Lorillard, Inc.

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March 16, 2011

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Re: Request for Correction of Information Disseminated to the Public and the Tobacco Products Scientific Advisory Committee

Dear Dr. Deyton and Mr. Weinstein:

Lorillard Tobacco Company submits this petition requesting that FDA and Center for Tobacco Products (CTP) correct certain data and information that was disseminated by FDA to the public and to the members of the Tobacco Products Scientific Advisory Committee (TPSAC) related to the scientific record on the use of menthol in cigarettes. This petition is submitted pursuant to the Data Quality Act (DQA), Pub. L. No. 106-554, tit. V, § 515, 114 Stat. 2763, 2763A-153, codified at 44 U.S.C. § 3516 note (2000), and implementing Office of Management and Budget (OMB), Health and Human Services (HHS), and FDA Guidelines.

Lorillard believes it is important for FDA and industry to work cooperatively if implementation of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) is to be truly effective. The company had hoped, and continues to believe, that FDA regulation of tobacco would be driven by an objective and rigorous assessment of the scientific record. This equally applies to matters placed before the TPSAC for its review and recommendation. Respectfully, however, in relation to TPSAC's review of menthol, pursuant to Section 907(e) of the FSPTCA, what has emerged is a pattern of incomplete and incorrect information being disseminated by FDA to the TPSAC members and the general public. Dissemination of incomplete and incorrect scientific reviews produced by FDA poses significant problems to any regulated industry because reports issued by FDA have the imprimatur of the U.S. government and, as such, are relied on, including in this instance by members of the TPSAC and the general public, as an accurate and objective summary of all of the available science on an issue.

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Lorillard has attempted to correct these significant issues with FDA through informal means. Lorillard's requests, however, do not appear to have been seriously considered by the agency. In light of these facts, Lorillard has reached the conclusion that it must submit this petition to FDA.

As discussed in greater depth below, the Data Quality Act and its implementing Guidelines are intended to ensure that information disseminated by federal agencies will enable users of the information to make reasonable decisions. To that end, the Act and the Guidelines (1) require that federal agencies ensure and maximize the "quality, objectivity, utility, and integrity" of information that they disseminate, and (2) require agencies to establish mechanisms by which affected persons can "seek and obtain" correction of information that violates these standards.[1] Under these standards, information disseminated by federal agencies must be presented in an "accurate, clear, complete, and unbiased manner" and "within a proper context," and an agency may be required to supplement the information that it wishes to disseminate with "other information . . . in order to ensure an accurate, clear, complete, and unbiased presentation."[2]

Contrary to these principles, however, FDA has released several documents that cannot be reconciled with the requirements of the DQA. The documents emanate from the first meeting of the TPSAC on March 31, 2010 where FDA provided to TPSAC a summary of the scientific literature involving menthol cigarettes. The presenters used slides for their presentations and FDA posted the slides on its website. In addition to the slides, FDA prepared two documents to summarize this scientific review to assist TPSAC in its charge to provide FDA with a report and recommendation on the impact of the use of menthol cigarettes. This petition focuses primarily on the documents that appear to have adopted the same analysis and conclusions as FDA's March 2010 presentation and which the agency released prior to the October 7, 2010 and November 18, 2010 TPSAC meetings.

First, FDA released numerous "White Papers" that purport to present the scientific literature on various issues related to menthol before the October 7, 2010 TPSAC meeting. Not only have these papers not been subject to peer review, but they suffer from a lack of objectivity, contain misleading analyses of pertinent data, and often fail to report on highly relevant findings contained in the articles discussed. Second, FDA released Table 1.1, summarizing conclusions from articles on menthol published in peer-reviewed journals, prior to the November 18, 2010 TPSAC meeting. That document contained numerous inaccuracies, omissions, and distortions of the scientific literature. Although FDA corrected some of these errors after receiving two emails from TPSAC industry representative Dr. Dan Heck, many

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[1] *See* 44 U.S.C. § 3516 note; *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies*, Republication, 67 Fed. Reg. 8452, 8459 (Feb. 22, 2002) (OMB Guidelines).

[2] 67 Fed. Reg. at 8459 (Part V(3)(a)).

problems remain. By any objective standard, neither of these documents meet the requirements for quality, utility, objectivity, and integrity demanded by the DQA.

For this reason, Lorillard requests that FDA correct these documents as quickly as possible. In addition, Lorillard requests that these corrections and any other corrections made in the future be announced conspicuously and on the record. When FDA corrected Table 1.1, it simply posted an "Updated Table 1.1" as part of the January 10-11, 2011 TPSAC briefing materials. FDA did not highlight which portions of the table had been changed. Further, the previous Table 1.1 remains on the website as part of the November 18, 2010 TPSAC briefing materials with no indication that an updated table exists. It is important to correct these inaccuracies and distortions, but TPSAC members and stakeholders must also be aware of the corrections.

We hope, moreover, that this petition will highlight what Lorillard has seen as a pervasive problem with the information disseminated by FDA in connection with the proceedings of TPSAC. Our hope is that by virtue of the agency's consideration of this petition, the agency will endeavor to be more complete, accurate and fair in its dissemination of documents related to menthol and tobacco products generally. The obligation for FDA to provide complete and accurate reviews of the scientific literature is obvious and mandated by the DQA. With regard to its menthol review, there is significant research that TPSAC and others must assess in a relatively short period of time. FDA's synthesis of that research plays an important role in TPSAC's review and ultimate recommendation to FDA on the impact of the use of menthol in cigarettes. That synthesis also plays an important role in impacting the general public's views and attitudes about whether menthol cigarettes present an increased harm over non-menthol cigarettes. Therefore, it is paramount that any information disseminated by FDA fairly, completely and accurately represents the scientific evidence.

Background

I. Materials Disseminated by FDA to TPSAC and the Public

The FSPTCA directed FDA to establish the Center for Tobacco Products and to create the Tobacco Products Scientific Advisory Committee (TPSAC). The statute directed that "[n]ot later than 6 months after the date of enactment" of the Act, FDA must establish the TPSAC by appointing "individuals who are technically qualified by training and experience in medicine, medical ethics, science, or technology involving the manufacture, evaluation or use of tobacco products."[3] In addition to conflicts of interest rules in the FSPTCA, members of the TPSAC are also subject to conflict of interest restrictions of the Federal Advisory Committee Act and FDA's regulations and guidance on conflicts of interest.[4] Congress directed that

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[3] FSPTCA § 912.

[4] Several companies, including Lorillard, have submitted letters or other submissions to FDA pointing out that members of TPSAC appear to have both financial conflicts of interest and clear biases. *See, e.g.*, Letter of Lorillard Tobacco Company to Lawrence Deyton, (January 31, 2011); Comment of R.J.
(continued...)

"immediately upon establishment" of the TPSAC, FDA must "refer to the Committee for report and recommendation . . . the issue of the impact of the use of menthol in cigarettes on the public health . . . . ."[5] The TPSAC was officially composed and first met on March 30, 2010 and immediately took up the issue of menthol in cigarettes.

From the start, FDA has played a prominent role in presenting to TPSAC members the scientific research on menthol cigarettes by providing the Committee with extensive briefing materials and making numerous presentations to the Committee. Unfortunately, however, FDA's presentations and briefing materials have been fraught with significant problems and demonstrated a clear bias. The very first set of presentations made by FDA to the TPSAC illustrates this point. As an initial matter, in the briefing materials released by FDA to the public and TPSAC, FDA placed a red asterisk next to every "industry funded" study, a "scarlet letter" clearly intended to tell the public and TPSAC that the studies should be ignored or afforded less weight, regardless of their scientific merit.[6] In doing so, FDA appears to have applied different standards to the scientific literature, based not on any principled scientific basis, but solely on the author's relationship with tobacco companies.[7]

The FDA presentations to the TPSAC at the March 30 and 31 meetings were similarly inaccurate and biased. As an example, one FDA employee, Dr. Allison Hoffman, presented what was styled as an overview of the available scientific record on the toxicology of menthol.[8] This presentation contained numerous inaccuracies and distortions of the scientific record:

- The presentation included misrepresentations of the conclusions of the scientific literature. As just one example, in one slide (Slide 31) Dr. Hoffman cited Carpenter

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Reynolds to Draft Guidance for the Public, Food and Drug Administration Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members Financial Interest Information and Waivers (Docket No. FDA-2002-D-0094). More recently, because FDA did not take action to correct these serious issues, Reynolds and Lorillard filed a lawsuit in federal court, requesting a injunction to require the agency to compose an advisory committee with members that do not have conflicts of interest. *See Lorillard, Inc., et al. v. FDA, et al.*, D.D.C., No. 1:11-cv-00440.

[5] FSPTCA § 906.

[6] *See, e.g.*, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM217521.pdf

[7] This denigration of industry science, of course, is fundamentally inconsistent with other areas of FDA regulation, which regularly rely on industry supported science for approving new products or making other critical regulatory decisions.

[8] Possible Health Effects of Cigarette Mentholation (March 30, 2010) Allison Hoffman, Ph.D, Center for Tobacco Products, FDA. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM207164.pdf

et al. (1999),[9] stating that this study "suggested an increased risk for male menthol smokers and lung cancer." In fact, the study's conclusion was that the "results from this study suggest little or no increase in lung cancer associated with mentholated cigarette smoking compared to non-mentholated smoking."[10]

- The presentation cited numerous studies that had little scientific merit and which should play no part in the TPSAC's consideration. For example, the presentation included a study by Ciftici et al.,[11] which was a Turkish study performed with unidentified cigarettes of unknown composition. How the cigarettes compare to menthol cigarettes in the U.S. marketplace is not discussed in the report not did FDA explain how the results should be extrapolated to the U.S.

- The presentation included conclusions drawn from decades-old industry documents of dubious value scientifically which have no scientific basis or value.[12]

- The presentation excluded numerous valid scientific studies without explanation.[13] Most of these excluded studies reached conclusions contrary to those presented by Dr. Hoffman.

Lorillard responded to Dr. Hoffman's presentation -- as well as to numerous inaccuracies in other FDA presentations -- in a comprehensive letter sent to Dr. Deyton on June

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[9] Carpenter C.L., et al. 1999. Metholated cigarette smoking and lung-cancer risk. Annals of Epidemiology 9, 114-120.

[10] *Id.* at 119.

[11] Ciftci O., et al. 2008. Mentholated cigarette smoking induced alterations in left and right ventricular functions in chronic smokers. Anadolu Kardiyol Derg 8(2): 116-22.

[12] *See* Hoffman Presentation Slide 17, citing Wayne and Connolly 2004, which drew conclusions from a two paragraph statement from a 1964 Philip Morris document. Wayne G.F., et al. 2004. Assessing internal tobacco industry knowledge of the neurobiology of tobacco dependence. Nicotine and Tobacco Research 6(6):927-940.

[13] For example, Dr. Hoffman failed to include Nil and Battig, Caskey et al., Miller et al., McCarthy et al., and Pickworth et al., all of which concluded that menthol cigarettes had no effect on cardiovascular disease. Nil R., Battig K. 1989. Separate effects of cigarette smoke yield and smoke taste on smoking behavior. Psychopharmacology 99, 54-59. Caskey N.H., et al. 1983. Rapid smoking of menthol and non-menthol cigarettes by black and white smokers. Pharmacology Biochemistry and Behavior 46, 259-263. Miller G.E., et al. 1994. Cigarette mentholation increases smokers' exhaled carbon monoxide levels. Experimental and Clinical Psychopharmacology 2, 154-160. McCarthy W.J., et al. 1995. Menthol vs. non-menthol cigarettes: effects on smoking behavior. American Journal of Public Health 85, 67-72. Pickworth W.B., et al. 2002. Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery. Pharmacology, Biochemistry and Behavior 71, 55-61.

29, 2010.[14] Lorillard also submitted the same letter to FDA in briefing materials for the July 2010 TPSAC meeting.[15] In that letter, Lorillard wrote:

> 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.
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> ...
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> 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.

The company then went on to describe at length the specific problems and issues with the government's presentations. Rather than substantively responding to these concerns, FDA's responded to Lorillard with a cursory letter.[16] Without addressing Lorillard's concerns, the agency merely responded that it stood by its presentations. The letter concluded by stating that Lorillard had an opportunity to present its analysis of the science at the July TPSAC meeting.[17]

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[14] Letter from Bill True, Lorillard Tobacco Company, to Lawrence R. Deyton, M.S.PH., M.D, Director, Center for Tobacco Products (June 29, 2010).

[15] Briefing Information for the July 15-16 Meeting of the Tobacco Product Scientific Advisory Committee, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm218720.htm.

[16] Letter from Lawrence R. Deyton, M.S.P.H., M.D., FDA to Bill True, Lorillard (October 18, 2010).

[17] *Id.*

However, during the July 2010 meeting, Lorillard and other industry participants were asked to respond to certain questions posed by TPSAC. During subsequent meetings, Lorillard's ability to address TPSAC has been limited to short presentations given during the public session of the meeting. Moreover, even if Lorillard were given an ample opportunity to address these issues, it is unreasonable for industry to be expected to correct the record established by FDA. Presentations by FDA carry an implicit imprimatur of the government (regardless of their actual merit), which is precisely the reason why federal law requires that government-issued information meet high standards codified in the DQA. The DQA requires that government -- not industry -- correct erroneous information that is disseminated by government agencies.

Many of these concerns can be traced to FDA's treatment of industry representatives on the TPSAC. FDA's own regulations provide that "[a] nonvoting member of an advisory committee . . . has the same rights as any other committee member."[18] Rather than treat industry representatives as bona fide members of the committee, however, FDA has repeatedly relegated the industry representatives to an inferior role on the committee. For example, FDA has adopted the practice of disseminating materials to industry representatives only two days before TPSAC meetings (and at the same time those materials are made available to the general public). This practice permits industry representatives essentially no time to review the material or prepare for the meeting. Industry representatives have extensive experience with the research, manufacturing, and scientific literature for tobacco products. Were industry representatives provided with briefing materials at the same time as other TPSAC representatives, many of these errors and biases could have been raised and addressed.

The materials disseminated by FDA have continued to be plagued by similar problems and biases, even after the initial March meeting presentations. FDA has continued to release documents that fail to characterize the literature in an evenhanded and accurate manner. In October, FDA released several "White Papers," each of which purport to FDA's summary of the scientific literature on various issues related to menthol. The White Papers are largely a written documentation of FDA's presentations at the March 31, 2010 TPSAC meeting.[19] As discussed in Exhibit A, these White Papers distort the literature in numerous ways.[20]

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[18] 21 C.F.R. § 14.86(a). The regulation provides two exceptions to the general rule that nonvoting members are to be treated equally with voting members: (1) nonvoting members can vote on procedural matters only; and (2) nonvoting members may not have access to confidential commercial information, in certain situations. 21 C.F.R. § 14.86(a)(1)-(2). Neither of these exceptions is relevant to the matters discussed in this petition.

[19] Briefing Information for the October 7 Meeting of the Tobacco Products Scientific Advisory Committee, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProducts ScientificAdvisoryCommittee/ucm228064.htm

[20] Exhibit A is contains the briefing materials that Lorillard submitted prior to the March 2011 TPSAC meeting, which included a detailed analysis of the flaws in FDA's White Papers.

Finally, in advance of the November 18, 2010 TPSAC meeting, FDA released briefing materials for the TPSAC.[21] FDA characterized these materials as documents to assist TPSAC members as they prepare the report on menthol. Included in FDA's materials was Table 1.1., a table that purported to summarize in tabular form the available peer-reviewed literature on menthol in cigarettes that FDA referenced in its presentation to TPSAC on March 31, 2010 and in its White Papers issued for the October 7, 2010 meeting. As described in Exhibit B, this table was riddled with inaccuracies and omissions. This table was placed on FDA's website and provided to the TPSAC members. It was provided to Dan Heck, the industry representative to TPSAC, only two days before the TPSAC meeting, which permitted no time for the inaccurate information to be corrected. After Dr. Heck voiced concern about various inaccuracies in the table, FDA asked Dr. Heck to provide a response detailing all of the problems present in the 87 page document within three days. Dr. Heck submitted two emails communications -- on November 17, 2011 (within the requested 3 days) and on December 4, 2010 – highlighting the errors and inaccuracies along with corrections. FDA has made some corrections to the table, but many errors remain.

