



James E. Dillard III
Senior Vice President
Regulatory Affairs

June 30, 2011

Ms. Caryn Cohen
Office of Science
Center for Tobacco Products
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: July 21, 2011 and July 22, 2011 Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Dear Ms. Cohen:

Altria Client Services (ALCS), on behalf of Philip Morris USA Inc. (PM USA)¹, resubmits its March 22, 2011 “Philip Morris USA Inc. Report to the FDA on the Use of Menthol in Cigarettes” (PM USA Report) as background information for the July 21, 2011 and July 22, 2011 meeting of the Tobacco Products Scientific Advisory Committee (TPSAC).

The PM USA Report provides information that we believe is relevant to the TPSAC as it evaluates proposed changes to its March 18, 2011 report regarding the impact of the use of menthol in cigarettes on the public health. The information in the PM USA Report is fully releasable.

If you have any questions, please contact me at (804) 335-2679.

Sincerely,

A handwritten signature in black ink, appearing to read "James E. Dillard III", with a stylized flourish at the end.

James E. Dillard III

Attachment

¹ Philip Morris USA Inc. (PM USA) is a wholly-owned subsidiary of Altria Group, Inc. Altria Client Services (ALCS) is providing this information on behalf of PM USA. ALCS provides certain services to PM USA, including tobacco regulatory and health sciences.



James E. Dillard III
Senior Vice President
Regulatory Affairs

March 22, 2011

Lawrence R. Deyton, M.D., M.S.P.H.
Director, Center for Tobacco Products
U.S. Food and Drug Administration
9200 Corporate Boulevard, Room 100
Rockville, MD 20850

Re: Philip Morris USA Inc. Report on the Use of Menthol in Cigarettes

Dear Dr. Deyton:

Altria Client Services (ALCS), on behalf of Philip Morris USA Inc. (PM USA),¹ provides the attached written report summarizing the science and evidence on the impact of the use of menthol in cigarettes on the public health. The Family Smoking Prevention and Tobacco Control Act tasked the Tobacco Products Science Advisory Committee ("TPSAC") with producing for FDA a report and recommendations on this same topic (the "TPSAC Report").

When FDA determined that industry representatives would not be permitted to participate in drafting the TPSAC Report, it invited the industry to provide a separate report. We are providing this report to contribute our perspective to FDA as it considers the use of menthol in cigarettes.

The information in the attached submission is entirely available for public release.

If you have any questions, please contact me at (804) 335-2679.

Sincerely,

A handwritten signature in blue ink, appearing to read "James E. Dillard III", with a stylized flourish at the end.

James E. Dillard III

cc: via e-mail to TPSAC@FDA.HHS.gov

¹ Altria Client Services (ALCS) provides this information on behalf of PM USA. ALCS provides certain services, including regulatory affairs, to the Altria family of companies.

PM USA Report to the FDA on the Use of Menthol Cigarettes

Prepared and submitted by Altria Client Services on behalf of
Philip Morris USA
for the
Food and Drug Administration

March 22, 2011

This Information is Fully Releasable.

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Executive Summary

The Family Smoking Prevention and Tobacco Control Act (FSPTCA or the Act) tasks the Tobacco Products Scientific Advisory Committee (TPSAC) with producing for FDA a report and recommendations on the impact of the use of menthol in cigarettes on the public health, including among children, African Americans, Hispanics and other racial and ethnic minorities (the TPSAC Report).

The tobacco industry comprises many separate companies, each with its own perspective. When FDA determined that the industry representatives would not be permitted to participate in drafting the TPSAC Report, it invited the industry to provide a separate report. Philip Morris USA (PM USA)¹ welcomes the opportunity to provide this report to FDA summarizing the evidence on that question and our conclusions.²

Our review of the science- and evidence-based information demonstrates that regulatory actions or restrictions related to the use of menthol in cigarettes are neither necessary nor justified. Significant restrictions, like eliminating menthol in cigarettes, would not reduce the population harm caused by cigarette smoking, and would lead to severe and lasting unintended consequences detrimental to public health objectives and society.

Below we address the following topics:

1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes
2. Assessment of Individual and Population Harm
3. Marketing
4. Assessment of Countervailing Effects
5. Impact of Menthol Related Regulatory Actions on Public Health and Society
6. Considerations for FDA

We provide key conclusions on each topic in this Executive Summary and further analysis and supporting information in the individual chapters. We also provide a detailed reference list and study summary tables as appendices. These detailed references and study summary tables support our analysis and conclusions, while promoting brevity and conciseness of this Report.

Chapter 1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes

The Act requires FDA to take multiple, equally important considerations into account in assessing potential menthol-related regulatory actions or restrictions. These include scientific evidence concerning the risks and benefits to the population as a whole and information concerning countervailing effects, such as the creation of a significant demand for contraband tobacco products. The Agency must also adhere to Executive Orders that govern federal regulatory policy and procedure.

¹ Altria Client Services (ALCS) is making this submission on behalf of PM USA. ALCS provides certain services, including regulatory affairs, to the Altria family of companies. “We” is used throughout to refer to PM USA.

² We use the terms “use of menthol in cigarettes” and “menthol cigarettes” interchangeably in this Report. Both terms refer to cigarettes that are marketed by reference to their menthol characteristics or flavoring and which consumers recognize as containing menthol flavoring. The terms “cigarettes that do not use menthol” and “non-menthol cigarettes” are also used interchangeably, referring to cigarettes that are not so marketed or recognized.

FDA's assessment of menthol should first be guided by the six foundational principles we outlined in a December 22, 2009 submission:³

- Decisions should be science- and evidence-based.
- Clarity and transparency will promote compliance.
- Reasonable regulation requires a balanced approach.
- Adult consumers are entitled to accurate and non-misleading information about tobacco products.
- Regulated industry is an important resource for FDA as it implements the FSPTCA.
- Implementation should leverage other available federal government resources.

We also urge FDA to consider three additional points. First, adult tobacco consumer choice is an appropriate consideration for FDA in order to faithfully implement the Act in the manner that Congress intended. Second, decisions about menthol must reflect the present day legal and regulatory environment related to cigarettes. Third, FDA has a powerful array of tools to reduce the harm caused by menthol and non-menthol cigarette smoking without adopting unsupported menthol-specific regulatory actions.

Chapter 2. Assessment of Individual and Population Harm

The question at hand is *not* whether cigarettes, menthol or non-menthol, cause disease or other adverse health effects. They do. PM USA agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases and is addictive. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no safe cigarette. It can be very difficult to quit smoking, but this should not deter smokers who want to quit from trying to do so. To reduce the health effects of cigarette smoking, the best thing to do is to quit. This applies equally to menthol and non-menthol cigarettes.

Rather, the issue here is whether menthol cigarettes are *different* from non-menthol cigarettes in the context of harm. Unfortunately, the TPSAC appears to assess menthol cigarettes against a completely hypothetical, "counterfactual" environment where menthol cigarettes never existed. The more appropriate question to answer is whether menthol cigarettes are more harmful than non-menthol cigarettes.

In this PM USA Report, we rely on an established scientific and evidentiary framework to answer it. This framework defines population harm as a combination of measurable outcomes – primarily, health risks and smoking prevalence. To analyze the evidence concerning these and related outcomes, we applied a traditional science-based approach. This included identifying and examining the available evidence, giving the most weight to the most directly relevant information and classifying the strength of the scientific evidence.

With respect to evaluating the strength of the scientific evidence, we urge FDA to follow the well-established and widely accepted classification system described in the 2004 Surgeon

³ See Letter from James E. Dillard, Senior Vice President, ALCS Regulatory Affairs, to docket FDA-2009-N-0294, December 22, 2009 (Guiding Principles for Implementation).

General’s Report⁴. This approach is informed by a long history of use in the context of tobacco products, relies on terms that are consistent with common and scientific usage, and takes a risk assessment approach.

The classification system that TPSAC proposes, based on the concept of “equipoise,” is not an appropriate tool for evaluating the menthol question at hand. This system arose in a unique historical context – establishing veterans’ eligibility to receive service-related benefits – that does not apply here. Also, this approach is entirely untested in the context of tobacco products. Further, it introduces confusion and bias and is too imprecise to support informed and transparent decision-making. Finally, it does not comport with scientific integrity principles issued by the Obama administration.⁵

To address the ultimate question about population harm, we applied the 2004 Surgeon General’s criteria to answer the following questions.⁶

| APPLYING THE 2004 SURGEON GENERAL’S CRITERIA TO THE CRITICAL QUESTIONS | |
|--|---|
| Critical Question | Conclusion |
| Does menthol alter the inherent toxicity of cigarette smoke? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in the inherent toxicity of smoke. |
| Do menthol cigarettes affect average daily smoke exposure differently than non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in average daily smoke exposure. |
| Is there a difference, caused by menthol, in the health risks of smoking menthol and non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased health risk. |
| Do menthol cigarettes affect smoking initiation differently than non-menthol cigarettes? | The evidence is inadequate to infer the presence or absence of a causal relationship between the use of menthol in cigarettes and smoking initiation. |
| Do menthol cigarettes affect dependence differently than non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased dependence. |
| Do menthol cigarettes affect smoking cessation differently than non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking cessation. |

⁴ USDHSS (2004).

⁵ Memorandum for the Heads of Executive Departments and Agencies, from John P. Holden, Assistant to the President for Science and Technology and Director of the Office of Science and Technology Policy, issued December 17, 2010, at 1.

⁶ These conclusions are consistent with and further substantiated in our March 2010 and June 2010 Submissions.

| APPLYING THE 2004 SURGEON GENERAL'S CRITERIA TO THE CRITICAL QUESTIONS (CONT.) | |
|--|---|
| Critical Question | Conclusion |
| Do menthol cigarettes affect smoking prevalence differently than non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking prevalence. |
| Do menthol cigarettes affect population harm differently than non-menthol cigarettes? | No. The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in population harm. |

Taken as a whole, the scientific evidence demonstrates that there is no unique menthol effect on the components of population harm. Thus, menthol cigarettes do not affect population harm differently than non-menthol cigarettes. Menthol cigarettes are no more harmful than non-menthol cigarettes.

Chapter 3. Marketing

PM USA is committed to responsibly marketing its cigarette brands by building relationships between those brands and adult smokers while using methods designed to minimize reach to unintended audiences. Our responsible marketing practices reflect a fundamental approach that kids should not smoke or use any tobacco products. PM USA does not direct any of its cigarette brand marketing to persons who are under legal age or to non-smokers. And PM USA markets its menthol cigarette brands using the same marketing approaches as for its non-menthol brands.

In the declining U.S. cigarette market, brand competition is intense. PM USA maintains or grows its cigarette brand market share by encouraging adult smokers of PM USA cigarette brands not to switch to, or make alternate purchases of, competitive cigarette brands; and by encouraging competitive brand adult smokers to make alternate purchases of, and to switch to, PM USA cigarette brands.

The TPSAC Report relied, in part, on selected historical industry documents to speculate on a number of factors claimed to influence consumer choice of menthol cigarette brands, including “targeting” of marketing communications; the use of color and imagery in marketing and advertising; and perception of risk. We demonstrate in Chapter 3 why TPSAC’s conclusions in these areas are incorrect and unsubstantiated by the evidence.

Chapter 4. Assessment of Countervailing Effects

The Act requires FDA to take into account the countervailing effects of potential menthol-related regulatory actions or restrictions. Congress intended FDA to take concerns about countervailing effects as seriously as concerns about the other risks and benefits to the population as a whole, its effects on initiation, and its effects on cessation.

PM USA provided a lengthy, detailed and well-sourced written report to TPSAC and FDA⁷ summarizing the potential countervailing effects of a ban on menthol cigarettes. That report demonstrates that radical regulatory action, such as eliminating menthol in cigarettes from the market, would be certain to trigger a series of lasting and severe unintended consequences and other countervailing effects detrimental to public health and to society.

A recent U.S. Government Accountability Office report also underscored that numerous incentives for and manifestations of contraband activity already exist within the current tobacco regulatory environment.⁸ Additionally, many other stakeholders similarly provided information to TPSAC demonstrating the existence of global contraband and counterfeit market that has the capacity to supply the U.S. market with illicit menthol cigarettes should the opportunity be created for them.

The TPSAC Report acknowledges the potential for contraband cigarettes existing, should FDA ban or restrict menthol cigarettes.⁹

FDA should not propose any actions to eliminate or otherwise restrict menthol cigarettes -- a product that millions of adult consumers use today -- without first (i) consulting with law enforcement and other relevant government authorities on the extent of the existing and potential expansion of a contraband market, and (ii) obtaining their assurances that they have the resources to respond to a substantial increase in contraband. FDA should conduct this consultation openly, publicly and transparently with all relevant stakeholders, including other government agencies.

Chapter 5. Impact of Menthol Related Regulatory Actions on Public Health and Society

The assessments of individual and population harm (Chapter 2) and countervailing effects (Chapter 4), independently and together, provide compelling evidence that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted by the science and are not necessary. It bears special mention that the U.S. government similarly has said, in official papers filed with the World Trade Organization, that banning menthol cigarettes is not appropriate to protect public health.

Chapter 6. Considerations for FDA

The science and evidence demonstrate that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted. That said, we are aware of the ongoing debate respecting issues of menthol cigarettes and offer some additional perspective to contribute constructively to the Agency's consideration of these issues. For example, the Agency could consider additional research on topics, such as menthol-specific interactions on smoking initiation, where the evidence could be more robust. Additionally, the Agency could consider

⁷ *Countervailing effects of a ban on menthol cigarettes*, prepared and submitted by ALCS on behalf of PM USA, December 30, 2010.

⁸ GAO (2011).

⁹ See TPSAC Report, *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, Chapter 8, available online at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pdf>

possible actions to further ensure that adult smokers are fully informed respecting menthol in cigarettes. And FDA could consider whether public education campaigns and programs would be appropriate ways to address concerns about any consumer perceptions that are supported by the science. We address each of these considerations in the final chapter of this Report.

The Act has been in place for less than two years and FDA is in the midst of implementing its substantial provisions that are bringing sweeping changes for the tobacco industry and adult tobacco consumers. These provisions provide ample opportunity for FDA to undertake an overall approach to reducing the harm from cigarette smoking. Sound public policy warrants that FDA give these provisions an opportunity to achieve their intended purposes before proposing further or supplemental – and possibly countervailing – steps.

Chapter 1. Guiding Principles for FDA Decision-Making about Menthol Cigarettes

The FSPTCA authorizes FDA to adopt tobacco product standards if FDA “finds that a tobacco product standard is appropriate for the protection of the public health.”¹ In making such a finding, FDA must take multiple considerations into account.

One is scientific evidence concerning: (i) the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard; (ii) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (iii) the increased or decreased likelihood that those who do not use tobacco products will start using such products.²

Other equally important considerations are the “technical achievability of compliance with a proposed standard” and “all other information submitted in connection with a proposed standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or nontobacco users, such as the creation of a significant demand for contraband or other tobacco products that do not meet the requirements of this chapter.”³ Further, the Agency must adhere to Executive Orders that govern federal regulatory policy and procedure.⁴

FDA has stated that it will consider the TPSAC Report, as well as other scientific evidence concerning menthol cigarettes, and determine what actions, if any, are warranted.⁵ In so doing, the Agency has an important opportunity to demonstrate that it will base decisions about tobacco products on scientific evidence.

We hope that FDA has been informed by our several substantive submissions and presentations,⁶ in addition to our December 22, 2009 Submission which outlined six foundational principles important to the successful implementing of the FSPTCA:

- Decisions should be science- and evidence-based.
- Clarity and transparency will promote compliance.
- Reasonable regulation requires a balanced approach.
- Adult consumers are entitled to accurate and non-misleading information about tobacco products.

¹ FSPTCA § 907(a)(3)(A).

² *Id.* § 907(a)(3)(B)(i).

³ *Id.* § 907(b)(1-2).

⁴ *See, e.g.*, Exec. Order No. 12,866, 58 Fed. Reg. 51,735 (October 4, 1993); Exec. Order No. 13,563, 76 Fed. Reg. 3,821 (January 18, 2011).

⁵ *See* “FDA Remarks on the Report and Recommendation on the Public Health Impact of Menthol Cigarettes,” <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm247617.htm>?

⁶ *See* PM USA submissions to FDA dated March 22, 2010; PM USA submission to FDA dated June 30, 2010; PM USA presentations to TPSAC dated July 15, 2010; and PM USA submission to FDA dated December 30, 2010. We incorporate these submissions, which are part of the TPSAC record on menthol, here by reference.

Guiding Principles for FDA Decision-Making about Menthol Cigarettes

- Regulated industry is an important resource for FDA as it implements the FSPTCA.
- Implementation should leverage other available federal government resources.⁷

We also urge FDA to consider the following three points.

First, Congress intended for FDA to respect adult tobacco consumer choice. To be sure, concerns about underage tobacco use and the public health impact of cigarettes motivated Congress to grant FDA authority to regulate tobacco products. However, Congress explicitly preserved tobacco products as products that adults may use. Congress stated that a purpose of the FSPTCA is “to continue to permit the sale of tobacco products to adults in conjunction with measures to ensure that they are not sold or accessible to underage purchasers.”⁸ It also prohibited FDA from banning all cigarettes.⁹ Together, these provisions reflect the policy determination that adult tobacco consumer choice is to be respected.

One such choice millions of them make is to smoke menthol cigarettes. In fact, more than 26% of U.S. adult smokers choose menthol cigarettes. Moreover, menthol has been an accepted flavor segment in the cigarette category for decades. FDA must carefully assess menthol based on these facts, not on some hypothetical, “counterfactual” model where menthol never existed. Sound policy analysis and decision making requires no less.

In stating these facts, we do not minimize in any way the issue of underage smoking. While adults comprise the vast majority of smokers¹⁰, we agree that any underage use of cigarettes – either menthol or not -- is a legitimate concern. PM USA, like many others, has worked towards addressing this issue, and in fact, youth smoking rates have dropped significantly since peak levels in the late 1990’s. As compared to those peak levels, current rates of reported past 30-day cigarette use represent declines of 66% (8th graders), 55% (10th graders), and 47% (12th graders).¹¹

Our point is that menthol cigarettes are very different from cigarettes with characterizing flavors as defined and prohibited by the Act. The U.S. government shares this view, and stated so in submissions to the World Trade Organization regarding the Act’s prohibition of clove cigarettes. For example:

149. Additionally, while a small fraction of adults smoke clove cigarettes (and, therefore will not, on balance, be affected by the ban), *a large number of adults smoke menthol cigarettes, both in terms of percentage of the population and in absolute numbers, and many cite them as their daily, regular cigarette.*

⁷ See Letter from James E. Dillard, Senior Vice President, ALCS Regulatory Affairs, to docket FDA-2009-N-0294, December 22, 2009 (Guiding Principles for Implementation).

⁸ FSPTCA § 3(7).

⁹ *Id.* § 907(d)(3).

¹⁰ Based on ALCS analysis of 2009 National Survey on Drug Use and Health public use data, 96.3% of past 30-day smokers are age 18 or older. NSDUH data are available for download at: <http://www.icpsr.umich.edu/icpsrweb/SAMHDA/series/64/studies?sortBy=7>.

¹¹ See <http://monitoringthefuture.org/pubs/monographs/mtf-overview2010.pdf>

189....It is simply not the case, as Indonesia submits, that clove cigarettes are smoked primarily by adults, *as are tobacco and menthol cigarettes....*

242. In contrast, increasing the scope of the ban to include *either one or both* of the noncovered flavorings – tobacco and menthol – would not fulfill Congress’s legitimate objective as it would prohibit the sale of cigarettes whose consumption by addicted adults is *far from “negligible,”* accounting for the vast majority of cigarettes sold and consumed in the United States.¹²

Second, decisions about menthol cigarettes must reflect the present day legal and regulatory environment related to cigarettes. Cigarette sales, marketing, and use have become substantially restricted over the last 15 years, and even more so since FSPTCA’s enactment in 2009. According to FDA, steps it has already undertaken (such as implementing the final rule restricting access and marketing of cigarettes to youth and the statutory ban on cigarettes with certain characterizing flavors) or is taking (such as implementing new graphic warning labels for cigarettes) will be even more effective in preventing the initiation of cigarette smoking, particularly among youth, and encouraging smokers to quit.¹³ Such steps are part of a broad, coordinated strategy to reduce tobacco use. This is in contrast to some data TPSAC emphasized, like selectively chosen industry documents relating to consumers or marketing of decades ago, long before the current regulatory environment.

