THE INDUSTRY MENTHOL REPORT

Menthol Cigarettes: No Disproportionate Impact on Public Health

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Submitted to FDA by the Non-Voting Industry Representatives on TPSAC
and Other Tobacco Industry Stakeholders

March 23, 2011

Available for Public Disclosure without Redaction

Under the Family Smoking Prevention and Tobacco Control Act (the Act), the Tobacco Products Scientific Advisory Committee (TPSAC) must issue a report and recommendation to the Food and Drug Administration (FDA) on "the issue of the impact of the use of menthol in cigarettes on the public health, including such use among children, African-Americans, Hispanics, and other racial and ethnic minorities" (Act at § 907(e)).

Report Title: Menthol Cigarettes: No Disproportionate Impact on Public Health

Dated: March 23, 2011

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Commonwealth Brands, Inc.

Dosal Tobacco Corporation

Fair Products, Inc.

IOTA USA, LLC

JT International U.S.A., Inc.

Kentucky Farm Bureau

King Maker Marketing Inc.

Liggett Group LLC

North Carolina Farm Bureau

Shamrock Specialty Papers, Ltd.

Sherman's 1400 Broadway, NYC Ltd. (D/B/A Nat Sherman)

Swisher International, Inc.

Tobacco Rag Processors

U.S. Tobacco Cooperative Association

Vector Tobacco Inc.

EXECUTIVE SUMMARY

Under the Family Smoking Prevention and Tobacco Control Act (the Act), the Tobacco Products Scientific Advisory Committee (TPSAC) must issue a report and recommendation to the Food and Drug Administration (FDA) on "the issue of the impact of the use of menthol in cigarettes on the public health, including such use among children, African-Americans, Hispanics, and other racial and ethnic minorities" (Act at § 907(e)).

THE INDUSTRY MENTHOL REPORT

The Industry Menthol Report is submitted to FDA, at its request, by the non-voting Industry Representatives on TPSAC and other tobacco industry stakeholders.[1] Consistent with FDA's commitment to science-based regulatory decisions that rely on the best available data, the Industry Menthol Report provides FDA with a complete and thorough evaluation and assessment of the best available scientific data.

The only appropriate focus for FDA is to assess whether menthol cigarettes have a disproportionate public health effect when compared to nonmenthol cigarettes. The Industry Menthol Report adopts this focus. All cigarettes are hazardous to health. It does not require a scientific analysis by TPSAC or FDA to conclude that removal of menthol cigarettes from the market plausibly would have some public health benefit. It is axiomatic that removing any type of cigarette preferred by a substantial number of American smokers – whether that be menthol, nonmenthol, lower tar, higher tar, filtered or unfiltered – might result in some smokers quitting when their preferred type of cigarette is taken away by the government. However, this is a very different issue than that contemplated in the Act.

The Industry Menthol Report takes into account the statutory considerations that TPSAC must address in its report and recommendation and that FDA must consider before deciding whether to propose any regulatory action. One of the issues Congress specifically recognized was the need to address the countervailing effects resulting from any regulatory decision, particularly "the creation of a significant demand for contraband." The illicit sale of cigarettes is a well-documented problem that poses significant threats to both the public health and the public safety.

The Industry Menthol Report outlines the demographics of menthol cigarette smoking and assesses whether menthol cigarettes have any impact over that of nonmenthol cigarettes on disease occurrence, as well as smoking behavior. The Industry Menthol Report also responds to speculative hypotheses that have been advanced with respect to menthol in cigarettes. In addition, the Industry Menthol Report pulls together numerous studies and reports, many from government agencies, along with written submissions and public comments to TPSAC on the likely countervailing effects resulting from an overly restrictive regulation of menthol cigarettes.

[1] See the list of non-voting Industry Representatives and other tobacco industry stakeholders on Page i.

PROVEN FRAMEWORK TO ASSESS THE WEIGHT OF THE EVIDENCE

In systematically evaluating the studies and data on menthol in cigarettes, both study methodology and ability to support inferences with respect to menthol were assessed using a scientifically rigorous approach. The scientific standards and processes used in the Surgeon General's Reports (SGRs) guided the conclusions reached in the Industry Menthol Report. The four categories adopted by the 2004 SGR to classify the strength of causal inferences, with modifications required to address the specific menthol topics, are used in the Industry Menthol Report to describe the weight of evidence with respect to any impact of menthol cigarettes on public health above the impact of nonmenthol cigarettes. The Surgeon General's causality framework has been applied for many decades to questions of smoking and health, and has also been adopted by other major public health authorities such as the Institute of Medicine (IOM) and the International Agency for Research on Cancer. The Surgeon General's categories include:

- **"Evidence is sufficient to infer a causal relationship" (Sufficient)**
- **"Evidence is suggestive but not sufficient to infer a causal relationship" (Suggestive)**
- **"Evidence is inadequate to infer the presence or absence of a causal relationship" (Inadequate)**
- **"Evidence is suggestive of no causal relationship" (No Causal Relationship)**

SGR 2004 also noted that "[t]here is no category beyond 'suggestive of no causal relationship' as it is extraordinarily difficult to prove the complete absence of a causal association" (USDHHS 2004). If an assessment falls into the category of "Suggestive," it may be appropriate for FDA to recommend further study of the issues. However, if an assessment of the totality of available scientific evidence falls into either of the final two categories ("Inadequate" or "No Causal Relationship"), no regulatory action on menthol is warranted by FDA.

This approach contrasts sharply with TPSAC's adoption of an unorthodox standard using the amorphous concept of equipoise, which historically has been used to address issues not relevant here – such as how to ethically conduct randomized clinical trials or award veterans' benefits. The IOM has used equipoise to evaluate veterans' benefits, but TPSAC does not adhere to the IOM equipoise categories. Most importantly, TPSAC's approach omits a category used by the IOM to encompass the conclusion of "*Against:* The evidence suggests the lack of a causal relationship." Ironically, that is the category into which the majority of the evidence regarding menthol falls.

MAJOR CONCLUSIONS OF THE REPORT

The conclusions of the Industry Menthol Report comply with FDA's mandate to "follow the science."

Using the Surgeon General's framework for assessing causality, a synthesis of the reliable data on the use of menthol in cigarettes, including data relating to its impact on disease and smoking behavior, leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol cigarettes and any disproportionate impact on the public health as a whole or for any

demographic group when compared to nonmenthol cigarettes. As a result, there is no scientific basis to support the regulation of menthol cigarettes any differently than nonmenthol cigarettes.

Demographics of Menthol Cigarette Preference and Current Trends in Smoking Prevalence

Smoking prevalence refers to estimates of cigarette use among the overall population, whereas smoking preference refers to the percentage of smokers who smoke a particular type of cigarette (e.g., menthol versus nonmenthol). An increase in smoking prevalence in the population could represent an adverse population-level effect, while higher preference for a particular cigarette type that does not provide any increased risk for disease or adversely impact smoking behavior among a declining smoking population would not. Cigarette smoking in the overall population (prevalence) has steadily declined during the last two decades, irrespective of race/ethnicity, sex and age category. Menthol cigarettes are used by only a quarter of the smoking population (preference). The majority of all menthol smokers are White. The vast majority of African American smokers prefer menthol cigarettes, and it is reported that female smokers prefer menthol more than male smokers. Some studies appear to suggest that menthol cigarette preference is also higher among younger as compared to older smokers. During the last two decades, declines in smoking prevalence have generally been more pronounced for minorities (including African Americans), females and adolescents, despite their preference for menthol. Also, prevalence of African American adolescent smoking is far below that of White adolescent smoking.

Menthol in Cigarettes Does Not Change the Inherent Health Risks of Cigarette Smoking

The available epidemiologic studies clearly demonstrate that smokers of menthol cigarettes are at no greater risk of developing chronic smoking-related diseases than are nonmenthol smokers. The number of studies and their consistency make it possible to draw this conclusion with confidence. While all epidemiology studies have limitations, the available studies are well-designed and well-analyzed. The diseases studied include lung cancer (the most common smoking-related cancer), cancers of the upper aerodigestive tract (esophagus, larynx, oropharynx), and other cardiac and lung outcomes. The studies provide data on risks specific to both sexes and to both Whites and African Americans, and do not find that there is any subpopulation of menthol smokers who incur increased risks compared to nonmenthol smokers. Thus, it can be concluded that, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol cigarettes and increased smoking-related disease risk above that caused by use of nonmenthol cigarettes.

Menthol in Cigarettes Has No Meaningful Effect on Smoking Biomarkers

The vast majority of studies of biomarkers of exposure to smoke constituents and biomarkers of potential harm have found no meaningful differences between menthol and nonmenthol smokers. The body of available scientific evidence from biomarker studies leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol cigarettes and increases in biomarkers of exposure and potential harm over and above those caused by the smoking of nonmenthol cigarettes.

Evidence on Menthol and Smoking Topography is Inadequate to Support a Conclusion that Menthol Cigarettes are Smoked More Intensely

The available studies on menthol cigarettes and smoking topography differ in the ways that they attempt to measure smoking variables such as puffing, depth, volume and frequency; and many have weaknesses (e.g., small numbers of subjects, use of cigarettes differing in yield and menthol content, etc.). This makes it difficult to compare the studies and to reach definitive overall conclusions regarding these aspects of smoking topography. Although the findings are somewhat inconsistent, the majority of studies find no significant differences between menthol and nonmenthol smokers in smoking topography variables. These data provide no support for the presence of a clear and consistent association between menthol smoking and an adverse impact on smoking topography and provide no convincing support for the suggestion that menthol increases the exposure to smoke constituents through effects on smoking behavior. However, given the inconsistencies that exist, the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between use of menthol cigarettes and adverse impacts on smoking topography. When placed in the context of the epidemiology and biomarker evidence referenced above, there is no reason to conclude that smoking topography differences, if any, lead to any increased health risks over those of nonmenthol cigarettes.

Menthol in Cigarettes Does Not Adversely Impact the Toxicologic Properties of Mainstream Smoke

Toxicology studies show that menthol has no notable effects at exposures spanning the ranges typical for its flavor application in cigarettes. Additionally, the weight of the evidence on the toxicologic properties of the mainstream smoke from menthol cigarettes compared with nonmenthol cigarettes provides no indications of increased toxicity, consistent with a broader conclusion that menthol has no causal relationship to adverse impacts on public health. This leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol added to cigarettes and increases in the toxicity of cigarette smoke.

Menthol in Cigarettes Does Not Meaningfully Alter the Chemical Composition of Mainstream Smoke

The weight of the evidence clearly shows that the chemical compositions of the mainstream smoke from menthol and nonmenthol cigarettes are very similar, apart from the presence of menthol itself. Thus, the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and potentially harmful changes in mainstream smoke chemistry.

Evidence is Inadequate to Conclude that Menthol in Cigarettes Influences Smoking Initiation

Smoking initiation rates have not changed significantly over the past decade. In addition, menthol smokers report later onset of initiation as compared to nonmenthol smokers. While some studies report that younger smokers have a higher preference for menthol cigarettes than older smokers, there are no studies that directly examine cigarette type (menthol versus nonmenthol) at the time of initiation. Although these data are suggestive of no causal relationship between menthol cigarette use and adverse smoking initiation behaviors, they do not directly address the cigarette type used to initiate smoking. Thus, using the Surgeon General's framework for assessing causality, it must be

concluded that the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between menthol cigarette use and adverse smoking initiation behaviors, including higher or earlier smoking initiation by the general population or by subpopulations.

Menthol in Cigarettes Has No Meaningful Impact on Smoking Cessation

Review of the methodologically sound literature on menthol smoking and cessation demonstrates that the most relevant studies – those that address successful long-term quitting – do not indicate that smokers of menthol cigarettes are less likely to quit than smokers of nonmenthol cigarettes. There are a sufficient number of high-quality studies that consistently find that menthol has no meaningful impact on smoking cessation. A few studies (three cross-sectional studies and one of a smoking cessation clinic) reported some lower cessation rates among non-White menthol smokers only. However, if menthol is a factor that affects the ability to quit smoking, one would expect to see consistency among White and non-White subjects. This race-associated inconsistency suggests that some other factor, possibly related to socioeconomic status or genetics, affects the ability to quit, rather than menthol itself. Given the number of high-quality studies that consistently find that menthol cigarette use has no meaningful impact on smoking cessation, using the Surgeon General's framework for assessing causality leads to the conclusion that the **"evidence is suggestive of no causal relationship."**

Menthol in Cigarettes Has No Meaningful Impact on Nicotine Dependence

Review of the methodologically sound literature on menthol smoking and measures of nicotine dependence demonstrates that menthol smokers are not any more dependent on nicotine than nonmenthol smokers, as assessed by a variety of measures including cigarettes per day (CPD), time to first cigarette (TTFC), and Fagerström Test for Nicotine Dependence (FTND). There are a sufficient number of studies, and they are consistent in their results. Menthol smokers do not smoke significantly more CPD than nonmenthol smokers; in fact, half of the studies reported that menthol cigarette smokers report significantly fewer CPD than nonmenthol smokers. Similarly, menthol and nonmenthol smokers do not differ significantly on composite measures of dependence. With respect to the studies that evaluated TTFC, half found no difference between menthol and nonmenthol smokers and about half found that menthol smokers had significantly shorter TTFC than nonmenthol smokers, but this was true only among limited subgroups of subjects. Given both the number of high-quality studies and their overall consistent findings, it is reasonable to conclude that the **"evidence is suggestive of no causal relationship"** between smoking menthol cigarettes and significantly increased levels of nicotine dependence.

Numerous Hypotheses Put Forth by TPSAC are Speculative and Cannot Serve as the Basis for Regulatory Policy

From review of meeting transcripts and presentations given at TPSAC meetings, it is apparent that committee members are concerned about a number of unfounded hypotheses. For example, TPSAC has addressed whether menthol cigarettes are perceived by menthol smokers as less harmful than nonmenthol cigarettes. The data show that this is not true. This and other speculative hypotheses are addressed in Chapter 6.

A Ban on Menthol Cigarettes Will Result in Significant Countervailing Effects

If a ban were imposed on menthol cigarettes, despite the scientific evidence that does not support regulating menthol cigarettes differently than nonmenthol cigarettes, the evidence unequivocally shows that the result would be a dramatically larger illegal cigarette market than currently exists. As a result, there also would be severe negative impacts on public health, including exposure of smokers to more harmful contraband cigarettes, increased access of youth to tobacco, increased criminal activity particularly in urban communities, reduced government revenues and loss of jobs.

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INTRODUCTION

Under the Family Smoking Prevention and Tobacco Control Act (the Act), the Tobacco Products Scientific Advisory Committee (TPSAC) must issue a report and recommendations to the Food and Drug Administration (FDA) on "the issue of the impact of the use of menthol in cigarettes on the public health, including such use among children, African-Americans, Hispanics, and other racial and ethnic minorities" (Act at § 907(e)).

THE INDUSTRY MENTHOL REPORT

While FDA had invited all members of the TPSAC to participate in developing the menthol report and recommendation, FDA allowed only the voting members to participate in writing the report. FDA invited the three non-voting members representing industry interests to collaborate in providing an industry perspective. This report (Industry Menthol Report) provides the industry perspective on the use of menthol in cigarettes.

The hallmark of FDA regulation long has been a commitment to science-based decisions that rely on the best available data. Consistent with the FDA's commitment, the purpose of the Industry Menthol Report is to provide the FDA with a complete and thorough evaluation and assessment of the best available scientific data to determine whether the use of menthol in cigarettes disproportionately impacts public health compared to nonmenthol cigarettes.

The focus of the Industry Menthol Report on the assessment of any disproportionate public health effects of menthol cigarettes over nonmenthol cigarettes is the only appropriate focus for FDA. All cigarettes are hazardous to health. A conclusion that removal of menthol cigarettes from the market plausibly would have some public health benefit does not require any scientific analysis by TPSAC or FDA. It is axiomatic that removal of the segment of any cigarette taste preference – whether that be menthol, nonmenthol, lower tar, higher tar, filtered or unfiltered cigarettes – may result in some smokers quitting and thus some public health benefit. However, that is a very different question than that posed in the Act. Failing to examine the public health impact in terms of any disproportionate harm from menthol cigarettes when compared to nonmenthol cigarettes inevitably leads first to a removal of menthol cigarettes from the market and eventually could lead to a complete ban of all cigarettes, which would violate §907(d)(3) of the Act.

The Industry Menthol Report takes into account the statutory considerations that TPSAC and FDA must consider: (1) "the risks and benefits to the population as a whole, including users and nonusers of tobacco products" (Act at § 907(a)(3)(B)(i)); (2) "the increased or decreased likelihood that existing users of tobacco products will stop using such products" ((Act at § 907(a)(3)(B)(i)); (3) "the increased or decreased likelihood that those who do not use tobacco products will start using such products." (Act at § 907(a)(3)(B)(i)); and (4) "information concerning the countervailing effects of the proposed standard [or recommendation] . . ., such as the creation of a significant demand for contraband." (Act at § 907(b(3)(B)).

Any decision by FDA regarding menthol must be grounded in accurate and reliable scientific data. The Industry Menthol Report is a complete and thorough scientific review that FDA can use in determining whether to take any action with respect the use of menthol in cigarettes.

A strict scientific standard was applied in the Industry Menthol Report to evaluate the studies and data relating to the impact of the use of menthol in cigarettes on the public health. The standard included objectivity and inclusiveness in evaluation of the scientific literature and data, as well as consideration for the full spectrum of worthy scientific interpretations of the data. The Industry Menthol Report is science-based and data-driven and includes an evaluation of the totality of the scientific data regarding the use of menthol in cigarettes, including data presented in published studies, as well as data provided to FDA by the Industry[1] and others. Studies that were properly designed and provide direct measurable data and outcomes which have been evaluated with statistical precision and rigor form the basis for the conclusions in the Industry Menthol Report.

Organization of the Industry Menthol Report

The Industry Menthol Report is designed to address whether the use of menthol in cigarettes disproportionately impacts public health compared to nonmenthol cigarettes, including such use among children, African American, Hispanics and other racial and ethnic minorities. Mindful of the requirements of the Act, the Industry Menthol Report specifically considers:

1. The risks and benefits to the population as a whole of smoking menthol cigarettes compared to smoking nonmenthol cigarettes;
2. The increased or decreased likelihood that existing smokers of menthol cigarettes will have disproportionate rates of quitting compared to smokers of nonmenthol cigarettes;
3. The increased or decreased likelihood that non-smokers will have disproportionate rates of initiation with menthol cigarettes compared to nonmenthol cigarettes; and
4. The countervailing effects of any recommendation on the public health including the creation of a significant demand for contraband menthol cigarettes.

Therefore, the Industry Menthol Report assesses the disproportionate impact, if any, that menthol cigarettes have over nonmenthol cigarettes on disease occurrence, initiation, cessation and

[1] Tobacco product manufacturers and other stakeholders have expended extraordinary efforts to provide TPSAC, as well as FDA, with relevant information regarding menthol. Since the enactment of the Act in 2009, Lorillard Tobacco Company, R.J. Reynolds Tobacco Company and Altria Client Services Inc. on behalf of Philip Morris USA, Inc., and possibly others (collectively Tobacco Manufacturers) have cooperated with FDA in implementing the provisions of the Act and have invested significant time and resources to provide TPSAC and FDA with relevant science and information so that TPSAC can meets its statutory charge of evaluating the science on menthol and provide FDA with its report and recommendation. Tobacco Manufacturers have submitted numerous written submissions and made numerous presentations to TPSAC during the course of its menthol review. Tobacco Manufacturers and possibly others have spent hundreds of hours collecting, reviewing and submitting documents to FDA in order to respond to specific requests from TPSAC about the use of menthol in cigarettes. Additionally, Tobacco Manufacturers have provided written comments to numerous regulatory proposals or other notices for information posted in the Federal Register relating to tobacco products, many of which have relevance to the use of menthol in cigarettes.

dependence while considering the countervailing effects that a ban on the use of menthol cigarettes (considered only in order to fully assess the countervailing effects) would have on the public health.

The chapters included in the Industry Menthol Report are:

- Chapter 1. APPROACH TO DATA ANALYSIS AND DECISION MAKING
- Chapter 2. DEMOGRAPHICS OF MENTHOL CIGARETTE PREFERENCE AND CURRENT TRENDS IN SMOKING PREVALENCE
- Chapter 3.
  - 3A. MENTHOL IN CIGARETTES DOES NOT CHANGE THE INHERENT HEALTH RISKS OF SMOKING
  - 3B. MENTHOL IN CIGARETTES HAS NO MEANINGFUL EFFECT ON BIOMARKERS OF EXPOSURE AND POTENTIAL HARM
  - 3C. EVIDENCE IS INADEQUATE TO CONCLUDE THAT MENTHOL IN CIGARETTES ADVERSELY IMPACTS SMOKING TOPOGRAPHY
  - 3D. MENTHOL IN CIGARETTES DOES NOT ADVERSELY IMPACT THE TOXICOLOGIC PROPERTIES OF MAINSTREAM SMOKE
  - 3E. MENTHOL DOES NOT MEANINGFULLY ALTER THE CHEMICAL COMPOSITION OF MAINSTREAM SMOKE
- Chapter 4. EVIDENCE IS INADEQUATE TO CONCLUDE THAT MENTHOL IN CIGARETTES ADVERSELY IMPACTS SMOKING INITIATION BEHAVIORS
- Chapter 5.
  - 5A. MENTHOL IN CIGARETTES HAS NO MEANINGFUL IMPACT ON SMOKING CESSATION
  - 5B. MENTHOL IN CIGARETTES HAS NO MEANINGFUL IMPACT ON NICOTINE DEPENDENCE
- Chapter 6. SEVERAL HYPOTHESES POSED BY TPSAC ARE SPECULATIVE
- Chapter 7. A BAN ON MENTHOL CIGARETTES WILL RESULT IN SIGNIFICANT COUNTERVAILING EFFECTS
- Chapter 8. CONCLUSIONS

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CHAPTER 1.
APPROACH TO DATA ANALYSIS AND DECISION MAKING

STUDIES AND DATA EVALUATED

The conclusions of the Industry Menthol Report are based on a comprehensive and inclusive review of the available literature and data related to the use of menthol in cigarettes. The Industry Menthol Report is science-based and data-driven and includes an evaluation of the totality of the scientific data regarding the use of menthol in cigarettes, including data presented in published studies, as well as data provided to FDA by the Industry[1] and others. Scientific data were examined from observational epidemiology, experimental and clinical studies, as well as large, nationally representative surveys and individual studies of specific populations.

The available literature and reported data on epidemiology, biomarkers of exposure and harm, smoking topography, toxicology and analytical chemistry studies comparing menthol cigarettes to nonmenthol cigarettes were evaluated using well-established procedures that have been used by public health authorities, such as the U.S. Surgeon General, the International Agency for Research on Cancer (IARC) and the National Academy of Sciences Institute of Medicine (IOM), to determine the weight of evidence for or against causal inferences with respect to menthol.

Data regarding the use of menthol and nonmenthol cigarettes have also been collected by large, nationally representative surveys that typically capture only self-reported statements of behavior and subjective intent. Survey data have not been considered in prior deliberations by FDA Advisory Committees, Surgeon General's Report authors or IARC Working Groups in developing causal inferences or assessing the strength of causal relationships because survey instruments are, by nature, less controlled in terms of taking into account or correcting for confounding or mediating factors.

Data related to the demographics of smoking prevalence and the preference of smokers for menthol and nonmenthol cigarettes can be obtained primarily from two major sources: nationally representative surveys and individual studies of specific populations. Demographic data from studies based on national surveys were generally determined to be more informative because the sample populations have been weighted to reflect nationally representative estimates aligned with the U.S. population; hence, study findings are considered to be representative of the entire smoking population. This was not always the case for individual studies based on specific populations. Findings from individual studies were only considered to be representative of the entire smoking population if external validity was demonstrated through appropriate comparisons.

Data and studies of smoking behaviors such as initiation, cessation and dependence comparing menthol and nonmenthol cigarette smokers were also primarily derived from nationally representative surveys and individual studies of specific populations. Published studies of these types of smoking behaviors were given an additional level of review. The published literature in the

[1] The written comments, submissions and presentations to TPSAC or to FDA by Lorillard Tobacco Company (Lorillard), R.J. Reynolds Tobacco Company (RJRT) and Altria Client Services Inc. (Altria) on behalf of Philip Morris USA, Inc. regarding the use of menthol in cigarettes and the marketing of cigarettes, generally, are incorporated herein by this reference.

areas of smoking initiation, cessation and dependence was independently identified and was systematically evaluated by an independent organization (Covance Market Access Services Inc. (Covance)) for methodologic quality (using criteria developed by the Agency for Healthcare Research and Quality (Ranney et al. 2006)), and for ability to support inferences related to menthol. Rating categories included: "good," "good to fair," "fair," "fair to poor," and "poor." Based on the review, the studies were categorized into three tiers:[2]

- Tier 1 studies were those rated by Covance as fair or better with respect to both overall quality and ability to support inferences related to menthol cigarette use;
- Tier 2 studies were those rated by Covance as fair or better with respect to overall quality, but lower than fair with respect to ability to support inferences related to menthol cigarette use; and
- Tier 3 studies were those rated by Covance as lower than fair with respect to both categories.

APPROACH FOR ANALYZING THE STRENGTH OF EVIDENCE

Scientific standards for determining the strength of evidence regarding any health effects related to menthol have guided the conclusions reached in the Industry Menthol Report. The approach taken by the Surgeon General's Reports (SGR) provides a reasonable basis to develop conclusions and determine the weight of scientific evidence in regard to any effect of the use of menthol in cigarettes on the public health.

Beginning in 1964, the Office of the Surgeon General periodically has issued reports on smoking and health, which have included syntheses of epidemiologic and other evidence supporting inferences of causation and evaluating the strength of those inferences for a number of smoking-related diseases (USPHS 1964). The scientific standards and processes employed by the SGR authors in support of inferences of causation have continued to evolve over the course of the series of SGRs as increasingly diverse data accumulated. This evolution culminated in a major report issued in 2004 (USDHHS 2004) that formalized and delineated the standards and processes employed in determinations of causal inferences for diseases and conditions associated with smoking, as well as specific categorization of the strengths of any causal inferences (USDHHS 2004).

The causal inference paradigm and categories describing the strength of the inference advanced in the 2004 SGR were not novel; they represented the essence of standards and terminology that had already been established by the IOM and IARC. The 2004 SGR sought to provide clarity regarding judgments of the strength and weight of available evidence for or against a given causal inference between smoking and a specific disease.

The authors of the original 1964 SGR on smoking and health had offered a similar philosophy and process for judgments of causal inference at a time when the available biomedical and epidemiologic

[2] Covance Market Access Services Inc., "The Role of Menthol Flavoring in Smoking Initiation, Cessation and other Smoking Behaviors: A Search and Methodological Evaluation of the Literature" Final Study Report Version 3.1, March 16, 2011. An earlier version of this report was provided to TPSAC and a summary of the findings was presented to TPSAC on February 10, 2011. Analysis of recent additional studies was added in the Final Study Report Version 3.1.

information on smoking was at a far less advanced state of maturity. The process for the development of causal inferences for smoking and disease that were set forth by the 1964 SGR authors included considerations later specified by A. Bradford Hill in 1965 (Hill 1965), as well as a component of scientific judgment beyond those criteria (USPHS 2004).

The Bradford Hill criteria comprise an itemization of the qualities of available scientific data and of the process of reasoning required to develop a defensible scientific judgment in regard to whether an established association between an exposure and a health outcome may be inferred to be causal. As recognized in the 2004 SGR "[a]ll of these criteria were meant to be applied to an already established statistical association; if no association has been observed, then these criteria are not relevant" (USDHHS 2004).

The quality and quantity of available data determine the degree of strength of the final judgment and the ultimate conclusion of whether a causal inference is (1) confirmed with high confidence, (2) suspected but not confirmed in the face of substantive remaining uncertainties, (3) equivocal in the face of sparse or conflicting data, or (4) rebutted by substantial contrary data. The nine Bradford Hill criteria have been frequently distilled and represented as the qualities of *consistency, strength, specificity, temporality*, and *coherence* that characterize the strength of the available data for a potential cause and effect relationship (Hill 1965). Each of these dimensions of overall data quality is encompassed in the Surgeon General's 2004 guidance for evaluating the existence and strength of causality in regard to smoking. As recognized in the 2004 SGR, "[t]hese criteria, which were just emerging into public health [in 1964], have since become widely accepted and used in epidemiology and public health" (USDHHS 2004).

The statistical significance of thoughtfully designed and well-executed scientific or epidemiologic investigations into a potential cause and effect relationship is a starting point in assessing the *consistency* and *strength* of the data. The magnitude of measurable study outcomes and the consistency of findings developed from multiple independent investigations build confidence in the development (or refutation) of causal inferences (Hill 1965). In the 2004 SGR, *consistency* refers to "the persistent finding or an association between exposure and outcome in multiple studies of adequate power [emphasis added], and in different persons, places, circumstances, and time" and its purpose "is to make the hypothesis of a chance effect unlikely…" (USDHHS 2004). *Strength* of an association refers to "the magnitude of the association and its statistical strength" (USDHHS 2004). The *specificity* of the relationships between smoking and a disease can be an important consideration because all smoking-related diseases are known to occur in nonsmokers as well, reflecting other environmental or genetic causes or spontaneous disease occurrence. The *coherence* of data derived from diverse areas of study may be evaluated by an inclusive consideration of all available information on a given topic or subtopic.

Importantly, however, both Hill and the SGR 2004 authors recognized that neither exposure and effect associations nor the statistical significance of those associations are in themselves sufficient to warrant an inference of causation (Hill 1965, USDHHS 2004). As stated in the 2004 SGR, although inferences, whether about causality or statistical associations, are always uncertain to a degree, the goal of the SGR approach "is to explain and communicate scientific judgments as to whether observed associations … are likely to be causal, based on the totality of scientific evidence." The 2004 SGR was also careful to separate causal conclusions from public health recommendations (USDHHS 2004).

The 2004 SGR adopted a four-level hierarchy of categories (2004 SGR Categories) to classify the strength of causal inferences between smoking and diseases, based on available evidence:[3]

- Evidence is sufficient to infer a causal relationship (i.e., smoking is proven to cause the disease).
- Evidence is suggestive but not sufficient to infer a causal relationship. (i.e., smoking more likely than not causes the disease).
- Evidence is inadequate to infer the presence or absence of a causal relationship (i.e., there is not enough proof that smoking does or does not cause the disease).
- Evidence is suggestive of no causal relationship (i.e., smoking probably does not cause the disease) (USDHHS 2004).

Importantly, SGR 2004 noted that "[t]here is no category beyond 'suggestive of no causal relationship' as it is extraordinarily difficult to prove the complete absence of a causal association" (USDHHS 2004). The general and inherent limitation of the scientific method in providing absolute proof of the absence of an effect must be borne in mind in the present consideration of menthol.

APPLICATION OF THE 2004 SGR CATEGORIES REGARDING CAUSAL INFERENCES RELATED TO MENTHOL CIGARETTES COMPARED TO NONMENTHOL CIGARETTES

In the present question of whether the use of menthol in cigarettes may adversely affect the public health, FDA must consider the potential of menthol to adversely impact the disease risks to the individual smoker; to the smoking population, generally; or to subpopulations of smokers. Well-established, proven general guidance and scientific principles for such a consideration are provided in the 2004 SGR, with some modifications required to address the specific menthol topics delineated in the text of the Act and reiterated in FDA's charge to the TPSAC.

The possible four conclusions relative to the review of the scientific literature on menthol expressed in terms of the four 2004 SGR categories are stated as follows:

- Evidence is sufficient to infer a causal relationship between the use of menthol in cigarettes and an adverse impact on public health (i.e., smoking menthol cigarettes is proven to cause disease in the smoker, in the general population, or in subpopulations over and above that caused by smoking nonmenthol cigarettes; or smoking menthol cigarettes is proven to cause increased or earlier smoking initiation or reduced smoking cessation over and above that caused by smoking nonmenthol cigarettes). (Sufficient)
- Evidence is suggestive but not sufficient to infer a causal relationship between the use of menthol in cigarettes and an adverse impact on public health (i.e., smoking menthol cigarettes is more likely than not to cause disease in the smoker, in the general population, or in subpopulations over and above that caused by smoking nonmenthol cigarettes; or

[3] Similar hierarchical approaches have also been used by the Institute of Medicine committees (IOM 1999) to classify causal conclusions and by the International Agency for Research on Cancer (IARC 1986) to classify conclusions regarding whether substances are carcinogenic.

smoking menthol cigarettes is more likely than not to cause increased or earlier smoking initiation or reduced smoking cessation over and above that caused by smoking nonmenthol cigarettes). (Suggestive)

- Evidence is inadequate to infer the presence or absence of a causal relationship between the use of menthol in cigarettes and an adverse impact on public health (i.e., there is not enough proof that smoking menthol cigarettes does or does not cause disease in the smoker, in the general population, or in subpopulations over and above that caused by smoking nonmenthol cigarettes; or there is not enough proof that smoking menthol cigarettes does or does not cause increased or earlier smoking initiation or reduced smoking cessation over and above that caused by smoking nonmenthol cigarettes). (Inadequate)
- Evidence is suggestive of no causal relationship between the use of menthol in cigarettes and an adverse impact on public health (i.e., the evidence does not suggest that smoking menthol cigarettes causes disease in the smoker, in the general population, (or in subpopulations) over and above that caused by smoking nonmenthol cigarettes; or the evidence does not suggest that smoking menthol cigarettes causes increased or earlier smoking initiation or reduced smoking cessation over and above that of caused by smoking nonmenthol cigarettes). (No Causal Relationship)

As noted above, because it is difficult to prove the complete absence of a causal relationship, the SGR 2004 does not provide a category beyond the final category -- "evidence is suggestive of no causal relationship."

In terms of the evaluation of menthol, if an assessment falls into the category of "Suggestive," it may be appropriate for FDA to recommend further study of the issues. However, if an assessment of the totality of available scientific evidence falls into either of the final two categories ("Inadequate" or "No Causal Relationship"), no regulatory action on menthol is warranted by FDA. Also, as Hill pointed out, his criteria were to be used only if an association was "perfectly clear-cut and beyond what we would care to attribute to the play of chance" (Hill 1965). This indicates that if a statistically significant association cannot be established between menthol and a given health effect, the "evidence is suggestive of no causal relationship."

EQUIPOISE

The use of the categories adopted by the U.S. Surgeon General in the Industry Menthol Report differs from the report to be issued by TPSAC, which uses the concept of equipoise. Equipoise has been used historically to provide an ethical basis for conducting medical research involving treatments of patients in clinical trials and more recently to evaluate veterans' eligibility for certain medical benefits. Although the concept of equipoise has been used to express the "strength of *overall* evidence" [emphasis in original] for or against a causal relationship between exposure and disease (IOM 2008), TPSAC applied the concept in a framework very different from IOM (TPSAC 2011). It is important to consider whether or not equipoise, as used by TPSAC, is the best approach for determining causation issues and questions related to any public health impact of the use of menthol as a cigarette ingredient above and beyond that for nonmenthol cigarettes. The simple answer is that it is not.

To understand why TPSAC's unique application of the equipoise concept is inappropriate, a short discussion of the background use of equipoise is necessary. The use of equipoise in determining causation was employed in the IOM 2008 report on determining veterans' benefits (IOM 2008). First, the IOM report described equipoise "to refer to the point at which the evidence is in balance between favoring and not favoring causation" (IOM 2008). Freedman, however, in his seminal article on equipoise and clinical research noted that this type of "theoretical equipoise" is near unattainable:

> Theoretical equipoise exists when, overall, the evidence on behalf of two alternative treatment regimens is exactly balanced. This evidence may be derived from a variety of sources, including data from the literature, uncontrolled experience, considerations of basic science and fundamental physiological processes, and perhaps a "gut feeling" or "instinct" resulting from (or superimposed on) other considerations…. Theoretical equipoise is overwhelmingly fragile; that is, it is disturbed by a slight accretion of evidence favoring one arm of the trial…. Theoretical equipoise is also highly sensitive to the vagaries of the investigator's attention, and perception. Because of its fragility, theoretical equipoise is disturbed as soon as the investigator perceives a difference between the alternatives – whether or not any genuine difference exists…. Finally, as described by several authors, theoretical equipoise is personal and idiosyncratic. It is disturbed when the clinician has, in Shafer's words, what "might be labeled as bias or a hunch," a preference of a "merely intuitive nature." (Freedman 1987).

As noted in the 2008 IOM report, equipoise is based on the underlying scientific data. Discussing the evidence necessary for an association between an agent and a disease, the IOM report states "[a]lthough it is not sufficient for establishing causation, association is nevertheless prima facie evidence for causation, and the lack of association is prima facie evidence for lack of causation" (IOM 2008). Much like the Hill criteria, the lack of an association must certainly stop the analysis. As described earlier, Hill notes in introducing his criteria "[o]ur observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance" (Hill 1965).

Similar to the 2004 SGR, the 2008 IOM Report also proposed "a four-level categorization of the strength of the *overall evidence* for or against a *causal relationship* between exposure and disease:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests a lack of a causal relationship.

The term "equipoise" is used to refer to the point at which the evidence is in balance between favoring and not favoring causation (IOM 2008).

The 2008 IOM report provides valuable insight into the lack of rigor the equipoise method employs as compared to the Surgeon General's Criteria. For example, the equipoise concept seemingly

rejects the consistency requirement. The Surgeon General's consistency requirement seeks "persistent finding of an association between exposure and outcome in multiple studies of adequate power, and in different persons, places, circumstances, and times" (USDHHS 2004 at 21).

The IOM's description and application of the equipoise concept is in stark contrast to the approach adopted by TPSAC. Although TPSAC adopts a "hierarchical classification for the strength of evidence," the categories adopted by TPSAC can be contrasted with those used by the 2008 IOM Report:

> TPSAC - "The evidence is sufficient to conclude that a relationship is more likely than not" (contrasted to IOM 2008 - "*Sufficient:* The evidence is sufficient to conclude that a causal relationship exists").
>
> TPSAC - "The evidence is sufficient to conclude that a relationship is at least as likely as not" (contrasted to IOM 2008 – "*Equipoise and Above:* The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists").
>
> TPSAC - "The evidence is insufficient to conclude that a relationship is more likely than not" (contrasted to IOM 2008 – "*Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment').
>
> TPSAC – "There is insufficient evidence to determine whether a relationship exists" (contrasted to IOM 2008 - *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment").

Most important, TPSAC completely eliminates the fourth category adopted by IOM: "*Against*: The evidence suggests the lack of a causal relationship." This omission alone means that TPSAC cannot conclude that there is evidence that the use of menthol in cigarettes suggest no impact on public health, even though, as described in the following Chapters of the Industry Menthol Report, this is the appropriate category for the majority of the scientific evidence on menthol. This omission is a serious flaw in TPSAC's approach.

In addition to this critical omission, the equipoise concept as described by TPSAC lacks specific common assessment criteria to be followed in evaluating the evidence. As opposed to the specific criterion set forth in the Surgeon General's Criteria, TPSAC did not propose specific criteria that would be applied uniformly. The absence of uniform, specified criteria severely limits conclusions that can be drawn from such a methodology. The scientific underpinning of reproducibility is cast to the wind because no one, other than the two-to-three person subcommittee for each chapter, could review the evidence and come to the same or similar conclusions based on the described method. As a result, the methodology TPSAC has reported also lacks the type of scientific rigor envisioned by Congress and expressed by FDA, particularly when the result of a recommendation from TPSAC could result in a consumer product being permanently removed from the market.

The modified equipoise concept adopted by TPSAC is, therefore, an inappropriate tool to be used in an objective, data-driven, science-based evaluation due to the critical omission of a complete category of causal inference, along with the susceptibility of any determination to be impacted by instinct, bias, and hunches of the evaluator.

PROPER INTERPRETATION OF DATA

When determining the weight that should be given to any scientific research or data, it is essential to interpret the research findings and data appropriately and objectively. Many of the studies related to cigarette mentholation are observational studies that examine whether an association exists between the use of menthol in cigarettes and specific public health issues such as disease incidence, smoking initiation, dependence or smoking cessation. The existence of an association is a necessary condition of any eventual causal inference; however, variables may be associated without there being any causal relationship. Thus, the existence of an association does not prove causation and in many instances does not even support a causal inference.

Often, the magnitude of an association is expressed by a comparative risk estimate (such as a relative risk, odds ratio, or hazard ratio), with a 1.0 risk estimate representing no increased risk. A risk estimate, however, is just that: an estimate of the strength of an association. Generally, the greater the risk estimate, the more likely that association is real (i.e., not due to bias or confounding). Confounding refers to the distortion of an observed association between two variables by a third factor associated with both the exposure and the outcome, but not considered in the analysis. Potential confounding factors must be considered in any reported association between the use of menthol in cigarettes and the outcome being examined. Examples of potential confounding factors in many studies of menthol cigarettes include race, sex, body mass index, socioeconomic status, residence of study participants, and tar, nicotine and carbon monoxide levels of the cigarettes studied, among other things. Caution must be exercised when inferring any causal relationship when risk estimates are below 2.0, because risk estimates of this magnitude can be produced by bias or confounding. Many respected epidemiologists believe that risk estimates below 2.0 are too weak to support a causal inference, especially when the related body of literature is inconsistent or even shows a non-significant reduced risk (e.g., Wynder 1996).

Statistical significance of research results, including risk estimates, is an important consideration with respect to the scientific weight accorded those results. The confidence interval of a statistical estimate of the strength of an association between two variables is an indication of whether the association is likely to be due to chance. The confidence interval is the range within which the true mean value is believed to be contained, with a given probability (typically 95%). The statement that a given result is statistically significant (usually at the $\alpha=0.05$ level, or below) means that it has a *low probability* of being due to chance. However, chance or sampling variability can never be completely ruled out as an explanation for a result.

A risk estimate is judged to be statistically significant if the 95% confidence interval does not contain 1.0. Further, although a risk estimate may be greater or lower than 1.0, if the confidence interval includes 1.0, the risk estimate is not considered to be statistically significant. A risk estimate that is not statistically significant means that chance or sampling variability cannot be ruled out as an explanation for the observed association. Importantly, a statistically non-significant elevated or reduced risk estimate (one that is greater or lower than 1.0, respectively) with a confidence interval that includes 1.0 cannot be interpreted as indicating a trend toward an increased risk or as being suggestive of an increased risk. In addition, statistically significant scientific findings are the essential foundation of any defensible causal inference, but may not in themselves be sufficient to infer

causation, particularly for complex associations such as those between multidimensional smoking behaviors and multifactorial disease conditions.

Note that in the Industry Menthol Report when study results or data are discussed as being "significant" or "non-significant," those terms mean "statistically significant" or "statistically non-significant," respectively.

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CHAPTER 2.
DEMOGRAPHICS OF MENTHOL CIGARETTE PREFERENCE AND CURRENT TRENDS IN SMOKING PREVALENCE

It has been suggested that individuals that smoke menthol cigarettes may be more likely to transition from cigarette experimentation to established smoking (i.e., initiate smoking), may be more likely to exhibit evidence of nicotine dependence and/or may be less likely to successfully quit smoking. This chapter reviews what is known about current smokers and the demographic characteristics that may be associated with higher menthol compared to nonmenthol cigarette preference. Properly interpreted, such demographic data can provide the necessary context for subsequent examinations of potential population-level effects (i.e., smoking initiation, dependence and/or cessation) that may be associated with higher menthol cigarette preference.

The available data indicates that menthol compared to nonmenthol cigarette preference is significantly higher among current smokers that are African American[1] and, to a lesser extent, female. Some studies appear to suggest a higher menthol cigarette preference among younger compared to older smokers; however, these data are less consistent than for African American and female smokers.

Also discussed are current trends in smoking prevalence, i.e., the proportion of the overall population (or subpopulation) that smoke cigarettes. Evidence that a specific group of smokers reports a higher preference for menthol cigarettes, or that preference among a group of smokers is increasing over time must not be interpreted as evidence of increased smoking prevalence. The reality is that smoking prevalence for the U.S. population has been steadily declining for the past two decades, regardless of demographic characteristics associated with race/ethnicity, sex or age category.

DEMOGRAPHICS DATA FOR MENTHOL CIGARETTE PREFERENCE

Information on the demographics of menthol compared to nonmenthol cigarette preference is available from nationally representative surveys and from individual studies of specific populations. Demographic data from studies based on national surveys are generally more informative due to the fact that the sample populations have been weighted to reflect nationally representative estimates aligned with the U.S. population; hence, study findings are considered to be representative of the entire smoking population. This is not the case for individual studies based on specific populations; findings from these studies would only be considered representative of the entire smoking population if external validity was demonstrated though appropriate comparisons.

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[1] Studies refer to racial/ethnic subgroups in different ways. When citing specific studies, this Industry Menthol Report uses the terms used by the study authors. When discussing race/ethnicity in general terms, the term African Americans is used and includes African Americans, Blacks, and non-Hispanic Blacks. The term Whites is used to refer to Whites, Caucasians, European Americans and non-Hispanic Whites. The term Hispanics is used to refer to Hispanics and Latinos.

Demographics data on menthol compared to nonmenthol cigarette preference among nationally representative populations of smokers are provided by five nationally representative surveys, as follows:

- National Health and Nutrition Examination Survey (NHANES),
- National Health Interview Survey (NHIS),
- National Survey on Drug Use and Health (NSDUH),
- National Youth Tobacco Survey (NYTS), and
- Tobacco Use Supplement to the Current Population Survey (TUS-CPS).

A brief description for each of the surveys is provided.

National Health and Nutrition Examination Survey (NHANES)

The NHANES is a major program of the National Center for Health Statistics (NCHS) that is designed to assess the health and nutritional status of adults and children. This nationally representative survey provides samples of the U.S. civilian, non-institutionalized population (~5,000 persons/year), completed in two-year cycles. Information on smoking is collected in similar fashion for older and younger participants, using computer aided self-reports and not direct interviews. For adult respondents (aged ≥20 years), interviews are completed prior to a physical examination, in the home, using the Computer-Assisted Personal Interviewing system. For respondents aged 12-19 years, smoking information is obtained during a physical examination, at the Mobile Examination Center (MEC), in the MEC Interview Room; respondents used audio computer-assisted, self-interviews. To estimate menthol cigarette use, current adult smokers are asked, "What brand of cigarettes [do you] usually smoke?" Brand is visually confirmed, but in the absence of visual confirmation adult smokers are asked, "Is the cigarette product mentholated or nonmentholated?" Youth respondents (aged 12-19 years) are asked to indicate the specific brand name cigarettes in response to the question, "During the past 30 days, on the days that you smoked, which brand of cigarettes did you usually smoke?" For Marlboro, Winston, Benson and Hedges, and "other," respondents are asked, "Was the [brand] cigarettes menthol or nonmenthol?"

National Health Interview Survey (NHIS)

The NHIS is a cross-sectional survey conducted by the NCHS that collects information on a variety of health indicators. This continuing nationwide sample survey collects data using personal household interviews with individuals aged ≥18 years. The NHIS includes an Adult Health Behavior section that contains questions related to cigarette smoking. All adults that indicate that they currently or formerly smoked are asked whether their usual cigarette brand is or was mentholated, whether they had ever tried to quit smoking, and the method(s) they used the last time they tried to stop smoking. To estimate menthol cigarette use, current adult smokers are asked the following question, "Earlier you said you smoke cigarettes. Is your usual cigarette brand menthol or nonmenthol?"

National Survey on Drug Use and Health (NSDUH)

The NSDUH, formerly called the National Household Survey on Drug Abuse (NHSDA), was initiated in 1971 as a result of legislation enacted in 1970 that created the Commission on Marijuana and Drug Abuse. This survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), and has grown in size and complexity from its initial sample size of ~3,000 to its current sample of nearly 70,000 persons. Participants of the survey represent the U.S. civilian, non-institutionalized population, aged ≥12 years. The survey is currently conducted via computer-assisted interviewing. To estimate menthol cigarette use, respondents are asked the following questions, "During the past 30 days, what brand of cigarettes did you smoke most often?" and "Were the [FILL] cigarettes you smoked during the past 30 days menthol?" Menthol status is typically assigned based on response to the latter question only, as many leading cigarette brands have menthol and nonmenthol sub-brands and these details are not collected in the survey.

National Youth Tobacco Survey (NYTS)

In collaboration with the Centers for Disease Control and Prevention (CDC), the American Legacy Foundation developed the NYTS to measure the tobacco-related beliefs, attitudes and behaviors of youth. This survey is a self-administered, school-based survey that targets students in grades 6 through 12 (aged 9-21 years). Surveys are completed anonymously, in a group setting, during the school day and on school property. The 1996, 1998 and 2000 surveys used passive parental consent, while the 2002 and 2004 surveys used active parental consent. In contrast, the 2006 and 2008 surveys used a mixed parental consent procedure. The NYTS uses a multi-stage sampling design to produce a nationally representative sample of students. The survey questions used to assess menthol cigarette smoking changed slightly from survey to survey between 1999 and 2006, but have consistently attempted to determine cigarettes usually smoked; for example, respondents were asked the following question during the 2004 and 2006 surveys, "Are the cigarettes you usually smoke menthol cigarettes?"

Tobacco Use Supplement to the Current Population Survey (TUS-CPS)

The Tobacco Use Supplement of the Current Population Survey (TUS-CPS) is a survey of tobacco use that is co-sponsored by the National Cancer Institute (NCI) and the CDC. TUS-CPS has been conducted approximately every three years, and uses a nationally representative sample that contains information on ~240,000 individuals within a survey period. Smoking information is collected for a U.S. civilian, non-institutionalized population aged ≥15 years. Approximately 70% of the respondents complete the survey by telephone, and ~30% complete the survey in person. The survey contains mostly self-reported data, although ~20% of the data for a few measures of tobacco use are collected by proxy (i.e., data are collected about others in the household indirectly from the survey respondent). To estimate menthol cigarette use in 2003 and 2006/07, current smokers were asked the following question, "Is your usual cigarette brand menthol or nonmenthol?"

EXAMINATION OF AVAILABLE DATA ON SMOKING DEMOGRAPHICS

As noted above, there are two sources for data on the demographics of menthol compared to nonmenthol cigarette preference: nationally representative surveys and individual studies of specific populations.

Eleven publications were identified that provided data on the demographics of menthol compared to nonmenthol cigarette preference. Of these studies, six analyses were based on data from four national surveys, appropriately weighted to be representative of the overall smoking population, including:

Table 2-1. National Surveys Examining the Demographics of Menthol Cigarette Preference

National Survey	Citation	Target Population	Size
2005 NHIS	Cubbin et al. 2010	Adult smokers (aged 25-64 years)	3,902
	Mendiondo et al. 2010	Adult smokers (aged ≥18 years)	6,055
2003, 2006/07 TUS-CPS	Fernander et al. 2010	Adult smokers (aged ≥18 years)	66,145
	Lawrence et al. 2010	Adult smokers (aged ≥18 years)	63,193
2004-2008 NSDUH	Rock et al. 2010	Adult smokers (aged ≥12 years)	71,605
2006 NYTS	Hersey et al. 2010	Adolescent smokers (aged 9-21 years)	3,281

Five additional studies provide data on the demographics of menthol compared to nonmenthol cigarette preference among specific populations not necessarily representative of the overall smoking population, including those listed in Table 2-2 below:

Table 2-2. Additional Studies Examining the Demographics of Menthol Cigarette Preference

Citation	Study	Target Population	Size
Hyland et al. 2002	COMMIT (1988)	Adult smokers (aged 25-64 years)	13,268
Murray et al. 2007	Lung Health Study, 1986-1989	Adult smokers (aged 35-60 years)	5,887
Muscat et al. 2002	Case-control study of lung cancer, 1981-1999	Adult smokers	19,545
Pletcher et al. 2006	CARDIA (1985)	Adults (aged 18-30 years)	1,535
Stahre et al. 2010[1]	2005 NHIS	Adult smokers (aged ≥18 years)	6,055

[1] Although Stahre et al. 2010 provides an analysis of data from the NHIS, which is a nationally representative survey, their sample population did not appear to be weighted to provide nationally representative estimates, likely limiting the generalizability of study findings to the overall population of smokers.

Cross-sectional Studies Based on Nationally Representative Populations of Smokers

Six studies are considered to be the "best available science" for examining the demographics of current menthol compared to nonmenthol cigarette preference. These studies are listed in Appendix Table 2-4, and are summarized below based on data source:

National Health Interview Survey (NHIS)

Analyses from both studies examining data from the 2005 NHIS indicated that African American and female smokers were significantly more likely to report current menthol versus nonmenthol cigarette preference compared to White and male smokers, respectively. None of the analyses based on NHIS data suggested that young adult smokers were more likely than older adult smokers to report menthol cigarette preference. These studies are described below:

Cubbin et al. (2010) reported findings for menthol versus nonmenthol cigarette preference among current daily smokers (aged 18-64 years; N=3,902). The proportion of smokers that reported using menthol cigarettes was highest for African Americans; after adjusting for age, education and income, 69.7% (99% CI:61.5-77.8%) of males and 77.9% (99% CI:71.1-84.7%) of females reported current use of menthol cigarettes; for Hispanics, 16.5% (99% CI:9.2-23.8%) of male and 35.6% (99% CI:25.6-45.7%) of female smokers reported using menthol cigarettes; and, the proportions of White male and female smokers that reported using menthol cigarettes were 14.6% (99% CI:11.9-17.3%) and 24.5% (99% CI:21.4-27.7%), respectively. Based on non-overlapping confidence intervals, African American smokers were significantly more likely to smoke menthol cigarettes than Whites (for both sexes) ($p<0.01$); and, female smokers were significantly more likely to smoke menthol cigarettes than males among both Hispanics and Whites ($p<0.01$).