II. Legal Principles

A. The Data Quality Act

Enacted in December 2000 as part of the Consolidated Appropriations Act for FY 2001, the Data Quality Act requires OMB to issue guidelines to "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies in fulfillment of the purposes and provisions of . . . the Paperwork Reduction Act."[22]

The Paperwork Reduction Act, whose purposes undergird the Data Quality Act, seeks to ensure government dissemination of useful and objective information in the service of informed decision-making and agency accountability. As the pertinent House and Senate reports state, the Paperwork Reduction Act seeks to promote the dissemination of public information "in useful forms and formats" and to strengthen "agency accountability for managing information resources in support of efficient and effective accomplishment of agency missions and programs."[23] The overarching goal is to enable reasonable users of information disseminated by the government to make reasonable decisions:

> For the American public, Government information often seems to serve either of two quite different purposes. It can

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[21] Briefing Information for the November 18 Meeting of the Tobacco Products Scientific Advisory Committee, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProducts ScientificAdvisoryCommittee/ucm233416.htm

[22] 44 U.S.C. § 3516 note.

[23] H.R. Rep. No. 104-37, at 2 (1995); S. Rep. No. 104-8, at 2 (1995).

> be the means by which the dedicated public servant uncovers problems . . . and informs the public. But it can also be the means by which the faceless bureaucrat . . . forces seemingly arbitrary changes in business practices or personal behavior, and imposes significant costs on the economy.[24]

Once OMB has issued guidelines serving the purposes of the Paperwork Reduction Act, the Data Quality Act requires each federal agency to which the OMB Guidelines apply (including HHS) to issue guidelines similarly "ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency."[25] The DQA further requires each such agency to establish administrative mechanisms enabling affected persons "to seek *and obtain* correction of information maintained and disseminated by the agency that does not comply" with the OMB Guidelines.[26] That Congress required agencies to establish such corrective mechanisms makes clear that it intended the quality standards stated in the Data Quality Act to be mandatory and not merely aspirational. If an agency defaults, it must correct the default. The Data Quality Act's twin goals of informed decision-making and accountable government cannot otherwise be realized.

B. OMB Guidelines

OMB published its Guidelines under the Data Quality Act on February 22, 2002.[27] The OMB Guidelines impose on agencies several quality standards with respect to the dissemination of "information," which the Guidelines define to include, *inter alia*, information that an agency disseminates to the public from a web page.[28] The OMB Guidelines also define the statutory terms "quality," "objectivity," "utility," and "integrity."

1. Quality. The OMB Guidelines define "quality," in pertinent part, as "an encompassing term comprising utility, objectivity, and integrity," and specify that the term "quality" may refer collectively to all four of the statutory terms.[29]

2. Utility. The OMB Guidelines define "utility," in pertinent part, as "the usefulness of the information to its intended users, including the public."[30]

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[24] H.R. Rep. No. 104-37 at 5; S. Rep. No. 104-8 at 4.

[25] 44 U.S.C. § 3516 note.

[26] *Id.* (emphasis added).

[27] 67 Fed. Reg. at 8452.

[28] *Id.* at 8460 (Part V(5)).

[29] *Id.* at 8459 (Part V(1)).

[30] *Id.* (Part V(2)).

3. **Objectivity.** The OMB Guidelines define "objectivity," in pertinent part, as meaning that the information is being presented in "an accurate, clear, complete, and unbiased manner"; this, in turn, requires the information to be "presented within a proper context," and sometimes may require the agency to supplement the information that it wishes to disseminate with "other information . . . in order to ensure an accurate, clear, complete, and unbiased presentation."[31] In defining "objectivity" in connection with an agency's dissemination of information defined as "influential," the OMB Guidelines state, in pertinent part:

> With regard to analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C. 300g-1(b)(3)(A) & (B)).[32]

The Guidelines define "influential" information to mean that "the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions."[33] The Guidelines specify that each agency may define the term "influential" "in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible."[34]

4. **Integrity.** Finally, the OMB Guidelines define "integrity" as the "security of information" against "unauthorized access or revision, to ensure that the information is not compromised through corruption or falsification."[35]

In summarizing these four standards, OMB stated:

> It is *crucial* that information Federal agencies disseminate meets these guidelines. . . . [T]he fact that the Internet enables agencies to communicate information quickly and easily to a wide audience not only offers great benefits to society, but also increases the potential harm that can result

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[31] *Id.* (Part V(3)(a)).

[32] *Id.* at 8460 (Part V(3)(b)(ii)(C)).

[33] *Id.* (Part V(9)).

[34] *Id.*

[35] *Id.* (Part V(4)).

> from the dissemination of information that does not meet basic information quality guidelines."[36]

C. HHS and FDA Guidelines

HHS announced final Guidelines on September 30, 2002.[37] The HHS Guidelines, which became effective on October 1, 2002, consist of two parts: Part I contains a general overview of the OMB and HHS Guidelines and adopts verbatim the standards and framework of the OMB Guidelines. Part II contains the quality assurance policies of each of the HHS operating divisions; the quality assurances policies for FDA are found in Subpart F of Part II. In Subpart F, FDA emphasizes that "We only disseminate information that we believe will be useful to the public or a segment of the public"[38] and notes the "many different systems [we have] in place to ensure that the information we disseminate is presented in an accurate, clear, and unbiased manner."[39]

Discussion

The White Papers and Table 1.1 Violate the Data Quality Act and Implementing Guidelines Because the Information Presented Is Not "Objective" or "Useful"

Under the OMB and HHS Guidelines, information disseminated by FDA must be "objective" and "useful." As both sets of Guidelines recognize, objectivity requires that information be "presented within a proper context."[40] In addition, as explained by HHS, "objectivity" "involves a focus on ensuring accurate, reliable, and unbiased information."[41] Because the information presented in the White Papers and Table 1.1 is riddled with errors and omissions, these documents fail to achieve objectivity for purposes of the Data Quality Act.

Despite FDA's attempts to limit the definition of "dissemination" by its disclaimer that "the information in these materials is not a formal dissemination of information by FDA," materials on FDA's website such as Table 1.1 and the White Papers clearly qualify as dissemination of information that is subject to the Data Quality Act. The Data Quality Act

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[36] *Id.* at 8452 (emphasis added).

[37] 67 Fed. Reg. 61343 (Sept. 30, 2002); HHS, *Guidelines for Ensuring the Quality of Information Disseminated by HHS Agencies, at* http://www.hhs.gov/infoquality (last revised Dec. 13, 2006) (HHS Guidelines).

[38] HHS, *Guidelines for Ensuring the Quality of Information Disseminated to the Public*, Part II.F, *Food and Drug Administration, at* http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml, at Part V(A) (FDA Guidelines).

[39] *Id.* at Part V(B).

[40] 67 Fed. Reg. at 8459 (Part V(3)(a)), incorporated in HHS Guidelines at Part I(D)(2)(c).

[41] HHS Guidelines at PartI(D)(2)(c).

does not distinguish between any type of "formal" or informal dissemination of information. OMB and HHS Guidelines define dissemination as "agency initiated or sponsored distribution of information to the public."[42] Thus, FDA-initiated distribution of information on its website will be considered a dissemination of information subject to the Data Quality Act, regardless of FDA's characterization of the information.

The concept of "utility" under the Data Quality Act requires that the information be useful to its intended users.[43] The disseminating agency must "consider the uses of the information not only from the perspective of the agency but also from the perspective of the public."[44] Because the information presented in the White Papers and Table 1.1 is inaccurate and incomplete, the utility of this information to the TPSAC and the public is extremely limited.

In Exhibit A, which is a copy of the briefing materials submitted by Lorillard in advance of the March 2, 2011 TPSAC meeting, we address the inaccuracies and distortions present in the White Papers. In Exhibit B, we present the glaring errors and omissions in the updated Table 1.1 and propose recommendations for correcting these errors and omissions. These suggestions were included in Dr. Dan Heck's November 17. 2010 and December 4, 2010 emails to FDA, but FDA has not addressed all of these issues.

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In short, far from providing objective, useful and unbiased information about menthol as described in the scientific literature, the White Papers and Table 1.1 are inaccurate, misleading, and incomplete. This information violates the Data Quality Act and implementing Guidelines. For all of the reasons presented above, we request that FDA correct the White Papers as proposed in Exhibit A so that these papers will similarly comply with the Act. In addition, we request that FDA correct updated Table 1.1 as proposed in Exhibit B so that Table 1.1 will comply with the requirements of the Data Quality Act.

Because FDA documents are relied upon by the public, TPSAC, and others, it is critical that FDA fully and effectively correct these documents. FDA should ensure that its correction provides adequate notice to TPSAC and the public. FDA must prominently denote on its website that the original materials posted by FDA were inconsistent with the DQA and, as a result, have been corrected. FDA should also announce these same matters during the next TPSAC meeting. Moreover, to the extent that TPSAC issues a report on

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[42] 67 Fed. Reg. at 8460, incorporated into HHS Guidelines at Part I(D)(2)(h). Although the HHS Guidelines discuss limited exceptions to this definition, they do not apply here.

[43] 67 Fed. Reg. at 8459, incorporated into HHS Guidelines at Part I(D)(2)(b).

[44] *Id.*

menthol that incorporates the same research or conclusions, FDA should not consider or rely upon those portions of the report.

These points, comments and suggestions are offered to assist the FDA in achieving its stated objective of conducting a sound, science-based, inclusive and objective evaluation of scientific matters relating to the regulation of tobacco products. Lorillard appreciates the agency's attention to this important matter.

Sincerely,

/S/

Ronald Milstein
Senior Vice President, Legal and External Affairs,
General Counsel and Secretary

Enclosures

EXHIBIT A TO LORILLARD DATA QUALITY ACT PETITION

Meeting of the Tobacco Products Scientific Advisory Committee

March 2, 2011

Briefing Regarding FDA-CTP White Papers on the Science Relating to the Use of Menthol in Cigarettes

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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, called for the establishment of a Tobacco Products Scientific Advisory Committee (TPSAC). FDA announced the creation of the TPSAC on August 26, 2009 (Final Rule (Aug. 26, 2009)). On March 23, 2010 FDA announced the membership of TPSAC. Among the topics on which TPSAC 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" (Menthol Report). On January 6, 2011, FDA announced a meeting of TPSAC on March 1-2, 2001 to "(1) receive updates from the Menthol Report Subcommittee and (2) receive and discuss presentations regarding the data requested by the Committee at the March 30 and 31, 2010, meeting of the Tobacco Products Advisory Committee." The announcement also provided that '[w]ritten submissions may be made to the contact person on or before February 15, 2011."

During the first meetings of TPSAC on March 30-31, 2010 (March 2010 Meetings), the FDA staff stated that a white paper on the science related to menthol in cigarettes (White Paper) was being prepared to facilitate TPSAC's preparation of the Menthol Report. Also during the March 2010 Meetings, FDA-CTP staff and other invited presenters provided briefings to TPSAC on several topics related to menthol cigarettes (TPSAC Briefings).

On June 29, 2010, Lorillard Tobacco Company submitted a critical review and identification of omissions and misstatements in the TPSAC Briefings. Lorillard was very concerned about the inaccuracies in the TPSAC Briefings and believes that TPSAC cannot rely on inaccurate representations of the science in preparing the Menthol Report. Lorillard's June 29th comments were intended to accompany the proposed White Paper for the TPSAC members' consideration.

It was not until immediately prior to the October 7, 2010 TPSAC meeting, that FDA posted to the FDA webpage the following White Papers (FDA White Papers) on the various topics addressed in the prior TPSAC Briefings:

- Rising and Alexander, "Marketing of menthol cigarettes and consumer perceptions."
- Lawrence *et al.*, "Sensory properties of menthol and smoking topography."
- Rising and Wasson-Blader, "Menthol and initiation of cigarette smoking."
- Hoffman and Simmons, "Menthol cigarette smoking and nicotine dependence."
- Hoffman and Miceli, "Menthol cigarettes and smoking cessation behavior."
- Hoffman, "The health effects of menthol cigarettes as compared to nonmenthol cigarettes."
- Caraballo and Asman, "Epidemiology of menthol cigarette use in the United States."

Many of the omissions and misstatements identified by Lorillard with respect to the TPSAC Briefings were carried over into the FDA White Papers without correction. In this submission, Lorillard sets forth examples of errors and omissions by FDA-CTP staff and other authors in the FDA White Papers. The FDA White Papers suffer, in the main, from the same lack of objectivity as the TPSAC Briefings, contain misleading analyses of pertinent data, and often fail to report on highly relevant findings contained in the papers discussed. Frequently, the FDA White Papers exclude or underemphasize strong, relevant data that demonstrate no public health effects of menthol in cigarettes in favor of stressing non-statistically significant data purporting to demonstrate a menthol effect. In addition, the FDA White Papers omit discussions of recent scientific publications which are highly relevant with respect to any health effects of the use of menthol in cigarettes. Before TPSAC or FDA can rely in any way on the FDA White Papers, all errors, omission and misrepresentations in these materials must be corrected.

Lorillard provides the following examples of the continuing errors, omissions and misrepresentations in the FDA White Papers.

Hoffman, A.C., "The health effects of menthol cigarettes as compared to non-menthol cigarettes" (Health Effects White Paper).

The Health Effects White Paper presents conclusions regarding various health effects of menthol cigarettes. Two conclusions particularly merit discussion.

With regard to the body of epidemiological literature addressing menthol cigarettes, the Health Effects White Paper states: "Overall, the data regarding menthol cigarette smoke and cancer do not support a link between menthol cigarette smoke and increased risk of cancer, however there are some limited data that suggest possible menthol x gender x disease interactions" (Health Effects White Paper at 20). The substantial body of epidemiological evidence does not support any increased risk of any disease for menthol smokers when compared to nonmenthol smokers. The Health Effects White Paper attempts to highlight elevated risks in subgroups – "some limited data that suggest a possible menthol x gender x disease interaction." This conclusion is not sound. These "suggestive" studies do not provide statistically significant data – data upon which scientific conclusions can be based. Rather, the authors merely suggest a possible interaction. Statistically non-significant findings should not be used by TPSAC in its preparation of the Menthol Report.

Addressing biomarkers of exposure, the Health Effects White Paper concludes: "Data on menthol's effects on biomarkers of smoke exposure, including nicotine/cotinine, CO (expired CO, blood carboxyhemoglobin) and some TSNAs are inconclusive" (Health Effects White Paper at 19). Describing the vast weight of evidence showing no differences in biomarkers of exposure as inconclusive is imprecise and misleading. In fact, 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)). Most importantly, recently published studies reported measurements of both biomarkers of exposure (Wang et al. (2010)) and putative biomarkers of harm (Frost-Pineda et al. (2010)) for an extremely large, nationally representative population of approximately 3,600 smokers of menthol and nonmenthol cigarettes. Neither blood carboxyhemoglobin nor urinary nicotine equivalents differed statistically significantly between menthol and nonmenthol smokers. In addition, not a single putative biomarker of harm differed between menthol and nonmenthol smokers.

In many instances, the Health Effects White Paper ascribes too much import to statistically non-significant data in attempting to suggest a menthol effect on health and underemphasizes or fails

to report findings where no menthol effect is found. For example, the Health Effects White Paper, in discussing three major epidemiology papers (Brooks *et al.* (2003); Friedman *et al.* (1998) and Hebert and Kabat (1988)), provided minimal discussion of statistically significant findings that menthol smokers showed no increased risk of disease over nonmenthol smokers.

> *Possible interactions between menthol and smoking-related disease, either as a disease state or on the cellular level, have been studied. The data do not suggest that smoking menthol cigarettes is associated with an altered likelihood of developing cancer. Several studies have failed to find that menthol cigarette smoking alters the likelihood of developing several kinds of cancers, including lung and non-lung smoking related cancers, as well as cardiovascular disease or coronary heart disease [79–81] in the population as a whole.* (Health Effects White Paper at 17).

By consolidating the discussion of these studies, the importance of the studies' findings is diminished. For example, Brooks *et al.* (2003) examined data from a large, multi-hospital case-control study to examine whether smoking menthol cigarettes might be associated with higher lung cancer risk as compared to smoking nonmenthol cigarettes. The authors found that menthol smokers did not have an elevated risk of lung cancer (OR= 0.89, 95% CI: 0.69 – 1.14) relative to nonmenthol smokers. The authors reported that: *"Odds ratios were also close to 1.0 in separate analyses of male, female, Black and White subjects. The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking nonmenthol cigarettes."* Simply reporting that these studies "failed to find that menthol cigarette smoking alters the likelihood of developing cancer" places far too little emphasis on the substantial data showing no menthol effect on disease risk set forth in the studies.

