who predominantly smoked nonmenthol cigarettes, but also smoked at least one menthol cigarette during the preceding month, are incorrectly classified as menthol smokers. Dr. Caraballo's analysis also fails to disclose that the NSDUH data from 2000-2003 when the menthol smoking question was worded differently ("During the past 30 days, did you smoke menthol or regular cigarettes most often?") may have been the cause of a dramatic increase (19%) in the alleged youth menthol smoking rate beginning in 2004, when the more imprecise question began to be used. All of Dr. Caraballo's conclusions regarding youth menthol smoking rates appear to be based solely on the flawed NSDUH data. In addition, no supporting or conflicting data from several other available national surveys were presented.

**D. Presentation to TPSAC on Perceptions and Marketing of Mentholated Cigarettes, by Josh Rising, M.D., M.P.H.**

Lorillard offer these specific comments on the Rising Perceptions and Marketing presentation

1. **Rising Perceptions and Marketing Slide #8, Adult Perceptions:** This slide purported to report on the conclusions of Hymowitz *et al.* (1995). Dr. Rising failed to disclose that the Hymowitz conclusions were not contained in a peer-reviewed publication, but rather were set forth in a Letter to Editor of Tobacco Control. Dr. Rising also did not include additional responses from the questionnaire used, which are relevant to the issue of adult perceptions of menthol cigarettes: members of my family smoke menthol cigarettes (30% African-Americans, 15% Whites); my friends that smoke, smoke menthol cigarettes (41% African-Americans, 18% Whites) and menthol cigarettes suit my self-image better (14% African-Americans, 5% Whites). Dr. Rising further did not disclose that Hymowitz acknowledged that "several studies, however, indicate that menthol cigarette smokers inhale less frequently and less deeply than non-menthol smokers (citing Sidney 1989 and Cummings 1987).

2. **Rising Perceptions and Marketing Slide #9, Adult Perceptions:** In his presentation of a focus group study of Black smokers conducted by Richter *et al.* (2008), Dr. Rising did not disclose the focus group's conclusion that: "In general, taste was the main reason for continuing to smoke a particular brand and was overwhelmingly offered as a reason for smoking menthol rather than non-menthol cigarettes."
3. **Rising Perceptions and Marketing Slide #23, Black Individuals:** In the presentation of a study by Allen *et al.* (2007) involving retrospective recall of exposure to tobacco advertising by low-income Black smokers in one urban setting, Dr. Rising reported that 70% of respondent smoked menthol cigarettes, men and women more likely to use menthol cigarettes with current exposure to menthol ads and women more likely to smoke menthol cigarettes if they were exposed to menthol ads as children. Dr. Rising failed to include that respondents were also asked why they smoke menthols, with "taste" being the most common response. The following conclusions were also omitted from the presentation: "Despite the proliferation of advertisements for menthol cigarettes in African American magazines, newspapers, neighborhoods, and entertainment venues, self-reported exposure to menthol advertising was not a significant correlate of menthol smoking in the present study" and the correlations of smoking menthol cigarettes with exposure to ads in childhood or at present were not significant (See table 2).

## V. MENTHOL IN CIGARETTES DOES NOT MEANINGFULLY AFFECT SMOKING BEHAVIOR

### A. Smoking Behavior Studies Overview

Many studies have attempted to measure any effects of menthol in cigarettes on human smoking behavior. These studies have attempted to measure differences in puff volume, number and frequency, depth of inhalation, duration of smoke retention in the lungs, percentage of cigarette smoked and other variables between menthol and nonmenthol smokers. These variables are typically referred to as elements of "smoking topography." Notably, some investigators in this area have employed unrealistic laboratory smoking regimes or intrusive devices and instrumentation in attempts to measure the dimensions of human smoking behavior. The results of the studies are mixed and any differences reported between menthol and nonmenthol smokers may be dependent on the method used and the lack of specificity of the outcome attempted to be measured. Despite the somewhat mixed results of the studies, overall the studies are not inconsistent with the studies on biomarkers of exposure, discussed above, which report that menthol does not meaningfully affect exposure of smokers to smoke constituents. The lack of any consistent inter-individual differences in either smoking topography or exposure biomarkers among smokers of menthol and nonmenthol cigarettes is, further, consistent with the similarity of chronic disease risks developed from repeated epidemiological inquiries that are discussed above.