Mendiondo et al. (2010) reported findings for menthol cigarette preference among current smokers (aged ≥18 years; N=6,055). The proportion of current smokers that reported using menthol cigarettes was estimated to be ~25%. After controlling for race/ethnicity, sex and age category, current smokers of menthol cigarettes were significantly more likely to be female than male (OR=1.74; 95% CI:1.30-2.33), and African American (OR=11.52; 95% CI:8.86-14.98) or Hispanic (OR=1.85; 95% CI:1.35-2.55) than White. There were no significant differences based on age category (OR=0.99; 95% CI:0.99-1.00).

Tobacco Use Supplement to the Current Population Survey (TUS-CPS)[2]

Analyses from both studies examining data from the 2003 and 2006/07 TUS-CPS indicated that African American and female smokers were significantly more likely to report current menthol cigarette preference compared to White and male smokers, respectively. Unlike findings from the NHIS, both analyses of TUS-CPS data suggested that younger smokers were significantly more likely to report menthol versus nonmenthol cigarette preference than older smokers, i.e. aged ≥65 years. These studies are described below:

Fernander et al. (2010) reported findings from descriptive analyses and logistic regression models examining menthol versus nonmenthol cigarette preference among current smokers (aged ≥18 years). Descriptive analyses suggested that ~28% of current smokers reported using menthol cigarettes (17,441/63,193). Results from regression models that controlled for demographic characteristics, age at smoking initiation and purchasing unit suggested the odds of using menthol cigarettes were 11-fold higher for African American smokers compared to Whites (OR=11.10; 95% CI:10.01-12.31). Other sociodemographic categories were associated with relatively smaller magnitude differences in the odds of smoking menthol versus nonmenthol cigarettes. For example, male smokers had a 42% lower odds of using menthol cigarettes than females (OR=0.58; 95% CI:0.55-0.61); Hispanic smokers had 55% higher odds of using menthol cigarettes than Whites (OR=1.55; 95% CI:1.40-1.71); and, smokers aged 18-24 years had 66% higher odds of using menthol cigarettes compared to smokers aged ≥65 years (OR=1.66; 95% CI:1.47-1.88).

Lawrence et al. (2010) examined sociodemographic correlates of using menthol cigarettes based on analyses of current smokers who participated in the TUS-CPS (N=63,193). Descriptive analyses suggested that ~28% of current smokers reported using menthol cigarettes (95% CI:27.14-28.10%). The proportions of current smokers that reported using menthol cigarettes were similar (i.e., 20-30% range) for all categories of race/ethnicity, except for African Americans, who were much more likely to prefer menthol to nonmenthol cigarettes (73.6%; 95% CI:71.97-75.16%). Stratifying by sex, female current smokers (32.4%; 95% CI:31.7-32.99%) were more likely than males (23.5%; 95% CI:22.86-24.06%) to report using menthol cigarettes, and this pattern was repeated within strata defined by each of the race/ethnicity groups. Findings from regression models suggested that African American smokers were approximately 11-fold more likely to prefer menthol cigarettes compared with Whites (OR=10.92; 99% CI:9.58-12.44). White females were more likely to report menthol cigarette preference than males (OR 1.67; 99% CI:1.53-1.82), as were African American

[2] Taures et al. (2010) examined the differential effect of price structures and indoor air quality regulations on smokers of menthol versus nonmenthol cigarettes, but did not provide any additional demographic data beyond that provided by cited analyses from the TUS-CPS.

females (OR=1.57; 99% CI:1.26-1.96). The odds of reporting menthol cigarette preference were 2.5- to 3-fold higher ($p<0.01$) among younger African American smokers compared to those aged ≥65 years; no age-related differences were suggested for White smokers. For Hispanic smokers, differences were limited to females being more likely to report menthol cigarette preference compared to males (OR=1.51; 99% CI:1.19-1.91).

National Survey on Drug Use and Health (NSDUH)

A single study examining data from the 2004-2008 NSDUH suggested that significantly higher percentages of African American and female smokers report menthol versus nonmenthol cigarette preference compared to White and male smokers. Moreover, the percentage of current smokers reporting menthol versus nonmenthol cigarette preference was significantly higher among adolescent and younger adult smokers compared to older adults. This study is described below:

Rock et al. (2010) reported findings for menthol versus nonmenthol cigarette preference among past-month smokers (aged ≥12 years; N=71,605). The proportion of past-month smokers that reported using menthol cigarettes was estimated to be ~36%. Among female smokers, a significantly larger proportion smoked menthol compared to nonmenthol cigarettes (52.2% vs. 43.0%; $p<0.01$). African American smokers were almost 10 times more likely to smoke menthol than nonmenthol cigarettes (29.4% vs. 3.0%; $p<0.01$). For Hispanics, 11.7% (95% CI:10.9–12.5%) smoked menthol cigarettes, while 11.5% (95% CI:11.0–12.1%) smoked nonmenthol cigarettes. Preference for past-month menthol cigarette preference was highest in smokers aged 12-17 years (44.7%; 95% CI:43.2-46.2%), and lower among young smokers aged 18-25 years (36.1%; 95% CI:35.3–36.9%) and aged ≥26 years (30.2%; 95% CI:29.4–31.1%).

It has been suggested that estimates of menthol cigarette preference from the NSDUH are based on an overly inclusive question that may misclassify smokers whose usual brand is nonmenthol but have smoked any menthol cigarette(s) in the past month. Estimates of menthol preference among current smokers from the NSDUH are typically higher (e.g., ~36%, as suggested by Rock et al. above) than those from surveys that base estimates of menthol preference on usual cigarette (or brand) smoked (~28%, as suggested by Lawrence et al. 2010 using the TUS-CPS; ~25%, as suggested by Mendiondo et al. 2010 using the NHIS). Additionally, current smokers in the NSDUH estimates were defined as having smoked all or part of a single cigarette in the last 30 days, a much more inclusive definition of smoking compared to that used by other surveys (i.e., having smoked ≥100 cigarettes lifetime and currently smoking on some days or every day). Hence, the potential exists that estimates provided by the NSDUH are somewhat exaggerated, particularly among younger, less experienced smokers.

National Youth Tobacco Survey (NYTS)

A single study examining data from the 2006 NYTS suggested that African American adolescent smokers were significantly more likely to report current menthol versus nonmenthol cigarette preference compared to White smokers; no sex differences were reported. This study is described below:

Hersey et al. (2010) reported that among middle school students, there were no significant differences in the proportions of smokers using menthol versus nonmenthol cigarettes by sex. African American smokers were significantly more likely to report using menthol cigarettes (80.6%; 95% CI:72.0–89.3%), and significantly more likely to prefer menthol cigarettes compared to Whites (43.1%; 95% CI:36.2-50.0%). Among high school students, there were no sex differences for menthol versus nonmenthol cigarette preference (39.4%; 95% CI:33.6- 45.2% for males; and, 46.9%; 95% CI:38.9-54.9% for females). However, there were significant differences for menthol cigarette preference between African American smokers (84.8%; 95% CI:77.3-92.3%) and White smokers (37.6%; 95% CI:31.0-44.3%)

The NYTS differs from the other surveys with regard to both target population (i.e., restricted to adolescents enrolled in public and private schools, grades 6-12) and data collection methodology (i.e., survey is completed in a group versus private setting). The potential for a group versus private survey setting to impact data collection is suggested by a comparison of adolescent responses to identically worded items from the school-based (group setting) Youth Risk Behavior Surveillance System (YRBSS) and household-based (private setting) NHIS (Kann et al. 2002). Published findings indicated that 39 of the 42 identically worded items produced higher risk estimates for the YRBSS compared to the NHIS. For 24 of the items, comparisons yielded significant differences, including higher estimates for ever tried cigarette smoking, smoked a whole cigarette prior to age 13, ever smoked regularly and smoked regularly prior to age 13. Estimates may likewise be exaggerated due to the fact that current smokers were identified based on smoking all or part of a single cigarette in the past month, which overestimates established smoking particularly among younger, less experienced smokers.

Studies Based on Specific Populations of Smokers

Five studies examined the demographics of menthol compared to nonmenthol cigarette preference among current smokers, but have significant weaknesses that preclude drawing sound conclusions regarding demographic information. They are mentioned here briefly because they have been discussed at TPSAC meetings.

- **Hyland et al. (2002)** analyzed baseline characteristics from a randomized community-based intervention trial (N=13,286) for smoking cessation; controlling for covariates suggested that menthol cigarette preference was more common among female compared to male smokers, African American compared to White smokers, and among smokers aged 25-34 years compared to aged 35-64 years.
- **Murray et al. (2007)** analyzed baseline characteristics from a smoking cessation study of adults (N=5,887) with early evidence of obstructive lung impairment; African American smokers were more likely to prefer menthol versus nonmenthol cigarettes at baseline.
- **Muscat et al. (2002)** reported cross-sectional analyses of baseline characteristics for current smokers (N=19,545) participating in a case-control study of tobacco-related cancers; smokers of menthol cigarettes were significantly more likely to be African American, female and aged <55 years.

- **Pletcher et al. (2006)** reported analyses of baseline characteristics for current smokers (N=5,115) participating in a longitudinal study of pulmonary disease; menthol cigarette preference was reported to be strongly related to being African American, female and younger aged (estimated means).
- **Stahre et al. (2010)** reported findings for menthol cigarette preference among current smokers in the NHIS (aged ≥18 years; N=6,055); African American smokers reported a significantly higher preference for menthol cigarettes compared to White smokers (76.0% vs. 20.2%; $p<0.001$); female smokers likewise reported a significantly higher preference for menthol cigarettes compared to male smokers (33.1% vs. 22.0%; $p<0.001$); and, preference for menthol cigarettes was highest among smokers aged 18-24 years (31.6%), but was not significantly different compared to older age groups.

The data from these five studies likewise indicate that menthol cigarette preference is higher among African American smokers compared to White smokers, and to a lesser extent, female smokers compared to male smokers. Some studies appear to suggest that menthol cigarette preference is also higher among younger compared to older smokers, although the data are less consistent than for African American and female smokers.

UNPUBLISHED ANALYSES PRESENTED TO TPSAC

In July 2010 and January 2011, a number of unpublished analyses that addressed the demographics of menthol versus nonmenthol cigarette preference were presented to TPSAC. Although these analyses have not undergone peer review, the authors' conclusions are mentioned here briefly:

- **Curtin (unpublished)** analyzed data from several large nationally representative surveys and reported that:
  - According to data from the 2005/06 and 2007/08 NHANES (aged ≥12 years), menthol cigarette preference among current smokers overall was ~26%; significantly higher proportions of African American and female smokers reported menthol cigarette preference compared to White and male smokers (by ~49% and ~9%, respectively), with no significant differences between younger and older smokers (26.4%, 31.7%, 25.5% and 24.5% for aged 12-17, 18-24, 25-29 and ≥30 years, respectively).
  - According to data from the 2005 NHIS (aged ≥18 years), menthol cigarette preference among current smokers overall was ~27%; significantly higher proportions of African American and female smokers reported menthol cigarette preference compared to White and male smokers (by ~57% and ~11%, respectively), with no significant differences between younger and older smokers (31.5%, 27.4% and 25.9% for aged 18-24, 25-29 and ≥30 years, respectively).

- According to data from the 2007 NSDUH (aged ≥12 years), menthol cigarette preference among currents smokers overall was ~32%; a significantly higher proportion of African American smokers reported menthol cigarette preference compared to White smokers (by ~58%), with no significant difference for female compared to male smokers; smokers aged 12-17 and 18-23 reported significantly higher preferences for menthol cigarettes compared to smokers aged 24-29 and ≥30 years (46.7%, 40.8%, 35.1% and 29.5% for aged 12-17, 18-23, 24-29 and ≥30 years, respectively).
- According to data from the 2007 NYTS (aged 9-21 years), menthol cigarette preference among current smokers overall was ~43%; a significantly higher proportion of African American smokers reported menthol cigarette preference compared to White smokers (by ~41%), with no significant differences based on sex.

- **Delnevo et al.(unpublished)** analyzed ever-smoker data from the 2003 and 2006/07 TUS-CPS; controlling for covariates, menthol cigarette preference was suggested to be higher for African American compared to White smokers, female compared to male smokers, and young adult (aged 18-24 years) compared to older adult smokers.
- **Giovino (unpublished)** analyzed data from the 2004-2008 NSDUH (aged ≥12 years), and reported that menthol cigarette preference among past-month smokers overall was ~33%; higher proportions of African American and female smokers reported menthol cigarette preference compared to White and male smokers (by ~62% and ~8%, respectively), with evidence of an age gradient for menthol cigarette preference (49.3%, 37.5%, 29.9%, 31.4% and 30.2% for aged 12-17, 18-25, 26-34, 35-49 and ≥50 years, respectively).
- **Hyland and Rivard (unpublished)** analyzed adult smoker data from the 2002-2008 International Tobacco Control Four Country Survey (aged ≥18 years), and reported that menthol cigarette preference among currents smokers overall was ~27%; higher proportions of African American and female smokers reported menthol cigarette preference compared to White and male smokers, with no reported analyses based on age category.

In addition, **Thorne et al. (2010)** (researchers from the CDC) presented an analysis from the 2001-2006 NHANES at the 2010 American Public Health Association meeting (on behalf of the FDA). They reported that menthol cigarette preference among past month smokers overall was ~25%; higher proportions of African American and female smokers reported menthol cigarette preference compared to White and male smokers (by ~59% and ~10%, respectively), with no differences between younger and older smokers (28.9%, 26.1%, 23.6%, 25.3% and 23.7% for aged 20-24, 24-34, 35-44, 45-64 and ≥65 years, respectively).

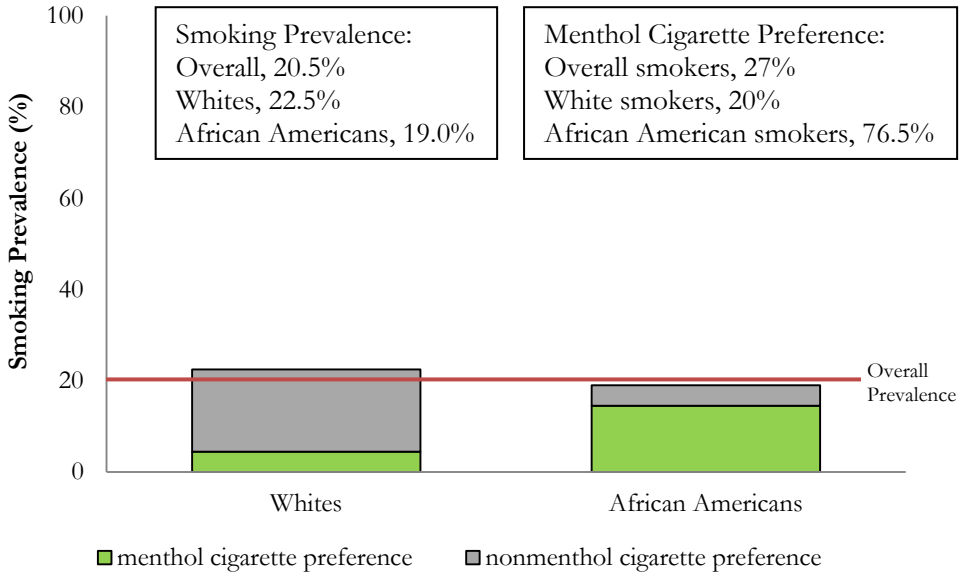
CIGARETTE PREFERENCE IS NOT INDICATIVE OF SMOKING PREVALENCE

Data indicating that specific groups of smokers (e.g., African Americans) report a higher preference for menthol versus nonmenthol cigarettes or that menthol preference is increasing over time must not be interpreted as evidence of increased smoking prevalence. Researchers have, in some instance, confused cigarette "preference" with smoking "prevalence," which in turn has led to inappropriate conclusions related to population-level harm.

Smoking prevalence provides an estimate of cigarette use among the overall population, i.e., the proportion of individuals in the population (or subpopulation) that currently smoke cigarettes. According to a recent report by the National Cancer Institute (NCI 2010), estimates provided by the NHIS indicate that smoking prevalence (i.e., established smoking) among all U.S. adults in 2008 was ~20.5%; stratifying by race/ethnicity, ~22.5% of Whites and ~19% of African Americans reported having smoked ≥100 cigarettes lifetime and currently smoking on some days or every day (Figure 2.1).

In contrast, estimates of cigarette preference provide information on the percentage of current smokers that choose to smoke a particular type of cigarette, such as higher versus lower tar or menthol versus nonmenthol. Estimates provided by the 2005 NHIS indicate that ~20% of White smokers report using menthol cigarettes, while ~76.5% of African American smokers report using menthol cigarettes (Curtin unpublished). As is clearly indicated in Figure 2-1, the disproportionate preference for menthol versus nonmenthol cigarettes estimated for African American compared to White smokers does not translate to a higher smoking prevalence for African Americans compared to Whites; in fact, smoking prevalence among African Americans is similar or slightly lower than that for Whites.

Figure 2-1. Smoking Prevalence and Cigarette Preference



Smoking prevalence data based on 2008 NHIS (NCI 2010); cigarette preference data based on 2005 NHIS (Curtin unpublished). Nationally representative surveys indicate that the majority (>50%) of menthol smokers are White; there are approximately two times more White menthol smokers than African American smokers (based on menthol smoking prevalence and census data for White and African American populations).

SMOKING PREVALENCE IS DECLINING REGARDLESS OF RACE/ETHNICITY, SEX OR AGE CATEGORY

An increase in smoking prevalence in the population could represent an adverse population-level effect, while higher preference for a particular cigarette type that does not provide any increased risk for disease or adversely impact smoking behavior among a declining smoking population would not. Recent estimates for the proportion of the U.S. population reporting established smoking (i.e., having smoked ≥100 cigarettes lifetime, and currently smoking some days or every day) indicate that smoking prevalence has been steadily declining during the last two decades, regardless of race/ethnicity, sex or age category.

As shown in Figure 2-2, smoking prevalence has declined among adults (aged ≥18 years) of all races from 1991 to 2008. The prevalence of smoking among African Americans and Hispanics declined more dramatically than smoking prevalence among Whites. Additionally, smoking prevalence among Hispanics, and to a lesser extent, African Americans tends to be lower than for Whites.

Smoking prevalence among both adult males and females (aged ≥18 years) has steadily declined since 1991 (from ~26% to ~21%), with a more pronounced reduction for females compared to males during the period of 2000 to 2006. Among adults aged 18-24 years, smoking prevalence initially increased but began declining in 1997 among males and in 1999 among females. Smoking prevalence among males and females aged ≥25 years steadily declined over the entire period.

Figure 2-2. Smoking Prevalence among US Adults (by race/ethnicity, 1991-2008)

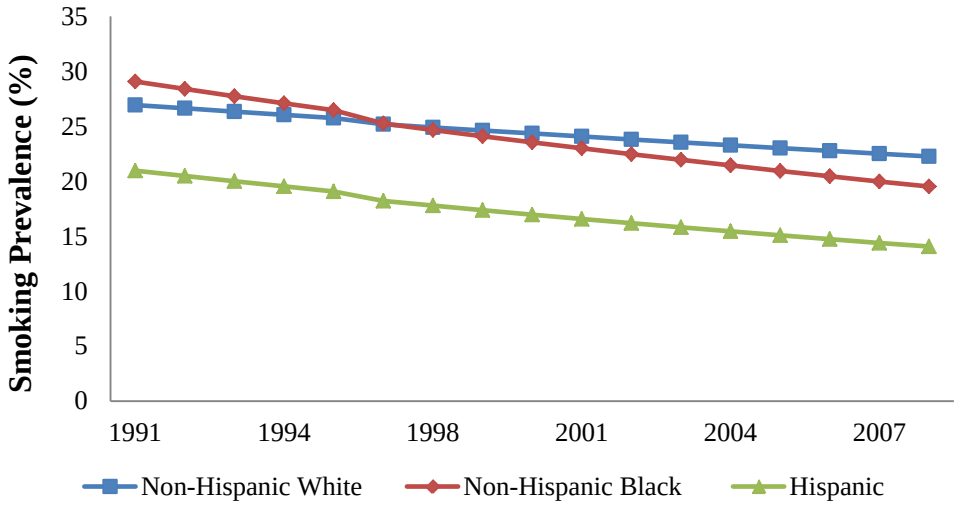


Figure reproduced from NCI 2010

Figure 2-3 depicts trends in smoking prevalence among adolescents (past month smoking, grades 9-12) and adults (established smoking, aged ≥18 years) over the period of 1997 to 2007. For

adolescents, smoking prevalence initially increased from 1991 to 1997 but was followed by a dramatic decline (from ~37% to ~19%) from 1997 to 2007. Comparatively, smoking prevalence among adults declined from ~24% to ~20.5% from 1997 to 2007.

Figure 2-3. Smoking Prevalence among U.S. Adolescents and Adults (1997-2007)

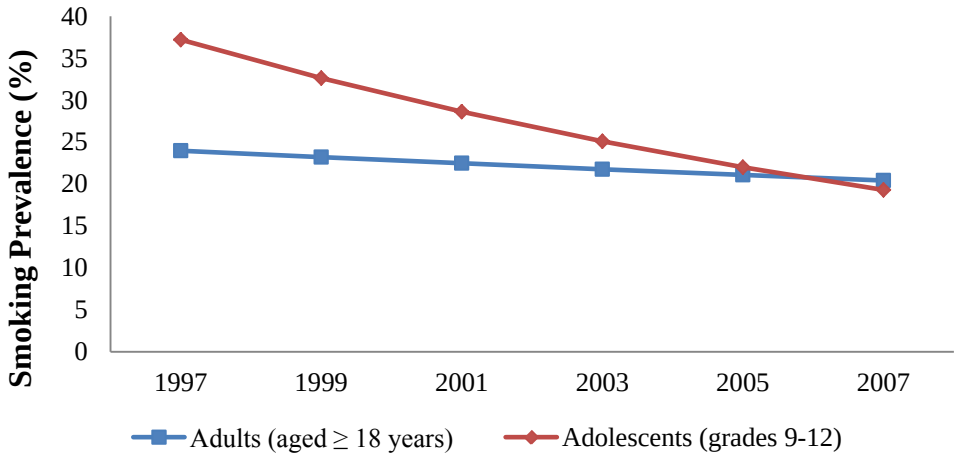


Figure reproduced from NCI 2010

Thus, estimates from a nationally representative sampling of the U.S. population indicate that cigarette smoking prevalence has steadily declined for all demographic groups, regardless of race/ethnicity, sex or age category; and, that these declines have been more pronounced for minorities (including African Americans), females and adolescents, despite their higher preference for menthol versus nonmenthol cigarettes.

Corresponding trends analyses of smoking prevalence based on menthol versus nonmenthol cigarette preference are not currently available from the published literature. Nonetheless, original trend analysis data from the NSDUH (aged 12-25 years) were provided to the TPSAC during the November 2010 meeting. Findings suggested that menthol smoking prevalence among African Americans, females and adolescents had generally declined from 2004 to 2008 (Table 2-3; derived from Giovino unpublished). Similar to findings from the NCI 2010 report, these data indicate that higher menthol cigarette preference among demographic groups that report higher menthol versus nonmenthol cigarette preference has not translated to an increased smoking prevalence.

Table 2-3. Menthol Smoking Prevalence (by demographic characteristics; Giovino unpublished)

	Non-Hispanic Black		Female		Aged 12-17 years	
	%	95% CI	%	95% CI	%	95% CI
2004	5.3	4.20-6.34	6.0	5.32-6.63	5.3	4.82-5.76
2005	6.1	4.69-7.53	5.2	4.46-6.03	4.8	4.23-5.31
2006	5.7	4.39-6.97	5.3	4.87-5.79	4.8	4.43-5.18
2007	5.8	4.44-7.11	5.0	4.44-5.61	4.9	4.46-5.42
2008	4.9	3.80-5.92	4.7	4.19-5.28	4.6	4.12-4.99

CONCLUSION

This review of the best available literature on the demographics of menthol cigarette preference indicates that substantially higher proportions of African American smokers report using menthol cigarettes compared to White smokers. While the difference is decidedly less pronounced, the available data consistently suggest that higher proportions of female compared to male smokers report using menthol cigarettes.

The available literature on the existence of an age gradient, whereby youth and younger adult smokers report higher menthol cigarette preference compared to older smokers, are inconsistent. Descriptive analyses based on data from the NHIS and NHANES consistently suggest no significant age-related differences for current menthol cigarette preference, while data from the NSDUH and, to a lesser extent, the TUS-CPS appear to suggest an age gradient for menthol cigarette preference. It bears mentioning that menthol status for respondents to the NSDUH is assigned based on any past month menthol cigarette use and not necessarily based on usual brand, leading to somewhat higher estimates of menthol cigarette preference relative to other nationally representative surveys. Moreover, interpretation of published findings from the TUS-CPS is complicated, to some extent, by use of the ≥65 years age category (i.e., those with the lowest preference for menthol cigarettes) as the reference group for comparative analyses. Regardless of whether the available data support the existence of an age gradient, the reality is that youth and young adult smokers will likely continue to be viewed as groups of particular interest during subsequent analyses of potential population-level effects associated with menthol cigarette preference.

Evidence that a specific group of smokers reports a higher preference for menthol cigarettes, or that preference among a group of smokers is increasing over time must not be interpreted as evidence of increased smoking prevalence. Current cigarette type preference is not informative with regard to the use of menthol versus nonmenthol cigarettes during experimentation with cigarettes or transitioning from cigarette experimentation to established smoking. The NCI recently reported that smoking prevalence has steadily declined during the past two decades for all demographic groups, and that these declines have been more pronounced for minorities (including African Americans), females and adolescents – the same groups that report higher menthol cigarette preference. Demographic data detailed in this chapter are most appropriately used to inform

subsequent examinations of potential population-level effects (i.e., smoking initiation, dependence and/or cessation) that may be associated with menthol cigarette preference.

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Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Cubbin et al. 2010 The intersection of sex and race/ethnicity in smoking behaviors among menthol and nonmenthol smokers in the United States	Cross-sectional data from the 2005 National Health Interview Survey (NHIS) linked with the Cancer Control Supplement Analytical sample included 21,196 subjects aged 25–64; included current (N=3,902), former (N=3,786) and never (N=13,508) smokers who reported menthol status. Data adjusted by race/ethnicity, age, income and education; imputed income from the National Center for Health Statistics was used for subjects whose income was unknown.	**Every Day Smokers** **Black** Women Men **Hispanic** Women Men **White** Women Men	**Menthol Smoking Preference Percent (99% CI)** 77.9 (71.1–84.7) 69.7 (61.5–77.8) 35.6 (25.6–45.7)* 16.5 (9.2–23.8) 24.5 (21.4–27.7)* 14.6 (11.9–17.3) Adjusted for age, income and education.	Black every day smokers, both men and women, were significantly ($p<0.01$) more likely to smoke menthol cigarettes than nonmenthol cigarettes compared to White or Hispanic every day smokers. Hispanic or White female smokers were significantly ($p<0.01$) more likely to smoke menthol cigarettes than Hispanic or White men; no significant differences were reported for Black female and male smokers. This study used 99% confidence intervals for statistical tests.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6) (Continued)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Fernander et al. 2010 Age of smoking initiation and purchasing patterns and associations with menthol smoking	Cross-sectional data from the 2003 and the 2006/07 Tobacco Use Supplement to the Current Population Survey (TUS CPS) Analytical sample included 66,145 subjects, self-responders only, aged 18 years or older; included respondents that smoked menthol (N=16,294) or nonmenthol (N=46,899) cigarettes, or were unresponsive (2,952). Proxy respondents were excluded from this study because it was assumed that certain items pertaining to smoking would be less accurate when answered by a proxy respondent.	**Current Smokers (every or some days)** **Sex** Male Female **Ethnicity** Black Hispanic Other White non-Hispanic **Age Cohorts** 18-24 25-44 45-64 65+	**Odds Ratio Associated with Menthol Smoking (95% CI)** 0.58 (0.55–0.61)** 1.00 (reference) 11.10 (10.01-12.31)* 1.55 (1.40-1.71) 1.35 (1.19-1.54) 1.00 (reference) 1.66 (1.47-1.88)* 1.20 (1.07-1.34)* 1.36 (1.22-1.51)* 1.00 (reference)	Female current smokers were significantly ($p<0.05$) more likely to smoke menthol cigarettes than males. Black current smokers were significantly ($p<0.05$) more likely than any other ethnic group to smoke menthol cigarettes, followed by Hispanic smokers. Current smokers aged 18-24, 25-44 and 45-64 years were significantly ($p<0.05$) more likely to smoke menthol cigarettes than smokers aged 65+ years.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6) (Continued)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Hersey et al. 2010 Menthol cigarettes and the appeal and addiction potential of smoking for youth	Cross-sectional data from the 2006 National Youth Tobacco Survey (NYTS) Sample included 27,038 subjects in Grades 6-12; analyses were restricted to those who had smoked in the past 30 days and could identify whether the usual brand was menthol or nonmenthol (N=3,281; 771 middle school and 2,510 high school).	**Past Month Smokers** **Middle school** All youth smokers **Sex** Male Female **Race/ethnicity** Black Asian American Hispanic White (non-Hispanic) **High school** All youth smokers **Sex** Male Female **Race/ethnicity** Black Asian American Hispanic White (non-Hispanic)	**Menthol Smoking Preference Percent (95% CI)** 51.7 (45.8-57.5) 55.1 (43.9-54.7) 48.1 (28.1-51.6) 80.6 (72.0-89.3) 57.4 (27.7-87.1) 57.9 (48.8-67.0) 43.1 (36.2-50.0) 43.1 (37.0-49.1) 39.4 (33.6-45.2) 46.9 (38.9-54.9) 84.8 (77.3-92.3) 43.6 (24.3-63.0) 56.4 (48.7-64.2) 37.6 (31.0-44.3)	There were no significant differences in menthol smoking preference between males and females in either age group (middle school or high school). Black middle school and high school students reported the highest menthol smoking preference among the race/ethnicity groups, and Whites reported the lowest. Among middle school students, menthol preference among Blacks was significantly higher than White (non-Hispanic) and Hispanic participants. Among high school students, preference for menthol among Blacks was significantly higher than any other race/ethnicity. Only 6.3% (95% CI, 5.1-7.5) of middle school smokers and 19.7% (95% CI, 18.1-21.4) of high school smokers reported a usual brand of cigarette.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6) (Continued)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Lawrence et al. 2010 National patterns and correlates of mentholated cigarette use in the United States	Cross-sectional data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey (TUS CPS) Analytical sample included 63,193 subjects aged 18 years or older; 16,294 (25.8%) smoked menthol and 46,899 (74.2%) smoked nonmenthol cigarettes.	**Regular Smokers** **Sex** Male Female **Age Cohorts** 18-24 25-44 45-64 65+ **Ethnicity** White (non-Hispanic) Black (non-Hispanic) Hispanic A. Indian/ Alaskan Native (non-Hispanic) Asian/Pacific Islander (non-Hispanic) Multiple races **Age by Sex** **Males** 18-24 25-44 45-64 65+ **Female** 18-24 25-44 45-64 65+	**Adjusted Odds Ratio Associated with Menthol Smoking (99% CI)** 1.00 (reference) 1.64 (1.53-1.76)* 1.39 (1.12-1.73)* 1.07 (0.89-1.28) 1.29 (1.09-1.53)* 1.00 (reference) 1.00 (reference) 10.92 (9.58-12.44)* 1.92 (1.66-2.21)* 1.19 (0.87-1.63) 2.07 (1.57-2.73)* 1.61 (1.29-2.01)* 1.46 (1.05-2.02)* 0.92 (0.69-1.23) 1.08 (0.82-1.44) 1.00 (reference) 1.31 (0.98-1.75) 1.21 (0.97-1.52) 1.48 (1.19-1.84)* 1.00 (reference)	Menthol cigarette smoking among regular smokers was significantly associated with race/ethnicity, sex and age. The most significant factor was race/ethnicity, with Black smokers being nearly 11 times more likely to use menthol cigarettes than White smokers; Hispanic and API smokers were approximately twice as likely. Female smokers were 1.6 times more likely to smoke menthol cigarettes than were males smokers. Smokers aged 18-24 and 45-64 years were approximately 1.4 and 1.3 times as likely, respectively, to use menthol cigarettes than smokers aged 65 years.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6) (Continued)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Lawrence et al. 2010 (continued)			Adjusted for socio-demographic and smoking behavior variables that were associated significantly with mentholated cigarette smoking in bivariate logistic regression models.	
Mendiondo et al. 2010 Health profile differences for menthol and nonmenthol smokers: findings from the national health interview survey	Cross-sectional data from the 2005 National Health Interview Survey (NHIS) linked with the Cancer Control Supplement Analytical sample included 12,004 subjects aged 18 years and older who were either current (N=6,055) or former (N=5,949) smokers and reported menthol status. Reported use of menthol cigarettes was 25.2% among current smokers. Post-stratification adjustments based on sex, race/ethnicity and age using the Census Bureau data were applied.	**Current Smokers (every or some days)** **Sex** Male Female **Ethnicity** Non-Hispanic White Black Hispanic **Age**	**Adjusted Odds Ratio Associated with Menthol Smoking (95% CI)** 1.00 (reference) 1.74 (1.30-2.33)* 1.00 (reference) 11.52 (8.86–14.98)* 1.85 (1.35–2.55)* 0.99 (0.99-1.00) Adjusted for age, education, region, race/ethnicity, income and sex.	African American and female smokers were significantly more likely to be menthol versus nonmenthol smokers compared to Whites and males, respectively. There were no significant differences based on age.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 2-4. Higher Quality Studies on Menthol Preference Demographics (N=6) (Continued)

CITATION	STUDY TYPE	GROUPS	RESULTS	CONCLUSIONS
Rock et al. 2010 Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008	Cross-sectional data from the 2004-2008 National Survey on Drug Use and Health (NSDUH) Analytical sample included 71,605 subjects (35.7% menthol smokers and 64.3% nonmenthol smokers), aged 12 years or older, who reported and menthol smoking in the past 30 days. Data were adjusted for non-response and weighted to provide national estimates of smoking preference.	**Age Cohorts** **12-17 years** Total Male Female White Black Hispanic Asian A. Indian/Alaska Native **18-25 years** Total Male Female White Black Hispanic Asian A. Indian/Alaska Native **26+ years** Total Male Female White Black Hispanic Asian Indian/Alaska Native	**Menthol Smoking Preference Percent (95% CI)** 44.7 (43.2–46.2) 42.2 (40.3–44.2) 47.3 (45.5–49.1)* 41.0 (39.4–42.6) 71.9 (67.1–76.2) 47.0 (42.5–51.5) 51.5 (39.2–63.6) 34.7 (24.3–46.8) 36.1 (35.3–36.9) 33.9 (32.9–34.9) 38.8 (37.9–39.8)* 28.8 (28.0–29.6) 85.0 (83.8–86.5) 38.2 (36.1-40.4) 35.8 (31.0–40.9) 27.4 (22.7–32.8) 30.2 (29.4–31.1) 26.1 (25.1–27.2) 35.0 (33.8–36.2)* 21.9 (20.9–22.9) 82.2 (80.1–84.1) 29.5 (27.4–31.8) 28.6 (23.2–34.7) 23.0 (16.4–31.3)	Preference for menthol cigarettes was higher among 12-17 year old smokers than among other age groups, for the overall sample, for males and females, and for Whites and Hispanics. Preference for menthol cigarettes was lower among Black smokers age 12-17 years compared to older age groups. In general, preference for menthol cigarettes was higher among Black smokers than among any other ethnic group. In general, preference for menthol cigarettes was higher among female smokers than males.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

CHAPTER 3A.
MENTHOL IN CIGARETTES DOES NOT CHANGE THE INHERENT HEALTH RISKS OF SMOKING

Menthol is one of the most widely studied ingredients in cigarettes. This review of the scientific evidence, which includes epidemiology studies, as well as those of biomarkers of exposure and harm, smoking topography, and toxicology and chemistry, clearly demonstrates that smokers of menthol cigarettes are at no greater risk of developing smoking-related diseases than are nonmenthol smokers.

The tobacco industry acknowledges that smoking any type of cigarette carries significant health risks. However, the science clearly shows that the addition of menthol to a cigarette does not affect the inherent health risks associated with smoking. FDA and the TPSAC must evaluate all available data in an impartial and comprehensive manner and base any recommendations or regulatory decisions on a rigorous evaluation of sound science.

The associations between cigarette smoking and various chronic diseases have been studied by epidemiologists for decades. Studies conducted in a variety of different populations during the past 60 years have given the same basic message: the risk of smoking-related diseases increases with amount and duration of smoking. Number of cigarettes smoked per day and years of smoking have been shown to be robust and reproducible predictors of the risks of developing smoking-related diseases. To the extent that smoking exposure is characterized accurately, well-conducted epidemiology studies are capable of measuring associated health risks. The epidemiology studies comparing smokers of menthol and nonmenthol cigarettes provide strong evidence that there is no difference between the two types of cigarettes with respect to health risks.

Findings from epidemiology studies are consistent with the available data on biomarkers of exposure and harm (which provide quantitative measures of smokers' systemic exposures and incorporate all aspects of smoking behavior), smoking topography, as well as studies of toxicology and chemistry. These studies indicate that menthol in cigarettes does not expose the smoker to any additional health risks over those associated with nonmenthol cigarettes.

Using the framework for causal inferences set forth by the Surgeon General in 2004, a collective assessment of the available literature on epidemiology, biomarkers of exposure and harm, smoking topography, toxicology and chemistry leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and increased chronic disease risk above that of nonmenthol cigarettes.

SUFFICIENT EPIDEMIOLOGY DATA ARE AVAILABLE TO DRAW CONCLUSIONS

Chronic disease epidemiology provides an essential foundation for the Surgeon General's conclusions on disease causation associated with smoking (e.g., USDHHS 2004[1]). Most importantly, epidemiology studies integrate all aspects of cigarettes and smoking, including the composition and design of cigarettes, smoking duration, smoking behavior and intensity (topography), and smoking cessation on public health. The Institute of Medicine (2001) has stated: "Most of what is known about harmful tobacco products has resulted from epidemiology. … [E]pidemiological studies can provide the most definitive data about tobacco harm." The recognition by the Surgeon General, the National Academy of Sciences, and the Institute of Medicine that, of all disciplines, epidemiology provides the most important evidence concerning risks to public health, is particularly relevant to the evaluation of any health effects of menthol in cigarettes.

Having sufficient, methodologically-sound epidemiology data is key to being able to draw reliable conclusions about the impact of menthol cigarettes on disease risk. While there may be debate about how many, and what type of, studies constitute the ideal dataset for any given public health problem, sufficient data exist to draw reliable conclusions about the health effects of menthol cigarettes compared to those of nonmenthol cigarettes, for the following reasons:

- There are more than a dozen relevant individual epidemiology studies which are of reasonable methodologic quality
- Most of these analyses were specifically designed to test hypotheses related to menthol's health effects
- These studies directly compared health risks between smokers of menthol and nonmenthol cigarettes
- There are multiple studies of different designs, which were done by different researchers
- Most of the studies had large sample sizes and good representation of menthol smokers
- Most studies controlled for the most relevant potential confounding factors and many performed race-specific and sex-specific analyses
- Several different health effects have been considered, most importantly, lung cancer and cancers of the upper aerodigestive tract; lung cancer is the most common smoking-related cancer, and cancers of the lung, esophagus, larynx, and oropharynx are the cancers most strongly associated with smoking
- There is also a recent, high-quality meta-analysis that examined the outcome of lung cancer
- Cardiovascular disease and respiratory disease have also been considered
- Especially important is the fact that epidemiology studies effectively incorporate all aspects of smoking behavior, including those that are not easily quantified

Given the number of studies and overall methodologic quality, there is adequate information to allow for a causal determination as outlined by the Surgeon General's framework (USDHHS 2004). As noted previously, the **"evidence is suggestive of no causal relationship"** between menthol in cigarettes and chronic disease risk compared to nonmenthol cigarettes.

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[1] Other Surgeon General reports that have relied on epidemiology include those published in 1964, 1967, 1968, 1969, 1971, 1972, 1973, 1974, 1975, 1977-78, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1989, 1990, 1992, 1998, 2001, 2006.

As will be discussed in detail in the next section, these studies consistently show that the health risks associated with smoking menthol cigarettes are no greater than those associated with smoking nonmenthol cigarettes. The consistency of these studies is striking, and helps to rule out even small elevations in risk. This is important, as the only way to avoid drawing erroneous conclusions is to evaluate the overall pattern of study results, as well as individual study findings.

Studies on the health risks of menthol cigarettes were first proposed in the late 1980s when epidemiologists noticed two striking facts. First, incidence rates of lung cancer were higher among African American men than White men, and incidence rates of esophageal cancer were much higher among African Americans of both sexes compared to Whites. Second, African American smokers strongly favored menthol cigarettes compared to Whites; by the mid-1980s, approximately 62% of African American smokers preferred menthol cigarettes compared to 23% of Whites (Hebert and Kabat 1988, 1989). However, as described above, large epidemiology studies that assessed the association between type of cigarette smoked (menthol versus nonmenthol) and risk of lung cancer (the most common smoking-related cancer) did not support this hypothesis. A smaller number of studies of other tobacco-related cancers with higher incidence among African Americans compared to Whites also did not provide evidence of a menthol effect. As will be demonstrated in the following section, higher rates of certain smoking-related diseases among African Americans compared to Whites cannot be explained by the greater preference for menthol cigarettes among African Americans. It is notable that the higher rate of lung cancer among African Americans, both men and women, is a phenomenon that has also been observed among those who have never smoked, suggesting that constitutional differences or factors other than cigarette preference underlie these differences (Thun et al. 2008).

PROPER INTERPRETATION OF EPIDEMIOLOGY FINDINGS IS ESSENTIAL

Because epidemiology serves as the foundation for understanding the health effects of menthol smoking, it is essential to interpret the findings of these studies properly and objectively. Review of TPSAC meeting minutes and FDA staff presentations to TPSAC suggests that epidemiology findings are sometimes not interpreted correctly. Thus, before discussing the relevant studies, it may be helpful to review the discussion of some of the most fundamental concepts provided in Chapter 1.

EPIDEMIOLOGY SHOWS NO DIFFERENCE IN RISK OF TOBACCO-RELATED DISEASE BETWEEN MENTHOL AND NONMENTHOL SMOKERS

The epidemiologic evidence provides a compelling basis to conclude that the risk of cancer and other smoking-related diseases is not materially affected by the use of menthol in cigarettes. To date, 13 published studies, a meta-analysis, and two unpublished studies have directly compared the risk of smoking-related diseases between menthol and nonmenthol cigarette smokers. These studies have addressed the following endpoints: lung cancer, esophageal cancer, oropharyngeal cancer, other smoking-related cancers (including those of the upper aerodigestive tract, pancreas, kidney, urinary tract and uterine cervix), as well as various other cardiac and lung conditions (coronary calcification, decline in pulmonary function, and mortality due to coronary heart disease, cardiovascular disease, and all causes). The overwhelming weight of the evidence shows no

difference between the disease risks of smoking menthol cigarettes and nonmenthol cigarettes. Consequently, the claims that this literature is equivocal or mixed are scientifically invalid; according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship."** Each study is discussed briefly below, and summarized in detail in the attached Tables 3-9 through 3-13.

Lung Cancer

Lung cancer is the most common smoking-related cancer and the one most strongly associated with cigarette smoking. According to the American Cancer Society, there were an estimated 222,500 new cases of lung cancer in the U.S. in 2010 (ACS 2010). Eight individual epidemiology studies and one meta-analysis have addressed this endpoint (Kabat and Hebert 1991, Sidney et al. 1995, Carpenter et al. 1999, Brooks et al. 2003, Stellman et al. 2003, Jöckel et al. 2004, Murray et al. 2007, Etzel et al. 2008, Lee 2011). All but one of these studies reported no significant differences between menthol versus nonmenthol smokers in risk of lung cancer. Only one study (Sidney et al. 1995) reported a statistically elevated risk (relative risk=1.45; 95% CI:1.03-2.02) for lung cancer in a single subgroup (men but not women) who smoked menthol cigarettes compared those who smoked nonmenthol cigarettes. Because this finding was not replicated in other studies, the authors later stated that it may have been "merely a chance finding" (Friedman et al. 1998).

While all epidemiology studies have limitations, the available studies of menthol smoking and lung cancer are well-designed and well-analyzed, for the most part have adequate numbers of lung cancer cases, and are able to detect effects of smoking parameters, including amount smoked, duration of smoking, and smoking cessation. This literature provides no evidence that smoking menthol cigarettes, as opposed to smoking nonmenthol cigarettes, increases the risk of lung cancer. The consistency of the studies is impressive. There is no consistent evidence of an effect of menthol in the study populations overall or in subgroups: males or females, or African Americans or Whites.

Each study is described below and summarized in more detail in Table 3-1 (including all relevant risk estimates).

Kabat and Hebert (1991) examined risk of lung cancer among current smokers of menthol or nonmenthol cigarettes in a hospital-based case-control study. The study involved a large number of subjects (1,044 cases, 1,324 controls), with a substantial number of menthol smokers (from 24-37%, depending on sex and race). The investigators obtained detailed information on types of tobacco products used throughout life, and considered many important confounders in their analysis (inhalation, race, body mass index (BMI), age, education, cigarettes/day, and duration of smoking). No statistically significant associations were observed between either short-term (1-14 years) or long-term (15+ years) menthol use and lung cancer for either men or women in logistic regression analyses adjusting for covariates. There was also no indication of any association with specific histological types of lung cancer. The authors concluded that "Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types of lung cancer in this study."

Sidney et al. (1995) examined menthol cigarette use and lung cancer incidence among 11,761 participants in the Kaiser Permanente Medical Care Program who were current smokers with a self-reported smoking history of 20 or more years. There were 93 cases of lung cancer among 3,654

menthol smokers and 225 cases of lung cancer among 8,107 nonmenthol smokers over a mean of approximately 8 years of follow-up. There were no statistically significant elevations in risk associated with any duration of menthol smoking (1-9; 10-19; or ≥20 years). However, there was a modest elevation in the risk of lung cancer associated with menthol cigarette use by men only (all races combined) (RR=1.45; 95% CI:1.03-2.02) after adjustment for age, race, education, cigarettes/day, and smoking duration. A similar finding was not seen for women (RR=0.75; 95% CI:0.51-1.11), despite the greater preference for menthol among women as opposed to men (34.6% vs. 27.4%, respectively). The authors concluded that: "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."

Importantly, a later study by some of the same authors (including Sidney) acknowledged that the elevated risk of lung cancer seen in this study among male menthol smokers may have been merely a chance finding, since it was not seen in women and has not been replicated elsewhere (Friedman et al. 1998 discussed below).

Carpenter et al. (1999) conducted a case-control study comparing 337 incident cases of lung cancer with 478 population controls who were current or former smokers. Among African American subjects, 85 men and 101 women had ever smoked menthols; among Caucasians, 66 men and 122 women had ever smoked menthols. The adjusted odds ratio for exclusive menthol smokers was not different from that of nonmenthol smokers (OR=1.04; 95% CI:0.62-1.75), after adjustment for age, sex, race, total pack-years, and years since quitting smoking. Similarly, odds ratios calculated by sex, race, and duration of menthol cigarette smoking (up to 32+ pack-years) revealed no statistically significant differences between menthol and nonmenthol cigarette smokers. The authors concluded: "Our results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes."

Brooks et al. (2003) examined data from a large, multi-hospital case-control study to examine whether smoking menthol cigarettes might be associated with higher lung cancer risk as compared to smoking nonmenthol cigarettes. The analysis was restricted to 643 cases and 4,110 controls for whom cigarette brand information could be identified for at least 60% of the total duration of smoking. There were 114 ever smokers of menthol cigarettes among the cases and 1,093 among the controls. Overall, menthol smokers did not have an elevated risk of lung cancer relative to nonmenthol smokers (OR=0.89; 95% CI:0.69-1.14), after adjustment for sex, age, race, year of interview, number years smoking, cigarettes/day, years since quitting, and proportion of years smoking filter cigarettes. Odds ratios were also close to 1.0 in separate analyses of male, female, Black, and White subjects that considered duration of smoking menthols (1-15 years >15 years). The authors concluded: "The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking nonmenthol cigarettes."

Stellman et al. (2003) conducted a hospital-based case-control study to investigate whether risk of lung cancer differs between Blacks and Whites for equivalent exposure to tobacco smoke. The study was large, including 3,031 White and 417 Black cases with lung cancer, and 8,151 control subjects. Smoking of menthol cigarettes was one of several variables examined; the prevalence of menthol smoking ranged from 13-24% among White subjects and was substantially higher (41-52%) among Black subjects. Among current smokers, the ORs associated with menthol smoking were almost the same as those associated with nonmenthol smoking for White men, Black men, White women, and Black women (after adjustment for age, education, BMI, and pack-years). The authors

concluded: "Smokers of flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands."
Jöckel et al. (2004) provided a brief description (abstract only) of a hospital-based case-control study of menthol cigarette smoking and lung cancer in a White population in Germany (1,004 cases and 1,004 controls matched for region, sex, and age). After adjustment for total amount of tobacco smoking, smoking menthol cigarettes was not associated with increased risk of lung cancer. The authors stated: "The present study gives no indication for an additional risk [of lung cancer] of ever smoking menthol cigarettes if total amount of smoking is taken into account." It should be noted that relatively few subjects had ever smoked menthol cigarettes (5% of cases and 4% of controls).

Murray et al. (2007) described an analysis of data from the Lung Health Study, a clinical trial of smoking cessation that included 5,887 current or former smokers with mild to moderate airway obstruction. About 20% had smoked menthol cigarettes at baseline. Over 14 years of follow-up, there were 240 deaths due to lung cancer. The hazard ratio associated with smoking menthol cigarettes at baseline was not elevated (RR=0.96; 95% CI:0.70-1.32) compared to nonmenthol cigarettes. The authors concluded: "We found no evidence in our data that mentholation of cigarettes is an attribute that contributes to the health risks of smoking."

Etzel et al. (2008) developed and validated a lung cancer prediction model specific to African Americans using data from a case-control study of lung cancer (491cases, 497 controls). There was a high prevalence of menthol use among these African American subjects (41% of cases, 47% of controls), although it was just one of many factors evaluated. Risk of lung cancer was not elevated among current or former menthol smokers (ORs were 0.69 and 0.99, respectively) compared to smokers of nonmenthol cigarettes, after adjustment for age, sex, and smoking status. The authors reported that their data were consistent with a possible "protective" effect of menthol cigarettes relative to nonmenthol cigarettes for current smokers. The authors stated: "...we observed no significant risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes . . ."

This study is particularly important because it shows that when the range of risk factors is considered for inclusion in a "prediction equation" for lung cancer in African Americans, a number of factors make a significant contribution and are retained in the final equation (smoking status, pack-years of smoking, age at smoking cessation, exposure to asbestos or dusts, and history of COPD or hay fever); however, menthol did not contribute to risk of lung cancer in the prediction equation and was not retained in the equation.

Lee (2011) recently conducted a meta-analysis that examined the relationship between smoking menthol cigarettes and risk of lung cancer. Meta-analysis is a technique for statistically combining the results of a number of individual studies to obtain a summary risk estimate that is more precise because of the larger sample size.

A systematic search of the literature revealed only the eight studies of lung cancer described individually above. Lee (2011) described these studies as "...generally of good quality, with valid cases and controls, and appropriate adjustment made for age, gender, race and smoking habits."

Combining the data from the eight studies yielded an overall adjusted RR of 0.93 (95% CI:0.84-1.02). In subgroup analyses, there was also no evidence of increased risk among men or women separately, among Blacks or Whites separately, among ever smokers, current smokers, or former smokers, or among long-term smokers of menthol cigarettes (15+ years). In fact, RRs were almost all 1.0 or less. Lee (2011) concluded: "The data do not suggest any effect of mentholation on lung cancer risk. While some study weaknesses exist, the epidemiological evidence is consistent with mentholation having no effect on the lung carcinogenicity of cigarettes."

Esophageal Cancer

Two publications (one of which is a letter to the editor) describing the same hospital-based case-control study (Hebert and Kabat 1988, 1989) found no evidence that smoking menthol cigarettes is associated with increased risk of esophageal cancer (see Table 3-2). The study involved 303 cases and 453 controls, all of whom were current smokers. The number of subjects who had ever smoked menthol cigarettes was small: 45 among the cases and 66 among the controls. Logistic regression analyses revealed no significant increase in ORs associated with smoking menthol cigarettes (either for <10 years or for ≥10 years) among men, after adjustment for covariates (education, religion, alcohol consumption, race, cigarettes/day, and smoking duration). Among women who smoked menthol cigarettes, adjusted ORs were elevated (1.5 for <10 years, 2.3 for ≥10 years), but were not statistically significant. The authors concluded: "Our results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer." Given the small number of cases (especially African Americans), the authors recommended that additional studies of adequate size be performed.