In contrast, the Health Effects White Paper gives ample consideration to papers finding statistically non-significant gender or race interactions:

> *Although some studies specifically discussed the absence of a menthol x gender x disease interaction [78, 81], other studies have suggested that such an interaction*

may exist. One prospective study of the health of smokers found that male (but not female) menthol smokers had a modestly increased risk of lung cancer, with a relative risk of 1.45 (95% CI = 1.03–2.02) [84]. Another case control study suggested a small positive association between pharyngeal cancer in menthol-smoking males, but not females (OR = 1.7; 95% CI = 0.8–3.4), <u>but this difference was not statistically significant</u> [85]. A third case control study found that menthol use was not associated with changes in risk for esophageal cancer in males, but suggested that females may have a modestly increased risk (OR = 2.3; 95% CI = 0.93–5.72). <u>These differences also failed to reach statistical significance</u> [86]. A fourth case control study suggested that menthol may modestly increase risk of lung cancer in men with histories of more than 32 pack years of smoking menthol cigarettes (OR = 1.48; 95% CI = 0.71–3.05), but the <u>findings were not statistically significant</u> and limited by the small study size [87]. (Health Effects White Paper at 17-18 [Emphasis Added]).

The Health Effects White Paper reports on four studies that find statistically non-significant differences between menthol and nonmenthol smokers in certain subgroups, but fails to mention the overall findings of those studies. For example, Kabat and Herbert (1994) reported *"[t]hese results indicate that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer;"* Herbert and Kabat (1989) stated *"[o]ur results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer;"* and Carpenter et al. (1999) found *"[o]ur results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking nonmentholated 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."*

The Health Effects White Paper also focuses on one study which found a single statistically significant finding showing a menthol x gender x disease interaction, fails to address a subsequent study of the same population which stated that the finding might be chance:

One prospective study of the health of smokers found that male (but not female) menthol smokers had a modestly increased risk of lung cancer, with a relative risk of 1.45 (95% CI = 1.03–2.02) [84]. (Health Effects White Paper at 17-18).

As noted above only Sidney *et al.* (1995) reported a small statistically significant elevated risk [relative risk (RR) 1.45; 95% CI: 1.03-2.02] for lung cancer among men (all races combined) who smoked menthol cigarettes compared with men who smoked non-menthol cigarettes. No statistically 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 the following about the earlier study: "*... 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)).

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. In addition, biomarkers of exposure studies, which integrate and reflect the impact of all of the diverse elements on complex human smoking behaviors, demonstrate that menthol in cigarettes has no meaningful effect on cigarette smoke constituent exposures. Given this weight of scientific evidence, claims that this evidence is equivocal or mixed is scientifically invalid.

Hoffman, A.C., Miceli, D., "Menthol cigarettes and smoking cessation behavior" (Cessation White Paper).

The Cessation White Paper underemphasizes relevant data showing no menthol effect on cessation, overemphasizes selected data showing a menthol effect on cessation and often omits important data:

There were several studies that found no association between adult use of menthol cigarettes and cessation success, including a national survey [4], a local/regional survey [6], a longitudinal study [13] a clinical study [12], and secondary data analysis of a large-scale randomized intervention study [14]. There were also several studies that found that adult menthol smokers have lower levels of abstinence/successful quitting, including several clinical studies with both moderate/heavy smokers and light smoker,[sic] [6,9] and in a national survey [3]. There were some clinical and cohort analysis studies that found that efficacious behavioral and pharmacotherapy treatments were less effective when used by menthol smokers as compared to non-menthol smokers [7, 10, 11]. In addition, a possible interaction between menthol and race/ethnicity was suggested, with worse outcomes for adult Black/African American and Hispanic/Latino menthol smokers than White menthol smokers [3, 15]. There was no consistent interaction between menthol cigarette use and quitting success for White smokers. (Cessation White Paper at 11-12).

The Cessation White Paper reports that "several studies found that adult menthol smokers have lower levels of abstinence/successful quitting, including several clinical studies with both moderate/heavy smokers and light smoker, [sic] [6, 9] and in a national survey [3]" (Cessation White Paper at 11). Gunderson *et al.* (2009) is referenced as the national survey finding lower abstinence/successful quitting than nonmenthol smokers. But Gunderson's findings were not so straightforward. Gunderson reported a lower likelihood among African-American and Hispanic smokers (collapsed as a "non-white" identity) reporting themselves to be ex-smokers compared to White smokers. The White menthol smokers in the study, however were *more* likely to report apparently spontaneous quitting than were White nonmenthol smokers:

We found that the association of menthol smoking and cessation differs among whites and non-whites. Specifically, we found a statistically significant relationship among non-white menthol smokers such that they were less likely to have quit relative to non-white nonmenthol smokers. This was not the case

among whites. Indeed, white menthol smokers were more likely to be a former smoker than were white nonmenthol smokers. (Gunderson *et al.* (2009) at 555-556).

The Cessation White Paper also does not discuss the fact that no coherent scientific basis whatsoever has been reported in the published literature to support speculation that menthol can exert profoundly opposing effects in White and non-white ethnic groups.

Regarding the clinical studies, the Cessation White Paper concludes that Okuyemi, *et al.* (2004) [Cessation White Paper FN 6] shows lower levels of abstinence/successful quitting. Again, the study's findings were not so simple:

> *We examined four measures of past cessation experiences: lifetime number of quit attempts, time since most recent quit attempt, and duration of abstinence for both longest-ever and most recent quit attempts. While both groups did not differ in their lifetime number of quit attempts, menthol smokers on average had a non-significantly (20%) higher number of more recent quit attempts compared to nonmenthol smokers. A more interesting finding, however, is that menthol smokers reported shorter periods of abstinence for both their longest-ever and most recent quit attempts compared to nonmenthol smokers. <u>While these differences did not reach statistical significance</u>, the consistency and direction of the three measures of success with smoking cessation <u>suggest</u> that menthol smokers were less successful in past quit attempts compared to nonmenthol smokers.* (Okuyemi, *et al.* (2004) at 1210 [Emphasis added]).

The conclusions from Okuyemi above do not support a finding that menthol smokers have poorer cessation outcomes, rather the authors merely "suggest" such a finding based on statistically non-significant data.

The Cessation White Paper also reports that "some clinical and cohort analysis studies that found that efficacious behavioral and pharmacotherapy treatments were less effective when used by

menthol smokers as compared to non-menthol smokers [7, 10, 11]" (Cessation White Paper at 11-12). When discussing these studies, however, the Cessation White Paper omits several relevant study findings.

Okuyemi *et al.* (2003) [Cessation White Paper FN 7] reported a difference in short-term cessation results between menthol and nonmenthol cigarette smokers using buproprion as a smoking cessation aide, but the Cessation White Paper failed to report that the study did not show a statistically significant cessation difference at 6 months:

> *Overall 28.3% of menthol smokers were abstinent at 6 weeks (end of treatment, n= 535) compared to 41.5% of non-menthol smokers (P = 0.006). <u>The abstinence rate at 6 months (n = 518) was also lower among menthol smokers but the difference was not statistically significant</u> (21.4% versus 27.0% for non-menthol smokers; (P = 0.21).* (Okuyemi *et al.* (2003) at 1390 [Emphasis added]).

Further, the Okuyemi study found no differences in the placebo group for cessation rates between menthol and nonmenthol smoking study participants, which the Cessation White Papers did not report:

> *Abstinence rates did not differ by menthol status among those who receive placebo (23.3% non-menthol versus 20.5% menthol; P=0.63).* (Okuyemi *et al.* (2003) at 1390).

Foulds *et al.* (2006) [Cessation White Paper FN 10] reported on various factors affecting smoking cessation outcomes for smokers undergoing counseling and various cessation medications, which the Cessation White Papers failed to disclose. Foulds reported:

> *Those with only a high school education were significantly less likely to be abstinent at both 4- and 26-week follow-up compared with those who had a degree. Unemployment predicted poor outcome at 4 weeks, and not having*

private health insurance predicted poor outcome at 26 weeks. All of these variables are indicators of socioeconomic status. (Foulds *et al.* (2006) at 409).

The Cessation White Paper also cites Okuyemi, *et al.* (2007) [Cessation White Paper FN 11] for the conclusion that behavioral and pharmacotherapy were less effective for menthol smokers. Okuyemi *et al.* (2007) reported on whether African-American light menthol smokers had lower cessation rates than those who smoke nonmenthol cigarettes following treatment with nicotine gum and counseling.

The Cessation White Paper fails to disclose that, in this study, menthol and nonmenthol smoker cessation rates at 26 weeks were no different when using placebo gum:

> *Abstinence rates among those who received placebo gum (P=0.196) or MI (P=0.244) were not significantly different by menthol status.* (Okuyemi *et al.* (2007) at 1981).

Further, the Cessation White Paper does not discuss data which show that combination treatments in the study participants produced no statistically significant differences in cessation success:

> *With the exception of MI + placebo combination, abstinence rates for non-menthol smokers were <u>non-significantly</u> higher than for menthol smokers for all other treatment combination groups.* (Okuyemi, *et al.* (2007) at 1981 [Emphasis Added]).

Finally, the Cessation White Paper does not mention the serious study limitations recognized by the study authors:

> *First all participants in the study were African Americans and therefore the findings may not generalize to light smokers of other ethnicities.... Secondly, this study was a secondary analysis that used data from a clinical trial that was not*

designed for testing differences in smoking cessation by menthol status.... Thirdly, although the use of menthol cigarettes may partially explain lower cessation rates for African Americans in clinical trials, this is somewhat at odds with the current overall decline in smoking prevalence in African Americans to a level below that for European Americans..... Finally, because menthol use was not the primary focus of the parent study, menthol status was determined by self-report and we did not assess how long participants have used menthol cigarettes. (Okuyemi *et al.* (2007) at 1984).

Ultimately, conclusions offered in the Cessation White Paper largely ignore the body of evidence from large, nationally representative cessation studies that show no differences in cessation success between menthol and nonmenthol cigarette smokers (Hyland *et al.* (2002); Li *et al.* (2005); Muscat *et al.* (2002); NHANES (2005-2006, 2007-2008); Murray *et al.* (2007)).

The Cessation White Paper, however, devotes substantial discussion to smaller studies – most notably studies that find a menthol effect on cessation. On pages 3 and 4, the Cessation White Paper reports on Hyland *et al.* (2002), Muscat *et al.* (2002) and Okuyemi *et al.* (2004) referring to these as the only three studies assessing smoking patterns in adult menthol smokers. In its treatment of the studies, the Cessation White Paper underemphasizes the importance of the Hyland study:

Hyland et al [4] analyzed the Community Intervention Trial for Smoking Cessation (COMMIT) dataset to assess whether use of menthol cigarettes was associated with quitting. This large-scale telephone survey was first completed in 1988, with a follow up (re-interview) in 1993. No association between smoking menthol cigarettes and quitting success was found. (Cessation White Paper at 4).

The Cessation White Paper fails to report that the Hyland study included 13,000 participants and fails to discuss important findings: "For the entire sample, the estimated relative risk was 1.00 (95% confidence interval (CI (0.90 to 1.11), and none of the race/ethnicity specific analysis revealed <u>any</u> significant associations" (Hyland *et al.* (2002) at 137 [Emphasis Added]).

In other instances, the Cessation White Paper does not mention serious limitations in studies finding a menthol effect on cessation and overemphasizes the studies' findings:

> *In an effort to better understand the smoking patterns and cessation experiences of Black/African American smokers, Okuyemi et al [6] conducted a cross-sectional survey of 600 Black/African American smokers at an inner-city health center. To examine past cessation attempts, survey questions focused on the number of lifetime quit attempts, time since most recent quit attempt, and the duration of abstinence for both the longest-ever and most recent quit attempts. There was no difference between menthol and non-menthol smokers in the number of lifetime quit attempts, but menthol smokers had significantly less time since their last quit attempt. Additionally, there was a suggestion that smokers of menthol cigarettes had shorter durations of abstinence for both their most recent and their longest-ever quit attempts, but the results were not statistically significant ($p = .187$ and $p = .111$, respectively). Based on the consistency of the direction of the three measures of cessation success, the authors suggested that Black/African American individuals who smoke menthol cigarettes may be less likely to be successful in their quit attempts.* (Cessation White Paper at 4-5).

The Cessation White Paper fails to mention the serious limitations reported in the Okuyemi study which found a menthol effect on cessation: "Second, being a cross-sectional study, causal relationship between menthol and smoking cessation cannot be implied. Sample size was also limited to that of the primary data. Third, our study was also limited to African-American smokers, and findings may not apply to smokers of other ethnic groups as there are well-documented differences in smoking patterns among various ethnic groups" (Okuyemi *et al.* (2004) at 1211).

In contrast to the omission of a discussion of limitations for many studies which find a menthol effect, the Cessation White Paper finds "caveats" when interpreting the data reported in Cropsey *et al.* (2009) which showed no menthol effect on cessation measures:

Female prisoners in a clinical trial studying smoking cessation treatment were given 10 weeks of treatment (group psychotherapy and nicotine replacement therapy) and followed for 12 months [12]. At the 12-month follow-up, there were no significant differences in abstinence rates when menthol smokers were compared to non-menthol smokers. <u>There are a few caveats when interpreting these data, however</u>.... (Cessation White Paper at 7-8 [Emphasis added]).

Further, the Cessation White Paper focuses on one set of study results (*e.g.*, short-term versus long-term) or statistically non-significant results in reporting findings of a menthol effect on cessation:

> *...Okuyemi et al [7] analyzed data from the first double-blind, placebo-controlled, randomized trial of bupropion in Black/African-American smokers [8] and reported that although bupropion increased successful abstinence, the 7-day point prevalence of abstinence for menthol smokers was only half that of non-menthol smokers (36.2% compared to 60.3%). Overall, at the 6-week follow-up, menthol smokers were only half as likely to remain abstinent as compared to non-menthol smokers (24.9% and 44.4%, respectively). These findings suggest that smoking menthol cigarettes contributes to difficulty in remaining abstinent while using bupropion as a cessation aid.* (Cessation White Paper at 5).

Okuyemi *et al.* (2003), however, reported no statistically significant differences between menthol and nonmenthol smokers' cessation rates at 6 months. The Cessation White Paper did not discuss this finding.

The examples provided above demonstrate an unbalanced presentation of the data on menthol and smoking cessation in the Cessation White Paper.

Hoffman, A.C. and Simmons, D., "Menthol cigarette smoking and nicotine dependence" (Dependence White Paper).

The Dependence White Paper draws a number of conclusions finding that menthol cigarette smokers are more dependent on nicotine than nonmenthol cigarette smokers:

> *The majority of indicators of nicotine dependence, including time to first cigarette upon waking (youth and adults), night waking to smoke (adults), and some other indications of dependence (youth) suggest that menthol cigarette smokers are more heavily dependent on nicotine. Although some other indicators of nicotine dependence, including CPD and FTND, failed to consistently differentiate menthol and non-menthol smokers, these indicators are not thought to be as robust as time to first cigarette.* (Dependence White Paper at 10).

These conclusions typically are based on single measures of dependence such as time to first cigarette on waking (TTFC) and waking at night to smoke and discount the validated Fagerström Test for Nicotine Dependence (FTND). The Dependence White Paper suggests that TTFC and night-waking to smoke are more robust indicators of nicotine dependence than the multifactorial FTND which includes a measure of TTFC. The Dependence White Paper does not discuss several recently published studies which report either no statistically significant differences for TTFC among menthol and nonmenthol smokers or that TTFC was statistically significantly delayed among White and African-American menthol smokers compared to nonmenthol smokers (Lawrence *et al.* (2010); Fagan *et al.* (2010); Ahijevych & Ford (2010); Fu *et al.* (2008); Hyland *et al.* (2002)). In addition, night-waking to smoke was evaluated only in a single smoking population. Moreover, in this study population 14 additional study variables were statistically significantly associated with night-waking to smoke (Bover *et al.* (2008); Gandhi *et al.* (2009)).

For example, the Dependence White Paper emphasizes a conclusion by Gandhi *et al.* (2009) that menthol smokers were more likely to wake at night to smoke than nonmenthol smokers.

> *Waking at night to smoke also appears to be a marker for tobacco dependence. Gandhi et al [12] conducted a retrospective cohort analysis of 1,688 consecutive patients who attempted to quit smoking. More menthol smokers than non-menthol*

smokers reported waking at night to smoke (55.3% and 44.9%, respectively; $p < .001$). (Dependence White Paper at 4).