**B. Presentation on Menthol Sensory Properties and Possible Effects on Topography, by D. Lawrence, Ph.D., M.P.H.**

Lorillard offers these specific comments on the Lawrence Topography presentation:

1. **Lawrence Slide #9, Sensory Properties: Flavor:** As in Rising Perceptions and Marketing Slide # 8 (discussed above), Dr. Lawrence referenced the 1995 letter to the Editor, Tobacco Control, authored by Hymowitz. The letter reported findings of a survey presented to 473 menthol cigarette smokers enrolled in a smoking cessation study. Since the survey included only menthol-preferring smokers, the findings that the subjects' stated taste preference for mentholated brands was their predominant reason for smoking them, and that 60% of these menthol-smoking subjects stated a willingness to pay more for the cigarette type they prefer are hardly surprising. Since the Hymowitz survey subjects are not compared to a reference group of non-menthol smokers within the cessation program population, it is not possible to determine whether menthol smokers' self-reported perceptions are any different from those of otherwise-similar smokers of nonmenthol products.

The 1995 Hymowitz letter is again cited on slide 14 in support of the last bullet point that "Menthol smokers believe menthol cigarettes are more soothing to the throat than nonmenthol." In fact, the Hymowitz letter reported that only 51% of white subjects (20 of 39) and 52% of black subjects (90/174) selected this response on the questionnaire. The subjects' responses to this question were therefore essentially the same as the 50/50 distribution that might be anticipated from a random distribution.

The presenter did not discuss Hymowitz' other findings, including the reported observation that "[r]elatively few smokers of either race endorsed 'image' or 'advertising' as the reasons for smoking menthol cigarettes" or that only 3% of white subjects and 10% of black subjects reported seeing menthol cigarette advertising more often than non-menthol cigarette advertising.

With respect to smoking topography, Dr. Lawrence's presentation failed to mention at least five peer-reviewed publications reporting direct measures of smoking topography of menthol cigarettes. See Nil and Bättig (1989), Pickworth *et al.* (2002), Strasser *et al.* (2007), O'Connor *et al.* (2007) and St. Charles *et al.* (2009).

2. **Lawrence Slide #22, Does Mentholation Result in Larger Puff Volumes and Increased Frequency:** Dr. Lawrence failed to list

studies by Nil and Battig(1989), Pickworth *et al.* (2002), Strasser *et al.* (2007), O'Connor *et al.* (2007), and St.Charles *et al.* (2009). None of these omitted studies reported findings consistent with increased smoking intensity for menthol cigarettes and these findings must be appropriately considered, discussed and presented to the TPSAC in an objective manner to inform a sound, science-based advisory opinion.

Nil and Battig examined the influence of several commercial cigarette taste categories and of different machine-measured smoke yield categories on smoking topography for 15 smokers, and reported a decreased puff volume and frequency for menthol cigarettes as compared to nonmenthol cigarettes.

In a group of 36 menthol and non-menthol smokers, Pickworth *et al.* studied the potential of menthol and nicotine acting together to affect physiological and subjective measures of commercial cigarettes' strength and satisfaction. No significant effect by menthol was reported in *ad libitum* puffs per cigarette, time to smoke the cigarette, or subjective evaluations of smoke "strength."

Strasser *et al.* investigated the effect of three human phenotypes of the nicotine metabolizing enzyme CYP2A6 on smoking topography. Smokers (n=119) in a smoking cessation trial smoked their preferred commercial brand as they desired. No significant differences in total puff volumes per cigarette or mean puff volumes were reported between menthol and non-menthol cigarette smokers.

O'Connor *et al.* examined exhaled CO, both before and after smoking, and smoking topography for 20 volunteer smokers who smoked commercial cigarettes *ad libitum*. While the menthol content of the tested flavored cigarette was not indicated, the brand listed included mint as a characterizing flavor and so almost certainly contained menthol.. The authors found a decreased puff volume and no significant difference in puffs per cigarette for the flavored cigarette compared to a nonmenthol cigarette.