Oropharyngeal Cancer

A single study (a hospital-based case-control study conducted by Kabat and Hebert in 1994) found no evidence that smoking menthol cigarettes was associated with increased risk of oropharyngeal cancer (see Table 3-3). Detailed information on lifetime smoking habits and other variables was obtained for 276 cases and 1,256 controls, all of whom were current smokers. Menthol use was not common among these subjects; only 5% had smoked menthol cigarettes exclusively, and 24% had smoked both menthol and nonmenthol cigarettes. Odds ratios for smoking menthol cigarettes for either 1-14 or ≥15 years were not elevated either for men or for women, after adjustment for covariates of age, education, filter use, race, BMI, hospital, alcohol, and cigarettes/day. Additional analyses examined risk by anatomic site within the oropharynx; menthol use was positively associated only with pharyngeal cancer in men, but the elevation in risk was small and not statistically significant. The authors concluded: "These results indicate that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer."

Other Smoking-Related Cancers

In a large prospective study of data from the Kaiser Permanente Medical Care Program in California, Friedman et al. (1998) investigated whether their previous finding of a higher risk of lung cancer among men who smoked menthol cigarettes compared to men who smoked nonmenthols (reported by Sidney et al. 1995) also applied to other smoking-related cancers (see Appendix Table 3-12). The analysis involved 11,761 subjects who were current smokers with a smoking history of 20 or more years. There were 69 cases of lung cancer among 3,654 menthol smokers and 212 cases of lung cancer among 8,106 nonmenthol smokers over more than 10 years of follow-up.

Smoking menthol cigarettes was not associated with an increased rate of cancer in either sex or in any of the sites examined (upper aerodigestive, pancreas, renal adenocarcinoma, other urinary tract, and uterine cervix). In fact, for 9 of the 11 tumor sites examined, the point estimates associated with menthol use were below 1.0. For all smoking-related cancers combined, the menthol/nonmenthol rate ratio was 0.76 (95% CI:0.52-1.11) for men and 0.79 (95% CI:0.53-1.18) for women. The authors concluded: "Risk was not increased among persons who currently smoked mentholated compared with plain cigarettes for all of the non-lung smoking-related cancers combined or for most sites studied." Referring to the Sidney et al. 1995 publication, they further stated: "...the association of mentholation with lung cancer in this study population may be merely a chance finding, particularly as it was absent in women and has not been replicated elsewhere."

Coronary Calcification and Lung Function

Pletcher and colleagues (2006) investigated whether smoking menthol cigarettes had a greater effect on the development of atherosclerotic disease and changes in pulmonary function than did smoking nonmenthol cigarettes among subjects enrolled in the Coronary Artery Risk Development in Young Adults Study (CARDIA) (see Appendix Table 3-13). The prospective study followed 5,115 subjects for 15 years; of these, 972 smoked menthol cigarettes and 563 smoked nonmenthols at baseline. Smokers of menthol cigarettes and those of nonmenthol cigarettes did not differ in coronary calcification (p=0.75) or decline in pulmonary function (p=0.88); the authors stated that the two types of cigarettes seem to be equally harmful with respect to these endpoints. The authors concluded: "Mentholation of cigarettes does not seem to explain disparities in ischemic heart disease and obstructive pulmonary disease between African Americans and European Americans in the United States . . ."

Mortality Due to Cardiovascular Disease

Murray et al. (2007) reported on mortality due to various causes in the Lung Health Study, a clinical trial of smoking cessation that included 5,887 current or former smokers with mild to moderate airway obstruction (see Appendix Table 3-13). About 20% had smoked menthol cigarettes at baseline. Over 14 years of follow-up, there were 77 deaths due to coronary heart disease (CHD), 163 deaths due to cardiovascular disease, and 731 deaths due to any cause. The authors reported no differences between menthol and nonmenthol smokers in risk of death due to CHD (HR=1.31; 95% CI:0.77-2.22), cardiovascular disease (HR=1.03; 95% CI:0.70-1.52), or any cause (HR=0.99; 95% CI:0.83-1.20). The authors concluded: "We found no evidence in our data that mentholation of cigarettes is an attribute that contributes to the health risks of smoking." However, they speculated that the hazard ratio associated with smoking menthol cigarettes and CHD was of sufficient magnitude that it might reach statistical significance in a study with a larger sample size.

ADDITIONAL UNPUBLISHED EPIDEMIOLOGY STUDIES

In addition to the published, peer-reviewed articles described above, two unpublished analyses prepared at the request of the FDA and submitted to TPSAC are relevant. Because these have not been peer-reviewed, they must be considered to represent a lower level of evidence than the studies described above.

Stellman and Neugut (unpublished) used existing data from a hospital-based, multi-center case-control study to evaluate the relationship between menthol smoking and risk of five tobacco-related cancers (including oral cavity, esophagus, larynx, lung, and bladder). Their analysis involved 5,771 cases with various cancers and 7,906 controls. Menthol smoking was not associated with elevations in risk of any of these cancers, compared to nonmenthol smoking. In fact, all odds ratios associated with menthol smoking were 1.0 or lower. The authors concluded that their data "… do not provide evidence of increased risk of lung or other cancers in smokers of menthol cigarettes over and above the well-known risks of cigarette smoking." While they suggested that the small numbers of cases of some of the cancers may have limited their ability to detect small effects due to menthol, they conceded that a menthol "effect," if any, is unlikely to be of substantive magnitude in comparison to the effects of smoking, generally.

Hyland and Kasza (unpublished) used data from two hospital-based case-control studies to evaluate the association between menthol smoking and lung diseases. One study involved 503 lung cancer cases and 1,081 controls from 1957-1965; the other involved 144 lung cancer cases, 238 cases of COPD/emphysema, and 58 cases of premalignant lung disease (defined as being at high risk for lung cancer, e.g., having long pack-year histories) from 2005-2010. The findings of the more recent cases are interesting, as their smoking behaviors and cigarette brand styles are most like those of the contemporary U.S. smoking population.

Using the conventional statistical threshold of $p=0.05$, the authors did not find any main effects (i.e., menthol smoking was not associated with significantly elevated risk of the various diseases compared to nonmenthol smoking). For lung cancer, the odds ratio associated with menthol smoking (men and women combined) in the 2005-2010 sampling, adjusted for age, sex, race, smoking behaviors and smoking duration was 0.76 (95% CI:0.41-1.44). The authors stated that: " . . . no clear pattern of risk was observed between menthol smokers in the populations and disease endpoints examined." Although they found no main effect of menthol, the authors highlighted several second-order findings (i.e., among subgroups) that achieved statistical significance according to a more liberal p value of <0.10. They cited three odds ratios that gave "slight suggestions" of elevated risk, although all of the confidence intervals included 1.0, and thus are not statistically significant using traditional standards. Critical review of this unpublished study shows that it is another null study that is consistent with the vast majority of published studies in finding no significantly elevated risks associated with menthol cigarette smoking.

EPIDEMIOLOGY STUDIES ARE SUPPORTED BY ECOLOGICAL DATA

As noted above, it was noticeable differences between African Americans and White smokers in rates of certain tobacco-related cancers that first drew attention to the possible health effects of menthol cigarettes. Consequently, it is of interest to compare rates of these cancers over the past 20 years (using NCI's Surveillance Epidemiology and End Results (SEER) data) to trends in menthol preference.

In 1989, the age-adjusted incidence rate of lung cancer per 100,000 was much higher in Black men than in White men (142.8 vs. 97.1, or a 47.1% excess in Blacks), but was only slightly higher in Black women compared to White women (51.4 vs. 47.2, or a 9% excess in Blacks) (Altekruse 2010). Rates had changed dramatically by 2007. At that time, age-adjusted incidence had decreased to 93.5 for Black men and to 69.1 for White men. In other words, there was a 35% decrease in the incidence rate among Black men and a 28% decrease in White men. In contrast, rates among women were slightly higher in 2007: 53.4 for Black women and 54.1 for White women. Thus, in spite of the higher preference for menthol cigarettes among smokers who are Black or female, the rate of lung cancer has decreased among Black men but remained stable among Black and White women. This fails to support a relationship between menthol cigarette smoking and lung cancer, especially among Black men.

Examination of esophageal cancer incidence rates also fails to support an association with the use of menthol cigarettes. In 1989, the age-adjusted incidence rate of esophageal cancer per 100,000 was greater in Black men compared to White men (17.3 vs. 6.2) and in Black women compared to White women (5.4 vs. 2.0). By 2007, the rate had declined in Black men to 7.9, while the rate among White men had increased slightly to 8.2. Incidence of esophageal cancer also decreased dramatically in Black women (to 2.8), while the rate in White women remained unchanged. The dramatic decline in esophageal cancer among Black men and women, but not White men or women, provides no support for the notion that menthol plays any role in the etiology of this cancer.

While the limitations of using ecologic data to make causal inferences are well-known, and while it would be desirable to distinguish between squamous cell cancer and adenocarcinoma of the esophagus, one can still conclude that the SEER data cited above comparing changes in the rates of lung and esophageal cancer among Blacks and Whites over the past 20 years are not suggestive of any contribution of menthol to the risk of these diseases.

EPIDEMIOLOGY ALSO SHOWS NO SEX-SPECIFIC OR RACE-SPECIFIC ASSOCIATIONS

Despite the fact that the substantial body of epidemiology studies has consistently found that menthol cigarette smoking is not associated with increased risk of any of the diseases evaluated, there appears to be the perception that, if one looks hard enough, one may find an elevated risk among a specific subgroup (either race or sex) of the population. The data do not support this notion, as described below.

It is important to remember that to avoid drawing erroneous conclusions, it is essential to evaluate the overall pattern of study findings, their consistency, and study quality. Isolated elevated risk estimates, especially when not statistically significant, should not be given undue weight. When

many analyses are conducted, statistically significant associations can arise by chance (i.e., it is to be expected that, on average, 1 in 20 results (or 5%) could be statistically significant due to chance alone, when the conventional criterion for statistical significance of 5% is used) (Fleiss 2003). The only safeguard against giving isolated results undue weight is to focus on the overall pattern of results. Doing so leads to the conclusion that there are no subgroups of smokers that have increased disease risks due to menthol in cigarettes.

Sex-Specific Associations

Much has been made of the single statistically significant finding in this literature: that by Sidney et al. (1995) in an analysis of the Kaiser Permanente cohort. As discussed above, those investigators found a modest elevation in risk of lung cancer (RR=1.45; 95% CI:1.03-2.02) among men (all races combined) who smoked menthol cigarettes, but not women (RR=0.75; 95% CI:0.51-1.11), despite the greater preference for menthol use among women. The authors considered this a suggestive finding, but a later analysis of smoking-related cancers in this cohort by some of the same investigators did not support this suggestion.

That later study (Friedman et al. 1998) examined the relationship between menthol smoking and other smoking-related cancers. It found that menthol smokers did not have a significantly increased risk of all of the non-lung smoking related cancers combined, or of any of the individual sites studied. The authors (including Sidney) concluded that the earlier finding by Sidney et al. may have been merely a chance finding, since it was not seen in women and has not been replicated elsewhere.

Numerous studies have examined risks among men and women menthol and nonmenthol smokers and found that neither sex had elevated risk of several important outcomes (i.e., Kabat and Hebert 1991, Kabat and Hebert 1994, Carpenter et al. 1999, Brooks et al. 2003, Stellman et al. 2003, Friedman et al. 1998).

Information presented to TPSAC[2] has suggested that there might be a menthol x disease x sex interaction, citing some point estimates that were >1.0, although not statistically significant. Specifically, the supporting evidence cited included:

- The finding by Carpenter et al. (1999) of an odds ratio of 1.48 (95% CI:0.71-3.05) for lung cancer associated with 32+ pack-years of menthol smoking among men;
- The finding by Kabat and Hebert (1994) of an odds ratio of 1.7 (0.8-3.4) for pharyngeal cancer associated with ever menthol smoking among men; and
- The finding by Hebert and Kabat (1989) of an odds ratio of 2.30 (95% CI:0.93-5.72) for esophageal cancer associated with $\geq$10 years of smoking menthols among women.

This suggestion of an interaction is unfounded for a number of reasons. First, none of the results is statistically significant. Second, there is no consistent pattern. In the first two instances, it appears that males have a higher risk, whereas in the third instance, females appear to have a higher risk. Third, if certain selected elevated risks are highlighted, similar focused discussion of reports of relative risks that are below 1.0 (and there are many in this literature) must also be considered.

[2] This information was provided to TPSAC in a presentation made in March 2010 and a white paper submitted in October 2010 (both by Dr. Allison Hoffman, NIDA/NIH).

Rather than cherry-picking individual results, it is more appropriate to conduct a meta-analysis to determine the overall association based on all available studies and to look at consistency of results in subgroups. As noted previously, none of the ORs reported in the meta-analysis on lung cancer by Lee (2011) associated with menthol smoking (by race, sex, and length of menthol smoking) were statistically significant, and virtually all were less than 1.0.

Race-Specific Associations

TPSAC has been specifically charged with evaluating the impact of menthol cigarettes on African Americans, Hispanics, and other racial and ethnic minorities. With respect to smoking-related diseases, the epidemiology literature mainly provides risk estimates among African American and White smokers. This has been the focus of interest for two reasons: African Americans have higher rates of certain smoking-related cancers than Whites, and the percentage of African American smokers who prefer menthol cigarettes (69%) is much higher than that of White smokers who prefer menthols (22%) (Giovino et al. 2004). As was noted in Chapter 2 of this report on the demographics of menthol use, the number of White menthol smokers greatly exceeds the number of African American menthol smokers. According to NSDUH (2004-2008), 53% of menthol smokers are White and 30% are African American (Caraballo unpublished).

However, not a single study has shown that African Americans who smoke menthols have statistically significant elevations in risk of any of the diseases examined (compared to African Americans who smoke regular cigarettes), as detailed in Appendix Tables 3-9 to 3-13. The bulk of the data on race come from studies that examined the endpoint of lung cancer. These studies drew the following conclusions:

- Carpenter et al. (1999): In this case-control study, odds ratios for lung cancer associated with menthol smoking among African Americans (either >1-15, 16-31, or 32+ pack years) were all less than 1.0. The authors concluded: "The lung-cancer risk associated with menthol smoking was similar to that for exclusive nonmentholated cigarette smoking both in the total sample and within ethnic groups."
- Brooks et al. (2003): In this case-control study, odds ratios for lung cancer associated with menthol smoking among Blacks (1-15 and >15 years) relative to nonmenthol smoking were not statistically significant. The authors stated: "In separate analyses of men, women, Blacks, and Whites, long-term use of menthol cigarettes was not associated with an increase in lung cancer relative to exclusive use of nonmenthol cigarettes."
- Stellman et al. (2003): Odds ratios for lung cancer associated with menthol smoking were 1.34 (95% CI:0.79-2.29) for Black men and 0.79 (95% CI:0.41-1.54) for Black women. The authors noted: "While Black smokers in our study were more likely to choose menthol than nonmenthol brands, our data provide no evidence that menthol cigarettes per se produce greater lung cancer risk than do nonmenthol brands."
- Etzel et al. (2008): In a case-control study of only African American subjects, neither current nor former smokers of menthol cigarettes had increased risk of lung cancer (odds ratios were 0.69 and 0.99). They concluded: "We observed no significant risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes and our data suggested a possible protective effect of mentholated cigarettes for current smokers."

- Lee (2011): This recent analysis found no significantly increased risk of lung cancer among Blacks who had ever smoked menthol cigarettes (OR=0.96; 95% CI:0.80-1.15) or those who had long-term use (15+ years) of menthol cigarettes (OR=1.08; 95% CI:0.79-1.47). Lee (2011) concluded: "The data do not suggest any effect of mentholation on lung cancer risk." He also stated: "There is also no evidence of an increase in men or women separately, in Blacks or Whites separately, or in estimates for ever smokers, current smokers, or former smokers." And finally: "Higher lung cancer rates in Black men cannot be due to their greater preference for mentholated cigarettes."

Two studies provide some data on other health outcomes; again, these did not find any significant elevations in risks for African American menthol smokers:

- Friedman et al. (1998) did not present much race-specific information in their analysis of the Kaiser Permanente cohort, but they did discuss prostate cancer because of its higher incidence rate among African Americans. They found no statistically significant excess risk associated with mentholation in analyses not controlled for race (rate ratio=1.15; 95% CI:0.82-1.62), and in Cox proportional hazards regression controlling for age and race (rate ratio=1.12; 95% CI:0.80-1.58).
- Pletcher et al. (2006): In the CARDIA longitudinal cohort study, there was no association between menthol exposure and coronary calcification among either European Americans or African Americans. With respect to pulmonary function, European Americans tended to have larger declines associated with menthol cigarettes than did African Americans. The authors concluded: "Mentholation of cigarettes does not seem to explain disparities in ischemic heart disease and obstructive pulmonary disease between African Americans and European Americans in the United States . . ."

TPSAC panel members are concerned that it may be difficult to interpret studies of menthol smoking and lung cancer, given that baseline rates of lung cancer differ by race, sex, and smoking status. This concern is unfounded, as every study of menthol smoking and lung cancer has considered race in some way. Some studies have been limited to only one race; for example, some compared African American menthol smokers to African American nonmenthol smokers (e.g., Etzel et al. 2008). In those studies that had adequate numbers of subjects of each race, separate analyses were conducted among Whites and African Americans (e.g., Brooks et al. 2003, Carpenter et al. 1999, Stellman et al. 2003). Other studies combined races but adjusted for race (e.g., Kabat and Hebert 1991, Murray et al. 2007, Sidney et al. 1995). This adjustment can be made through the study design (i.e., by matching cases and controls on race) or through statistical adjustment (by including a term for race in the multivariate model).

Differences in incidence of lung cancer by sex have been handled in the same manner (either sex-specific analyses, matching or statistical adjustment). Finally, all of these studies are limited to smokers (current or former). This analytic approach avoids any baseline difference in lung cancer risk among never smokers of different races. By focusing on menthol versus nonmenthol, the studies appropriately isolate the potential effect of menthol.

TPSAC members have pointed out that African American menthol smokers smoke fewer cigarettes per day than nonmenthol smokers, but have contended that those smokers do not have lower biomarker levels or reduced incidence of smoking-related diseases. TPSAC members have theorized

that African American smokers smoke their fewer cigarettes more intensely, thus increasing their exposure. However, a review of the biomarker studies (discussed in Chapter 3B) and epidemiology studies do in fact suggest lower levels of exposure and lower levels of disease risk, although these findings are not statistically significant. For example, Etzel et al. (2008) studied lung cancer rates among African American smokers and found that current menthol smokers had lower odds ratio (OR=0.69; 95% CI:0.46-1.03) for lung cancer compared to current nonmenthol smokers, which is what one would expect with smoking fewer cigarettes per day.

CONCLUSION

This review of available epidemiology studies clearly demonstrates that smokers of menthol cigarettes are at no greater risk of developing chronic smoking-related diseases than are nonmenthol smokers. Importantly, with more than a dozen published studies as well as a meta-analysis of the eight studies on lung cancer, there are sufficient data available to draw this conclusion with confidence. Furthermore, the literature is very consistent, which rules out the possibility that there are even small elevations in risk associated with menthol cigarettes. While all epidemiology studies have limitations, the available studies are well-designed and well-analyzed, for the most part have adequate numbers of cases, and are able to detect effects of smoking parameters. The diseases studied include lung cancer (the most common smoking-related cancer), cancers of the upper aerodigestive tract (esophagus, larynx, oropharynx), and other cardiac and lung outcomes. The studies provide data on risks specific to both sexes and to both Whites and African Americans, and do not find that there is any subpopulation that is especially susceptible to effects from menthol smoking. Thus, it can be concluded that, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol cigarettes and increased smoking-related disease risk above that caused by use of nonmenthol cigarettes.

CHAPTER 3B.
MENTHOL IN CIGARETTES HAS NO MEANINGFUL EFFECT ON BIOMARKERS OF EXPOSURE AND POTENTIAL HARM

As described above, epidemiology studies show no significant difference in the risk of smoking-related disease among menthol smokers as compared to nonmenthol smokers. Consistent with the epidemiology, biomarker studies show that menthol in cigarettes does not increase exposure of smokers to smoke constituents, including some constituents that are believed to cause disease.

A considerable number of soundly-designed and well-conducted studies comparing biomarkers of exposure and potential harm among menthol smokers and nonmenthol smokers have been conducted. Sensitive methods are currently available to measure biomarkers of smoke constituent exposures in body fluids (e.g., saliva, blood, urine) of smokers, primarily as metabolites of those constituents. A number of biomarkers of potential harm that may be related to chronic disease risk have also been investigated and reported, although they are at a lesser state of development and validation.

To evaluate the hypothesis that menthol in cigarettes affects exposure to smoke constituents, either directly or by influencing the manner in which cigarettes are smoked, various researchers have examined the relationship between menthol cigarettes and biomarkers of exposure, metabolism and potential harm. Overwhelmingly, the data show that biomarkers of exposure are not significantly different among menthol smokers compared with nonmenthol smokers. Similarly, menthol does not appear to meaningfully impact exposure to putative biomarkers of potential harm. These biomarker studies integrate and reflect the combined impacts of all the diverse elements of complex human smoking behaviors, including cigarettes smoked per day, puffing intensity (puff number, volume, interval and duration), amount of smoke inhalation, the percent of the cigarette smoked and the amount of filter ventilation hole blocking, if any. According to the Surgeon General's framework for assessing causality, a thorough assessment of the available scientific evidence from biomarkers studies leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between smoking menthol cigarettes and increases in biomarkers of exposure to smoke constituents or their metabolites or biomarkers of potential harm as compared to smoking nonmenthol cigarettes. The rationale for reaching this conclusion on each biomarker endpoint is provided in the appropriate section below.

SUFFICIENT DATA ON BIOMARKERS EXIST TO DRAW CONCLUSIONS

Included in the vast body of literature evaluating tobacco smoke biomarkers are 19 studies that compare biomarkers between menthol and nonmenthol smokers. These comparisons have been made on a wide variety of endpoints, some of which reflect acute exposures (e.g., exhaled carbon monoxide (CO) or increases ("boosts") in plasma nicotine from the smoking of a single cigarette) and others which provide far more meaningful representations of daily exposures (e.g., a mid-afternoon sampling of blood providing a near steady-state assessment of systemic exposure to CO (as blood carboxyhemoglobin) and nicotine (as plasma cotinine)). Those studies that have assessed acute pre- and post-smoking "boosts" in breath CO and plasma nicotine are considered primarily in

Chapter 3C on smoking topography, since these measures are intended to evaluate exposures resulting from the last cigarette smoked rather than systemic exposures integrated over the course of daily smoking. The volume of the literature available for each of the endpoints considered in the following biomarkers section varies. The breakdown of the 19 studies and a summary of their findings are as follows:

- 4 of 4 studies comparing systemic carbon monoxide exposure found no significant differences
- 12 of 17 studies comparing levels of nicotine or its metabolites found no significant differences
- 4 of 4 studies comparing levels of carcinogens found no significant differences[3]

Details of these studies are provided in Appendix Table 3-14.

MENTHOL SMOKERS DO NOT HAVE HIGHER SYSTEMIC CARBON MONOXIDE EXPOSURE

Carbon monoxide (CO), a combustion product of cigarette tobacco and other organic materials, can be estimated through measurement of expired-air carbon monoxide (expressed as parts per million) or as blood carboxyhemoglobin (as the percent of hemoglobin saturation). Breath CO measurements are readily influenced by short-term changes in smoke inhalation and reflect very recent smoking since the half-life for CO elimination in the breath is approximately 1-4 hours (Scherer 2006). Exhaled breath CO has been reported to correlate relatively poorly with daily cigarette consumption (Rosenblatt et al. 1998; Ho et al. 2009). Blood carboxyhemoglobin measurement is more reflective of daily systemic exposures to CO from smoking than is exhaled breath analysis, since CO has a very high affinity for stably-circulating hemoglobin and carboxyhemoglobin accumulates over the course of the smoker's day to attain a near steady-state level, typically by mid-afternoon (Smith et al. 1998). Blood carboxyhemoglobin level is not as sensitive to the time since the last cigarette and is a preferred biomarker to assess daily or chronic CO exposures from smoking. Studies reporting exhaled breath CO measurements are therefore discussed primarily in the following section (Chapter 3C) on smoking topography, while those reporting blood carboxyhemoglobin as a biomarker of smoke exposure are discussed in the present biomarkers section.

Four studies have compared blood carboxyhemoglobin between menthol and nonmenthol smokers. As shown in Table 3-1, none of these studies found a statistically significant difference between menthol and nonmenthol smokers. Importantly, Wang et al. (2010) evaluated carboxyhemoglobin levels in more than 3,000 smokers as part of the Total Exposure Study (discussed in more detail below). Given the size of the study population and inclusion of a significant number of menthol and nonmenthol smokers (1,044 and 2,297, respectively), any meaningful difference that existed between the groups should have been detected.

[3] One study found a small difference in a carcinogen metabolite ratio (i.e., NNAL-glucuronide/NNAL); the relevance of this finding to disease risk is unknown.

Table 3-1. Comparison of Carboxyhemoglobin between Menthol and Nonmenthol Smokers (N=4)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
- No Studies -	Benowitz et al. 2004	- No Studies -
	Heck 2009	
	Jarvik et al. 1994	
	Wang et al. 2010	

Conclusion about Exposure to Systemic Carbon Monoxide

The four studies that have compared blood carboxyhemoglobin are consistent in finding no significant difference between menthol and nonmenthol smokers in carboxyhemoglobin, a sensitive measure of systemic carbon monoxide exposure. Wang et al. (2010) included an adequate sample size to detect a meaningful difference. Thus, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and elevated levels of systemic carbon monoxide above those caused by smoking nonmenthol cigarettes.

MENTHOL SMOKERS DO NOT HAVE HIGHER EXPOSURE TO NICOTINE OR NICOTINE METABOLITES

Nicotine and its metabolites are perhaps the most-studied among the available biomarkers employed in smoking research. Seventeen studies[4] have reported on comparisons of exposure to nicotine or nicotine metabolites in menthol and nonmenthol cigarette smokers; details of each study are provided in Appendix Table 3-14. The measures of exposure in these studies include nicotine; acute "nicotine boost;" nicotine/cigarette; unlabeled nicotine in plasma; salivary and plasma cotinine; cotinine/cigarette ratio; urinary recovery of nicotine, nicotine-glucuronide, cotinine, cotinine-glucuronide, 3'-hydroxycotinine and 3'-hydroxycotinine-glucuronide; urinary nicotine equivalents; and cotinine/3'-hydroxycotinine ratio.

Nicotine is a major tobacco and cigarette smoke constituent which is absorbed in the lungs and rapidly metabolized in the liver, with a half-life of only about 2 hours. Acute measures of "nicotine boost" before and after the laboratory smoking of an experimental cigarette are intended to assess nicotine exposure from the last cigarette smoked and are considered a correlate of puffing intensity (smoking topography). Studies reporting "nicotine boost" are therefore discussed in the subsequent section, Chapter 3C, on smoking topography.

The main metabolite of nicotine is cotinine, which has a much longer half-life of 16-18 hours (Roethig et al. 2009). This longer half-life of cotinine makes it a more practical biomarker of systemic tobacco smoke exposure than nicotine. Cotinine can be measured in saliva, blood or urine. Salivary cotinine has been reported to have a relatively stable and predictable relationship to plasma cotinine and offers a relatively convenient means to assess systemic nicotine exposure.

[4] Ahijevych and Parsley 1999, Ahijevych and Wewers 1994, Ahijevych et al. 2002, Allen and Unger 2007, Benowitz et al. 2004, Benowitz et al. 2010, Clark et al. 1996, Gan et al. 2008, Heck 2009, Ho et al. 2009, Muscat et al. 2009, Mustonen et al. 2005, Patterson et al. 2003, Signorello et al. 2009, Strasser et al. 2011, Wang et al. 2010, Williams et al. 2007.

Cotinine is further metabolized into 3'-hydroxycotinine and other minor metabolites. Nicotine-glucuronide and cotinine-glucuronide are the primary conjugated metabolites of nicotine and cotinine that can be measured in excreted urine to assess exposure, as well as the efficiency of glucuronide conjugation. Some studies report urinary nicotine equivalents, typically as the molar sum of nicotine and the five principal metabolites that account for a majority of nicotine clearance (sum of nicotine, cotinine, *trans*-3'-hydroxycotinine and their respective glucuronides) (Roethig et al. 2009). The ratio of cotinine/3'-hydroxycotinine represents a measure of cytochrome P450 2A6 activity, the primary hepatic enzyme responsible for nicotine metabolism in humans.

Of these seventeen studies, twelve found no elevation in nicotine or any of its metabolites in menthol smokers as compared to nonmenthol smokers. Included among these are seven studies that included more than 100 to 500 smokers, two studies of more than 500 to 1,000 smokers and two studies with sample sizes exceeding 1,000 smokers. Table 3-2 below lists the studies according to their overall results: those in which subjects who smoked nonmenthols had significantly greater levels of nicotine or nicotine metabolites than those who smoked menthols; those in which there was no significant difference, and those in which subjects who smoked menthols had significantly greater levels of nicotine or nicotine metabolites than those who smoked nonmenthols.

Table 3-2. Comparison of Nicotine or Nicotine Metabolites Between Menthol and Nonmenthol Smokers (N=17)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
- No Studies -	Ahijevych and Wewers 1994[1]	Ahijevych and Parsley 1999[2]
	Allen and Unger 2007[1]	Ahijevych et al. 2002[2]
	Benowitz et al. 2004	Clark et al. 1996[2]
	Benowitz et al. 2010[1]	Mustonen et al. 2005[3]
	Gan et al. 2008[1]	Williams et al. 2007[4]
	Heck 2009[1]	
	Ho et al. 2009[1]	
	Muscat et al. 2009[1]	
	Patterson et al. 2003[1]	
	Signorello et al. 2009[1]	
	Strasser et al. 2011	
	Wang et al. 2010[1]	

[1] No significant difference in cotinine, cotinine/cigarette or cotinine/CPD
[2] Significantly higher cotinine in menthol smokers
[3] Significantly higher cotinine/CPD in menthol smokers
[4] Significantly higher serum cotinine and serum nicotine

Wang et al. (2010) published analyses of the Total Exposure Study (TES) dataset, which is discussed in more detail below. This study is important to consider due to its substantial size (3,341 smokers) and its inclusion of a substantial number of menthol, as well as nonmenthol smokers (1,044 and 2,297, respectively). Additionally, the study evaluated a broad number of biomarkers and subject characteristics, including extensive demographic and physical traits, CPD, nicotine equivalents, nicotine equivalents per cigarette and serum cotinine. Analysis of unadjusted data found statistically significantly higher nicotine equivalents per cigarette in menthol smokers while CPD and nicotine equivalents per 24 hours were found to be significantly lower in menthol smokers as compared to nonmenthol smokers. There was no reported difference in serum cotinine between smokers of the two cigarette types. After adjustment for variables which were found to be statistically significant in

the initial model[5], there were no longer any statistically significant effects of menthol cigarettes on nicotine equivalents per 24 hours, serum cotinine or nicotine equivalents per cigarette.

Similarly, the findings of Gan et al. (2008), a study of 840 men and 680 women among the large 1999-2000 NHANES sampling which evaluated the effect of sex on cotinine levels, showed significantly higher plasma cotinine in menthol smokers as compared to nonmenthol smokers, but only in the univariate analysis. After adjustment for sex, CPD, age, race, BMI, poverty status and nicotine content per cigarette, the difference was no longer significant.

In addition to Wang et al. (2010) and Gan et al. (2008), eight studies found no significant differences between menthol and nonmenthol smokers in levels of cotinine (Table 3-2, footnote 1) and five studies reported higher cotinine levels in menthol smokers compared to nonmenthol smokers (Table 3-2, footnotes 2-4).

One of the five studies that reported higher cotinine levels in menthol smokers, Mustonen et al. (2005), collected salivary samples for cotinine analysis from 307 smokers (28.7% menthol smokers) recruited for a clinical smoking cessation trial. Although there was no difference observed in CPD or measures of salivary cotinine, the authors observed a significantly higher cotinine/CPD ratio among menthol smokers as compared to nonmenthol smokers ($p=0.004$). It should be noted that these analyses were unadjusted. Given that Mustonen et al. (2005) reported a significant effect of the interaction between sex, race and cigarette type on salivary cotinine and cotinine/CPD, the differences observed in cotinine/CPD may have been due to these factors, which were not accounted for in the univariate analysis.

However, Williams et al. (2007), in a study of 89 schizophrenic smokers and 53 control smokers (comprising 79 menthol smokers), found no significant difference in cotinine/CPD but found significantly elevated serum cotinine levels in menthol smokers as compared to nonmenthol smokers after adjustment for schizophrenic status, race and CPD. In addition to the differences observed in serum cotinine, Williams et al. (2007) found significant elevations in serum nicotine, but not in nicotine/CPD in menthol smokers as compared to nonmenthol smokers. The discrepancies in these results depending on the method used to adjust for CPD imply that some other variable is responsible for the difference.

Clark et al. (1996) collected samples from 161 smokers following a 1-hour smoking abstention for determination of serum cotinine. Serum cotinine levels were found to be significantly elevated in menthol smokers versus nonmenthol smokers (84.5 ng/ml increase in menthol smokers after adjustment for race, CPD and mean amount of cigarette smoked). However, the question of whether differences in the mainstream smoke nicotine yields of the subjects' preferred cigarettes may at least partially account for the reported cotinine differences limits the conclusions that can be drawn from this study with respect to menthol.

Two additional studies (Ahijevych and Parsley 1999 and Ahijevych et al. 2002) of all female smokers reported increased cotinine/cigarette ratios at baseline among menthol smokers as compared to nonmenthol smokers. Neither of these studies considered the machine-measured mainstream smoke nicotine yields of the cigarettes smoked by the study subjects, an adjustment that is lacking

[5] Those tested included menthol, age, sex, BMI, race, smoking machine derived tar category, CPD, U.S. Census region, annual household income, education and the two-way and three-way interactions of the factors.

from the majority of biomarkers studies. For example, in Williams et al. (2007), subjects reported smoking a variety of different full-flavor, lights and ultra-lights brands. The most frequently smoked menthol brand among study subjects was Newport, which at the time of the study delivered 9% more machine-determined (FTC) nicotine and 13% more carbon monoxide than did the most frequently-reported nonmenthol brand (Marlboro) in the study. Thus, attribution of reported differences to the presence of menthol cannot be scientifically justified. In Heck (2009), in which 112 smoking subjects were provided with designated menthol and nonmenthol brands closely matched for machine-determined "tar," nicotine and CO yields, the two groups of smokers did not have significantly different levels of cotinine or urinary nicotine equivalents.

The few differences reported between menthol and nonmenthol smokers in these measures of nicotine and nicotine metabolites in body fluids, especially differences that remain when taking into account cigarettes per day, may reflect differences in the ways that the two types of cigarettes are smoked. However, whether this can be attributed to the inclusion of menthol in cigarettes is unclear. Another important consideration when evaluating a measure of exposure per cigarette is the accuracy of the cigarette per day data. For many of these studies, data on cigarette consumption were self-reported, and as shown by Ahijevych and Wewers (1994), this method of data collection can be subject to substantial underreporting of cigarette consumption.

Benowitz et al. 2004, Benowitz et al. 2010, Heck 2009 and Patterson et al. 2003 found no differences in any measures of nicotine exposure. One study (Muscat et al. 2009) also compared levels of thiocyanate, a metabolite of hydrogen cyanide, in menthol smokers versus nonmenthol smokers and reported no difference.

Conclusion about Exposure to Nicotine and Nicotine Metabolites

In drawing conclusions about type of cigarette smoked and nicotine and nicotine metabolites, it must be remembered that there are a good number of studies (N=17) and many endpoints assessed among those studies. It is not surprising that there might be a few significant findings when doing this number of analyses; however, it is important to focus on the overall pattern of results. Of the 17 studies that compared exposure to nicotine or nicotine metabolites between menthol and nonmenthol smokers, the majority (N=12) showed no significant differences in any of the endpoints measured. This includes the two largest studies (Wang et al. 2010, Gan et al. 2008), which presented data on nationally representative populations (TES and NHANES).

Among the five studies that found significant differences between menthol and nonmenthol smokers, all observed differences in cotinine levels. Two of these involved only relatively small groups of female smokers. Additionally, results were not internally consistent, with discrepant findings in cotinine and cotinine/CPD in two of the studies (Mustonen et al. 2005, Williams et al. 2007) that could not be easily explained. Thus, the combined weight of available published, peer-reviewed studies of biomarkers of systemic nicotine exposure clearly supports a conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and elevated systemic nicotine exposure above that caused by smoking nonmenthol cigarettes.

MENTHOL DOES NOT INHIBIT THE METABOLISM OF TOBACCO SMOKE COMPONENTS

The studies discussed above that evaluated measures of nicotine metabolites provide information both on systemic nicotine exposure and on the impact of menthol on the metabolism of certain tobacco smoke components. With the majority showing no significant difference between menthol and nonmenthol smokers in levels of nicotine metabolites, it can be concluded that menthol does not meaningfully affect the metabolism of tobacco smoke components. Benowitz et al. (2004), discussed in further detail below, suggested that menthol may affect the metabolism of nicotine, and these authors explored the potential of such an effect to influence smoke constituent exposures accompanying menthol cigarette smoking. An earlier report by MacDougall et al. (2003) had reported inhibitory effects of menthol and similar compounds on the in vitro oxidation of nicotine by human microsomes, but the rather modest potency of menthol in affecting these enzyme activities (Ki value for inhibition of cotinine formation by menthol = 69.7 μM vs. systemic menthol from smoking ~1 μM or less) does not suggest a likelihood of a meaningful effect in vivo at exposure levels resulting from menthol's use in cigarettes. Indeed, a number of subsequent studies in humans have not observed metabolic interactions between menthol and a number of drugs that are well-characterized as human cytochrome P450 substrates (Gelal et al. 2003, 2005).

Benowitz et al. (2004), was a forced crossover study of 14 smokers, half African American and half White. Each subject was randomly assigned to smoking either a menthol or nonmenthol cigarette of similar FTC smoke yield (Kool Kings or Marlboro Kings) for a one-week period. Following the treatment period, subjects were administered an intravenous dose of deuterated nicotine and cotinine and deuterated nicotine metabolites were analyzed in collected urine to assess nicotine and metabolite clearance. Subjects' menthol and nonmenthol group assignments were then switched for another week of smoking followed by another intravenous administration of deuterated nicotine and urinary metabolite collection and analysis.

The disposition kinetics of nicotine and cotinine were evaluated through a number of measures including clearance, half-life and volume of distribution at steady state. The only significant differences that were observed were slower total and nonrenal clearance of nicotine among menthol smokers and a lower nicotine-glucuronide/nicotine ratio in menthol smokers. These differences were not found for cotinine. There were also no significant differences in urinary recovery of nicotine, nicotine-glucuronide, cotinine, cotinine-glucuronide, 3'-hydroxycotinine or 3'-hydroxycotinine-glucuronide when comparing the menthol group to the nonmenthol group. These results led the authors to conclude that menthol inhibits nicotine, but not cotinine, metabolism. However, given the lack of consistent evidence of an effect of menthol on the metabolism of tobacco smoke components (e.g., Heck 2009, Ho et al. 2009, Benowitz et al. 2010, Wang et al. 2010, Strasser et al. 2011, Williams et al. 2007), the practical implications of this as-yet unconfirmed observation that menthol may affect the metabolism of intravenously-administered nicotine are not readily apparent.

The extremely large study of Wang et al. (2010), in particular, addressed the discrepancy in their results versus those observed by Benowitz et al. (2004). As stated above, Wang et al. (2010), along with nine other studies, found no difference in serum cotinine levels between menthol and nonmenthol smokers; the authors also reported no significant differences in nicotine metabolite ratios, suggesting that menthol has no effect on the metabolism of nicotine derived from smoking. This is in contrast to the conclusion of Benowitz et al. (2004) that menthol cigarettes significantly

inhibit nicotine metabolism by slower oxidative metabolism to cotinine and slower glucuronide conjugation. Wang et al. (2010) explained that the reason for the discrepancy between the two studies could be due to the differences in the study designs (i.e., Benowitz et al. 2004) compared urine cotinine levels collected for eight hours after an intravenous infusion of deuterium-labeled nicotine and cotinine in a controlled setting, whereas Wang et al. (2010) compared serum cotinine levels taken at a single time-point from smokers in an ambulatory setting. Furthermore, the sample sizes between the two studies are vastly different (N=14 vs. N=3,341). The absence of statistically significant differences in serum cotinine levels or any other nicotine metabolites measured in the large Wang et al. (2010) study suggests that an effect, if any, of menthol on nicotine metabolism is most likely small since it could not be detected in such a large study.

Heck (2009) was a parallel-arm study of 112 smokers who were assigned to specific brands of menthol or nonmenthol cigarettes with similar machine-measured tar yields. Smokers were assigned either to menthol or nonmenthol cigarettes based on their stated preference and smoked commercial cigarettes of similar machine-measured "tar" yields (~9-10 mg) ad libitum for a 2-week study interval. Measures of metabolism included nicotine-glucuronide, cotinine-glucuronide, *trans*-3'-hydroxycotnine and *trans*-3'-hydroxycotinine-glucuronide; there were no significant differences between the menthol and nonmenthol group in any of these measures. In addition, Strasser et al. (2011) and Williams et al. (2007) reported 3'-hydroxycotinine to cotinine ratios, a measure of CYP2A6-mediated nicotine metabolism, that did not show significant differences between menthol and nonmenthol smokers.

Conclusion about Effects on Metabolism of Tobacco Smoke Components

Of the four studies most relevant to this topic, there was only a single significant finding, which suggested that menthol inhibits metabolism. This finding came from a study of only 14 subjects and it has not been confirmed in three subsequent analyses (one of which was an analysis of the extremely large TES dataset). Thus, there is no clear and consistent association between menthol smoking and an effect on nicotine metabolism. This conclusion is supported by the lack of significant differences in studies that have compared levels of nicotine metabolites, as discussed in the previous section. The combined weight of available published, peer-reviewed studies comparing levels of nicotine metabolites and other measures of metabolism supports a conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and altered nicotine metabolism when compared the use of nonmenthol cigarettes.

MENTHOL DOES NOT INCREASE EXPOSURE TO CARCINOGENS

Tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs) are among the carcinogens present in measurable quantities in tobacco smoke. Prominent among the TSNAs is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and a urinary metabolite of this compound, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL) that has been broadly employed as a sensitive and specific urinary biomarker for NNK exposures resulting from tobacco use.

Urinary levels of excreted NNAL and its glucuronide conjugates (NNAL-gluc) have been measured in several studies to compare the relative NNK exposures resulting from the smoking of menthol and nonmenthol cigarettes. Although NNAL has itself been classified by IARC as a Group 2B carcinogen (i.e., possibly carcinogenic to humans), the relatively efficient urinary clearance of the glucuronide conjugate of NNAL has led some authors to propose that a higher urinary NNAL-gluc/NNAL ratio may be indicative of a metabolic detoxification capacity that is consistent with lower cancer risks. Notably, this speculation that NNAL-gluc/NNAL ratio may determine smokers' lung cancer risks has not been borne out in studies of populations having substantially different metabolite profiles and lung cancer risks (Derby et al. 2008).

Four studies have evaluated concentrations of NNAL and its metabolites among menthol smokers and nonmenthol smokers, and none of these have reported higher total NNAL excretion by menthol cigarette smokers (see Table 3-3). One of these studies reported menthol-related differences in NNAL-gluc/NNAL ratio, as discussed below.

Table 3-3. Comparison of NNAL and NNAL Metabolites Between Menthol and Nonmenthol Smokers (N=4)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
- No Studies -	Benowitz et al. 2010	- No Studies -
	Heck 2009	
	Muscat et al. 2009	
	Xia et al. 2010	

One of the studies which measured NNAL concentrations (Xia et al. 2010) included an analysis of 1,373 tobacco users who participated in the 2007-2008 NHANES. Urinary total NNAL concentrations were determined from analysis of urine samples of all participants aged 6 years or older. The authors reported no significant difference between menthol and nonmenthol smokers (285 vs. 331 pg/ml, respectively) in this analysis. Likewise, Heck (2009), discussed in more detail above, found no difference in total NNAL concentrations between menthol and nonmenthol smokers nor any difference in its metabolite, NNAL-glucuronide. Benowitz et al. (2010) included a comparison of urine NNAL in menthol smokers to that measured in nonmenthol smokers and reported that there was no significant difference.

The study reported by Muscat et al. (2009) found no significant difference between menthol and nonmenthol smokers in total urinary NNAL, but these authors reported a significantly higher NNAL-glucuronide/NNAL ratio for nonmenthol smoking subjects than for the menthol smokers. This finding was in contrast to the analysis reported in a prior publication by this group for the same study population, which had concluded African American race, but not menthol preference, appeared to be associated with apparent reduced glucuronidation efficiency for NNAL (Richie et al. 1997). The authors hypothesized that the 2009 finding could be due to inhibition of UDP-glucuronosyltransferase enzymes responsible for glucuronidation of nicotine and NNAL. The authors offered the findings of a single in vitro experimental incubation of human S-9 in support of their hypothesis. However, this experiment used menthol levels roughly equivalent to those that would result from smoking several hundred cigarettes, and the experimental NNAL level used was approximately 5 million times greater than what is measured in human smokers. The authors acknowledged that the levels of menthol and substrate in the in vitro enzyme incubation were not representative of those from actual smoking. No prior or subsequent studies in human smokers

have confirmed the speculation of Muscat et al. (2009) that menthol in cigarettes may affect NNAL metabolism. The alternate explanation offered by Ritchie et al. (1997) (i.e., metabolic differences between Black and White smokers as opposed to an effect by menthol), is also supported by the findings of the large Total Exposure Study.

One study, Benowitz et al. (2010), compared urine total PAHs, the molar sum of all PAH metabolites, in menthol smokers to those of nonmenthol smokers. In this analysis of 127 smokers (60 menthol and 62 nonmenthol), nonmenthol smokers were found to have significantly higher levels of total PAH in the urine than menthol smokers. The authors conducted various statistical analyses to understand the relationship between measures of menthol exposure and other variables, including nicotine equivalents, NNAL and total PAHs. They concluded that menthol exposure does not add to the predictive value of nicotine exposure in determining exposure to TSNAs or PAHs from cigarette smoking.

Conclusion about Exposure to Carcinogens

None of the four studies that compared levels of NNAL or PAH found significant differences between menthol and nonmenthol smokers. One of these (Xia et al. 2010) included an analysis of data collected as part of a nationally representative survey, NHANES. The only study that reported a significant finding was Muscat et al. (2009), which reported a significantly lower NNAL-glucuronide/NNAL ratio among menthol smokers compared to nonmenthol smokers (but no difference in total urinary NNAL). This finding conflicted with earlier studies by the same group that attributed the difference to race. The combined weight of available published, peer-reviewed studies of biomarkers of potential harm support the conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and increased levels of TSNAs and PAHs above that caused by smoking nonmenthol cigarettes.

LACK OF EFFECT OF MENTHOL CONFIRMED BY TOTAL EXPOSURE STUDY

The largest dataset measuring a variety of biomarkers was generated from PM USA's Total Exposure Study (TES). The TES was a stratified, multi-center, cross-sectional study specifically designed to estimate exposure to selected cigarette smoke constituents in a population of U.S. adult smokers (Roethig et al. 2009). The study included 3,585 evaluable adult smokers (1,104 menthol smokers and 2,481 nonmenthol smokers) and 1,077 evaluable non-smokers from 39 investigative sites located in 31 states across the U.S. Various biomarkers were measured in blood and urine samples and comparisons were made between menthol and nonmenthol smokers, and also between Black and White smokers. Wang et al. (2010) is the only available publication to date reporting these data with regard to menthol and focuses on biomarkers of exposure. The study findings have been presented to TPSAC and to the broader scientific community at the 2010 meeting of the Society for Research on Nicotine and Tobacco. Given its size and the comprehensive measurements made in this study, additional details from further analyses of the dataset are presented in Table 3-4 below.

The results of TES found:

- Overall, no statistically significant differences (p>0.05) in biomarkers of exposure were observed between menthol and nonmenthol smokers
- Overall, no statistically significant differences (p>0.05) in metabolite ratios were observed between menthol and nonmenthol smokers
- Menthol had no statistically significant effect (p>0.05) on the biomarkers of potential harm investigated; there were no statistically significant menthol-related interaction terms

Table 3-4 Summary of Results of TES

Measure	Menthol (N=1044)	Nonmenthol (N=2297)
Biomarkers of Exposure[a]		
CPD	15.0 (8.7)	16.8 (9.0)
Tar yield (mg)	10.6 (6.2)	8.5 (4.9)
NE (mg/24 h)	12.8 (7.8)	13.5 (7.9)
Total NNAL (ng/24 h)	399.9 (294.8)	436.7 (309.5)
Serum cotinine (ng/ml)	188.9 (108.4)	183.4 (105.4)
Carboxyhemoglobin (% saturation)	5.2 (2.27)	5.4 (2.23)
Metabolite Ratios[b]		
3OHC/cotinine	2.67	2.52
Nicotine gluc./nicotine	1.12	1.09
Cotinine gluc./cotinine	2.85	2.59
3OHC gluc./3OHC	1.07	1.09
NNAL gluc./NNAL	3.16	3.06
Biomarkers of Potential Harm[c]		
HDL cholesterol (mg/dl)	52.6 (15.3)	51.0 (16.3)
LDL cholesterol (mg/dl)	114 (36.4)	116 (36.3)
Oxidized LDL (U/L)	73.5 (21.4)	74.5 (21.0)
Total cholesterol (mg/dl)	194 (42.3)	198 (41.6)
Triglycerides (mg/dl)	142 (106)	164 (141)
hs C-Reactive Protein (mg/L)	2.91 (2.69)	2.69 (2.55)
FEV_1 (% predicted)	83.5 (19.0)	84.1 (18.0)
8-epi-Prostaglandin-F2-α (ng/24h)	1882 (1082)	1893 (1040)
11-dehydrothromboxane-B2 (ng/24h)	1397 (1016)	1310 (1045)
White blood cells (x100/uL)	7.74 (2.33)	8.05 (2.27)

[a] Data shown as unadjusted mean (SD)
[b] Data shown as LSMeans
[c] Data shown as Mean (SD)
No statistically significant differences
CPD=cigarettes per day; NE=nicotine equivalents; 3OHC=3'-hydroxycotinine; HDL=high-density lipoprotein; LDL=low-density lipoprotein; FEV1=forced expiratory volume in 1 second

CONCLUSION

Overall, the vast majority of studies comparing biomarkers of exposure to tobacco smoke constituents and their metabolites and biomarkers of potential harm have found no difference between menthol and nonmenthol smokers. Sporadic findings of differences have been reported in smaller studies, but substantive differences in biomarkers of exposure are not seen in analyses of body fluids from large study populations. According to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and increases in biomarkers of exposure and potential harm over and above those caused by the smoking of nonmenthol cigarettes.

CHAPTER 3C.
EVIDENCE IS INADEQUATE TO CONCLUDE THAT MENTHOL IN CIGARETTES ADVERSELY IMPACTS SMOKING TOPOGRAPHY

Some researchers have attempted to measure the effect of menthol in cigarettes on human smoking behavior. These studies have attempted to measure differences between menthol and nonmenthol smokers in puff volume, number and frequency of puffs; depth of inhalation; duration of smoke retention in the lungs; percentage of cigarette smoked and other variables. These variables are typically referred to as elements of "smoking topography." The results of the studies are mixed in regard to whether they find a significant difference between menthol and nonmenthol smokers and also, among the studies that do report differences, the results are mixed with regard to the direction of the change observed. Any differences reported between menthol and nonmenthol smokers may be dependent on the method of measurement used and the lack of specificity of the outcome measured. Despite the somewhat contradictory results of the studies, overall the studies are consistent with the studies on biomarkers of exposure, discussed above, which report that menthol does not affect exposure of smokers to smoke constituents. In addition, any clinically meaningful differences in smoking topography among smokers of menthol and nonmenthol cigarettes would be reflected in the epidemiology studies discussed above which show no increase in tobacco-related disease risk due to menthol. According to the Surgeon General's framework for assessing causality, the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between the use of menthol cigarettes and adverse impacts on smoking topography.

METHODS OF MEASURING SMOKING TOPOGRAPHY PARAMETERS

A variety of methodologies are used to capture data on smoking behavior, and have been applied in experimental comparisons of menthol and nonmenthol cigarettes. Each of the available methods has distinct shortcomings that have contributed to the mixed and inconsistent findings in published work to date.

Some investigators have reported acute changes in exposure biomarkers (e.g., exhaled CO or plasma nicotine "boosts") as indirect indices of smoking topography. Although CO accumulation and elimination from the body has been well characterized, the kinetics of these processes are complex due to physiological variables such as lean body mass, the partitioning of CO into myoglobin and cytochrome protein sinks, and the endogenous production of CO by heme catabolism (Lloyd and Rowe 1999). Smoking-related exposures to CO are also influenced by the design and mainstream smoke yields of specific cigarettes. Cigarette filter ventilation and paper porosity both have a marked effect in lowering mainstream smoke CO yield and the smoker's consequent CO exposure.

Other available methods to assess smoking topography have included the smoking of cigarettes through pressure and flow-sensing mouthpiece devices that to varying degrees influence the experimental smoker's normal manner of smoking since the test cigarette is not held in the smoker's lips or hands in the normal way. The more the methods of data collection interfere with a subject's ability to smoke normally, the less meaningful the data. A less intrusive approach to the estimation

of inhaled puff volumes, inspiratory flow rates and puff retention times uses chest band transducers to record chest expansion patterns during the smoking process (Nil and Bättig 1989, St. Charles et al. 2009).