Third, Congress gave the Agency a powerful array of tools to reduce the harm caused by cigarette smoking. Any regulatory actions and restrictions depriving adult smokers of menthol cigarettes would be a highly intrusive way to reduce harm. Such regulatory actions would infringe on adult consumer choice, depriving millions of adult smokers of a product they prefer. Significant menthol-specific restrictions also would impose enormous burdens upon federal, state, and local governments, including those responsible for law enforcement and budgets. And, they would intrude – with no rational scientific basis – on the legitimate business of the regulated industry and cause harm to hundreds of thousands of others across the tobacco value chain. Such steps should never be taken lightly, and certainly should not be taken at all when the scientific evidence is non-existent or sparse, conflicting, or of inadequate quality.

¹² U.S. WTO (2010). (emphases added); see also U.S. WTO (2011).

¹³ See, e.g., Press conference re: “Protecting Kids from Tobacco” (March 18, 2010), <http://www.fda.gov/TobaccoProducts/ProtectingKidsfromTobacco/default.htm>; Transcript for FDA’s Media Briefing on Ban on Cigarettes with Certain Characterizing Flavors (September 22, 2009), <http://www.fda.gov/NewsEvents/Newsroom/MediaTranscripts/ucm121371.htm>; Webcast for FDA’s Graphic Health Warnings Announcement (November 10, 2010), <http://www.fda.gov/TobaccoProducts/NewsEvents/ucm232556.htm>.

Chapter 2. Assessment of Individual and Population Harm

Population harm, as we use that term here, refers to the adverse health outcomes in the U.S. population resulting from the use of cigarettes. Population harm is a component of public health impact, which we address in Chapter 5.

We organize our assessment of population harm into three sections. First, we outline an established framework and identify the critical questions to be answered. We then describe our approach for weighing and classifying the relevant evidence to answer those questions. Finally, we answer the critical questions relating to health risk, smoking prevalence, and population harm of menthol cigarettes as compared with non-menthol cigarettes.

As shown next, the evidence is suggestive of no causal relationship between the use of menthol in cigarettes and

- changes in the inherent toxicity of smoke;
- changes in average daily smoke exposure;
- changes in the health risks from smoking;
- dependence;
- cessation-related outcomes;
- smoking prevalence.

With respect to smoking initiation, the evidence is inadequate to infer the presence or absence of a causal relationship.

Because there is no unique menthol effect on individual outcomes, menthol cigarettes do not affect population harm differently than non-menthol cigarettes. This collective evidence is, therefore, suggestive of no causal relationship between the use of menthol in cigarettes and changes in population harm. Menthol cigarettes are no more harmful than non-menthol cigarettes.

I. Analytical Framework

To begin, we emphasize a point we have made repeatedly over the last year: the question is not whether cigarettes, menthol or non-menthol, cause disease or other adverse health effects. They do. PM USA agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers and is addictive. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no safe cigarette. It can be very difficult to quit smoking, but this should not deter smokers who want to quit from trying to do so. To reduce the health effects of cigarette smoking, the best thing to do is to quit. This applies equally to menthol and non-menthol cigarettes.¹

¹ When the U.S. Surgeon General, the International Agency for Research on Cancer, and other government and public health authorities concluded that smoking causes lung cancer, heart disease, and chronic obstructive pulmonary disease, among other diseases, they did not distinguish between menthol and non-menthol cigarettes. They relied on epidemiology and other scientific evidence related to cigarettes that used menthol and cigarettes that did not.

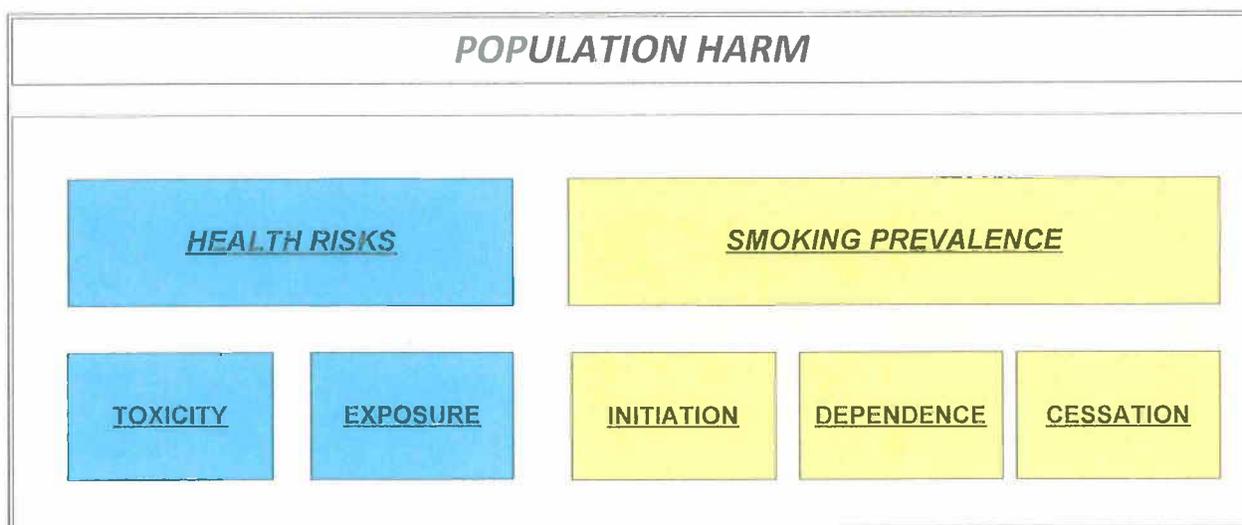
Rather, the issue is whether menthol cigarettes are *different* from non-menthol cigarettes in the context of harm. TPSAC’s Report appears to assess menthol cigarettes against a completely hypothetical, “counterfactual” environment where menthol cigarettes never existed. The more appropriate question to answer is whether menthol cigarettes are more harmful than non-menthol cigarettes.

We address this question using an established framework for assessing population harm.

A. Population Harm Framework

Various models for assessing population harm from cigarette smoking have been proposed in the scientific literature. We use a framework derived from two recent models,² as depicted in Figure 2.1:

Figure 2.1. Measurable Outcomes for Population Harm Assessment



This framework defines population harm as a combination of measurable outcomes. The primary outcomes are *health risks* and *smoking prevalence*. Each primary outcome is informed by related secondary outcomes. Thus, health risks are determined by toxicity and exposure; smoking prevalence is determined by initiation, dependence, and cessation. Figure 2.2 summarizes methods to measure these outcomes.

² See IOM (2001) and Carter et al. (2009).

B. The Critical Questions

To assess the impact on population harm, we examine the following questions:

- **Is there a difference, caused by menthol, in the health risks of smoking menthol and non-menthol cigarettes?**
 - Does menthol alter the inherent toxicity of cigarette smoke?
 - Do menthol cigarettes affect average daily smoke exposure differently than non-menthol cigarettes?
- **Do menthol cigarettes affect smoking prevalence differently than non-menthol cigarettes?**
 - Do menthol cigarettes affect smoking initiation differently than non-menthol cigarettes?
 - Do menthol cigarettes affect dependence differently than non-menthol cigarettes?
 - Do menthol cigarettes affect smoking cessation differently than non-menthol cigarettes?
- **Do menthol cigarettes affect population harm differently than non-menthol cigarettes?**

II. Weighing and Classifying the Evidence

A. Weight of Evidence

We evaluated scientific studies, data, and other information using a weight of evidence approach. Thus, we gave greater weight to evidence most directly tied to population harm and less weight to evidence less directly linked to population harm. Figure 2.2 depicts this approach:

Figure 2.2. Weight of Evidence for Population Harm Assessment

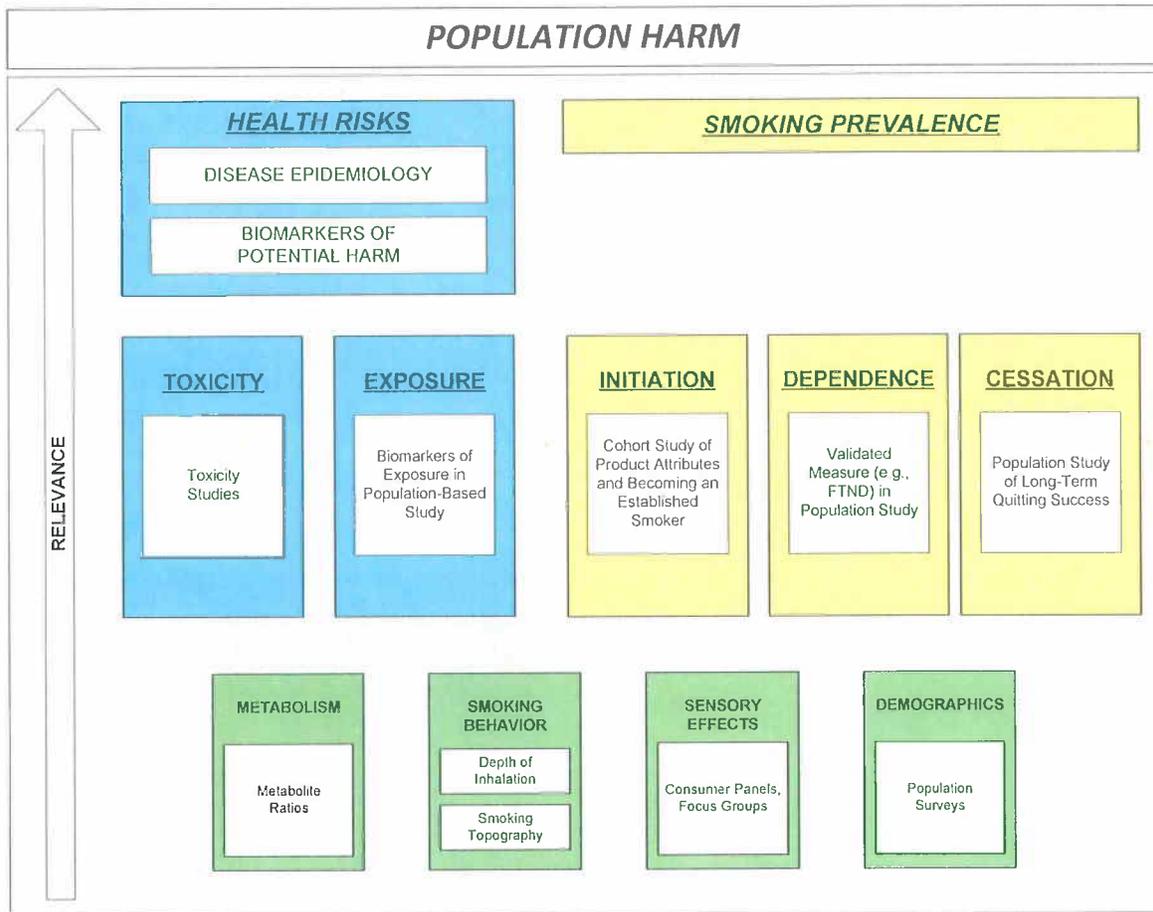


Figure 2.2 depicts primary outcomes, related secondary outcomes, and examples of direct and indirect methods for measuring each outcome (shown in the white boxes). The most relevant outcomes and measures are at the top; the least relevant are at the bottom.

Evidence from well-conducted, high-relevance studies have been given more weight than findings from less-relevant studies.

B. Classifying the Strength of Evidence

An appropriate evidence classification system supports sound regulatory decision-making by ensuring that proposed regulatory actions are supported by the scientific evidence pertaining to a potential risk.

1. Classification approach

A major aspect of classifying the strength of evidence has to do with causal inference. The 2004 U.S. Surgeon General Report described a four-tiered system to categorize the strength of scientific evidence:

- A. Evidence is **sufficient** to infer a causal relationship.
- B. Evidence is **suggestive but not sufficient** to infer a causal relationship.
- C. Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
- D. Evidence is suggestive of no causal relationship.

These categories rely upon the Hill criteria³ to assess causal inference and provide a standardized way of classifying strength of evidence. We use this 2004 U.S. Surgeon General classification approach and urge FDA to do the same.

2. TPSAC's classification approach

Instead of following this well-established approach for evidence review and classification, the TPSAC inappropriately relied on a modified version of a relatively new, four-level approach outlined in a 2008 IOM Report for the Veterans Administration (IOM-VA Report).⁴ Moreover, the TPSAC significantly modified this untested approach and adopted the following four-level classification scheme based on the concept of “equipoise”:

- The evidence is sufficient to conclude that a relationship is more likely than not.
- The evidence is sufficient to conclude that a relationship is at least as likely as not (equipoise).
- The evidence is insufficient to conclude that a causal relationship is more likely than not.
- There is insufficient evidence to make a determination of strength of evidence.

There are several reasons TPSAC erred in using this approach. First, this approach arose in a unique context not relevant here – implementing a policy giving veterans the benefit of the doubt in claims for injury and illness resulting from military service. We are not aware of any other instance in which equipoise has been used to assess the strength of scientific evidence. The only other statutory application of the equipoise concept involved reparations to Japanese-Americans for their forced internment by the government during World War II.⁵ The policy drivers of such an approach – to provide veterans with benefits or to compensate victims – do not apply here.

Other policy rationales for the equipoise-based classification scheme are also inappropriate. For example, one rationale for establishing a presumption in favor of veterans was that they lacked the financial and other resources to prove scientific and technical elements of their claim.⁶ There is no such concern here. FDA has access to vast scientific and technical expertise throughout the federal government and within the scientific community. Another rationale was that veterans could not access information needed to prove their claims because it was designated as classified or secret.⁷ Again, there is no such concern here. FDA has statutory authority to obtain confidential and trade secret information from the regulated industry, and has done so.⁸

³ Hill (1965).

⁴ IOM (2008) at 19.

⁵ See 50 U.S.C. § 1989b-4(a)(3).

⁶ See IOM (2008) at 37, 42.

⁷ *Id.* at 326.

⁸ See, e.g., FSPTCA § 904(b).

Second, using the equipoise classification suggests policy-driven outcomes rather than objective, data-driven risk assessment based on scientific evidence. It is entirely untested in the context of tobacco products, in contrast to traditional approaches used by the U.S. Surgeon General, International Agency for Research on Cancer, and the National Toxicology Program

Third, the proposed equipoise classification is too imprecise to support informed decision-making. A designation of perfect equipoise – “as likely as not” – would signify that the evidence is evenly divided between supporting and not supporting the existence of a causal relationship. However, TPSAC proposes a much broader classification – “*at least* as likely as not.” This classification establishes a structural bias, because the *same* classification level would be used for evidence that is *at* equipoise and evidence that is *above* equipoise. At best, this is confusing. At worst, it can provide a vehicle for policy preferences to make weak evidence appear strong.

Finally, the proposed approach does not comport with scientific integrity principles issued by the Obama administration. By Executive Order, “each [federal] agency shall ensure the objectivity of any scientific and technological information and processes used to support the agency’s regulatory actions.”⁹ A December 17, 2010 memorandum provides guidance to federal agencies regarding scientific integrity, emphasizing that “[s]uccessful application of science in public policy depends on the integrity of the scientific process both to ensure the validity of the information itself and to engender public trust in Government.”¹⁰ The TPSAC’s proposed classification approach simply does not meet these standards.

III. Answering the Critical Questions

Our analysis draws on all the available evidence, particularly the detailed information provided in our March 2010 and June 2010 submissions, which are incorporated into this document by reference, and to which we refer FDA for more detail.¹¹ In addition, there now are available subsequent published literature and analyses. All this forms the basis for our analysis and conclusions. As noted above, we are also providing here a reference list of scientific evidence (Appendix A) and detailed study summary tables (Appendix B).

A. Background

1. The Sensory Experience

As described in our June 2010 Submission, we design our menthol cigarettes to meet the taste preferences of adult smokers who wish to smoke menthol cigarettes. We do this by balancing the amount of menthol with the design features that affect the amount of tar and menthol in smoke.

⁹ Exec. Order No. 13,563, 76 Fed. Reg. 3,821, at § 5 (January 18, 2011).

¹⁰ Memorandum for the Heads of Executive Departments and Agencies, from John P. Holden, Assistant to the President for Science and Technology and Director of the Office of Science and Technology Policy, issued December 17, 2010, at 1.

¹¹ *Submission re: March 30-31, 2010 Meeting of the Tobacco Products Scientific Advisory Committee*, prepared and submitted by ALCS on behalf of PM USA, March 22, 2010; *Background Information to Tobacco Products Scientific Advisory Committee, Menthol Discussion*, prepared and submitted by ALCS on behalf of PM USA, June 30, 2010.

Many studies have examined the effects of menthol *per se* on sensory responses. Research studies have shown that menthol *per se* produces a cooling sensation by binding with the TRPM8 channel and irritation by binding with the TRPA1 channel. Other reports in the scientific literature suggest that menthol *per se* can act as an anesthetic or analgesic, particularly for dermal application. However, mechanistic studies do not support a local anesthetic effect for menthol in the airways (respiratory tract, mouth and throat).

With regard to an analgesic effect, a desensitizing effect of menthol on nicotine-induced activation of TRPA1 channels has been observed in cultured cells. A published clinical study concluded that pre-treatment with menthol appears to desensitize the tongue to nicotine-induced irritation.¹² However, findings from a PM USA-funded clinical study indicate that menthol does not desensitize the upper respiratory tract to irritation caused by nicotine, even in the presence of a cooling sensation.¹³

In contrast to studies of menthol *per se*, there are very limited data on the sensory effects of menthol in cigarette smoke. The desensitizing effects of menthol observed in cell studies or in oral irritation models (tongue) should not be assumed to be the same as the effects of menthol in smoke or in the airways. Smoke contains a number of reactive molecules that can bind with TRPA1 receptors. The interaction of menthol with the TRPA1 channel, in the presence of numerous reactive smoke constituents, is likely to be more complex than the interaction of menthol alone. Published studies that have examined the interaction between reactive molecules and menthol at the TRPA1 channel have reported that such molecules eliminated menthol's ability to influence the activation of this channel.¹⁴

Unconjugated or free menthol has not been detected in the blood of individuals smoking menthol cigarettes.¹⁵ Thus, it seems unlikely that sensory effects resulting from the direct action of menthol from smoke occurs outside the airways. Whether menthol in cigarette smoke produces an anesthetic or analgesic effect on the respiratory tract has not been directly examined. Indirect evidence, however, suggests none. For example, studies of the effect of menthol cigarettes on depth of inhalation show no difference between menthol and non-menthol cigarettes.¹⁶ If menthol were exerting a significant physiological effect related to reducing sensations in the respiratory tract, these inhalation patterns would be expected to change.

In the framework for population harm, evidence about the sensory experience of smoking menthol cigarettes provides, at most, indirect information for answering the critical questions. Therefore, the current incomplete understanding of how menthol in smoke affects sensory responses and receptors does not impact the overall assessment of population harm. Yet, the TPSAC relied on sensory data regarding menthol *per se* to conclude biological plausibility for population harm.

¹² Dessierier et al. (2001).

¹³ Renner & Schreiber (Manuscript Submitted for Publication).

¹⁴ Karashima et al. (2007).

¹⁵ Ahijevych et al. (2002).

¹⁶ Jarvik et al. (1994); St. Charles et al. (2009); Ahijevych et al. (1996).

2. Demographics of Menthol Cigarette Use

The Tobacco Use Supplement to the Current Population Survey estimated that 26.6% of adult smokers in the United States smoke menthol cigarettes.¹⁷ The proportion of adult menthol smokers varies in different sociodemographic groups as menthol cigarette smokers are not a homogenous population. Several recent papers have examined the prevalence of menthol smoking and further characterized differences in gender, race, age, education, income and employment and other differences between menthol and non-menthol smokers.¹⁸

The comparison of menthol-related demographic patterns with patterns of health effects in certain U.S. subpopulations – African Americans in particular – have led to speculation that menthol may have a unique contribution to the health risks from smoking. Analyses of the general population and subpopulations, including African Americans, show that it does not. Several factors unrelated to menthol cigarettes, such as lack of control for confounding factors and social and environmental differences, are likely to explain observed disparities in health risks between different subpopulations.