St. Charles *et al.* investigated puff depth and volume for subjects smoking commercial cigarettes having a range of machine-measured smoke yields. The authors compared inhalation patterns for 18 menthol smokers and 56 nonmenthol smokers. All participants smoked the commercial brand of their choice as desired. No significant effect of menthol on puff volume was reported.

The omission of these five smoking topography studies that are inconsistent with an assertion that menthol in cigarettes may increase smoking intensity is exemplary of the bias evident in the FDA staff

briefings that were represented to the TPSAC as objective summaries of published scientific literature.

3. **Lawrence Slide #23, Menthol's Effect on Puff Volume Compared to Nonmenthol Cigarettes:** Dr. Lawrence failed to list four studies which have reported either decreased or no significant effect on puff volume by the smoking of menthol cigarettes. Two studies by Nil and Battig (1989) and O'Connor *et al.* (2007) reported a decreased puff volume, while the studies of Strasser *et al.* (2007) and St.Charles *et al.* (2009) reported no significant effect of menthol on puff volume. The omission of these four studies from the TPSAC briefing misrepresents the reality that the overwhelming majority (eight of nine papers) have found no increase in puff volume by smokers of menthol cigarettes.
4. **Lawrence Slide #24, Menthol's Effect on Puffs per Cigarette Compared to Nonmenthol Cigarettes:** Dr. Lawrence failed to include the three studies by Pickworth *et al.* (2002), Strasser *et al.* (2007), and O'Connor *et al.* (2007), which all found no significant effect of menthol on puff number. No published studies have reported an increase in puff volume for smokers of menthol versus nonmenthol cigarettes.
5. **Lawrence Slide #26, Self-Reported Topography:** Dr. Lawrence noted that a published letter by Hymowitz reported that a survey of menthol smokers indicated "ease of inhalation" to be one of the three main reasons for smoking menthol cigarettes. The Hymowitz letter states that 473 smokers participated in the survey, but only 213 participants are accounted for in the data table in the published letter. The "ease of inhalation" question was answered in the affirmative by 48% of African-American respondents (84 of 184), but by only 21% of White smokers (8 of 39 respondents), suggesting that social or demographic factors may markedly influence such subjective responses. Dr. Lawrence failed to note that a simple stated taste preference for menthol cigarettes and acquaintances' menthol preferences were also reported by participants as primary reasons for smoking menthol cigarettes (Hymowitz,1995).
6. **Lawrence Slide 27, Limitations of Topography Studies:** Because Dr. Lawrence did not include all available studies in her analysis, several of the conclusions in this slide are incorrect. Three of the published studies included more than 40 subjects. The largest was 119 (not 95) participants. While two studies included only females and four included only males, five studies (not zero) included both sexes.

Not mentioned as a limitation was the fact that the measurement of smoking topography without influencing the parameters being measured can be difficult. Most of the devices used today for

topography measurements rely on the use of a mouthpiece through which the cigarette is smoked. Smoking topography as measured through a mouthpiece may differ from that of natural smoking. In fact, the use of a mouthpiece has been shown to increase puff duration and puff number and to decrease interpuff interval (Nil and Battig (1989), Pickens et al., (1983); Hofer et al. (1991)). It has been reported that smokers take more puffs and longer puffs in clinical or laboratory settings than in “naturalistic” smoking (Ossip-Klein *et al.* 1983). Smoking topography has also been shown to vary significantly based on differences between individual smokers. Morgan *et al.* (1985) reported that puffs per cigarette, puff duration, and total puff time per cigarette for each smoker varied considerably over the day. It has also been noted that smoking topography may change significantly based on the number cigarettes smoked (Fant *et al.* (1995)).

Unfortunately, most studies of smoking topography have been limited to measurements from one or two cigarettes. Morgan *et al.* (1985) noted that “[g]iven the degree to which the subjects demonstrated change in topography across the smoking day, the data suggest that to study how a subject smokes a single cigarette or a small number of cigarettes during a limited period of the day may not allow accurate description of the subject’s smoking behavior.” Hammond *et al.* (2005) also noted that such studies that seek to estimate the effect of brand switching (or switching between menthol and nonmenthol) on topography “rely on transient reactions to brand switching which may not relate well to longer-term changes in smoking topography.”