An emerging method to compare at least some aspects of the differences in smoking topography among smokers or between different types of cigarettes uses chemical analyses of segments of the expended filter butt as an indication of the quantity of mainstream smoke that has been drawn from the cigarette by the normal smoking process. This "mouth level exposure" method offers the advantage of allowing completely naturalistic smoking. An international effort to develop and validate standard methods for mouth level exposure is underway (under the auspices of the Cooperation Centre for Research Relative to Tobacco (CORESTA)).

Several of the studies that have sought to determine whether there may be differences in smoking topography between menthol and nonmenthol cigarettes have applied some combination of pressure and/or flow transducer-equipped mouthpieces, plethysmography/spirometry, laboratory smoke-delivery devices, and modified rapid smoking procedures. The lack of standardized methods in this area of study has contributed to the mixed and inconsistent nature of this literature. Only a few of the studies that present comparisons of menthol and nonmenthol smokers have gathered data on subjects during natural smoking (Pickworth et al. 2002, St. Charles et al. 2009). In general, the topography studies have yielded inconsistent results, which could be attributable to variation in the data collection methods and the ability of participants to smoke naturally in a clinical setting. Although differences in various smoking topography parameters may be measured in the laboratory setting, it is not always clear that these differences are present or meaningful in real-life smoking scenarios.

EXHALED BREATH CARBON MONOXIDE AS AN INDICATOR OF PUFFING INTENSITY

Exhaled breath CO may be reported as a measure of smoking intensity as either a single exhaled breath concentration or as a change in that concentration ("CO boost") after smoking a cigarette under laboratory conditions. The transient nature of increases in breath carbon monoxide level and the relatively short half-life for CO elimination by exhalation render exhaled CO measurements informative in assessing the topography of cigarette smoking rather than cumulative daily systemic exposures.

Among the eight studies comparing exhaled CO concentrations, five found no significant differences between menthol and nonmenthol smokers (see Table 3-5). While three studies found significant differences, the results were inconsistent in that two found higher CO concentrations among menthol smokers while a third study found the opposite, i.e., higher CO concentrations among nonmenthol smokers.

Table 3-5. Comparison of CO concentrations between menthol and nonmenthol smokers (N=8)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
Rosenblatt et al. 1998: 10 smokers; 50% menthol; race not provided	Allen and Unger 2007: 432 smokers; 68.5% menthol; 100% African American	Miller et al. 1994: 12 smokers; 50% menthol; 100% African American
	Clark et al. 1996: 161 smokers; 47.2% menthol; 40.4% Black, 59.6% White	Williams et al. 2007: 142 smokers; 55.6% menthol; 53.1% Black, 28.1% White, 18.8% Hispanic/Latino[1]
	Ho et al. 2009: 700 smokers; 81.3% menthol; 100% African American	
	Jarvik et al. 1994: 20 smokers; 50% menthol; 50% Black, 50% White	
	McCarthy et al. 1995: 29 smokers; 38% menthol; 55.2% Black, 44.8% White	

[1] Race breakdown provided for menthol smokers only

It should be noted that the studies that included the largest sample sizes (Allen and Unger 2007, Ho et al. 2009) found no differences in exhaled breath CO measurements.

The study of Rosenblatt et al. (1998) was designed to compare olfactory thresholds for nicotine and menthol between menthol and nonmenthol smokers. Among the 10 smokers included in the study, menthol smokers were found to have significantly lower exhaled carbon monoxide levels than nonmenthol smokers and this was not correlated with CPD as there was no difference in CPD between the two groups.

Two studies that have applied exhaled breath CO measurements as a measure of smoking/puffing intensity have reported that menthol smokers had statistically significantly higher levels of CO as compared to nonmenthol smokers (Miller et al. 1994, Williams et al. 2007).

Miller et al. (1994) evaluated the effect of increasing menthol concentrations (0 mg, 4 mg, 8 mg per cigarette) on carbon monoxide boost after subjects had inhaled a specific volume of smoke through an experimental apparatus from the test cigarettes. The authors concluded that this study demonstrated that adding menthol to cigarettes causes a significant increase in exhaled carbon monoxide despite a constant volume of smoke exposure.

The analyses in Williams et al. (2007) were designed to compare the effect of menthol smoking in smokers with and without schizophrenia and found statistically significantly higher exhaled carbon monoxide levels in menthol smokers. It should be noted that the measures of carbon monoxide levels in this study resulted from the smoking of a variety of cigarette types (full-flavor, as well as low tar brands). Adjustments were made for group (schizophrenic versus control), CPD and race but not for cigarette brand or FTC yield.

PUFF VOLUME

Several studies have examined the relationship between mentholation of cigarettes and inhaled puff volume. Although it has been suggested that menthol in cigarettes could allow for greater inhalation of cigarette smoke (i.e., increased puff volume), there is little support for this hypothesis as shown in Table 3-6 below. In fact, only one of eight studies found a significantly increased puff volume among menthol smokers as compared to nonmenthol smokers. The table below lists the studies according to their overall results: those in which subjects who smoked nonmenthols had significantly greater puff volumes than those who smoked menthols; those in which there was no significant difference; and those in which subjects who smoked menthols had significantly greater puff volumes than those who smoked nonmenthols.

Table 3-6. Comparison of Puff Volume Between Menthol and Nonmenthol Smokers (N=8)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
Jarvik et al. 1994: 20 smokers; 50% menthol; 50% Black, 50% White	Ahijevych et al. 1996: 37 smokers; 48.6% menthol; 48.4% Black, 51.4% White	Ahijevych and Parsley 1999: 95 smokers; 53% menthol; 50.5% Black, 49.5% White
McCarthy et al. 1995: 29 smokers; 38% menthol; 55.17% Black, 44.83% White	Miller et al. 1994: 12 smokers; 50% menthol; 100% African American	
Nil and Bättig 1989[1]: 15 smokers; menthol preference not provided[2]; race not provided	St. Charles 2009: 74 smokers; 24.3% menthol; race not specified	
	Strasser 2007: 119 smokers; 38% menthol; 62% White, 31% African American, 2.5% Hispanic or Latino	

[1] Significant difference between high yield menthol and: low yield menthol, high and low yield blond tobacco (aka flue-cured bright tobacco), own brand.

[2] All subjects smoked 6 experimental cigarettes including 1 high smoke yield and 1 low smoke yield menthol, and 1 cigarette of their own brand.

Note that three of these studies (Jarvik et al. 1994, McCarthy 1995, Nil and Bättig 1989) found that menthol smokers had a significantly decreased puff volume compared to nonmenthol smokers. The majority of studies (4 of 8) found no statistically significant effect of menthol on puff volume and only one study (Ahijevych and Parsley 1999) reported a significantly increased (by 8 mL) puff volume among menthol smokers compared to nonmenthol smokers.

These studies represent a broad range of study designs and smoking conditions. The study conducted by Ahijevych and Parsley (1999) assessed smoking parameters in a laboratory setting and found significantly larger puff volumes in menthol compared to nonmenthol smokers (45.8 vs. 37.8 ml, p=0.03). However, it was unclear whether these values were adjusted for potential confounding factors, such as race or body physiology. Ahijevych et al. (1996) used the same laboratory setting and data collection procedures and found no significant difference in puff volume; however, the sample size was much smaller in this earlier study (37 vs. 95).

PUFFS PER CIGARETTE

It has also been hypothesized that menthol could contribute to taking more puffs per cigarette. Eight studies compared this parameter and none found that menthol smokers took more puffs per cigarette than nonmenthol smokers (see Table 3-7 below). Three studies found that nonmenthol smokers took significantly more puffs per cigarette than menthol smokers and five studies found no difference between the two groups. The table below lists the studies according to their overall results: those in which subjects who smoked nonmenthols had significantly greater puffs per cigarette than those who smoked menthols; those in which there was no significant difference; and those in which subjects who smoked menthols had significantly greater puffs per cigarette than those who smoked nonmenthols.

Table 3-7. Comparison of Puffs Per Cigarette Between Menthol and Nonmenthol Smokers (N=8)

Nonmenthol > Menthol	No significant difference	Menthol > Nonmenthol
Jarvik et al. 1994: 20 smokers; 50% menthol; 50% Black, 50% White	Ahijevych et al. 1996: 37 smokers; 48.6% menthol; 48.4% Black, 51.4% White	- No studies -
McCarthy et al. 1995: 29 smokers; 38% menthol; 55.17% Black, 44.83% White	Caskey et al. 1993: 28 smokers; 43% menthol; 61% Black, 39% White	
Nil and Bättig 1989[1]: 15 smokers; menthol preference not provided[2]; race not provided	Miller et al. 1994: 12 smokers; 50% menthol; 100% African American	
	Pickworth et al. 2002: 36 smokers; 50% menthol; 55.6% African America, 44.4% Caucasian	
	Strasser 2007: 119 smokers; 38% menthol; 62% White, 31% African American, 2.5% Hispanic or Latino	

[1] Significant difference between high yield menthol and: low yield menthol, low yield dark tobacco (aka air-cured European-style tobacco), high and low yield blond tobacco, own brand.

[2] All subjects smoked 6 experimental cigarettes including 1 high smoke yield and 1 low smoke yield menthol, and 1 cigarette of their own brand.

Contrary to the suggestion that the menthol smokers have greater exposure to smoke constituents from taking more puffs per cigarette, those studies that found a significant difference between menthol and nonmenthol smokers in puffs per cigarette reported significantly more puffs per cigarette among nonmenthol smokers. While the results across the eight studies are inconsistent, there are none that suggest that menthol smokers take more puffs per cigarette.

OTHER TOPOGRAPHY VARIABLES

Some of the studies noted above also examined a number of other smoking topography measures, but found few differences between menthol and nonmenthol smokers. For example, although Jarvik et al. (1994) found significant increased puff volume and puffs per cigarette among nonmenthol smokers, the study found no significant differences between menthol and nonmenthol smokers in puff duration, peak puff flow, interpuff interval, inhaled volume and lung retention time. St. Charles (2009) compared total lung exposure time between menthol and nonmenthol smokers and found no difference. In addition to finding no differences in puff volume and number of puffs, Ahijevych et al. (1996) compared puff duration, interpuff interval, inhalation duration and exhalation duration between menthol and nonmenthol smokers and found no significant differences. Nil and Bättig (1989) found that postpuff inspiratory times (the time during which the subject continues to inhale following a cigarette puff) increased across cigarette taste categories from menthol to dark tobacco to blond tobacco. The inconsistencies within these studies argue that one must be cautious about placing too much importance on the finding of a significant difference in any single measure, as no single measure has yet been proven and validated as an adequate representation of the complexities of human smoking behavior. Rather the findings from all measures of topography should be assessed as a whole.

A few studies have evaluated the relationship between menthol, nicotine, and tar yield to smoking topography (e.g., Miller et al. 1994, Nil and Bättig 1989, Pickworth et al. 2002). However, these studies were not able to clearly delineate the relative importance of smoke taste (menthol) or smoke yield (e.g., nicotine, smoke condensate, CO) on measures of smoking topography. The one study that measured mouth level exposures to tar and nicotine resulting from natural smoking found no significant differences between menthol and nonmenthol cigarettes (Nelson et al. 2010). This study included six menthol brand styles among the total of 26 brands and styles smoked by a sampling of 1,330 smokers at multiple nationwide study sites.

CONCLUSION

There is a reasonable body of literature on menthol cigarette smoking and smoking topography. The available studies are quite different in the ways that they measure smoking topography variables, and many have significant weaknesses, including differences in study design, small study sizes, use of only men or women in a study, and use of cigarettes differing in yield and menthol content. These differences make it difficult to compare the studies and to reach definitive overall conclusions regarding these aspects of smoking topography. Although the findings are somewhat inconsistent, overall the majority of studies find no significant differences between menthol and nonmenthol smokers in smoking topography variables. Many of the studies that do find significant differences report smoking behaviors that would lead to greater exposures among nonmenthol smokers as compared to menthol smokers. These data provide no support for the presence of a clear and consistent association between menthol smoking and an adverse impact on smoking topography and provide no convincing support for the suggestion that menthol increases the exposure to smoke constituents through effects on smoking behavior. However, given the inconsistencies that exist, according to the Surgeon General's framework for assessing causality, the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between use of menthol cigarettes and

adverse impacts on smoking topography. Moreover, topography studies purport to be proxies for exposure and risk that are more directly measured by biomarker and epidemiology studies. The biomarker and epidemiology studies summarized above show that menthol cigarettes are not associated with increased risk of exposure or disease as compared to nonmenthol cigarettes.

CHAPTER 3D.
MENTHOL IN CIGARETTES DOES NOT ADVERSELY IMPACT THE TOXICOLOGIC PROPERTIES OF MAINSTREAM SMOKE

Since menthol and nonmenthol cigarettes are very similar in design characteristics (such as tobacco blend, paper characteristics, and filter design), they have been shown to produce mainstream smoke (MSS) that is also very similar (except of course, for the differential presence of menthol) (see Table A1 in (Heck 2010)). Therefore, it would be expected that the toxicologic profile for menthol and nonmenthol MSS would be very similar. The relevant data show that to be the case.

The toxicologic properties of the mainstream smoke (MSS) from menthol cigarettes have received considerable attention, and there are recent reviews on the subject (Werley et al. 2007, Heck 2010). These reviews describe three ways in which toxicologic assessments have been performed:

- On the neat compound
- On menthol added as a single ingredient to experimental cigarettes
- On menthol added as one of several ingredients to experimental cigarettes

NEAT MENTHOL HAS NO NOTABLE TOXICOLOGIC PROPERTIES

As reviewed below, the toxicity of menthol has been extensively evaluated. Menthol does not burn at the temperatures seen in cigarettes: rather, it sublimes at approximately 212 °C and is carried nearly quantitatively into smoke as the intact parent molecule. There are repeated cycles of sublimation and condensation that take place as the cigarette is smoked, but in none of these cycles is the menthol pyrolyzed or combusted (Jenkins et al. 1970a, 1970b; Wilson 1993). Because menthol in cigarettes is transferred to the smoker as the intact parent molecule, and may be recovered primarily as urinary metabolites identical to those resulting from oral exposures (Benowitz 2010), the literature on the safety of the neat compound is in fact quite relevant to the present consideration. A total of twelve such analyses, representative of a larger literature on the safety of menthol in flavoring applications, are briefly reviewed below.

Belsito et al. (2008). This general toxicology review considered the various toxicologic characteristics of menthol that have been published elsewhere. The broad conclusion was that there were no safety concerns regarding the use of menthol.

National Toxicology Program (1979). Menthol was tested for carcinogenicity by the National Cancer Institute in the predecessor to the National Toxicology Program, using lifetime feeding studies in male and female Fischer 344 rats and B6C3F1 mice. The details of the test were: "Groups of 50 rats of each sex and 50 mice of each sex were administered d,l-menthol at one of the following doses, either 3,750 [0.375%] or 7,500 ppm [0.75%] for the rats and either 2,000 [0.2%] or 4,000 ppm [0.4%] for the mice, for 103 weeks, then observed for 1 or 2 additional weeks. Matched controls consisted of 50 untreated rats of each sex and 50 untreated mice of each sex. All surviving rats were killed at 105 weeks and all surviving mice at 104 weeks. Mean body weights of dosed rats and mice were only slightly lower than those of corresponding controls. No other clinical signs

related to administration of the d,l-menthol were noted in the dosed groups of animals. A dose-related trend in mortality was observed only in the female mice. Survival at the end of the bioassay was at least 62% in all dosed and control groups of animals of each species, and sufficient numbers of animals were at risk for the development of late-appearing tumors. In male rats, no tumors occurred at incidences which were considered to be related to the administration of d,l-menthol. In female rats, no tumors occurred at higher incidences in the dosed groups than in the control groups. Fibroadenomas of the mammary gland occurred at lower incidences in the low-dose (10/49) and high-dose (7/49) groups than in the control group (20/50), and alveolar/bronchiolar adenomas or carcinomas of the lung occurred only in the controls (3/50). In mice of either sex, no tumors occurred in dosed groups at incidences that were significantly different from those for corresponding control groups. It is concluded that under the conditions of this bioassay, d,l-menthol was not carcinogenic for either Fischer 344 rats or B6C3F1 mice." Subsequently, several genetic toxicology tests were performed to confirm the results of this study (see below).

In Vitro Genotoxicity

Most of the remaining studies with the neat compound involve in vitro genotoxicity, with menthol being evaluated in several different types of cell cultures.

Ishidate et al. (1984). One of the first studies used six different strains of *Salmonella typhimurium* in the presence and absence of the S9 metabolic activation mix: this procedure is known as the "Ames test." These authors also evaluated chromosomal aberrations using a Chinese hamster fibroblast cell line. Menthol was negative in all tests performed.

Andersen and Jensen (1984). This study replicated the results of Ishidate et al. (1984) (Ames test only), and again no mutagenic activity was noted for menthol.

Zeiger et al. (1988). Menthol was one of 300 chemicals tested for mutagenicity using the Ames test. This work was part of the evaluation by the NTP to correlate results in genetic toxicology testing with those obtained in the long-term rodent carcinogenicity studies described above. The authors described the results as "negative."

Ivett et al. (1989). Menthol was one of 15 individual compounds tested in Chinese Hamster Ovary (CHO) cells, using the endpoints chromosomal aberrations and sister chromatid exchange (SCE), in the presence and absence of the S9 metabolic mix. This work was part of the evaluation by the NTP to correlate results in genetic toxicology testing with those obtained in the long-term rodent carcinogenicity studies described above. In both assays menthol was tested "up to toxic or near-toxic levels as evidenced by the reduction of cell confluence at the highest doses." The authors considered menthol to be negative in both assays.

Myhr and Caspary (1991). Menthol was one of 31 compounds tested for mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells (the "mouse lymphoma" assay) in the presence and absence of the S9 metabolic mix. This work was part of the evaluation by the NTP to correlate results in genetic toxicology testing with those obtained in the long-term rodent carcinogenicity studies described above. The authors reported that "no evidence for mutagenicity was found."

Shelby et al. (1993). Menthol was one of 49 chemicals tested in a mouse bone marrow micronucleus test that involved three daily exposures by intraperitoneal injection. This work was part of the evaluation by the NTP to correlate results in genetic toxicology testing with those obtained in the long-term rodent carcinogenicity studies described above. The authors noted that the "The initial test was negative to 1000 mg/kg and was not repeated."

Murthy et al. (1991). Tests were performed using in vitro exposures of human lymphocytes, the aim being to determine whether menthol had any effect in these cells on chromosome aberration and SCE. The authors concluded that "menthol does not have a chromosome-damaging effect in human lymphocytes."

Foureman et al. (1994). The last of the five comparisons with the results of the NTP long-term rodent carcinogenicity studies used the sex-linked recessive lethal assay in *Drosophila*. Administration of menthol to flies was by either feeding (up to 50,000 ppm, 5.0%) or injection (10,000 ppm, 1.0%). The lethality rate was very low for both routes of administration, and the authors termed the response "negative."

Gomes-Carneiro et al. (1998). Menthol was one of a group of essential oils again tested using the *Salmonella* assay (only four strains, tested with and without S9). The authors compared other published data with their own and concluded that "menthol is not mutagenic in the Ames test."

Additional studies on menthol metabolism and other properties in toxicology test systems are available, and these have been considered in extensive reviews of the menthol literature (Adams et al. 1996, Belsito et al. 2008).

Menthol has also been studied as a potential modifier of the speed of permeation of exogenous compounds across biological tissues, particularly in topical applications, but also in porcine oral and esophageal preparations (Kitagawa and Li 1999, Azzi et al. 2006, Squier et al. 2010). Speculation that such effects may promote the speed or efficiency of penetration of tobacco smoke constituents is not substantiated as biologically consequential when considered in light of the extensive body of smoke biomarkers data showing no significant differences between menthol and nonmenthol cigarette smokers (discussed previously in this report).

Menthol Added to Experimental Cigarettes Has No Adverse Impact on Smoke Toxicology

Several experiments have evaluated menthol as a single ingredient added to experimental cigarettes or as a component of ingredient mixtures (e.g., minor top flavorings, humectants, casings) that reflect typical commercial manufacturing practice. These published reports and their underlying data have been provided to the FDA and presented to the TPSAC, and are briefly listed and summarized below.

Gaworski et al. (1997). "A 13-wk comparative nose-only smoke inhalation toxicity study was conducted using an American-style, cellulose acetate-filtered, non-menthol reference cigarette and a similarly blended test cigarette containing 5000 ppm [0.5%] synthetic l-menthol tobacco. Male and female Fischer 344 rats were exposed for 1 hr/day, 5 days/wk for 13 weeks at target mainstream smoke particulate concentrations of 200, 600 or 1200 mg/m^3, while control rats were exposed to filtered air. Internal dose biomarkers (blood carboxyhemoglobin, serum nicotine and serum cotinine) indicated equivalent exposures were obtained for the two cigarettes. Effects typically noted

in rats exposed to high levels of mainstream tobacco smoke were similar for both cigarette types and included reduced body weights (males slightly more affected than females), increased heart-to-body weight ratios and lung weights, and histopathological changes in the respiratory tract. Rats exposed to reference cigarette smoke displayed a dose-related increase in nasal discharge that was not observed in menthol smoke exposed rats. All smoke-related effects diminished significantly during a 6-week non-exposure recovery period. The results of this 13-week smoke inhalation study indicated that the addition of 5000 ppm (0.5%) menthol to tobacco had no substantial effect on the character or extent of the biological responses normally associated with inhalation of mainstream cigarette smoke in rats."

Previously unpublished work performed by the R. J. Reynolds Tobacco Company and appearing as Appendix B in a recent review (Heck 2010) used a comparative approach to assess the mutagenic activity of menthol addition in experimental cigarettes. Two types of cigarettes were used, identical except for the addition of 1.03% menthol to one of them. This addition rate is about twice as high as that typically used commercially. The cigarettes contained a standard commercial blend of tobaccos. Ames testing was done on cigarette smoke condensate with 5 bacterial strains, both with and without the S9 mix. The authors concluded that "there was no evidence that the addition of menthol increases the mutagenicity of smoke particulate material."

The same experimental cigarettes as mentioned above were used to make a comparative evaluation of the cytotoxicity of the smoke condensates (Heck 2010), using the neutral red uptake (NRU) assay. This cytotoxicity assay is among the tests specified by Health Canada for comparative assessments of cigarette smoke condensates and is widely used elsewhere for that purpose. These workers used CHO cells to assess the proportion of cells killed by the treatment (and therefore unable to accumulate the vital dye neutral red). The authors concluded that "there was no evidence that menthol addition increases the cytotoxic potential of cigarette smoke condensate" of menthol versus nonmenthol cigarettes.

The same experimental cigarettes as mentioned above were used to generate data on chromosomal aberrations, using the sister chromatid exchange (SCE) assay in CHO cells treated with different concentrations of cigarette total particulate matter (TPM) (Heck 2010). The SCE assay is not a common component of batteries of genotoxicity assays, probably because interpretations of the data obtained are considered to be difficult. Smokers have been reported however to have elevated numbers of SCEs in circulating lymphocytes in a number of studies, so this in vitro assay may reflect processes occurring in smokers. The authors stated that "cigarette smoke TPM from menthol cigarettes was not significantly different from that of nonmenthol cigarettes either in the presence or absence of S9 activation under conditions of this study."

There are several major studies that have examined the toxicologic properties of menthol as one of several ingredients added to experimental cigarettes (Gaworski et al. 1998, Gaworski et al. 1999, Carmines 2002, Baker et al. 2004); these studies report in vitro and in vivo toxicology data. These studies of combinations of commonly-used cigarette ingredients model potential interactions that may exist among ingredients used in commercial cigarettes.

Carmines (2002). The Carmines work used menthol added at a target concentration of 18,000 ppm (1.8%) to experimental cigarettes (as part of Ingredient Group 3); the other components added in this group were cocoa shells, licorice extract, and corn syrup sugar. Toxicology endpoints included the Ames mutagenesis test and the NRU cytotoxicity assay (Roemer et al. 2002), plus a standard

battery of endpoints classically used in 90-day inhalation studies with cigarette smoke (Vanscheeuwijck et al. 2002). None of the in vitro or in vivo toxicology endpoints were significantly elevated in the groups with added menthol when compared with no added menthol.

Baker et al. (2004). The Baker work used menthol added at a target concentration of 23,400 ppm (2.34%) to experimental cigarettes, with five other compounds (cocoa, ethanol, licorice, propylene glycol, and raisin juice) added in the "B4" group (plus water). Toxicology endpoints included the Ames test, the in vitro micronucleus assay of disruption to chromosomal segregation, and the NRU cytotoxicity assay, plus a standard battery of classically used endpoints in 90-day inhalation studies. 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 changes.

Gaworski et al. (1998). The experimental design used in a 90-day smoke inhalation study reported by Gaworski used 172 added ingredients allocated to one of four different experimental cigarettes, including menthol at a concentration of 5,000 ppm (0.5%) (Gaworski et al. 1998). "Male and female Fischer 344 rats were exposed 1 h/day, 5 days/wk, for 13 week to smoke from cigarettes containing mixtures of flavor ingredients at target mainstream smoke particulate concentrations between 150 and 1200 mg/m^3. For comparison, separate groups of rats were exposed to smoke from non-flavored reference cigarettes of similar construction and tobacco blend, or to filtered air. Internal dose biomarkers (carboxyhemoglobin, serum nicotine, and serum cotinine) were measured during the studies to monitor smoke exposure. Effects typically noted in rats exposed to mainstream tobacco smoke were similar for both flavored and non-flavored cigarette types. Dose-related reductions in body weights, increased organ-to-body weight ratios for the heart and lungs, and a trend toward decreased blood glucose concentrations in males were noted in the smoke-exposed groups. Exposure-related histopathologic changes occurred only in the respiratory tract. These changes were primarily associated with epithelial tissue, and presented as hyperplasia and/or metaplasia in the nose and larynx. The anterior sections of the nose were more severely affected than were the more posterior regions. Macrophages and areas of epithelial hyperplasia were observed in the lungs of smoke-exposed animals. All smoke-related histopathologic effects diminished significantly during a 6-week post-exposure recovery period. The results indicate that the addition of these flavoring ingredients to cigarette tobacco had no discernible effect on the character or extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats."

Gaworski et al. (1999). A similar approach as in the previous section was used in a 26-week mouse skin painting study of cigarette smoke condensate (CSC) using female SENCAR mice: there were 150 added ingredients allocated to one of six different experimental cigarettes, including menthol at a concentration of 5,000 ppm (0.5%). "Groups of 30-50 female SENCAR mice each were initiated topically with 50 μg of 7,12-dimethylbenz(a)anthracene (DMBA), and promoted thrice weekly for 26 weeks with either 10 or 20 mg of CSC from test cigarettes containing ingredient mixtures. For comparison, separate groups of mice received concurrent treatment with CSC from reference cigarettes prepared without added ingredients. Negative and positive controls were treated with acetone or 12-0-tetradecanoyl-phorbol-13-acetate (TPA) as a promoter, respectively. CSC-only groups served as promotion controls. Tumors developed in >80% of the TPA-treated mice by study week 11, with a <3% background tumor formation in the acetone treated controls at termination. Tumor incidence in CSC-only promotion control groups was <20%, with no apparent difference between reference and test CSC groups. Approximately 70% of the DMBA-initiated

mice promoted with 20 mg CSC developed tumors. Tumors first appeared around week 9, with about five tumors per tumor bearing animal. Tumor incidence, latency and multiplicity were CSC dose related, with a lower tumor incidence (approximately 50%), longer latency (12 weeks), and reduced tumor burden (four tumors/tumor bearing animal) at the 10 mg CSC dose level. While tumor incidence, latency and multiplicity data occasionally differed between test and comparative reference CSC groups, all effects appeared to be within normal variation for the model system. Furthermore, none of the changes appeared to be substantial enough to conclude that the tumor promotion capacity of CSC obtained from cigarettes containing tobacco with ingredients was discernibly different from the CSC obtained from reference cigarettes containing tobacco processed without ingredients."

As a result of the inclusion of several other compounds in the experimental menthol-containing cigarettes, compared with controls, it is difficult to make definitive statements on the role of menthol per se in the overall toxicologic responses noted in the studies of ingredient combinations reviewed here. Nevertheless, no meaningful increases in biological activity were noted in any study involving the addition of menthol to cigarettes. These results further suggest that menthol does not participate in chemical interactions with other ingredients that are commonly used in commercial cigarettes.

CONCLUSION

Among a broad range of toxicologic endpoints evaluated with respect to the neat compound menthol, including several different genotoxicity assays (e.g., *Salmonella* mutagenicity using 5 different bacterial strains, cytotoxicity (using the NRU), different measures of chromosomal aberrations, micronucleus testing, the mouse lymphoma assay, and the sex-linked recessive lethal assay in *Drosophila)*, menthol did not show any positive toxicologic findings. These in vitro tests broadly support the results of the NTP rat and mouse chronic feeding studies, which unequivocally showed no carcinogenic activity of menthol. Neat menthol clearly has very low toxicologic activity.

In studies with menthol added to experimental cigarettes (either on its own or as part of a mixture), including a 26-week dermal carcinogenicity study in mice and multiple nose-only 90-day smoke inhalation studies in rats, the addition of menthol did not modify the toxicologic profile in any way when the results obtained were compared with those produced by comparable nonmenthol cigarettes.

Overall, the weight of the evidence on wide-ranging toxicology testing of the neat material shows that menthol has no notable effects at exposures spanning the ranges typical for its flavor applications. Additionally, the weight of the evidence on the toxicologic properties of the mainstream smoke from menthol cigarettes compared with nonmenthol cigarettes provides no indications of increased toxicity, consistent with a broader conclusion that menthol has no causal relationship to adverse impacts on public health. According to the Surgeon General's framework for assessing causality, **"the evidence is suggestive of no causal relationship"** between menthol added to cigarettes and increases in the toxicity of cigarette smoke.

CHAPTER 3E.
MENTHOL DOES NOT MEANINGFULLY ALTER THE CHEMICAL COMPOSITION OF MAINSTREAM SMOKE

The chemical composition of the mainstream smoke (MSS) from nonmenthol cigarettes has received considerable attention, and there are many publications on the subject (Rodgman and Perfetti 2009). In contrast, the MSS from menthol cigarettes has been of much less interest scientifically, and consequently publications are sparse. Comparisons of the two data sets reveal that, apart from menthol itself, the MSS from menthol cigarettes is very similar to that from nonmenthol cigarettes. The main reason for this common MSS composition is that the design characteristics (e.g., tobacco blends, paper, filter, to name just a few) of the two cigarette types are very comparable, except for the addition of small amounts of menthol. Because the formulations are broadly similar, the combustion products of the cigarettes are broadly similar.

A brief technical note from 1968 (Schmeltz and Schlotzhauer 1968) indicated that neat menthol when heated to 800 °C produced small amounts of benzo[a]pyrene (BAP). At 800 °C, approximately 400 μg of BAP were calculated to be produced per gram of menthol, with no BAP produced at 600 °C. Identification and quantification of BAP was made using (by today's standard) a very crude analytical technology (paper chromatography), and the results do not seem to have been confirmed by other workers. In any case, "the correlation of pyrolysis products formed this way with those formed during the burning of a cigarette is extremely difficult, if not impossible, without knowing the quantitative relationship between the precursor and its products in the cigarette smoke" (Jenkins et al. 1970a, 1970b). In a review of pyrolysis work on cigarette components, more recent authors commented that "unless they are performed under dynamic conditions that are relevant to those that occur during tobacco burning, results can be obtained which have little resemblance to those obtained during cigarette smoking" (Baker and Bishop 2004).

A subsequent study used menthol that was universally-labeled with ^{14}C (Jenkins et al. 1970a, 1970b) and clearly showed that in the matrix of MSS there is "very little, if any, pyrolysis and combustion of menthol during the puffing of the cigarette," with approximately 99% of the labeled material recovered being in the form of unchanged menthol. Thus, menthol itself does not add to or otherwise modify MSS composition, because menthol does not burn at the temperatures seen in cigarettes; rather, it sublimes, at approximately 212 °C. The menthol in the tobacco near the burning cone of the cigarette (at about 850 °C, see Figure 7 in Wilson 1993) is (1) converted from a solid to gaseous menthol and (2) drawn downstream into adjacent cooler tobacco, where (3) it condenses back into a solid. There are repeated cycles of sublimation and condensation that take place as the cigarette is smoked, but in none of these is the menthol itself pyrolyzed or combusted (Jenkins et al. 1970a, 1970b; Wilson 1993). A variety of other processes that occur in menthol cigarettes (e.g., in the filter) has been described elsewhere (Wilson 1993).

A recent review (Heck 2010) described the MSS composition of directly comparable cigarettes whose only difference was the addition of menthol (at a target rate of 1.03%). A total of 25 analytes in MSS were measured in each pair, and the results are presented in Table 3-8 as the ratio (percent) of the concentration in the menthol cigarettes to the concentration in the nonmenthol cigarettes. In general, the chemical composition of the smoke from the menthol cigarettes was very similar to the

smoke from nonmenthol cigarettes, with the exception of menthol itself. The lowest ratio was 69.2% (nitrogen), and the highest was 124% (formaldehyde). This difference in mainstream smoke formaldehyde yield achieved statistical significance for these carefully matched experimental cigarettes, but the levels of this constituent for the menthol cigarette were well within the ranges reported for many contemporary nonmenthol commercial cigarettes. Concentrations of BAP were not significantly different between the two cigarettes, confirming other independent work (Rustemeier et al. 2002) which indicates that the evolution from menthol upon furnace pyrolysis under inert atmosphere that was reported in the very early study by Schmeltz and Schlotzhauer (1968) has no relevance to the burning and distillation processes that occur in an actual cigarette.

Table 3-8. Comparison of Mainstream Analyte Concentrations in Menthol and Nonmenthol Cigarettes

Component	Menthol	Nonmenthol	M/NM (%)
Menthol (mg/cig)	0.41	0	--
Ammonia (μg/cig)	4.6	4.49	102
Benzo[a]pyrene (BAP) (ng/cig)	2.65	2.87	92.3
Puffs	9	8.8	102
Formaldehyde (μg/cig)	4.2	3.4	124*
Acetaldehyde (μg/cig)	284.6	275.8	103
Acetone (μg/cig)	114.8	117.1	98.0
Acrolein (μg/cig)	22.1	21.4	103
Hydrogen cyanide (μg/cig)	40.8	43.3	94.2
Carbon (%)	69	65.25	106*
Hydrogen (%)	9.71	8.57	113*
Nitrogen (%)	3.7	5.35	69.2*
Total particulate matter (mg/cig)	4.6	4.1	112
Nicotine (mg/cig)	0.35	0.35	100
Water (mg/cig)	0.3	0.3	100
Tar (mg/cig)	3.9	3.5	111
Carbon monoxide (mg/cig)	5.2	5.3	98.1
Carbon dioxide (mg/cig)	22.1	22.5	98.2
Hydroquinone (μg/cig)	17.36	17.56	98.9
Catechol (μg/cig)	20.98	21.38	98.1
Phenol (μg/cig)	2.56	2.42	106
Cresol (μg/cig)	2.5	2.34	107
N-nitrosonornicotine (NNN) (ng/cig)	29	35	82.9
N-nitrosoanatabine (NAB) (ng/cig)	30	33	90.9
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (ng/cig)	22	28	78.6

Data obtained from Heck (2010).
* Statistically significant difference between menthol and nonmenthol ($p<0.05$); (N=6 cigarettes).

CONCLUSION

The weight of the evidence clearly shows that the chemical compositions of the MSS from menthol and nonmenthol cigarettes are very similar, apart from the presence of menthol itself. Thus, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and harmful changes in mainstream smoke chemistry.

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Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Brooks et al. 2003 United States	**Lung cancer** Case-control study (643 cases, 4,110 controls) Subjects were current or former smokers with ≥20 yrs smoking. Among the cases, 61 men and 53 women had ever smoked menthols; among the controls, 453 men and 640 women had ever smoked menthols.	**Tobacco Use** Nonmenthol only Ever menthol Current menthol (>15 yrs) 1-15 yrs smoking menthol >15 yrs smoking menthol **Subgroups** **Men** Nonmenthol only 1-15 yrs smoking menthol >15 yrs smoking menthol **Women** Nonmenthol only 1-15 yrs smoking menthol >15 yrs smoking menthol **Whites** Nonmenthol only 1-15 yrs smoking menthol >15 yrs smoking menthol **Blacks** Nonmenthol only 1-15 yrs smoking menthol >15 yrs smoking menthol	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 0.89 (0.69-1.14) 0.90 (0.62-1.31) 0.80 (0.57-1.13) 0.97 (0.79-1.34) 1.0 (reference) 0.67 (0.43-1.05) 0.91 (0.57-1.46) 1.0 (reference) 1.14 (0.66-1.95) 1.00 (0.63-1.60) 1.0 (reference) 0.86 (0.59-1.28) 1.01 (0.68-1.51) 1.0 (reference) 0.60 (0.27-1.35) 1.21 (0.64-2.26) Adjusted for sex, age, race, year of interview, number years smoking, cigarettes/day, years since quitting, proportion of years smoking filter cigarettes.	The lung cancer risk for long-term smokers of menthol cigarettes was similar to that for smokers of nonmenthol cigarettes. The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking nonmenthol cigarettes. In separate analyses of men, women, Blacks, and Whites, long-term use of menthol cigarettes was not associated with an increase in lung cancer relative to exclusive use of nonmenthol cigarettes.

* denotes statistically significant increase in risk

Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Carpenter et al. 1999 United States	**Lung cancer** Case-control study (337 cases, 478 population controls) Subjects were ever-smokers (current or former). Among the cases, 85 African Americans and 66 Caucasians had ever smoked menthols; among the controls, 101 African Americans and 122 Caucasians had ever smoked menthols.	**Entire Population** Exclusive regular Exclusive menthol Mixed menthol/regular **Subgroups** **Caucasians** Exclusive regular >1-15 pk-yrs menthol 16-31 pk-yrs menthol 32+ pk-yrs menthol **African Americans** Exclusive regular >1-15 pk-yrs menthol 16-31 pk-yrs menthol 32+ pk-yrs menthol **Men** Exclusive regular >1-15 pk-yrs menthol 16-31 pk-yrs menthol 32+ pk-yrs menthol **Women** Exclusive regular >1-15 pk-yrs menthol 16-31 pk-yrs menthol 32+ pk-yrs menthol	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 1.04 (0.62-1.75) 1.01 (0.71-1.42) 1.0 (reference) 1.01 (0.61-1.68) 1.01 (0.41-2.47) 1.06 (0.47-2.36) 1.0 (reference) 0.96 (0.54-1.70) 0.69 (0.30-1.60) 0.90 (0.38-2.12) 1.0 (reference) 0.87 (0.57-1.37) 1.21 (0.56-2.62) 1.48 (0.71-3.05) 1.0 (reference) 1.58 (0.77-3.22) 0.51 (0.19-1.34) 0.41 (0.15-1.11) Adjusted for age, sex, race, total pack-years, and years since quitting.	Our results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes. The lung-cancer risk associated with menthol smoking was similar to that for exclusive nonmentholated cigarette smoking both in the total sample and within ethnic groups. Our data does not support the hypothesis that the increased risk of lung cancer among African Americans is due to the increased prevalence of menthol smoking.

* denotes statistically significant increase in risk

Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Etzel et al. 2008 United States	**Lung cancer** Case-control study (491 cases, 497 population controls; all African Americans). Prevalence of menthol smoking was 41% among cases and 47% among controls. Subjects were never, current, or former smokers.	**Current Smokers** Nonmenthol smokers Menthol smokers **Former Smokers** Nonmenthol smokers Menthol smokers	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 0.69 (0.46-1.03) 1.0 (reference) 0.99 (0.62-1.56) Adjusted for age, sex, and smoking status (current vs. former).	We observed no significant risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes and our data suggested a possible protective effect of mentholated cigarettes for current smokers. Existing lung cancer prediction models may not be appropriate for predicting risk for African Americans.
Jöckel et al. 2004 (abstract) Germany	**Lung cancer** Case-control study (839 male and 165 female cases; 839 male and 165 female population controls). It appears that all subjects were White. It appears that subjects were ever-smokers.	**Tobacco Use** Not defined Ever menthol smoking	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 1.12 (0.68-1.83) Adjusted for total amount of tobacco smoking.	The present study gives no indication for an additional risk of ever smoking menthol cigarettes if total amount of smoking is taken into account. However, the number of exposed subjects is small hindering definitive conclusions with respect to dose.

* denotes statistically significant increase in risk

Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Kabat and Hebert 1991 United States	**Lung cancer** Case-control study (588 male and 456 female cases; 914 male and 410 female hospital controls). Prevalence of menthol smokers ranged from 24-37%, depending on age and sex. All were current smokers.	**Men** Nonmenthol smokers 1-14 yrs smoking menthol 15+ yrs smoking menthol **Women** Nonmenthol smokers 1-14 yrs smoking menthol 15+ yrs smoking menthol	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 1.14 (0.82-1.19) 0.98 (0.70-1.38) 1.0 (reference) 0.82 (0.52-1.28) 0.76 (0.53-1.16) Adjusted for inhalation, race, BMI, age, education, cigarettes/day, and duration of smoking,	Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types of lung cancer in this study. If our results are confirmed by other researchers, the implication would be that use of mentholated cigarettes does not explain black-white differences in lung cancer incidence rates or time trends. Other hypotheses need to be formulated to explain these differences.
Lee [submitted]	**Lung cancer** Meta-analysis of 8 studies: Sidney et al. 1995 Brooks et al. 2003 Murray et al. 2007 Kabat & Hebert 1991 Carpenter et al. 1999 Stellman et al. 2003 Jockel et al. 2004 Etzel et al. 2008	**Use of Menthol Cigarettes Among Ever Smokers (or Current if not Available)** Overall Men Women Whites Blacks **Long-Term Use (15+ Yrs) of Menthol Cigarettes** Overall Men Women Whites Blacks	**Adjusted Relative Risks (95% CI)** 0.93 (0.84-1.02) 1.01 (0.88-1.15) 0.80 (0.67-0.95) 0.87 (0.75-1.03) 0.90 (0.73-1.10) 0.95 (0.80-1.13) 1.11 (0.88-1.39) 0.78 (0.60-1.01) 1.02 (0.71-1.46) 1.09 (0.66-1.81)	The data do not suggest any effect of mentholation on lung cancer risk. There is also no evidence of an increase in men or women separately, in Blacks or Whites separately, or in estimates for ever smokers, current smokers, or former smokers. While some study weaknesses exist, the epidemiological evidence is consistent with mentholation having no effect on the lung carcinogenicity of cigarettes. Higher lung cancer rates in Black men cannot be due to their greater preference for mentholated cigarettes.

* denotes statistically significant increase in risk

Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Murray et al. 2007 United States (Lung Health Study)	**Lung cancer** Clinical trial of smoking cessation among 5,887 smokers with mild-moderate airway obstruction. About 20% (1,216) smoked menthol cigarettes at baseline. There were 240 deaths due to lung cancer in 14 years of follow-up. All were current or former smokers.	**Tobacco Exposure** **Death Due to Lung Cancer** Plain cigarettes Menthol smokers	**Adjusted Hazard Ratios (95% CI)** 1.0 (reference) 0.96 (0.70-1.32) Adjusted for age, sex, cigarettes/day at baseline, FEV1 percentage of predicted, randomization group, race, and baseline years of education.	We found no evidence in our data that mentholation of cigarettes is an attribute that contributes to the health risks of smoking.
Sidney et al. 1995 United States (Kaiser Permanente)	**Lung cancer** Cohort study (11,761 subjects; 93 lung cancers among 3,654 menthol smokers and 225 lung cancers among 8,107 nonmenthol smokers followed for a mean of approximately 8 years) All were current smokers of ≥20 years.	**Men** Nonmenthol smokers Menthol smokers 1-9 yrs smoking menthol 10-19 yrs smoking menthol ≥20 yrs smoking menthol **Women** Nonmenthol smokers Menthol smokers 1-9 yrs smoking menthol 10-19 yrs smoking menthol ≥20 yrs smoking menthol	**Adjusted Relative Risks (95% CI)** 1.0 (reference) 1.45 (1.03-2.02)* 1.10 (0.65-1.87) 1.32 (0.84-2.08) 1.59 (0.96-2.63) 1.0 (reference) 0.75 (0.51-1.11) 0.72 (0.38-1.39) 1.01 (0.61-1.69) 0.70 (0.40-1.23) Adjusted for age, race, education, cigarettes/day, and duration of smoking.	Mentholated cigarette use was associated with a statistically significant 45% increase in the incidence of lung cancer relative to nonmentholated cigarette use in men who were long-term smokers. 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. We cannot explain why the association between mentholated cigarette use and lung cancer was present in men only.

* denotes statistically significant increase in risk

Table 3-9. Comparative Risk of Lung Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=9) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Stellman et al. 2003 United States	**Lung cancer** Case-control study (1,710 White male and 1,321 White female cases, 254 Black male and 163 Black female cases; 8,151 hospital controls). Prevalence of menthol smoking was 13.5-23.7% for White subjects and 40.8-51.8% for Black subjects. Subjects were non-, current, or former smokers. Data presented here are for current smokers.	**White Men** Nonmenthol Menthol **Black Men** Nonmenthol Menthol **White Women** Nonmenthol Menthol **Black Women** Nonmenthol Menthol	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 0.83 (0.63-1.09) 1.0 (reference) 1.34 (0.79-2.29) 1.0 (reference) 0.61 (0.44-1.06) 1.0 (reference) 0.79 (0.41-1.54) Adjusted for age, education, BMI, and pack-years.	Smokers of menthol flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands. ORs among smokers of menthol cigarettes were practically the same as among smokers of nonmenthol cigarettes. While Black smokers in our study were more likely to choose menthol than nonmenthol brands; our data provide no evidence that menthol cigarettes per se produce greater lung cancer risk than do nonmenthol brands.

* denotes statistically significant increase in risk

Table 3-10. Comparative Risk of Esophageal Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=2)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Hebert and Kabat 1988 (letter to the editor) United States	**Esophageal cancer** Case-control study (216 male and 96 female cases; 305 male and 157 female hospital controls)	**Men** Not specified ≥10 yrs smoking menthol **Women** Not specified ≥10 yrs smoking menthol	**Relative Risks (95% CI)** 1.0 (reference) 0.70 (0.29-1.73) 1.0 (reference) 1.53 (0.61-3.86) Not clear if risk estimates are adjusted for confounders.	We analyzed existing data from a case-control study of esophageal cancer and found no menthol effect.
Hebert and Kabat 1989 United States	**Esophageal cancer** Case-control study (209 male and 94 female cases; 301 male and 152 female hospital controls). There were 45 ever-smokers of menthol among the cases and 66 among the controls. All subjects were current smokers.	**Men** Nonmenthol only <10 yrs smoking menthol ≥10 yrs smoking menthol **Women** Nonmenthol only <10 yrs smoking menthol ≥10 yrs smoking menthol	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 0.50 (0.23-1.07) 1.03 (0.39-6.89) 1.0 (reference) 1.50 (0.54-4.17) 2.30 (0.93-5.72) Adjusted for education, religion, alcohol consumption, race, cigarettes/day, and smoking duration.	Our results do not support the hypothesized relationship between menthol cigarette smoking and esophageal cancer. Because of the limitations of this study we feel the issue of menthol cigarette smoking and esophageal cancer is not resolved. We recommend additional studies of ample size in appropriate populations or hospitals whose 'catchment' areas include typical American Blacks.

Table 3-11. Comparative Risk of Oropharyngeal Cancer Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=1)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Kabat and Hebert 1994 United States	**Oropharyngeal cancer** Case-control study (194 male and 82 female cases; 845 male and 411 female hospital controls). Only 5% of subjects had smoked menthol exclusively; ever-use of menthol was also low (26% of men, 34% of women). All subjects were current smokers.	**Men** Nonmenthol only 1-14 yrs smoking menthol ≥15 yrs smoking menthol **Women** Nonmenthol only 1-14 yrs smoking menthol ≥15 yrs smoking menthol **By Subsite Among Men Who Ever Smoked Menthol*** Tongue Gum, floor of mouth, other Pharynx **By Subsite Among Women Who Ever Smoked Menthol*** Tongue Gum, floor of mouth, other Pharynx *Reference group for subsite analyses is smokers of nonmenthol only.	**Adjusted Relative Risks (95% CI)** 1.0 (reference) 0.6 (0.3-1.1) 0.9 (0.5-1.6) 1.0 (reference) 1.0 (0.7-2.1) 0.7 (0.5-1.7) 0.4 (0.1-1.0) 0.6 (0.3-1.2) 1.7 (0.8-3.4) 1.3 (0.5-3.2) 0.5 (0.2-1.3) 1.2 (0.4-3.7) Adjusted for age, education, filter use, race, BMI, hospital, alcohol, and cigarettes/day.	These results indicate that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer. In analyses by subsite, menthol use was positively associated only with cancer of the pharynx in males, although the magnitude of the association was small.

Table 3-12. Comparative Risk of Other Smoking-Related Cancers Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=1)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Friedman et al. 1998 United States (Kaiser Permanente)	**Smoking-related cancers other than lung** Cohort study (11,760 subjects; 69 cancers among 3,654 menthol smokers and 212 cancers among 8,106 nonmenthol smokers followed for more than 10 years). All were current smokers of ≥20 years.	**Men Who Smoked Menthol*** All cancers other than lung Upper aerodigestive Pancreas Renal adenocarcinoma Other urinary tract **Women Who Smoked Menthol*** All cancers other than lung Upper aerodigestive Pancreas Renal adenocarcinoma Other urinary tract Uterine cervix *Reference group for all comparisons is smokers of plain cigarettes.	**Rate Ratios (95% CI)** 0.76 (0.52-1.11) 0.68 (0.36-1.28) 0.60 (0.25-1.44) 1.28 (0.39-4.15) 0.83 (0.45-1.55) 0.79 (0.53-1.18) 0.70 (0.30-1.67) 0.76 (0.32-1.81) 0.73 (0.08-7.00) 0.71 (0.30-1.68) 1.06 (0.53-2.12) Adjusted for age.	Risk was not increased among persons who currently smoked mentholated compared with plain cigarettes for all of the non-lung smoking-related cancers combined or for most sites studied. Results were similar when current smokers of mentholated and plain cigarettes were restricted, respectively, to persons who reported smoking mentholated cigarettes for at least 10 years and for less than six months. 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. Most analyses did not present risks by race. However, the authors did discuss prostate cancer because of its higher incidence rate among African Americans. They found no statistically significant excess risk associated with mentholation in analyses not controlled for race (rate ratio=1.15, 95% CI:0.82-1.62), and in Cox proportional hazards regression controlling for age and race (rate ratio=1.12; 95% CI:0.80-1.58).

Table 3-13. Comparative Risk of Other Cardiac/Lung Outcomes Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=2)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Murray et al. 2007 United States (Lung Health Study)	**Coronary heart disease** **Cardiovascular disease** Clinical trial of smoking cessation among 5,887 subjects (age 35-60) with mild-moderate airway obstruction. About 20%(1,216) smoked menthol cigarettes at baseline. There were 731 deaths due to any cause, 77 deaths due to CHD, and 163 deaths due to CVD in 14 years of follow-up. All were current or former smokers.	**Menthol Smokers*** **Death Due To** Coronary heart disease Cardiovascular disease Any cause	**Adjusted Hazard Ratios (95% CI)** 1.31 (0.77-2.22) 1.03 (0.70-1.52) 0.997 (0.83-1.20) Adjusted for age, sex, cigarettes/day at baseline, FEV1 percentage of predicted, randomization group, race, and baseline years of education.	We found no evidence in our data that mentholation of cigarettes is an attribute that contributes to the health risks of smoking. Still, the hazard ratio associated with smoking menthol cigarettes and coronary heart disease (1.31) is of sufficient magnitude that one can imagine that it might reach statistical significance in a study of sufficient sample size.

* denotes statistically significant increase in risk

Table 3-13. Comparative Risk of Other Cardiac/Lung Outcomes Associated with Menthol Cigarettes vs. that Associated with Nonmenthol Cigarettes (N=2) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS
Pletcher et al. 2006 United States (CARDIA study)	**Atherosclerotic disease** **Lung function** Cohort study (5,115 subjects; 972 smoked menthol and 563 smoked nonmenthol at baseline); 15-year follow-up.	**Coronary Calcification** Nonmenthol cigarettes (per pk-yr increase) Menthol cigarettes (per pk-yr increase) p-value comparing strength of association (nonmenthol vs. menthol) **Lung Function** Nonmenthol cigarettes (per pk-yr increase) Menthol cigarettes (per pk-yr increase) p-value comparing strength of association (nonmenthol vs. menthol)	**Adjusted Odds Ratios (per 10-pack-year increase) (95% CI)** 1.27 (1.01-1.60)* 1.33 (1.06-1.68)* 0.75 **Excess Decline in FEV1 (mL) (95% CI)** 84 (32-137) 80 (30-129) 0.88 Adjusted for age, sex, ethnicity, socioeconomic status (education, income), habits (alcohol consumption and exercise), cumulative exposure to cigarettes, and differential loss to follow-up.	Menthol and nonmenthol cigarettes seem to be equally harmful per cigarette smoked in terms of atherosclerosis and pulmonary function decline. Mentholation of cigarettes does not seem to explain disparities in ischemic heart disease and obstructive pulmonary disease between African Americans and European Americans in the United States.