B. Health Risks, Smoke Toxicity and Exposure

With respect to health risk, the effects of menthol in cigarettes have been extensively studied. Investigations provide direct evidence about the health risks (disease epidemiology), smoke exposure (biomarker studies) and the toxicity of smoke (non-clinical testing and the safe use of menthol in other products). A considerable amount of indirect evidence also exists (*e.g.*, study of puffing topography, effect on metabolism). We examine and summarize three main areas of concern as they relate to possible differences in health effects of menthol cigarettes compared with non-menthol cigarettes: (i) smoke toxicity, (ii) exposure and, (iii) health risks in humans.

1. Does menthol alter the inherent toxicity of cigarette smoke?

The safety profile of menthol has been extensively investigated in pre-clinical studies.¹⁹ Menthol has a long history of safe use in a wide range of consumer products. Further, the addition of menthol to cigarettes has been extensively studied using a variety of non-clinical tests including smoke chemistry, *in vitro* biological tests and animal studies.²⁰

During TPSAC's review of menthol, some members hypothesized that menthol might affect smoke toxicity by altering the metabolism of other compounds in smoke, particularly NNK and nicotine.²¹ However, the most definitive assessment of this possible effect has been investigated in the PM USA Total Exposure Study (TES), which found no significant effect of menthol on either NNK or nicotine metabolism based on evaluation of metabolite ratios. This information was presented at a public meeting of the American College of Clinical Pharmacology,²² and we have provided to FDA all data needed to replicate this analysis.

¹⁷ NCI (2010).

¹⁸ Rock et al. (2010); Cubbin et al. (2010); Lawrence et al. (2010).

¹⁹ Belsito et al. (2008); Bhatia et al. (2008).

²⁰ See Appendix Table B-3.

²¹ Benowitz et al. (2004).

²² Sarkar et al. (2010).

Based on the consistency of the evidence highlighted above, the evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in the inherent toxicity of smoke.

2. Do menthol cigarettes affect average daily smoke exposure differently than non-menthol cigarettes?

During TPSAC's review of menthol, some opined that menthol makes it easier to inhale cigarette smoke, resulting in more intense smoking and increased smoke constituent exposure. The proposed mechanism is that menthol may desensitize the respiratory tract to irritating effects of tobacco smoke by either local anesthetic or analgesic effects.

Generally, exposure to cigarette smoke occurs as a result of a multi-step process. First, smoke is drawn into and held briefly within the mouth. Various parameters, such as puff volume, puff frequency, and puff duration, can be measured in puffing topography studies.

Second, smoke is inhaled into the lungs. Inhalation topography data are limited because the associated parameters are relatively difficult to measure. Finally smoke is exhaled. Throughout this process, the body absorbs nicotine and other smoke constituents. As multiple cigarettes are smoked, this process repeats itself to determine a smoker's average daily exposure.

Average daily exposure can be directly measured using biomarkers of exposure (BOE). An important advantage of well-designed BOE studies is their ability to account for puffing and inhalation behaviors as well as other factors, such as smoke constituent metabolism and disposition. Measurements of nicotine and its major metabolites in urine have been demonstrated to provide a robust biomarker of average daily smoke exposure.²³

Studies of puffing topography show mixed results while studies of depth of inhalation show no significant difference from the use of menthol in cigarettes.²⁴ More importantly, the largest and most thoroughly conducted BOE studies, including the PM USA TES, indicate no difference in exposure between smokers of menthol vs. non-menthol cigarettes. A 2010 study,²⁵ which was not available at the time of our June 2010 Submission, found that "[m]enthol is not independently associated with carcinogen exposure when nicotine intake is considered." This finding corroborates the findings from previous BOE studies that menthol has no effect on cigarette smoke constituent exposure.

Consistency and small effect sizes are illustrated by the TES and Heck.²⁶ In both studies, the main analysis found no statistically significant differences in exposure between smokers of menthol and non-menthol cigarettes. These studies employed different experimental designs and yet reached the same conclusion. Coherence in these findings is illustrated by the finding of no significant effect in exposure studies and the studies of inhalation patterns.

The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and changes in average daily smoke exposure.

²³ Wang et al. (2011).

²⁴ Jarvik et al. (1994); St. Charles et al. (2009); Ahijevych et al. (1996).

²⁵ Benowitz et al. (2010).

²⁶ Wang et al. (2010); Heck (2009).

3. Is there a difference, caused by menthol, in the health risks of smoking menthol and non-menthol cigarettes?

Direct evidence about the use of menthol in cigarettes and health risks comes from studies of disease epidemiology and studies of biomarkers of potential harm (BOPH). Thirteen epidemiological studies, summarized in Appendix Table B-1, comparing smoking-related health effects among menthol vs. non-menthol smokers, have been published.²⁷ PM USA provided a summary of these thirteen studies in its June 2010 Submission and during the July 15-16, 2010 TPSAC meeting.

Twelve of these thirteen studies reported no significant differences between menthol vs. non-menthol smokers for any of the health outcomes evaluated. The other study, Sidney et al. (1995), reported a weak but statistically significant increase in lung cancer risk (RR = 1.45; 95% CI: 1.03-2.02) among men who smoked menthol cigarettes compared with men who smoked non-menthol cigarettes.²⁸ No such effect was observed among women. The same investigators conducted a follow-up investigation using the same study population to determine if menthol-related increases in other smoking-related cancers would be observed.²⁹ No menthol-related increases for cancer risk were observed for the upper aerodigestive tract, pancreas, kidney, other parts of the urinary tract, uterine cervix and all smoking-related sites. In discussing this finding in the context of their previous report, as well as other studies, the investigators commented, “*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.*” The single finding of increased lung cancer risk for menthol cigarettes reported was not replicated in six subsequent epidemiological studies (which are included among the thirteen studies noted above) that examined the possible effects of menthol on lung cancer risks.

We have analyzed BOPH data from the TES. Our June 2010 Submission describes the results, which we also presented at a public meeting of the Society for Research on Nicotine and Tobacco scientific conference.³⁰ That analysis demonstrates that menthol has no statistically significant effects on any of the BOPHs and no statistically significant menthol-related interactions.

There has historically been a disparity in lung cancer risk independent of smoking status between African American men and White men.³¹ However, this disparity is narrowing due primarily to a faster rate of decline in lung cancer prevalence among African Americans versus Whites. Differences in background susceptibility, historical smoking prevalence, and socioeconomic disparities are more likely than menthol to account for the observed smoking-related lung cancer risk disparity between African Americans and Whites.

The epidemiological results are supported by the results of exposure and toxicity studies, both of which show no effect of menthol. Together, this evidence demonstrates that there is no

²⁷ Health outcomes evaluated in this collective body of research include all cause mortality, lung cancer, esophageal cancer, oropharyngeal cancer, all smoking-related cancers, coronary calcification, cardiovascular heart disease mortality, and lung function.

²⁸ Sidney et al. (1995).

²⁹ Friedman et al. (1998).

³⁰ Frost-Pineda et al. (2010); Frost-Pineda et al. (2011).

³¹ USDHHS (1998).

significant association between the use of menthol in cigarettes and health risk, exposure, or toxicity. No studies have demonstrated a specific action of menthol in cigarettes on smoke toxicity. To the contrary, non-clinical studies have shown that there is no dose-related effect (biological gradient) between menthol level and smoke toxicity.

The extensive evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased health risk.

C. Effects on Smoking Prevalence, Initiation, Dependence and Cessation

Smoking prevalence is the second primary outcome in the population harm framework. Smoking prevalence is measured using surveys to estimate the number of smokers in the population. Using these data, it is possible to characterize the prevalence of smoking menthol and non-menthol cigarettes overall and within various subgroups. These data can also be used to generate hypotheses about the possible effects of menthol. However, because many factors influence smoking trajectories from initiation to cessation,³² prevalence measures alone are not sufficient to evaluate causal relationships between the use of menthol in cigarettes and the number of people who smoke.

Numerous studies related to initiation, dependence, and cessation have been published since our June 2010 Submission. We focus here on summarizing and synthesizing these new studies with the results presented in our June 2010 Submission.³³

1. Do menthol cigarettes affect smoking initiation differently than non-menthol cigarettes?

In our June 2010 Submission, we reviewed the published literature and data related to menthol cigarettes and smoking initiation. There we concluded, based on the limited available information, that menthol cigarettes do not appear to play a unique role in smoking initiation. For the reasons discussed below, these conclusions remain unchanged. We acknowledge, however, the relative lack of evidence in this area, inconsistencies in findings and the lack of prospective longitudinal research designed specifically to answer this question.

a. Recent evidence is inconsistent with the view that menthol cigarettes play a unique role in smoking initiation.

Overall, the evidence suggests that the age of smoking initiation does not differ between menthol and non-menthol cigarette smokers; in fact, some evidence suggests that it may be later for menthol smokers.³⁴ Two recent studies found no difference between menthol and non-menthol smokers in age of initiation.³⁵ A third study showed some tendency for longer delays in initiation associated with menthol cigarette smoking,³⁶ while a fourth study indicated rates of menthol cigarette use were higher for women who started smoking at age 18 or older (vs. ages 15 to 17).³⁷ An earlier study, which was not included in our June 2010 Submission, also found no

³² NCI (2009).

³³ See Appendices B-4, B-5, B-6, B-7, and B-8 for additional detail on the scientific evidence in these areas.

³⁴ Fernander et al. (2010); Lawrence et al. (2010).

³⁵ Cubbin et al. (2010); Stahre et al. (2010)

³⁶ Fernander et al. (2010).

³⁷ Lawrence et al. (2010).

significant difference by menthol status on age at time of first cigarette smoked among a sample of African-American smokers.³⁸

The relationship between menthol cigarette use and recency of smoking initiation is inconsistent. A 2010 Hersey analysis of 2006 National Youth Tobacco Survey (NYTS) data indicated that the proportion of middle-school smokers whose reported usual brand was menthol was *lower* among those who smoked for less than a year (42.2%) than those who smoked one year or more (54.7%)³⁹. A 2006 Hersey analysis of 2002 NYTS data reported opposite findings.⁴⁰

Similarly, analyses using the National Survey on Drug Use and Health (NSDUH) data produced inconsistent results.⁴¹ As our June 2010 Submission detailed, prior to 2004, when the question to discern menthol use included a forced choice between “Regular” or “Menthol” brands,⁴² reported usual use of menthol cigarettes was lower for adolescents who said they first smoked in the past year than for those who said they had smoked for more than a year. Beginning in 2004, when the question to discern menthol use was changed to a “Yes” or “No” response,⁴³ the recency pattern was largely reversed. In 2008 the observed recency pattern reversed yet again.

Since our June 2010 Submission, we analyzed 2009 NSDUH data and found a pattern consistent with 2008. Thus, even using the current measure, the association between menthol use and recency of smoking initiation remains inconsistent. This suggests that patterns of menthol use may fluctuate over time and that there is an opportunity for improved measures⁴⁴ and longitudinal data.

New analyses suggest no differences in reported use of menthol by number of cigarettes ever smoked. Hersey et al. (2010) observed no differences in the proportions of respondents reporting menthol use by lifetime number of cigarettes smoked, regardless of how menthol use was categorized (“self-described,” “likely menthol,” or “broad menthol”).⁴⁵

Evidence suggests that the relationship between menthol cigarette use and age varies among samples and over time. Current data suggest that among Whites, underage smokers report

³⁸ Allen & Unger (2007).

³⁹ Hersey et al. (2010).

⁴⁰ Hersey et al. (2006).

⁴¹ On November 18, 2010, Dr. Gary Giovino presented an overview of the NSDUH to the TPSAC. In the course of his presentation and corresponding written submission, Dr. Giovino expressed concern that tobacco industry analyses may be inclusive of only a small subset of respondents – those who were not able to identify a usual cigarette brand smoked. His concern does not apply to our analyses which were based on all respondents to the menthol questions, whether they cited a brand or not. Page 116 of our June 2010 submission contains sample size information. The question regarding brand smoked most often preceded the menthol question in all survey years.

⁴² Question: “During the past 30 days, did you smoke [insert brand name if identified] menthol or regular cigarettes most often?” Response alternatives: Menthol, Regular, *Don’t Know/Refused/Blank*.

<http://www.oas.samhsa.gov/nsduh/methods.cfm#top>. Brand name inserted refers to brand smoked most often.

⁴³ Question: “Were the [insert brand name if identified] cigarettes you smoked during the past 30 days menthol?” Response alternatives: Yes, No, *Don’t Know/Refused/Blank*. <http://www.oas.samhsa.gov/nsduh/methods.cfm#top>. Brand name inserted refers to brand smoked most often.

⁴⁴ The current menthol question appears to measure “any use” of menthol cigarettes; compared to the prior question it may include a greater proportion of individuals who smoke both menthol and non-menthol cigarettes. Also, it does not allow for a direct assessment of non-menthol use.

⁴⁵ Cf. Hersey et al. (2010).

menthol use at higher rates than older smokers, but among African Americans, underage smokers report menthol use at lower rates than older smokers.⁴⁶ These patterns stand in contrast to data collected from 1979 to 1986 among 29,037 current smokers who were Kaiser Permanente Medical Care Program members.⁴⁷ These data indicate “relatively little difference” in menthol cigarette use with age in White smokers. At the same time, and in contrast to current trends, the proportion of menthol smokers was higher among 15 to 19 year old African Americans than older African American age groups. The authors attributed this latter pattern to a cohort effect.

Similar inconsistencies have been observed in analyses of middle-school and high-school students. A recent analysis of 2006 NYTS data suggested that a higher proportion of Asian-American middle-school smokers (57.4%) use menthol cigarettes than their high-school counterparts (43.6%),⁴⁸ while an earlier analysis of 2000 NYTS data suggested this was not the case. Reported use of menthol equaled 59.9% among Asian-American high-school smokers and 50.9% among their middle-school counterparts.⁴⁹

b. Analyses regarding the potential role of menthol cigarettes in smoking initiation should account for important differences between underage and adult smokers.

Underage and adult smokers differ in their smoking behaviors. Most underage smokers are experimenters and do not progress to regular smoking,⁵⁰ whereas most adult smokers smoke on a regular basis.⁵¹ Where 46.8% of past 30-day smokers aged 12 to 17 reported smoking less than 100 lifetime cigarettes in 2009, this percentage drops to 4.0% among those who are 26 or older.⁵² Unlike adults, underage smokers rely heavily on social sources to access cigarettes, in particular those who are younger or smoke on an infrequent basis.⁵³ High percentages of underage experimental smokers coupled with social sourcing of cigarettes are likely to affect the reports of type of cigarette smoked.

Underage and adult smokers also differ in their awareness and knowledge of cigarette brands and types. It takes time to learn specific brand characteristics (e.g., menthol vs. non-menthol).⁵⁴ Many underage smokers, particularly those who are only starting to experiment with cigarettes or those who do not typically buy their cigarettes, are likely less knowledgeable than adult smokers about the brand characteristics of the cigarettes they smoke. As a consequence, underage

⁴⁶ Rock et al. (2010). Patterns among Hispanic, Asian, and American Indian/Alaska Native smokers were similar to those observed among White smokers.

⁴⁷ Sidney et al. (1989).

⁴⁸ Hersey et al. (2010).

⁴⁹ Appleyard et al. (2001).

⁵⁰ CDC (2009); Tucker et al. (2003).

⁵¹ <http://oas.samhsa.gov/NSDUH/2k9NSDUH/tabs/Index.pdf>.

⁵² Based on ALCS analysis of National Survey on Drug Use and Health data available through: <http://www.icpsr.umich.edu/cocoon/SAMHDA/SERIES/00064.xml>. Data were weighted to provide population estimates.

⁵³ CDC (2009); Croghan et al. (2003); Emery et al. (1999); Harrison et al. (2000); Ma et al. (2003).

⁵⁴ Caraballo & Asman (Manuscript Submitted for Publication). Downloaded from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM228105.pdf>, February 25, 2011.

smokers may be more likely to fail to respond correctly to questions about the brands and types of cigarettes they smoke. Several studies provide evidence consistent with this view.⁵⁵

Evidence related to recency of smoking initiation and the association between age and reported menthol use lacks consistency. Moreover, no differences in underage smokers' subjective reactions to the first inhaled cigarette argue against plausibility⁵⁶, as does the difficulty that some underage smokers have in identifying the cigarette(s) they smoked. No differences in age of initiation (apart from recent evidence of an association with delayed initiation) and no apparent relationship between menthol use and number of cigarettes ever smoked demonstrate a lack of coherence.

We continue to believe, based on the limited available evidence, there is no effect on initiation. However, in applying the Surgeon General's criteria, we recognize the inconsistent findings and lack of prospective longitudinal research specifically designed to answer questions about menthol and initiation.

As a result, the evidence is inadequate to infer the presence or absence of a causal relationship between the use of menthol in cigarettes and smoking initiation.

2. Do menthol cigarettes affect dependence differently than non-menthol cigarettes?

We considered studies with large representative samples that used a generally-accepted, widely-used measure of dependence like the Fagerström Test for Nicotine Dependence (FTND) to be the most informative in answering this question. Since the proportion of menthol smokers varies in age, gender, racial/ethnic, and socio-economic groups, and since these variables are also associated with differences in dependence, we considered whether the analysis controlled for these potential confounders. If both univariate and multivariate comparisons were done, we assigned greater weight to the multivariate results.

In our June 2010 Submission, we reviewed relevant evidence from the published scientific literature and the TES, concluding that the evidence does not support the hypothesis that menthol makes cigarettes more addictive or that menthol increases cigarette dependence. Since then, several new studies have been published that included dependence-related variables and analysis. These studies confirmed that menthol smokers smoke the same⁵⁷ or significantly fewer cigarettes per day (CPD)⁵⁸ as compared with non-menthol smokers. For example, Cubbin et al.⁵⁹ reported no significant difference in CPD by menthol status and race/ethnicity among males or females.

Recent studies also have reported the following:

- No association between menthol status and smoking within the first 30 minutes of waking among daily smokers⁶⁰

⁵⁵ See, e.g., DiFranza et al. (2004); Hersey et al. (2006); Hersey et al. (2010).

⁵⁶ DiFranza et al. (2004).

⁵⁷ Ahijevych & Ford (2010); Cubbin et al. (2010); Lawrence et al. (2010); Mendiondo et al. (2010) [African-American, Hispanic].

⁵⁸ Fagan et al. (2010); Mendiondo et al. (2010) [Current, former and White menthol smokers]; Stahre et al. (2010).

⁵⁹ Cubbin et al. (2010).

⁶⁰ Ahijevych & Ford (2010).

- No significant difference in odds of smoking within the first five minutes versus greater than five minutes for those who smoke 1-5, 11-20, or 20+ CPD in menthol versus non-menthol smoker⁶¹
- Among African Americans, Whites, Hispanics, American Indians/Alaska Natives, and Asian/Pacific Islanders, no significant difference in Adjusted Odds Ratio (AOR) by menthol status in any CPD category, or in time to first cigarette (TTFC) \leq or $>$ thirty minutes⁶²
- Among underage smokers reporting a “usual brand”, no significant increased odds for menthol smokers to report “feeling restless or irritable without smoking” or “experiencing cravings after going without smoking for a few hours”; among those reporting a “usual brand” and “established smokers”, underage menthol smokers had higher odds of reporting “needing a cigarette within one hour after smoking”⁶³
- No significant difference by menthol status in FTND scores or in mean TTFC⁶⁴
- Menthol smokers had statistically significantly lower mean scores on the Nicotine Dependence Syndrome Scale (NDSS) in the unadjusted analysis and no significant difference between menthol and non-menthol smokers in AOR of dependence on the NDSS in the multivariate analysis⁶⁵
- Subsequent to our June 2010 Submission, we identified a 2007 study which found no significant differences by menthol status in odds of higher score on FTND, age first smoked or in wanting to stop smoking completely for African-American women and men⁶⁶

Most studies have found no effect of menthol on established and widely used measures of dependence.