A promising new method for determining actual smoke yield, and therefore smoking topography, is the “yield in use” (YIU) method. This method, which has recently been explored by the CDC (Polzin *et al.*, (2009)), relies on the collection of cigarette filter butts from smokers and the analysis of these filters for nicotine and/or markers of tar content. St. Charles *et al.* (2010) reported a YIU study that analyzed spent cigarette filters from human smoked cigarettes to develop estimates of actual exposures from cigarettes as smoked by 784 subjects. No trend was apparent between self-reported cigarettes smoked per day and tar yield, either on a tar band basis or an individual brand basis, for both mentholated and nonmentholated cigarettes. Nelson *et al.* (2008) have also presented a national YIU survey of 26 commercial brands, both menthol and nonmenthol, with 50 smokers per brand. Menthol had had no significant impact on YIU values. The similarity of menthol and nonmenthol cigarettes’ apparent smoking intensities reported by these authors is not consistent with

the speculated increase in inhalation depth by smokers of mentholated cigarettes.

7. **Lawrence Slide #28, Summary:** Several of Dr. Lawrence's conclusions cite incorrect numbers of studies. Eight (not four) studies reported decreased or no effect on puff volume. Six (not three) studies reported no significant effect on puff frequency. In two of the three available self reported topography assessments, including a large study of 29,037 smokers (Sidney (1989)), participants reported similar subjective measures of smoking topography or cigarette strength.

## **VI. MENTHOL IN CIGARETTES DOES NOT MEANINGFULLY AFFECT SMOKE CHEMISTRY OR INCREASE THE TOXICITY OF SMOKE**

The overwhelming weight of the *in vitro* and *in vivo* animal studies on menthol in cigarette smoke and cigarette smoke condensate demonstrates that menthol is neither a toxic nor carcinogenic hazard. Experiments with vastly exaggerated menthol levels show no increase in mutagenic, cytotoxic or tumorigenic responses in a variety of cigarette test systems, including *in vitro* cytotoxicity and mutagenesis assays, skin painting tumor bioassays and smoke inhalation studies. The weight of the toxicological studies do not indicate that menthol increases the hazards of cigarette smoking beyond those of regular cigarettes (Gaworski *et al.* (1997); Gaworski *et al.* (1999); (Heck 2010)).

As discussed above in Hoffman Health Effects Slide #15, Cytotoxicity or Reduced Cell Proliferation, The characterization of menthol as “[t]oxic in *in vitro* biologic model systems” in the presentation is scientifically unsupportable. Menthol is certainly among the most-studied flavoring and aroma ingredients in existence in terms of its safety in use in foods and consumer products around the world. It has been repeatedly evaluated and approved for these uses by authoritative national and international scientific and regulatory bodies. No substantive safety concerns have arisen in the course of these repeated assessments, and a summary of menthol's toxicity presented to the TPSAC should certainly reflect the wealth of prior science-based safety evaluation as well as a full and balanced treatment of the considerable volume of information that is available on the safety of menthol's use in tobacco products.

## **VII. THE REPEATED REFERENCE IN SEVERAL PRESENTATIONS TO PUBLISHED ARTICLES WHICH CONTAIN A HANDFUL OF SELECTED INDUSTRY DOCUMENTS IS ALSO SCIENTIFICALLY INAPPROPRIATE.**

Several of the presentations at the TPSAC Meetings included slides which referenced purported “industry” knowledge and conduct. At best, these slides are often inaccurate and misleading; at worst, they reflect an approach by the presenters which is biased, irresponsible, and deliberately at odds with a careful and objective assessment of the relevant facts. The following points are illustrative.