* denotes statistically significant increase in risk

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Ahijevych and Parsley 1999	95 female smokers 49 menthol and 46 nonmenthol smokers 48 Black and 47 White CO measured 2 min prior to smoking and 2 min after Blood sample for nicotine and baseline cotinine obtained 1 min before smoking and for nicotine 1 min after	**Cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Cotinine/cigarette ratio** Menthol smokers Nonmenthol smokers	 239* 189 17.8* 13.1 *p<0.05 (unadjusted), menthol greater than nonmenthol No significant interaction effects of ethnicity and menthol preference on smoke constituent exposure	Menthol smokers had higher cotinine levels (p=0.02) and higher cotinine/cigarette ratios (p=0.04) compared to nonmenthol smokers.
Ahijevych and Wewers 1994	142 female smokers 130 menthol and 12 nonmenthol smokers 142 Black Self-reported average daily cigarette consumption Saliva sample for cotinine analysis obtained while completing questionnaire	**Cigarettes per day (CPD)** Menthol smokers Nonmenthol smokers **Cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Cotinine/cigarette (ng/ml/cigarette)** Menthol smokers Nonmenthol smokers	 14.8 ± 9.7 11.4 ± 5.7 394 369 37.9 33.6 No significant difference (unadjusted)	The average cotinine concentration for women smoking menthol cigarettes was not significantly different from the mean cotinine concentration for nonmenthol smokers. Menthol smokers in this study tended to have a nonsignificantly higher smoking rate than nonmenthol smokers. Fifty-eight percent of the total sample had cotinine/cigarette ratios >25 ng/ml/cigarette and were classified as underreporters.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Ahijevych et al. 2002	32 female smokers 20 menthol and 12 nonmenthol smokers 16 African American and 16 Caucasian Subjects smoked *ad libitum* on day 1. Plasma samples for cotinine assays were obtained every 8 h to establish a baseline. Subjects abstained from smoking day 2-7; samples were obtained for cotinine analysis every 8 h until discharge at 7 PM of day 7. Abstinence was confirmed via exhaled CO measurement.	**CPD** Menthol smokers Nonmenthol smokers **Baseline cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Cotinine/cigarette ratio** Menthol smokers Nonmenthol smokers **Cotinine half-life (hr)** Menthol smokers Nonmenthol smokers	 19.8 ± 7.5 21.6 ± 7.3 342 ± 123* 230 ± 123 20.7 ± 12.8* 12.4 ± 8.8 23.1 ± 7.9 18.1 ± 7.9 p<0.05 (unadjusted), menthol greater than nonmenthol	There was a significantly (p=0.019) greater baseline cotinine concentration among smokers of menthol compared with nonmenthol cigarettes, with a similar number of cigarettes smoked per day. The cotinine/cigarette ratio was significantly (p=0.05) higher in menthol smokers compared with nonmenthol smokers. Menthol smokers had a nonsignificantly longer cotinine half-life than nonmenthol smokers.
Allen and Unger 2007	432 smokers 296 menthol smokers 136 nonmenthol smokers 199 men and 233 women 432 African American Breath and saliva samples provided; timing unspecified	**Cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Carbon monoxide (CO) (ppm)** Menthol smokers Nonmenthol smokers	 347.7 ± 182.73 386.0 ± 192.51 16.88 ± 8.06 16.46 ± 8.32 No significant differences (unadjusted)	Menthol and nonmenthol smokers did not differ significantly on CO or salivary cotinine.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Benowitz et al. 2004	14 smokers 12 men and 2 women 7 African American and 7 White Two-period crossover study. Subjects randomly assigned to smoking either menthol or nonmenthol cigarettes for a one-week period. All subjects smoked nonmenthol cigarettes during 1st week as washout. Blood sample for baseline nicotine analysis obtained at time of eligibility evaluation While hospitalized on days 3 to 6 of each treatment period, subjects smoked 20 cigarettes per day, one every 45 min, from 8 AM to 11 PM. On day 5 each subject received a 30-min infusion of a 50:50 mixutre of nicotine-d_2 and cotinine-d_4. Blood samples were collected at 8 AM, noon, then 10, 20, 30, 45, 60 and 90 min and 2, 3, 4, 8, 12, 16,	**CPD** Menthol smokers Nonmenthol smokers **Nicotine intake (mg)** Menthol smokers Nonmenthol smokers **Nicotine/cigarette (mg)** Menthol smokers Nonmenthol smokers **Unlabeled nicotine in plasma (ng/ml·h)** Menthol smokers Nonmenthol smokers **Blood carboxyhemoglobin (%·h)** Menthol smokers Nonmenthol smokers **Disposition Kinetics of Nicotine** **Total clearance (ml/min)** Menthol smokers Nonmenthol smokers **Renal clearance (ml/min)** Menthol smokers Nonmenthol smokers **Nonrenal clearance (ml/min)** Menthol smokers Nonmenthol smokers	 28.3 22.1 29.8 30.6 1.49 1.53 404 388 109.8 116.1 1289 1431** 87 82 1202 1339**	Our data do not support the hypothesis that mentholated cigarette smoking results in a greater absorption of tobacco smoke toxins. Our finding of impaired metabolism of nicotine while mentholated cigarette smoking suggests that mentholated cigarette smoking enhances systemic nicotine exposure.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Benowitz et al. 2004 (continued)	20, 24, 44 and 68 h postinfusion. Urine was collected for analysis of nicotine and metabolites for the first 8 h after start of infusion and for 24 h on each hospital day for analysis of menthol concentration. Blood samples were obtained two days after discharge at 44 and 68 h.	**T1/2 (min; half-life)** Menthol smokers Nonmenthol smokers **Vss (L; volume of distribution at steady state)** Menthol smokers Nonmenthol smokers **F (ml/min; fractional conversion of nicotine to cotinine)** Menthol smokers Nonmenthol smokers **CLnic→ cot (ml/min; clearance)** Menthol smokers Nonmenthol smokers **<u>Disposition Kinetics of Cotinine</u>** **Total clearance (ml/min)** Menthol smokers Nonmenthol smokers **Renal clearance (ml/min)** Menthol smokers Nonmenthol smokers **Nonrenal clearance (ml/min)** Menthol smokers Nonmenthol smokers **T1/2 (min; half-life)** Menthol smokers Nonmenthol smokers	 156 140 223 219 0.66 0.65 850 940 47.1 50.0 10.3 11.3 36.8 38.7 1039 1049	

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Benowitz et al. 2004 (continued)		**Vss (L; volume of distribution at steady state)** Menthol smokers Nonmenthol smokers **Urinary Recovery** **Nicotine (%)** Menthol smokers Nonmenthol smokers **Nicotine glucuronide (%)** Menthol smokers Nonmenthol smokers **Cotinine (%)** Menthol smokers Nonmenthol smokers **Cotinine glucuronide (%)** Menthol smokers Nonmenthol smokers **3'-hydroxycotinine (%)** Menthol smokers Nonmenthol smokers **3'-hydroxycotinine glucuronide (%)** Menthol smokers Nonmenthol smokers	 64 65 43.3 32.9 13.7 14.8 24.5 29.0 8.7 9.8 7.0 11.1 2.7 4.1 **p<0.05 (unadjusted), nonmenthol greater than menthol	

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Benowitz et al. 2010	127 smokers 60 menthol and 67 nonmenthol smokers 62 African American and 65 non-African American Blood samples were obtained for nicotine and cotinine. Urine samples were obtained for creatinine, nicotine and its five major metabolites, NNAL, and metabolites of several PAHs. The time of smoking the last cigarette prior to blood and urine sampling was recorded.	**CPD (mean over 3 days)** Menthol smokers Nonmenthol smokers **Plasma cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Urine nicotine equivalents (pmol/mg creat)** Menthol smokers Nonmenthol smokers **Urine menthol (µg/mg creat)** Menthol smokers Nonmenthol smokers **Urine NNAL (pmol/mg creat)** Menthol smokers Nonmenthol smokers **Urine total PAHs (pmol/mg creat)** Menthol smokers Nonmenthol smokers	 18.8 17.0 202 217 47.2 59.8** 4.8* 2.1 0.9 1.2 81.6 115.2** *p<0.05 (unadjusted), menthol greater than nonmenthol **p<0.05 (unadjusted), nonmenthol greater than menthol	Urine menthol is measurable in the great majority of menthol cigarette smokers, and urine menthol is highly correlated with exposure to nicotine. Menthol is not independently associated with carcinogen exposure when nicotine intake is considered. Reviewer comment: Neither plasma cotinine nor urinary nicotine equivalents was higher in menthol smokers as compared to nonmenthol smokers (urinary nicotine equivalents were significantly higher in nonmenthol smokers as compared to menthol smokers).

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Clark et al. 1996	161 smokers 76 menthol and 85 nonmenthol smokers 74 men and 87 women 65 Black and 96 White Subjects abstained from smoking for 1 h followed by blood sampling for cotinine analysis. Subjects then smoked 1 cigarette. CO measurements were obtained prior to smoking and within 120 s of smoking and within 120 s of completing the test cigarette. Butts of all cigarettes smoked for 1 week were collected.	**Serum cotinine (ng/ml)** Menthol smokers Nonmenthol smokers Difference (menthol –nonmenthol) **Expired-air CO (ppm)** Menthol smokers Nonmenthol smokers	 478.2* 349.1 84.5*** 40.3 35.8 *p<0.05 (unadjusted data), menthol greater than nonmenthol ***p<0.05 (adjusted for race, CPD and mean amount of cigarette smoked), menthol greater than nonmenthol	After adjusting for race, CPD, and mean amount of each cigarette smoked, menthol was associated with higher cotinine levels (p=0.03) and carbon monoxide concentrations (p=0.02).

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Gan et al. 2008	1,520 smokers 346 menthol and 1,174 nonmenthol smokers 840 men and 680 women 189 Black and 1331 non-Black Blood samples obtained during clinical examination in NHANES 1999-2002	**Cotinine (nmol/L)** Menthol smokers Nonmenthol smokers	 1333.8 ± 40.1 1230.3 ± 24.5 No significant difference (adjusted for sex, CPD, age, race, BMI, poverty status and nicotine content per cigarette)	We observed higher serum cotinine concentrations in those who used mentholated cigarettes compared with nonmentholated cigarettes (103.4 nmol/L; p=0.037). Reviewer comment: This difference was no longer significant in the multivariate analysis which includes adjustment for other factors (p=0.632).
Heck 2009	112 smokers 54 menthol smokers and 58 nonmenthol smokers 50 men and 62 women 28 Black and 84 White Subjects smoked specified brands of their preferred cigarette type *ad libitum* for 2 weeks prior and during the 1-week study interval. 24-h urine collections and a blood sample were obtained on the 1st day and 7th day of the study period.	**CPD (median)** Menthol smokers Nonmenthol smokers **Carboxyhemoglobin (%)** Menthol smokers Nonmenthol smokers **Nicotine (µg/ml)** Menthol smokers Nonmenthol smokers **Cotinine (ug/ml)** Menthol smokers Nonmenthol smokers **Total nicotine equivalents (µg/ml)** Menthol smokers Nonmenthol smokers	 27 27 5.9 6.5 1.5 1.7 3.3 4.3 15.5 17.7	There were no significant differences between menthol and nonmenthol smokers in any biomarker concentrations (unadjusted and creatinine-adjusted); p-values ranged from 0.2 to 0.8. The present blood (carboxyhemoglobin) and urine (total nicotine equivalents, total NNAL) biomarkers findings are not consistent with speculation that smokers of mentholated cigarettes may exhibit an increased smoking intensity or smoke constituent exposures relative to those smoking nonmentholated cigarettes of broadly similar design and FTC smoke yield.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Heck 2009 (continued)	Cigarette butts were collected during two 24-h intervals preceding blood and urine collections.	**Total nicotine equivalents (mg/24 h)**		
		Menthol smokers	21.1	
		Nonmenthol smokers	24.2	
		Nicotine-glucuronide (µg/ml)		
		Menthol smokers	0.3	
		Nonmenthol smokers	0.5	
		Cotinine-glucuronide (µg/ml)		
		Menthol smokers	1.9	
		Nonmenthol smokers	2.7	
		***trans*-3'-hydroxycotinine (µg/ml)**		
		Menthol smokers	5.9	
		Nonmenthol smokers	6.6	
		***trans*-3'-hydroxycotinine-glucuronide (µg/ml)**		
		Menthol smokers	1.3	
		Nonmenthol smokers	1.6	
		NNAL (pg/ml)		
		Menthol smokers	67.9	
		Nonmenthol smokers	77.15	
		NNAL-glucuronide (pg/ml)		
		Menthol smokers	164.6	
		Nonmenthol smokers	212.4	
		Total NNAL (pg/ml)		
		Menthol smokers	239.4	
		Nonmenthol smokers	303.6	
		Total NNAL (ng/24-h urine)		
		Menthol smokers	300.3	
		Nonmenthol smokers	419.4	

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Heck 2009 (continued)			No significant differences (unadjusted)	
Ho et al. 2009	700 light smokers (≤10 CPD) 569 menthol smokers 131 nonmenthol smokers 233 men and 467 women 700 African American All subjects were participants in a double-blind, placebo-controlled smoking cessation study. Cigarettes per day were self-reported. Blood sample for nicotine and its metabolites was collected at study randomization. Expired CO levels were also measured.	**CPD** Menthol smokers Nonmenthol smokers **Expired CO (ppm)** Menthol smokers Nonmenthol smokers **Plasma cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Plasma 3'-hydroxycotinine (Correlation coefficient)** Menthol smokers Nonmenthol smokers	7.07 7.53 13.49 14.74 242.93 246.84 0.45 0.46 No significant differences (unadjusted)	Those who smoked mentholated cigarettes trended toward reporting fewer CPD compared with those who did not (p=0.05), although no difference was found for expired CO or plasma cotinine levels between mentholated and nonmentholated cigarette smokers. The correlation coefficients between CPD and expired CO with plasma nicotine and its metabolites were generally not altered when analyzed separately by mentholated cigarettes.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Jarvik et al. 1994	20 male smokers 10 menthol and 10 nonmenthol smokers 10 Black and 10 White Study participants attended 2 testing sessions of 1-2 h each separated by at least 1 week. In one session they smoked an experimenter-supplied commercial menthol cigarette and in the other a regular cigarette. Blood samples were obtained prior to smoking and at 2-5 min after completion of smoking for analysis of carboxyhemoglobin. End-expired CO samples were obtained immediately prior to and approximately 1 min after smoking.	**Total particulate matter, inhaled (mg)** Menthol smokers Nonmenthol smokers **Total particulate matter, (% retained)** Menthol smokers Nonmenthol smokers **Carboxyhemoglobin boost (% change)** Menthol smokers Nonmenthol smokers **CO boost (change in ppm)** Menthol smokers Nonmenthol smokers	 10.16 9.31 69.9 72.0 1.27 0.98 6.53 5.79 No significant differences (unadjusted)	Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide. Reviewer comment: Although the authors conclude that there were significant differences between menthol and nonmenthol smokers, the results of the statistical analysis do not support this finding.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Muscat et al. 2009	525 smokers 284 menthol smokers and 241 nonmenthol smokers 258 men and 267 women 237 Black and 288 White Urine was collected at 9 AM. Subjects were asked to abstain from smoking from midnight the previous night.	**Plasma cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Urinary cotinine (µg)** Menthol smokers Nonmenthol smokers **Thiocyanate (µm/L)** Menthol smokers Nonmenthol smokers **NNAL+NNAL-Gluc (pmol/mg creatinine)** Menthol smokers Nonmenthol smokers **NNAL-Gluc/NNAL** Menthol smokers Nonmenthol smokers	 371 ± 252 330 ± 249 4246 ± 4143 4193 ± 4532 166 ± 48 167 ± 50 2.9 ± 2.1 3.2 ± 2.2 3.0 ± 1.6 3.8 ± 2.5** **p<0.05 (adjusted for age, education, CPD, race and sex), nonmenthol greater than menthol	There were no significant differences in the mean concentrations of all cigarette smoke metabolites between menthol and nonmenthol smokers in Blacks and Whites, after adjustment for sex and other factors. The ratio of NNAL-Gluc to NNAL, a possible indicator of lung cancer risk, was significantly lower in menthol versus nonmenthol smokers. These data indicate that menthol is not associated with a higher exposure to tobacco smoke carcinogens. Menthol may not be more hazardous than other cigarette formulations for most smokers, although it cannot be ruled out at this time that some menthol smokers are possibly at increased risk for lung cancer because of selective inhibition of UDP-glucuronosyltransferase enzymes.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Mustonen et al. 2005	307 smokers 88 menthol and 219 nonmenthol smokers 149 men and 158 women 51 Black and 256 White Subjects were all smokers recruited for a clinical smoking cessation trial Salivary cotinine samples and CO levels were obtained at first two pre-cessation visits which were scheduled to allow at least 6 waking hours for each participant to reach his or her typical level of cigarette consumption. CPD was self-reported.	**CPD** Menthol smokers Nonmenthol smokers Sex x race x cigarette type interaction **Salivary cotinine (ng/ml)** Menthol smokers Nonmenthol smokers Sex x cigarette type interaction Sex x race x cigarette type interaction **Cotinine/CPD** Menthol smokers Nonmenthol smokers Sex x cigarette type interaction Sex x race x cigarette type interaction	 Not provided Not provided p=0.002 476.1 ± 218.3 441.9 ±197.3 p=0.05 p=0.05 23.3 ± 13.6* 19.4 ± 9.4 p=0.01 p<0.001 *p=0.004 (unadjusted); menthol is greater than nonmenthol	No differences in CPD were found between smokers of nonmenthol and menthol cigarettes (p=0.44). Cotinine levels were higher among menthol smokers than among nonmenthol smokers, but this difference did not reach statistical significance. The cotinine/CPD ratio was, however, higher among menthol smokers than nonmenthol smokers. We found a significant sex x race x menthol interaction on salivary cotinine level as well as cotinine/CPD ratio.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Patterson et al. 2003	190 smokers 55 menthol and 135 nonmenthol smokers 95 men and 95 women 63% Caucasian 25% African American 12% Hispanic, Asian, other or mixed Subjects were all treatment-seeking smokers; data were collected at baseline assessment. Subjects were instructed to smoke 1 cigarette immediately prior to entering research center at which time CO levels were measured. Approximately 40 min later, subjects smoked 1 cigarette. Blood samples for nicotine and cotinine analyses were obtained before and after (within 3 min) of "boost cigarette.	**Nicotine boost (ng/ml)** Menthol smokers Nonmenthol smokers **Baseline cotinine (ng/ml)** Menthol smokers Nonmenthol smokers **Baseline nicotine (ng/ml)** Menthol smokers Nonmenthol smokers	**Median (SD)** 11.2 ± 5.5 10.8 ± 5.0 316.5 ± 147.5 276.5 ± 119.2 20.9 ± 10.3 19.3 ± 10 No significant differences (unadjusted)	Menthol/nonmenthol brand was not associated with nicotine boost or baseline nicotine. Baseline cotinine was significantly elevated among menthol smokers as compared to nonmenthol smokers ($p<0.10$). Reviewer comment: Although the authors conclude that there was a significant difference between menthol and nonmenthol smokers, the results of the statistical analysis do not support this finding.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Signorello et al. 2009	225 smokers 139 menthol and 116 nonmenthol smokers 128 men and 127 women 130 Black and 125 White Blood samples for cotinine analysis were obtained at time of enrollment. Subjects self-reported number of cigarettes smoked in previous 24 h at time of blood collection.	**Difference in cotinine (ng/ml) in menthol vs. nonmenthol** Black men White men Black women White women	 -6.2 -1.0 -12.4 -18.1 No significant difference (adjusted)	We observed no positive association between cotinine levels and menthol cigarette use.
Strasser et al. 2011	109 smokers 32 menthol and 77 nonmenthol smokers 64 men and 45 women 105 Caucasian and 4 non-Caucasian Blood samples for nicotine metabolite analysis and urine samples for total NNAL were obtained. Time since last cigarette not provided.	**Nicotine metabolite ratio (ratio of cotinine and 3'-hydroxycotinine)** Menthol smokers Nonmenthol smokers	 Not provided Not provided No significant difference (unadjusted)	NMR was non-significantly higher among participants who smoked nonmenthol cigarettes (p=0.10).

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Wang et al. 2010	3341 smokers 1044 menthol and 2297 nonmenthol smokers 1419 men and 1922 women 614 African American and 2727 White 24 h urine samples were collected for determination of nicotine and five major metabolites. Blood samples were collected for serum cotinine analysis and carboxyhemoglobin determination. Subjects collected all cigarettes butts during 24 h urine collection period.	**CPD** Menthol smokers Nonmenthol smokers **Nicotine equivalents (mg/24 h)** Menthol smokers Nonmenthol smokers **Nicotine equivalents per cigarette (mg/cig)** Menthol smokers Nonmenthol smokers **Carboxyhemoglobin (% sat)** Menthol smokers Nonmenthol smokers **Serum cotinine (ng/ml)** Menthol smokers Nonmenthol smokers	 15.0 ± 8.7 16.8 ± 9.0** 12.78 ± 7.80 13.51 ± 7.94** 0.96 ± 0.67* 0.90 ± 0.67 5.18 ± 2.27 5.35 ± 2.28** 188.94 ± 108.43 183.44 ± 105.39 *p<0.05 (unadjusted); menthol greater than nonmenthol **p<0.05 (unadjusted); nonmenthol greater than menthol	Smoking mentholated cigarettes does not increase daily exposure to smoke constituents as measured by nicotine equivalents (NE) and carboxyhemoglobin (COHb). Analyses of variance revealed no statistically significant effects of mentholated cigarettes on NE/24 h, COHb, serum cotinine and NE/cigarette. Reviewer comment: The statistically significant difference found in the univariate analysis (higher nicotine equivalents in menthol vs. nonmenthol) disappeared after adjustment for other factors (age, sex, BMI, race, smoking machine derived tar delivery category, CPD, U.S. Census region, annual household income, education and two- and three-way interactions)

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Williams et al. 2007	142 smokers 79 menthol (47 schizophrenic, 32 control) and 63 nonmenthol (42 schizophrenic, 21 control) smokers 89 schizophrenic smokers and 53 control smokers Menthol smokers included 33 Blacks, 33 Whites, 8 Hispanic/Latino, 4 Asians and 1 Other. Exhaled CO measurements and blood samples for nicotine, cotinine and trans-3'-hydroxycotinine were obtained on the afternoon of a normal smoking day approximately 2 min after smoking their usual cigarettes.	**Serum nicotine (ng/ml)[a]** Menthol smokers Nonmenthol smokers **Nicotine/CPD[b]** Menthol smokers Nonmenthol smokers **Serum cotinine (ng/ml)[a]** Menthol smokers Nonmenthol smokers **Cotinine/CPD[b]** Menthol smokers Nonmenthol smokers **CO[a]** Menthol smokers Nonmenthol smokers **3-HC/cotinine ratio[a]** Menthol smokers Nonmenthol smokers **Predictors of serum nicotine level[c]** Menthol smokers Nonmenthol smokers [a] Adjusted for group, CPD and race [b] Adjusted for group and race [c] Regression model included variables for FTC nicotine machine-measured delivery, age, education, marital status, age at onset of smoking, sex, race, CPD, employment status, time of blood draw, and number of past quit attempts.	 27.2 ± 10.9* 22.4 ± 10.8 1.3 ± 0.8 1.2 ± 0.7 294.3 ± 172.2* 239.8 ± 121.2 13.5 ± 9.8 12.4 ± 8.5 25.1 ± 10.9* 20.6 ± 8.5 0.41 ± 0.32 0.43 ± 0.27 **Odds Ratio** 1.30* 1.0 (Reference) *p<0.05; menthol greater than nonmenthol	Serum nicotine levels, serum cotinine levels, and expired CO were higher in smokers of menthol compared with nonmenthol cigarettes, with no differences in 2-hydroxycotinine/cotinine ratios between groups when controlling for race. Backward stepwise linear regression models showed that, in addition to having a diagnosis of schizophrenia, smoking menthol cigarettes was a significant predictor of nicotine and cotinine levels. Reviewer comment: The results of the linear regression analyses were presented for predictors of serum nicotine only; no data were provided on predictors of serum cotinine levels.

Table 3-14. Comparison of Biomarkers of Tobacco Smoke Exposure (N=19) (Continued)

CITATION	STUDY POPULATION AND DESIGN	FACTORS MEASURED	MEASURE OF EFFECT	AUTHORS' CONCLUSIONS/COMMENTS
Xia et al. 2010	1373 tobacco users 1053 of 1373 tobacco users were cigarette smokers; % menthol smokers not reported 844 men and 533 women 349 non-Hispanic Black, 703 non-Hispanic White, 145 Mexican-American and 180 Other Sample included all tobacco users from NHANES 2007-2008 (N=9762) Urine samples for urinary total NNAL were collected from all NHANES participants 6 years of age or older.	**NNAL** Menthol smokers Nonmenthol smokers	**Geometric Means (95% CI)** 285 (243-334) 331 (304-360) No significant difference (adjusted for serum cotinine, urinary creatinine, CPD and FTC tar levels)	Although NNAL concentrations among menthol smokers were lower than those among nonmenthol smokers, the difference did not achieve statistical significance (p=0.095).

CHAPTER 4.
EVIDENCE IS INADEQUATE TO CONCLUDE THAT MENTHOL IN CIGARETTES ADVERSELY IMPACTS SMOKING INITIATION BEHAVIORS

One element of FDA's consideration is the question of whether menthol versus nonmenthol cigarette use may adversely impact smoking initiation behaviors. Speculative adverse effects include an increase in smoking initiation rate and/or an earlier onset of established smoking among menthol versus nonmenthol cigarette smokers. Smoking initiation has been defined as the transition from never smoking to becoming an experimenting smoker (i.e., smoking >1 cigarette but <100 cigarettes lifetime), experimenting smoking to becoming an established smoker (i.e., >100 cigarettes lifetime and smoking on some days), and/or from established smoking to becoming a daily smoker. This latter transition may be more appropriately examined as a measure of smoking dependence, as it provides the clearest distinction between smoking experimenters and true initiators of established smoking.

An assessment of whether menthol versus nonmenthol cigarette use impacts smoking initiation rate should begin with an examination of the cigarette type used by experimenting smokers to initiate established smoking. Currently, no published studies report data on this issue or any other transition. In the absence of such published studies, data from nationally representative surveys and individual studies of specific populations have been used to infer a role for menthol versus nonmenthol cigarettes during smoking initiation. However, the available information from these sources is not currently adequate to draw any firm conclusions about the specific relationship between menthol smoking (as compared to nonmenthol smoking) and becoming an established smoker.

Although nationally representative surveys do not currently collect respondent data on cigarette type used during smoking initiation, they do provide important information on smoking initiation behaviors. For example, available data allow researchers to estimate the proportion of respondents that began smoking within the last 12 months preceding the survey, and thus allow trend analyses of estimated year-to-year smoking initiation rates. These data can be further stratified based on demographic and smoking behavior characteristics, including race/ethnicity, sex, current age and current cigarette type preference. Existing trend analyses of year-to-year initiation rates suggest that the percentage of individuals initiating smoking, as represented by never smokers transitioning to established or daily smoking has not significantly changed over the last several years. This finding is consistent with national survey data indicating a steady decline in smoking prevalence during the past two decades.

National surveys also collect data that allow researchers to estimate average ages of smoking initiation (i.e., age at first cigarette smoked, age at first regular smoking and/or age at first daily smoking); these data can be further stratified based on race/ethnicity, sex, current age and current cigarette type preference. Although such survey data may inform questions of whether cigarette type preference impacts onset of smoking experimentation and subsequent transition to established (or daily) smoking, a given observational association cannot be regarded as conclusive evidence for a

cause-and-effect relationship in this or any other area of study. Nevertheless, earlier onset of smoking might be interpreted as evidence of an adverse population-level effect since total duration of smoking and early age of smoking initiation have been observed to be substantial predictors of chronic disease risk among smokers.

Conversely, findings from a number of nationally representative surveys consistently indicate that current menthol cigarette smokers are more likely to report significantly older initiation ages (i.e., later onset of smoking) compared to nonmenthol smokers. Findings from epidemiology studies of smoking-associated chronic diseases among menthol versus nonmenthol smokers (discussed in Chapter 3 of this report) are consistent with the smoking initiation data discussed in this chapter. As expected with a similar to later (but not earlier) initiation age among smokers who report a preference for menthol cigarettes, the epidemiology studies report no increase in disease risk associated with the use of menthol versus nonmenthol cigarettes.

Existing data from nationally representative surveys as well as studies based on populations that are not necessarily representative of the overall (smoking) population, do not provide data on cigarette type (menthol versus nonmenthol) used during smoking initiation. Trend analyses based on nationally representative smoking populations suggest that smoking initiation rates (including those among menthol cigarette smokers) have remained largely unchanged during the past several years, and that current smokers of menthol cigarettes are more likely to delay onset of smoking compared to nonmenthol smokers. Although these data are suggestive of no causal relationship between menthol cigarette use and adverse smoking initiation behaviors, they do not directly address the cigarette type used to initiate smoking. Thus, using the Surgeon General's framework for assessing causality, it must be concluded that the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between menthol cigarette use and adverse smoking initiation behaviors.

This chapter reviews what is known about the complex process of smoking initiation, discusses the most appropriate way to assess smoking initiation, and reviews the available data on initiation behaviors. Although there are a limited number of methodologically sound studies that attempt to examine the impact of cigarette type on smoking initiation, the available evidence discussed below suggests that menthol versus nonmenthol cigarette use does not adversely impact smoking initiation behaviors.

FACTORS ASSOCIATED WITH SMOKING INITIATION BEHAVIORS

Most studies report that experimentation with cigarette smoking and transition to established smoking typically begins during adolescence. Research indicates that this process is associated with a complex interplay among cultural, sociodemographic, intrapersonal, environmental, genetic and behavioral factors. Some of the factors that influence or correlate with the uptake of smoking include age; ethnicity/race; family socioeconomic status and personal income; use or approval of tobacco use by peers or siblings; lack of skills to resist influences to use tobacco; smoking by parents or guardians; lack of parental involvement or support; psychological reactance to adult authority or parental control; accessibility, availability or price of tobacco products; a perception that tobacco use

is the norm; low levels of academic achievement; low self-image or self-esteem; stress, depression or distress; and aggressive behavior such as fighting or carrying weapons (Batra et al. 2003; Campaign for Tobacco-Free Kids 2010a; Miller et al. 2006; USDHHS 1994, 2000). Adolescents who use tobacco are likewise at an increased risk for other potentially harmful behaviors (e.g., the use of alcohol/other drugs, high-risk sexual behavior). The sheer number of these factors documented to influence early smoking behaviors, each constrained by unique biases, interactions and imprecisions, suggests that the definitive study and conclusive identification of a role for menthol cigarette use as an independent factor for smoking initiation behavior(s) will be difficult.

DIFFICULTIES IN ASSESSING SMOKING INITIATION BEHAVIORS

There are inherent difficulties in studying smoking initiation behaviors. Most studies report that smoking experimentation and transition to established smoking typically begins at a time when young people cannot purchase cigarettes legally. Hence, young smokers often do not make choices about brand preference, or obtain cigarettes in the manner that adults do. Young smokers are undoubtedly strongly influenced by the types of cigarettes used by the smokers around them. To the degree that young smokers obtain cigarettes from others, they may know little about what type of cigarette they are smoking. As noted by researchers who have studied this issue, "It is not surprising that many youths could not recall any details regarding the brand, strength, or mentholation of their first cigarette, since the first cigarette is most commonly provided by others and this information is rarely written on the cigarette" (DiFranza et al. 2004). Moreover, brand or style of the cigarette with which young smokers initiate smoking may bear no predictable relationship to a future brand purchased legally. An additional complication is that, adolescents may not report their smoking activities accurately. Some may be unwilling to report that they engage in an activity that is illicit, as well as unhealthful, while others may view reporting smoking in a positive light as evidence of rebellion and a challenge to authority.

Analyses are further complicated by the fact that there is no single definition of what constitutes "smoking initiation," with researchers often employing different definitions that are dictated by available data sets. Secondary analyses of baseline data from studies designed to examine disease risk or smoking initiation are limited by the original study design. Even nationally representative surveys collect respondent data based on different definitions of smoking initiation, ranging from first cigarette (or puff) smoked to established (or even daily) smoking. Caution is warranted when interpreting (and comparing) findings from individual studies. An additional complexity is the knowledge that only about 25% of self-reported youth smokers actually transition to established or daily smoking (Deyton 2010). While it is encouraging that only 1 in 4 youths experimenting with cigarettes actually transition to established smoking (a more appropriate measure of smoking initiation), it is clear that study findings based on first cigarette (or puff) smoked or other early experimentation-phase smoking behaviors significantly overestimate the true initiation of established smoking.

Ideal Study for Assessing Role of Menthol Cigarette Use During Smoking Initiation

The ideal study evaluating whether menthol versus nonmenthol cigarette use adversely impacts smoking initiation behaviors would enroll a large, nationally-representative cohort of young people; enrollment would likely include an over-sampling of African American and Hispanic youth. This cohort would be followed for a number of years to capture data through the age 20 or 21 years, when most long-term smokers have established their smoking behaviors. All participants would be re-interviewed (in person) at regular intervals, e.g., at least every 6 months, to minimize the impact of recall bias. Individuals would be asked about experimentation with different types of cigarettes, their smoking intensity (cigarettes per day), and would provide a urine sample for cotinine analysis to verify smoking status. In addition, detailed information would be collected at baseline (and, for certain variables, at each follow-up visit) on sociodemographic factors, smoking behavior (amount smoked, timing of first and last cigarette, whether smoking is done mainly socially), nicotine dependence, alcohol consumption, body mass index, and health/respiratory symptoms. Such a study would make it possible to monitor smoking initiation behaviors, to verify the stability of cigarette type smoked (menthol versus nonmenthol), and to assess the development of dependence. It would also enable researchers to confidently adjust for numerous variables that might confound the association between menthol cigarette use and initiation behaviors.

None of the available studies meets all of the criteria described above, including the unpublished secondary analysis of Nonnemaker et al. (unpublished) that TPSAC heavily relied upon in the developments of its menthol model and its conclusions with respect to the effects of menthol on smoking initiation. The ideal study described above would, in fact, likely be difficult to conduct.

BEST AVAILABLE SCIENCE WAS DETERMINED THROUGH A RIGOROUS PROCESS

There are two potential sources of data on menthol cigarette use and smoking initiation behaviors: nationally representative surveys and individual studies of specific populations. Data from studies based on nationally representative surveys are generally more informative due to the fact that the sample populations have been weighted to achieve nationally representative estimates aligned with the U.S. population; hence, study findings are considered to be representative of the entire smoking population. This is not the case for individual studies based on specific populations; findings from these studies may only be considered representative of the entire smoking population if the authors demonstrated the external validity of the study through appropriate comparisons.

As previously discussed, the available studies do not collect information on the cigarette type used by experimenting smokers to initiate established smoking. However, these studies collect data that allow researchers to estimate average ages of smoking initiation; and, these data can be further stratified based on race/ethnicity, sex, current age and current cigarette type preference. Such data are informative as to whether cigarette type preference impacts the onset of smoking initiation, with earlier onset of smoking likely to be suggestive of an adverse population-level effect.

A comprehensive search of the literature and methodologic evaluation of the identified studies on the association between menthol cigarette use and smoking initiation behaviors was performed by Covance at the request of Lorillard. The report of their analysis has been provided to TPSAC and a summary of the findings were presented to TPSAC on February 10, 2011. An updated report from Covance (as referenced in Chapter 1) includes an evaluation of additional recent studies.

The Covance report describes in detail the rigorous and objective process used to identify and evaluate the available published literature on this topic. Briefly, a systematic search of the published literature was conducted to identify studies that addressed use of menthol cigarettes and smoking initiation behaviors. Covance then evaluated these articles for overall methodologic quality (using criteria developed by FDA for Healthcare Research and Quality (Ranney et al. 2006)), and for ability to support inferences related to menthol cigarette use. Study quality ratings for these two measures included poor, poor/fair, fair, fair/good, and good. The studies were categorized into three tiers as follows:

- Tier 1 studies were those rated by Covance as fair or better with respect to both overall quality and ability to support inferences related to menthol cigarette use;
- Tier 2 studies were those rated by Covance as fair or better with respect to overall quality, but lower than fair with respect to ability to support inferences related to menthol cigarette use; and
- Tier 3 studies were those rated by Covance as lower than fair with respect to both categories.

Six articles were identified that evaluated menthol cigarettes and smoking initiation behaviors. Of these, Covance's ratings placed four studies in Tier 1, no studies in Tier 2, and two studies in Tier 3, as shown below.

Table 4-1. Studies of Menthol Smoking and Initiation Behaviors (N=6) Quality Ratings by Covance

	Citation	Overall Quality Rating	Rating: Menthol Inferences
Tier 1	Appleyard et al. 2001	Good	Fair
	Cubbin et al. 2010	Fair/Good	Fair/Good
	Fernander et al. 2010	Fair/Good	Fair
	Lawrence et al. 2010	Good	Good
Tier 2	No studies identified		
Tier 3	Ahijevych and Parsley 1999	Poor	Poor
	Okuyemi et al. 2004	Poor	Poor

Tier 1 Studies on Menthol Smoking and Initiation Behaviors

The Tier 1 studies are considered to be the "best available science" for assessing the effect of menthol versus nonmenthol cigarette use on smoking initiation behaviors. All four studies provide findings based on nationally representative populations, although one limited analyses to specific demographic groups (i.e., Asian American and Hawaiian/Pacific Islander youth). None of the nationally representative surveys asked respondents about the type of cigarette smoked during the initial smoking experience, the type of cigarette used when regular smoking began or the type first purchased (which may better reflect preference). The studies are summarized in Appendix Table 4-3 and discussed below.

Appleyard et al. (2001) conducted an analysis of data from the 2000 National Youth Tobacco Survey (NYTS) to better understand smoking behaviors among Asian American and Hawaiian/Pacific Islander youth. The analysis is not very useful in understanding what, if any, role menthol cigarette use plays during smoking initiation, as it does not compare initiation among youth who smoked menthol cigarettes with those who smoked nonmenthol cigarettes. A few findings of interest did relate to menthol cigarette use. For example, White and Hispanic youth were more likely to smoke menthol cigarettes in middle school than in high school; the opposite was true for Asian Americans, Hawaiian/Pacific Islanders and African Americans (specific percentages not provided).

Cubbin et al. (2010) conducted a cross-sectional analysis of data from the 2005 National Health Interview Survey (NHIS) and Cancer Control Supplement. Adult daily smokers (aged ≥18 years; N=66,145) were asked how old they were when they started smoking cigarettes "fairly regularly." Among menthol cigarette smokers, Whites became regular smokers earlier than their Black and Hispanic counterparts, i.e., age of initiation was about 2 years younger for White females and 1.5-3 years younger for White males. Among nonmenthol smokers, Whites similarly initiated smoking earlier, but the differences were only significant in comparison with Hispanic males and females. There were no sex differences among any racial/ethnic group for either cigarette type (menthol or. nonmenthol); and, within each demographic group, there were no differences in age of initiation by cigarette type. The authors concluded that the results do not support the hypothesis that menthol smokers initiate smoking at an earlier age compared to nonmenthol smokers. Note that the survey did not collect information on whether respondents initiated with menthol or nonmenthol cigarettes; thus, it does not provide insight into whether early experiences with menthol cigarettes may be associated with subsequent regular smoking.

Fernander et al. (2010) conducted a cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey (TUS-CPS). After adjustment for demographic and smoking variables, findings from multivariate logistic models suggested that the longer the delay of initiation (established smoking), the more likely that individual respondents reported smoking menthol cigarettes as an adult. The authors concluded that menthol smokers tend to start smoking at significantly older ages (i.e., later onset of smoking initiation) than smokers of nonmenthol cigarettes. As with the NHIS, this survey did not collect information on whether respondents started out smoking menthol or nonmenthol cigarettes; thus, it does not provide insight

into whether early experiences with menthol cigarettes may be associated with subsequent regular smoking.

Lawrence et al. (2010) conducted a cross-sectional analysis of data from the 2003 and 2006/07 TUS-CPS. After adjustment for sociodemographic and smoking variables in the multivariate logistic regression model, no significant associations between age at onset of regular smoking and menthol use among all current smokers were found. When the analysis was stratified by sex, older onset of established smoking (aged ≥18 years compared to aged 15-17 years) was significantly associated with current menthol versus nonmenthol cigarette use among female smokers; there were no significant differences among male smokers. As mentioned previously, this survey did not collect information on whether respondents started out smoking menthol or nonmenthol cigarettes; thus, it does not provide insight into whether early experiences with menthol cigarettes may be associated with subsequent regular smoking.

The weight of evidence provided by these highest-quality studies does not support the contention that menthol in cigarettes is causally associated with earlier initiation of smoking among the general population or among ethnic subpopulations. In fact, menthol smokers are more likely to report later onset of smoking initiation when compared with nonmenthol smokers.

Tier 3 Studies on Menthol Smoking and Initiation Behaviors

Two Tier 3 studies (**Ahijevych and Parsley 1999, Okuyemi et al. 2004**) were rated poor in overall quality and in their ability to draw menthol inferences, and are not discussed in detail here.

Studies Not Designed to Address Initiation Behaviors

Covance assigned studies to behavior classification categories (initiation, cessation or dependence) according to the study's primary outcomes. This resulted in some studies that are often discussed in the context of initiation to be assigned to other behavior categories. Because they have been discussed in TPSAC meetings, they are mentioned briefly here.

DiFranza et al. (2004) was categorized by Covance as a Tier 1 dependence study and is presented in detail in Chapter 5B. In this study, authors conducted a "retrospective/prospective" longitudinal analysis of seventh graders followed for 30 months as part of the Development and Assessment of Nicotine Dependence in Youth Study. The subjects were interviewed three times per year for three years, with the goal of understanding whether the recalled reaction to a first cigarette was predictive of later nicotine dependence. This analysis focused on 237 subjects who reported that they had inhaled cigarette smoke; only about half of these could recall whether the first cigarette they had smoked was menthol or nonmenthol. The authors found that reactions to the initial smoking experience were unrelated to cigarette mentholation; reactions were likewise unrelated to sex, cigarette brand or strength of cigarette.

Hersey et al. (2006) was categorized by Covance as a Tier 3 study addressing cessation and dependence. Given its low rating, the study is not discussed in detail in Chapters 5A or 5B. However, because the findings of this study have been mentioned in discussion of initiation in

TPSAC meetings, they are mentioned here briefly. In this study, the authors analyzed data from the 2000 and 2002 NYTS, and reported that menthol cigarette smoking was more prevalent among students who had smoked <1 year (i.e., beginner smokers) than among students who had smoked >1 year (i.e., experienced smokers). The authors suggested that menthol cigarettes may be a "starter product" during youth uptake of smoking, but cautioned against interpreting findings as predictive of future smoking (i.e., "gateway" effect). Study findings were likely compromised by the significant loss of sample (i.e., due to nonresponse to the survey and indeterminate menthol status), inconsistency between survey items in the 2000 and 2002 NYTS, and the study's cross-sectional design. A subsequent analysis by the same authors (Hersey et al. 2010, discussed below) did not substantiate the "starter product" assertions made in this earlier study.

Additional studies provided data on smoking initiation behaviors among menthol versus nonmenthol cigarette smokers (Hyland et al. 2002, Hymowitz et al. 1995, Pletcher et al. 2006). Corresponding findings were based on baseline characteristics of specific populations and are not discussed here despite their findings of no differences in menthol versus nonmenthol in age at which smoking was started (Hyland et al. 2002; Hymowitz et al. 1995) or at which first cigarette was smoked (Pletcher et al. 2006).

Recent Publications of Data from National Cross-Sectional Surveys

There were three additional publications (included in the recent *Nicotine and Tobacco Research* December 2010 Supplement and March 2011 issue) that examined smoking initiation behaviors and menthol versus nonmenthol cigarette use based on data from nationally representative surveys (NYTS and NSDUH). Due to the timing of publication, these studies were not included in the Covance review; thus, they have not been placed into a specific quality tier. These studies are discussed briefly.

Hersey et al. (2010) analyzed cross-sectional data from the 2006 NYTS, and provided findings from youth (i.e., past month smokers) that had a usual brand of cigarette and could identify that usual brand as either menthol or nonmenthol (N=3,281). Menthol cigarette use was found to be more common among more experienced smokers (i.e., those having smoked for >1 year) of middle school age than among beginner smokers (i.e., those having smoked <1 year), 54.7% vs. 42.2%, respectively. Among high school smokers, the proportions smoking menthol cigarettes as their usual brand were similar among more experienced and beginner smokers (43.1% vs. 42.8%, respectively). No statistical tests were performed on these data to determine whether the observed differences were significant. Nonetheless, these findings directly contradicted earlier findings from the same authors examining data from the 2000 and 2002 NYTS (Hersey et al. 2006, discussed previously), that were used to support the contention that menthol cigarettes might serve as a "starter product" during youth uptake of smoking.

Rock et al. (2010) conducted an analysis of data from the 2004-2008 NSDUH, the objective being to examine menthol versus nonmenthol cigarette use patterns among racial and ethnic groups; similar analyses were performed on different age groups. These data do not address initiation directly as participants were not asked which type of cigarette they used when they began smoking; rather, analyses focused on trends of menthol versus nonmenthol cigarette type preference.

Findings suggested that menthol cigarette preference (i.e., use among current smokers, and not smoking prevalence among the overall population) increased during the period of 2004-2008 among White adolescent smokers, but not among African American or Hispanic adolescent smokers. Increases were likewise reported for Hispanic and White young adult smokers. For all race/ethnic groups except African Americans, menthol cigarette smoking was more common among the youngest smokers (age 12-17 years) compared to smokers in the older age groups (age 18-25 years or age ≥26 years). Among African Americans, menthol cigarette smoking was more common among smokers in the older age groups.

As discussed in Chapter 2, estimates of menthol cigarette preference from the NSDUH are based on an overly inclusive question that may misclassify smokers whose usual brand is nonmenthol but have smoked any menthol cigarette(s) in the past month. Estimates of menthol preference among current smokers from the NSDUH are typically higher than those from surveys that base estimates of menthol preference on usual cigarette (or brand) smoked. Additionally, current smokers in the NSDUH estimates were defined as having smoked all or part of a single cigarette in the last 30 days, a much more inclusive definition of smoking compared to that used by other surveys (i.e., having smoked ≥100 cigarettes lifetime and currently smoking on some days or every day). Hence, the potential exists that estimates provided by the NSDUH are somewhat exaggerated, particularly among younger, less experienced smokers.

Yu (2011) reported an analysis of a national sampling of 305 American Indian/Alaska Native adolescent smokers in grades 6-12 who were participants in the 2006 National Youth Tobacco Survey. Just over half of the respondents reported ever having experimented with or initiating the cigarette smoking (54%). However, only 12% of these respondents reported experience with menthol cigarettes, suggesting that menthol added to cigarettes does not lead to an increase in experimentation or initiation of smoking among this American Indian/Alaska Native adolescent subpopulation compared to nonmenthol cigarettes.

Unpublished Analyses Presented to TPSAC

In July 2010 and January 2011, unpublished analyses that examined menthol versus nonmenthol cigarette use and smoking initiation behaviors were presented to TPSAC. Although these analyses have not undergone peer review, the authors reported conclusions are mentioned here briefly:

- **Curtin (unpublished)** analyzed data from several large nationally representative surveys and reported that:
    - Among demographic groups reporting higher menthol versus nonmenthol smoking preference, female smokers indicated significantly older mean ages for initiating established smoking. Significant differences were suggested for age at first cigarette smoked (0.80 years; NSDUH), age at first regular smoking (1.18 years; NHANES) and age at first daily smoking (0.96 years; NSDUH). No significant differences were suggested for non-Hispanic Black, adolescent or young adult menthol versus nonmenthol smokers based on estimated mean initiation ages.

- Regression models that controlled individually for sex or current age suggested an association between older smoking initiation age and menthol cigarette use, i.e., for age at first cigarette smoked (NHANES and NSDUH), age at first regular smoking (NHANES and NHIS) and age at first daily smoking (NSDUH). Significant differences persisted when controlling for the combinations of race/ethnicity and current age or sex and current age.
- For first daily smoking, a significantly older (0.63 years; $p<0.05$) smoking initiation age among menthol smokers was indicated after controlling for the combination of current age, sex and race/ethnicity.

- **Nonnemaker et al. (unpublished)** conducted a secondary analysis of a longitudinal cohort of middle/high school youth to examine the influence of early menthol and nonmenthol cigarette use (and switching) on the progression from experimentation to established/daily smoking over a 3-year interval. Results were not entirely consistent, but the authors suggested that an early stated preference for menthol cigarettes was associated with indicators of progression to established smoking and higher levels of nicotine dependence. This study has numerous limitations, including use of a sample population that was not representative of the overall youth population and sample sizes that were likely insufficient to draw valid conclusions. Notably in this regard, the numbers of African American daily, regular and established smokers ranged from 11-13 subjects up to Wave 3 of the survey, with 5-6 added in the Third Wave for each categorical definition of initiation. These extremely small sample numbers are, by any standard, inadequate to support estimations of initiation behaviors of the general national population of African American adolescents.

In summary, an analysis of the studies described above (those not designed to directly address cigarette type used during smoking initiation, recently published studies that were not rated by Covance, and unpublished analyses presented to TPSAC) do not support the conclusion that menthol in cigarettes adversely effects smoking initiation or progression to regular smoking.

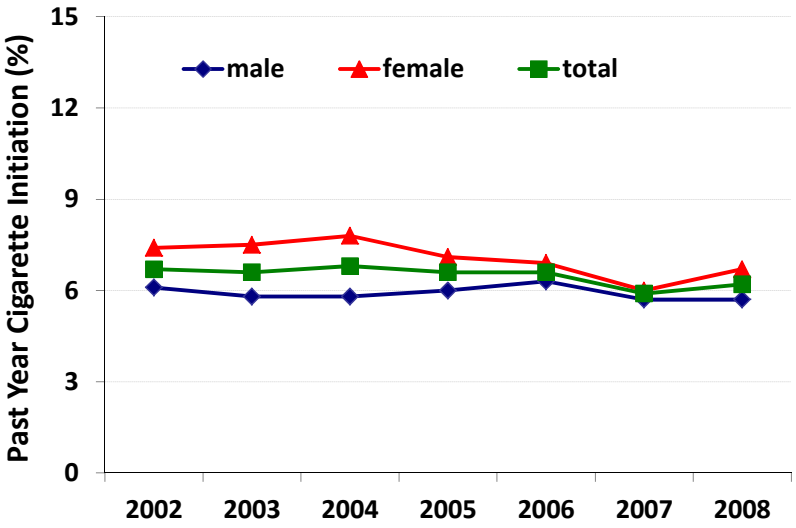
TREND DATA FOR SMOKING INITIATION RATES

The weakness in national survey data with regard to evaluating the effect of menthol cigarettes on smoking initiation is that they have historically not collected respondent data on cigarette type preference during initiation. Although cross-sectional analyses of national survey data are limited to assessments based on current cigarette type preference (e.g., usual brand smoked), comparisons across survey years are possible based on combined sample populations. This allows researchers to identify the proportion of respondents that began smoking within the 12 months preceding participating in each survey, and thereby examine year-to-year smoking rates based on sociodemographic and smoking behavior characteristics, including current cigarette type preference. Existing trend analyses of year-to-year initiation rates indicate that the percentage of never smokers transitioning to established or daily smokers has not significantly changed over the last several years.

Data provided by the NSDUH indicate that adolescent smoking initiation rates, overall or stratified by sex, were not significantly different from 2002 to 2008 (Figure 4-1). Among youths aged 12-17

years who had not smoked cigarettes prior to the past year, the smoking initiation incidence rate (i.e., transition to daily smoking) showed no significant difference between 2002 and 2008. Among males in this group, the decrease in past year initiation rate from 6.1% in 2002 to 5.7% in 2008 was not significant; nor was the decrease from 7.4% in 2002 to 6.7% in 2008 among females (SAMHSA 2009).

Figure 4-1. Annual smoking initiation* rate as percent of respondents (NSDUH, 2002-2008)



*Smoking initiation (daily smoking) estimates based on percent of survey respondents that reported initiating smoking ≤12 months prior to survey participation (SAMHSA 2009).

Analyses, conducted by the tobacco industry and presented to the TPSAC during the July 2010 meeting, examined the transition from never smoking to established smoking (i.e., smoking on ≥10 of the last 30 days) based on nationally representative data from the 1999-2008 NHANES. Year-to-year smoking initiation rates were estimated based on the proportion of respondents that began smoking ≤12 months prior to the survey; current menthol versus nonmenthol cigarette use was approximated based on usual cigarette (or brand) smoked, and analyses were conducted for the overall study population, as well as for demographic groups stratified by race/ethnicity, sex, current age and menthol status.

While somewhat underpowered (N=267), these analyses suggest no significant differences over time for rates of smoking initiation (i.e., transitioning to established smoking) among all new smokers, or after stratifying (all new smokers) by current cigarette type preference (menthol versus nonmenthol) (see Table 4-2; full demographics data is provided in Appendix Table 4-4). While currently unpublished, these data are readily available for confirmatory re-analysis from the original data source (CDC 2009).