However, a more objective interpretation of the study results indicates that measures of dependence are impacted by socioeconomic status (SES):

> *Further sub-analysis indicated that the strength of the 'menthol effect' was related to SES, even within different ethnic/racial groups. Taking employment status as an example (unemployed vs. full-time employed), the difference between quit rates in menthol and non-menthol smokers was greater among those who were unemployed as compared with those who were employed. Among Whites, 4-week quit rates were identical for menthol and non-menthol smokers who were fully employed (56%), whereas among unemployed white smokers, the quit rate was non-significantly lower for menthol smokers (23% vs. 37%, $\chi^2[1] = 3.160$, $p = 0.07$). Similarly, the 4-week quit rate was significantly lower for menthol smokers than non-menthol smokers among unemployed AAs (16% vs. 43%, $\chi^2[1] = 4.38$, $p = 0.03$), <u>but the effect of mentholation was not significant for full-time employed AAs</u> (42% vs. 56%, $p = 0.20$) (Figure 2).* (Gandhi *et al.* (2009) at 364 [Emphasis Added]).

Similarly, when discussing Bover *et al.* (2008), which examined the same study population as Gandhi *et al.* (2009), the Dependence White Paper's analysis relating menthol cigarettes to waking at night to smoke and TTFC is misleading:

> *Similar results were found by Bover et al [12], in a large study of more than 1,350 smokers at a tobacco dependence clinic. Menthol cigarette smokers (58%) reported waking at night to smoke compared with 45% of non-menthol cigarette smokers ($p \leq .0001$). Furthermore, night-waking smokers had a significantly shorter time before smoking their first cigarette after waking in the morning, with 72% of menthol smokers reporting smoking their first cigarette of the day within five minutes or less, compared to 28% of non-menthol smokers ($p \leq .0001$). Taken*

together, these data indicate that menthol smokers have greater nicotine dependence. (Dependence White Paper at 4-5).

Bover *et al.* (2008), however, did not analyze TTFC by menthol/nonmenthol status. Rather, this study reported TTFC by waking at night to smoke versus not waking to smoke. The percentages given in the Dependence White Paper are presumably taken from Table 1 at page 185. These percentages *do not* represent a menthol/nonmenthol analysis. Further, the Dependence White Paper based its erroneous claim that menthol smokers are more nicotine dependent than nonmenthol smokers on this inaccurately reported data.

Ultimately, the strongest measure of nicotine dependence is borne out in cessation results and health risks. In the case of menthol cigarettes, the large, nationally representative studies show that menthol cigarette smokers quit smoking at equivalent rates as do nonmenthol smokers. In addition, menthol smokers do not show an increased risk of smoking related disease as compared to nonmenthol smokers in the sizable body of epidemiological literature.

Rising, J. and Wasson-Blader, K., "Menthol and initiation of cigarette smoking" (Initiation White Paper).

The Initiation White Paper recognizes the severe limitations that exist in the published literature relating to menthol cigarettes and smoking initiation. The author states that "retrospective data and adult recollections of smoking initiation may not provide an accurate representation of the product used" (Initiation White Paper at 8). As such, these studies should not be relied upon in forming conclusions with regard to menthol and smoking initiation. However, despite the lack of relevant data, the Initiation White Paper draws several conclusions regarding an effect of menthol on smoking initiation.

Two of the Initiation White Paper's conclusions do not provide data helpful in forming opinions with regard to menthol cigarettes and smoking initiation. Conclusion 1 ("The vast majority of individuals who become regular smokers begin smoking as youth or young adults" (Initiation White Paper at 9)) and conclusion 6 ("Reviews of publically available internal tobacco industry

documents suggest an industry awareness of the appeal of menthol cigarettes to newer smokers" (Initiation White Paper at 9)) report no information relevant to the question of menthol cigarette smoking initiation. The conclusion regarding industry documents is based on a very limited review of industry documents. Suggestions in a limited number of documents from years, and in some instances decades, ago regarding vague industry knowledge is not relevant to the issue of menthol cigarette smoking initiation.

White Paper conclusion 4 ("Results are inconsistent regarding the frequency and direction of switching and the direction of switching between menthol and non-menthol cigarettes" (Initiation White Paper at 9)) is inconsistent with recent data provided to FDA. Hyland, in a recent submission to FDA (Analysis of Mentholated Cigarettes using the COMMIT Data -- Summary Report, November, 2010) reported that "...switching between menthol and non-menthol cigarettes is uncommon for all smokers, regardless of race" (Hyland (2010) unpublished data at 21).

White Paper conclusion 2 ("Menthol cigarettes are widely used among youth who have smoked for less than one year and are used less frequently by youth who have smoked for more than one year" (Initiation White Paper at 9)) ignores important facts about youth menthol smoking. Foremost, the majority of adolescent smokers choose nonmenthol brands (NSDUH, 2009). Linking the popularity of a certain style or brand of product to a causal relationship with smoking initiation or smoking trajectory is unfounded.

The Initiation White Paper's conclusion 3 ("Although limited data are available, there appears to be no differences in age of initiation between those who start smoking with menthol cigarettes and those who start smoking with non-menthol cigarettes..." (Initiation White Paper at 9)) and conclusion 5 ("No data exist on whether menthol cigarette use alters the trajectory from initiating cigarette use to regular smoking" (Initiation White Paper at 9)) both support a conclusion that menthol in cigarettes has no causal effect on youth smoking initiation. It is well documented that African-Americans, the vast majority of whom prefer menthol cigarettes, begin smoking at an older age than Whites. In addition, African-American youth report themselves to be smoking at about half the rate reported by White youth.

The Initiation White Paper also omits discussion of some relevant limitations of the published literature on menthol cigarettes and smoking initiation. For example, in its treatment of Hersey *et al.* (2006), the Initiation White Paper fails to report on the limitations of the study:

> *A study by Hersey et al [5] examined data from the 2002 National Youth Tobacco Survey regarding the duration of smoking and menthol cigarette use. Middle school students (grades 6–8) who had been smoking less than 1 year were significantly more likely to smoke menthol cigarettes than were middle school students who had been smoking more than 1 year (62.4% vs. 53.3%, $p < .002$). A similar, though not statistically significant, pattern was found for high school students (grades 9–12); 46% of the high school students who had been smoking for less than 1 year smoked menthol cigarettes, compared with 42% of students who had been smoking more than 1 year.* (Initiation White Paper at 4).

While this text accurately reports the study findings, it fails to list three major limitations noted by the study authors:

> *The present study had a number of limitations. Some misclassification in the reporting of menthol use may have occurred. However, the sensitivity analyses indicated similar findings using various definitions of menthol cigarettes. Moreover, any misclassification is likely to have reduced the differences between menthol and nonmenthol groups, given that the results of misclassification have been to mix actual menthol cigarette smokers with nonmenthol smokers and vice versa.*
>
> *Also, differences in the smoking patterns of menthol versus nonmenthol users may not have been adequately controlled for in our models. Further, 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. Such a study also would be able to address issues related to brand switching. Findings about nicotine dependence would be strengthened by confirmation with biochemical data on nicotine absorption.

Finally, the present study could not determine the extent to which the popularity of menthol cigarettes among younger, newer smokers is a result of product characteristics, marketing (Giovino et al., 2004), or other influences. Even so, the fact that menthol is one of the most prevalent types of cigarettes used by younger, newer smokers suggests that further investigation of the role of mentholated cigarettes deserves close attention. (Hersey *et al.* (2006) at 412).

The Initiation White Paper relies on conclusions regarding industry documents from Kreslake *et al.* (2008a) and (2008b). The Kreslake papers are not relevant to the issue of whether or not adolescent smokers initiate with menthol cigarettes. In the discussion of the Kreslake papers, the Initiation White Paper cites to only two documents, one authored by R.J. Reynolds and another authored by Brown & Williamson, from the mid-1980s. The fact that these two companies studied the appeal of different menthol levels, or that any company studied such issues, is irrelevant as to whether or not new smokers choose menthol brands.

In addition, one of the allegations made in Kreslake *et al.* (2008b) was that cigarette brands reported to be preferred by younger smokers have lower levels of menthol than do brands reported to be preferred by older smokers, and further that cigarette manufacturers had lowered menthol levels as a general strategy to attract youthful smokers in recent years. Lorillard has publically and without reservation denied this assertion and has provided extensive evidence of the inaccuracy of this assertion to TPSAC and FDA (see, e.g. Response to FDA Request for Information Regarding Youth Smoking, and Advertising and Promotion of Cigarettes, August 2, 2010, Lorillard Tobacco Company, Docket ID: FDA-2010-N-0295).

Lawrence et al., "Sensory properties of menthol and smoking topography" (Topography White Paper).

The ultimate conclusion in the Topography White Paper is that "...the extant literature does not bridge the gap between what is known about menthol's multifaceted sensory effects and the mechanism by which menthol may alter a smoker's behavior." (Topography White Paper at 20). The conclusion overreaches. Studies attempting 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 show mixed results with any differences reported likely dependent upon the method used and lack of the specificity of the outcome attempted to be measured. Any differences in these measures of "smoking topography" would be reflected in the biomarkers and epidemiology studies – which show no statistically significant differences in exposure or risks between menthol and nonmenthol cigarette smokers.

The Topography White Paper reports that Dessirier *et al.* (2001) conclude that menthol reduces the degree of nicotine-induced irritation and goes on to conclude that this effect could "enhance the acceptance of tobacco products...." Important limitations of this study, however, are not included in the Topography White Paper. For example, the White Paper fails to report that Dessirier did not study nicotine and menthol in a smoking environment. This study design prevents broad conclusions regarding menthol and nicotine in cigarette smoke because other sensory and chemical components of the complex mixture of cigarette smoke are not accounted for in the study. Therefore no conclusions regarding any effect of menthol in cigarettes can be drawn.

In discussing the perception of airflow and respiratory rates, the Topography White Paper cites an industry document review to support a hypothesis that menthol may alter inhalation patterns during smoking:

By inhibiting respiratory rates and increasing the perception of airflow, it has been postulated that menthol may alter inhalation patterns during smoking [8]. (Topography White Paper at 5).

Using selected industry documents reported by tobacco control advocates in "document dredging" publications is not sound science. Wayne & Connolly (2004), in reporting on "respiratory effects" of menthol state:

> *Often used as a nasal decongestant, menthol alters perception of breathing patterns, allowing the inhaler to feel that they are breathing freely. An R.J. Reynolds review cites published studies in concluding that "menthol can increase perceived openness of nasal airway in the absence of actual changes in nasal resistance" (Warren, Drake, Liu & Walker, 1991). In another published study found within industry documents, Eccles (1988) noted that increased sensation of nasal airflow is accompanied by reflective alteration of breathing patterns and activity of the upper airway muscles. These changes in breathing and airflow perception may alter inhalation patterns during smoking. A series of R.J. Reynolds studies suggested that although menthol inhalation produces a sensation of free breathing, "reflex reactions include inhibition of respiratory rate" (Hayes et al. 1989). As described in a related study, "At concentrations, the authors reported a decrease in respiratory frequency initially, but noted that the responses faded over the 30 minute exposure period indicating 'desensitization'" (Yermakoff, 1987).* (Wayne & Connolly at S49).

In the underlying Wayne & Connolly report, the 'data' upon which the Topography White Paper relies to postulate that menthol cigarette smoking may alter inhalation patterns during smoking is not human study data – a fact unreported in the Topography White Paper and Wayne & Connolly (2004). Review of the underlying R.J. Reynolds documents cited shows that these studies were conducted on mice which were only exposed to menthol – not menthol under smoking conditions (Hayes, *et al.* (1989) [Bates Number 508296951–6989]; Yermakoff, J. (1987) [Bates Number 505347068–7070]).

The Topography White Paper also states that Clark, *et al.* (1996) reported on increased mouth "wetness" that may increase saliva and facilitate absorption of nicotine in the mouth.

> *Similarly, in a cross-sectional study with 161 participants, menthol smokers reported an increased feeling of "wetness" in the mouth with menthol cigarettes; the researchers hypothesized that increased saliva may facilitate dissolution and absorption of nicotine in the mouth [25].* (Topography White Paper at 5).

But the underlying study comments were not so powerful:

> *We offer mechanisms by which menthol use may increase serum cotinine levels or expired-air carbon monoxide concentration. The menthol smokers in our laboratory reported, anecdotally, an increased feeling of "wetness" in the mouth with menthol cigarettes. Duner-Engstrom and coworkers[25] reported that chewing menthol gum gave a significantly higher amount of stimulated saliva compared to nicotine chewing gum or placebo for nicotine gum. Most of the body burden of nicotine is delivered by way of inhalation into the lungs, but a part of each puff is held in the mouth. If menthol delivered by way of a burning cigarette also increases salivary flow (relative to nonmenthol cigarettes,), the result may be an increase in dissolution in the mouth of the particulate phase of tobacco smoke. Because saliva raises pH, this would not be a particularly efficient delivery mechanism, but it may contribute somewhat to total nicotine absorption. It cannot explain the increase in carbon monoxide levels."* (Clark *et al.* (1996) at 1196).

The Clark study does not provide data that menthol smokers reported an increase in "wetness" in the mouth to any degree of certainty as compared to nonmenthol smokers. Rather, it suggests that anecdotal reports indicate such a phenomenon. Anecdotal reports are far from the type of data necessary to draw conclusions.

The Topography White Paper also reports "mixed" data and fails to disclose that the overwhelming weight of the literature shows no menthol effect. Unfortunately, this is consistent with the approach throughout the White Papers where the authors view the data in the light most favorable in finding or suggesting a menthol effect. When reporting on puff volume the Topography White Paper concludes:

> *Although it has been postulated that mentholation of cigarettes would allow larger puff volumes, of the seven studies, three of the studies discussed found that menthol cigarettes were associated with decreased puff volume. Two studies failed to find any association between menthol cigarettes and puff volume, and one found that menthol cigarettes was associated with an increased puff volume. There were many methodological differences that may impact generalizability of these findings, including small study sizes, use of only men or only women in a study, differences in study design with regard to smoking as usual (ad libitum) smoking vs. rapid-smoking, and differing yield and menthol content of the cigarettes used in the study. These methodological differences make it difficult to make comparisons and draw firm conclusions.* (Topography White Paper at 11 [Table omitted]).

Further, when reporting on number of puffs per cigarette the Topography White Paper concludes:

> *In summary, as was the case the puff volume data, the data for number of puffs per menthol cigarette vs. non-menthol cigarette are mixed: ...*

Significantly Fewer Puffs per Cigarette	***No Statistically Significant Difference in Number of Puffs per Cigarette***
Jarvik et al 1994 [31] *McCarthy et al 1995 [32]* *Nil and Battig 1989 [35]*	*Ahijevych et al 1996 [29]* *Caskey et al 1993 [36]* *Miller et al 1995 [33]* *Strasser et al 2007 [34]*

> *As with the studies of puff volume, there are several methodological weaknesses, including small study sizes, use of only men or only women in a study, differences*

in study design with regard to smoking as usual (ad libitum) vs. rapid-smoking, and differing cigarette nicotine yields and menthol content. (Topography White Paper at 13-14).

These conclusions are misleading. Six of seven studies found no difference in puff volume and no studies found a difference in puffs per cigarette – statistically significant or not.

Rising, J., "Marketing of Menthol Cigarettes and Consumer Perceptions" (Marketing White Paper).

The Marketing White Paper draws the following conclusions:

> *The marketing and advertising of menthol cigarettes is a possible contributing factor to the higher rates of menthol cigarette use among several population subgroups. However, it is difficult to draw definitive conclusions because of the limited research that is available and the cross-sectional nature of the research (which can demonstrate associations but are limited with regard to assessing causality). Furthermore, limitations of the studies that have been published include retrospective designs, small sample sizes, a small geographic survey area, and reliance on focus groups, make it difficult to generalize the research findings.* (Marketing White Paper at 21-22).

Given a general inability to draw definitive conclusions with regard to menthol cigarette marketing and consumer perception, the Marketing White Paper attempts to draw conclusions that are unsupported or irrelevant.

Current literature on menthol and consumer perception does not support conclusion 1 ("Research studies and reviews of publicly available internal tobacco industry documents suggest that menthol cigarettes may be perceived to be safer choices than non-menthol cigarettes" (Marketing White Paper at 22)).

- Richter *et al.* (2008): menthols were ranked as worse than lights and better than full-flavor. P.176.

- Richter *et al.* (2006): menthols were ranked differently with regard to perceived safety by various groups. However, menthol was only viewed as less harmful by a small group of participants. *See generally*, Table 4 p. 306.