Most findings from population studies that have appropriately controlled for confounding factors indicate no difference in dependence between smoking menthol as compared with non-menthol cigarettes. Where a statistically significant association was observed in either direction, the effect was small. Together, this evidence demonstrates that there is no significant association between the use of menthol in cigarettes and dependence. Additionally, in these limited instances where statistically significant menthol effects have been reported, mixed results are observed, demonstrating lack of consistency. There has been no study of a biological gradient with regard to changing menthol levels and dependence measures. There is no scientific evidence for an analogous situation that can be used to explore the effect of the use of menthol in cigarettes on dependence.

The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and increased dependence.

⁶¹ Fagan et al. (2010).

⁶² Lawrence et al. (2010).

⁶³ Hersey et al. (2010).

⁶⁴ Benowitz et al. (2010).

⁶⁵ Hooper et al. (2011).

⁶⁶ Allen & Unger (2007).

3. Do menthol cigarettes affect smoking cessation differently than non-menthol cigarettes?

Studies with large representative samples with actual quitting and long term follow-up are most informative in answering this question. The proportion of current and former menthol smokers varies in different age, gender, racial/ethnic, and socio-economic groups. Since these sociodemographic variables are also associated with differences in cessation-related outcomes, we relied on studies that appropriately controlled for potential confounders. If both univariate and multivariate comparisons were done, we assigned greater weight to the multivariate results.

In our June 2010 Submission, we reviewed and summarized studies including cessation-related variables and outcomes, concluding that the evidence does not support the hypothesis that there is an effect of menthol on smoking cessation. Since that time, several new studies have been published. One review article, that included ten of the studies previously examined, reported that, “None of the studies found a significant overall effect of menthol on smoking cessation at the last study follow-up point, after controlling for other relevant measured variables.”⁶⁷

Other recent analyses have found the following:

- No difference in number of quit attempts, longest length of cessation, or if had ever stopped smoking by menthol status; menthol smokers were more likely to have stopped smoking in the last 12 months⁶⁸
- No difference in quit attempts in the past 12 months or in length of smoking abstinence among those who made a quit attempt between menthol and non-menthol smokers (for ≤5, 6-10, 11-19 and 20+ CPD groups in the multivariate analysis)⁶⁹
- No difference in past year quit attempts among menthol and non-menthol smokers.⁷⁰
- No significant difference in quit attempts between menthol and non-menthol, no significant difference in length of abstinence by menthol status by race or gender except that White female menthol smokers had statistically significantly longer abstinence (2.5 years longer) as compared with White female non-menthol smokers⁷¹
- No difference reported for odds of quitting by menthol status within any of the racial ethnic groups (White, African American, American Indian/Alaska Native, Asian), no difference between menthol and non-menthol in odds of using any type of quit aid⁷²
- Current African American and Hispanic menthol smokers were more likely to be “seriously thinking about quitting” and have a positive estimation of their success, but reported lower odds of six months or more cessation among former menthol as compared with non-menthol smokers⁷³
- Menthol smoking was not significantly related to abstinence at six months post-cessation⁷⁴

⁶⁷ Foulds et al. (2010).

⁶⁸ Alexander et al. (2010).

⁶⁹ Fagan et al. (2010).

⁷⁰ Hooper et al. (2011).

⁷¹ Cubbin et al. (2010).

⁷² Stahre et al. (2010).

⁷³ Trinidad et al. (2010).

⁷⁴ Steinberg et al. (2011).

Most studies indicate no difference in smoking cessation between menthol and non-menthol smokers. Additionally, in those limited instances where statistically significant menthol effects have been reported, mixed results are reported, demonstrating a lack of consistency. No studies have reported a specific action of menthol in cigarettes on cessation. Of note, there has been no study of a biological gradient with regard to changing menthol levels and cessation outcomes, nor have there been randomized clinical trials that specifically examined the question of the effect of the use of menthol in cigarettes on cessation; therefore, experimental data are lacking.

The evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking cessation.

4. Do menthol cigarettes affect smoking prevalence differently than non-menthol cigarettes?

As documented in our previous Submissions, the evidence is lacking that menthol cigarettes facilitate cigarette smoke inhalation, increase exposure, enhance smoking initiation, increase dependence, or inhibit smoking cessation.

We cannot infer a menthol-specific effect because of the numerous non-menthol factors associated with smoking initiation, dependence, and cessation related behaviors. Moreover, the strength of any observed associations of menthol on any outcomes is not particularly strong, and these associations lack consistency. The collective body of evidence suggests no causal relationship between menthol and increased dependence or reduced cessation. With respect to smoking initiation, the evidence is inadequate to infer the presence or absence of a causal relationship.

Because menthol does not affect these individual components, we conclude that, taken as a whole, the evidence is suggestive of no causal relationship between the use of menthol in cigarettes and smoking prevalence.

D. Population Harm

1. Do menthol cigarettes affect population harm differently than cigarettes which do not use menthol?

The evidence demonstrates that the scientific evidence is suggestive of no causal relationship between the use of menthol in cigarettes and

- changes in the inherent toxicity of smoke;
- changes in average daily smoke exposure;
- changes in the health risks from smoking;
- dependence;
- cessation-related outcomes; and
- smoking prevalence.

With respect to smoking initiation, the evidence is inadequate to infer the presence or absence of a causal relationship.

Thus, one can directly answer the population harm question. The use of menthol in cigarettes does not increase health risks for smokers and does not have a unique effect on smoking prevalence. Because there is no demonstrated unique menthol effect on these individual components of population harm, the evidence taken as a whole is suggestive of no causal relationship between the use of menthol in cigarettes and changes in population harm.

Menthol cigarettes are no more harmful than non-menthol cigarettes.

Chapter 3. Marketing

PM USA has provided to TPSAC and the FDA extensive information related to its marketing practices. Importantly, all cigarette marketing has been subject for many years to significant restrictions. For example, extensive restrictions agreed upon in the Tobacco Settlement Agreements have been in place for nearly 13 years.¹ With the enactment of the FSPTCA in 2009, cigarette marketing is now subject to more regulation than ever before. In addition to these restrictions, PM USA has adopted a number of voluntary practices related to marketing and advertising, all of which have been described in detail previously.

As FDA has considered other regulatory matters such as the Final Tobacco Rule (the 1996 Rule), the development of mandatory graphic warnings for all cigarette packages and the removal of descriptors, PM USA has provided additional detailed submissions to FDA.² Together, they show that the current marketing environment for all cigarettes, including menthol, is restricted and constrained.

PM USA is committed to responsibly marketing its cigarette brands by building relationships between those brands and adult smokers while using methods designed to minimize reach to unintended audiences. Our responsible marketing practices start with a fundamental commitment that kids should not smoke. PM USA does not direct any of its tobacco brand marketing to persons who are under legal age. Additionally, PM USA does not direct any of its tobacco brand marketing to non-smokers.

In the declining U.S. cigarette market, brand competition is intense. PM USA maintains or grows its cigarette brand market share by encouraging:

- adult smokers of PM USA cigarette brands not to switch to, or make alternate purchases of, competitive cigarette brands; and
- by encouraging competitive brand adult smokers to make alternate purchases of, and ultimately to switch to, PM USA cigarette brands.

PM USA markets its menthol cigarette brands using the same limited marketing approaches it uses for its non-menthol brands.

In its review of menthol-related marketing issues, TPSAC made a number of assertions that are incorrect and unsubstantiated by the evidence. These include issues related to “targeting”, the use of color and imagery in marketing and advertising, and perception of risk. We demonstrate below why FDA should disregard these assertions in its review.

¹ In 1998, the nation’s leading cigarette manufacturers, including Philip Morris USA and the other Original Participating Manufacturers (OPMs), signed a contract called the Master Settlement Agreement (MSA) with the Attorneys General of 46 states, five U.S. territories and the District of Columbia. Prior to entering into the MSA, OPMs had already reached similar agreements with Florida, Minnesota, Mississippi and Texas. These agreements with the Previously Settled States, combined with the MSA, are collectively referred to as the Tobacco Settlement Agreements (TSAs).

² See PM USA Submissions to FDA: December 22, 2009, Docket No. FDA-2009-N-0294 (1996 Rule); February 18, 2010, Docket No. FDA-2009-N-0020 (Use of Marketing Descriptors to Convey Modified Risk); January 11, 2011, Docket No. FDA-2010-N-0568 (Required Warnings for Cigarette Packages and Advertisements).

I. Historical Documents are not Necessarily “Scientific Evidence”

The TPSAC’s charge has been to assess the “scientific evidence” related to menthol cigarettes.³ The hallmarks of “scientific evidence” include adherence to a scientific method, thoroughness, documentation, reliability, and perhaps most importantly, objectivity. In making conclusions related to the tobacco industry’s marketing practices, the TPSAC inappropriately relied upon certain historical industry documents -- many of which do not constitute “scientific evidence.” For example, in our January 27, 2011 letter to FDA, we outlined the deficiencies in the University of California San Francisco’s (UCSF) analyses of historical documents, some of which were marketing related; and we objected to TPSAC’s consideration and reliance on them.⁴ Some specific deficiencies include:

- Very few of the historical documents relied upon by UCSF were prepared as scientific studies. For example, documents prepared by outside marketing consultants,⁵ are not in accordance with scientific principles. Others simply represent the thoughts of individuals, whose backgrounds and experience are not reflected in the documents (assuming the individuals are identified at all).⁶
- For the few documents that might possibly qualify as scientific studies, they provide little scientific utility because the UCSF staff ignored a basic scientific approach of gathering evidence. As some of the UCSF authors acknowledged:

“In analyzing the documents in a limited time frame, context may have been lost ... Understanding the time period when a document was written, who wrote a document, why a document was written, or why a study was performed requires time for reviewing and linking documents together.”⁷

Context is essential to interpreting any document that contains scientific data. Without sufficient context, it is impossible for the FDA to assess the quality, objectivity, utility, and integrity of scientific information within a document. Such considerations include

³ 21 U.S.C. § 387g(a)(3)(A)-(B).

⁴ Letter from James E. Dillard, Senior Vice President, Altria Client Services, Inc., to Lawrence R. Deyton, M.D., M.S.P.H., Director, Center for Tobacco Products, U.S. Food and Drug Administration (Jan. 27, 2011). The University of California San Francisco (UCSF) Legacy Tobacco Documents library contains approximately 11 million publicly-available tobacco industry documents. Over 173,000 documents in the “Philip Morris” collection of that library contain the word menthol. The TPSAC received information based on analyses of a tiny fraction of these documents, only approximately 80 of which purportedly related to PM USA. In preparing these analyses, UCSF staff appear to have apparently selected documents without regard to their context, authorship, currency, true content, or intrinsic scientific value.

⁵ See Bates Document Numbers 2041511968; 1002483819; 2057096413; 2023000218; 2057095502; 2045812301; 2042371833; 2041511968; 2040814402.

⁶ Indeed, sixteen of the cited documents do not even identify their authors. See Bates Document Numbers 2028813524; 2501018276; 2042256026; 2045435898; 2045737946; 2048491303; 2023062878; 2023680852; 2504009076; 2044950973; 2063105812; 2025988759; 2048224025; 2029252228; 2501503404; 2073096785.

⁷ See generally briefing materials from October 7, 2010 meeting of the TPSAC: “Menthol Cigarettes and Smoking Cessation Behavior” at 8-9; “Marketing of Menthol Cigarettes and Consumer Perceptions” at 8; “Potential Health Effects of Menthol” at 18; “Menthol’s Potential Effects on Nicotine Dependence” at 7; “Menthol Sensory Qualities and Possible Effects on Topography” at 8.

information about the study objective, description of the study design, and how data were collected, analyzed and reported.

- Most of the documents reviewed were outdated and the UCSF analyses ignored more recent, reliable data. This presents significant scientific limitations to an inquiry into the current-day impact of the use of menthol in cigarettes on the public health. Of the approximately 80 PM USA documents cited in the UCSF analyses, 72 were more than 15 years old,⁸ and 20 of the documents were authored more than 30 years ago.⁹ These documents do not reflect the current thinking of PM USA specifically, or of the current state of affairs vis-à-vis menthol generally.

Selected historical industry documents should not have played a role in TPSAC's inquiry. They do not aid in understanding the current-day impact of the use of menthol in cigarettes on the public health. Even if an analysis of such documents were appropriate to the TPSAC's charge – which it is not – the process undertaken by UCSF in selecting anecdotal documents purportedly related to PM USA was flawed. The result is the inclusion of and reliance on documents that are not representative of the universe of menthol documents.

II. Targeting

For consumer packaged goods companies like PM USA, the term “targeting” refers to the way in which a consumer goods manufacturer directs its marketing efforts to reach a particular audience. TPSAC acknowledged that targeting is a basic and fundamental aspect of marketing.¹⁰

For PM USA, marketing a particular cigarette brand is targeted to those segments of adult smokers who have shown interest in the brand, as well as adult smokers of competitive brands with similar attributes. PM USA directs communications for its menthol cigarette brands to adult smokers who are interested in menthol cigarettes.

III. Use of Color and Imagery

PM USA uses color and imagery in packaging and advertising for the same reasons that other companies do: trademark colors and imagery communicate to adult consumers brand and product distinctions in an efficient and effective manner. The use of color and imagery differentiate products in the marketplace, and is constitutionally protected commercial speech. As discussed

⁸ See Bates Document Numbers 1001811426; 1002483819; 2042789367; 1003700764; 2022211023; 1003293355; 1000352160; 2042506843; 2023780305; 1002646151; 2062951249; 1002480974; 1002478682; 2044219555; 2501018276; 2049455309; 1000035986; 2058122435; 1000385226; 2023780237; 1000793283; 2040214488; 1000800650; 2058037687; 1003723688; 20519902170; 2040333014; 2042256026; 2024941088; 2045300800; 2045435898; 25052350055; 2063105829; 2022945953; 2023177501; 2045737946; 2023062285; 2048491303; 2022203430; 2023062580; 2031466749; 2023062681; 2022167545; 2028813524; 2024475617; 2023148679; 2023069480; 2028817004; 2029082255; 2024059422; 2024059406; 2024847429; 2023062895; 2023680852; 2023062878; 2023062962; 2023105127; 2031421329; 2504009076; 2028817734; 2057096413; 2023000218; 2044950973; 2057095502; 2042371833; 2025986845; 2023160346; 2063105812; 2025988759; 2048224025; 2045812301.

⁹ See Bates Document Numbers 1001811426; 1002483819; 2042789367; 1003700764; 2022211023; 1003293355; 1000352160; 2042506843; 2023780305; 1002646151; 2062951249; 1002480974; 1002478682; 2044219555; 2501018276; 2049455309; 1000035986; 2058122435; 1000385226; 2023780237.

¹⁰ Comments of Dr. Melanie Wakefield, March 2, 2011 TPSAC Meeting.

in detail in prior submissions, FDA must respect Congress's determination that informed adult consumers have the right to use tobacco products and they have the right to receive information related to those products.¹¹ FDA should recognize the role of responsible marketing and advertising practices tailored to current adult cigarette smokers.

IV. Risk Perception

A variety of factors affect an adult smoker's cigarette brand choice, including the choice of menthol cigarette brands. These factors vary from smoker to smoker. In light of the variety of factors affecting brand choice, it is impossible to conclude that any single factor dominates the brand choice of those smokers who choose a particular brand. Taste preference, however, is an important factor in an adult smokers' brand choice.

Several published studies confirm the importance of taste preferences for both menthol and non-menthol adult smokers. Some adult smokers prefer the taste of menthol while other do not. Allen and Unger reported that, "Nearly equal proportions of menthol smokers (49%) and non-menthol smokers (45%) reported taste as their major motivation for choosing their cigarette type."¹² A 2010 study also reported preference for menthol taste was highest among menthol smokers, followed by those who smoked both menthol and non-menthol cigarettes and was lowest for non-menthol smokers.¹³ We include additional detail about these studies in Appendix Table B-9.

Studies also show the influence of parental, extended family and social networks on adult smokers' choice of menthol cigarette brands. Among adult African-American smokers, women reporting that their mothers and fathers smoked menthols were more likely to smoke menthols.¹⁴ In addition, men and women who endorsed the statement that "most African-American smokers smoke menthols" had higher odds of smoking menthol as compared to non-menthol cigarettes.¹⁵ Studies have also reported that adult African-American menthol smokers (41%) were more likely than Whites (18%) to endorse, "My friends that smoke, smoke menthol cigarettes."¹⁶ Exclusive menthol smokers, and those who smoke both menthol and non-menthol cigarettes, are more likely to have menthol smokers in their current social network as compared to exclusive non-menthol smokers.¹⁷

With respect to risk perception, several studies have examined consumer perceptions of risks of menthol cigarettes, both overall and in subpopulations. The literature shows that most consumers perceive menthol cigarettes as equally or more harmful than non-menthol cigarettes. A 2010 quantitative study among a national sample of over 4,500 adults found that "few adults (0.6%), including smokers, perceived menthol cigarettes to be less harmful than non menthol

¹¹ See PM USA Submissions to FDA: December 22, 2009, Docket No. FDA-2009-N-0294 (1996 Rule); February 18, 2010, Docket No. FDA-2009-N-0020 (Use of Marketing Descriptors to Convey Modified Risk); January 11, 2011, Docket No. FDA-2010-N-0568 (Required Warnings for Cigarette Packages and Advertisements).

¹² Allen & Unger (2007).

¹³ Unger et al. (2010).

¹⁴ Allen & Unger (2007).

¹⁵ Allen & Unger (2007).

¹⁶ Hymowitz et al. (1995).

¹⁷ Unger et al. (2010).

cigarettes.”¹⁸ This study also reported 12.6% thought menthol cigarettes were more harmful than non-menthol cigarettes.¹⁹ In another 2010 quantitative study, the authors concluded, “few menthol smokers (2.4%) and survey respondents overall (4.0%) believed menthol cigarettes to be less risky than non-menthol cigarettes. In contrast, 30.2% of menthol smokers and 25.9% of all respondents (including nonsmokers) believed menthol cigarettes to be more risky than non-menthol cigarettes.”²⁰ Overall, about 70% of both groups believed that menthol and non-menthol cigarettes have the same risk. Over one-third of African Americans and almost half of 18-24 year-olds in this study believed menthol cigarettes were riskier than non-menthol. In the study’s multivariate analysis, overall, menthol smokers, non-menthol smokers and former smokers (as compared to never smokers) all had significantly higher odds of believing menthol cigarettes were more risky than non-menthol cigarettes. Among current smokers, African Americans and 18-24 year olds had significantly higher odds of believing that menthol cigarettes were more risky as compared to White smokers and smokers ≥ 65 years of age, respectively.

A qualitative study reported similar findings for menthol cigarettes being generally perceived as the same or more harmful than non-menthol cigarettes.²¹ In focus groups with smokers between the ages of 18-22 years of age, African Americans and non-Hispanic Whites perceived menthol cigarettes as having “the same risk” or to be “more harmful” than non-menthol cigarettes.

An additional study found that more than 90% of White and African-American smokers disagreed with the statement that “menthol cigarettes are better for you than regular non-menthol cigarettes.”²²

The scientific evidence does not support a conclusion that menthol cigarettes are perceived as less harmful. Further, this evidence is counter to the conclusion in the TPSAC Report. The disconnect between what the evidence shows and what the TPSAC concluded may be due to the fact that TPSAC approached the question in a non-scientific, non-objective way. By asking, “what health reassurances were/are used in menthol marketing messages?”²³, the TPSAC assumed that there are health reassurances and essentially assured that its conclusion on risk perception would focus on historical documents and marketing practices. By failing to meaningfully differentiate between past and present, TPSAC’s flawed approach resulted in speculation about “implicit claims,” “oblique references to health,” “coded messages,” and “verbal cues.” It also led to further speculation that TPSAC could dismiss recent findings of peer-reviewed surveys – in which respondents overwhelmingly responded that menthol cigarettes are not less harmful – simply because “it is uncommon to state an explicit belief that

¹⁸ Davis et al. (2010).