Table 4-2. Analysis of time trends for smoking initiation* (NHANES, 1999-2008)

		All New Smokers[1]		New Smokers[1]			
				Nonmenthol		Menthol	
		Estimate	p-value	Estimate	p-value	Estimate	p-value
Total	Initiation rate[2]	0.40	0.01*	0.35	0.010*	0.05	0.38
	2 year change[3]	0.04	0.17	0.01	0.65	0.03	0.17
Sex							
Male	Initiation rate[2]	0.63	0.006*	0.55	0.012	0.08	0.30
	2 year change[3]	0.00	0.88	-0.02	0.60	0.01	0.56
Female	Initiation rate[2]	0.19	0.09	0.17	0.114	0.02	0.68
	2 year change[3]	0.07	0.05	0.03	0.24	0.04	0.08
Race/Ethnicity							
Non-Hispanic White	Initiation rate[2]	0.35	0.01*	0.33	0.03*	0.11	0.20
	2 year change[3]	0.05	0.09	0.02	0.46	0.00	0.80
Non-Hispanic Black	Initiation rate[2]	0.37	0.01*	0.07	0.13	0.18	0.09
	2 year change[3]	0.02	0.33	0.05	0.04*	0.04	0.18
Other	Initiation rate[2]	0.63	0.10	0.51	0.11	0.11	0.30
	2 year change[3]	0.00	0.99	-0.02	0.78	0.02	0.49
Age Group (years)							
12 to 17	Initiation rate[2]	1.41	0.03*	1.13	0.03*	0.28	0.07
	2 year change[3]	-0.08	0.51	-0.05	0.62	-0.03	0.38
18 to 24	Initiation rate[2]	0.84	0.10	0.64	0.15	0.21	0.54
	2 year change[3]	0.24	0.11	0.12	0.32	0.12	0.29
25 to 29	Initiation rate[2]	0.60	0.10	0.30	0.27	0.30	0.31
	2 year change[3]	-0.03	0.68	-0.02	0.74	-0.01	0.93
30 +	Initiation rate[2]	0.31	0.05	0.30	0.01*	0.01	0.82
	2 year change[3]	0.00	0.91	-0.02	0.35	0.02	0.25

[1] New smokers initiated smoking ≤12 months prior to survey participation, and reported using cigarettes ≥10 of the last 30 days.

[2] The average initiation rate is the y-intercept from the linear regression model. The p-value indicates whether the initiation rate is statistically significantly different from zero (* indicates $p<0.05$).

[3] The NHANES is implemented over a two year interval. The two year change indicates change in smoking initiation over the two year interval compared to the average initiation rate for each stratum. The p-value indicates whether the difference from the average initiation rate is statistically significant (* indicates $p<0.05$).

A borderline significant (p=0.0517) increase over time was suggested for the rate of smoking initiation among females overall, but there were no significant differences in smoking initiation rates among females or males currently smoking menthol compared to nonmenthol cigarettes.

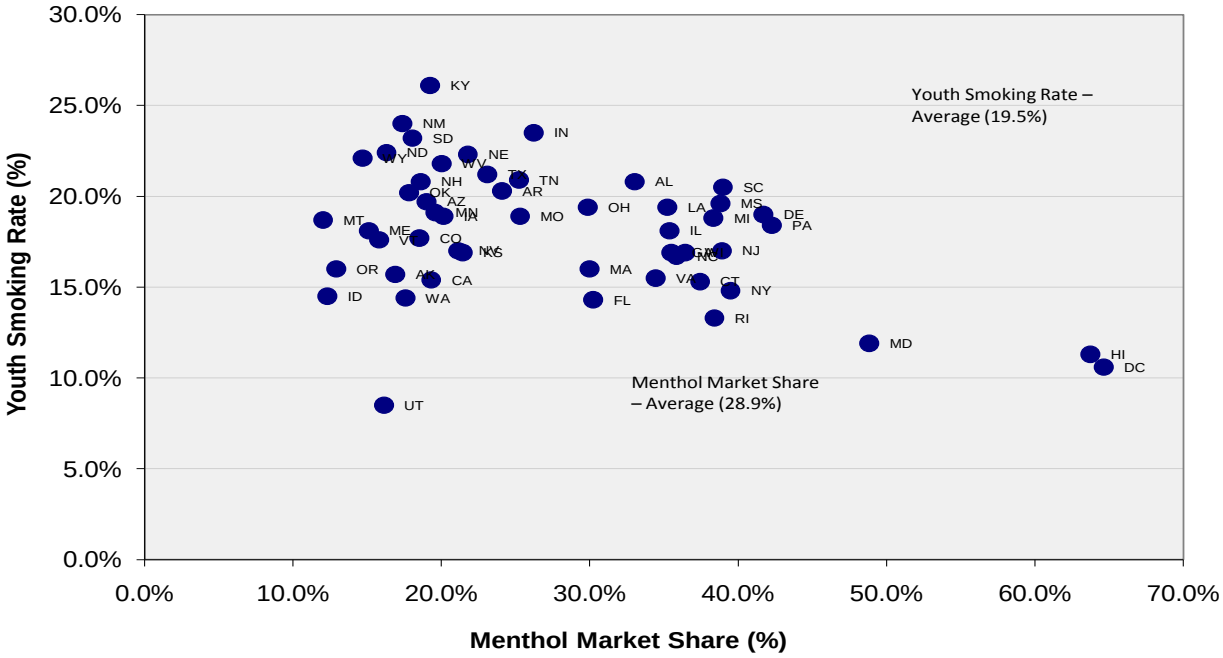
Likewise, there were no significant differences over time for smoking initiation rates among non-Hispanic Whites or respondents of "other" race/ethnicity, overall or after stratifying by current menthol or nonmenthol cigarette use; there was a small but significant increase for non-Hispanic Blacks currently smoking nonmenthol cigarettes (p=0.04).

Finally, there was a slight decline suggested over time for smoking initiation among respondents aged 12-17 and 25-29 years, overall and after stratifying by current menthol or nonmenthol cigarette use; however, there were no significant trends for smoking initiation rates by age at survey.

MENTHOL MARKET SHARE COMPARED TO YOUTH SMOKING RATES

Although an analysis of the preference for menthol cigarettes (expressed as menthol share-of-market) compared to youth smoking rates does not directly address the topic of initiation, it provides additional supportive evidence that youth smoking rates are not influenced by the availability of menthol. A state-by-state comparison of menthol share-of-market and youth smoking incidence in 2009 shows a poor correlation between the two (see Figure 4-2).

Figure 4-2. Menthol Market Share Compared to Youth Smoking Rates (2009)

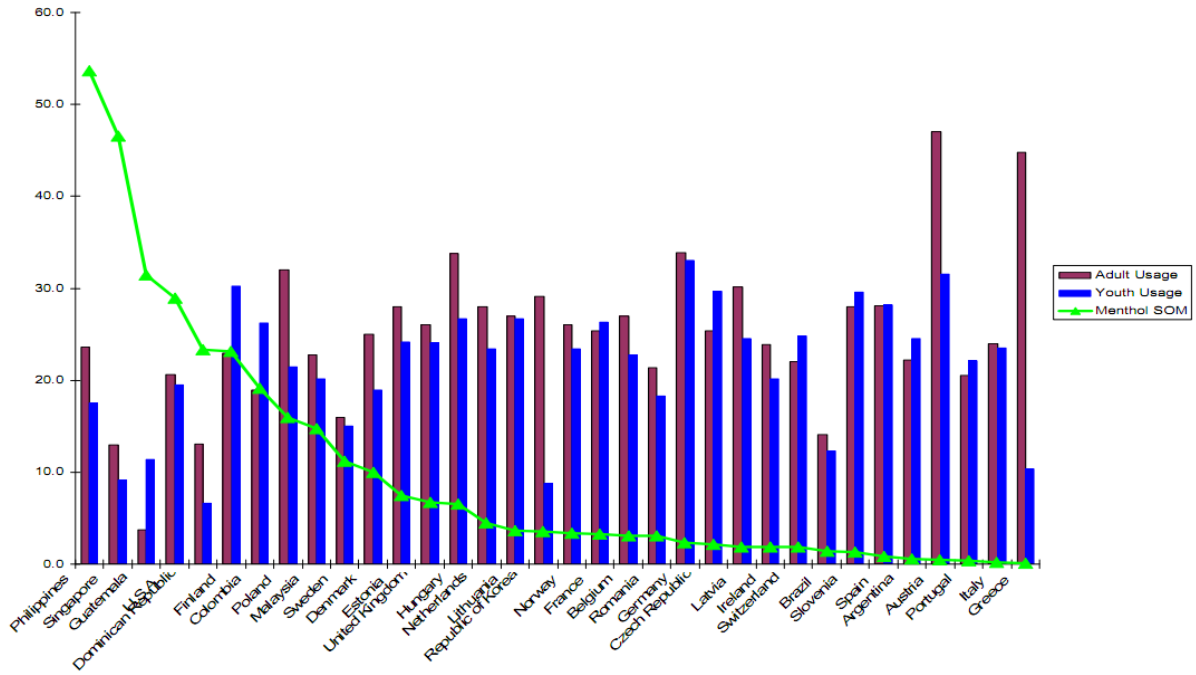


Sources: For youth smoking rates, Campaign for Tobacco-Free Kids (2010b); for menthol market share, Management Science Associates, Inc. (confidential industry data).

Notably, menthol market share is *inversely* related to youth smoking among all 50 states to a statistically significant degree. These data indicate that youth smoking rates are generally lower in states with higher menthol market share. There is no evidence that youth smoking rates in the U.S. would decline if menthol cigarettes were not available.

The lack of correlation between menthol market share and youth smoking rates is also indicated on a global basis. In many countries, the share of menthol is very low and, in some, menthol cigarettes are effectively unavailable. Many of these countries continue to have adult and youth smoking rates that are higher than those in the U.S. (see Figure 4-3). There is no relationship between menthol share and youth usage or smoking incidence globally. Absence of menthol cigarettes in the marketplace has not resulted in lower youth smoking rates.

Figure 4-3. Menthol Market Share Compared to Youth and Adult Smoking Rates - International



Sources: For smoking prevalence, WHO (2009); for menthol market share from foreign countries, A.C. Nielsen (confidential industry data); for menthol market share in U.S., Management Science Associates, Inc. (confidential industry data).

SWITCHING BETWEEN MENTHOL AND NONMENTHOL

It has been suggested during the TPSAC meetings that there could be an adverse population-level effect as a result of switching patterns among menthol and nonmenthol cigarette smokers. Data were presented to suggest that among African Americans (aged ≤40 years) participating in the Kaiser Permanente Cohort Study (1979-1986), nonmenthol smokers were ~4-times more likely (i.e., 14.6% vs. 3.6%) to switch to menthol cigarettes than menthol smokers were to switch to

nonmenthol cigarettes (Sidney et al. 1989). A second study analyzed data from a small population of smokers (N=178), and reported no difference in switching behavior based on menthol status (Pletcher et al. 2006). Neither study was based on a nationally representative population of smokers.

More recent data on switching behaviors were provided as an unpublished analysis during the November 2010 TPSAC meeting. In contrast to findings from the earlier studies, current smokers (aged 16-24 years) participating in the National Youth Smoking Cessation Survey (2003-2005) provided data to suggest that 15.0% (95% CI:10.8-19.2) of menthol smokers at baseline had switched to nonmenthol cigarettes after two years of follow-up, while 6.9% (95% CI:4.9-8.9) of nonmenthol smokers had switched to menthol cigarettes (Giovino unpublished). The likelihood of switching cigarette types was notably higher for White menthol and nonmenthol smokers (20.4% and 5.6%, respectively) than for other racial groups.

While the Giovino findings were presented as a nationally representative survey that included 1,045 youth smokers, only 58 menthol and 55 nonmenthol cigarette smokers actually reported switching during the 24-month study, i.e., ~90% of participants did not switch cigarette type. Despite the small numbers of menthol and nonmenthol smokers included in the analysis, and despite the low rate of switching, study findings were suggested to "lend further credence on menthol as a starter product for young smokers." These data have similarly been suggested to provide strong evidence that younger smokers are more likely to initiate smoking with mentholated products and progress to smoking nonmentholated varieties in a short period of time. Neither of these statements is supported by the available data.

In summary, available published data on reported switching between menthol and nonmenthol cigarettes is mixed and inconclusive, and does not support a conclusion that such switching, generally or within subpopulations of smokers, has any meaningful effect on the individual or population risks associated with smoking.

CONCLUSIONS

This review of the methodologically sound literature on menthol cigarette use and smoking initiation behaviors demonstrates that smoking initiation rates (i.e., transitioning from never smoking to established or daily smoking) have not significantly changed during the last decade; and, that current menthol cigarette smokers are more likely to report later onset of smoking initiation than nonmenthol smokers.

The weight of evidence provided by the highest-quality studies does not support the contention that menthol in cigarettes is causally associated with earlier initiation of smoking among the general population or among demographic groups. An analysis of available studies not designed to directly address cigarette type used during smoking initiation, along with several unpublished or very recently published studies, provides no evidence that menthol in cigarettes adversely effects smoking initiation or progression to regular smoking.

An analysis of available published data on reported switching between menthol and nonmenthol cigarettes is mixed and inconclusive, and does not support a conclusion that such switching, generally or within subpopulations of smokers, has any meaningful effect on the individual or population risks that attend smoking.

Although these data are suggestive of no causal relationship between menthol cigarette use and adverse smoking initiation behaviors, they do not directly address the cigarette type used to initiate smoking. Thus, using the Surgeon General's framework for assessing causality, it must be concluded that the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between menthol cigarette use and adverse smoking initiation behaviors.

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Table 4-3. Higher Quality Studies on Menthol Cigarette Smoking and Initiation Behaviors (N=4)

CITATION	OUTCOME STUDY TYPE	MEASURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Appleyard et al. 2001 United States	**Initiation of smoking** **Prevalence of menthol cigarette use among youth by race** Analysis of 2000 National Youth Tobacco Survey (NYTS) dataset comprising a nationally representative sample of 35,828 middle and high school students. This analysis focused on a nationally representative sample of Asian American youth (n=1,742) and a smaller sample of Hawaiian/Pacific Islander youth that is not nationally representative (n=487). Current smokers were defined as those reporting smoking a cigarette on at least one of the past 30 days. Participants were asked: "How old were you when you smoked a whole cigarette for the first time?" and "Is the brand of cigarettes that you usually smoked during the past 30 days mentholated?"	**Percentage of Youth Who Usually Smoke Mentholated Cigarettes** Asian American Hawaiian/Pacific-Islander African American Hispanic White	**Percentage Estimates (95% CI)** 58.4% (50.8-66.0) 46.1% (33.4-58.8) 73.6% (68.9-78.2) 51.3% (47.2-55.3) 32.2% (28.2-36.3)	NYTS 2000 data indicate that during the last year of high school, one third of Asian American youth are smokers. Of these youth, 60% report that their usual brand of cigarettes is a menthol brand. White and Hispanic youth are more likely to smoke menthol cigarettes in middle school than in high school; the opposite is true for Asian Americans, Hawaiian/Pacifc Islanders, and African Americans (specific percentages not provided).	The reported conclusions are supported by the study data. However, this study does not compare initiation among youth who smoke menthol cigarettes with those who smoke nonmenthols. It only presents data on percent of each race that initiated smoking (of any type) in grade, middle, and high school. Initiation was defined as age at which the subject first smoked a whole cigarette. This paper focuses on smoking among Asian American and Hawaiian/Pacific Islander youth.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 4-3. Higher Quality Studies on Menthol Cigarette Smoking and Initiation Behaviors (N=5) (Continued)

CITATION	OUTCOME STUDY TYPE	MEASURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Cubbin et al. 2010 United States	**Age of initiation** Cross-sectional analysis of data from the 2005 National Health Interview Survey Cancer Control Supplement. Analysis was based on 21,196 Black, Hispanic, and White women and men aged 25-64 years (current, former, and never-smokers who reported menthol status). Menthol use was defined as "usual cigarette brand was menthol." Age of initiation question was not provided in report. Cessation data are included in Table 5-3; dependence data are included in Table 5-4.	 **Menthol Smokers** Black women Black men Hispanic women Hispanic men White women White men **Nonmenthol Smokers** Black women Black men Hispanic women Hispanic men White women White men	**Predicted Mean Age of Initiation by Cigarette Type (99% CI)** 19.8 (18.9, 20.8) 18.6 (17.8, 19.5) 19.9 (18.0, 21.9) 20.5 (17.6, 23.5) 17.7 (17.0, 18.5) 17.2 (16.3, 18.1) 19.2 (17.4, 20.9) 17.5 (16.0, 19.1) 19.9 (18.2, 21.6) 18.6 (17.6, 19.7) 17.5 (17.1, 17.8) 17.1 (16.7, 17.5) Adjusted for age, income, and education.	The results do not support the hypothesis that menthol smokers initiate earlier. Among menthol smokers, White women and men started smoking earlier than their Black and Hispanic counterparts. There were no sex differences for any racial/ethnic group for either cigarette type. Within each demographic group, there were no differences in age of initiation by type of cigarette.	Conclusions are supported by study data. Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Authors do not have information on type of cigarette used at initiation (menthol vs. nonmenthol). Thus, "menthol smoker" refers to preference as an adult. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 4-3. Higher Quality Studies on Menthol Cigarette Smoking and Initiation Behaviors (N=5) (Continued)

CITATION	OUTCOME STUDY TYPE	MEASURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Fernander et al. 2010 United States	**Age of initiation** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 66,145 current smokers (age 18 and older). 16,294 smoked menthol, 46,899 smoked nonmenthol, and 2,952 did not respond. Menthol use was assessed by: "Is your usual cigarette brand menthol or nonmenthol?" Age of initiation was assessed by: "How old were you when you first started smoking cigarettes fairly regularly?" (answer given as age in years)	**Smoking Preference** Nonmenthol Menthol **Mean age of Initiation** **All Smokers** <18 ≥18 **Menthol Smokers** <18 ≥18 **Nonmenthol Smokers** <18 ≥18	**Adjusted Odds Ratio of Delayed Initiation (95% CI)** 1.0 (reference) 1.01 (1.00-1.01)* Adjusted for demographic and smoking variables. **Percent (95% CI)** 55.3 (±0.5) 44.7 (±0.5) 53.2 (±0.9) 46.8 (±0.9) 56.2 (±0.6) 43.8 (±0.6)	Menthol smokers in the U.S. tend to start smoking later than smokers of other types of cigarettes. This finding is suggestive only and requires further study.	Conclusions are supported by study data. Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Authors do not have information on type of cigarette used at initiation (menthol vs. nonmenthol). Thus, "menthol smoker" refers to preference as an adult. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 4-3. Higher Quality Studies on Menthol Cigarette Smoking and Initiation Behaviors (N=5) (Continued)

CITATION	OUTCOME STUDY TYPE	MEASURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Lawrence et al. 2010 United States	**Age at onset of regular smoking** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 69,193 current smokers (age 18 and older). 16,294 (25.8%) smoked menthol cigarettes and 46,899 (74.2%) smoked non-menthol cigarettes. Analyses were restricted to self-respondents who comprised 64.6% of the 2003 sample and 75.1% of the 2006/07 sample. Dependence data are included in Table 5-4.	<u>**Age at Onset of Regular Smoking**</u> **All Current Smokers** ≤14 15-17 18+ **Current Male Smokers** ≤14 15-17 18+ **Current Female Smokers** ≤14 15-17 18+	<u>**Adjusted Odds Ratio of Menthol Use (95% CI)**</u> 0.99 (0.90-1.09) 0.95 (0.89-1.02) 1.0 (reference) 1.10 (0.95-1.28) 1.01 (0.91-1.12) 1.00 (reference) 0.89 (0.79-1.01) 0.90 (0.82-0.99)** 1.0 (reference) Adjusted for other sociodemographic and smoking behavior variables that were significant in the bivariate regression analysis.	Race/ethnicity, sex and age are significant correlates of mentholated cigarette smoking among current smokers. The age of smoking onset was associated significantly with mentholated cigarette use among women but not among men or among the total sample.	Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Authors do not have information on type of cigarette used at initiation (menthol vs. nonmenthol). Thus, "menthol smoker" refers to preference as an adult. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 4-4. Distribution of Menthol versus Nonmenthol Current Cigarette Smoking[a] (NHANES, 1999-2008); Demographic Characteristics for New Smokers (Smoking for 1 year or less)

Variable	Survey Year	Frequency	Regular (nonmenthol)			Menthol			
			Weighted frequency[b]	Percent	95% CI[c]	Frequency	Weighted frequency[b]	Percent	95% CI[c]
Total	1999-2000	41	1,532,287	91.0	82.7, 99.3	9	151,989	9.0	0.7, 17.3
	2001-2002	47	1,470,946	65.5	51.2, 79.8	22	774,736	34.5	20.2, 48.8
	2003-2004	45	1,411,493	74.0	57.1, 90.8	17	496,282	26.0	9.2, 42.9
	2005-2006	38	1,106,681	73.9	55.3, 92.5	12	390,458	26.1	7.5, 44.7
	2007-2008	20	924,677	66.7	42.8, 90.5	16	462,253	33.3	9.5, 57.2
Sex									
Males	1999-2000	25	1,192,276	94.1	85.9, 100	3	74,565	5.9	0.0, 14.1
	2001-2002	32	907,469	69.9	52.1, 87.7	11	390,587	30.1	12.3, 47.9
	2003-2004	27	823,380	79.2	62.3, 96.2	8	215,595	20.8	3.8, 37.7
	2005-2006	21	616,418	75.4	40.4, 100	6	200,787	24.6	0.0, 59.6
	2007-2008	10	593,603	81.2	56.9, 100	7	137,361	18.8	0.0, 43.1
Females	1999-2000	16	340,011	81.5	50.4, 100	6	77,424	18.5	0.0, 49.6
	2001-2002	15	563,477	59.5	30.3, 88.6	11	384,149	40.5	11.4, 69.7
	2003-2004	18	588,113	67.7	38.7, 96.7	9	280,686	32.3	3.3, 61.3
	2005-2006	17	490,263	72.1	55.9, 88.3	6	189,670	27.9	11.7, 44.1
	2007-2008	10	331,075	50.5	29.8, 71.2	9	324,892	49.5	28.8, 70.2
Race/ethnicity									
Non-Hispanic White	1999-2000	15	1,205,419	100.0	100, 100			0.0	
	2001-2002	18	924,462	68.7	58.0, 79.5	8	420,488	31.3	20.5, 42.0
	2003-2004	19	988,547	79.9	53.6, 100	5	248,017	20.1	0.0, 46.4
	2005-2006	16	741,267	75.0	35.4, 100	4	247,224	25.0	0.0, 64.6
	2007-2008	13	826,011	78.7	52.0, 100	5	223,070	21.3	0.0, 48.0
Non-Hispanic Black	1999-2000	9	58,625	35.5	11.6, 59.5	6	106,442	64.5	40.5, 88.4
	2001-2002	10	67,471	33.0	0.0, 97.8	5	137,178	67.0	2.2, 100
	2003-2004	12	110,581	51.4	24.1, 78.7	7	104,624	48.6	21.3, 75.9
	2005-2006	4	78,781	49.1	48.2, 49.9	4	81,808	50.9	50.1, 51.8
	2007-2008	0	0	0.0	0	5	124,568	100.0	0

Table 4-4. Distribution of Menthol versus Nonmenthol Current Cigarette Smoking[a] (NHANES, 1999-2008); Demographic Characteristics for New Smokers (Smoking for 1 year or less) (Continued)

Variable	Survey Year	Frequency	Regular (nonmenthol)			Menthol			
			Weighted frequency[b]	Percent	95% CI[c]	Frequency	Weighted frequency[b]	Percent	95% CI[c]
Other	1999-2000	17	268,244	85.5	42.7, 100	3	45,547	14.5	0.0, 57.3
	2001-2002	19	479,013	68.8	35.4, 100	9	217,071	31.2	0.0, 64.6
	2003-2004	14	312,365	68.5	40.1, 96.9	5	143,641	31.5	3.1, 59.9
	2005-2006	18	286,633	82.4	54.6, 100	4	61,426	17.6	0.0, 45.4
	2007-2008	7	98,667	46.3	16.6, 75.9	6	114,615	53.7	24.1, 83.4
Current age (years)									
12 to 17	1999-2000	13	253,684	85.3	50.5, 100	2	43,606	14.7	0.0, 49.5
	2001-2002	14	191,992	74.9	74.0, 75.9	3	64,189	25.1	24.1, 26.0
	2003-2004	16	292,765	85.8	74.1, 97.4	4	48,578	14.2	2.6, 25.9
	2005-2006	13	292,094	81.2	44.7, 100	3	67,594	18.8	0.0, 55.3
	2007-2008	3	168,902	95.6	0	1	7,730	4.4	0
18 to 24	1999-2000	12	496,587	90.5	51.1, 100	2	52,033	9.5	0.0, 48.9
	2001-2002	11	258,171	41.3	11.0, 71.6	13	367,137	58.7	28.4, 89.0
	2003-2004	12	469,666	59.0	35.0, 83.0	10	326,663	41.0	17.0, 65.0
	2005-2006	10	270,980	72.0	0.0, 100	2	105,198	28.0	0.0, 100
	2007-2008	8	417,678	62.5	9.8, 100	8	251,046	37.5	0.0, 90.2
25 to 29	1999-2000	0				0			
	2001-2002	2	95,827	39.4		3	147,156	60.6	
	2003-2004	1	65,699	48.2	0.0, 100	1	70,492	51.8	0.0, 100
	2005-2006	1	67,531	67.6		2	32,322	32.4	
	2007-2008	1	24,863	24.8		1	75,392	75.2	
≥30	1999-2000	16	782,017	93.3	82.2, 100	5	56,350	6.7	0.0, 17.8
	2001-2002	20	924,955	82.5	69.6, 95.4	3	196,254	17.5	4.6, 30.4
	2003-2004	16	583,363	92.0	73.3, 100	2	50,549	8.0	0.0, 26.7
	2005-2006	14	476,076	72.0	59.3, 84.7	5	185,344	28.0	15.3, 40.7
	2007-2008	8	313,235	71.0	25.7, 100	6	128,085	29.0	0.0, 74.3

[a] Current cigarette smoking defined as having smoked on 10 or more of the last 30 days
[b] Frequency among survey respondents weighted to represent the population of the United States
[c] 95% confidence interval around estimated percentages

CHAPTER 5A.
MENTHOL IN CIGARETTES HAS NO MEANINGFUL IMPACT ON SMOKING CESSATION

Concern has been raised about whether it may be harder to quit smoking menthol cigarettes than nonmenthol cigarettes. Information on this issue comes from two major sources: nationally representative surveys and individual studies of specific populations. While these data sources provide some opportunities to examine adolescent smoking behaviors, virtually all of the existing data on smoking cessation come from studies of adults.

When assessing this literature, it is imperative to base conclusions on those studies that are methodologically sound. Many of the published studies have serious flaws or do not make appropriate inferences based on their findings. Although a limited number of studies may suggest that menthol cigarette smokers have lower rates of cessation compared to nonmenthol smokers, critical evaluation of the findings often indicates that the stated conclusions are not truly supported by the data. FDA must base its regulatory policy only on those studies that present strong science. And, because smoking cessation attempts are plagued by relapses, it is also essential that FDA give greatest weight to those studies that examine long-term successful cessation (6 months or longer) rather than short-term (past 7 days) cessation (Pierce and Gilpin 2003).

This chapter reviews what is known about the complex process of quitting smoking, discusses the most appropriate way to assess cessation, and reviews the available data, with emphasis placed on the most methodologically sound studies. Critical review of the best available studies indicates that individuals who smoke menthol cigarettes do not have significantly lower rates of quitting smoking compared to individuals who smoke nonmenthol cigarettes. Given the overall consistency of this lack of significant findings among the best studies, using the Surgeon General's framework for assessing causality leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol cigarette use and reduced smoking cessation. Further, as discussed later in Chapter 5B, the methodologically sound studies that compare nicotine or smoking dependence between menthol and nonmenthol smokers do not suggest that menthol cigarette smokers are any more dependent on or addicted to cigarettes. With respect to this endpoint, the **"evidence is suggestive of no causal relationship"** between menthol cigarette use and nicotine or smoking dependence. The rationale and scientific basis for these conclusions are discussed in further detail below.

FACTORS ASSOCIATED WITH SMOKING CESSATION

Quitting smoking is a difficult process. Every year, many smokers try to quit but most do not succeed. There has been much interest in identifying factors associated with making a quit attempt and with successful long-term smoking cessation. Research indicates that changing smoking behavior usually involves a series of stages (pre-contemplation, contemplation, and preparation), with each stage influenced by different factors. Many studies have evaluated individual aspects of smokers' characteristics to determine the predictors of successful smoking cessation, and have

identified a number of demographic, behavioral (including smoking behavior), psychological, and environmental factors that play a role.

A recent analysis by investigators associated with the Centers for Disease Control and Prevention (Lee and Kahende 2007) evaluated data from a representative sample of the U.S. Population (2000 National Health Interview Survey (NHIS)) to determine significant predictors of smoking cessation. The authors reported that successful quitters tended to have rules against smoking in their homes, were less likely to have switched to light cigarettes for health concerns, and were more likely to be aged ≥35 years, married or living with a partner, be non-Hispanic White, and have at least a college education.

There are ethnic and social differences in smoking cessation among various subgroups of the population. Although many factors are recognized to play a role in smoking cessation, major reviews of the literature have not identified menthol cigarette use as a significant factor. In recent years, researchers have raised the question of whether smoking menthol cigarettes adversely impacts cessation behavior or success in quitting.

DIFFICULTIES IN ASSESSING SMOKING CESSATION

Assessing smoking cessation is not straightforward. Studies differ in terms of how cessation is defined, study design and methodology used, and population evaluated. Therefore, it is not surprising that some studies provide more useful information about the relationship between menthol cigarette smoking and cessation than others.

It is especially important to clarify what is meant by smoking cessation. Many smokers who attempt to quit smoking manage only short-term abstinence; 75-80% of people who try to quit smoking will relapse within six months (NIDA 2009). Hence, the most valuable and definitive studies are those that define cessation as long-term abstention from smoking, which in practice can be defined as not smoking any cigarettes for six months or more.

The ideal study of whether smoking menthol cigarettes reduces a smoker's ability to quit would enroll a large cohort of subjects representative of smokers in the general smoking population (with over-sampling of African American smokers to ensure adequate numbers of menthol and nonmenthol smokers) and follow the cohort for a number of years. All participants would be re-contacted in person at 1-year intervals and would answer questions about their smoking, whether they had quit, and would provide a urine sample (for cotinine analysis[1]) to verify quitting. In addition, detailed information would be collected at baseline (and, for certain variables, at each annual visit) on sociodemographic factors, smoking behavior, nicotine dependence, alcohol consumption, body mass index, and health and respiratory symptoms. Such a study would make it possible to verify the stability of type of cigarette smoked (menthol versus nonmenthol), to assess long-term cessation, and to validate nonsmoking status at multiple points in time with urinary cotinine measurements. It would also enable researchers to adjust for numerous variables that might confound the association of menthol cigarette use and smoking cessation.

[1] Measurement of cotinine, a primary metabolite of nicotine that has a half-life of 16 to 18 hours and that can be detected in urine, saliva, or serum, provides a reliable means of determining smoking status and other tobacco product use or exposure over a period of 2 to 3 days (Montalto and Wells 2007).

None of the available studies meets all of these criteria. However, some of the studies are superior to others. Prospective studies that follow current smokers over time and document long-term cessation provide the most informative data. Second, cross-sectional studies of large, nationally representative populations with high participation rates that gather data on quit attempts and length of time without smoking are informative. Finally, studies of individuals in randomized trials of cessation medications or attending short-term smoking cessation clinics that employ multiple assistance strategies may have biased samples of subjects and, while they should be considered, cannot reflect quitting patterns in the general population (Freund et al. 1992).

BEST AVAILABLE SCIENCE WAS DETERMINED THROUGH A RIGOROUS PROCESS

As noted above, there are two potential sources of data on menthol smoking and cessation: nationally representative surveys and individual studies of specific populations. These sources of information are fairly consistent in showing that smokers of menthol cigarettes are no less likely to quit smoking than smokers of nonmenthol cigarettes.

At the request of the Lorillard Tobacco Company, Covance conducted a comprehensive search of the literature on the association between menthol cigarette use and smoking cessation and evaluated the identified studies for methodologic quality. The report of Covance's analysis has been provided to TPSAC and the findings were presented to TPSAC in summary fashion on February 10, 2011. An updated report from Covance (as referenced in Chapter 1) includes an evaluation of additional recent studies.

The Covance report describes in detail the rigorous and objective process used to identify and evaluate the available published literature. Briefly, a systematic search of the published literature was conducted to identify studies that addressed use of menthol cigarettes and a variety of cessation behaviors. Covance then evaluated these articles for methodologic quality (using criteria developed by FDA for Healthcare Research and Quality (Ranney et al. 2006)), and for ability to support inferences related to menthol. Quality ratings for these two measures included: poor, poor/fair, fair, fair/good, and good. The studies were categorized into three tiers as follows:

- Tier 1 studies were those rated by Covance as fair or better with respect to both overall quality and ability to support inferences related to menthol cigarette use;
- Tier 2 studies were those rated by Covance as fair or better with respect to overall quality, but lower than fair with respect to ability to support inferences related to menthol cigarette use; and
- Tier 3 studies were those rated by Covance as lower than fair with respect to both categories.

Twenty-five articles were identified that evaluated the relationship between menthol cigarette use and smoking cessation. Of these, Covance's ratings placed 15 studies in Tier 1, four studies in Tier 2, and six studies study in Tier 3, as shown below.

Table 5-1. Studies of Menthol Smoking and Cessation Behaviors (N=25) Quality Ratings by Covance

	Citation	Overall Quality Rating	Rating: Menthol Inferences
Tier 1	Alexander et al. 2010	Fair/Good	Fair/Good
	Berg et al. 2010	Fair	Fair
	Cubbin et al. 2010	Fair/Good	Fair/Good
	Fagan et al. 2010	Fair/Good	Fair
	Foulds et al. 2006	Fair	Fair
	Gandhi et al. 2009	Good	Fair
	Gundersen et al. 2009	Good	Fair/Good
	Hyland et al. 2002	Fair	Fair
	Murray et al. 2007	Fair/Good	Fair/Good
	Muscat et al. 2002	Fair	Fair
	Okuyemi et al. 2003	Fair	Fair
	Okuyemi et al. 2007	Good	Fair
	Pletcher et al. 2006	Good	Good
	Stahre et al. 2010	Fair	Fair
	Trinidad et al. 2010	Good	Fair/Good
Tier 2	Bover et al. 2008	Fair	Poor
	Cropsey et al. 2009	Good	Poor
	Fu et al. 2008	Fair	Poor
	Hymowitz et al. 1995	Fair	Poor
Tier 3	Ahijevych and Parsley 1999	Poor	Poor
	Fagan et al. 2007	Poor/Fair	Poor
	Harris et al. 2004	Poor	Poor
	Hersey et al. 2006	Poor/Fair	Poor/Fair
	Li et al. 2005	Poor	Poor
	Okuyemi et al. 2004	Poor	Poor

Tier 1 Studies on Menthol Cigarette Smoking and Cessation Behaviors

The 15 Tier 1 studies are considered to be the "best available science" for assessing the effect of menthol cigarette use and smoking cessation. These studies are summarized in Appendix Table 5-3 and are assessed below in a hierarchical fashion, as follows:

- Prospective or cross-sectional studies that assess long-term (at least 6 months) cessation: Hyland et al. 2002, Murray et al. 2007, Muscat et al. 2002, Pletcher et al. 2006.
- Cross-sectional studies of nationally representative populations with high participation rates that examined quit attempts and time since quitting: Alexander et al. 2010, Cubbin et al. 2010, Fagan et al. 2010, Gundersen et al. 2009, Stahre et al. 2010, Trinidad et al. 2010.
- Studies from smoking cessation clinics that examined only short-term (7-day) cessation: Berg et al. 2010, Foulds et al. 2006, Gandhi et al. 2009, Okuyemi et al. 2003, Okuyemi et al. 2007.

There are important differences between those studies in the first two categories and those in the third. Studies in the first two categories tend to be larger, have subjects that are more representative of the general smoking population, and evaluate spontaneous quitting (which is how the majority of people quit). Those studies in the third category tend to be smaller, enroll subjects that are not representative of the general smoking population (e.g., two are composed of only African American light smokers), and consist solely of individuals who sought smoking cessation assistance. Smokers who seek assistance from cessation clinics consider themselves to be more highly dependent than smokers who are representative of the general population (Etter et al. 2009). Based on the findings from the first two categories of studies combined, smoking menthol cigarettes does not adversely impact the ability to achieve long-term cessation compared to smoking nonmenthol cigarettes.

Prospective and Cross-Sectional Studies that Examined Long-Term Cessation

Four studies (three prospective and one cross-sectional) compared long-term cessation (6 months or more) among menthol and nonmenthol smokers. Three of these found no significant difference in long-term quitting among menthol compared to nonmenthol smokers (Hyland et al. 2002, Murray et al. 2007, Muscat et al. 2002). The fourth study (Pletcher et al. 2006) found no significant differences in 4 of 5 cessation measures, but there was a significant increase in the remaining measure, i.e, documented relapse, among menthol cigarette smokers. These studies are described briefly below:

> **Hyland et al. (2002)** examined the association between smoking menthol cigarettes and quitting in the COMMIT trial of smoking cessation. The study was large, involving a random sample of more than 13,000 smokers (aged 25-64 years) from a representative sample of households in ten U.S. communities. Approximately 24% of current smokers smoked menthol cigarettes at baseline in 1988. Multivariate regression was used to assess the association between baseline menthol cigarette use and cessation in 1993 (defined as not having smoked any cigarettes in the past 6 months). Nearly one-quarter of baseline smokers quit smoking between 1988 and 1993; the adjusted relative risk of quitting was no different for menthol compared to nonmenthol smokers (RR=1.00; 95% CI:0.90-1.11). The authors concluded that "Use of mentholated cigarettes was not associated with quitting." Furthermore, none of the race/ethnicity-specific analyses revealed any significant associations with menthol cigarette use.
>
> **Murray et al. (2007)** describe an analysis of data from the Lung Health Study, a clinical trial of smoking cessation that included 5,887 current smokers at baseline with mild to moderate airway obstruction. About 20% had smoked menthol cigarettes at baseline. Sustained quitting was assessed at five annual visits, and required biochemical confirmation as well as no recollection (at any annual visits) of any months in which ≥1 cigarette per day was smoked. After 5 years of follow-up, there were no significant differences in the proportion of quitters among menthol smokers compared to nonmenthol smokers for either men or women. Effects by race were not addressed. The authors concluded, "We found no difference in success at smoking cessation with or without menthol."
>
> **Muscat et al. (2002)** performed a cross-sectional analysis of smoking habits among 19,545 subjects in a case-control study of smoking and lung cancer. The investigators examined whether menthol cigarette use was associated with heavy smoking or quitting, and whether menthol cigarette use explained racial differences in these smoking behaviors. All subjects

were current or former smokers; of these, 3,005 smoked menthol cigarettes. Quitting was defined as not smoking ≥1 cigarette each day in the past year. The adjusted prevalence odds ratio of continued smoking versus quitting associated with menthol cigarette use was 1.1 (95% CI:1.0-1.2) for both Blacks and Whites. The authors concluded that "The risk of quitting was not associated with cigarette menthol flavor." Furthermore, menthol cigarette use was not associated with continued smoking among either Blacks or Whites.

Pletcher et al. (2006) analyzed data on subjects in the CARDIA cohort study who were smokers at baseline, and assessed cessation after 15 years of follow-up. There were no significant associations between menthol smoking and 4 of 5 measures of cessation examined, including not currently smoking, recent quit attempts, cessation if recent quit attempt and sustained cessation. The most stringent of these measures was sustained cessation, which was defined as no current smoking in the past 2 CARDIA exams (2 to 5 years apart) (OR=0.70; 95% CI:0.48-1.03). The only significant association was with an outcome referred to as documented relapse, i.e., smoking at one follow-up visit after self-reported quitting at a prior visit (OR=1.89, 95% CI:1.17-3.05). Based on this single finding, the authors concluded that " . . . menthol cigarettes may be harder to quit smoking." The limited number of European American menthol smokers and African American nonmenthol smokers in this cohort made it difficult to differentiate the independent effects of menthol cigarette use from the confounding influence of ethnicity.

Cross-Sectional Studies of Nationally Representative Populations

Some of the nationally representative surveys described in Chapter 2 (the Tobacco Use Supplement to the Current Population Survey and the National Health Interview Survey) provide data on menthol cigarette use and smoking cessation. Findings from these surveys are more generalizable to the overall smoking population than those from tobacco cessation clinics, and are thus informative with respect to potential population-level effects. It is important to recognize that cessation is typically assessed in these surveys as a "quit attempt" (which could be defined as not smoking for even one day in the past 12 months), which is much less rigorous than the long-term (at least six months) smoking cessation definition in the studies evaluated above. Six analyses of menthol cigarette smoking and quit attempts based on these nationally representative surveys are summarized below.

Tobacco Use Supplement to the Current Population Survey (TUS-CPS)

Three analyses were based on the TUS-CPS; two found no evidence that quitting behaviors differ significantly between menthol and nonmenthol smokers.

Alexander et al. (2010) assessed life-time attempts to quit (defined as ever stopped smoking for ≥1 day) among 30,176 current smokers in the 2006/07 TUS-CPS. After controlling for occupational status and work-place cessation policies, menthol smokers did not differ significantly from nonmenthol smokers in life-time attempts to quit smoking (OR 0.98; CI:0.83-1.15).

Fagan et al. (2010) assessed slightly different cessation measures (i.e., was there a quit attempt of ≥1 day in past 12 months; abstinence >2 weeks vs. ≤2 weeks; and intent to quit in the next 30 days) among 46,273 adults who were current daily smokers in the 2003 and 2006/07 TUS-CPS.

Multivariate models did not show significant associations between usual cigarette type (menthol versus nonmenthol) and any of the three cessation outcomes evaluated. The authors concluded that their data do not support the hypothesis that menthol smokers experience greater difficulty quitting.

Trinidad et al. (2010) conducted a third analysis of data from the TUS-CPS, examining menthol cigarette use and smoking cessation among adults (aged 20-65 years) of different racial/ethnic groups (African American, Asian American/Pacific Islander, Hispanic/Latino, Native American, non-Hispanic White) in the 2003 and 2006/07 surveys. Researchers examined pre-quitting behaviors among current smokers and successful cessation (being quit for ≥6 months) among former smokers. Findings from adjusted logistic regression models indicated that African Americans and Hispanic/Latinos (but not other races) who smoked menthol cigarettes were significantly more likely to be seriously considering quitting in the next 6 months and to have a positive estimation of quitting successfully compared to those who smoked nonmenthol cigarettes. With respect to cessation, across race/ethnic groups, former regular smokers of menthol cigarettes were less likely to have experienced long-term quitting success.

National Health Interview Survey (NHIS)

Three analyses based on the 2005 NHIS compared long-term cessation among menthol and nonmenthol smokers; one of these found no evidence that menthol smokers have a harder time quitting than nonmenthol smokers.

Cubbin et al. (2010) analyzed 21,196 adults who reported their menthol status by race (Black, White, Hispanic) and sex; they found no significant differences by cigarette type in percent making a quit attempt in the past year. The only significant difference was in time since quitting in one racial subgroup; White women who smoked menthol cigarettes reported longer cessation than those who smoked nonmenthol cigarettes (15 vs. 12.5 years; $p<0.01$).

The two other analyses based on the 2005 NHIS reported some findings that suggested there could be poorer cessation outcomes among non-White menthol smokers.

Stahre et al. (2010) examined the population quit ratio (i.e., total number of former smokers divided by total life-time smokers), and use of quit aids among 12,004 current or former adult smokers. Curiously, the sample population was not weighted to provide nationally representative estimates, likely limiting the generalizability of study findings to the overall population of smokers. There were no significant differences in quit ratios for menthol versus nonmenthol smokers among Whites, Asian Americans or Hispanics, but there was for African Americans. Regression analysis showed a significant interaction between menthol status and African American race, such that African American menthol smokers were significantly less likely than White nonmenthol smokers to have quit smoking (AOR 0.72; CI:0.53-0.97).

Gundersen et al. (2009) analyzed 7,815 current and former smokers and found that the association between menthol smoking and cessation was different for Whites compared to non-Whites (Blacks and Hispanics combined). Non-White menthol cigarette smokers were significantly less likely to have stopped smoking compared to non-White nonmenthol smokers (OR=0.55; 95% CI:0.43-0.71), whereas White menthol smokers were significantly more likely to have quit compared to White nonmenthol smokers (OR=1.17; 95% CI:1.00-1.36). Study findings assumed that a causal connection between menthol smoking and an ability to quit operated in an opposite direction for

Whites and non-Whites, an assumption that is not supported by a plausible mechanism. When races were examined individually, there was no difference in cessation between Black menthol and nonmenthol smokers, and Hispanic menthol smokers were significantly less likely to have quit than Hispanic nonmenthol smokers. The findings from these two analyses suggest that variables other than menthol (e.g., socioeconomic status, metabolic issues, uncontrolled confounding) may account for the race-associated differences found in different analyses of the same survey data.

Studies from Smoking Cessation Clinics with Short-Term Cessation Measures

Five studies conducted in smoking cessation and tobacco treatment clinics provide relevant data on menthol and nonmenthol smokers. The clinic-based studies were all designed to assess the efficacy of various pharmacological and other therapies in promoting cessation, but not to evaluate menthol in a controlled fashion as an independent variable. In addition, these studies have important differences from those using more representative sample populations. The following studies involved specific groups of subjects who sought help in quitting smoking and thus are not representative of the general population; they followed the subjects for shorter durations (4 weeks to 26 weeks); and they defined cessation much less stringently (i.e., only 7 days of abstinence). These studies generally found no difference in rates of cessation for menthol and nonmenthol smokers, although one study (Gandhi et al. 2009) showed that African Americans and Latinos who smoked menthol cigarettes have reduced success in quitting compared with nonmenthol smokers in the same racial groups.

Berg et al. (2010) investigated factors predicting smoking reduction among Black light smokers (≤10 cigarettes/day) enrolled in a 26-week cessation trial. Quitters were defined based on self-reported cessation verified by salivary cotinine concentrations of ≤20 ng/mL (which indicates only that there was no tobacco use or nicotine replacement therapy in the past 2-3 days). The authors did not draw specific conclusions about the relationship between menthol smoking and cessation, even though 81% of the subjects smoked menthol cigarettes. However, examination of the data shows that smoking menthol cigarettes did not significantly affect either reduction of smoking or cessation in this study group.

Foulds et al. (2006) evaluated a cohort of the first 1,021 patients attending a free tobacco treatment clinic who made a quit attempt (41% of whom smoked menthol cigarettes).[2] Logistic regression was used to identify factors associated with abstinence at 4 weeks and 6 months of follow-up. Cessation was defined as not having used any tobacco in the past 7 days. Although the authors concluded that, "Those smoking nonmenthol cigarettes at assessment showed a trend toward being more likely to be abstinent" at 4 weeks (AOR=1.359; 95% CI:0.996-1.856, p=0.053), this finding was not significant. Cigarette type was not associated with 26 week abstinence. This study shows why it is important to follow subjects for more than just a few weeks, and why it is important to look beyond the stated conclusions to the actual data. Results were not presented by race but 66% of the subjects were White. It should be noted that one-third of subjects included in this study were lost to follow-up.

[2] Foulds et al. (2006), Gandhi et al. (2009) and Bover et al. (2008) all reported on consecutive patients from the same smoking cessation clinic. Given that the enrollment period overlapped, the study samples likely contained some subset of identical patients. Thus, these three studies should not be considered as entirely independent analyses.

Gandhi et al. (2009) evaluated quit rates among 1,688 consecutive patients (White, African American and Latino smokers) at a tobacco treatment clinic.[2] Cessation, which was defined as 7-day point prevalence, was assessed at 4 weeks and 6 months. The authors concluded that, despite smoking fewer cigarettes per day, African American and Latino menthol smokers had reduced success in quitting compared to nonmenthol smokers of the same racial groups. For African Americans, the odds ratio for abstinence at 6 months associated with menthol smoking (compared to nonmenthol smoking) was 0.48 (95% CI:0.25-0.90); for Latinos, it was 0.64 (95% CI:0.20-1.80). However, among Whites, who made up the majority (64%) of the study group, menthol smokers were no less likely to quit than nonmenthol smokers (OR=1.0; 95% CI:0.80-1.40). It should be noted that, at six months, 42% of subjects had been lost to follow-up.

Okuyemi et al. (2003) reported that African American menthol smokers had lower cessation rates after 6 weeks of treatment with bupropion. The randomized clinical trial involved 600 African Americans, 471 of whom were menthol smokers. Cessation was defined as 7 days of abstinence. While there was a significant difference between menthol and nonmenthol smokers in terms of percent abstinent at 6 weeks (p=0.006), that difference had disappeared by the terminal 6-month evaluation (p=0.21). Thus, if the reported effect of menthol on buproprion efficacy among African American smokers is real, it appears to be only transient in nature. Furthermore, abstinence rates did not differ by menthol status among those who received placebo, suggesting that menthol added to cigarettes does not influence spontaneous cessation (not aided by pharmaceuticals).

Okuyemi et al. (2007) reported that among African American light smokers (≤10 cigarettes/day), use of menthol cigarettes is associated with lower cessation rates. Researchers performed a secondary analysis of data from a randomized clinical trial involving 755 African Americans, 82% of whom were menthol smokers. Cessation was defined as 7 days of abstinence. At 26 weeks, 11.2% of menthol smokers versus 18.8% of nonmenthol smokers had achieved abstinence (p=0.015). However, these percentages are not adjusted, even though there were significant differences between menthol and nonmenthol smokers in potentially confounding factors, including age and duration of smoking in years. Other analyses that considered relevant confounders did not show a significant difference in cessation success for menthol compared with nonmenthol cigarette smokers. For example, adjusted logistic regression models stratified by age group (aged <50 and ≥50 years) did not indicate that menthol versus nonmenthol status was significantly associated with abstinence.

Tier 2 Studies on Menthol Smoking and Cessation Behaviors

Four Tier 2 studies address this topic but have major weaknesses that preclude drawing sound conclusions. The studies are mentioned here briefly because they have been discussed at the TPSAC meetings.

- **Bover et al. (2008)** found that menthol smoking was not a significant predictor of abstinence at 26 weeks among a group of smokers who sought treatment at a tobacco dependence clinic.[2] The study suffered from a high attrition rate (~40%), and was not designed to evaluate menthol smoking and cessation directly.
- **Cropsey et al. (2009)** found that smoking menthol cigarettes was not associated with different quit rates among Black and White female prisoners. The study had a high

attrition rate, and the results of this study cannot be generalized to a non-prison population.

- **Fu et al. (2008)** found pharmacotherapy was more likely to be effective among menthol than nonmenthol cigarette smokers, with no difference in cessation success associated with cigarette type among patients randomized to usual care.
- **Hymowitz et al. (1995)** analyzed data from the COMMIT trial by race/ethnicity, but did not attempt to link menthol smoking status with cessation outcomes.

Six Tier 3 studies (**Ahijevych and Parsley 1999, Fagan et al. 2007**, **Harris et al. 2004, Hersey et al. 2006, Li et al. 2005**, **Okuyemi et al. 2004**) were all rated poor overall and in their ability to draw menthol inferences, and are not discussed in detail here.

Unpublished Analyses Presented to TPSAC

In July 2010 and January 2011, a number of unpublished analyses that addressed menthol cigarette use and smoking cessation were presented to TPSAC. Although these analyses have not undergone peer review, the authors' reported conclusions are mentioned here briefly:

- **Curtin (unpublished)** analyzed data from several large surveys and reported that:
  - According to the 2005/06 and 2007/08 NHANES, adolescent (aged 12-17 years) menthol cigarette smokers overall were no less likely to have reported past-year cessation attempts than nonmenthol smokers (49.2% vs. 53.3%, respectively; p=0.72). Similarly, there were no significant differences in the likelihood of attempting to quit smoking for menthol compared to nonmenthol cigarette smokers when stratified by race/ethnicity or sex.
  - According to the 2005 NHIS, adult menthol cigarette smokers overall were significantly more likely to have reported any quit attempt during the past 12 months compared to nonmenthol smokers (48.6% vs. 41.0%, respectively; p<0.001). Stratifying by race/ethnicity, sex, or current age indicated that non-Hispanic Black female, and younger (aged 18-24 years) menthol smokers were significantly more likely to have reported any past-year quit attempt compared to nonmenthol smokers (49.1% vs. 43.6%, p=0.02; 53.4% vs. 38.6%, p<0.0001; and 57.9% vs. 46.4%, p=0.01). In regression models that controlled for the combination of race/ethnicity, sex and current age, the higher odds of reporting any past-year quit attempt associated with menthol compared to nonmenthol cigarette smoking was significant (OR 1.23; 95% CI:1.06-1.44; p=0.007).
  - According to the 2007 NYTS, adolescent (aged 9-21 years) menthol cigarette smokers overall were no less likely to have reported past-year cessation attempts than nonmenthol smokers (59.6% vs. 56.1%, respectively; p=0.27). Similarly, there were no significant differences in the likelihood of attempting to quit smoking for menthol compared to nonmenthol cigarette smokers when stratified by race/ethnicity or sex.
- **Delnevo et al. (unpublished)** attempted to replicate Gundersen et al. (2009) by examining menthol smoking and cessation in the 2003 and 2006/07 TUS-CPS. It was reported that menthol smokers were significantly less likely to have quit smoking than nonmenthol smokers, and that the effect was more pronounced among Blacks and Puerto Ricans.
- **Hyland and Kasza (unpublished)** evaluated data from the International Tobacco Control Four Country Survey and found that making a quit attempt, successful cessation and successful cessation among those making a quit attempt were generally similar among

menthol and nonmenthol smokers, although there were exceptions for some racial/ethnic/sex subgroups (Hispanic menthol smokers may be more dependent than Hispanic nonmenthol smokers).