- Wackowski *et al.* (2010) (omitted from the Marketing White Paper): 4.0% of all responding smokers perceived as less hazardous whereas 30.2% of menthol and 25.9% of all respondents viewed menthol cigarettes as more hazardous. See generally, Table 2 p. 3.

Smokers do not perceive menthol cigarettes as less hazardous than nonmenthol cigarettes. Published scientific research does not indicate a widespread perception that menthol cigarettes are less hazardous than nonmenthol cigarettes. This research shows that smokers generally perceive menthol cigarettes as equally, if not more, hazardous than nonmenthol cigarettes. In a study published in 2004, Bansal *et al.* asked survey respondents to indicate their level of agreement with a number of statements regarding the risk perception associated with menthol cigarettes including. "Menthol cigarettes are safer than regular cigarettes." (Bansal *et al.* (2004)). The research results showed a greater awareness that menthol cigarettes were as dangerous to health as nonmenthol cigarettes (Bansal *et al.* (2004)).

Very recent publications also found that smokers do not perceive menthol cigarettes as less hazardous than nonmenthol cigarettes. In June 2010, Wackowski *et al.* published a study analyzing data from the 2005 New Jersey Adult Tobacco Survey which asked participants to compare how risky menthol cigarettes were versus nonmenthol cigarettes (Wackowski *et al.* (2010)). Wackowski found few menthol smokers (2.4%) and few people overall (4.0%) perceive menthol cigarettes to be less risky than nonmenthol cigarettes (Wackowski *et al.* (2010)). To the contrary, a considerable proportion of menthol smokers (30.2%) and all respondents (25.9%) believed menthol cigarettes to be more risky than nonmenthol cigarettes (Wackowski *et al.* (2010)):

Despite what might be a popular and intuitive assumption, this study found that few people believed menthol cigarettes were less risky than nonmenthol cigarettes. In contrast, the main finding of interest is that a quarter of all survey respondents (including nonsmokers) and 30% of current menthol smokers believed that menthol cigarettes were somewhat more risky than nonmenthol cigarettes. Wackowski *et al.* (2010).

Recent government data demonstrates that menthol cigarette smokers perceive a greater risk of harm from smoking than nonmenthol cigarette smokers. From 2000 to 2008, as part of the National Survey on Drug Use and Health (NSDUH), sponsored by the Department of Health and Human Services, consumers were asked, "How much do people risk harming themselves physically and in other ways when they smoke one or more packs of cigarettes per day? A: No risk; Slight Risk; Moderate Risk; or Great Risk." (NSDUH (2000-2008)). Responses to this question by menthol and nonmenthol smokers indicated that menthol smokers perceive a greater health risk of smoking than nonmenthol smokers, and that the perception that smoking presents a great risk of harm increased for both menthol smokers and nonmenthol smokers from 2000 to 2008 (NSDUH). NSDUH data also indicates that Hispanic and African-American menthol smokers perceive a greater risk of harm from smoking than White menthol smokers, and that the perception that smoking presents a great risk of harm increased for Hispanic, African-American and White menthol smokers from 2000 to 2008 (NSDUH).

Other published survey data on this issue going back 25 years is consistent with NSDUH. The 1986 Adult Use of Tobacco Survey (AUTS) reported that menthol smokers' beliefs about the health effects of smoking differed little from the beliefs of nonmenthol smokers (Adult Use of Tobacco Survey (1986)). Data from the 1987 National Health Interview Study (NHIS) similarly indicated few differences between menthol and nonmenthol smokers' risk beliefs and further showed that menthol smokers were more likely than nonmenthol smokers to agree that smoking causes various ailments (NHIS (1987)).

Marketing White Paper conclusion 2 ("There is significant overlap between the themes of menthol cigarette campaigns and consumer perceptions of menthol cigarettes" (Marketing White Paper at 22)) overemphasizes the impact of marketing as compared to taste.

Marketing White Paper conclusion 3 ("Marketing of menthol cigarettes is higher in publications/venues whose target audiences are Black/African Americans" (Marketing White Paper at 22)) lacks relevance in a cigarette market after the settlement agreements between the tobacco industry and the state Attorneys General which placed severe limitations on the marketing practices for all cigarettes – including menthol brands. Issues raised with regard to marketing prior to 1998 are not relevant to draw conclusions with regard to menthol cigarette marketing practices today. Further, the adoption of the FDA 1996 Rule as Final in 2010 also makes past marketing practices no longer relevant.

Cigarettes sales continue a thirty-year pattern of substantial decline. Cigarette sales in the United States reached a peak almost thirty years ago in 1981. Since then, overall cigarette sales have fallen almost 50%. Sales in the menthol segment of the cigarette market are no different and have also fallen almost 50%. Since the mid-to-late 1990s, youth smoking rates have declined substantially as well and are at historic lows. Importantly, African-American youth smokers report themselves to be smoking at about half the rate reported by European-American youth. The majority of both adult and youth smokers prefer nonmenthol cigarettes.

The Marketing White Paper fails to consider the numerous submissions and presentations by Lorillard to TPSAC and FDA regarding its marketing practices. Lorillard's marketing activities are directed to adult smokers. Lorillard has taken substantial steps since the late 1990s to dramatically reduce exposure of youth and non-smokers to its cigarette advertising. Lorillard's retail price promotions and direct marketing activities are directed exclusively to adult smokers and are not based race/ethnicity. In addition, Lorillard has not disproportionately directed its advertising to African-Americans. For example, over the last 30 years, an average of 88% of Newport's magazine advertising has been in general market magazines, and only 11% has gone toward magazines directed primarily to African-Americans.

Conclusion 4 ("Publicly available internal tobacco industry documents differentiate the preferences of younger smokers with those of experienced smokers, with younger smokers preferring lower levels of menthol than experienced smokers" (Marketing White Paper at 22)) and conclusion 5 ("There have been changes in cigarette menthol content over the past decade as some brands have moved towards lower levels of menthol and others toward higher levels of menthol. This has been viewed as the tobacco industry modifying the menthol cigarette in order to attract different types of smokers, such as inexperienced versus experienced smokers" (Marketing White Paper at 22)) are inaccurate with respect to Lorillard's Newport cigarettes, the most popular menthol brand. Kreslake *et al.* (2008b) has been referenced as the basis for these allegations. As discussed above, Lorillard has thoroughly discredited the statements made regarding Newport cigarettes in the Kreslake paper.

Conclusion

This submission merely contains examples of the errors, omission and misrepresentations in the FDA White Papers. Lorillard continues to be concerned that, while many of the errors contained in the TPSAC Briefings were brought to FDA's and TPSAC's attention, the same errors continued to be perpetuated in the FDA White Papers. Lorillard also submitted an analysis of the errors and omissions in Table 1.1 ("Table of Evidence for Peer-Reviewed Journals included in the White Papers Submitted by the Food and Drug Administration, Center for Tobacco Products, Office of Science"), which purported to summarize the peer-reviewed literature on the use of menthol in cigarettes, and was provided to TPSAC to assist in its preparation of its report and recommendations on menthol. To date, many of the errors in Table 1.1 also remain uncorrected. Before TPSAC or FDA can rely in any way on the FDA White Papers or on Table 1.1, all errors, omission and misrepresentations in these materials must be corrected.

Respectfully submitted,

/S/

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EXHIBIT A TO LORILLARD DATA QUALITY ACT PETITION

Meeting of the Tobacco Products Scientific Advisory Committee

March 2, 2011

Briefing Regarding FDA-CTP White Papers on the Science Relating to the Use of Menthol in Cigarettes

Lorillard Tobacco Company
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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, called for the establishment of a Tobacco Products Scientific Advisory Committee (TPSAC). FDA announced the creation of the TPSAC on August 26, 2009 (Final Rule (Aug. 26, 2009)). On March 23, 2010 FDA announced the membership of TPSAC. Among the topics on which TPSAC 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" (Menthol Report). On January 6, 2011, FDA announced a meeting of TPSAC on March 1-2, 2001 to "(1) receive updates from the Menthol Report Subcommittee and (2) receive and discuss presentations regarding the data requested by the Committee at the March 30 and 31, 2010, meeting of the Tobacco Products Advisory Committee." The announcement also provided that '[w]ritten submissions may be made to the contact person on or before February 15, 2011."

During the first meetings of TPSAC on March 30-31, 2010 (March 2010 Meetings), the FDA staff stated that a white paper on the science related to menthol in cigarettes (White Paper) was being prepared to facilitate TPSAC's preparation of the Menthol Report. Also during the March 2010 Meetings, FDA-CTP staff and other invited presenters provided briefings to TPSAC on several topics related to menthol cigarettes (TPSAC Briefings).

On June 29, 2010, Lorillard Tobacco Company submitted a critical review and identification of omissions and misstatements in the TPSAC Briefings. Lorillard was very concerned about the inaccuracies in the TPSAC Briefings and believes that TPSAC cannot rely on inaccurate representations of the science in preparing the Menthol Report. Lorillard's June 29th comments were intended to accompany the proposed White Paper for the TPSAC members' consideration.

It was not until immediately prior to the October 7, 2010 TPSAC meeting, that FDA posted to the FDA webpage the following White Papers (FDA White Papers) on the various topics addressed in the prior TPSAC Briefings:

- Rising and Alexander, "Marketing of menthol cigarettes and consumer perceptions."
- Lawrence *et al.*, "Sensory properties of menthol and smoking topography."
- Rising and Wasson-Blader, "Menthol and initiation of cigarette smoking."
- Hoffman and Simmons, "Menthol cigarette smoking and nicotine dependence."
- Hoffman and Miceli, "Menthol cigarettes and smoking cessation behavior."
- Hoffman, "The health effects of menthol cigarettes as compared to nonmenthol cigarettes."
- Caraballo and Asman, "Epidemiology of menthol cigarette use in the United States."

Many of the omissions and misstatements identified by Lorillard with respect to the TPSAC Briefings were carried over into the FDA White Papers without correction. In this submission, Lorillard sets forth examples of errors and omissions by FDA-CTP staff and other authors in the FDA White Papers. The FDA White Papers suffer, in the main, from the same lack of objectivity as the TPSAC Briefings, contain misleading analyses of pertinent data, and often fail to report on highly relevant findings contained in the papers discussed. Frequently, the FDA White Papers exclude or underemphasize strong, relevant data that demonstrate no public health effects of menthol in cigarettes in favor of stressing non-statistically significant data purporting to demonstrate a menthol effect. In addition, the FDA White Papers omit discussions of recent scientific publications which are highly relevant with respect to any health effects of the use of menthol in cigarettes. Before TPSAC or FDA can rely in any way on the FDA White Papers, all errors, omission and misrepresentations in these materials must be corrected.

Lorillard provides the following examples of the continuing errors, omissions and misrepresentations in the FDA White Papers.

Hoffman, A.C., "The health effects of menthol cigarettes as compared to non-menthol cigarettes" (Health Effects White Paper).

The Health Effects White Paper presents conclusions regarding various health effects of menthol cigarettes. Two conclusions particularly merit discussion.

With regard to the body of epidemiological literature addressing menthol cigarettes, the Health Effects White Paper states: "Overall, the data regarding menthol cigarette smoke and cancer do not support a link between menthol cigarette smoke and increased risk of cancer, however there are some limited data that suggest possible menthol x gender x disease interactions" (Health Effects White Paper at 20). The substantial body of epidemiological evidence does not support any increased risk of any disease for menthol smokers when compared to nonmenthol smokers. The Health Effects White Paper attempts to highlight elevated risks in subgroups – "some limited data that suggest a possible menthol x gender x disease interaction." This conclusion is not sound. These "suggestive" studies do not provide statistically significant data – data upon which scientific conclusions can be based. Rather, the authors merely suggest a possible interaction. Statistically non-significant findings should not be used by TPSAC in its preparation of the Menthol Report.

Addressing biomarkers of exposure, the Health Effects White Paper concludes: "Data on menthol's effects on biomarkers of smoke exposure, including nicotine/cotinine, CO (expired CO, blood carboxyhemoglobin) and some TSNAs are inconclusive" (Health Effects White Paper at 19). Describing the vast weight of evidence showing no differences in biomarkers of exposure as inconclusive is imprecise and misleading. In fact, 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)). Most importantly, recently published studies reported measurements of both biomarkers of exposure (Wang et al. (2010)) and putative biomarkers of harm (Frost-Pineda et al. (2010)) for an extremely large, nationally representative population of approximately 3,600 smokers of menthol and nonmenthol cigarettes. Neither blood carboxyhemoglobin nor urinary nicotine equivalents differed statistically significantly between menthol and nonmenthol smokers. In addition, not a single putative biomarker of harm differed between menthol and nonmenthol smokers.

In many instances, the Health Effects White Paper ascribes too much import to statistically non-significant data in attempting to suggest a menthol effect on health and underemphasizes or fails

to report findings where no menthol effect is found. For example, the Health Effects White Paper, in discussing three major epidemiology papers (Brooks *et al.* (2003); Friedman *et al.* (1998) and Hebert and Kabat (1988)), provided minimal discussion of statistically significant findings that menthol smokers showed no increased risk of disease over nonmenthol smokers.

> *Possible interactions between menthol and smoking-related disease, either as a disease state or on the cellular level, have been studied. The data do not suggest that smoking menthol cigarettes is associated with an altered likelihood of developing cancer. Several studies have failed to find that menthol cigarette smoking alters the likelihood of developing several kinds of cancers, including lung and non-lung smoking related cancers, as well as cardiovascular disease or coronary heart disease [79–81] in the population as a whole.* (Health Effects White Paper at 17).

By consolidating the discussion of these studies, the importance of the studies' findings is diminished. For example, Brooks *et al.* (2003) examined data from a large, multi-hospital case-control study to examine whether smoking menthol cigarettes might be associated with higher lung cancer risk as compared to smoking nonmenthol cigarettes. The authors found that menthol smokers did not have an elevated risk of lung cancer (OR= 0.89, 95% CI: 0.69 – 1.14) relative to nonmenthol smokers. The authors reported that: *"Odds ratios were also close to 1.0 in separate analyses of male, female, Black and White subjects. The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking nonmenthol cigarettes."* Simply reporting that these studies "failed to find that menthol cigarette smoking alters the likelihood of developing cancer" places far too little emphasis on the substantial data showing no menthol effect on disease risk set forth in the studies.

In contrast, the Health Effects White Paper gives ample consideration to papers finding statistically non-significant gender or race interactions:

> *Although some studies specifically discussed the absence of a menthol x gender x disease interaction [78, 81], other studies have suggested that such an interaction*

may exist. One prospective study of the health of smokers found that male (but not female) menthol smokers had a modestly increased risk of lung cancer, with a relative risk of 1.45 (95% CI = 1.03–2.02) [84]. Another case control study suggested a small positive association between pharyngeal cancer in menthol-smoking males, but not females (OR = 1.7; 95% CI = 0.8–3.4), but this difference was not statistically significant [85]. A third case control study found that menthol use was not associated with changes in risk for esophageal cancer in males, but suggested that females may have a modestly increased risk (OR = 2.3; 95% CI = 0.93–5.72). These differences also failed to reach statistical significance [86]. A fourth case control study suggested that menthol may modestly increase risk of lung cancer in men with histories of more than 32 pack years of smoking menthol cigarettes (OR = 1.48; 95% CI = 0.71–3.05), but the findings were not statistically significant and limited by the small study size [87]. (Health Effects White Paper at 17-18 [Emphasis Added]).

The Health Effects White Paper reports on four studies that find statistically non-significant differences between menthol and nonmenthol smokers in certain subgroups, but fails to mention the overall findings of those studies. For example, Kabat and Herbert (1994) reported *"[t]hese results indicate that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer*;" Herbert and Kabat (1989) stated *"[o]ur results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer*;" and Carpenter et al. (1999) found *"[o]ur results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking nonmentholated 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."*

The Health Effects White Paper also focuses on one study which found a single statistically significant finding showing a menthol x gender x disease interaction, fails to address a subsequent study of the same population which stated that the finding might be chance:

One prospective study of the health of smokers found that male (but not female) menthol smokers had a modestly increased risk of lung cancer, with a relative risk of 1.45 (95% CI = 1.03–2.02) [84]. (Health Effects White Paper at 17-18).

As noted above only Sidney *et al.* (1995) reported a small statistically significant elevated risk [relative risk (RR) 1.45; 95% CI: 1.03-2.02] for lung cancer among men (all races combined) who smoked menthol cigarettes compared with men who smoked non-menthol cigarettes. No statistically 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 the following about the earlier study: *"... 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)).