¹⁹ Davis et al. (2010).

²⁰ Wackowski et al. (2010).

²¹ Ritcher et al. (2006).

²² Hymowitz et al. (1995).

²³ See TPSAC Report, *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, Chapter 5, available online at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pdf>

menthol cigarettes are safer...”²⁴ Such speculation is not an adequate scientific base on which to establish regulatory policy.

²⁴ See TPSAC Report, *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*, Chapter 5, at 41, available online at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pdf>

Chapter 4. Assessment of Countervailing Effects

PM USA provided a lengthy, detailed and well-sourced written report to TPSAC and FDA,¹ summarizing the potential countervailing effects of a ban on menthol cigarettes. That report demonstrates that radical regulatory action, such as eliminating menthol in cigarettes, would be certain to trigger a series of lasting and severe unintended consequences and other countervailing effects detrimental to public health and to society. Given the comprehensive treatment of this issue in our previous submission, we refer FDA there, and make some additional comments below.

First, a recent U.S. Government Accountability Office report underscored that numerous incentives for, and manifestations of, contraband activity exist within the current tobacco regulatory environment.² Additionally, many other stakeholders similarly provided information to TPSAC demonstrating the existence of global contraband and counterfeit market that has the capacity to supply the U.S. market with illicit menthol cigarettes should the opportunity be created for them.

Second, Executive Orders require that FDA consult with other government authorities when determining when and how to discharge their regulatory functions. In particular, federal agencies like FDA must: (i) “seek views of appropriate State, local, and tribal officials before imposing regulatory requirements that might significantly or uniquely affect those governmental entities,” where feasible; (ii) assess the effects of such regulation on State, local, and tribal governments, “including specifically the availability of resources to carry out those mandates,” (iii) “seek to minimize those burdens that uniquely or significantly affect such governmental entities,” and (iv) “avoid regulations that are inconsistent, incompatible, duplicative with... those of other Federal agencies.”³ President Obama recently reaffirmed these requirements in ordering that

- regulations be based, in part, on the open exchange of information and perspectives of state, local, and tribal officials;
- before issuing a notice of proposed rulemaking, each agency, where feasible and appropriate, seek the views of those who are likely to be affected; and
- each agency attempt to promote greater coordination across agencies in developing regulatory actions.⁴

Third, in conjunction with any “significant regulatory action,”⁵ FDA would have to undertake a cost-benefit analysis, including “an explanation of the manner in which the regulatory action

¹ *Countervailing effects of a ban on menthol cigarettes*, prepared and submitted by ALCS on behalf of PM USA, December 30, 2010.

² GAO (2011).

³ Exec. Order No. 12,866, 58 Fed. Reg. 51,735, at §§ 1(b)(9), (10) (Oct. 4, 1993) (emphasis added).

⁴ Exec. Order No. 13,563, 76 Fed. Reg. 3,821, at §§ 1-3 (January 18, 2011). Such consultation is of course consistent with and contemplated by the FSPTCA itself. See §§ 907(a)(6), (b)(2) (requiring FDA to consider “information concerning the countervailing effects of [a] tobacco product standard... such as the creation of a significant demand for contraband,” while also providing that in carrying out its duties FDA “shall endeavor” to consult with, and utilize technical support of, other federal agencies, and invite participation by “informed persons”).

...avoids undue interference with State, local, and tribal governments in the exercise of their government functions.”⁶ Where such regulatory action will have an annual effect on the economy of at least \$100 million or adversely and materially affect the economy, a sector of the economy, productivity, competition, jobs, the environment, public health, or state, local, or tribal governments, FDA must conduct an in-depth “regulatory analysis” that entails an “assessment, including the underlying analysis, of costs anticipated from the regulatory action (such as ...the direct cost to the government in administering the regulation...)” and “a quantification of those costs.”⁷

To accomplish the required cost-benefit analyses, FDA would need to engage with the federal, state, and local government entities, including law enforcement, which would be impacted by any increase in the illicit market.⁸ These entities are in a better position than FDA to understand their current budgetary and resource constraints and to evaluate their ability to manage added pressure on their resources.⁹

Consequently, FDA should not propose any rule to eliminate or otherwise restrict menthol in cigarettes without first (i) consulting with law enforcement and other relevant government authorities on the extent of the existing contraband market, and (ii) obtaining their assurances that they have the resources and capacity to respond to a substantial increase in contraband, as would be anticipated. FDA would need to conduct this consultation openly, publicly, and transparently¹⁰ across the spectrum of relevant government stakeholders. At the federal level, FDA would need to consult with, at minimum, the Alcohol and Tobacco Tax and Trade Bureau, the Bureau of Alcohol, Tobacco, Firearms, and Explosives, the Federal Bureau of Investigation, U.S. Customs and Border Protection, Immigration and Customs Enforcement, and the United

⁵ “Significant regulatory action” is defined as “any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of \$100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities; (2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) Materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) Raise novel legal or policy issues arising out of legal mandates, the President’s priorities, or the principles set forth in this Executive order.” Exec. Order No. 12,866 at § 3(f).

⁶ *Id.* § 6(a)(3)(B).

⁷ *Id.* § 6(a)(3)(C).

⁸ See GAO (2011) regarding identification of potentially relevant stakeholders and subject matter experts.

⁹ See OMB Circular A-4, at 3 (September 17, 2003) (“As you design, execute, and write your regulatory analysis, you should seek out the opinions of those who will be affected by the regulation... Consultation can be useful in ensuring that your analysis addresses all of the relevant issues and that you have access to all pertinent data. Early consultation can be especially helpful. You should not limit consultation to the final stages of your analytical efforts.”)

¹⁰ See Exec. Order No. 13,563 at § 2 (“Regulations shall be adopted through a process that involves public participation. To that end, regulations shall be based, to the extent feasible and consistent with law, on the open exchange of information and perspectives among State, local, and tribal officials, experts in relevant disciplines, affected stakeholders in the private sector, and the public as a whole.”); Exec. Order No. 12,866 at § 6 (stating that “[e]ach agency shall... provide the public with meaningful participation in the regulatory process” and requiring an agency to make available to the public its cost-benefit assessment and regulatory analysis with respect to a regulatory action).

States Postal Service (International Mail Centers).¹¹ FDA would need similarly to consult with, and obtain assurances from, relevant state and local law enforcement authorities and government officials.¹²

¹¹ As discussed elsewhere in this report and in other submissions, the contraband trade in menthol cigarettes presumably would encompass the failure to pay excise taxes, illicit activity by organized crime, and illegally imported product, and thus implicate the respective jurisdictions of these federal agencies.

¹² Selected examples of state and local law enforcement authorities that we believe, based on our experience, would be significantly affected include: the New York Department of Tax and Finance (Office of Tax Enforcement - Petroleum, Alcohol, Tobacco Bureau), New York City Department of Finance (Office of Tax Enforcement), New York City Sheriff's Office, California Board of Equalization (Investigations Division), Los Angeles Police Department, Los Angeles Sheriff's Office, Los Angeles City Attorney's Office, Illinois Department of Revenue, and the Chicago Police Department.

Chapter 5. Impact of Menthol-Related Regulatory Actions on Public Health and Society

Public health impact is a broad question that must take many considerations into account – not only any population harm that may be shown to be uniquely attributable to menthol cigarettes, but also countervailing effects and unintended consequences of potential regulatory actions concerning menthol cigarettes.

This report provides compelling evidence that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted by the science and evidence.

Further, the U.S. government recently considered the question of banning menthol cigarettes and came to the same conclusion. In a recent World Trade Organization submission, the U.S. government stated its plain and unambiguous conclusion that banning menthol cigarettes is not appropriate to protect public health:

147. Further, the level at which the United States considers is appropriate to protect public health is to eliminate from the market, not simply restrict access to, those products that are disproportionately used by young people, but not to eliminate from the market those products to which tens of millions of adults are addicted, and whose precipitous withdrawal from the market may cause negative consequences. This level is reflected in section 907(a)(1)(A). Members are entitled to choose for themselves which policy objectives they wish to pursue and the levels at which they wish to pursue them.

148. The means by which section 907(a)(1)(A) fulfils its legitimate objective is to ban products that are disproportionately used by young people while not banning products to which tens of millions of adults are addicted. Specifically, in only prohibiting those products that serve as “trainer” cigarettes for young smokers and which are not regularly used by adult smokers, namely cigarettes with characterizing flavors that appeal to young people, while not prohibiting those products to which tens of millions of adults are addicted, namely menthol and tobacco cigarettes, section 907(a)(1)(A) fulfills its objective to reduce youth smoking while avoiding the potential for negative public health consequences that might be associated with banning cigarettes to which tens of millions of adults are addicted.¹

As FDA begins to review the available science and evidence related to menthol cigarettes, it could consider the potential utility of a model to examine public health impact. However, the model in the TPSAC Report is insufficient for this purpose. First, the model is preliminary and has not been rigorously tested, published, or peer-reviewed; its validity in terms of robustness and reliability, therefore, is unknown. Second, the model relies on data inputs that have not been

¹ U.S. WTO (2011) (emphases added); *see also id.* at ¶ 172.

sufficiently validated. For example, one input parameter, the 1.68 ratio of “menthol experimenters that become established smokers to that for non-menthol smokers” was said to be not statistically significant by one of the TPSAC members.² Further, this ratio was generated from an analysis which included only 12 African Americans; this is unlikely to be representative of the U.S. population. Finally, the model is incomplete. It is a static model, not a dynamic model, and does not consider other mitigating external factors. As pointed out in NCI Monograph 18, “understanding of public health issues has evolved from simple cause-and-effect studies to complex models that involve feedback and evolving behavior.”³ This is lacking in the model. In its present state, the model cannot provide the basis for FDA to make science and evidence-based decisions about menthol.⁴

² Comments of Dr. Dorothy Hatsukami, March 17, 2011 TPSAC Meeting.

³ NCI (2007).

⁴ Another model funded by the American Legacy Foundation, a special interest group that wants to ban menthol cigarettes on a policy basis, is similarly deficient. A cursory description of the Legacy model was presented to the TPSAC during the open public session of the March 2, 2011 TPSAC meeting. From that description, it seems clear that the Legacy model does not consider the impact of a ban on the black market or other countervailing effects and unintended consequences. Greater transparency and the disclosure of additional information are needed so that stakeholders can assess the Legacy model more completely. *See* Presentation by Dr. David Levy to the TPSAC, February 10, 2011.

Chapter 6. Considerations for FDA

The science and evidence demonstrate that regulatory actions or restrictions related to the use of menthol in cigarettes are not warranted.

That said, we are of course aware of the ongoing debate respecting issues of menthol cigarettes and offer some closing perspectives to contribute constructively to the Agency's consideration of these issues. In doing so, we are guided by several principles, including

- an appreciation of and respect for FDA's mission and obligations under the Act;
- our uncompromising commitment – a commitment we know that FDA shares – to support the evaluation of tobacco regulatory policy solely on the best available science and evidence, not outcome-driven advocacy; and
- respect for Congress's determination that informed adult consumers have the right to use tobacco products – and respect for the choices that those adult consumers make.

Those principles suggest the following considerations.

First, while the available science and evidence taken as a whole demonstrate that there is no unique effect of menthol on harm, there may be areas where additional research might usefully be pursued. There appears to be, for example, some consensus that research on whether menthol uniquely affects smoking initiation could be more robust, including on the question of underage smoking. PM USA is opposed to any underage smoking of cigarettes, menthol or non-menthol, and has for many years taken multiple actions, including supporting research, to contribute to reducing underage smoking. FDA may consider whether additional research in that regard would further contribute to better understanding this complex phenomenon. We renew our previously communicated offer to partner with FDA on responsible, science-based initiatives to reduce underage smoking – an objective we share.

Second, the Agency could consider possible actions to further ensure that adult smokers are fully informed respecting menthol in cigarettes. For example, PM USA does not add menthol to its cigarettes except in its brands labeled as such, and FDA could consider whether it should require all cigarette manufacturers to similarly label any brand to which menthol is added, whether currently marketed as a menthol cigarette or not.

In a similar regard, we note that FDA has authority under 15 U.S.C. § 1333(d)¹ to revise, through rulemaking, the text of cigarette warning labels “if the Secretary finds that such a change would promote greater public understanding of the risks associated with the use of tobacco products.” Although no menthol-specific warning would be warranted by the scientific evidence available today, FDA has the authority to consider such an approach if new and contrary evidence were to emerge.

Third, the TPSAC process has produced some discussion of adult smoker perceptions of menthol cigarettes, including whether these consumers perceive that menthol cigarettes present less of a health hazard than non-menthol cigarettes. The evidence is quite clear: they do not. Nonetheless, we observe that FDA has announced its intention to develop and disseminate public education campaigns designed to decrease initiation of tobacco use and to launch a tobacco

¹ 15 U.S.C. Section 1333(d) (2010).

health literacy program targeted at various populations. FDA could consider whether such campaigns and programs would be appropriate ways to address concerns about consumer perceptions that are supported by the science.

Fourth, and related to adult smoker perceptions, we urge FDA to weigh very carefully the impact of any menthol-specific actions it might consider. Such actions might suggest to, or be understood by, adult smokers to mean that *non-menthol* cigarettes are somehow less hazardous than menthol cigarettes. That erroneous conclusion could provoke its own unintended contributions to individual and population harm.

Finally, it is worth remembering that the Act has been in place for less than two years and that FDA is still implementing substantial provisions that are bringing sweeping changes to the tobacco industry, from manufacturing to retail. These provisions provide ample opportunity for FDA to undertake an overall approach to reducing the harm from cigarette smoking and, in doing so, address any concerns respecting menthol cigarettes. We urge FDA to give these provisions an opportunity to achieve their intended purposes before proposing further or supplemental - and possibly countervailing - steps.

We appreciate the opportunity to submit this Report to the FDA and look forward to continued engagement with the Agency on this issue.

Appendices

Appendix A. Scientific Reference List

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Appendix B. Summary of Studies Tables

Appendix Table B-1. Summary of Epidemiological Studies Comparing Smoking-Related Health Effects Among Menthol vs. Non-Menthol Cigarette Smokers

| Study Authors, Year, Page No. | Health Outcome Investigated | Study Design | Number of Subjects | Authors Conclusions |
|--------------------------------|--|--------------|--------------------------------------|--|
| Hebert & Kabat, 1988, p. 986 | Esophageal cancer | Case-control | Cases = 312 Controls = 462 | "We analyzed existing data from a case-control study of esophageal cancer and found no menthol effect." |
| Hebert & Kabat, 1989, p. 41 | Esophageal cancer | Case-control | Cases = 311 Controls = 462 | "Our results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer." |
| Kabat & Hebert, 1991, 6511 | Lung cancer | Case-control | Cases = 1,044 Controls = 1,324 | "Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types of lung cancer in this study." |
| Kabat & Hebert, 1994, p. 183 | Oropharyngeal cancer | Case-control | Cases = 276 Controls = 1,265 | "These results indicate that use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer." |
| Sidney et al., 1995, p. 727 | Lung cancer | Cohort | Menthol: 3,654 Non-menthol: 8,107 | "This study suggests that there is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers." |
| Friedman et al., 1998, p. 202 | Upper aerodigestive, pancreas, renal, urinary tract, uterine cervix, and all smoking related cancers | Cohort | Menthol: 3,654 Non-menthol: 8,107 | "Risk was not increased among persons who currently smoked mentholated compared with plain cigarettes for all of the non-lung smoking related cancers combined or for most sites studies." |
| Carpenter et al., 1999, p. 114 | Lung cancer | Case-control | Cases = 337 Controls = 478 | "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." |
| Brooks et al., 2003, p. 609 | Lung cancer | Case-control | Cases = 643 Controls = 4,110 | "The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking non-menthol cigarettes." |
| Stellman et al., 2003, p. 294 | Lung cancer | Case-control | Cases = 3,448 Controls = 8,151 | "Smokers of menthol flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands." |
| Jockey et al., 2004, p. 33 | Lung cancer | Case-control | Cases = 1,004 Controls = 1,004 | "The present study gives no indication for an additional risk of ever smoking menthol cigarettes if total amount of smoking is taken into account." |

| Study Authors, Year, Page No. | Health Outcome Investigated | Study Design | Number of Subjects | Authors Conclusions |
|--------------------------------|--|---------------------------|--------------------------------------|--|
| Pletcher et al., 2006, p. 1919 | Coronary calcification, pulmonary function decline | Longitudinal, prospective | Menthol: 972 Non-menthol: 563 | "Although the present study does not rule out a difference in thrombosis or other non-atherosclerotic mechanisms leading to coronary events, we found no evidence that it plays a role in coronary heart disease disparities between African-Americans and European Americans." "Menthol seems unlikely to be a contributor to the pulmonary function decline associated with tobacco smoke exposure." |
| Murray et al., 2007, p. 101 | Mortality from coronary heart disease, cardiovascular disease, lung cancer, and all causes | Prospective | Menthol: 1,216 Non-menthol: 4,665 | "We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking." |
| Etzel et al., 2008, p. 261 | Lung cancer | Case-control | Cases = 491 Controls = 497 | "In our analysis, we observed no significant risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes (OR range, 0.69-0.99) and our data suggested a possible protective effect of mentholated cigarettes for current smokers." |