- **Hyland and Rivard (unpublished)** evaluated data from the COMMIT trial of smoking cessation and reported that menthol smokers were as likely as nonmenthol smokers to try to quit smoking and to be successful in quitting.
- **King et al. (unpublished)** evaluated data from a clinical trial of naltrexone/nicotine patch/counseling in smoking cessation and found that menthol status, race, and medication interacted to affect outcomes. Among Whites, menthol smoking had no effect on quit rates; however, among African Americans, menthol users had lower quit rates than nonmenthol users when given standard treatment of patch and counseling, which was reversed with the addition of naltrexone.
- **Reitzel (a) (unpublished)** analyzed data from the Project CARE longitudinal cohort study and found that menthol cigarette use was not significantly related to continuous abstinence from smoking through week 26 of follow-up.
- **Reitzel (b) (unpublished)** analyzed data from the BREAK FREE clinical trial of smoking cessation and found that menthol cigarette smokers had higher rates of continuous smoking abstinence than nonmenthol smokers at follow-up, but that these differences were not significant.
- **Reitzel (c) (unpublished)** analyzed data from the MOM clinical trial of smoking relapse prevention among post-partum women and found that menthol cigarette smokers had lower rates of continuous abstinence from smoking than nonmenthol smokers at follow-up but that these differences were not significant. White menthol smokers were less likely to maintain continuous smoking abstinence than White nonmenthol smokers, but the number of subjects in these analyses was small.
- **Unger et al. (unpublished)** analyzed intention to quit smoking in a community-based survey of African American smokers and found no significant differences between menthol, nonmenthol and combined-type smokers. Certain subgroups of African American menthol smokers (light smokers and those with a high school education) may be less likely to express intentions to quit than nonmenthol smokers in these subgroups.

MENTHOL CIGARETTES AND CESSATION BY RACE

As noted above, 7 of the 15 Tier 1 studies presented cessation results by race. Three studies found that menthol smoking was not significantly associated with lower cessation rates among any of the races examined. Hyland et al. (2002) and Cubbin et al. (2010) examined Whites, Blacks and Hispanics, while Muscat et al. (2002) examined Blacks and Whites.

Three studies reported different effects of menthol by race. Gandhi et al. (2009) found that, despite smoking fewer cigarettes per day, African American and Latino menthol smokers had reduced success in quitting compared to nonmenthol smokers of the same race. This was not true for White menthol smokers. Gundersen et al. (2009) and Stahre et al. (2010) both examined the data from the NHIS, and found some evidence that non-White menthol smokers had poorer cessation outcomes than nonmenthol smokers (contradicting the findings of Cubbin et al. 2010, cited above).

The seventh study (Trinidad et al. 2010) examined non-Hispanic Whites, African Americans, Hispanics, Asian American/Pacific Islanders and Native American/Alaska natives. Findings suggested that across all of these racial/ethnic groups, individuals who used to regularly smoke mentholated cigarettes were less likely to have experienced long-term quitting success.

The remaining eight studies included only African American subjects (Berg et al. 2010, Okuyemi et al. 2003, Okeuyemi et al. 2007) or did not present results by race (Alexander et al. 2010, Fagan et al. 2010, Foulds et al. 2006, Murray et al. 2007, Pletcher et al. 2006).

MENTHOL CIGARETTES AND CESSATION AMONG YOUNG PEOPLE

The published literature does not directly address smoking cessation among young people. However, some relevant information can be gleaned from the unpublished analyses of the nationally representative surveys by Curtin (unpublished) mentioned above. In the NHANES, adolescent (aged 12-17 years) menthol cigarette smokers overall were no less likely to have reported past-year cessation attempts than nonmenthol smokers (49.2% vs. 53.3%, respectively; p=0.72). In the 2005 NHIS, younger (aged 18-24 years) menthol cigarette smokers were significantly more likely to have reported any past-year quit attempt compared to nonmenthol smokers (57.9% vs. 46.4%, p=0.01). Finally, in the 2007 NYTS, adolescent (aged 9-21 years) menthol cigarette smokers overall were no less likely to have reported past-year cessation attempts than nonmenthol smokers (59.6% vs. 56.1%, respectively; p=0.27).

CONCLUSION

This review of the methodologically sound (Tier 1) literature on menthol cigarette smoking and cessation demonstrates that the most relevant studies, i.e., those that address successful long-term quitting, do not indicate that smokers of menthol cigarettes are significantly less likely to quit than are smokers of nonmenthol cigarettes. There is a sufficient number of high-quality studies that consistently find that menthol cigarette use has no meaningful impact on smoking cessation. Three of the cross-sectional studies, two of which only examined quit attempts on a single day (Gundersen et al. 2009, Stahre et al. 2010, Trinidad et al. 2010) and one of the three analyses of basically the same smoking cessation clinic population (Gandhi et al. 2009) reported some findings that suggested that among non-Whites, menthol smokers were less likely to be former smokers than nonmenthol smokers. However, if menthol is a factor that affects the ability to quit smoking, one would expect to see consistency among White and non-White subjects. This race-associated inconsistency suggests that some other factor affects the ability to quit, rather than menthol itself.

Thus, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between menthol cigarette use and success in smoking cessation. This is based on a consideration and synthesis of findings from a number of large, methodologically sound investigations of prospective cohorts and cross-sectional analyses of nationally representative population samples. The findings from these studies are more consistent and relevant than are the findings derived from, for example, smoking cessation clinic studies designed to evaluate various quit-smoking therapies.

CHAPTER 5B.
MENTHOL IN CIGARETTES HAS NO MEANINGFUL IMPACT ON NICOTINE DEPENDENCE

An important element of cessation is the degree of a smoker's dependence on nicotine. The more heavily dependent on nicotine an individual is, the harder it may be for that individual to quit. Dependence has been assessed by a variety of measures. While the best measures for assessing dependence have been debated, use of multiple measures or a composite measure is generally considered to be preferable to any single measure. For example, the Fagerström Test of Nicotine Dependence (FTND) is a reliable, validated and widely accepted composite measure of nicotine dependence (Heatherton et al. 1991). The FTND instrument provides an overall score based on 6 items:

- How soon after you wake up do you smoke your first cigarette?
- Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?
- Which cigarette would you hate most to give up?
- How many cigarettes per day do you smoke?
- Do you smoke more frequently during the first hours after awakening than during the rest of the day?
- Do you smoke if you are so ill that you are in bed most of the day?

The FTND has been correlated with biochemical measures of smoking intensity, including concentrations of exhaled air carbon monoxide, salivary cotinine and salivary nicotine. Also useful is the 10-item Hooked on Nicotine Checklist (HONC), a reliable and valid measure of loss of autonomy over nicotine that has been used for screening adolescents for nicotine dependence (DiFranza et al. 2002).

The methodologically sound studies that compare nicotine dependence between menthol and nonmenthol cigarette smokers do not suggest that menthol smokers are any more addicted to smoking. Using the Surgeon General's framework for assessing causality leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol cigarette use and nicotine dependence.

BEST AVAILABLE SCIENCE WAS DETERMINED THROUGH A RIGOROUS PROCESS

Relevant studies on menthol cigarette use and nicotine dependence were identified by Covance through the process described in Chapters 4 and 5A. Briefly, a systematic search of the published literature was conducted and Covance evaluated the relevant articles for methodologic quality (using criteria developed by FDA for Healthcare Research and Quality) and for ability to support inferences related to menthol. Rating choices for these two measures of study quality included: poor, poor/fair, fair, fair/good, and good. The studies were categorized into three tiers as follows:

- Tier 1 studies were those rated by Covance as fair or better with respect to both overall quality and ability to support inferences related to menthol cigarette use;
- Tier 2 studies were those rated by Covance as fair or better with respect to overall quality, but lower than fair with respect to ability to support inferences related to menthol cigarette use; and
- Tier 3 studies were those rated by Covance as lower than fair with respect to both categories.

Twenty-two articles were identified that evaluated the relationship between menthol cigarette use and nicotine dependence. Of these, Covance's ratings placed 10 studies in Tier 1, five studies in Tier 2, and seven studies study in Tier 3, as shown below.

Table 5-2. Studies of Menthol Smoking and Nicotine Dependence (N=22) Quality Ratings by Covance

	Citation[1]	Overall Quality Rating	Rating: Menthol Inferences
Tier 1	Ahijevych and Ford 2010	Fair/Good	Fair
	Cubbin et al. 2010	Fair/Good	Fair/Good
	DiFranza et al. 2004	Fair	Fair
	Fagan et al. 2010	Fair/Good	Fair
	Hyland et al. 2002	Fair	Fair
	Lawrence et al. 2010	Good	Good
	Mendiondo et al. 2010	Fair/Good	Fair
	Moolchan et al. 2006	Good	Good
	Muhammad-Kah et al. 2010	Fair/Good	Fair/Good
	Muscat et al. 2002	Fair	Fair
Tier 2	Ahijevych and Wewers 1993	Fair	Poor
	Ahijevych et al. 2002	Fair	Poor
	Bover et al. 2008	Fair	Poor
	Hymowitz et al. 1995	Fair	Poor
	Muscat et al. 2009	Fair	Poor
Tier 3	Ahijevych and Parsley 1999	Poor	Poor
	Collins and Moolchan 2006	Poor	Poor
	Hersey et al. 2006	Poor/Fair	Poor/Fair
	Li et al. 2005	Poor	Poor
	Muilenburg and Legge 2008	Poor	Poor
	Okuyemi et al. 2004	Poor	Poor
	Wackowski and Delnevo 2007	Poor/Fair	Poor

[1] A number of additional studies provide data on measures of dependence (e.g., CPD, TTFC); however, as these data were provided as measures at baseline and dependence was not considered to be a primary outcome, they are not included here. These studies include Stahre et al. 2010, Fu et al. 2008, Gandhi et al. 2009, Murray et al. 2007 and Mustonen et al. 2005.

Tier 1 Studies on Menthol Smoking and Nicotine Dependence

The 10 Tier 1 studies are considered to be the "best available science" for assessing the effect of menthol cigarette use on nicotine dependence. These studies are described below and summarized

in Appendix Table 5-4. Studies encompass a variety of designs, including the large, well-conducted Total Exposure Study, a prospective study of the COMMIT trial, 5 cross-sectional analyses of nationally representative surveys (NHIS and TUS-CPS), and analyses of data from smoking cessation clinics. These 10 studies assessed subjects using the best measures of dependence (TTFC, CPD, FTND and/or HONC), and consistently indicated that menthol cigarette smokers are not significantly more dependent on nicotine than nonmenthol smokers.

Ahijevych and Ford (2010) analyzed data on nicotine dependence from daily and non-daily young adult smokers (aged 18-24 years) in the 2006/07 TUS-CPS. Among daily smokers (N=2,241), there were no significant associations between menthol brand preference and either TTFC or CPD. Among non-daily smokers (N=688), menthol brand preference was not associated with cigarettes smoked per day but was associated with shorter time to first cigarette. Although the findings were mixed for the dependence outcomes examined, the authors concluded that, "Young adult non-daily smokers who preferred menthol cigarettes were significantly more dependent than those who preferred nonmenthol cigarettes, as shown by the shorter TTFC."

Cubbin et al. (2010) conducted a cross-sectional analysis of 21,196 adults from the 2005 NHIS and Cancer Control Supplement who reported their menthol status by race and sex. Menthol and nonmenthol smokers were compared on predicted mean CPD after adjustment for age, income and education. The authors found no significant differences for any group (stratified by race and sex) in the number of cigarettes smoked per day by cigarette type (menthol versus nonmenthol). The authors concluded that: "The results do not suggest that menthol smokers smoke more than nonmenthol smokers."

DiFranza et al. (2004) conducted a "retrospective/prospective" longitudinal analysis of seventh graders followed for 30 months as part of the Development and Assessment of Nicotine Dependence in Youth Study. The subjects were interviewed three times per year for three years, with the goal of understanding whether the recalled reaction to a first cigarette was predictive of later nicotine dependence. This analysis focused on 237 subjects who reported that they had inhaled cigarette smoke; only about half of them could recall whether the first cigarette they had smoked was menthol or nonmenthol. The authors found that reactions to the initial smoking experience were unrelated to cigarette mentholation; reactions were likewise unrelated to sex, cigarette brand or strength of cigarette. Only 59 subjects had smoked enough to establish a favorite brand; 42% indicated Newport as a favorite brand. The strength of the addiction, as measured by the HONC, did not differ according to the favorite brand, brand strength or menthol content. The mean HONC score was 6.0 for subjects whose favorite brand was menthol and 6.0 for subjects whose favorite brand was nonmenthol.

This study has a number of important strengths, including its prospective nature, the fact that subjects were not expected to recall experiences from a long time ago, the use of an unselected population, and the inclusion of a validated measure of dependence. The study also had a number of limitations, including a small sample size, the fact that it focused on a variety of subjective symptoms, the fact that half of the subjects could not recall whether the first cigarette they smoked was menthol or nonmenthol, and the small number of African American (i.e., 4% of subjects).

Fagan et al. (2010) analyzed 46,273 current adult daily smokers in the 2003 and 2006/07 TUS-CPS to determine whether there was association between menthol cigarette smoking and increased CPD or decreased TTFC after waking. Study data indicated that menthol smokers reported smoking

significantly fewer CPD than nonmenthol smokers (13.05 vs. 15.01, $p<0.001$). Comparisons of TTFC were made between menthol and nonmenthol smokers stratified by cigarettes smoked per day (≤5, 6-10, 11-19, ≥20). In general, there were no significant differences between menthol and nonmenthol smokers, regardless of whether TTFC was defined as ≤5 minutes or ≤30 minutes after waking. A single significant difference suggested that menthol smokers who smoked 6-10 CPD were more likely than nonmenthol smokers of 6-10 CPD to have their first cigarette within 5 minutes after waking (OR 1.22; 95% CI:1.05-1.43). The authors focused on this one marginally significant finding to conclude that menthol smokers who reported consuming 6-10 CPD show greater signs of nicotine dependence than comparable nonmenthol smokers. However, it is inappropriate to focus on this single finding when the overall pattern of results suggests no difference in TTFC between menthol and nonmenthol smokers. The authors acknowledge that the effect was not dose-dependent, as the odds ratios for TTFC after waking did not increase as smoking intensity increased for menthol smokers.

Hyland et al. (2002) examined the association between smoking menthol cigarettes and measures of nicotine dependence in the COMMIT trial of smoking cessation. The study involved a random sample of more than 13,000 smokers (aged 25-64 years) from a representative sample of households in ten U.S. communities. Data were collected first in 1988 and then 5 years later in 1993. Multivariate regression was used to assess the association between menthol cigarette use in 1988 and TTFC as reported in 1988. Overall, menthol smokers reported a significantly longer TTFC than nonmenthol smokers; this difference was no longer significant when the analyses were stratified by race. Linear regression was used to assess the association between menthol use in 1988 and estimated change in cigarettes smoked per day in 1993. There were no significant associations between menthol use and change in number of cigarettes smoked per day in either overall or race-specific analyses. The authors concluded that menthol smokers do not exhibit greater signs of nicotine dependence than do nonmenthol smokers.

Lawrence et al. (2010) conducted a cross-sectional analysis of 63,193 current adult smokers in the 2003 and 2006/07 TUS-CPS, 25.8% of whom smoked menthol cigarettes. This analysis was restricted to self-respondents who comprised 64.6% of the 2003 sample and 75.1% of the 2006/07 sample. Multivariate regression was used to evaluate the association between menthol use and CPD/ TTFC (≤30 minutes vs. >30 minutes). Among all current smokers, heavy smokers (≥20 cigarettes per day) were significantly less likely to be menthol smokers than were light smokers (≤5 cigarettes per day). This association was no longer significant when the analyses were stratified by sex. Also, whether subjects smoked their first cigarette within 30 minutes of waking was not a significant predictor of menthol smoking; this was true for all smokers, as well as male and female smokers when assessed separately. The authors did not draw any conclusions about menthol and dependence specifically, although they did note that prevalence of menthol use is significantly higher among individuals who smoke on some days than among individuals who smoke every day.

Mendiondo et al. (2010) analyzed cross-sectional data from 12,004 current or former adult smokers in the 2005 NHIS and Cancer Control Supplement. Multivariate regression was used to assess the association between menthol use and CPD in two separate analyses of current and former smokers. Current menthol smokers smoked significantly fewer CPD after controlling for sex, age and race compared to current nonmenthol smokers. There was no difference among former smokers.

Moolchan et al. (2006) conducted a clinical evaluation of 91 adolescent smokers who were recruited for a smoking cessation study. These authors examined nicotine metabolism (cotinine to *trans*-3'-hydroxycotinine ratio) in an effort to explain the lower smoking rates among African Americans compared to Caucasians. African Americans had similar FTND scores compared to Caucasians (FTND scores were not provided for menthol smokers only, although 86% of the subjects smoked menthol cigarettes), yet smoked significantly fewer CPD and had significantly lower nicotine metabolite ratios than Caucasians. Although the focus of the study was on racial differences in nicotine metabolism, the authors did note that the results were essentially unchanged when looking only at the subgroup who smoked menthol cigarettes. This suggested that the observed difference was due to factors other than menthol.

Muhammad-Kah et al. (2010) evaluated nicotine dependence in the Total Exposure Study, a large cross-sectional study of adult smokers. The analysis focused on 1,044 menthol and 2,297 nonmenthol smokers. Dependence was assessed by overall FTND score, as well as the scores on the six individual items that make up the FTND. The authors found that, when odds ratios were adjusted by race, sex, age, tar yield, income and education, menthol status had no statistically significant effect on any single item of the FTND or on the overall scores (OR=1.05; 95% CI:0.91-1.22) compared with nonmenthol smoking. In addition, menthol smokers did not have increased odds of smoking within the first 30 minutes after waking compared to nonmenthol smokers. The authors concluded that, "Our results add to the existing evidence that menthol does not increase nicotine dependence."

Muscat et al. (2002) performed a cross-sectional analysis of smoking habits among 19,545 subjects in a case-control study of smoking and lung cancer (see Chapter 3A). The investigators examined whether menthol cigarette use was associated with heavy smoking (defined as ≥21 CPD) and whether menthol cigarette use explained racial differences in these smoking behaviors. All subjects were current or former smokers; of these, 3,005 (15.4%) smoked menthol cigarettes. After adjustment for age, education, case-control status, sex and years of smoking, there were no significant differences in cigarette type (menthol versus nonmenthol) among White current or former heavy smokers. Among Black current and former smokers, heavy smokers were significantly less likely to be menthol smokers than nonmenthol smokers. According to the authors, the findings suggest that menthol does not increase the addictive properties of nicotine.

In summary, the available studies of highest methodological quality discussed above provide strong evidence that menthol in cigarettes does not contribute to higher nicotine dependence.

Tier 2 and 3 Studies of Menthol Smoking and Nicotine Dependence

Five Tier 2 studies address this topic but have weaknesses that preclude drawing sound conclusions. None of these studies examined CPD, TTFC or composite measures of nicotine dependence.[3] They are mentioned here briefly because they have been discussed at the TPSAC meetings.

- **Ahijevych and Wewers (1993)** tested a model of nicotine dependence in a convenience sample of 187 African American women who largely smoked menthol cigarettes; however, menthol status was not included as a variable in the model.

[3] One study (Muscat et al. 2009) did include these measures, but numerical inconsistencies in the paper make it difficult to interpret.

- **Ahijevych et al. (2002)** examined various factors, including menthol cigarette preference, on plasma cotinine half-life in African American and Caucasian women during 6 days of smoking abstinence. African American smoking of menthol cigarettes was a significant predictor of cotinine half-life in comparison to Caucasian nonmenthol cigarette smoking.
- **Bover et al. (2008)** found that menthol cigarette smoking was among many factors significantly associated with waking at night to smoke (a measure of nicotine dependence) among a group of smokers who sought treatment at a tobacco dependence clinic. The study suffered from a high attrition rate (approximately 40%), and the study was designed to assess efficacy of treatment rather than to evaluate menthol smoking and dependence.
- **Hymowitz et al. (1995)** analyzed data from the COMMIT trial by race/ethnicity but did not attempt to link menthol smoking status with dependence outcomes.
- **Muscat et al. (2009)** conducted a cross-sectional study of 525 Black and White volunteers, and reported that after adjustment for confounders menthol smoking was not significantly associated with several measures of dependence (high score on the FTND, time to first cigarette of ≤30 minutes, daily cigarette amount, or heavy smoking). Numerical inconsistencies in this paper make it difficult to interpret.

Seven Tier 3 studies (**Ahijevych and Parsley 1999**, **Collins and Moolchan 2006**, **Hersey et al. 2006, Li et al. 2005**, **Muilenburg and Legge 2008**, **Okuyemi et al. 2004, Wackowski and Delnevo 2007**) were all rated lower than fair overall and poor in their ability to draw menthol inferences, and are not discussed in detail here.

Unpublished Analyses Presented to TPSAC

In July 2010 and January 2011, a number of unpublished analyses that addressed menthol cigarette use and smoking cessation were presented to TPSAC. Although these analyses have not undergone peer review, the authors reported conclusions are mentioned here briefly:

- **Curtin (unpublished)** analyzed data from several large nationally representative surveys and reported that:
  - Based on data from the NHIS, female and young adult menthol smokers reported smoking significantly fewer CPD (12.60 vs. 14.34 CPD for females; 10.47 vs. 12.51 CPD for young adults) compared to nonmenthol smokers.
  - Based on data from the NSDUH, female menthol smokers were significantly more likely (p=0.0002) to be represented in lower versus higher cigarette use categories (70%, 22.6% and 7.3% reported smoking ≤10, 11-20 and >20 CPD, respectively) compared to nonmenthol smokers (59.7%, 30.4% and 9.9%, respectively). Menthol smokers aged 18-23 years were significantly more likely (p=0.01) to be represented in lower versus higher cigarette use categories (81.2%, 16.0% and 2.8% reported smoking ≤10, 11-20 and >20 CPD, respectively) compared to nonmenthol smokers (75.2%, 20.7% and 4.1%, respectively).
  - No significant differences for CPD were indicated for non-Hispanic Black or adolescent menthol versus nonmenthol smokers participating in the NHANES, NHIS or NSDUH.
  - Findings from the NYTS were markedly different from those provided by the larger NHANES, NHIS and NSDUH; as discussed in Chapter 2, analyses of NYTS data

identified demographic characteristics associated with menthol cigarette preference that were different from those provided by other nationally representative surveys. Specific to dependence outcomes, menthol smokers aged 9-21 years were significantly more likely ($p<0.0001$) to be represented in higher versus lower cigarette use categories compared to nonmenthol smokers; similar findings were suggested for both sexes, as well as non-Hispanic Whites.

  - Based on regression models that adjusted individually for demographic variables, significantly fewer CPD generally persisted for menthol versus nonmenthol smokers when controlling for current age, sex or race/ethnicity. This was the case regardless of whether CPD was provided as continuous (NHANES and NHIS) or categorized (NSDUH) data.
  - Significantly lower estimates for CPD among menthol smokers from the NHANES and NSDUH only persisted when controlling for the combination of current age and sex. Significantly lower CPD for menthol smokers from the larger NHIS generally persisted when controlling for all combinations of demographic variables.

- **Hersey et al. (unpublished)** evaluated data on 5,511 youth surveyed by Legacy for Health, of whom 216 reported past-month menthol smoking and 366 reported past-month nonmenthol smoking. Findings from regression models indicated that menthol versus nonmenthol smoking was not a significant predictor of nicotine dependence; and, there was no significant interaction between menthol versus nonmenthol smoking and mean CPD. Some evidence was provided to suggest that menthol smoking may be associated with higher levels of nicotine dependence among smokers smoking less than one year.
- **Hyland and Kasza (unpublished)** evaluated data from the International Tobacco Control Four Country Survey and found that indicators of dependence (TTFC and CPD) were generally similar among menthol and nonmenthol smokers, although there were exceptions for some racial/ethnic/sex subgroups (Hispanic menthol smokers may be more dependent than Hispanic nonmenthol smokers).
- **Hyland and Rivard (unpublished)** evaluated data from the COMMIT trial of smoking cessation and found that switching between menthol and nonmenthol cigarettes was uncommon, regardless of race. Furthermore, menthol smokers were as likely as nonmenthol smokers to increase the time to their first cigarette and decrease the number of cigarettes smoked per day.
- **Muscat (unpublished)** examined data from a community-based study of Black and White smokers and reported that smoking menthol cigarettes did not affect the significant association between TTFC and blood cotinine levels. Similar or slightly higher cotinine values were found for menthol smokers compared to nonmenthol smokers for each TTFC category, but the results were not significant.
- **Nonnemaker et al. (unpublished)** conducted a secondary analysis of a longitudinal cohort of middle/high school youth to examine the influence of early menthol and nonmenthol cigarette use (and switching) on the progression from experimentation to established/daily smoking over a 3-year interval. Results were not entirely consistent, but the authors suggested that an early stated preference for menthol cigarettes was associated with higher levels of nicotine dependence ($\beta=1.04$; 95% CI:0.26-1.82). This study has numerous limitations, including use of a sample population that was not representative of the overall youth population.
- **Reitzel (a) (unpublished)** analyzed data from the Project CARE longitudinal cohort study and found that menthol cigarette use was not significantly related to tobacco dependence (as

assessed by the WISDM-68 multi-dimensional measure of dependence, CPD or TTFC) through week 26 of follow-up. Post-hoc analyses showed a single significant finding; among Latinos, menthol smokers scored higher than nonmenthol smokers on the WISDM-68 Behavioral Choice/Melioration subscale, suggesting greater dependence.

- **Reitzel (b) (unpublished)** analyzed data from the BREAK FREE clinical trial of smoking cessation and found that menthol cigarette smoking was unrelated to the majority of dependence indicators, including 12 of 13 WISDM-68 subscales, the WISDM-68 total score, CPD and TTFC. However, menthol cigarette use was significantly associated with the Taste/Sensory Processes subscale of the WISDM-68 in adjusted analyses.
- **Reitzel (c) (unpublished)** analyzed data from the MOM clinical trial of smoking relapse prevention among post-partum women and found that although menthol cigarette use was significantly associated with some, but not all, indicators of tobacco dependence in unadjusted analyses, these associations were not maintained in adjusted analyses. Post-hoc analyses revealed that Black menthol users smoked significantly more pre-quit cigarettes per day than did Black nonmenthol users.
- **Unger et al. (unpublished)** analyzed nicotine dependence (as assessed by TTFC ≤30 minutes) in a community-based survey of African American smokers and found no significant differences among menthol, nonmenthol, and combined smokers.

In addition, **Thorne et al. (2010)** presented findings from the 2001-2006 NHANES on menthol cigarette use and dependence at the 2010 American Public Health Association meeting (on behalf of FDA). The data indicated that menthol cigarette smokers report significantly fewer CPD and shorter durations of smoking compared to nonmenthol smokers. There were no significant differences in TTFC or nicotine dependence scores (Heaviness of Smoking Index), leading to the conclusion of no difference in dependence levels between menthol and nonmenthol smokers.

MENTHOL CIGARETTES AND DEPENDENCE AMONG ADOLESCENTS

Several studies provide some insight into menthol cigarette use and indicators of dependence among adolescent smokers. Two published studies found to be high quality (i.e., Tier 1) during the Covance literature review failed to find evidence of a difference between adolescent menthol and nonmenthol cigarette smokers.

- **DiFranza et al. (2004)** found no difference in strength of addiction between menthol and nonmenthol adolescent smokers who had "ever inhaled on a cigarette," as measured by the Hooked on Nicotine Checklist.
- **Moolchan et al. (2006)** found no difference in FTND score between African American (86% of whom smoked menthols) and Caucasian smokers (adolescents aged 13 to 17 years).

Four other studies **(Collins and Moolchan 2006, Hersey et al. 2006, Muilenburg and Legge 2008, Wackowski and Delnevo 2007)** provided mixed results, but were judged by Covance to be poor both with respect to overall quality as well as ability to support menthol inferences related to dependence (i.e., Tier 3).

- **Collins and Moolchan (2006)** analyzed interview data for 572 adolescent smokers enrolled in an urban Baltimore smoking cessation treatment study, comprising 46.9% African

Americans and having an overall 92.8% population preference for menthol cigarettes. The study found that similar percentages of menthol and nonmenthol smokers report smoking their first cigarette 6-30, 31-60 or >60 minutes after waking; a single difference was suggested for menthol smokers reporting a TTFC less than 5 minutes after waking. The data likewise indicated no differences for CPD or FTND score based on menthol status.

- **Hersey et al. (2006)** analyzed data from the 2000-2002 NYTS and reported that menthol smokers had a 45% higher odds of being above the median on nicotine dependence; these data were inconsistent with data from the same population indicating that menthol smokers were significantly less likely to report smoking on ≥20 of the last 30 days or to smoke ≥6 cigarettes per day.
- **Muilenburg and Legge (2008)** examined data from a 2006 survey of six secondary schools in a large southeastern metropolitan area. The sample population was not representative of the overall adolescent smoking population, which was further underscored by the unique finding that menthol smokers, independent of race, "exhibit high risk levels" for "Days smoked in month," "Cigs. smoked in month," and "last time Smoked," contrary to virtually all other studies of menthol smokers.
- **Wackowski and Delnevo (2007)** analyzed data from the 2004 NYTS, reporting that menthol smoking was associated with an increased adjusted odds ratio of needing a cigarette within 1 hour (AOR=2.6; 95% CI:1.6-4.3) and experiencing cravings (AOR=1.2; 95% CI:1.1-2.2); no significant differences were reported for feeling irritable or an inability to quit, and no overall dependency score was reported. The study also reported considerably more variability in adolescents' reporting of usual, regular or exclusive smoking of menthol cigarettes than is typically reported by adult smokers. Also, the authors cautioned that "…[t]he NYTS was not designed to test hypotheses related to menthol use and dependence."

Additional information on dependence among adolescents is presented in three unpublished analyses provided during the TPSAC meetings; all three were discussed above.

- **Curtin (unpublished)** analyzed data from several large nationally representative surveys and found no significant differences in CPD between adolescent menthol versus nonmenthol smokers in the NHANES or NSDUH. In contrast, adolescent menthol smokers from the NYTS were suggested to be significantly more likely to be represented in higher versus lower cigarette use categories compared to nonmenthol smokers. This survey differs from the other surveys with regard to both target population and data collection methodology; the implications of these differences have been previously discussed (refer to Chapter 2).
- **Hersey et al. (unpublished)** evaluated data on 5,511 youth surveyed by Legacy for Health. Findings indicated that menthol versus nonmenthol smoking was not a significant predictor of nicotine dependence. Some evidence was provided to suggest that menthol smoking may be associated with higher levels of nicotine dependence among smokers smoking less than one year.
- **Nonnemaker et al. (unpublished)** analyzed a longitudinal cohort of middle/high school youth to examine the influence of early menthol and nonmenthol cigarette use (and switching) on the progression from experimentation to established/daily smoking over a 3-year interval. Results were not entirely consistent, but the authors suggested that an early stated preference for menthol cigarettes was associated with higher levels of nicotine

dependence. Among other limitations, this study used a sample population that was not representative of the overall youth population.

An additional publication examined smoking dependence among adolescents and menthol (versus nonmenthol) cigarette use based on data from the NYTS. Due to the timing of publication, this study was not included in the Covance review; thus, it was not placed into a specific quality tier. It is discussed here briefly.

- **Hersey et al. (2010)** analyzed cross-sectional data from the 2006 NYTS, and provided findings from past-month smokers to suggest that smoking menthol cigarettes was significantly associated with reduced time to "needing" a cigarette. Among established smokers, but not all smokers with a usual brand, smoking a menthol brand was significantly associated with feeling restless and irritable without smoking and with experiencing cravings after going without smoking for a few hours.

Collectively, the available studies on adolescent smokers are not conclusive with respect to any impact of menthol versus nonmenthol smoking on adolescent dependence. A combination of mixed findings in some studies (several showing no menthol effect) and overall lack of quality in study design precludes drawing definitive conclusions that menthol smoking has an effect on increased measures of adolescent dependence compared to nonmenthol smoking. Further, as discussed in Chapter 2, approximately only one-quarter of young smokers go on to become regular smokers, indicating that three-quarters of youth smokers quit smoking during the experimentation phase, which dramatically limits the inferences that can be drawn with respect to adolescent smoking dependence.

CONCLUSIONS

This review of literature on menthol cigarette smoking and measures of nicotine dependence demonstrates that the most methodologically sound studies do not find that menthol smokers are any more dependent on nicotine than are nonmenthol smokers. The 10 Tier 1 studies examined several measures of nicotine dependence, including multi-factor FTND and HONC, as well as single measures of CPD and TTFC.

- Three studies evaluated FTND, which is a more comprehensive measure of nicotine dependence; none of these three studies (including the very large Total Exposure Study) found a difference between menthol and nonmenthol smokers.
- A single study evaluating dependence among adolescents using the HONC found that the strength of the addiction did not differ according to the favorite brand of cigarette, brand strength or menthol content.
- Eight studies evaluated CPD; menthol cigarette smokers either smoked significantly fewer CPD than nonmenthol smokers (N=4 studies), or there were no differences (N=4 studies).
- Five studies evaluated TTFC; three found no differences between menthol and nonmenthol smokers. The other two studies do not provide compelling evidence of a significant difference. Ahijevych and Ford (2010) focused on their finding that non-daily menthol smokers had a significantly shorter TTFC than nonmenthol smokers. However, the fact that this was not true for daily smokers, nor was there a significant difference in CPD among

either daily menthol and nonmenthol smokers or non-daily menthol and nonmenthol smokers argues against greater dependence among menthol smokers. Fagan et al. (2010) found a significant difference between menthol and nonmenthol smokers in only one of eight subgroups examined, i.e., smokers of 6-10 CPD only when TTFC was defined as ≤5 minutes after waking.

Even those studies assessed to be of lower quality (Tier 2) generally show that menthol smokers are either less dependent or are no different in their dependence measures than nonmenthol smokers.

In the few studies in which differences were reported in measures of dependence between menthol and nonmenthol smokers, those differences were small for both adolescents and adult smokers.

Given the number of high-quality studies and their consistent findings with respect to adult dependence, and the lack of any conclusive evidence with respect to adolescents, using the Surgeon General's framework for assessing causality, it is reasonable to conclude that the **"evidence is suggestive of no causal relationship"** between smoking menthol cigarettes and significantly increased levels of nicotine dependence.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Alexander et al. 2010 United States	**Cessation** Cross-sectional analysis of data from the 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 30,176 current smokers (age 18 and older). Cessation was assessed by: ever stopped smoking for 1 day or longer because you were trying to quit; number of quit attempts in past 12 months; and longest length of time you quit smoking.	**Tobacco Preference** Nonmenthol smoker Menthol smokers **Tobacco Preference** Nonmenthol smoker Menthol smokers **Tobacco Preference** Nonmenthol smoker Menthol smokers	**Odds Ratio (95% CI) for Ever Stopped Smoking for 1 Day or Longer** 1.0 (reference) 0.98 (0.83-1.15) Adjusted for age, race, sex, education and income. **Mean No. Times Stopped Smoking in Past Month (%)** 3.8 (3.6-3.9) 4.0 (3.6-4.4) **Longest Length of Time Stopped Smoking (%)** 1.0 (1.7-2.3) 2.2 (1.9-2.5)	After controlling for occupational status and work-place smoking policies, smokers of menthol cigarettes in the United States appear to have similar self-reported life-time rates of attempts to stop smoking as nonmenthol smokers. In this exploratory study, menthol versus nonmenthol as a factor in quitting was not significant.	Conclusions are supported by study data. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Goal of this study was to examine the role of occupation status on the quitting behaviors of menthol versus nonmenthol smokers. Menthol use and quitting behaviors were self-reported. "Quitting" was not defined very strictly (i.e., ever stopped smoking for 1 day or longer).

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Berg et al. 2010 United States	**Cessation** Randomized clinical trial of smoking cessation among 539 Black light smokers (<10 CPD). About 81% smoked menthol cigarettes at baseline. 95 subjects quit by the end of the trial. Cessation was assessed at 26 weeks. There were 3 categories of smoking status. Reducers were those who reduced their smoking by ≥50% from baseline but did not quit. Nonreducers did not reduce their smoking by >50%. Quitters reported abstinence that was verified by salivary cotinine ≤20 ng/ml.	**% Smoking Menthol at Baseline** Whole group: 80.6	**% Smoking Menthol at 26 Weeks** No reduction: 83.9 Reduction: 80.8 Cessation: 72.6 p=0.07	Conclusions do not directly address menthol. Authors mention that, although using menthol cigarettes did not significantly contribute to the multivariate model, more nonreducers used menthol cigarettes than did reducers, as indicated by the bivariate analyses.	Study was not designed to examine the relationship between menthol smoking and cessation. Despite the authors' comment, smoking menthol cigarettes was not a statistically significant predictor of reduction or cessation. Clinical trial. Cessation was assessed at 26 weeks; defined as salivary cotinine ≤20 ng/ml. All subjects were Black light smokers, which limits generalizability of the findings.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Cubbin et al. 2010 United States	**Cessation** Cross-sectional analysis of data from the 2005 National Health Interview Survey and Cancer Control Supplement. Analysis was based on 21,196 Black, Hispanic, and White women and men aged 25-64 years (current, former, and never-smokers who reported menthol status). Menthol use was defined as "usual cigarette brand was menthol." Cessation was assessed by proportion with a quit attempt in the past year among every-day smokers, and time since quitting among former smokers. Initiation data are included in Table 4-3; dependence data are included in Table 5-4.	<u>**Menthol Smokers**</u> Black women Black men Hispanic women Hispanic men White women White men <u>**Nonmenthol Smokers**</u> Black women Black men Hispanic women Hispanic men White women White men	<u>**% Who Attempted to Quit in Past Year by Cigarette Type (99% CI)**</u> 49.9 (40.0, 59.9) 48.6 (37.1, 60.1) 46.7 (27.8, 65.7) 57.9 (38.0, 77.8) 43.2 (35.8, 50.7) 40.7 (31.2, 50.2) 39.7 (24.3, 55.2) 37.6 (21.6, 53.6) 42.5 (30.7, 54.3) 38.4 (28.3, 48.5) 39.8 (35.7, 43.9) 36.8 (32.6, 41.0) Adjusted for age, income, and education.	The results do not support the hypothesis that menthol smokers have a harder time quitting (making a quit attempt and length of time since quitting) than nonmenthol smokers. There were no statistically significant differences by race/ethnicity, sex or cigarette type in quit attempts. White women who smoked menthol cigarettes reported longer cessation compared with those who smoked nonmenthol cigarettes.	Conclusions are supported by study data. Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use was self-reported.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Fagan et al. 2010 United States	**Cessation** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 46,273 current daily smokers (age 18 and older). Cessation was assessed by: number of quit attempts (ever stopped smoking for 1 day or longer) in past 12 months; and length of smoking abstinence in past 12 months. Dependence data are included in Table 5-4.	**Quit Attempt in Past 12 Months vs. None** Nonmenthol ≤5CPD Menthol ≤5CPD Nonmenthol 6-10 CPD Menthol 6-10 CPD Nonmenthol 11-19 CPD Menthol 11-19 CPD Nonmenthol 20+CPD Menthol 20+ CPD **Abstinent >2 Weeks vs. ≤2 Weeks** Nonmenthol ≤5CPD Menthol ≤5CPD Nonmenthol 6-10 CPD Menthol 6-10 CPD Nonmenthol 11-19 CPD Menthol 11-19 CPD Nonmenthol 20+CPD Menthol 20+ CPD	**Odds Ratios (95% CI)** 1.0 (reference) 1.10 (0.91-1.34) 1.0 (reference) 0.92 (0.83-1.02) 1.0 (reference) 0.99 (0.85-1.16) 1.0 (reference) 0.97 0.88-1.07) 1.0 (reference) 1.03 (0.78-1.36) 1.0 (reference) 0.97 (0.82-1.14) 1.0 (reference) 1.05 (0.82-1.36) 1.0 (reference) 0.93 (0.79-1.12)	These data do not support the hypothesis that menthol smokers experience greater quitting difficulty. The multivariate models did not show significant associations between usual cigarette brand and quit attempts in past 12 months or duration of smoking abstinence >2 weeks in the past 12 months.	Conclusions are supported by study data. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use and quitting behaviors were self-reported. A "quit attempt" was not defined very strictly (i.e., ever stopped smoking for 1 day or longer).

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Foulds et al. 2006	**Cessation** Convenience sample of first 1,021 patients at a free tobacco treatment clinic who made a quit attempt. 41% smoked menthol cigarettes. 320 reported abstinence at 6 months. 66% of subjects were White. Abstinence (self-reported 7-day point prevalence) was assessed at 4 weeks and 6 months. Cessation was defined as not smoking in past 7 days. Biochemical confirmation of smoking abstinence was confirmed by CO level ≤10 ppm at in-person follow-ups.	**Current Brand Menthol?** Yes No	**Adjusted Odds Ratio (95% CI) for Abstinence at 4 Weeks** 1.00 (reference) 1.359 (0.996-1.856) p=0.053 Adjusted for age, education, employment status, time-to-first-cigarette, baseline stage of change, and number of face-to-face contacts with clinic ORs were not presented for abstinence at 26 weeks, as menthol versus nonmenthol was not a significant predictor of abstinence at 26 weeks.	Menthol smokers were less likely to achieve abstinence in univariate analyses and this item remained in the model predicting 4-week outcome. Menthol preference is one of many predictors of abstinence.	Conclusions are not fully supported by study data. While "menthol cigarettes remained in the model" at 4 weeks, it was only of borderline significance (p=0.053). The authors did not directly address the association between menthol smoking and abstinence at 26 weeks. It is reasonable to conclude that there was no significant relationship, since menthol was not included as a variable in the model at 26 weeks. Cessation was assessed at 4 weeks and 6 months. Defined as 7 days of abstinence; self-reported abstinence was biochemically verified at in-person follow-ups. This is a convenience sample of volunteers seeking treatment at a clinic; generalizability is limited. Results not presented by race. One-third of subjects were lost to follow-up at 26 weeks.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Gandhi et al. 2009 United States	**Cessation** Retrospective analysis of 1,688 patients attending a specialist smoking cessation service. Overall, 46.1% smoked menthol cigarettes (81% of African Americans, 66% of Latinos, 32% of Whites). Cessation (assessed at 4 weeks and 6 months was defined as 7-day point prevalence of abstinence. Abstinence was self-reported and biochemically verified (exhaled CO).	**Race** White Nonmenthol Menthol African American Nonmenthol Menthol Hispanic/Latino Nonmenthol Menthol **Race** White Nonmenthol Menthol African American Nonmenthol Menthol Hispanic/Latino Nonmenthol Menthol	**Adjusted Odds Ratios (95% CI) for Abstinence at 4 Weeks** 1.0 (reference) 0.96 (0.72-1.20) 1.0 (reference) 0.32 (0.16-0.62)** 1.0 (reference) 0.43 (0.10-0.90)** **Adjusted Odds Ratios (95% CI) for Abstinence at 6 Months** 1.0 (reference) 1.0 (0.80-1.40) 1.0 (reference) 0.48 (0.25-0.90)** 1.0 (reference) 0.64 (0.20-1.80) Adjusted for age, education, sex, employment status, type of insurance, CPD, age smoked for first time, awaken at night to smoke, TTFC, previous quit attempts, presence of smoking-related disease.	Despite smoking fewer cigarettes per day, African American and Latino menthol smokers experience reduced success in quitting as compared with nonmenthol smokers within the same ethnic/racial groups.	Conclusions are supported by study data. However, note that White subjects made up the majority (64%) of the study group; White menthol smokers were no less likely to quit than White nonmenthol smokers. Cessation was assessed at 4 weeks and 6 months; defined as not smoking for 7 days. Abstinence was self-reported and verified biochemically. Menthol use was self-reported. Loss to follow-up by 6 months was high (42%).

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Gundersen et al. 2009 United States	**Cessation** Cross-sectional analysis of data from the 2005 National Health Interview Survey. Subjects were 7,815 Black, White, and Hispanic current and former smokers who had made a quit attempt. 26.5% smoked menthol cigarettes. Former smokers were those who had smoked at some point but were now smoking "not at all." Current smokers now smoked every day or some days.	<u>**Race**</u> White Nonmenthol Menthol Hispanic Nonmenthol Menthol Black Nonmenthol Menthol Non-White (Black + Hispanic) Nonmenthol Menthol	<u>**Adjusted Odds Ratios for Cessation (95% CI)**</u> 1.0 (reference) 1.17 (1.00-1.36)* 1.0 (reference) 0.61 (0.39-0.97)** 1.0 (reference) 0.78 (0.56-1.09) 1.0 (reference) 0.55 (0.43-0.71)** Adjusted for age, education, sex, cigarettes per day, census region, and perceived risk of cancer.	Our findings provide some support for the hypothesis that menthol smoking can lead to poorer cessation outcomes, but only for non-White smokers. Non-White menthol smokers were less likely to have quit compared to non-White nonmenthol smokers, but White menthol smokers were more likely to have quit compared to White nonmenthol smokers.	Study does not permit definitive conclusions. It is true that cessation results differed by race. Non-White menthol smokers were less likely to be former smokers whereas White menthol smokers were more likely to be former smokers. However, when the analysis was restricted to Blacks, there was no difference in cessation between menthol and nonmenthol smokers. This suggests that variables other than menthol may be relevant. Study is large and subjects are nationally representative. Cross-sectional nature of analysis does not permit causal conclusions. Cessation was defined as now smoking "not at all" (apparently no duration requirement). Smoking status and menthol use was self-reported.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Hyland et al. 2002	**Cessation** Prospective study. Subjects were 13,286 baseline smokers (age 25-64) in the COMMIT trial of smoking cessation. 24% smoked menthols in 1988. Smoking was reassessed after 5 years. Cessation was defined as not having smoked any cigarettes in the past 6 months. Dependence data are included in Table 5-4.	**Race** Overall White, non-Hispanic Black, non-Hispanic Hispanic (Reference group not defined but appears to be smokers of nonmenthol cigarettes.)	**Relative Risks for Menthol Use in 1988 on Quitting in 1993 (95% CI)** 1.0 (0.90-1.11) 0.94 (0.83-1.05) 1.04 (0.73-1.47) 1.22 (0.80-1.87) Adjusted for sex, age, race/ethnicity, education, cigarettes smoked per day, time to first cigarette in the morning, history of past serious quit attempts, age started smoking, desire to stop smoking, frequency of alcohol consumption, use of non-cigarette tobacco product, pricing tier of cigarette smoked, and the presence of another smoker in the household.	Use of mentholated cigarettes was not associated with quitting. None of the race/ethnicity-specific analyses revealed any significant associations. Menthol users who had greater levels of dependence had lower quit rates than menthol users who had lower levels of dependence.	Conclusions are supported by study data. Large prospective study. Cessation was assessed at 5 years; defined as 6 months of abstinence. Subjects were a random sample from a representative sample of households in 10 U.S. communities. Menthol use and smoking status were assessed by self-report. Menthol status only collected at baseline in 1988. High rate of attrition (34%) over time.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Murray et al. 2007 United States (Lung Health Study)	**Cessation** Clinical trial of smoking cessation. There were 5,887 subjects (age 35-60), all current or former smokers with mild to moderate airway obstruction. About 20% (1,216) smoked menthol cigarettes at baseline. Cessation was assessed at 5 years. Sustained quitters were biochemically confirmed at 5 annual visits and did not recall at any annual visit any months where smoked >1 CPD. Intermittent smokers were biochemically confirmed as quitters at some but not all annual visits. Continuing smokers reported smoking at all annual visits.	 **Men** Sustained quitter Intermittent smoker Continuing smoker Chi square, p-value **Women** Sustained quitter Intermittent smoker Continuing smoker Chi square, p-value	**Cessation at 5 Years: Menthol vs. Plain Smoker at Baseline (%)** 16.6 vs. 17.2 26.0 vs. 26.9 57.3 vs. 55.9 0.80 13.8 vs. 15.4 30.4 vs. 28.7 55.9 vs. 55.9 0.57 Percentages are unadjusted.	We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking.	Conclusions are supported by study data. Large clinical trial. Cessation was assessed at 5 years of follow-up; sustained quitters were biochemically confirmed as quitters at the 5 annual visits and did not recall at any annual visit any month with mean smoking >1 cigarette per day. Results were not presented by race. Subjects had some degree of impaired lung function at baseline. Menthol use was self-reported.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Muscat et al. 2002	**Cessation** Cross-sectional analysis of data from case-control study on smoking and lung cancer. There were 19,545 subjects, 3,005 of whom smoked menthol cigarettes. All were current or former smokers. Ever-smokers smoked ≥1 CPD in one year. Former smoker were ever-smokers who did not smoke at least 1 CPD in the past year. Dependence data are included in Table 5-4.	**Whites** Current versus former nonmenthol smokers Current versus former menthol smokers **Blacks** Current versus former nonmenthol smokers Current versus former menthol smokers	**Adjusted Prevalence Odds Ratios of Continued Smoking vs. Quitting (95% CI)** 1.0 (reference) 1.1 (1.0-1.3) 1.0 (reference) 1.1 (0.8-1.4) Adjusted for age, sex, education, case-control status, years of smoking, and cigarettes per day.	The risk of quitting was not associated with cigarette menthol flavor. Cigarette mentholation was not associated with continued smoking in Blacks and in Whites. Blacks were less likely than Whites to have quit smoking regardless of the brand of cigarettes. The reason for the lower quit rate in Blacks is poorly understood but could be due to lack of perceived benefits, medical advice, and social support.	Conclusions are supported by study data. Cross-sectional analysis; consequently, does not permit causal conclusions. Cessation was defined as not smoking at least 1 CPD in the year prior to study interview. Menthol use was self-reported. Most subjects who smoked menthol during their lifetime also smoked nonmenthol cigarettes. Subjects were classified as menthol smokers if LAST brand smoked was menthol. Population was older and male; some were lung cancer patients.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Okuyemi et al. 2003 United States	**Cessation** Randomized clinical trial of sustained-release bupropion for smoking cessation. Subjects were 600 African American smokers, 471 of whom smoked menthol cigarettes. Cessation (7-day point prevalence) was assessed at 6 weeks and 6 months. Self-reported abstinence was confirmed by expired CO assessment. Dependence data are included in Table 5A-1.	**Tobacco Preference** Nonmenthol smokers Menthol smokers **Tobacco Preference** Nonmenthol smokers Menthol smokers	**Abstinence at 6 Weeks** 41.5% 28.3% p=0.006* **Abstinence at 6 Months** 27.0% 21.4% p=0.21	African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, thereby putting menthol smokers at greater risk from the health effects of smoking. The lower cessation rates among menthol cigarette smokers were found only in those younger than 50 years.	Conclusions are misleading. While there was a significant difference between menthol and nonmenthol smokers at 6 weeks, that difference had disappeared by 6 months. The difference was only seen among subjects treated with bupropion at 6 weeks, not among subjects who received placebo at 6 weeks. Clinical trial. Cessation was assessed at 6 weeks and 6 months. Defined as 7 days of abstinence; self-reported abstinence was biochemically verified. All subjects were African American, thus limiting ability to generalize.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Okuyemi et al. 2007 United States	**Cessation** Randomized clinical trial of nicotine gum and counseling for smoking cessation. Subjects were 755 African American light smokers (≤10 CPD). 81.7% smoked menthol cigarettes. Cessation (7-day point prevalence) was assessed at 8 weeks and 26 weeks. Self-reported abstinence was confirmed by urinary cotinine.	**Tobacco Preference** Menthol smokers Nonmenthol smokers **By Age** **<Age 50** Menthol smokers Nonmenthol smokers **>Age 50** Menthol smokers Nonmenthol smokers	**7-Day Verified Abstinence at 26 Weeks** 11.2% 18.8% p=0.015* Percentages are unadjusted. **Adjusted Odds Ratio (95% CI)** 1.0 (reference) 2.077 (0.944-4.569) 1.0 (reference) 1.676 (0.760-3.698) Adjusted for drug and counseling treatment assignments, as well as confidence to quit smoking (note that the ORs are not adjusted for duration of smoking in years, even though nonmenthol smokers had smoked significantly longer than menthol smokers at baseline).	Among African American light smokers, use of menthol cigarettes is associated with lower cessation rates.	Conclusions are not supported by study data. Percentages presented here are not adjusted, even though there were significant differences between menthol and nonmenthol smokers (age, duration of smoking in years, confidence in quitting). Analyses based on actual randomization showed no differences between menthol and nonmenthol smokers. Logistic regression by age group (<50 vs. ≥50) that considered some potential confounders did not find that menthol/nonmenthol status to be significantly associated with abstinence. Clinical trial. Cessation was assessed at 6 weeks; defined as 7-day point prevalence. Self-reported abstinence was biochemically verified. All subjects were African American light smokers, thus limiting ability to generalize.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Pletcher et al. 2006 United States (CARDIA study)	**Cessation** Cohort study. There were 5,115 subjects; 972 smoked menthol and 563 smoked nonmenthol at baseline. 15 years of follow-up. Cessation was measured at 2, 5, 7, 10, and 15 years of follow-up. Cessation assessed by 5 measures: not currently smoking; recent quit attempts; cessation if recent quit attempt; sustained cessation (no current smoking in past 2 CARDIA exams); and documented relapse (those who reported no smoking at one exam and then current smoking at their final exam).	**Measure of Cessation** Not currently smoking Recent quit attempt Cessation if recent quit attempt Sustained cessation Documented relapse	**Adjusted Odds Ratios (95% CI) for Menthol vs. Nonmenthol** 0.90 (0.68-1.19) 0.77 (0.57-1.06) 0.98 (0.69-1.39) 0.70 (0.48-1.03) 1.89 (1.17-3.05)* Adjusted for age, sex, ethnicity, social factors (education, marital status, employment, health insurance status) and cigarettes per day at baseline.	Menthol cigarettes may be harder to quit smoking.	Conclusions are not fully supported by study data. There were no significant associations between menthol smoking and 4 of 5 measures of cessation (including the most stringently defined outcome of sustained cessation. The only measure that was significantly associated was "documented relapse." Large prospective study with long-term follow-up. Cessation was assessed at 2-15 years; sustained cessation was defined as no smoking in the past 2 CARDIA exams. Cessation was self-reported, but was assessed at multiple visits. The limited number of European American menthol smokers (189) and African American nonmenthol smokers (95) made ethnicity-specific analyses somewhat imprecise.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Stahre et al. 2010 United States	**Cessation** Cross-sectional analysis of data from the 2005 National Health Interview Survey Cancer Control Supplement. Analysis was based on 12,004 current or former smokers age 18 or older for whom menthol cigarette status was known. Menthol use was defined as "usual cigarette brand was menthol." Cessation was assessed by the population quit ratio and the utilization of evidence-based smoking cessation aids.	**Predictors of Population Quit Ratio** **Interaction of Menthol/Race** Nonmenthol x White Menthol x African American Menthol x American Indian/Alaskan native Menthol x Asian **Predictors of Utilization of Any Quit Aid** **Current Smokers** Nonmenthol smoker Menthol smoker **Former Smokers** Nonmenthol smoker Menthol smoker	**Adjusted Odds Ratio (95% CI)** 1.00 (reference) 0.72 (0.53-0.97)* 2.00 (0.56-7.23) 0.74 (0.37-1.48) Adjusted for age group, sex, region, marital status, and average number of cigarettes per day. 1.00 (reference) 1.05 (0.80-1.36) 1.00 (reference) 1.29 (0.74-2.26)	Menthol cigarette smoking is associated negatively with successful smoking cessation among African Americans. African American menthol smokers were significantly less likely than White nonmenthol smokers to have quit smoking. Menthol smoking status was not associated with differences in utilization of quit aids.	Conclusions are supported by study data. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use and use of quit aids were self-reported.