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. In addition, biomarkers of exposure studies, which integrate and reflect the impact of all of the diverse elements on complex human smoking behaviors, demonstrate that menthol in cigarettes has no meaningful effect on cigarette smoke constituent exposures. Given this weight of scientific evidence, claims that this evidence is equivocal or mixed is scientifically invalid.

Hoffman, A.C., Miceli, D., "Menthol cigarettes and smoking cessation behavior" (Cessation White Paper).

The Cessation White Paper underemphasizes relevant data showing no menthol effect on cessation, overemphasizes selected data showing a menthol effect on cessation and often omits important data:

There were several studies that found no association between adult use of menthol cigarettes and cessation success, including a national survey [4], a local/regional survey [6], a longitudinal study [13] a clinical study [12], and secondary data analysis of a large-scale randomized intervention study [14]. There were also several studies that found that adult menthol smokers have lower levels of abstinence/successful quitting, including several clinical studies with both moderate/heavy smokers and light smoker,[sic] [6,9] and in a national survey [3]. There were some clinical and cohort analysis studies that found that efficacious behavioral and pharmacotherapy treatments were less effective when used by menthol smokers as compared to non-menthol smokers [7, 10, 11]. In addition, a possible interaction between menthol and race/ethnicity was suggested, with worse outcomes for adult Black/African American and Hispanic/Latino menthol smokers than White menthol smokers [3, 15]. There was no consistent interaction between menthol cigarette use and quitting success for White smokers. (Cessation White Paper at 11-12).

The Cessation White Paper reports that "several studies found that adult menthol smokers have lower levels of abstinence/successful quitting, including several clinical studies with both moderate/heavy smokers and light smoker, [sic] [6, 9] and in a national survey [3]" (Cessation White Paper at 11). Gunderson *et al.* (2009) is referenced as the national survey finding lower abstinence/successful quitting than nonmenthol smokers. But Gunderson's findings were not so straightforward. Gunderson reported a lower likelihood among African-American and Hispanic smokers (collapsed as a "non-white" identity) reporting themselves to be ex-smokers compared to White smokers. The White menthol smokers in the study, however were *more* likely to report apparently spontaneous quitting than were White nonmenthol smokers:

We found that the association of menthol smoking and cessation differs among whites and non-whites. Specifically, we found a statistically significant relationship among non-white menthol smokers such that they were less likely to have quit relative to non-white nonmenthol smokers. This was not the case

among whites. Indeed, white menthol smokers were more likely to be a former smoker than were white nonmenthol smokers. (Gunderson *et al.* (2009) at 555-556).

The Cessation White Paper also does not discuss the fact that no coherent scientific basis whatsoever has been reported in the published literature to support speculation that menthol can exert profoundly opposing effects in White and non-white ethnic groups.

Regarding the clinical studies, the Cessation White Paper concludes that Okuyemi, *et al.* (2004) [Cessation White Paper FN 6] shows lower levels of abstinence/successful quitting. Again, the study's findings were not so simple:

> *We examined four measures of past cessation experiences: lifetime number of quit attempts, time since most recent quit attempt, and duration of abstinence for both longest-ever and most recent quit attempts. While both groups did not differ in their lifetime number of quit attempts, menthol smokers on average had a non-significantly (20%) higher number of more recent quit attempts compared to nonmenthol smokers. A more interesting finding, however, is that menthol smokers reported shorter periods of abstinence for both their longest-ever and most recent quit attempts compared to nonmenthol smokers. <u>While these differences did not reach statistical significance</u>, the consistency and direction of the three measures of success with smoking cessation <u>suggest</u> that menthol smokers were less successful in past quit attempts compared to nonmenthol smokers.* (Okuyemi, *et al.* (2004) at 1210 [Emphasis added]).

The conclusions from Okuyemi above do not support a finding that menthol smokers have poorer cessation outcomes, rather the authors merely "suggest" such a finding based on statistically non-significant data.

The Cessation White Paper also reports that "some clinical and cohort analysis studies that found that efficacious behavioral and pharmacotherapy treatments were less effective when used by

menthol smokers as compared to non-menthol smokers [7, 10, 11]" (Cessation White Paper at 11-12). When discussing these studies, however, the Cessation White Paper omits several relevant study findings.

Okuyemi *et al.* (2003) [Cessation White Paper FN 7] reported a difference in short-term cessation results between menthol and nonmenthol cigarette smokers using buproprion as a smoking cessation aide, but the Cessation White Paper failed to report that the study did not show a statistically significant cessation difference at 6 months:

> *Overall 28.3% of menthol smokers were abstinent at 6 weeks (end of treatment, n= 535) compared to 41.5% of non-menthol smokers (P = 0.006). <u>The abstinence rate at 6 months (n = 518) was also lower among menthol smokers but the difference was not statistically significant</u> (21.4% versus 27.0% for non-menthol smokers; (P = 0.21).* (Okuyemi *et al.* (2003) at 1390 [Emphasis added]).

Further, the Okuyemi study found no differences in the placebo group for cessation rates between menthol and nonmenthol smoking study participants, which the Cessation White Papers did not report:

> *Abstinence rates did not differ by menthol status among those who receive placebo (23.3% non-menthol versus 20.5% menthol; P=0.63).* (Okuyemi *et al.* (2003) at 1390).

Foulds *et al.* (2006) [Cessation White Paper FN 10] reported on various factors affecting smoking cessation outcomes for smokers undergoing counseling and various cessation medications, which the Cessation White Papers failed to disclose. Foulds reported:

> *Those with only a high school education were significantly less likely to be abstinent at both 4- and 26-week follow-up compared with those who had a degree. Unemployment predicted poor outcome at 4 weeks, and not having*

private health insurance predicted poor outcome at 26 weeks. All of these variables are indicators of socioeconomic status. (Foulds *et al.* (2006) at 409).

The Cessation White Paper also cites Okuyemi, *et al.* (2007) [Cessation White Paper FN 11] for the conclusion that behavioral and pharmacotherapy were less effective for menthol smokers. Okuyemi *et al.* (2007) reported on whether African-American light menthol smokers had lower cessation rates than those who smoke nonmenthol cigarettes following treatment with nicotine gum and counseling.

The Cessation White Paper fails to disclose that, in this study, menthol and nonmenthol smoker cessation rates at 26 weeks were no different when using placebo gum:

> *Abstinence rates among those who received placebo gum (P=0.196) or MI (P=0.244) were not significantly different by menthol status.* (Okuyemi *et al.* (2007) at 1981).

Further, the Cessation White Paper does not discuss data which show that combination treatments in the study participants produced no statistically significant differences in cessation success:

> *With the exception of MI + placebo combination, abstinence rates for non-menthol smokers were <u>non-significantly</u> higher than for menthol smokers for all other treatment combination groups.* (Okuyemi, *et al.* (2007) at 1981 [Emphasis Added]).

Finally, the Cessation White Paper does not mention the serious study limitations recognized by the study authors:

> *First all participants in the study were African Americans and therefore the findings may not generalize to light smokers of other ethnicities.... Secondly, this study was a secondary analysis that used data from a clinical trial that was not*

> *designed for testing differences in smoking cessation by menthol status.... Thirdly, although the use of menthol cigarettes may partially explain lower cessation rates for African Americans in clinical trials, this is somewhat at odds with the current overall decline in smoking prevalence in African Americans to a level below that for European Americans..... Finally, because menthol use was not the primary focus of the parent study, menthol status was determined by self-report and we did not assess how long participants have used menthol cigarettes.* (Okuyemi *et al.* (2007) at 1984).

Ultimately, conclusions offered in the Cessation White Paper largely ignore the body of evidence from large, nationally representative cessation studies that show no differences in cessation success between menthol and nonmenthol cigarette smokers (Hyland *et al.* (2002); Li *et al.* (2005); Muscat *et al.* (2002); NHANES (2005-2006, 2007-2008); Murray *et al.* (2007)).

The Cessation White Paper, however, devotes substantial discussion to smaller studies – most notably studies that find a menthol effect on cessation. On pages 3 and 4, the Cessation White Paper reports on Hyland *et al.* (2002), Muscat *et al.* (2002) and Okuyemi *et al.* (2004) referring to these as the only three studies assessing smoking patterns in adult menthol smokers. In its treatment of the studies, the Cessation White Paper underemphasizes the importance of the Hyland study:

> *Hyland et al [4] analyzed the Community Intervention Trial for Smoking Cessation (COMMIT) dataset to assess whether use of menthol cigarettes was associated with quitting. This large-scale telephone survey was first completed in 1988, with a follow up (re-interview) in 1993. No association between smoking menthol cigarettes and quitting success was found.* (Cessation White Paper at 4).

The Cessation White Paper fails to report that the Hyland study included 13,000 participants and fails to discuss important findings: "For the entire sample, the estimated relative risk was 1.00 (95% confidence interval (CI (0.90 to 1.11), and none of the race/ethnicity specific analysis revealed <u>any</u> significant associations" (Hyland *et al.* (2002) at 137 [Emphasis Added]).

In other instances, the Cessation White Paper does not mention serious limitations in studies finding a menthol effect on cessation and overemphasizes the studies' findings:

> *In an effort to better understand the smoking patterns and cessation experiences of Black/African American smokers, Okuyemi et al [6] conducted a cross-sectional survey of 600 Black/African American smokers at an inner-city health center. To examine past cessation attempts, survey questions focused on the number of lifetime quit attempts, time since most recent quit attempt, and the duration of abstinence for both the longest-ever and most recent quit attempts. There was no difference between menthol and non-menthol smokers in the number of lifetime quit attempts, but menthol smokers had significantly less time since their last quit attempt. Additionally, there was a suggestion that smokers of menthol cigarettes had shorter durations of abstinence for both their most recent and their longest-ever quit attempts, but the results were not statistically significant ($p = .187$ and $p = .111$, respectively). Based on the consistency of the direction of the three measures of cessation success, the authors suggested that Black/African American individuals who smoke menthol cigarettes may be less likely to be successful in their quit attempts.* (Cessation White Paper at 4-5).

The Cessation White Paper fails to mention the serious limitations reported in the Okuyemi study which found a menthol effect on cessation: "Second, being a cross-sectional study, causal relationship between menthol and smoking cessation cannot be implied. Sample size was also limited to that of the primary data. Third, our study was also limited to African-American smokers, and findings may not apply to smokers of other ethnic groups as there are well-documented differences in smoking patterns among various ethnic groups" (Okuyemi *et al.* (2004) at 1211).

In contrast to the omission of a discussion of limitations for many studies which find a menthol effect, the Cessation White Paper finds "caveats" when interpreting the data reported in Cropsey *et al.* (2009) which showed no menthol effect on cessation measures:

> *Female prisoners in a clinical trial studying smoking cessation treatment were given 10 weeks of treatment (group psychotherapy and nicotine replacement therapy) and followed for 12 months [12]. At the 12-month follow-up, there were no significant differences in abstinence rates when menthol smokers were compared to non-menthol smokers. <u>There are a few caveats when interpreting these data, however</u>....* (Cessation White Paper at 7-8 [Emphasis added]).

Further, the Cessation White Paper focuses on one set of study results (*e.g.*, short-term versus long-term) or statistically non-significant results in reporting findings of a menthol effect on cessation:

> *...Okuyemi et al [7] analyzed data from the first double-blind, placebo-controlled, randomized trial of bupropion in Black/African-American smokers [8] and reported that although bupropion increased successful abstinence, the 7-day point prevalence of abstinence for menthol smokers was only half that of non-menthol smokers (36.2% compared to 60.3%). Overall, at the 6-week follow-up, menthol smokers were only half as likely to remain abstinent as compared to non-menthol smokers (24.9% and 44.4%, respectively). These findings suggest that smoking menthol cigarettes contributes to difficulty in remaining abstinent while using bupropion as a cessation aid.* (Cessation White Paper at 5).

Okuyemi *et al.* (2003), however, reported no statistically significant differences between menthol and nonmenthol smokers' cessation rates at 6 months. The Cessation White Paper did not discuss this finding.

The examples provided above demonstrate an unbalanced presentation of the data on menthol and smoking cessation in the Cessation White Paper.

Hoffman, A.C. and Simmons, D., "Menthol cigarette smoking and nicotine dependence" (Dependence White Paper).

The Dependence White Paper draws a number of conclusions finding that menthol cigarette smokers are more dependent on nicotine than nonmenthol cigarette smokers:

> *The majority of indicators of nicotine dependence, including time to first cigarette upon waking (youth and adults), night waking to smoke (adults), and some other indications of dependence (youth) suggest that menthol cigarette smokers are more heavily dependent on nicotine. Although some other indicators of nicotine dependence, including CPD and FTND, failed to consistently differentiate menthol and non-menthol smokers, these indicators are not thought to be as robust as time to first cigarette.* (Dependence White Paper at 10).

These conclusions typically are based on single measures of dependence such as time to first cigarette on waking (TTFC) and waking at night to smoke and discount the validated Fagerström Test for Nicotine Dependence (FTND). The Dependence White Paper suggests that TTFC and night-waking to smoke are more robust indicators of nicotine dependence than the multifactorial FTND which includes a measure of TTFC. The Dependence White Paper does not discuss several recently published studies which report either no statistically significant differences for TTFC among menthol and nonmenthol smokers or that TTFC was statistically significantly delayed among White and African-American menthol smokers compared to nonmenthol smokers (Lawrence *et al.* (2010); Fagan *et al.* (2010); Ahijevych & Ford (2010); Fu *et al.* (2008); Hyland *et al.* (2002)). In addition, night-waking to smoke was evaluated only in a single smoking population. Moreover, in this study population 14 additional study variables were statistically significantly associated with night-waking to smoke (Bover *et al.* (2008); Gandhi *et al.* (2009)).

For example, the Dependence White Paper emphasizes a conclusion by Gandhi *et al.* (2009) that menthol smokers were more likely to wake at night to smoke than nonmenthol smokers.

> *Waking at night to smoke also appears to be a marker for tobacco dependence. Gandhi et al [12] conducted a retrospective cohort analysis of 1,688 consecutive patients who attempted to quit smoking. More menthol smokers than non-menthol*

smokers reported waking at night to smoke (55.3% and 44.9%, respectively; $p < .001$). (Dependence White Paper at 4).

However, a more objective interpretation of the study results indicates that measures of dependence are impacted by socioeconomic status (SES):

> *Further sub-analysis indicated that the strength of the 'menthol effect' was related to SES, even within different ethnic/racial groups. Taking employment status as an example (unemployed vs. full-time employed), the difference between quit rates in menthol and non-menthol smokers was greater among those who were unemployed as compared with those who were employed. Among Whites, 4-week quit rates were identical for menthol and non-menthol smokers who were fully employed (56%), whereas among unemployed white smokers, the quit rate was non-significantly lower for menthol smokers (23% vs. 37%, $\chi^2[1] = 3.160$, $p = 0.07$). Similarly, the 4-week quit rate was significantly lower for menthol smokers than non-menthol smokers among unemployed AAs (16% vs. 43%, $\chi^2[1] = 4.38$, $p = 0.03$), <u>but the effect of mentholation was not significant for full-time employed AAs</u> (42% vs. 56%, $p = 0.20$) (Figure 2).* (Gandhi *et al.* (2009) at 364 [Emphasis Added]).

Similarly, when discussing Bover *et al.* (2008), which examined the same study population as Gandhi *et al.* (2009), the Dependence White Paper's analysis relating menthol cigarettes to waking at night to smoke and TTFC is misleading:

> *Similar results were found by Bover et al [12], in a large study of more than 1,350 smokers at a tobacco dependence clinic. Menthol cigarette smokers (58%) reported waking at night to smoke compared with 45% of non-menthol cigarette smokers ($p \leq .0001$). Furthermore, night-waking smokers had a significantly shorter time before smoking their first cigarette after waking in the morning, with 72% of menthol smokers reporting smoking their first cigarette of the day within five minutes or less, compared to 28% of non-menthol smokers ($p \leq .0001$). Taken*

together, these data indicate that menthol smokers have greater nicotine dependence. (Dependence White Paper at 4-5).

Bover *et al.* (2008), however, did not analyze TTFC by menthol/nonmenthol status. Rather, this study reported TTFC by waking at night to smoke versus not waking to smoke. The percentages given in the Dependence White Paper are presumably taken from Table 1 at page 185. These percentages *do not* represent a menthol/nonmenthol analysis. Further, the Dependence White Paper based its erroneous claim that menthol smokers are more nicotine dependent than nonmenthol smokers on this inaccurately reported data.