Appendix Table B-2. Summary of Studies Related to the Question of Average Daily Exposure

| Studies that Provide a Direct Measurement of Average Daily Exposure | | | | |
|---|------|---|---|---|
| Study Authors | Year | Subjects & Methods | Outcome(s) | Strengths and Limitations |
| Wagenknecht L.E., et al. | 1990 | 1,424 subjects Included White and Black men and women (age 18-30) who smoked at least 5 cigarettes per week [from the CARDIA Study]; Recruited from 4 urban areas: Birmingham, AL; Chicago, IL; Minneapolis, MN; Oakland, CA | Serum cotinine – some analysis of the effect of menthol was made (perhaps suggesting that menthol was associated with higher exposure (see last paragraph in results section)) but no direct statistical analysis was reported. | This study was focused on the question of racial differences in exposure. A number of linear models were evaluated, however none of these models had menthol as a significant factor suggesting that either this was not significant or not included in the model Authors acknowledge metabolic differences could be a potential confounder for exposure. |
| Clark, P.I., et al. | 1996 | 161 subjects Included non-Hispanic black and non-Hispanic white men and women (age 18-45) who smoked at least 5 cigarettes per day. [37 black women, 28 black men, 50 white women and 46 white men (83.1 % of blacks smoked menthol and 22.9 % of whites smoked menthol)]; Recruited through advertising and personal contact (appears to be in southern Florida) One week in ambulatory setting and a laboratory smoking at the end (serum cotinine was measured in the laboratory setting) | Serum Cotinine – statistically significantly higher in menthol smokers (~35% increase using unadjusted values); also higher in a model which adjusted for race, CPD and the mean amount of each cigarette smoked. | Subjects smoked in a natural setting prior to collecting baseline blood sample. Although the authors determined the machine measured nicotine content of the cigarettes (which is relates to machine measured tar yield) this factor was not included in the model. |

| Studies that Provide a Direct Measurement of Average Daily Exposure | | | | |
|---|------|--|---|--|
| Study Authors | Year | Subjects & Methods | Outcome(s) | Strengths and Limitations |
| Ahijevych, K., et al. | 1996 | <p>37 subjects</p> <p>Included only black and white women who smoked 20 or less CPD; (18 black and 19 white; 8 of 18 blacks smoked menthol and 10 of 19 whites smoked menthol)</p> <p>Recruited for a study on cigarette smoking through advertisement. (appears to be in the central Ohio area)</p> <p>Ambulatory setting with laboratory visit to collect blood for baseline measure of cotinine; blood was collected one minute before a subject smoked (other measures were made after smoking).</p> | <p>"Baseline cotinine was nonsignificantly higher in nonmenthol smokers compared to menthol smokers (254 ng/ml and 204 ng/ml, respectively).</p> | <p>Small sample size and only women limit generalization of results to a larger population. It was not clear whether the mean values provided were LS means or Arithmetic means, and no measure of variability was provided.</p> |
| Ahijevych and Parsley | 1999 | <p>95 subjects</p> <p>Included only black and white women; (48 black and 47 white; "about one half of each ethnic group preferring menthol cigarettes")</p> <p>Recruited through advertisement. (appears to be in the central Ohio area), stratification for ethnicity and menthol/nonmenthol preference.</p> <p>Ambulatory setting with laboratory visit to collect blood for baseline measure of cotinine</p> | <p>"Menthol smokers had higher cotinine levels (239 vs. 189 ng/ml, $p=.020$)..."</p> <p>"There were no significant interaction effects of ethnicity and menthol preference on smoke constituent exposure."</p> | <p>Study of only women limits generalization of results to a larger population.</p> |
| Mustonen, T. K. et al. | 2005 | <p>307 subjects</p> <p>Included White and Black men and women who smoked at least 10 CPD (256 White and 51 Black) (51.5% Women)</p> <p>Recruitment was for a smoking cessation treatment trial in the Boston area</p> | <p>Salivary cotinine –</p> <p>Unadjusted univariate analysis showed nonstatistically significant higher levels in menthol smokers (476.9 ± 218.7 ng/ml) than nonmenthol smokers (441.9 ± 197.3 ng/ml).</p> <p>Results from a GLM ANCOVA factorial model found a significant (gender X cigarette type) and a (gender X race X cigarette type) interaction.</p> | <p>These subjects were characterized as being "motivated to quit".</p> <p>The authors acknowledge that metabolism is an important factor that needs to be taken into consideration.</p> |

| Studies that Provide a Direct Measurement of Average Daily Exposure | | | | |
|---|------|--|--|---|
| Study Authors | Year | Subjects & Methods | Outcome(s) | Strengths and Limitations |
| Williams, J.M., et al. | 2007 | <p>142 subjects</p> <p>Included men and women 89 were outpatients with schizophrenia or schizoaffective disorder and 53 were without schizophrenia</p> <p>Blood sample taken in the afternoon of a "normal smoking day" 2 minutes after smoking a cigarette</p> <p>Recruitment was into a smoking cessation trial or studies of nicotine levels in smokers with schizophrenia.</p> | <p>Serum cotinine – significantly higher in menthol smokers (294.3 ± 172.2 vs. 239.8 ± 121.2ng/ml, respectively).</p> <p>ANOVA adjusted for schizophrenia, CPD and race/ethnicity).</p> | <p>Most subjects had schizophrenia and some were part of a smoking cessation trial making generalization to the larger population questionable.</p> <p>Demographic characteristics including smoking history were not provided.</p> |
| Muscat, J. E., et al. | 2009 | <p>147 – 500 subjects</p> <p>Included men and women and Blacks and Whites.</p> <p>Blood and urine samples were collected in the morning after an overnight fast and abstinence from smoking.</p> <p>Smokers of at least five CPD were recruited into a "community-based cross sectional study on cigarette smoke metabolism" in Westchester County, NY.</p> | <p>Plasma cotinine (481 Subjects)</p> <p>Urinary Cotinine (500 Subjects)</p> <p>Thiocyanate (394 subjects)</p> <p>NNAL+NNAL-Gluc (147 Subjects)</p> <p>No statistically significant differences between menthol and nonmenthol for any of the biomarkers levels.</p> <p>Adjustment was made for age, BMI, CPD, race and sex (in all subjects model).</p> | <p>Biomarkers were collected after overnight smoking abstinence.</p> <p>Relatively imbalanced groups, Black Menthol n=237, black non-menthol n=33.</p> |
| Signorello, L. B., et al. | 2009 | <p>264 subjects</p> <p>This was a subset of male and female smokers from the Southern Community Cohort Study. Subjects were 40-79 years of age. The study subset was balanced for race and sex.</p> | <p>Serum cotinine – no statistically significant effect of menthol. The statistical model adjusted for a number of factors "believed to influence nicotine or cotinine metabolism."</p> | |
| Heck, J.D. | 2009 | <p>112 subjects</p> <p>Included males or females;(54 menthol smokers; 31 white and 23 black);58 nonmenthol smokers; 53 white and 5 black)</p> <p>Ad lib smoking for one week of menthol or nonmenthol cigarettes in the 9-10 mg tar range (FTC);2 24-h urine collections, COHb determined at 2:30 PM during clinic visit</p> | <p>COHb - no difference between menthol and nonmenthol</p> <p>Nicotine Equivalents - no difference between menthol and nonmenthol</p> <p>Total NNAL - no difference between menthol and non menthol</p> | <p>Smoking was in a natural setting. Nicotine equivalents from a 24 h urine sample provides the most direct way of measuring average daily smoke exposure.</p> |

| Studies that Provide a Direct Measurement of Average Daily Exposure | | | | | |
|--|------|--|---|--|--|
| Study Authors | Year | Subjects & Methods | Outcome(s) | Strengths and Limitations | |
| Wang, J., et al. | 2010 | 3,341 subjects Included males and females who smoked at least one cigarette per day; [1044 menthol smokers (448 African-American) and 2297 non-menthol smokers (166 African American)] Multicenter (sites in many of the lower 48 states) cross sectional study. | Nicotine Equivalents (24 h urine) - no difference between menthol and non-menthol Serum Cotinine - no difference between menthol and non-menthol COHb - no difference between menthol and non-menthol | Large number of participants from a wide geographical distribution in the U.S. Large number of African-American non-menthol smokers makes possible an analysis of race/ethnicity and is likely more representative of the US population than other studies in this table. Smokers were in a natural setting. Nicotine equivalents from a 24 h urine sample provides the most direct way of measuring average daily smoke exposure. | |
| Chapter 4 of PM USA June 30, 2010 Submission to FDA ¹ | 2010 | 3,341 subjects Included males and females who smoked at least one cigarette per day; [1044 menthol smokers (448 African-American) and 2297 non-menthol smokers (166 African American)] Multicenter (sites in many of the lower 48 states) cross sectional study. | Total NNAL – no difference between menthol and non-menthol | Large number of participants from a wide geographical distribution in the U.S. Large number of African-American non-menthol smokers makes possible an analysis of race/ethnicity and is likely more representative of the U.S. population than other studies in this table. Smokers were in a natural setting. | |

¹ Data from the TES was provided to FDA

| Studies that Provide a Direct Measurement of Average Daily Exposure | | | | |
|---|------|--|---|--|
| Study Authors | Year | Subjects & Methods | Outcome(s) | Strengths and Limitations |
| Benowitz, N.L., et al. | 2010 | 127 subjects Included men and women cigarette smokers (at least 10 CPD) (age 18-65) from the general population (appears to be the San Francisco, CA area), all subjects were non-Hispanic Whites or African-Americans. | Plasma cotinine – No statistically significant difference in univariate analysis (Table 1) Spot urinary nicotine equivalents – significantly lower in menthol than regular smokers in univariate analysis (Table 1) Urine NNAL - No statistically significant difference in univariate analysis (Table 1) Urine total PAHs - -- significantly lower in menthol than regular smokers in univariate analysis (Table 1) In a multiple regression model which used a biomarker of menthol exposure included a measure for nicotine exposure, menthol did not have a significant effect. | Unique in conducting an analysis of menthol exposure using biomarkers. |
| Xia, Y., et al. | 2011 | 1,373 subjects Included men and women (age 12 and up) who were smokers based on serum cotinine measurement from the NHANES study. | Urinary total-NNAL – Based on multivariate regression analysis the authors concluded: "Although NNAL concentrations among menthol smokers were lower than those among non-menthol smokers, the difference did not achieve statistical significance (p=0.095)." | Large nationally representative sample. |

CO, carbon monoxide; COHb, carboxyhemoglobin; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; PAH, polycyclic aromatic hydrocarbon; TPM, total particulate matter

Appendix Table B-3. Summary of Studies Concerning Toxicity

| Smoke Chemistry | | | | | |
|--|--------------|---|---|---|---|
| Study Authors | Year | Methods | Test Cigarettes | Outcome(s) | Strengths and Limitations |
| Rustemeier et al. Carmines (provides general information) | 2002 2002 | 51 mainstream smoke constituents were measured using standard ISO smoking conditions | Cigarettes contained 2, 5 (Group 2) and 18,000 ppm menthol (Group 3). The focus of this analysis was on results from Group 3. | With respect to Group 3 the authors conclude: "Relative to the TPM yield (Fig. 3), the main changes, which were all ingredient level-dependent, were the increase in formaldehyde (low level: 30%; high level: 42%), resorcinol (low level: 23%; high level: 45%) and lead (high level: 13%). For most of the other compounds, decrease of 10-20% was observed and, a stronger decrease was observed for naphthalene (low level: 31%, high level: 36%) and for N-nitrosoamines (26-37%)." | Menthol was added to test cigarettes as part of a mixture of ingredients. Study conducted under GLP. |
| Baker et al. | 2004 | 45 mainstream smoke constituents were measured using standard ISO smoking conditions | Test cigarettes contained 23,400 ppm menthol. The focus of this analysis was on results from Group B4. | Phenol, m- + p-cresol and o-cresol were significantly lower in B4 than control (p. S71) and there were no statistically significant increases. Most of the changes for all test cigarettes relative to control were between 85% and 115% (Table 6). | Menthol was added to test cigarettes as part of a mixture of ingredients. |
| Heck (Appendix A) | 2010 | Mainstream smoke constituents (including about 25 chemicals, free radicals, and non-specific assessment of chromatographic peaks) were measured using standard smoking conditions (former FTC conditions) | Test cigarettes contained 103,000 ppm menthol | The author stated: "In conclusion, the addition of menthol to cigarettes did not meaningfully alter smoke chemistry in a manner consistent with an expectation of increased risk to health compared with similar cigarettes without added menthol." | Test and control cigarettes differed only by the addition of menthol. |

| in vitro biology | | | | | |
|--|--------------|--|---|---|---|
| Study Authors | Year | Methods | Test Cigarettes | Outcome(s) | Strengths and Limitations |
| Roemer et al. Carmines (provides general information) | 2002 2002 | Ames mutagenicity (5 tester strains \pm S9) (test material was TPM collected by impaction trap); Cytotoxicity (BALB/c - 3T3 cells and Neutral Red) (test material was TPM collected on glass fiber filters and gas/vapor phase trapped in PBS) Cigarette smoke was generated using standard ISO smoking conditions. | Cigarettes contained 2, 5 (Group 2) and 18,000 ppm menthol (Group 3). The focus of this analysis was on results from Group 3. | No statistically significant different results between cigarettes with and without menthol for any of the <i>in vitro</i> tests reported. | Menthol was added to test cigarettes as part of a mixture of ingredients. Study conducted under GLP. |
| Baker et al. | 2004 | Ames mutagenicity (5 tester strains \pm S9); Micronucleus assay (V79 cell line); Cytotoxicity (V79 Cells and Neutral Red) TPM from cigarette smoke was collected on a Cambridge filter pad. | Test cigarettes contained 23,400 ppm menthol. The focus of this analysis was on results from Group B4. | No statistically significant different results between cigarettes with and without menthol were observed for any of the <i>in vitro</i> tests reported. | Menthol was added to test cigarettes as part of a mixture of ingredients. |
| Heck (Appendix B) | 2010 | Ames mutagenicity (5 tester strains \pm S9); Sister Chromatid Exchange (CHO cells); Cytotoxicity (Neutral Red in CHO cells) Smoke particulate material was the test article. | Test cigarettes contained 103,000 ppm menthol | No statistically significant differences in results between cigarettes with and without menthol for any of the tests. | Test and control cigarettes differed only by the addition of menthol. |

| <i>in vivo biology</i> | | | | | | |
|---|--------------|--|--|---|--|--|
| Study Authors | Year | Methods | Test Cigarettes | Outcome(s) | Strengths and Limitations | |
| Vanscheeuwick et al. Carmines (provides general information) | 2002 2002 | 90-day cigarette smoke nose-only inhalation study in male and female Sprague-Dawley rats Cigarette smoke was generated using ISO standard conditions. | Cigarettes contained 2, 5 (Group 2) and 18,000 ppm menthol (Group 3). The focus of this analysis was on results from Group 3. | No toxicologically significant differences in outcomes between cigarettes with and without menthol | Menthol was added as part of a mixture of ingredients. Study conducted under GLP. | |
| Baker et al. | 2004 | 90-day nose-only cigarette smoke inhalation study in male and female Sprague-Dawley rats Cigarette smoke was generated using ISO standard conditions. | Test cigarettes contained 23,400 ppm menthol The focus of this analysis was on results from Group B4 | The authors report: "The response due to tobacco smoke exposure was not distinguishable between the test and control cigarettes, indicating that the presence of the ingredients had made no discernable differences to the type and severity of the treatment-related response." | Menthol was added as part of a mixture of ingredients. Study conducted under GLP. | |
| Gaworski et al. | 1997 | 13-week cigarette smoke inhalation study in male and female Fisher 344 rats. Smoke generated using FTC standards. | Test cigarettes contained 5000 ppm menthol | No biologically relevant differences in outcomes between cigarettes with and without menthol | Menthol was added as part of a mixture of ingredients. | |
| Gaworski et al. | 1998 | 13-week cigarette smoke inhalation study in male and female Fisher 344 rats. Smoke generated using FTC standards. | Test cigarettes contained 5353 ppm of menthol | No biologically relevant differences in outcomes between cigarettes with and without menthol | Menthol was added as part of a mixture of ingredients. | |

| <i>in vivo</i> biology | | | | | |
|--|------|--|---|--|---|
| Study Authors | Year | Methods | Test Cigarettes | Outcome(s) | Strengths and Limitations |
| Gaworski et al. | 1999 | SENCAR mouse skin painting of cigarette smoke condensate. Smoke condensate was generated using FTC methods and a cold trap. | Test cigarettes contained 5353 ppm of menthol | No biologically relevant differences in outcomes between cigarettes with and without menthol | Menthol was added as part of a mixture of ingredients. |
| Toxicity of menthol <i>per se</i> ² | | | | | |
| Study Authors | Year | Methods | Test Cigarettes | Outcome(s) | Strengths and Limitations |
| Jenkins et al. | 1970 | Smoke transfer - chemistry | Analysis of ¹⁴ C-menthol in cigarettes | 98.9% of the radiolabeled activity measured in mainstream smoke was menthol <i>per se</i> | Very specific method to assess menthol fate in a cigarette. Unfiltered cigarettes were used. |
| Belisto et al. | 2008 | Literature review | Not Applicable | Menthol has a low order of toxicity. | |
| Bhatia et al. | 2008 | Literature review | Not Applicable | Menthol has a low order of toxicity. | |

CHO, Chinese hamster ovary; FTC, Federal Trade Commission; GLP, good laboratory practice; ISO, International Organization for Standardization; PBS: phosphate buffered saline; TPM: total particulate matter

² Jenkins et al. (1970) show that menthol transfers intact into cigarette smoke. This finding suggests the value of examining the literature on the toxicology of menthol *per se*. However, this literature is vast and, therefore, we list only two review articles here.

Appendix Table B-4. Summary of Studies Concerning Menthol Smoking and Initiation

| Study Authors, Year | Population/Sample/Design | Suggestive of Decreased Effect on Initiation | Suggestive of Increased Effect on Initiation | Suggestive of No Effect on Initiation |
|------------------------|---|--|--|---|
| Allen & Unger, 2007 | Based on results of cross-sectional survey conducted in 2001 among African American smokers in Los Angeles (n = 432), examined variables associated with menthol vs. non-menthol cigarette use. | | | Age of initiation. Age first smoked was not significantly associated with menthol smoking |
| Cubbin et al. (2010) | Conducted secondary analyses of data from the 2005 National Health Interview Survey (NHIS) and Cancer Control Supplement (CCS) to "determine whether menthol is related to initiation, quantity or quitting..." (p. 32). Respondents were "Black, Hispanic, and white women and men aged 25 - 64 years" (p. 32). The final analytical sample (n = 21,196) included 3,902 current every day smokers and 3,786 former smokers. Note. 2005 NHIS question related to smoking initiation worded to reflect the age at which the person first started to smoke fairly regularly. | | | Age of initiation. Looking at the predicted mean age of initiation among current every day smokers by gender and race/ethnicity, age of smoking initiation did not differ by type of cigarette. |
| DiFranza et al. (2004) | To determine if reaction to the first smoking experience is predictive of future nicotine dependence, 237 7th graders who reported having inhaled on a cigarette were asked to recall their first smoking experience. | | | There were no significant differences in the percentage of respondents who reported irritation, dizziness, relaxation or positive/mixed reactions to their first inhaled cigarette between those who smoked menthol versus non-menthol cigarettes. This also was the case for self-reports of wanting to smoke again in the future. |

| Study Authors, Year | Population/Sample/Design | Suggestive of Decreased Effect on Initiation | Suggestive of Increased Effect on Initiation | Suggestive of No Effect on Initiation |
|-------------------------|--|---|--|--|
| Fernander et al. (2010) | <p>Conducted secondary analyses of data from 2003 and 2006/2007 Tobacco Use Supplement (TUS) to the Current Population Survey (CPS); menthol (vs. non-menthol) cigarette use was the dependent variable in a logistic regression, and potential predictor variables included age of initiation and cigarette purchasing type as well as demographic and other smoking variables. 66,145 adult current smokers completed the survey.</p> <p>Note. 2006 TUS CPS question related to smoking initiation worded to reflect the age at which the person first started to smoking cigarettes fairly regularly.</p> | <p><u>Age of initiation.</u> The results were taken by the authors to suggest that "the longer the delay of initiation, the more likely an individual smoked menthol cigarettes" (p. 42).</p> | | |
| Hersey et al. (2010) | <p>Reviewed earlier research and conducted secondary analyses of data from the 2006 NYTS "to assess the relationship between menthol cigarette use and needing a cigarette within 1 hr after smoking" (p. S136). There were 27,038 students in the 2006 NYTS. Analyses were based on consideration for menthol/non-menthol status (self-described menthol, likely menthol, broad menthol) and smoking status (current smokers; established smokers).</p> | <p><u>Recency of smoking (Middle school smokers).</u> "In the 2006 NYTS, the proportion of middle school smokers whose usual brand was menthol was higher among those who smoked for 1 year or more (54.7%) than among those who smoked for less than a year (42.2%...)" (p. S140).</p> | | <p><u>Recency of smoking (High school smokers).</u> The percentages of high school smokers who reported that their usual brand was menthol "were similar for smokers who had smoked for less than and for more than 1 year (42.8% vs. 43.1%)" (p. S140).</p> <p><u>Reported menthol use by number of cigarettes ever smoked.</u> Hersey et al. segmented respondents into categories based on number of lifetime cigarettes smoked: less than 6, 6-25, 26-99 and 100 or more. In all cases, there was a high degree of overlap in the confidence intervals reported concerning the use of menthol cigarettes (cf., Hersey et al., 2010; p. S142, Table 4).</p> |

| Study Authors, Year | Population/Sample/Design | Suggestive of Decreased Effect on Initiation | Suggestive of Increased Effect on Initiation | Suggestive of No Effect on Initiation |
|------------------------|---|---|---|---|
| Hersey et al. (2006) | Analyzed data from 2000 and 2002 National Youth Tobacco Survey (NYTS) administered to 6th - 12th graders, focusing on students who reported current smoking, usual brand and whether that brand is mentholated. Data from 1,552 menthol smokers and 1,650 non-menthol smokers were included in the main analyses. Observations related to recency of smoking were based on analyses of NYTS 2002 data. | | <u>Recency of smoking.</u> Middle school students who initiated smoking in the past year were more likely to report current smoking of menthol cigarettes than those who reported smoking for more than one year. | <u>Recency of smoking.</u> There was no difference in reported menthol use between high school students who initiated smoking in the past year and those who reported smoking for more than one year. |
| Hymowitz et al. (1995) | Analyzed survey data on smoking characteristics of different racial/ethnic groups. | | | <u>Age of initiation.</u> Menthol and non-menthol smokers did not differ on age started smoking: Odds Ratio Estimate, Menthol: 1.00 (0.96, 1.04). |
| Lawrence et al. (2010) | Conducted secondary analyses of data from 2003 and 2006/2007 TUS CPS to "examine the patterns and correlates of mentholated cigarette smoking among adult smokers in the United States" (p. 13). Data from 58,389 adult current smokers were included in the referenced analysis (Table 4). Note. 2006 TUS CPS question related to smoking initiation worded to reflect the age at which the person first started to smoking cigarettes fairly regularly. | <u>Age of initiation.</u> For women, later age at start of regular smoking (18 or older vs. 15 - 17) was associated significantly with menthol cigarette smoking. | | The effect observed for women was not observed among men or the total sample. For these samples, age at start of regular smoking was not associated with menthol cigarette smoking. |

| Study Authors, Year | Population/Sample/Design | Suggestive of Decreased Effect on Initiation | Suggestive of Increased Effect on Initiation | Suggestive of No Effect on Initiation |
|------------------------|---|---|---|---|
| Okuyemi et al. (2004) | Surveyed 480 African American adult smokers at an inner-city health center. The survey examined sociodemographics, smoking characteristics, and smoking cessation experiences. Analysis compared menthol (n = 407) and non-menthol (n= 73) smokers. | | | Age of initiation. Menthol and non-menthol smokers did not differ on age of first cigarette, years (Median - [range]): Menthol 15 (3-40), Non-menthol 16 (5-52), p = 0.692 or age of regular smoking, years: Menthol 18 (9-44), Non-menthol 18 (5-59), p = 0.884. |
| Pletcher et al. (2006) | As part of a longitudinal study of risk factors for coronary artery disease (CARDIA Study), assessed the relationship between menthol and non-menthol cigarette use and smoking cessation. Analyzed data from 1,535 African-American and European menthol (n = 972) and non-menthol (n = 563) smokers; age 18-30. | | | Age of initiation. Menthol and non-menthol smokers did not differ on age smoked first cigarette (Mean +/- SD, year): Menthol 16.7 (+/- 3.2), Non-menthol 16.8 (+/- 3.3), p = 0.61. |
| SAMHSA (2009) | Using data from current smokers (age 12 or older) from NSDUH, analyzed trend and combined data from 2004 to 2008 regarding menthol cigarette use ¹ | Recency of smoking. For African-Americans, recent smoking initiates were less likely to report menthol cigarette use than were longer-term smokers. | Recency of smoking. As shown for current smokers aged 12 or older, 12 to 17, 18 to 25, males, females, Hispanics and Whites, recent smoking initiates (i.e., those who started smoking in the past year) were more likely to report menthol cigarette use than more established smokers (i.e., those who started smoking more than one year ago). | |