It is inappropriate and irresponsible to make broad-brush assertions regarding so-called “industry” conduct, thus encompassing Lorillard, when such assertions are not based on any facts or documents from Lorillard. For example, the presentation by Dr. Hoffman (“Possible Health Effects of Cigarette Mentholation” (Slide 17)) makes broad assertions regarding alleged “industry” knowledge and conduct. This slide is based on the 2004 article from Wayne and Connolly, which purports to assess “internal tobacco industry knowledge of the neurology of tobacco dependence.” That article does not cite a single Lorillard document, nor does it provide any description of Lorillard’s internal scientific research on any topic. Lorillard’s knowledge and conduct are separate and distinct from its competitors. This is just one of multiple examples where so-called “industry” conduct and knowledge is wrongly attributed to Lorillard.

Far-reaching assertions and implications are made regarding alleged “industry” knowledge or conduct based on a mere handful of documents. These assertions often suggest current “industry” practices, when in fact the alleged supporting documents are decades old. Slides 36 and 37 from Dr. Rising’s presentation, “Perceptions and Marketing of Mentholated Cigarettes,” provide clear and disturbing examples. Slide 36, which purports to address tobacco industry information on “younger” smokers, cites a *single* document prepared over 20 years ago by R.J. Reynolds for an assertion that the “industry” has knowledge of the appeal of lower-menthol cigarettes to “younger” smokers. It is noted that the referenced document is explicitly restricted to a discussion regarding legal age, adult smokers; nonetheless, the presentation misleadingly refers to “younger” smokers. Slide 37 suffers similar flaws. This slide purports to describe industry marketing practices directed to “Black youth.” This assertion is based on a single document from Philip Morris dated almost 30 years ago. There is no discussion in this document of “youth” smokers; to the contrary, the document very explicitly discusses brand preference information among legal age smokers, age 18 and older.

Further, memoranda, technical reports and business communications from the internal files of tobacco companies that have been produced in the litigation discovery process and made public do not rise to the standard of published scientific works and may represent nothing other than their authors’ opinions on a given topic. These documents may contain opinions that are inconsistent with the scientific evidence and that may be at odds with company policies. It is inappropriate for persons other than their authors themselves or appropriately-designated company spokespersons to represent or interpret such documents before the TPSAC as substantive scientific works with a standing that some TPSAC members may confuse with published scientific data.

## **CONCLUSION**

An overwhelming body of epidemiology indicates that chronic smoking-related disease risks are not increased by smoking menthol cigarettes. The epidemiology results are powerfully supported by and consistent with available chemistry, toxicology and biomarkers data which indicate that menthol and nonmenthol cigarettes do not differ in

these evaluations. Both the epidemiology and biomarkers results are consistent with equivalent smoking cessation by menthol and nonmenthol cigarette smokers in the general population. Menthol has not been shown to be a factor in youth smoking initiation or to facilitate smoking among underage smokers. The best available science does not support an assertion that menthol in cigarettes impacts public health.

Lorillard calls upon the FDA-CTP to take sufficient steps to remedy any misconceptions about the true state of menthol science that may have resulted from the presentations made to the TPSAC at the March 2010 Meetings. To allow the omissions and inaccurate reporting to go uncorrected flies in the face of recent statements of FDA policy by Commissioner Hamburg, Principal deputy Commissioner Scharfstein, and others:

“...the public must trust the agency to base its decisions on science. We recognize the importance of a management approach that respects the expertise and dedication of the FDA's career scientists. In recent years, the agency has struggled to handle controversies involving the safety of regulated products, opening the door to legitimate questions from the media, the public, and Congress about whether the public interest is being served. Establishing the FDA as a public health agency requires a culture that encourages scientific exchange and respects alternative viewpoints along the path of decision making. It also requires that the agency define and protect integrity in its basic processes..”

“Transparency is a potent element of a successful strategy to enhance the work of the FDA and its credibility with the public. Whenever possible, the FDA should provide the data on which it bases its regulatory decisions and other guidance and explain its decision-making process to the public.”

This submission is intended to assist the CTP and TPSAC in fulfilling their respective obligations to develop sound, science-based regulatory processes and advisory opinions in regard to tobacco products. Lorillard remains ready to assist the FDA-CTP in meeting its charge to develop informative, inclusive and defensible science-based briefing papers to inform future TPSAC discussions.

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