Ultimately, the strongest measure of nicotine dependence is borne out in cessation results and health risks. In the case of menthol cigarettes, the large, nationally representative studies show that menthol cigarette smokers quit smoking at equivalent rates as do nonmenthol smokers. In addition, menthol smokers do not show an increased risk of smoking related disease as compared to nonmenthol smokers in the sizable body of epidemiological literature.

Rising, J. and Wasson-Blader, K., "Menthol and initiation of cigarette smoking" (Initiation White Paper).

The Initiation White Paper recognizes the severe limitations that exist in the published literature relating to menthol cigarettes and smoking initiation. The author states that "retrospective data and adult recollections of smoking initiation may not provide an accurate representation of the product used" (Initiation White Paper at 8). As such, these studies should not be relied upon in forming conclusions with regard to menthol and smoking initiation. However, despite the lack of relevant data, the Initiation White Paper draws several conclusions regarding an effect of menthol on smoking initiation.

Two of the Initiation White Paper's conclusions do not provide data helpful in forming opinions with regard to menthol cigarettes and smoking initiation. Conclusion 1 ("The vast majority of individuals who become regular smokers begin smoking as youth or young adults" (Initiation White Paper at 9)) and conclusion 6 ("Reviews of publically available internal tobacco industry

documents suggest an industry awareness of the appeal of menthol cigarettes to newer smokers" (Initiation White Paper at 9)) report no information relevant to the question of menthol cigarette smoking initiation. The conclusion regarding industry documents is based on a very limited review of industry documents. Suggestions in a limited number of documents from years, and in some instances decades, ago regarding vague industry knowledge is not relevant to the issue of menthol cigarette smoking initiation.

White Paper conclusion 4 ("Results are inconsistent regarding the frequency and direction of switching and the direction of switching between menthol and non-menthol cigarettes" (Initiation White Paper at 9)) is inconsistent with recent data provided to FDA. Hyland, in a recent submission to FDA (Analysis of Mentholated Cigarettes using the COMMIT Data -- Summary Report, November, 2010) reported that "...switching between menthol and non-menthol cigarettes is uncommon for all smokers, regardless of race" (Hyland (2010) unpublished data at 21).

White Paper conclusion 2 ("Menthol cigarettes are widely used among youth who have smoked for less than one year and are used less frequently by youth who have smoked for more than one year" (Initiation White Paper at 9)) ignores important facts about youth menthol smoking. Foremost, the majority of adolescent smokers choose nonmenthol brands (NSDUH, 2009). Linking the popularity of a certain style or brand of product to a causal relationship with smoking initiation or smoking trajectory is unfounded.

The Initiation White Paper's conclusion 3 ("Although limited data are available, there appears to be no differences in age of initiation between those who start smoking with menthol cigarettes and those who start smoking with non-menthol cigarettes..." (Initiation White Paper at 9)) and conclusion 5 ("No data exist on whether menthol cigarette use alters the trajectory from initiating cigarette use to regular smoking" (Initiation White Paper at 9)) both support a conclusion that menthol in cigarettes has no causal effect on youth smoking initiation. It is well documented that African-Americans, the vast majority of whom prefer menthol cigarettes, begin smoking at an older age than Whites. In addition, African-American youth report themselves to be smoking at about half the rate reported by White youth.

The Initiation White Paper also omits discussion of some relevant limitations of the published literature on menthol cigarettes and smoking initiation. For example, in its treatment of Hersey *et al.* (2006), the Initiation White Paper fails to report on the limitations of the study:

> *A study by Hersey et al [5] examined data from the 2002 National Youth Tobacco Survey regarding the duration of smoking and menthol cigarette use. Middle school students (grades 6–8) who had been smoking less than 1 year were significantly more likely to smoke menthol cigarettes than were middle school students who had been smoking more than 1 year (62.4% vs. 53.3%, $p < .002$). A similar, though not statistically significant, pattern was found for high school students (grades 9–12); 46% of the high school students who had been smoking for less than 1 year smoked menthol cigarettes, compared with 42% of students who had been smoking more than 1 year.* (Initiation White Paper at 4).

While this text accurately reports the study findings, it fails to list three major limitations noted by the study authors:

> *The present study had a number of limitations. Some misclassification in the reporting of menthol use may have occurred. However, the sensitivity analyses indicated similar findings using various definitions of menthol cigarettes. Moreover, any misclassification is likely to have reduced the differences between menthol and nonmenthol groups, given that the results of misclassification have been to mix actual menthol cigarette smokers with nonmenthol smokers and vice versa.*
>
> *Also, differences in the smoking patterns of menthol versus nonmenthol users may not have been adequately controlled for in our models. Further, 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. Such a study also would be able to address issues related to brand switching. Findings about nicotine dependence would be strengthened by confirmation with biochemical data on nicotine absorption.

Finally, the present study could not determine the extent to which the popularity of menthol cigarettes among younger, newer smokers is a result of product characteristics, marketing (Giovino et al., 2004), or other influences. Even so, the fact that menthol is one of the most prevalent types of cigarettes used by younger, newer smokers suggests that further investigation of the role of mentholated cigarettes deserves close attention. (Hersey *et al.* (2006) at 412).

The Initiation White Paper relies on conclusions regarding industry documents from Kreslake *et al.* (2008a) and (2008b). The Kreslake papers are not relevant to the issue of whether or not adolescent smokers initiate with menthol cigarettes. In the discussion of the Kreslake papers, the Initiation White Paper cites to only two documents, one authored by R.J. Reynolds and another authored by Brown & Williamson, from the mid-1980s. The fact that these two companies studied the appeal of different menthol levels, or that any company studied such issues, is irrelevant as to whether or not new smokers choose menthol brands.

In addition, one of the allegations made in Kreslake *et al.* (2008b) was that cigarette brands reported to be preferred by younger smokers have lower levels of menthol than do brands reported to be preferred by older smokers, and further that cigarette manufacturers had lowered menthol levels as a general strategy to attract youthful smokers in recent years. Lorillard has publically and without reservation denied this assertion and has provided extensive evidence of the inaccuracy of this assertion to TPSAC and FDA (see, e.g. Response to FDA Request for Information Regarding Youth Smoking, and Advertising and Promotion of Cigarettes, August 2, 2010, Lorillard Tobacco Company, Docket ID: FDA-2010-N-0295).

Lawrence et al., "Sensory properties of menthol and smoking topography" (Topography White Paper).

The ultimate conclusion in the Topography White Paper is that "...the extant literature does not bridge the gap between what is known about menthol's multifaceted sensory effects and the mechanism by which menthol may alter a smoker's behavior." (Topography White Paper at 20). The conclusion overreaches. Studies attempting 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 show mixed results with any differences reported likely dependent upon the method used and lack of the specificity of the outcome attempted to be measured. Any differences in these measures of "smoking topography" would be reflected in the biomarkers and epidemiology studies – which show no statistically significant differences in exposure or risks between menthol and nonmenthol cigarette smokers.

The Topography White Paper reports that Dessirier *et al.* (2001) conclude that menthol reduces the degree of nicotine-induced irritation and goes on to conclude that this effect could "enhance the acceptance of tobacco products...." Important limitations of this study, however, are not included in the Topography White Paper. For example, the White Paper fails to report that Dessirier did not study nicotine and menthol in a smoking environment. This study design prevents broad conclusions regarding menthol and nicotine in cigarette smoke because other sensory and chemical components of the complex mixture of cigarette smoke are not accounted for in the study. Therefore no conclusions regarding any effect of menthol in cigarettes can be drawn.

In discussing the perception of airflow and respiratory rates, the Topography White Paper cites an industry document review to support a hypothesis that menthol may alter inhalation patterns during smoking:

> *By inhibiting respiratory rates and increasing the perception of airflow, it has been postulated that menthol may alter inhalation patterns during smoking [8].* (Topography White Paper at 5).

Using selected industry documents reported by tobacco control advocates in "document dredging" publications is not sound science. Wayne & Connolly (2004), in reporting on "respiratory effects" of menthol state:

> *Often used as a nasal decongestant, menthol alters perception of breathing patterns, allowing the inhaler to feel that they are breathing freely. An R.J. Reynolds review cites published studies in concluding that "menthol can increase perceived openness of nasal airway in the absence of actual changes in nasal resistance" (Warren, Drake, Liu & Walker, 1991). In another published study found within industry documents, Eccles (1988) noted that increased sensation of nasal airflow is accompanied by reflective alteration of breathing patterns and activity of the upper airway muscles. These changes in breathing and airflow perception may alter inhalation patterns during smoking. A series of R.J. Reynolds studies suggested that although menthol inhalation produces a sensation of free breathing, "reflex reactions include inhibition of respiratory rate" (Hayes et al. 1989). As described in a related study, "At concentrations, the authors reported a decrease in respiratory frequency initially, but noted that the responses faded over the 30 minute exposure period indicating 'desensitization'" (Yermakoff, 1987).* (Wayne & Connolly at S49).

In the underlying Wayne & Connolly report, the 'data' upon which the Topography White Paper relies to postulate that menthol cigarette smoking may alter inhalation patterns during smoking is not human study data – a fact unreported in the Topography White Paper and Wayne & Connolly (2004). Review of the underlying R.J. Reynolds documents cited shows that these studies were conducted on mice which were only exposed to menthol – not menthol under smoking conditions (Hayes, *et al.* (1989) [Bates Number 508296951–6989]; Yermakoff, J. (1987) [Bates Number 505347068–7070]).

The Topography White Paper also states that Clark, *et al.* (1996) reported on increased mouth "wetness" that may increase saliva and facilitate absorption of nicotine in the mouth.

> *Similarly, in a cross-sectional study with 161 participants, menthol smokers reported an increased feeling of "wetness" in the mouth with menthol cigarettes; the researchers hypothesized that increased saliva may facilitate dissolution and absorption of nicotine in the mouth [25].* (Topography White Paper at 5).

But the underlying study comments were not so powerful:

> *We offer mechanisms by which menthol use may increase serum cotinine levels or expired-air carbon monoxide concentration. The menthol smokers in our laboratory reported, anecdotally, an increased feeling of "wetness" in the mouth with menthol cigarettes. Duner-Engstrom and coworkers[25] reported that chewing menthol gum gave a significantly higher amount of stimulated saliva compared to nicotine chewing gum or placebo for nicotine gum. Most of the body burden of nicotine is delivered by way of inhalation into the lungs, but a part of each puff is held in the mouth. If menthol delivered by way of a burning cigarette also increases salivary flow (relative to nonmenthol cigarettes,), the result may be an increase in dissolution in the mouth of the particulate phase of tobacco smoke. Because saliva raises pH, this would not be a particularly efficient delivery mechanism, but it may contribute somewhat to total nicotine absorption. It cannot explain the increase in carbon monoxide levels."* (Clark *et al.* (1996) at 1196).

The Clark study does not provide data that menthol smokers reported an increase in "wetness" in the mouth to any degree of certainty as compared to nonmenthol smokers. Rather, it suggests that anecdotal reports indicate such a phenomenon. Anecdotal reports are far from the type of data necessary to draw conclusions.

The Topography White Paper also reports "mixed" data and fails to disclose that the overwhelming weight of the literature shows no menthol effect. Unfortunately, this is consistent with the approach throughout the White Papers where the authors view the data in the light most favorable in finding or suggesting a menthol effect. When reporting on puff volume the Topography White Paper concludes:

> *Although it has been postulated that mentholation of cigarettes would allow larger puff volumes, of the seven studies, three of the studies discussed found that menthol cigarettes were associated with decreased puff volume. Two studies failed to find any association between menthol cigarettes and puff volume, and one found that menthol cigarettes was associated with an increased puff volume. There were many methodological differences that may impact generalizability of these findings, including small study sizes, use of only men or only women in a study, differences in study design with regard to smoking as usual (ad libitum) smoking vs. rapid-smoking, and differing yield and menthol content of the cigarettes used in the study. These methodological differences make it difficult to make comparisons and draw firm conclusions.* (Topography White Paper at 11 [Table omitted]).

Further, when reporting on number of puffs per cigarette the Topography White Paper concludes:

> *In summary, as was the case the puff volume data, the data for number of puffs per menthol cigarette vs. non-menthol cigarette are mixed: ...*

Significantly Fewer Puffs per Cigarette	***No Statistically Significant Difference in Number of Puffs per Cigarette***
Jarvik et al 1994 [31] *McCarthy et al 1995 [32]* *Nil and Battig 1989 [35]*	*Ahijevych et al 1996 [29]* *Caskey et al 1993 [36]* *Miller et al 1995 [33]* *Strasser et al 2007 [34]*

> *As with the studies of puff volume, there are several methodological weaknesses, including small study sizes, use of only men or only women in a study, differences*

in study design with regard to smoking as usual (ad libitum) vs. rapid-smoking, and differing cigarette nicotine yields and menthol content. (Topography White Paper at 13-14).

These conclusions are misleading. Six of seven studies found no difference in puff volume and no studies found a difference in puffs per cigarette – statistically significant or not.

Rising, J., "Marketing of Menthol Cigarettes and Consumer Perceptions" (Marketing White Paper).

The Marketing White Paper draws the following conclusions:

> *The marketing and advertising of menthol cigarettes is a possible contributing factor to the higher rates of menthol cigarette use among several population subgroups. However, it is difficult to draw definitive conclusions because of the limited research that is available and the cross-sectional nature of the research (which can demonstrate associations but are limited with regard to assessing causality). Furthermore, limitations of the studies that have been published include retrospective designs, small sample sizes, a small geographic survey area, and reliance on focus groups, make it difficult to generalize the research findings.* (Marketing White Paper at 21-22).

Given a general inability to draw definitive conclusions with regard to menthol cigarette marketing and consumer perception, the Marketing White Paper attempts to draw conclusions that are unsupported or irrelevant.

Current literature on menthol and consumer perception does not support conclusion 1 ("Research studies and reviews of publicly available internal tobacco industry documents suggest that menthol cigarettes may be perceived to be safer choices than non-menthol cigarettes" (Marketing White Paper at 22)).

- Richter *et al.* (2008): menthols were ranked as worse than lights and better than full-flavor. P.176.

- Richter *et al.* (2006): menthols were ranked differently with regard to perceived safety by various groups. However, menthol was only viewed as less harmful by a small group of participants. *See generally*, Table 4 p. 306.

- Wackowski *et al.* (2010) (omitted from the Marketing White Paper): 4.0% of all responding smokers perceived as less hazardous whereas 30.2% of menthol and 25.9% of all respondents viewed menthol cigarettes as more hazardous. See generally, Table 2 p. 3.

Smokers do not perceive menthol cigarettes as less hazardous than nonmenthol cigarettes. Published scientific research does not indicate a widespread perception that menthol cigarettes are less hazardous than nonmenthol cigarettes. This research shows that smokers generally perceive menthol cigarettes as equally, if not more, hazardous than nonmenthol cigarettes. In a study published in 2004, Bansal *et al.* asked survey respondents to indicate their level of agreement with a number of statements regarding the risk perception associated with menthol cigarettes including. "Menthol cigarettes are safer than regular cigarettes." (Bansal *et al.* (2004)). The research results showed a greater awareness that menthol cigarettes were as dangerous to health as nonmenthol cigarettes (Bansal *et al.* (2004)).

Very recent publications also found that smokers do not perceive menthol cigarettes as less hazardous than nonmenthol cigarettes. In June 2010, Wackowski *et al.* published a study analyzing data from the 2005 New Jersey Adult Tobacco Survey which asked participants to compare how risky menthol cigarettes were versus nonmenthol cigarettes (Wackowski *et al.* (2010)). Wackowski found few menthol smokers (2.4%) and few people overall (4.0%) perceive menthol cigarettes to be less risky than nonmenthol cigarettes (Wackowski *et al.* (2010)). To the contrary, a considerable proportion of menthol smokers (30.2%) and all respondents (25.9%) believed menthol cigarettes to be more risky than nonmenthol cigarettes (Wackowski *et al.* (2010)):

Despite what might be a popular and intuitive assumption, this study found that few people believed menthol cigarettes were less risky than nonmenthol cigarettes. In contrast, the main finding of interest is that a quarter of all survey respondents (including nonsmokers) and 30% of current menthol smokers believed that menthol cigarettes were somewhat more risky than nonmenthol cigarettes. Wackowski *et al.* (2010).