¹ Since recency of smoking initiation interacts with age category, analyses concerning menthol use on initiation should be restricted to earlier age categories versus the entire 12 or older sample. The latter comparison yields a confounded result: the effect appears larger for the total sample than for younger age groups where most initiation occurs (cf., Figure 5).

| Study Authors, Year | Population/Sample/Design | Suggestive of Decreased Effect on Initiation | Suggestive of Increased Effect on Initiation | Suggestive of No Effect on Initiation |
|-----------------------------|---|--|--|--|
| <p>Stahre et al. (2010)</p> | <p>Conducted secondary analyses of data from the 2005 NHIS and CCS to examine racial/ethnic differences in menthol cigarette use, population quit ratios, and use of evidence-based smoking cessation aids. The sample for the referenced analysis consisted of 6,055 current smokers and 5,949 former smokers for whom menthol status was known. Note. 2005 NHIS question related to smoking initiation worded to reflect the age at which the person first started to smoke fairly regularly.</p> | | | <p><u>Age of initiation.</u> The average age at which smokers (current or former) first started to smoke fairly regularly was not associated with reported menthol status.</p> |

Appendix Table B-5. Summary of Studies Concerning Relationship Between Menthol Cigarette Smoking and Age²

| Study Authors, Year | Population/Sample/Design | Evidence of Association with Higher Age | Evidence of Association with Lower Age | No Evidence of Relationship with Age |
|-------------------------|--|---|---|---|
| Appleyard et al. (2001) | Conducted secondary analysis of 2000 NYTS to explore possible differences in how tobacco differentially affects Asian American (n = 1,742) and Hawaiian/Pacific youth (n = 487) | | Among Whites, a higher proportion of middle-school smokers reported menthol cigarette use than their high-school counterparts (Confidence intervals did not overlap; Table A-4, p. 13). | Comparable proportions of Asian American smokers reported menthol cigarette use in middle school and high school. The same appeared true for H/Pi, African Americans and Hispanics (Confidence intervals overlapped; Table A-4, p. 13). |
| Fernander et al. (2010) | Conducted secondary analyses of data from 2003 and 2006/2007 Tobacco Use Supplement (TUS) to the Current Population Survey (CPS); menthol (vs. non-menthol) cigarette use was the dependent variable in a logistic regression, and potential predictor variables included age of initiation and cigarette purchasing type as well as demographic and other smoking variables. 66,145 adult current smokers completed the survey. | | Relative to current smokers in the 65 or older age group, current smokers in the 18 - 24, 25-44, and 45-64 age groups were more likely to smoke menthol cigarettes. | |

² Prevalence data of this nature provide little insight concerning the role of menthol cigarettes in smoking initiation. It is difficult to discern a causal relationship from prevalence data alone (e.g., Rock et al., 2010).

| Study Authors, Year | Population/Sample/Design | Evidence of Association with Higher Age | Evidence of Association with Lower Age | No Evidence of Relationship with Age |
|-----------------------|---|---|---|--|
| Giovino et al. (2004) | Summarized literature on health effects and patterns of use of menthol cigarettes as indicated by consumption and survey data from the United States and other nations. | National Household Survey on Drug Abuse, 2000. Black adults (18-25 and 26 or older) were more likely to report using menthol cigarettes than adolescents (12-17). | National Household Survey on Drug Abuse, 2000. Overall, 12-17 year olds were more likely to report using menthol cigarettes than 18 to 25 year olds. For Whites, 12 to 17 year olds were more likely to report using menthol cigarettes than adults (18-25 and 26 or older). Monitoring the Future (MTF). 1998 - 2000 -- The proportions of current smoking White 8th, 10th, and 12th graders reporting use of menthol brands was inversely related to grade, although there was some overlap in the confidence intervals. | National Household Survey on Drug Abuse, 2000. There was not a linear relationship between age categories and menthol cigarette use: The proportion of smokers reporting menthol cigarette use was higher in the 26 or older age category than in the 18-25 age category. Hispanics did not show a relationship between reported menthol cigarette use and age. MTF. Unlike the results for White 8th, 10th and 12th graders, there was no apparent pattern in the results for Blacks or Hispanics during these years (1998 - 2000). |
| Hersey et al. (2010) | Reviewed earlier research and conducted secondary analyses of data from the 2006 NYTS "to assess the relationship between menthol cigarette use and needing a cigarette within 1 hr after smoking" (p. S136). Data from 1,458 menthol smokers and 1,710 non-menthol smokers were included in the main analyses. | | Among smokers with a usual brand in the 2006 NYTS, middle-school students (51.7%) were more likely than high-school students (43.1%) to report that their usual brand was menthol. This appears to be case for males but not females. | For Blacks, Asian Americans and Hispanics, there was a fair degree of overlap in the confidence intervals when comparing reported usual use of menthol cigarettes between smokers in middle school and high school. |
| Hersey et al. (2006) | Analyzed data from 2000 and 2002 National Youth Tobacco Survey (NYTS) administered to 6th - 12th graders, focusing on students who reported current smoking, usual brand and whether that brand is mentholated. Data from 1,552 menthol smokers and 1,650 non-menthol smokers were included in the main analyses. | | Reported usual use of menthol cigarettes was higher for White smokers in middle school (53%) than high school (37%). The same was true for Hispanic smokers in middle school (63%) versus high school (52%). | Among African-Americans, there was no difference in middle school (88%) and high school (87%) students' reported use of menthol cigarettes. |

| Study Authors, Year | Population/Sample/Design | Evidence of Association with Higher Age | Evidence of Association with Lower Age | No Evidence of Relationship with Age |
|---------------------------------|---|---|--|---|
| Kreslake et al. (2008) | As part of their study, the authors analyzed 2006 National Survey on Drug Use and Health (NSDUH) data regarding the current use of menthol cigarettes among smokers in different age categories. | | The proportions of current smokers reporting menthol cigarette use declined with age: 12 to 17 (43.8), 18 – 24 (35.6), and 35 or older (30.6). | African-American adolescents, young adult, and older adult smokers reported using menthol equally frequently. |
| Lawrence et al. (2010) | Conducted secondary analyses of data from 2003 and 2006/2007 TUS CPS to "examine the patterns and correlates of mentholated cigarette smoking among adult smokers in the United States" (p. 13). Data from 69,193 adult current smokers were examined for the analysis. | | Among adult current smokers, menthol cigarette use was more likely for those 18–24 and 45-64 year than 65 or older. For men, menthol cigarette use was more likely for those 18–24 than 65 or older. For women, menthol cigarette use was more likely for those 45–64 than 65 or older age. For Blacks, menthol cigarette use was more likely for all age groups vs. the 65 or older age group. | Among adult current smokers menthol cigarette use was equally likely between those 25-44 and 65 or older. For men, menthol cigarette use was equally likely for those 25-44, 45-64, and 65 or older. For women menthol cigarette use was equally likely for those 18-24, 25-44, and 65 or older. For Whites and Hispanics menthol cigarette use was equally likely for all age groups. |
| Rock et al. (2010) ³ | Conducted secondary analyses of data from the 2004 - 2008 NSDUH to estimate the prevalence of menthol cigarette smoking among current smokers by race/ethnicity, gender, and age. Also "compared estimates for menthol and non-menthol use by demographic groups" (p. S117) and menthol smoking trends. The analysis was based on data from 277,960 respondents included in the public use files. | For African-Americans, prevalence of reported menthol use was comparable between smokers aged 18-25 (85.0%) and 26+ (82.2%) and lowest among smokers aged 12 to 17 (71.9%). | Overall, prevalence of reported menthol use was highest among 12 to 17 year olds and decreased among older age groups (18-25 and 26 or older). These percentages differed among current smoking Whites (12-17, 41.0%; 18-25, 28.8%; 26+, 21.9%), Hispanics (12-17, 47.0%; 18-25, 38.2%; 26+, 29.5%), and Asian Americans (12-17, 51.5%; 18-25, 35.8%; 26+, 28.6%). | |

³ Rock et al. (2010) and SAMHSA (2009) reported results of analyses of the same NSDUH data; Kreslake et al. (2008) reported results of analyses of a subset of these data.

| Study Authors, Year | Population/Sample/Design | Evidence of Association with Higher Age | Evidence of Association with Lower Age | No Evidence of Relationship with Age |
|----------------------|--|---|--|---|
| SAMHSA (2009) | Using data from current smokers (age 12 or older) from NSDUH, SAMHSA analyzed trend and combined data from 2004 to 2008 regarding menthol cigarette use. | | Among current smokers, reported use of menthol was highest among 12 to 17 year olds and decreased with age (statistical significance not reported). | |
| Sidney et al. (1989) | Studied menthol cigarette use in relation to age and race using data collected from 1979 to 1986 on 29,037 current smokers (Kaiser Permanente Medical Care Program members). | | Analyses revealed "a marked inverse relationship between age and mentholated cigarette use in Blacks and in Asians.." (p. 1425). Authors suggest that "the steep decline in the proportion of mentholated cigarette users with age in Blacks can be explained predominantly as a cohort effect..." (p. 1416) | Analyses revealed "... there was relatively little difference in mentholated cigarette use with age in Whites" (p. 1425). |

Appendix Table B-6. Summary of Studies of Dependence Measures and “Indicators” in Adult Menthol and/or Groups With High Menthol Cigarette Use

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|---------------------------|---|---|--|--|
| Ahijevych & Parsely, 1999 | 95 women | | Shorter TTFC among menthol cigarette smokers | |
| Ahijevych & Ford, 2010 | 2,241 daily and 688 non-daily young adult smokers (18-24) | | Menthol non-daily smokers were more likely to smoke within the first 30 min. of waking compared with non-menthol non-daily smokers. Note that <10% of non-daily smokers smoke within the first 30 min. | No association between menthol status and smoking within the first 30 min. of waking among daily smokers. No significant difference in CPD between menthol and non-menthol daily and non-daily smokers. |
| Ahijevych & Garrett, 2010 | Selected results from 19 studies | No new dependence-related information reported. The authors present selected results from selected studies. | | |
| Allen & Unger 2007 | 432 Adult African-American smokers | | | No significant difference by menthol status in odds of higher score on FTND, age first smoked or in wanting to stop smoking completely for women and men. |
| Benowitz et al., 2010 | 60 menthol and 67 non-menthol adult smokers. | | | No significant difference in FTND scores or in mean TTFC. |
| Bover et al., 2008 | 2,312 adult smokers | | | Menthol not significant predictor of 26-week cessation outcomes. |
| Cubbin et al., 2010 | 21,196 current, former and never smokers | | | No significant difference in CPD by menthol status and race/ethnicity among males or females. |
| Fagan et al., 2010 | 46,273 current smokers ages 18 and older, pooled TUS-CPS | Significantly fewer CPD among menthol smokers. | Multivariate analysis results included that menthol smokers of 6-10 CPD had higher odds of smoking within the first 5 min. | Multivariate analysis found no significant difference in odds of smoking within the first 30 min as compared with >30 min for menthol vs. non-menthol smokers in any CPD categories. No significant difference in odds of smoking within the first 5 minutes versus greater than 5 min for those who smoke 1-5, 11-20, or 20+ CPD. |

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|-------------------------|---|---|-------------------------------|--|
| Finkenauer et al., 2009 | 203 adult smokers | African-Americans (90% menthol) smoked significantly less CPD | | No difference by race in the percentage of smokers who were categorized as high dependent on measure of nicotine dependence. |
| Gandhi et al., 2009 | 1,688 patients in a smoking cessation study | Menthol cigarette smokers smoked significantly less CPD than non-menthol. African-American and Hispanic menthol cigarette smokers also smoked significantly less CPD than non-menthol same race/ethnicity. | | |
| Hooper et al., 2011 | 3,396 current smokers from the Florida 2007 BRFSS | Menthol smokers had statistically significantly lower mean scores on the NDSS in the unadjusted analysis. | | No significant difference between menthol and non-menthol smokers in AOR of dependence (NDSS) in the multivariate analysis |
| Hyland et al., 2002 | Cohort of 13,268 adult smokers with 5 years follow-up | At baseline, menthol use was associated with smoking <5 CPD, smoking >60 minutes after waking and with 2+ quit attempts. Menthol cigarette smokers were less likely to report smoking within 10 min. of waking. | | No baseline difference in desire to quit. No association between menthol use and CPD among those who continued to smoke at follow-up. |
| Kandel & Chen, 2000 | 12,550 White, 4903 African-American, 4839 Hispanic current smokers from the NHSDA | Minorities smoked significantly fewer CPD compared with Whites. Whites more likely than African-Americans to be DSM-IV dependent even controlling for CPD. | | |
| Lawrence et al., 2010 | 63,193 current and former smokers from 2003, 2006/07 TUS-CPS | Among all current smokers AOR of menthol use lower in the 20+ CPD category. | | Among AA, whites, Hispanic, AI/AN and Asian/PI, no significant difference in AOR by menthol status in any CPD category, or in TTFC \leq or $>$ 30 min. |

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|--------------------------------------|---|---|--|--|
| Luo et al., 2008 | 2,925 White and African-American adult smokers | Prevalence of ever smoking in lifetime was lower among African-Americans (24.1%) compared with Whites (40.6%). Current smoking lower for African-Americans (15.3%) than Whites (19.9%). African-American smokers had lower FTND scores compared with Whites. African-Americans smoked less CPD, were less likely to smoke when sick and were more likely to be able to refrain when prohibited. | Authors suggest by using TTFC as the measure of dependence, that "at the same level of CPD African-Americans have a higher likelihood of being dependent", with the largest difference observed at 15-19 CPD. However, <25% of African-Americans reported smoking \geq 15 CPD, while 58% of Whites smoked \geq 15 CPD. | No significant difference between White and African-American smokers on the FTND categories of TTFC (0-5, 6-30, 31-60 and 60+ minutes). Close to 50% of both groups reporting smoking within 30 minutes of waking. |
| Mendonzo et al., 2010 | 12,004 current and former smokers | Current, former and white menthol smokers smoked significantly fewer CPD as compared with non-menthol smokers. Overall, current menthol smokers have statistically significant reduced odds of smoking more CPD as compared with non-menthol smokers. | | No significant difference in CPD for AA (menthol 16, non-menthol 21 CPD, $p=0.069$) and Hispanic menthol versus non menthol smokers. Overall, no significant difference AOR of CPD for former menthol and non-menthol smokers. |
| Muhammad-Kah et al., 2010a and 2010b | 3,585 adult smokers (1,104 menthol and 2,481 non-menthol) | | | No significant increased odds of menthol use for any of the FTND questions. Menthol cigarette smoking did not increase the odds of higher FTND scores regardless of how scores were categorized. Higher FTND scores were not associated with increased odds of smoking menthol cigarettes. No difference in odds of TTFC more or <30 minutes after waking. |
| Muscat et al., 2002 | 19,545 current and former smokers | For African-Americans and Whites, menthol cigarette smokers smoked fewer CPD. | | Quitting was not associated with menthol status for Whites or African-Americans. |
| Muscat et al., 2009 | 525 adult smokers | | | No significant association between high FTND scores and the use of menthol cigarettes. |
| Murray et al., 2007 | 5,887 adult smokers | | | Among males and among females, respectively, there was no significant effect of menthol on partial FTND scores. |

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|-----------------------|--|---|---|--|
| Mustonen et al., 2005 | 307 White and African-American adult smokers in a clinical study of NRT. Smoked at least 10 CPD. | African-American and White male non-menthol cigarette smokers and White male menthol cigarette smokers smoked higher numbers of CPD as compared with all female smokers and as compared with African-American male menthol cigarette smokers. | | No significant difference was found between menthol and non-menthol cigarette smokers in number of CPD. No difference in FTQ scores between White males, White females, African-American males or African-American females. |
| Okuyemi et al., 2003 | 600 African-American smokers in a bupropion trial | | Menthol cigarette smokers more likely to smoke first cigarette within 30 minutes of waking. | No significant difference in mean number of CPD or FTND scores. |
| Okuyemi et al., 2004 | 480 adult African-American smokers at a inner-city health center | | | No significant difference in FTND scores between menthol and non-menthol cigarette smokers. Also no difference in average age of initiation (for either first cigarette or regular smoking) or in average number of CPD. |
| Okuyemi et al., 2007b | 755 African-American smokers in smoking cessation trial | | | No significant difference between menthol and non-menthol on the NDSS or MNWS. No difference in motivation to quit; duration of longest quit attempt; number of quit attempts in the last year; age of smoking initiation or in average number of CPD. |
| Pletcher et al., 2006 | 1,535 adult smokers | Menthol cigarette smokers had lower median number of CPD (10) as compared with non-menthol (15). | | |
| Stahre et al., 2010 | 6,511 current and 6,774 former smokers from the 2005 NHIS | Statistically significantly fewer CPD among menthol as compared with non-menthol smokers among current and former smokers. | | |

AA, African American; AI, American Indian; AN, Alaska Native; AOR, adjusted odds ratio; CPD, cigarettes per day; FTND, Fagerström Test for Nicotine Dependence; FTQ, Fagerström Tolerance Questionnaire; MNWS, Minnesota Withdrawal Scale; NDSS, Nicotine Dependence Syndrome Scale; NHIS, National Health Interview Survey; NRT, nicotine replacement therapy; PI, Pacific Islander; TFC, time to first cigarette; TUS CPS, Tobacco Use Supplements to the Current Population Surveys

Appendix Table B-7. Summary of Dependence Measures and “Indicators” in Underage Menthol and/or Groups with High Menthol Cigarette Use

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|--------------------------|--|--|---|---|
| Collins & Moolchan, 2006 | 572 adolescent smokers (531 smoked menthol) | | Significant difference in percent of menthol (45%, n=239) and non-menthol cigarette smokers (29%, n=12) only in the ≤ 5 minutes TTFC. | No significant difference between menthol and non-menthol in any other TTFC categories and no differences in number of CPD or FTND scores. |
| DiFranza et al., 2004 | 237 adolescents who had inhaled on a cigarette | | | Reactions to the initial smoking experience were unrelated menthol. No difference between menthol and non-menthol on the HONC. |
| Hersey et al., 2006 | 3,202 adolescents who knew menthol status and reported smoking in last month 2000, 2002 NYTS | | Report that menthol cigarette smokers had significantly higher odds of being above the median on the NDSA, but no details about the scores (means, medians) and 95% CI not provided. | Menthol and non-menthol smokers reported a similar frequency of quit attempts. |
| Hersey et al., 2010 | 3,303 adolescents from 2006 NYTS | | Among those reporting a “usual brand” and “established smokers”, menthol smokers had higher odds of reporting “needing a cigarette within 1 h after smoking”. Higher odds for menthol “established smokers” endorsing two other statements. | Among all reporting a “usual brand”, no significant increased odds for menthol smokers to report “feeling restless or irritable without smoking” or “experiencing cravings after going without smoking for a few hours”. Note models do not adjust for SES. |
| Kandel & Chen, 2000 | 12,550 White, 4,903 African-American, 4,839 Hispanic current smokers ages ≥12 (NHSDA) | Minorities smoked significantly fewer CPD compared with Whites. Whites more likely than African-Americans to be DSM-IV dependent even controlling for CPD. | | |

| Study Authors, Year | Population/Sample | Suggestive of Less Dependence | Suggestive of More Dependence | No Significant Difference in Dependence |
|---------------------------|---|---|---|--|
| Mullenburg & Legge, 2008 | 4,336 middle- and high-school students in five predominantly African-American inner city schools and one predominantly White suburban school in Mississippi | | Authors report that menthol cigarette smokers, and specifically that African-American underage menthol cigarette smokers had the highest rates of cigarette consumption. However, these findings should be read with caution, as 81% of the African-American smokers reported non-menthol cigarettes. | |
| Moolchan et al., 2000 | 115 treatment seeking adolescents | African-American adolescents had significantly lower FTND scores as compared with non African-Americans. | | |
| Wackowski & Delnevo, 2007 | 1,345 adolescents from the NYTS | African-American and Asian adolescents less likely to be a current smoker, or current and established smoker as compared with Hispanics and Whites. | Menthol cigarette smokers had higher odds of endorsing two of four dependence related statements. | No difference in odds of endorsing two other dependence statements by menthol status. African-American adolescent smokers (88% menthol) had no increased odds for any of the four statements compared with Whites. |

CPD, cigarettes per day; FTND, Fagerström Test for Nicotine Dependence; NHSDA, National Household Survey on Drug Abuse; NYTS, National Youth Tobacco Survey; TTFC, time to first cigarette

Appendix Table B-8. Summary of Studies Related to Menthol and Cessation

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|------------------------|--|---|--|--|
| Alexander et al., 2010 | 30,176 current smokers ages 18 and older, pooled TUS-CPS | Menthol smokers were significantly more likely to have stopped smoking in the last 12 months. | | No significant difference in mean number of number quits in last year or longest length of cessation. In the multivariate model, no significant difference by menthol status for ever stopped smoking. |
| Bover et al., 2008 | 2,312 adult smokers seeking treatment | | | Night waking to smoke, but not menthol, was a significant predictor of cessation at 26-weeks follow-up. |
| Cropsey et al., 2009 | 233 adult female prisoners | | | Whites had higher quit rates, regardless of menthol status, as compared with African-Americans at 6 weeks and 12 months. Menthol not significant main effect, no menthol by race interaction. |
| Cubbin et al., 2010 | 21,196 current, former and never smokers | White female menthol smokers had statistically significantly longer abstinence (2.5 years longer) as compared with non-menthol smokers. | | No significant difference in quit attempts between menthol and non-menthol (but trend for higher levels among menthol smokers for both genders and all racial/ethnic groups. No significant difference in length of abstinence by menthol status by race or gender (except White women). |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|---------------------|--|--|--|---|
| Fagan et al., 2007 | 7,912 young adults (ages 18-30) from TUS-CPS | | | No increased or decreased odds of having ≥ 1 quit attempt in last 12 months for menthol compared with non-menthol among all smokers, daily and non-daily smokers. No difference by menthol among those who had ≥ 1 quit attempt in last 12 months and intention to quit in 6 months. |
| Fagan et al., 2010 | 46,273 current smokers ages 18 and older, pooled TUS-CPS | | | No significant difference in quit attempts in the past 12 months or in length of smoking abstinence among those who made a quit attempt between menthol and non-menthol smokers (for ≤ 5 , 6-10, 11-19 and 20+ CPD groups) in the multivariate analysis. |
| Foulds et al., 2006 | 1,021 treatment seeking adults | | In multivariate analysis, a trend for non-menthol cigarette smokers to be more likely to be abstinent at 4-week follow-up. | Menthol status not a factor related to abstinence at 26-weeks. Factors related to successful cessation outcomes were age, education, number of children, health insurance, stage of change and number of face-to-face clinic contacts. |
| Foulds et al., 2010 | Review of 10 studies | | | No new information reported. The authors' results state "None of the studies found a significant overall effect of menthol on smoking cessation at the last study follow-up point, after controlling for other relevant measured variables." But they conclude that "certain subgroups of smokers find it harder to quit menthol versus non-menthol cigarettes." They mention the need for additional research. |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|------------------------|--|--|---|--|
| Fu et al., 2008 | 1,343 adults from five VA medical centers | Menthol smokers had trend of higher smoking abstinence in main effects model. Menthol smokers with intervention were more likely to be abstinent at 6 months (OR 1.80, 95% CI 1.18-2.76, p=0.006). | | There was no significant difference by menthol status or race in the unadjusted univariate analyses. |
| Gandhi et al., 2009 | 1,688 patients in a smoking cessation study (includes patients from Foulds et al., 2006) | | African-American and Hispanic menthol smokers had lower odds of quitting at 4 weeks than non-menthol smokers. At 6 months only difference for African-American smokers. Additional analysis, 4-week quit rate was lower among unemployed African-American menthol vs. African-American non-menthol (16% vs. 43%). | White menthol smokers did not have decreased odds of quitting as compared with White non-menthol smokers at 4 weeks or 6 months. No control for being in the "action stage" of change and predictors in Foulds et al., 2006. The effect of menthol at 4 weeks was not significant for full-time employed African-Americans. 6-month outcomes by employment not tested. |
| Gundersen et al., 2009 | 7,815 White, African-American and Hispanic adult current & former smokers (NHIS) | White menthol smokers had a significantly higher AOR for cessation vs. non-menthol smokers. African-Americans less likely to be ever or current smoker. | Hispanic menthol smokers had a significantly lower AOR for cessation. "Non-White" menthol smokers (but not African-Americans) had lower AOR of cessation. | No increased/decreased odds for cessation in menthol vs. non-menthol in Model 1. The AOR for quitting for African-American menthol smokers was not statistically significantly different than non-menthol smokers. |
| Harris et al., 2004 | 600 African-American adults from Okuyemi et al., 2003 study. | | Univariate analysis found higher 7 weeks abstinence rates in non-menthol smokers. | Menthol status was not a significant predictor of long-term cessation outcomes. Factors which were significant and independent baseline predictors were assignment to bupropion treatment, lower cotinine, TTFC > 30 minutes. |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|---------------------|--|--|--|---|
| Hersey et al., 2006 | 3,202 adolescents who knew menthol status and reported smoking in last month | | | Menthol and non-menthol smokers reported a similar frequency of quit attempts. |
| Hooper et al., 2011 | 3,396 current smokers from the Florida 2007 BRFSS | | | No significant difference in past year quit attempts among menthol and non-menthol smokers. |
| Hyland et al., 2002 | Cohort of 13,268 adult smokers with 5 years follow-up | Baseline, menthol use was associated with smoking <5 CPD, smoking >60 minutes after waking and with 2+ quit attempts. Menthol smokers less likely to report smoking in ≤10 min. of waking. | | No baseline difference in desire to quit. Among smokers overall, no difference in relative risk (RR 1.0 95% CI 0.90-1.11) for quitting in 1993 based on menthol status in 1988. No significant menthol associations in the race/ethnicity specific analysis. |
| Murray et al., 2007 | Cohort of 5,887 adult smokers with 5-year follow-up | | | For both men and women, no significant difference by menthol status in becoming a sustained quitter, intermittent quitter, or continuing smoker over the five years of annual follow-up. At the five year visit, approximately 35% of all baseline smokers and baseline menthol smokers had quit smoking. |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|----------------------|---|---|---|---|
| Muscat et al., 2002 | 19,545 current and former smokers | | | No significant difference in the prevalence odds ratios (POR) of quitting for menthol smokers compared with non-menthol smokers among Whites or among African-Americans. |
| Muscat et al., 2009 | 525 adult smokers | | More menthol smokers reported "never thought about quitting" (17% vs. 3.6%). | Similar reasons for not quitting were reported by menthol and non-menthol smokers with one exception. |
| Okuyemi et al., 2003 | 600 African-American smokers in a bupropion trial | Difference at 6-weeks could have been a "spurious finding" or could be due to delayed quitting among menthol smokers or higher relapse among non-menthol smokers. | Among those who received bupropion, non-menthol smokers had significantly higher abstinences rates at 6-weeks. Among those who were <50 years of age, African-American non-menthol smokers were twice as likely to have quit smoking at the 6-week follow-up. | No significant difference in 6-week abstinence rates of menthol and non-menthol smokers in the placebo group. For those ≥50 years old, bupropion was the only predictor of abstinence at 6 weeks. At 6-months, overall abstinence rates of menthol and non-menthol smokers not statistically significantly different. |
| Okuyemi et al., 2004 | 480 adult African-American smokers at an inner-city health center | More recent quit attempts were reported by menthol smokers (12 days) as compared with non-menthol smokers (24 days). | | Menthol and non-menthol smokers reported a similar number of quit attempts over their lifetimes. No difference in readiness to quit (60% either contemplating or preparing to quit). |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|-----------------------|--|--|--|--|
| Okuyemi et al., 2007a | 755 adult African-American smokers in smoking cessation trial | | Non-menthol smokers as compared with menthol smokers had statistically significantly higher abstinence rates at 26 weeks (18.8% vs. 11.2%). This difference between menthol and non-menthol smokers at 26-weeks was statistically significant only for those who received NRT gum or health education. | No significant difference between menthol and non-menthol on motivation to quit, duration of longest quit attempt, number of quit attempts in the last year. 8-week abstinence rates did not differ between menthol and non-menthol smokers. No difference in cessation at 26-weeks for those who received placebo gum or motivational interview. African-American non-menthol smokers who were <50 years of age had cessation odds that trended higher than menthol smokers at 26 weeks, but the difference was not statistically significant. No difference by menthol status among those who were ≥50 years of age. |
| Pletcher et al., 2006 | Prospective study of 1,535 adult smokers followed for 15 years | | Baseline menthol smokers compared with non-menthol had higher odds of relapse. | No statistically significant difference by menthol in odds for not currently smoking, recent quit attempt, cessation if recent quit attempt or sustained smoking cessation. |

| Study Authors, Year | Population/Sample | Suggestive of Better Cessation Indicator/Outcome | Suggestive of Poorer Cessation Indicator/Outcome | No Significant Difference |
|------------------------|---|---|--|--|
| Stahre et al., 2010 | 6,511 current and 6,774 former smokers | Past year quit attempts was higher among menthol (49%) as compared with non-menthol (41%) smokers. | AA menthol smokers had lower AOR of quitting as compared with White non-menthol smokers. Note that quit ratios are lower among AA as they are less likely to be ever smokers. | No difference between menthol and non-menthol in odds of using any type of quit aid. Univariate analysis found no difference in quit ratio by menthol status among whites. After controlling for age, sex, region, marital status and average CPD, no difference reported for odds of quitting by menthol status within any of the racial ethnic groups (White, AA, AI/AN, Asian) |
| Steinberg et al., 2011 | Retrospective cohort of 723 smokers who received cessation treatment. | | | Menthol smoking was not significantly related to abstinence at 6 months post cessation. No higher AOR for menthol smokers for 6 month abstinence. |
| Trinidad et al., 2010 | 283,441 current and former smokers | AA and Hispanic menthol smokers were statistically significantly more likely to be "seriously thinking about quitting in the next 6 months" and to have a positive estimation of their success in quitting in the next 6 months as compared with non-menthol smokers. | Among former smokers, menthol smokers had lower AOR for "successfully quitting for at least six months" across race/ethnic groups. (Model adjusted for age group, gender, education and use of other tobacco products). Note some numbers are questionable in the table, i.e. former smokers quit less than 6 months, approx. 10,000 non-menthol, 3,000 menthol and close to 38,000 "no usual type." | No difference by menthol status for seriously thinking about quitting or estimation of successfully quitting in the next 6 months for non-Hispanic whites, Asian Americans/Pacific Islanders or Native Americans/Alaska Natives. |

AA, African American; AI, American Indian; AN, Alaska Native; AOR, adjusted odds ratio; CPD, cigarettes per day; NHIS, National Health Interview Survey; NRT, nicotine replacement therapy; PI, Pacific Islander; TTFC, time to first cigarette

Appendix Table B-9. Summary of Studies Related to Predictors of Use and Risk Perception

| Study authors, Year | Population/Sample Type of Study | Study Measures | Study Findings |
|---------------------|--|---|--|
| Allen & Unger 2007 | 432 adult AA smokers in CA | <p>Predictors of menthol smoking (vs. non-menthol) among women</p> <p>Predictors of menthol smoking (vs. non-menthol) among men</p> <p>Factors tested that were not predictors of menthol vs. non-menthol use</p> | <p>Increased odds of menthol use for women who responded "father smoked menthols", "mother smoked menthols", and "most African American smokers smoke menthols".</p> <p>Decreased odds for menthol use for women who responded "mother smoked nonmenthols" and "smoking menthol cigarettes is a 'Black thing'".</p> <p>Increased odds of menthol use for men who responded "most African American smokers smoke menthols".</p> |
| Davis et al., 2010 | <p>4,556 adults 2009 HealthStyles survey</p> <p>Results included by race/ethnicity, gender, age education, income and smoking status</p> | <p>Perception of harmfulness</p> <p>Perception of health benefit</p> <p>Perceptions about addiction</p> <p>Perceptions about cessation</p> | <p>For both men and women, no significantly increased or decreased odds of menthol use by various school/neighborhood composition factors, physical characteristics, taste preference, nicotine addiction (FTND) and smoking history, exposure to menthol advertising in childhood or currently, by attitudes toward tobacco companies or by emotional distress.</p> <p>"Nearly equal proportions of menthol smokers (49%) and nonmenthol smokers (45%) reported taste as their major motivation for choosing their cigarette type..." (p. 451).</p> <p>Less than 1% thought menthol cigarettes were less harmful than non-menthol cigarettes. 12.6% perceived them as more harmful. The remainder thought they were equally harmful or did not know.</p> <p>76.8% reported menthol cigarettes have no health benefit, 18.9% did not know and 4.3% believed there was some health benefit to menthol cigarettes.</p> <p>49.4% of smokers reported they thought menthol and non-menthol cigarettes are equally addictive, 24.2% believed menthol were more and 21% believed non-menthol were more addictive</p> <p>74.5% of smokers reported menthol and non-menthol cigarettes as equally hard to quit, 12.1% perceived menthol and 6.1% perceived non-menthol harder to quit.</p> |

| Study authors, Year | Population/Sample Type of Study | Study Measures | Study Findings |
|-----------------------|--|---|---|
| Hymowitz et al., 1995 | 473 adult menthol smokers who participated in a smoking cessation study. Results of comparisons between menthol smokers based on N=213 | Compared White and AA menthol smokers on reasons for smoking menthol cigarettes | Only statistically significant difference between White and AA menthol smokers was more AA (41%) were more likely than Whites (18%) to report "My friends that smoke, smoke menthol cigarettes". The majority of AA (83%) and White (74%) menthol smokers reported "menthol cigarettes taste better than regular non-menthol cigarettes". More than 90% of menthol smokers did not think that menthol cigarettes are "better for you" than non-menthol. AA as compared with White menthol smokers were significantly more likely to say that they would not smoke a non-menthol cigarette if they could not smoke a menthol cigarette. The authors report "Relatively few smokers of either race endorsed 'image' or 'advertising' as a reason for smoking menthol cigarettes." (p.194). |
| Richter et al., 2006 | 16 focus groups with smokers between 18-22 years of age in TN (36 White, 40 AA) and TX (34 NH-White, 31 Hispanic) | Compared perceived risk of light, regular and menthol cigarettes and non-traditional tobacco and non-tobacco products | Among NH-Whites, menthol as compared with regular cigarettes were perceived to have "the same risk" or were perceived as "more harmful" by all participants. Among Hispanics, the majority of those who were not in college perceived menthol cigarettes as "more harmful" while those in college were split between the same risk, safer and don't know. Among AA, menthol as compared with regular cigarettes were perceived to have "the same risk" or were perceived as "more harmful" by all participants. AA in college rated marijuana, herbal smokeless and Shisha as "safer" than their preferred (primarily menthol) cigarettes. |
| Unger et al., 2010 | 720 Black adult smokers identified through community intercept locations | Predictors of menthol by various characteristics | In the menthol only vs. non-menthol only comparison and the combined (smokes menthol and non-menthol cigarettes) vs. non-menthol only comparison: menthol smokers and combined smokers had a significantly higher odds of having menthol smokers in their current social network and higher odds in what is reported to be "medicinal effects" (note that these questions were rated on a four point scale from strongly agree to strongly disagree and statements included the comparison as "better than non-menthols" [p.400]). No significant differences in the menthol only vs. non-menthol only or combined group vs. non-menthol only in odds ratios for ethnic identity, perceived discrimination, depressive symptoms, anxiety symptoms, sensation seeking, stress, image, less harmful, tradition, menthol smokers in childhood network, or in exposure to menthol marketing. |

| Study authors, Year | Population/Sample Type of Study | Study Measures | Study Findings |
|------------------------|---|--------------------------------------|--|
| Wackowski et al., 2010 | Data from 3,062 adults in the 2005 New Jersey Adult Tobacco Survey (over sampled 18-24 year olds, smokers and recent quitters | Prevalence of perceptions about risk | Few respondents overall (4%) and menthol smokers (2.4%) reported a belief that menthol cigarettes were less risky than non-menthol cigarettes, whereas 25.9% overall and 30.2% of menthol smokers believed menthols were more risky. Overall, 70% of respondents believed menthol and non-menthol had the same risk. Among menthol smokers, over 1/3 of AA and almost half of 18-24 year-olds believed menthol cigarettes were riskier than non-menthol. |
| | | AOR of "somewhat less risky" | Among all respondents: those in age categories of 25-44 and 45-64 (as compared to those 65+) had significantly lower odds of believing that menthol cigarettes were less risky than non-menthol cigarettes. Among current smokers: males as compared to females had significantly lower odds of believing that menthol cigarettes were less risky than non-menthol cigarettes. |
| | | AOR of "somewhat more risky" | Among all respondents: menthol smokers, non-menthol smokers and former smokers (as compared to never smokers) all had significantly higher odds of believing menthol cigarettes were more risky than non-menthol cigarettes; Males had higher odds of perceiving menthol to be more risky as compared to females; those in age categories of 18-24 and 25-44 (as compared to those 65+) had significantly higher odds of believing that menthol cigarettes were more risky. Among current smokers: Menthol smokers had significantly lower odds of believing that menthol cigarettes were more risky as compared to non-menthol smokers; AA had significantly higher odds of believing that menthol cigarettes were more risky as compared to White smokers; Smokers ages 18-24 years had significantly higher odds of believing that menthol cigarettes were more risky as compared to smokers ages 65+. |

AA, African American; AOR, adjusted odds ratio; FTND, Fagerström Test for Nicotine Dependence; NH, non-Hispanic;