Recent government data demonstrates that menthol cigarette smokers perceive a greater risk of harm from smoking than nonmenthol cigarette smokers. From 2000 to 2008, as part of the National Survey on Drug Use and Health (NSDUH), sponsored by the Department of Health and Human Services, consumers were asked, "How much do people risk harming themselves physically and in other ways when they smoke one or more packs of cigarettes per day? A: No risk; Slight Risk; Moderate Risk; or Great Risk." (NSDUH (2000-2008)). Responses to this question by menthol and nonmenthol smokers indicated that menthol smokers perceive a greater health risk of smoking than nonmenthol smokers, and that the perception that smoking presents a great risk of harm increased for both menthol smokers and nonmenthol smokers from 2000 to 2008 (NSDUH). NSDUH data also indicates that Hispanic and African-American menthol smokers perceive a greater risk of harm from smoking than White menthol smokers, and that the perception that smoking presents a great risk of harm increased for Hispanic, African-American and White menthol smokers from 2000 to 2008 (NSDUH).

Other published survey data on this issue going back 25 years is consistent with NSDUH. The 1986 Adult Use of Tobacco Survey (AUTS) reported that menthol smokers' beliefs about the health effects of smoking differed little from the beliefs of nonmenthol smokers (Adult Use of Tobacco Survey (1986)). Data from the 1987 National Health Interview Study (NHIS) similarly indicated few differences between menthol and nonmenthol smokers' risk beliefs and further showed that menthol smokers were more likely than nonmenthol smokers to agree that smoking causes various ailments (NHIS (1987)).

Marketing White Paper conclusion 2 ("There is significant overlap between the themes of menthol cigarette campaigns and consumer perceptions of menthol cigarettes" (Marketing White Paper at 22)) overemphasizes the impact of marketing as compared to taste.

Marketing White Paper conclusion 3 ("Marketing of menthol cigarettes is higher in publications/venues whose target audiences are Black/African Americans" (Marketing White Paper at 22)) lacks relevance in a cigarette market after the settlement agreements between the tobacco industry and the state Attorneys General which placed severe limitations on the marketing practices for all cigarettes – including menthol brands. Issues raised with regard to marketing prior to 1998 are not relevant to draw conclusions with regard to menthol cigarette marketing practices today. Further, the adoption of the FDA 1996 Rule as Final in 2010 also makes past marketing practices no longer relevant.

Cigarettes sales continue a thirty-year pattern of substantial decline. Cigarette sales in the United States reached a peak almost thirty years ago in 1981. Since then, overall cigarette sales have fallen almost 50%. Sales in the menthol segment of the cigarette market are no different and have also fallen almost 50%. Since the mid-to-late 1990s, youth smoking rates have declined substantially as well and are at historic lows. Importantly, African-American youth smokers report themselves to be smoking at about half the rate reported by European-American youth. The majority of both adult and youth smokers prefer nonmenthol cigarettes.

The Marketing White Paper fails to consider the numerous submissions and presentations by Lorillard to TPSAC and FDA regarding its marketing practices. Lorillard's marketing activities are directed to adult smokers. Lorillard has taken substantial steps since the late 1990s to dramatically reduce exposure of youth and non-smokers to its cigarette advertising. Lorillard's retail price promotions and direct marketing activities are directed exclusively to adult smokers and are not based race/ethnicity. In addition, Lorillard has not disproportionately directed its advertising to African-Americans. For example, over the last 30 years, an average of 88% of Newport's magazine advertising has been in general market magazines, and only 11% has gone toward magazines directed primarily to African-Americans.

Conclusion 4 ("Publicly available internal tobacco industry documents differentiate the preferences of younger smokers with those of experienced smokers, with younger smokers preferring lower levels of menthol than experienced smokers" (Marketing White Paper at 22)) and conclusion 5 ("There have been changes in cigarette menthol content over the past decade as some brands have moved towards lower levels of menthol and others toward higher levels of menthol. This has been viewed as the tobacco industry modifying the menthol cigarette in order to attract different types of smokers, such as inexperienced versus experienced smokers" (Marketing White Paper at 22)) are inaccurate with respect to Lorillard's Newport cigarettes, the most popular menthol brand. Kreslake *et al.* (2008b) has been referenced as the basis for these allegations. As discussed above, Lorillard has thoroughly discredited the statements made regarding Newport cigarettes in the Kreslake paper.

Conclusion

This submission merely contains examples of the errors, omission and misrepresentations in the FDA White Papers. Lorillard continues to be concerned that, while many of the errors contained in the TPSAC Briefings were brought to FDA's and TPSAC's attention, the same errors continued to be perpetuated in the FDA White Papers. Lorillard also submitted an analysis of the errors and omissions in Table 1.1 ("Table of Evidence for Peer-Reviewed Journals included in the White Papers Submitted by the Food and Drug Administration, Center for Tobacco Products, Office of Science"), which purported to summarize the peer-reviewed literature on the use of menthol in cigarettes, and was provided to TPSAC to assist in its preparation of its report and recommendations on menthol. To date, many of the errors in Table 1.1 also remain uncorrected. Before TPSAC or FDA can rely in any way on the FDA White Papers or on Table 1.1, all errors, omission and misrepresentations in these materials must be corrected.

Respectfully submitted,

/S/

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EXHIBIT B TO LORILLARD DATA QUALITY ACT PETITION

UPDATED TABLE 1.1 Errors and Omissions

Table 1.1, *Table of Evidence for Peer-Reviewed Journals included in the White Papers Submitted by the FDA-CTP,* was among the meeting materials distributed for the November 18 TPSAC meeting. After Dan Heck, Ph.D, the industry representative to TPSAC, sent an email to FDA on December 4, 2010 setting forth the inaccuracies, omissions, and distortions of the scientific literature, FDA made some necessary corrections and posted "Updated Table 1.1" as part of the January 2011 TPSAC meeting briefing materials. The updated table, however, still contains a number or errors and omissions that should be corrected before it is used by the menthol report writing groups. Many of these errors fall into the following categories:

- **Table 1.1 does not include key conclusions of many of the articles.** For example, the agency's summary of the 2004 Benowitz article (on page 20 of Table 1.1) includes the last sentence of the authors' abstract but omits the very significant conclusion presented in the sentence before: "Our data so not support the hypothesis that mentholated cigarette smoking results in a greater absorption of tobacco smoke toxins." On pages 44-45 of Table 1.1, the agency, in its summary of the 2009 Gundersen et al. paper, summarizes the authors' conclusion that non-white menthol smokers had poorer cessation outcomes, but the agency omits the authors' finding that white menthol smokers had statistically significant greater cessation success than white nonmenthol smokers. An objective summary should include this observation as well. Similarly, the agency's summary of the 2003 Stellman et al. paper (on page 74 of Table 1.1) still omits many of the authors' key menthol-related findings.

- **The agency erroneously describes many of the journal articles listed in Table 1.1.** For some of the articles, the agency incorrectly summarizes the conclusions of a particular article by listing as the summary of the article, the article's discussion of another study. For example, the agency's summary of the 2008 Gan et al. study on page 41 of Table 1.1 states, as part of the authors' conclusions about menthol, that "menthol inhibits nicotine metabolism." This statement was part of the authors' discussion with reference to a 2004 report by Benowitz et al. The cited Gan paper included no metabolism work. Table 1.1 should summarize the authors' conclusions described in the study, not their discussion of other literature and speculation.

- **FDA incorrectly characterizes the nature of several of the articles listed in Table 1.1.** For example, the agency describes the two 2008 papers by Kreslake et al. and the 2004 paper by Wayne et al. as "reviews." The term "review" is typically used to refer to a review paper of published, peer-reviewed literature. The Kreslake and Wayne papers discussed and interpreted tobacco company documents. There was no discussion of peer-reviewed literature in these papers. These papers should more accurately be characterized as "commentary." The

agency's mischaracterization of the nature of the articles may cause members of the TPSAC and the public to assign undue weight to the articles.

The list below sets forth errors, omissions, and misstatements that remain unaddressed in the updated Table 1.1. These points, comments and suggestions are offered to assist the FDA-CTP in achieving its stated objective of conducting a sound, science-based, inclusive and objective evaluation of scientific matters relating to the regulation of tobacco products.

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Page 16 (Marketing/Consumer Perceptions) Allen and Unger (2007) – Table 1.1 does not mention certain relevant elements of the authors' conclusions, e.g., "Controlling for age and employment, we found that the significant correlates of menthol use among women were parents' menthol smoking, the belief that most African American smokers smoke menthols, and disagreement with the belief that smoking menthol cigarettes is a 'Black thing.' Among men, the only significant correlate of menthol smoking was the belief that most African American smokers smoke menthols. Results indicate that menthol smoking among adult African Americans is at least partly a consequence of a complex set of social and cultural norms." (p. 449). In addition, Table 1.1 does not note that the study measures of exposure to menthol advertising were not found to be significant correlates of menthol use (authors' Table 2, p 450).

The FDA staff should appropriately summarize these points and conclusions that are directly relevant to TPSAC's consideration of menthol.

Page 20 Benowitz, 2004: A very significant conclusion from the authors' abstract that is directly relevant to TPSAC's deliberations is omitted here and should be added to the summary:

"Our data do not support the hypothesis that mentholated cigarette smoking results in a greater absorption of tobacco smoke toxins."

Page 38, Rescission of FTC Guidance re the Cambridge Filter Method: The summary appears to comprise some random phrasing from this FTC guidance. The key summary point is that this notice ended FTC's implied endorsement of the former "FTC" smoking method and required that the term "FTC method" no longer be employed.

Page 39 Ferris Wayne, Connolly *et al.*: This paper comprises commentary, interpretation and re-interpretation of selected, unpublished tobacco industry internal business documents released to the public as a result of litigation. It is not a "literature review" as described here, since this term of reference is properly reserved for reviews of published literature. It is more appropriately described as a commentary. The authors' conclusions developed from their readings of such documents seem to be accurately

stated, but TPSAC should be aware that these conclusions were not developed from any primary scientific data.

Page 41 Gan et al., 2008: The summary statement includes a phrase that "menthol inhibits nicotine metabolism." This was part of the authors' discussion with reference to the report of Benowitz et al., 2004. **The Gan paper included no metabolism work. The Gan paper's conclusions should be summarized here, not discussion of other literature and speculation offered by the authors.**

Page 42, Garten, 2003 and 2004 papers: The author's hypotheses and speculations based upon a selective review of the literature are reported here as conclusions. These "review" papers (actually more akin to opinion pieces or commentaries) did not contain any primary data.

Page 44-45, Gundersen 2009: The authors' conclusion that non-white menthol smokers had poorer cessation outcomes is summarized here, **but the authors' finding that white menthol smokers had statistically significantly greater cessation success than white nonmenthol cigarette smokers is omitted**. An objective summary here should include this observation as well.

Page 48-49, Ho *et al.*, 2009: The FDA staff summary here has omitted <u>all</u> of the authors' key menthol-related scientific findings, including:

"Those who smoked mentholated cigarettes trended toward reporting fewer CPD compared with those who did not (P = 0.05), although no difference was found for expired CO or plasma COT levels between mentholated and nonmentholated cigarette smokers." (page 3428)

"The correlation coefficients between CPD and expired CO with plasma nicotine and its metabolites were not greatly altered by CYP2A6 genotype or 3HC/COT quartiles (Table 3). Similarly, these relationships were generally not altered when analyzed separately by gender, mentholated cigarettes, BMI, or age." (page 3428)

"In this current study of African-American light smokers, mentholated cigarette users did not have significantly higher expired CO or plasma COT levels despite our large sample, with 131 nonmenthol smokers examined. Thus, cigarette mentholation did not seem to contribute to increased intensity of cigarette smoking or increased absorption of nicotine in our sample of African-American light smokers." (page 3431)

"In summary, the results from this study suggest that the commonly used biomarkers of cigarette smoke exposure, expired CO and plasma COT, are significantly but weakly correlated with self-reported CPD. Furthermore, these relationships are not greatly altered by variables that were previously reported to have an influence on these parameters, such as CYP2A6 activity, smoking mentholated cigarettes, or age, although the relationships may differ slightly by gender and BMI." (page 3433)

The authors' menthol findings should be accurately summarized here in appropriately condensed form.

p. 49 Hymowitz et al. (1995): Table 1.1 does not report the lack of association between type of cigarette smoked (menthol/non-menthol) and the age that one started to smoke that was found in this study (author's Table 3a, p. 506).

p. 49 Hymowitz et al. (1995):

The present statement of the authors' conclusions regarding menthol does not state the study's scientific findings, but rather the author's call for further research and regulation. For TPSAC's purposes, the scientific findings and conclusions should be provided here.

In the updated table, it appears that a summary of the Pletcher study now mistakenly appears here.

P. 52-53, Kreslake *et al.*, (2008) This paper comprises an interpretive analysis of selected internal business documents released by tobacco companies in litigation, as well as some original data on menthol in commercial cigarettes and smoke. It is not properly characterized as a "review".

Page 53, Kreslake et al. (2008): This paper comprises an interpretive analysis of tobacco company documents, and is more properly described as a commentary than a "review", as this latter term should be reserved for a review paper of published, peer-reviewed literature.

p. 60-61 Mustonen et al. (2005): FDA summary states:

"Menthol smokers have been found to have higher cotinine/cigarette ratios as compared to non-menthol smokers."

The study also reported that menthol and nonmenthol smokers did not differ statistically in cotinine levels or cigarettes per day. Although FDA has updated the summary of conclusions, the menthol findings are still not clear.

p. 62-63 Okuyemi et al. (2003): Some of the authors' menthol findings were omitted from the summary, including the observation that Fagerstrom scores for menthol and nonmenthol smokers were similar, and that the quit success for menthol and nonmenthol smokers were not statistically different in the placebo group, and cessation success for menthol and nonmenthol smokers did not differ at the terminal 6-month follow up.

p. 63 Okuyemi et al. (2004): These authors also reported that their study ". . .did not find differences in addiction between menthol and non-menthol smokers.", a reference to their Fagerstrom scores.

p. 67 Rabinoff et al. (2007) : The Rabinoff paper develops speculation and hypotheses about cigarette ingredients, generally, from the authors' online perusal of published literature on (primarily botanically-derived) flavoring substances and some unpublished tobacco industry documents. The paper contains no primary data whatsoever.

p. 69 Ruch and Sigler (1994) Please confirm that the "Funded by" listing of a grant from AICR to RJR is correct, rather than vice-versa, which would seem to make more sense.

p. 70-71 Scanlon et al. (2000): The FDA summary omits a briefly stated menthol conclusion reported by these authors: "...Smoking mentholated cigarettes did not affect the rate of decline in lung function in Year 1 or between Year 1 and Year 5 ($p = 0.229$ and 0.64, respectively, data not shown)". The observation that menthol preference did not affect the decline in smokers' lung function was not further detailed in this paper, but was later confirmed in the study of Pletcher et al., 2006.

p. 72 Sidney et al. (1995): The FDA summary omits many of the menthol findings from this 20-year cohort study of lung cancer in smokers. FDA should provide a balanced summary that includes the race-specific lung cancer Relative Risk estimates for males and females, in addition to the combined males conclusion.

p. 74 Stellman et al. (2003): The present FDA summary <u>entirely omits</u> the menthol findings. These include:

"...ORs among smokers of menthol cigarettes were practically the same as among smokers of non-menthol cigarettes".

"...[s]mokers of menthol flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands"

"...[w]hile black smokers in our study were more likely to choose menthol than non-menthol brands..., our data provide no evidence that menthol cigarettes per se produce greater lung cancer risk than do non-menthol brands".

"...[e]xperimental data show no increase in NNK-induced adduct formation in NNK-treated rats that were administered menthol in their drinking water (NNK is a tobacco-specific nitrosamine, which experimentally produces lung adenocarcinoma in rodents), further supporting our conclusion that menthol does not play a role in risk for lung cancer".

p. 78 Wackowski and Delnevo (2007): FDA summary mentions that menthol was statistically associated with two measures of dependence, but neglects to mention that it was not associated with two others.

p. 80 Wayne et al. (2004). A discussion and interpretive analysis of tobacco industry documents is more appropriately characterized as a "Commentary" than a "Review", as the latter term implies a review of peer-reviewed, published literature of the type that should be considered by TPSAC.

p. 80 Werley et al. (2007). In addition to its broad review content, the paper included a formal meta analysis of available menthol data on lung cancer risk at the time of its writing. The findings of this primary analysis should be briefly mentioned. Although it appears FDA updated the summary of conclusions for this paper, the summary does not best reflect the contents of the paper.

p. 82 Yerger et al. (2007) : Again, a discussion and re-interpretation of unpublished, non peer-reviewed internal industry documents does not qualify as a true "Review." Such papers are more appropriately characterized as "Commentaries."