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Table 5-3. Higher Quality Studies on Menthol Smoking and Cessation Behaviors (N=15) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Trinidad et al. 2010 United States	**Cessation** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on current and former smokers (age 20-65). Successful cessation was assessed at being quit for ≥6 months. Pre-quitting behaviors (intention of quitting in the next 6 months and positive estimation of quitting success in the next 6 months) were also examined.	**Former Smokers** **Non-Hispanic Whites** Nonmenthol Menthol **African American** Nonmenthol Menthol **Hispanics** Nonmenthol Menthol **Asian American/ Pacific Islander** Nonmenthol Menthol **Native American/ Alaska Native** Nonmenthol Menthol	**Adjusted ORs (95% CI) of Cessation >6 Mos** 1.0 (reference) 0.28 (0.25-0.33)** 1.0 (reference) 0.23 (0.17-0.31)** 1.0 (reference) 0.48 (0.34-0.69)** 1.0 (reference) 0.22 (0.11-0.45)** 1.0 (reference)** 0.49 (0.14-1.71)	Across race/ethnic groups, those who used to regularly smoke mentholated cigarettes were less likely to have experienced long-term quitting success. African Americans and Hispanics/Latinos (but not other races) who smoked menthols were significantly more likely to be seriously considering quitting in the next 6 months and were significantly more likely to have a positive estimation of quitting successfully in the next 6 months compared to those who smoked nonmenthols.	Conclusions are supported by study data. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use and quitting behaviors were self-reported. Quitting was defined more rigorously in this analysis (quit for ≥6 months) than in other analyses of this survey. The large number of statistical comparisons increases the likelihood that some findings may be due to chance.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Ahijevych and Ford 2010 United States	**Dependence** Cross-sectional analysis of data from the 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 2,241 daily and 688 non-daily young adult smokers (age 18-24). Dependence was assessed by: cigarettes per day and time to first cigarette after waking (≤30 min after waking vs. >30 min)..	**Association of Menthol Brand Preference with TTFC (<30 min)** Among daily smokers Among non-daily smokers **Association of Menthol Brand Preference with Average CPD** Among daily smokers Among non-daily smokers	**Binary Logit Model Coefficient (SE)** 0.151 (0.088) 0.709 (0.317)* (p<0.05) **Poisson Model Coefficient (SE)** 0.022 (0.031) -0.018 (0.110)	Young adult non-daily smokers who preferred menthol cigarettes were significantly more dependent than those who preferred nonmenthol cigarettes, as shown by the shorter TTFC. Among daily smokers, there was no association between menthol brand preference and smoking within 30 minutes of waking. However, among non-daily smokers, menthol users were more likely to smoke with 30 minutes of waking compared to those who smoked nonmenthol cigarettes. Menthol brand preference was not significantly associated with cigarettes per day.	Conclusions are not fully supported by study data. If non-daily smokers were truly more nicotine dependent, this should have been reflected in a higher CPD. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use and dependence behaviors were self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Cubbin et al. 2010 United States	**Dependence** Cross-sectional analysis of data from the 2005 National Health Interview Survey and Cancer Control Supplement. Analysis was based on 3,902 Black, Hispanic, and White women and men aged 25-64 years who were current everyday smokers. Menthol use was defined as "usual cigarette brand was menthol." Dependence was assessed by predicted mean number of cigarettes smoked per day. Initiation data are included in Table 4-3; cessation data are included in Table 5-3.	<u>**Menthol Smokers**</u> Black women Black men Hispanic women Hispanic men White women White men <u>**Nonmenthol Smokers**</u> Black women Black men Hispanic women Hispanic men White women White men	<u>**Predicted Mean Number of Cigarettes Smoked per Day by Cigarette Type (99% CI)**</u> 11.5 (10.0, 13.0) 13.9 (12.1, 15.8) 8.8 (6.7, 11.0) 12.9 (9.6, 16.2) 16.2 (14.9, 17.5) 18.9 (17.3, 20.6) 11.7 (9.4, 13.9) 13.0 (10.3, 15.7) 10.0 (8.5, 11.4) 12.5 (10.6, 14.5) 16.9 (16.2, 17.6) 20.7 (19.8, 21.6) Adjusted for age, income and education.	The results do not support the hypothesis that menthol smokers smoke more than nonmenthol smokers. There were no significant differences for any group in the number of cigarettes smoked per day by cigarette type (menthol versus nonmenthol).	Conclusions are supported by study data. Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
DiFranza et al. 2004 United States	**Dependence** Retrospective/prospective longitudinal analysis of a cohort of 7th graders followed for 30 months (part of the Development and Assessment of Nicotine Dependence in Youth study). Detailed information was collected (3 times annually for 3 years), including first puff, first inhalation, first monthly and daily use, and first occurrence of 10 indicators of lost autonomy over use of nicotine (using the Hooked on Nicotine Checklist). Subjects were considered to be tobacco users if they had ever used any form of tobacco. This analysis focused on 237 subjects who had inhaled a cigarette.	**Strength of Addiction** Favorite brand is nonmenthol Favorite brand is menthol Of the 237 subjects who reported they had inhaled a cigarette, only 51% could recall whether it was mentholated. Menthol cigarettes accounted for 42% of the first inhaled cigarettes. 59 subjects had smoked enough to establish a favorite brand; for 42%, it was Newport.	**Mean Score on Hooked on Nicotine Checklist** 6.0 (s.d.=3.3) 6.0 (s.d.=3.4) t=0.22	The strength of the addiction, as measured by the Hooked on Nicotine Checklist, did not differ according to the favorite brand, brand strength or menthol content. It is not surprising that many youths could not recall any details regarding the brand, strength, or mentholation of their first cigarette, since the first cigarette is most commonly provided by others and this information is rarely written on the cigarette.	Conclusions are supported by study data. Dependence was assessed by the 10-item Hooked on Nicotine Checklist, a reliable and valid measure of loss of autonomy over nicotine that has been used for screening adolescents for nicotine dependence. Strengths include: prospective nature of study; short recall time for subjects; use of unselected population; inclusion of a measure of dependence. Limitations include: small sample size; subjective nature of symptoms; small number of African Americans (only 4% of subjects.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Fagan et al. 2010 United States	**Dependence** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 46,273 current daily smokers (age 18 and older). Dependence was assessed by: cigarettes per day and time to first cigarette after waking. Responses were grouped into TTFC ≤30 min after waking vs. >30 min; TTFC ≤5 min after waking vs. >5 min. Cessation data are included in Table 5-3.	**CPD** Nonmenthol Menthol No usual type **TTFC (≥30 min vs. <30 min)** Nonmenthol ≤5CPD Menthol ≤5CPD Nonmenthol 6-10 CPD Menthol 6-10 CPD Nonmenthol 11-19 CPD Menthol 11-19 CPD Nonmenthol 20+CPD Menthol 20+ CPD **TTFC (≥5 min vs. <5 min)** Nonmenthol ≤5CPD Menthol ≤5CPD Nonmenthol 6-10 CPD Menthol 6-10 CPD Nonmenthol 11-19 CPD Menthol 11-19 CPD	**Geometric Mean (95% CI)** 15.01 (14.88-15.14) 13.05 (12.86-13.23) 12.53 (11.81-13.31) p<0.001 for nonmenthol versus menthol and nonmenthol versus no usual type **Adjusted Odds Ratio (95% CI)** 1.0 (reference) 1.20 (0.96-1.50) 1.0 (reference) 1.09 (0.97-1.22) 1.0 (reference) 0.98 (0.84-1.14) 1.0 (reference) 1.05 (0.95-1.16) 1.0 (reference) 0.94 (0.60-1.47) 1.0 (reference) 1.22 (1.05-1.43)* 1.0 (reference) 1.18 (0.97-1.45)	Findings from this national survey of daily smokers demonstrate that menthol smokers in the United States who report consuming 6-10 cigarettes per day show greater signs of nicotine dependence than comparable nonmenthol smokers. The ORs for TTFC after waking did not increase as smoking intensity increased for menthol smokers; the relationship was non-linear.	Conclusions are supported by study data. However, the authors focused on the single statistically significant finding among a number of nonsignificant findings. It is inappropriate to focus on this single finding (shorter TTFC among menthol smokers of 6-10 cigarettes when TTFC is defined as <5 minutes, but not <30 minutes) and ignore the overall pattern of results: that TTFC is generally similar among menthol and nonmenthol smokers. Large nationally representative survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use and dependence behaviors were self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Fagan et al. 2010 (continued) United States		Nonmenthol 20+CPD Menthol 20+ CPD	1.0 (reference) 1.03 (0.95-1.13) Adjusted for sociodemographic and smoking behavior characteristics.		

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Hyland et al. 2002 United States	**Dependence** Prospective study. Subjects were 13,286 baseline smokers (age 25-64) in the COMMIT trial of smoking cessation. 24% smoked menthols in 1988. Smoking was reassessed after 5 years. There were 2 measures of nicotine dependence: time to first cigarette (TTFC) in the morning in 1988, and amount smoked among continuing smokers in 1993 (weighted average of number of cigarettes smoked per weekday and weekend day). Cessation data are included in Table 5-3.	**Race** Overall White, non-Hispanic Black, non-Hispanic Hispanic **Race** Overall White, non-Hispanic Black, non-Hispanic Hispanic (Reference group not defined but appears to be smokers of nonmenthol cigarettes.)	**Odds Ratios for Menthol Use in 1988 on TTFC in 1988 (95% CI)** 0.90 (0.81-0.99)* 0.91 (0.81-1.02) 0.89 (0.69-1.28) 0.86 (0.50-1.45) **Estimated Change in CPD in 1993 Associated with Menthol use in 1988** 0.11 (-0.38-0.60) 0.00 (-0.56-0.56) 0.47(-1.4-2.3) 1.16 (-1.3-3.6) Adjusted for sex, age, race/ethnicity, education, cigarettes smoked per day, time to first cigarette in the morning, history of past serious quit attempts, age started smoking, desire to stop smoking, frequency of alcohol consumption, use of non-cigarette tobacco product, pricing tier of cigarette smoked, and the presence of another smoker in the household.	Mentholated cigarette smokers do not exhibit greater signs of nicotine dependence as measured by the likelihood of future cessation, TTFC in the morning, or number of cigarettes smoked per day. Overall, menthol smokers were slightly less likely to report smoking within 10 minutes after waking. Race/ethnicity-specific analyses show similar effect sizes. No associations were observed between menthol use in 1988 and amount smoked among continuing smokers in 1993.	Conclusions are supported by study data. Large prospective study. In addition to cessation at 5 years, there were two measures of dependence (TTFC in 1988 and estimated change in CPD among continuing smokers in 1993). Subjects were a random sample from a representative sample of households in 10 U.S. communities. Menthol use and smoking status were assessed by self-report. Menthol status only collected at baseline in 1988. High rate of attrition (34%) over time.

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** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Lawrence et al. 2010 United States	**Dependence** Cross-sectional analysis of data from the 2003 and 2006/07 Tobacco Use Supplement to the Current Population Survey. Analysis was based on 69,193 current smokers (age 18 and older). 16,294 (25.8%) smoked menthol cigarettes and 46,899 (74.2%) smoked non-menthol cigarettes. Analyses were restricted to self-respondents who comprised 64.6% of the 2003 sample and 75.1% of the 2006/07 sample. Dependence was assessed by cigarettes per day and TTFC (≤30 minutes vs. >30 minutes). Initiation data are included in Table 4-3.	**Cigarettes Per Day** **All Current Smokers** ≤5 6-10 11-19 20+ **Current Male Smokers** ≤5 6-10 11-19 20+ **Current Female Smokers** ≤5 6-10 11-19 20+ **Cigarettes Within 1st 30 min of Waking** **All Current Smokers** No Yes **Current Male Smokers** No Yes **Current Female Smokers** No Yes	**Adjusted Odds Ratio of Menthol Use (95% CI)** 1.0 (reference) 1.03 (0.91-1.16) 0.96 (0.84-1.11) 0.84 (0.74-0.96)** 1.0 (reference) 1.09 (0.90-1.31) 1.00 (0.81-1.25) 0.85 (0.69-1.03) 1.0 (reference) 0.98 (0.84-1.15) 0.93 (0.77-1.12) 0.84 (0.71-1.00) 1.0 (reference) 1.05 (0.96-1.14) 1.0 (reference) 1.05 (0.92-1.19) 1.0 (reference) 1.04 (0.95-1.15) Adjusted for sociodemographic and smoking behavior variables.	Prevalence of menthol use is significantly higher among individuals who smoke on some days than among individuals who smoke every day. Time to first cigarette was not found to be a significant predictor of menthol cigarette smoking.	Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use was self-reported. Where sufficient numbers permitted race-specific analyses, there were no differences between menthol and nonmenthol users in cigarettes per day (Whites, Blacks) or TTFC (Whites, Hispanics).

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** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Mendiondo et al. 2010 United States	**Dependence** Cross-sectional analysis of data from the 2005 National Health Interview Survey and Cancer Control Supplement. Analysis was based on 12,004 women and men aged 25-64 years who were current everyday or former smokers. Menthol use was defined as "usual type of cigarette smoked." Dependence was assessed by predicted mean number of cigarettes smoked per day.	**Current Smokers** Nonmenthol Menthol **Former Smokers** Nonmenthol Menthol	**Adjusted Odds Ratios (95% CI) for Number Cigarettes Per Day** 1.0 (reference) 0.99 (0.98-1.00)** 1.0 (reference) 1.00 (1.00-1.00) Adjusted for age, race and sex.	Menthol smokers reported smoking fewer cigarettes per day than their nonmenthol counterparts. Further studies may need to tease out the health-related significance of smoking fewer menthol cigarettes per day but having similar health outcomes to those who smoke more nonmenthol cigarettes per day.	Conclusions are supported by study data. Large national population-based survey with many menthol smokers. Cross-sectional nature of analysis does not permit causal conclusions. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Moolchan et al. 2006 United States	**Dependence** Clinical evaluation of 91 adolescent smokers (age 13-17) who were recruited for a smoking cessation study. They had to smoke ≥10 CPD, score ≥5 on the FTND, and be motivated to quit. 86% (n=79) of them smoked menthols. To investigate the potential mechanism of lower smoking rates among African Americans (compared to Caucasians), two nicotine metabolite ratios were measured as markers of the metabolic disposition of nicotine (3HC to COT, and COT to CPD).	**<u>Entire Group</u>** **CPD (Mean)** Caucasians African Americans **FTND Score (Mean)** Caucasians African Americans **3HC/COT Ratio (Mean)** Caucasians African Americans **COT/CPD Ratio (Mean)** Caucasians African Americans **<u>Menthol Smokers</u>** **Cigarettes/Day (Mean)** Caucasians African Americans **3HC/COT Ratio (Mean)** Caucasians African Americans **COT/CPD Ratio (Mean)** Caucasians African Americans	 19.6 15.1 p=0.013* 7.1 6.7 NS 0.35 0.26 p=0.026* 8.5 12.1 p=0.033* 20.3 15.1 p=0.007* 0.35 0.27 p=0.041* 8.2 12.1 p=0.028*	Among the entire group, African American adolescents smoked significantly fewer cigarettes per day and had significantly lower nicotine metabolite ratios than Caucasian adolescents. Results were essentially unchanged when looking at the subgroup who smoked menthols, suggesting that the observed differences are due to factors other than menthol smoking.	Conclusions are supported by study data. Clinical evaluation of subjects in a smoking cessation study. Note that this study focused on racial differences in nicotine metabolism. There are limited data related to menthol/nonmenthol smoking. All subjects were adolescents who sought cessation treatment, thus limiting the generalizability of the results. Dependence was assessed by the FTND. FTND scores were not provided for the subgroup of menthol smokers, although most of the subjects (86%) were menthol smokers.

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** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Muhammad-Kah et al. 2010 United States	**Dependence** Stratified, cross-sectional, observational, multi-center ambulatory study (the Total Exposure Study). Subjects were adult men and women in generally good health who had smoked at least one cigarette per day for at least the past 12 months. This analysis focused on 1,044 menthol and 2.297 nonmenthol smokers. Dependence was assessed by the Fagerström Test of Nicotine Dependence (FTND), as well as its 6 individual elements.	**Overall FTND Score** Nonmenthol smokers Menthol smokers **TTFC (>30 min vs. <30 min)** Nonmenthol smokers Menthol smokers	**Adjusted Odds Ratios (95% CI)** 1.0 (reference) 1.05 (0.91-1.22) Menthol smokers did not have higher FTND scores than nonmenthol smokers. 1.0 (reference) 0.88 (0.72-1.05) Menthol smokers did not have increased odds of smoking within the 1st 30 minutes after waking compared to nonmenthol smokers. Odds ratios adjusted for race, sex, age, income, education, and tar yield category.	Our results add to the existing evidence that menthol does not increase nicotine dependence. Adult menthol smokers had no increased odds of having higher FTND scores as compared to nonmenthol smokers. When adjusted by race, sex, age, tar yield category, income and education, menthol status had no statistically significant effect on any single item of FTND or on the overall scores.	Conclusions are supported by study data. Large cross-sectional analysis. Cross-sectional nature of study does not permit causal conclusions. Dependence was assessed by the FTND, as well as its individual elements. Menthol use was self-reported.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

Table 5-4. Higher Quality Studies on Menthol Smoking and Indicators of Dependence (N=10) (Continued)

CITATION	OUTCOME STUDY TYPE	EXPOSURE	RESULTS	AUTHORS' CONCLUSIONS	STRENGTHS AND WEAKNESSES
Muscat et al. 2002 United States	**Dependence** Cross-sectional analysis of data from case-control study on smoking and lung cancer. There were 19,545 subjects, 3,005 of whom smoked menthol cigarettes. All were current or former smokers. Dependence was assessed as the prevalence of heavy smoking (≥21 CPD). Cessation data are included in Table 5-3.	**Whites** **Current Smokers** Nonmenthol Menthol **Former Smokers** Nonmenthol Menthol **Blacks** **Current Smokers** Nonmenthol Menthol **Former Smokers** Nonmenthol Menthol	**Adjusted Prevalence Odds Ratios of Heavy Smoking (>21 CPD) (95% CI)** 1.0 (reference) 0.9 (0.8-1.0) 1.0 (reference) 0.9 (0.8-1.0) 1.0 (reference) 0.7 (0.5-0.9)** 1.0 (reference) 0.6 (0.4-0.9)** Adjusted for age, education, case-control status, sex, and years of smoking.	Menthol was inversely associated with smoking more than one pack per day. Both Black and White smokers of mentholated cigarettes smoked fewer cigarettes per day than smokers of other cigarettes. The findings suggest that menthol does not increase the addictive properties of tobacco nicotine.	Conclusions are supported by study data. Cross-sectional analysis; consequently, does not permit causal conclusions. Nicotine dependence was assessed as the prevalence of heavy smoking (≥21 CPD). Menthol use was self-reported. Most subjects who smoked menthol during their lifetime also smoked nonmenthol cigarettes. Subjects were classified as menthol smokers if LAST brand smoked was menthol. Population was older and male; some were lung cancer patients.

* denotes statistically significant increase in risk
** denotes statistically significant decrease in risk

CHAPTER 6.
SEVERAL HYPOTHESES POSED BY TPSAC ARE SPECULATIVE

A review of meeting transcripts and presentations given at TPSAC meetings makes it apparent that some committee members are concerned about a number of issues not addressed in the previous chapters. Although these issues are discussed often, little information has been presented to date to support the validity of these claims. TPSAC should be reminded that with no increase in disease risk, as demonstrated by numerous high-quality epidemiology studies, and no convincing evidence that use of menthol cigarettes affects biomarkers of exposure or potential harm, smoking topography, or smoking behavior, the issues described below are primarily of academic interest. This chapter briefly reviews some of the hypotheses that have been discussed at TPSAC meetings and points out the speculative nature of each one.

HYPOTHESIS: SMOKERS PERCEIVE MENTHOL CIGARETTES AS BEING LESS HARMFUL

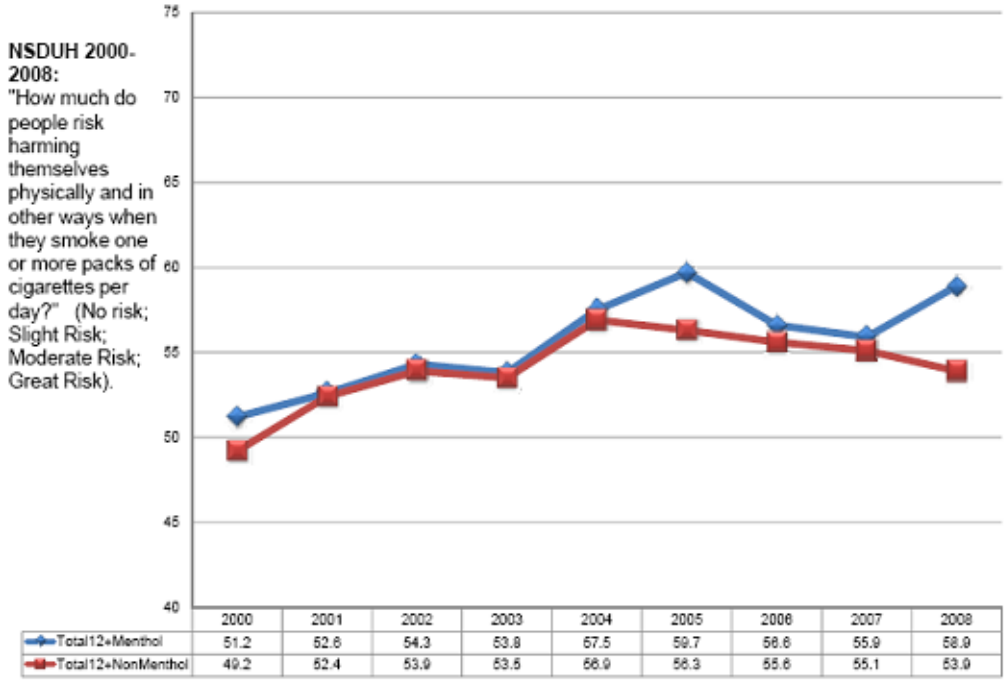
Published scientific research does not indicate that contemporary smokers have a perception that menthol cigarettes are less hazardous than nonmenthol cigarettes. This research shows that smokers generally perceive menthol cigarettes as equally, if not more, hazardous than nonmenthol cigarettes. In a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

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

Recent government data also demonstrate that menthol cigarette smokers perceive a greater risk of harm from smoking than nonmenthol cigarette smokers. From 2000 to 2008, as part of the NSDUH, consumers were asked, "How much do people risk harming themselves physically and in other ways when they smoke one or more packs of cigarettes per day? Answer options were: No Risk; Slight Risk; Moderate Risk; or Great Risk." (NSDUH 2000-2008).

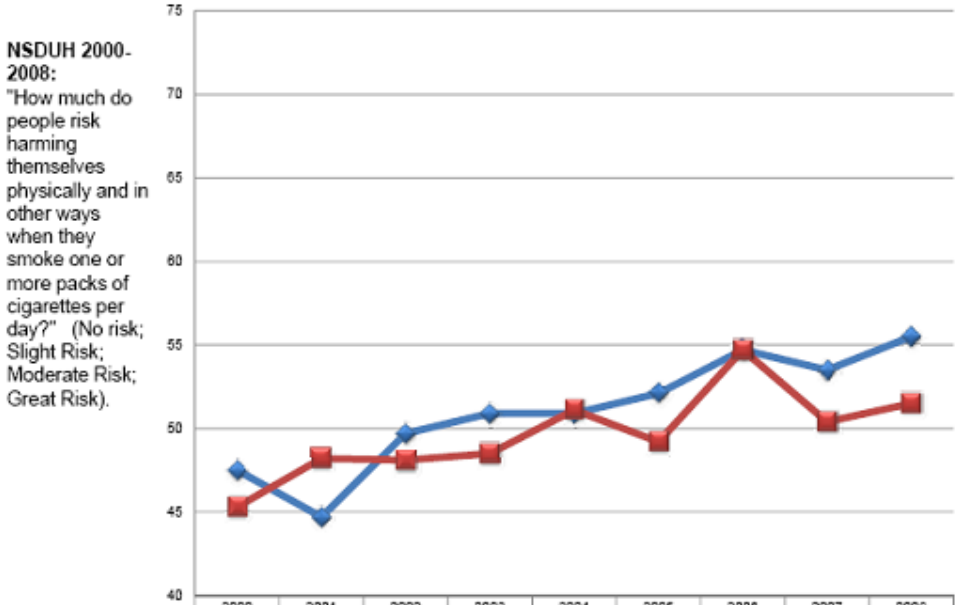
Responses to this question showed that menthol smokers perceive an equal or slightly greater health risk from smoking than nonmenthol smokers. Moreover, the perception that smoking presents a great risk of harm increased for both menthol smokers and nonmenthol smokers from 2000 to 2008 (see Figure 6-1). The same perception is true among adolescent smokers (see Figure 6-2).

Figure 6-1. Percentage of Menthol vs. Nonmenthol Smokers Who Believe Smoking Presents a Great Risk of Harm (NSDUH)



	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total12+Menthol	51.2	52.6	54.3	53.8	57.5	59.7	56.6	55.9	58.9
Total12+NonMenthol	49.2	52.4	53.9	53.5	56.9	56.3	55.6	55.1	53.9

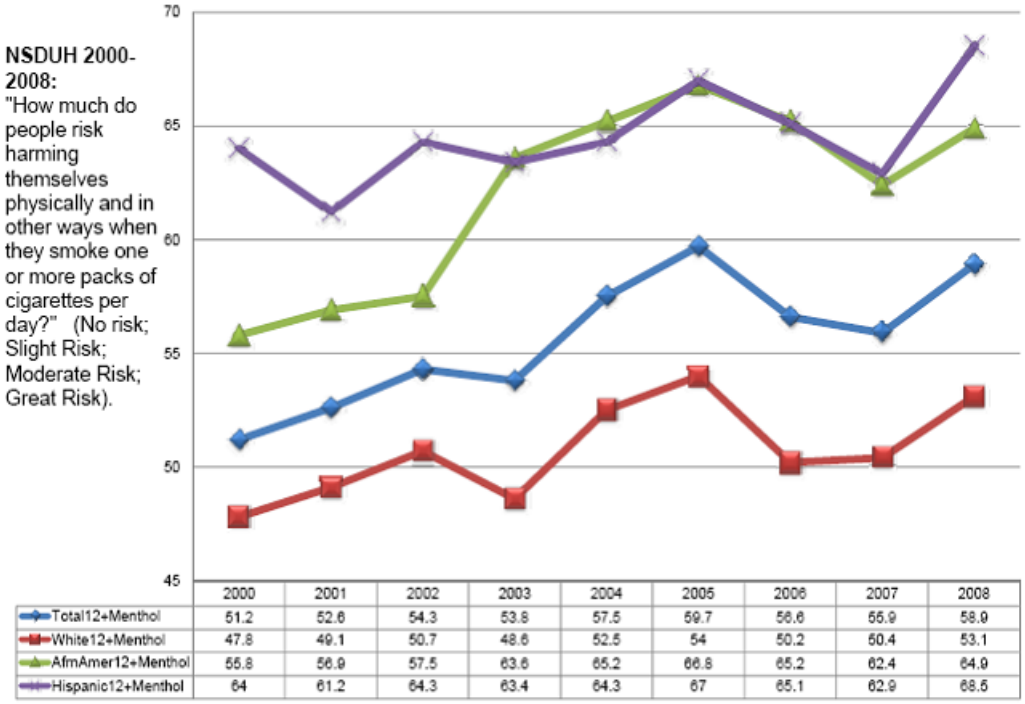
Figure 6-2. Percentage of Menthol vs. Nonmenthol Smokers (Age 12-17) Who Believe Smoking Presents a Great Risk of Harm (NSDUH)



	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total12-17Menthol	47.5	44.7	49.7	50.9	50.9	52.1	54.7	53.5	55.5
Total12-17Non-Menthol	45.3	48.2	48.1	48.5	51.1	49.2	54.7	50.4	51.5

NSDUH data also show that Hispanic and African American menthol smokers perceive a greater risk of harm from smoking than White menthol smokers. Moreover, the perception that smoking presents a great risk of harm increased for Hispanic, African American and White menthol smokers from 2000 to 2008 (see Figure 6-3).

Figure 6-3. Percentage of Menthol Smokers by Race/Ethnicity Who Believe Smoking Presents a Great Risk of Harm (NSDUH)



	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total12+Menthol	51.2	52.6	54.3	53.8	57.5	59.7	56.6	55.9	58.9
White12+Menthol	47.8	49.1	50.7	48.6	52.5	54	50.2	50.4	53.1
AfrAmer12+Menthol	55.8	56.9	57.5	63.6	65.2	66.8	65.2	62.4	64.9
Hispanic12+Menthol	64	61.2	64.3	63.4	64.3	67	65.1	62.9	68.5

Other published survey data on this issue going back 25 years are consistent with NSDUH. The 1986 Adult Use of Tobacco Survey reported that menthol smokers' beliefs about the health effects of smoking differed little from the beliefs of nonmenthol smokers (AUTS 1989). Data from the 1987 National Health Interview Study (NHIS) also indicated few differences between menthol and nonmenthol smokers' risk beliefs; further, the NHIS showed that menthol smokers were more likely than nonmenthol smokers to agree that smoking causes various ailments (NHIS 1987).

HYPOTHESIS: MENTHOL INCREASES HARM THROUGH CHEMOSENSORY EFFECTS

Some authors have speculated that menthol increases the harm of smoking through its chemosensory effects. They have suggested that menthol goes beyond its role as just a flavoring by masking irritation and pain sensations associated with smoking, enabling easier smoking initiation and increased exposure due to changes in respiratory patterns (e.g., Kreslake et al. 2008, Wayne and Connolly 2004). It is important to note, however, that support for menthol's purported desensitization and anesthetic properties is very limited and information on this topic has been largely obtained from laboratory and clinical protocols using methods of administration and doses unlike those in actual smoking. Experience with cigarette product development indicates no special

role of menthol in this regard, particularly with respect to the chemosensory properties (primarily irritation) of nicotine in smoke.

The aroma, flavor, and cooling thermal properties of menthol have made it popular in personal and health care products, particularly in topical and oral care formulations. In the majority of instances (most of which precede any modern mechanistic research or the structural characterization of the receptor for thermal coldness), use of menthol rests simply on its simple sensory properties explored empirically. Understanding the role of menthol in cigarettes has very much an empirical basis, just as understanding its' role in personal care and over-the-counter products. Admittedly, marketing once implied that a menthol cigarette could soothe the irritated throat, but whether it did or not was never explored with scientific rigor. The tobacco industry has relied principally on traditional taste and sensory evaluation, using panels of internal expert smokers and consumer panels to develop its products. The characteristic taste and sensory notes imparted by menthol in some tobacco products marketed as having a mentholated character is simply preferred by a minority of smokers and is not preferred or even regarded as quite distasteful by the majority of smokers. Ultimately, menthol is a characterizing flavor used in cigarettes to meet the taste preferences of some smokers; it is recognized that reactions to menthol vary considerably, and range from aversion to liking among individual smokers.

Menthol can impart not only cooling, but also a minty aroma and flavor to products (Eccles and Jones 1994, Werley et al. 2007) and can even impart bitterness, depending on the location of application on the tongue (Green and Schullery 2003). These actions derive from a pattern of activity of smell, taste, and chemesthetic receptors. Contemporary research in the chemosensory and food technology fields has provided a considerable insight into the mechanistic basis of receptor-mediated chemesthetic stimuli that are subjectively perceived very differently by different individuals. Those perceptions span the entire spectrum of preferences from enjoyment to powerful aversion. These sensory notes include the cooling properties of menthol and other natural and synthetic compounds; the hot, peppery properties of red and black pepper principles; and the tingling sensations imparted by beverage carbonation. Menthol and similar sensory stimuli mediate their effects through mixed agonism, antagonism, sensitization, and desensitization across neural fibers, as is the normal rule for any flavor or sensory component of a complex product mixture.

In recent years, the characterization of the TRP (transient receptor potential) super-family of receptors illustrates how one set of receptors can actually respond to more than one type of stimulation. TRPM8 receptors react in sensations of cooling, TRPV1 receptors respond to warmth and the burning from capsicum compounds, TRPA1 receptors react to a broad range of noxious compounds, such as those in wasabi and mustard, as well as compounds such as carbonyls that are present as normal constituents of tobacco smoke. Different parts of TRPA1 channels respond to different irritants and, it seems, to some cooling compounds, giving it an enormous breadth of "tuning." The responses may also change with level of stimulation (Dessirier et al. 2001, Eccles and Jones 1983, McKemy 2005, Patel et al. 2007). For example, application of menthol at low concentrations to skin or mucosal surfaces produces a cooling sensation, whereas at higher exposure levels it can produce sensation of burning, irritation, or pain. The effect of just one among many level-dependent chemosensory stimuli found in cigarette smoke, demonstrated in isolation or in simple interaction experiments, is in all likelihood an inadequate basis to represent phenomena that may occur from inhalation exposure to the exceedingly complex smoke aerosol. Some of the major sensory components of the cigarette smoking experience, such as "throat grab" or "chest impact," as well as the taste of cigarette smoke itself, are subjectively perceived as desirable or powerfully

aversive by smokers and nonsmokers, or among different smokers. The intensity of the taste or sensory contributions of menthol are similarly perceived very differently by different smokers, so simplistic general conclusions drawn from experimental dosing with pure menthol are entirely inadequate to account for the very different subjective taste perceptions that different smokers report for menthol and nonmenthol cigarettes.

It has been suggested by some authors that menthol desensitizes the airway to irritation from the components of smoke, including nicotine, and thereby makes it easier or more desirable to smoke more (e.g., Dessirier et al. 2001). Experimental and clinical studies have shown both increased and decreased sensitivity due to the presence of menthol (e.g., Dessirier et al. 2001, Foster et al. 1993, Green and McAuliffe 2000, Hans 2006, Lee et al. 2007, Reeh and Kichko 2006, Renner et al. 2008, Talavera et al. 2009, Xiao et al. 2008, Zanotto et al. 2008). Most of these studies have involved use of in vitro experimental systems to examine mechanistic aspects of the interaction of menthol with peripheral receptors and individual compounds (e.g., nicotine) or topical application of compounds. Whereas such studies may have contributed some understanding of the action of menthol, they do not provide a sound scientific basis for the hypothesis that menthol may alter perception in the complex matrix of cigarette smoke, beyond the familiar characterizing flavor that it imparts. The degree of promiscuity for ligands by the TRP family of receptors, the ranges and degree of overlap in their sensory signals, and the complex mixture that is cigarette smoke have rendered a determination of any net effect of mentholated cigarette smoke elusive. Further confounding the pharmacology is research indicating that nicotine itself has nicotinic acetylcholine receptor-independent irritant properties mediated through TRPA1 (Talavera et al. 2009) in addition to local nicotinic receptor-mediated irritation in the respiratory tract (Lee et al. 2007). A further example is provided by the Philip Morris USA-funded clinical study of Renner et al. (2008) that found menthol had no effect on the perception of stinging and burning from nicotine pulses administered as a vapor to the nasal mucosa in adult smokers. Although this study did not evaluate the effects of menthol in cigarette smoke, it did evaluate exposures in routes and target receptors more directly relevant to the actual smoking experience than in vitro or ex vivo experimental systems.

Some have asserted that menthol may, through local anesthetic effects, attenuate irritation produced by inhaled cigarette smoke (e.g., Ahijevych and Garrett 2004, Patel et al. 2007, Wayne and Connolly 2004); this claim is poorly supported by mechanistic data. Galeotti et al. (2001) is often cited in support of such a local anesthetic effect. That report showed that menthol reduced muscle contractions under experimental conditions in the rat (in vitro phrenic nerve hemidiaphragm preparation) and the rabbit (in vivo), but did not block the action potentials of sensory nerves, a key feature of local anesthetics. Other researchers have also provided mechanistic evidence that menthol fails to block action potentials (e.g., Haeseler et al. 2002, Hans 2006, Swandulla et al. 1987). It has been suggested that menthol in topical preparations at high concentrations may relieve pain via production of a warming sensation similar to that of heat therapy (Harris 2006). Nevertheless, menthol does not exhibit features characteristic of local anesthetic action in that it does not appear to block current-induced neuronal action potentials nor have any effect on neuronal sodium channels.

Menthol also has proalgesic properties (Sherkheli et al. 2008). The relative strength of menthol as an analgesic is weak compared to other over-the-counter (OTC) sore throat medications, including Cepacol (benzocaine) and Sucrets (dyclonine), as evidenced by their use of other main active ingredients in place of or in conjunction with menthol. The amount of menthol used is ~4-7 times higher in Cepacol lozenges than the 0.5 mg estimate of smoke menthol, and menthol is not a

primary therapeutic compound for the treatment of cough of any origin (Irwin et al. 2006). Menthol is similarly not useful as a clinical anesthetic for oral or dental procedures (i.e., laryngoscopy, endotracheal intubation, endoscopy, cavity preparation, or endodontics). The lack of clinical use as an anesthetic or antitussive, even for these relatively minor procedures runs counter to the claims that menthol is an effective topical anesthetic in the oral and upper respiratory regions. Markedly more efficacious drugs (Cetacaine®, injectable lidocaine, injectable bupivicaine, etc.) are readily available and are widely used to achieve clinically significant local anesthesia.

Further, it has been speculated that menthol causes smokers to inhale more deeply. This claim appears to be based on reports that menthol increases the perception of nasal airflow and decreases respiratory rates (Wayne and Connolly 2004). While it has been reported that menthol increases the *perception* of nasal airflow, this perception is not accompanied by any actual physical changes in the airway (e.g., Eccles and Jones 1983, Eccles et al. 1989, Eccles et al. 1990, Houghton and Beardsmore 1998). Enhanced stimulation of cold receptors is likely to account for this sensation of increased nasal airflow and respiratory ease (Nishino et al. 1997). Some reports have suggested that menthol can decrease respiratory rates in experimental animals (e.g., Orani et al. 1991, Sant'Ambrogio et al. 1992) and humans (Sloan et al. 1993). However, these studies have limited relevance to real-world smoking exposures to menthol in that they involve measurements in anesthetized animals exposed to menthol by inhalation and of voluntary breath-holding in humans who ingested menthol lozenges. Doubts about the ability of menthol to affect breathing patterns in smokers significantly and uniformly are especially appropriate in light of the mixed and inconsistent findings regarding the effects of menthol in clinical smoking topography studies.

Any case for added harm due to menthol based on existing scientific data surrounding these hypotheses is not convincing. The arguments discussed before TPSAC appear to be constructed largely by citing behavioral principles and effects out of context, and fall far short of providing a sound scientific basis of evidence for any real, incrementally adverse public health outcome. Basing any conclusion or recommendation on evidence of this type directly contradicts the mandate issued by the Director of the Center for Tobacco Products, Dr. Lawrence Deyton, at the first TPSAC meeting during which he stated that the success of TPSAC was dependent on being "guided by the best science" and that "the advice you give us [must be] based on the science and the science alone" (TPSAC 2010a p.39). Claims regarding the role of menthol in encouraging smoking initiation and maintenance, discouraging quitting by making satisfying low-yield cigarettes, or increasing the addictiveness of smoking are not supported by clear evidence (as discussed in detail in previous sections of this report). Furthermore, there is a lack of sound data connecting available knowledge of the physiologic, pharmacologic, and neurochemical mechanisms of menthol's sensory impact to specific smoking-related behaviors. These behaviors are more informatively measured by other, more direct methods by extrapolation from laboratory research on menthol in isolation in experimental systems to complex human behaviors.

HYPOTHESIS: MENTHOL "MAKES THE POISON GO DOWN EASIER"

At many TPSAC meetings, committee members and attendees have repeatedly made the assertion that menthol makes the "poison go down easier." While exactly what this means has never been stated, it may be another way of saying that menthol cigarettes make it easier to start smoking, inhale more deeply, or make it harder to quit. The literature discussed in the previous chapters (3-5) does not provide evidence in support of this hypothesis. FDA and TPSAC have received written and verbal information that menthol added to cigarettes does not in fact reduce the harshness or irritation of cigarette smoke. Product developers in the tobacco industry have long appreciated that increases in smokers' perceptions of smoke harshness by product design features such as filter tip ventilation or excessive dryness of the cigarette tobacco filler are not ameliorated by added menthol. Neither the available body of scientific evidence on smoking topography nor comparisons of biomarkers of smoke exposure in menthol and nonmenthol cigarette smokers have not substantiated the facilitation of deeper smoke inhalation. Most importantly, the epidemiology studies, which incorporate the combined influences of all aspects of smoking behavior, consistently fail to show that menthol smoking is associated with any significant increase in disease risk compared to nonmenthol smoking.

Smokers' stated reasons for choosing a particular cigarette brand are numerous and complex, and vary considerably from smoker to smoker. Menthol content is only one factor related to consumer acceptability. Smokers accept or reject cigarettes based on a variety of product attributes and sensory characteristics, including strength of taste, strength of menthol flavor, smoothness of taste, harshness of taste, refreshment of taste, tobacco taste, and balance of menthol taste and tobacco taste. Other factors such as price and the cigarette brand favored by an individual's family or social group also may be important determinants in making choices regarding preferred cigarette brands.

Consumer research consistently shows that smokers who prefer menthol over nonmenthol cigarettes do so primarily because of taste. Some of the industry's studies of the physiologic, pharmacologic, and neurochemical mechanisms of sensory impact have been carried out to better understand how different cigarette ingredients may affect chemosensory responses and to understand consumers' reactions to different products. The findings of these types of mechanistic studies are not typically used to design and develop cigarette products, but rather to understand how flavors or other design components might be adjusted to compensate for reported taste and sensory deficits. Taste preferences and even how menthol taste characteristics are described are not consistent among individuals, but some menthol cigarette smokers are able to detect slight differences in menthol levels and can taste the differences among different cigarette brands. These perceptions are not unlike those for tobacco taste itself among smokers who prefer nonmenthol brands. Individuals have their own perceptions and preferences of the menthol taste characteristics, and the majority of U.S. smokers prefer no menthol taste at all.

Speculative explanations of how menthol may mask nicotine or other components of cigarette smoke based on existing mechanistic data do not appear to be as likely or important reasons for brand selection as are simple subjective taste preferences. In fact, some menthol smokers appear to prefer the taste impact associated with cigarettes having a lower nicotine yield balanced with the menthol flavoring characteristic. It is worthwhile to note, of course, that nonmenthol smokers also make choices regarding their preferred brand based on taste and reject the menthol flavor characteristic in favor of preferred choices among tobacco flavor characteristics. This spectrum of tobacco taste characteristics includes such elements as burley tobacco character, bright tobacco

character, oriental/Turkish notes, and a variety of other terms of the cigarette developer's art that are typically interpreted by the smoker as a simple taste preference for one cigarette over another.

DiFranza et al. (2004) conducted a "retrospective/prospective" longitudinal analysis of a cohort of seventh graders who were followed for 30 months (part of the Development and Assessment of Nicotine Dependence in Youth Study) to assess subjects' reactions to their first cigarettes and whether these reactions were predictive of later nicotine dependence. The analysis focused on 237 subjects who reported that they had inhaled a cigarette; only about half of them could recall whether the first cigarette they had smoked was mentholated or not. The authors found that reactions to the initial smoking experience (irritation; nausea; dizziness; relaxation; felt good, or good and bad; desire to smoke again, yes or maybe) were unrelated to mentholation. They were also unrelated to sex, cigarette brand, or strength of cigarette. In addition, for the 59 subjects who smoked enough to have established a favorite brand, the strength of the addiction, as measured by the Hooked on Nicotine Checklist, did not differ according to the favorite brand, brand strength, or menthol content. Although this study has some limitations (small sample size, subjectivity of symptoms, few subjects who could recall mentholation of first cigarette, few African American subjects), it argues against the assertion that menthol in cigarettes alters the smoking experience to make it more pleasurable and easier to continue than nonmenthol cigarettes, i.e., menthol does NOT "make the poison go down easier."

HYPOTHESIS: MENTHOL INCREASES POTENTIAL FOR ABUSE

The concept of abuse liability has been raised by some members of TPSAC. The FDA defines products with abuse potential (a term interchangeable with abuse liability) as "a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their central nervous system (CNS) activity" (FDA 2010b). The applicability of this concept to menthol cigarettes is unclear, as the central nervous system effects of menthol cigarettes have not been documented (Ahijevych and Garrett 2004). Furthermore, drugs with abuse potential often (but not always) produce dependence and may lead to addiction (FDA 2010b). As discussed in Chapter 5, a review of the methodologically sound literature on menthol smoking and cessation demonstrates that the most relevant studies – those that address successful long-term quitting – do not indicate that smokers of mentholated cigarettes are less likely to quit than are smokers of nonmentholated cigarettes. Additionally, the studies that address other measures of nicotine dependence do not find that menthol smokers are any more dependent on nicotine than nonmenthol smokers.

HYPOTHESIS: MENTHOL SMOKERS WHO SMOKE 6-10 CIGARETTES/DAY ARE UNIQUELY AFFECTED

Based on the findings of a recent study (Fagan et al. 2010), TPSAC members speculated that menthol smokers who smoke fewer than 10 cigarettes per day are more dependent than those who smoke more than 10 cigarettes per day. Fagan et al. conducted an analysis of the pooled datasets of

the 2003 and 2006/07 TUS-CPS. The data showed that after adjustment for multiple factors,[1] subjects who smoked their first cigarette within 5 minutes of waking were more likely to be menthol smokers of 6-10 cigarettes per day than nonmenthol smokers of 6-10 cigarettes per day (OR=1.22, 95% CI: 1.05-1.43). When the same analysis was conducted on smokers of <5, 11-19 and ≥20 cigarettes per day, there were no significant differences between menthol and nonmenthol smokers. No significant differences were found in any other measures of dependence, including whether subjects smoked their first cigarette within 30 minutes of waking, had a quit attempt lasting 1 day or longer within the past 12 months, and length of smoking abstinence. As discussed in Chapter 5B, the authors focused on this one significant finding to conclude that menthol smokers who reported consuming 6-10 CPD show greater signs of nicotine dependence than comparable nonmenthol smokers. However, it is inappropriate to focus on this single finding when the overall pattern of results suggests no difference in TTFC between menthol and nonmenthol smokers. The authors acknowledge that the effect was not dose-dependent, as odds ratios for TTFC after waking did not increase as smoking intensity increased for menthol smokers.

Given that Fagan et al. (2010) is the only study that looks specifically at menthol smokers of 6-10 cigarettes per day, at the request of TPSAC, Altria conducted an analysis of the Total Exposure Study (TES) dataset that included only those subjects who smoked ≤10 cigarettes per day and compared menthol to nonmenthol smokers on biomarkers of exposure (nicotine equivalents, carboxyhemoglobin, serum cotinine, total NNAL), FTND scores and TTFC. There were no significant differences in exposure and dependence measures among menthol smokers as compared to nonmenthol smokers of ≤10 cigarettes per day. These results were consistent with the previous findings from the TES, observed among all adult smokers. Additionally, this analysis adds to the substantial body of evidence that indicates no effect of menthol on exposure or dependence measures.

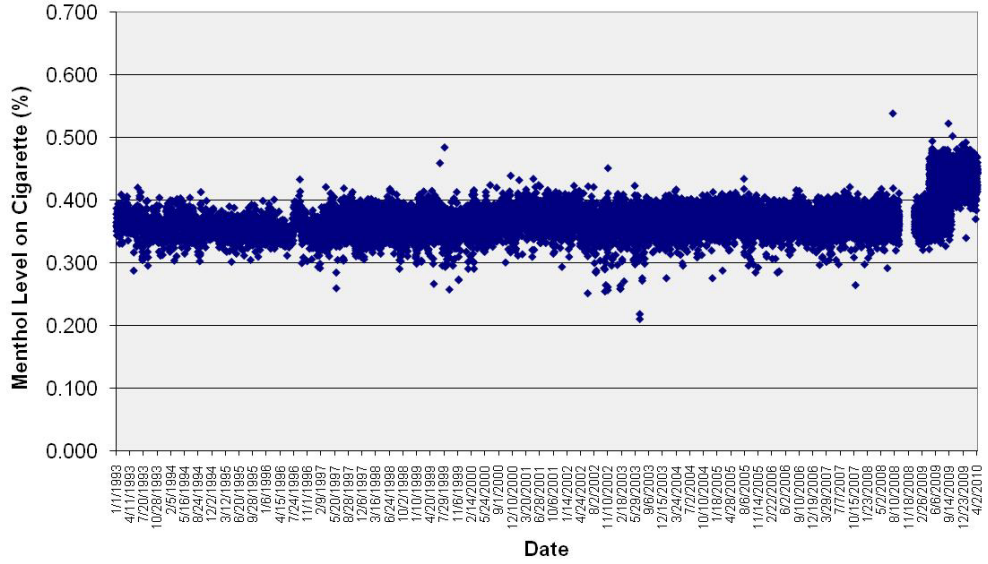
HYPOTHESIS: VARIATIONS IN MENTHOL LEVEL DRIVE BRAND POPULARITY

TPSAC has discussed a single published paper that has asserted that the tobacco industry has manipulated levels of menthol downward to increase the appeal of menthol cigarettes to adolescents (Kreslake et al. 2008). The Industry has previously submitted detailed product data to the FDA that refutes this assertion. The industry led a discussion with TPSAC on this subject during the July 15-16, 2010 TPSAC meeting (TPSAC 2010b p.17) with the example of the leading menthol brand, Newport, discussed in some detail. It should not be surprising that some competitors of the manufacturer of Newport may have speculated internally with regard to the reasons for Newport's increasing success in the marketplace in prior decades, as such analysis and hypothesis is a normal component of free market competition. Some of these analyses included hypotheses relating to the moderately lower levels of menthol in Newport compared to those found in some competitive brands. The fact is that menthol levels in existing products have generally remained stable over time and any significant changes can be explained by changes in regulations or other business reasons, such as blend consolidations or target level adjustments due to revised (improved) analytical methodology for determining menthol. As a compelling example of this fact, the amount of

[1] Odds ratios were adjusted for sex, age, race/ethnicity, marital status, educational attainment, annual family income, employment/occupational status, region, metropolitan status, survey year, age of onset, total years smoked daily and smoking status 12 months ago.

menthol in the most popular menthol brand, Newport Kings Box, did not change substantially from 1972 through 2009.[2] As Figure 6-4 demonstrates, the pack menthol levels have not changed beyond normal production variation parameters for years prior to the design changes employed as a result of compliance with new fire safe cigarette standards. Pursuant to Section 904 of the Act, the Industry has reported to the FDA the amounts of menthol applied to each brand and sub-brand of its cigarettes.

Figure 6-4. Newport Full Flavor 80mm Menthol Level (1993-2010)



Introduction of Fire Standards Compliant (FSC) Cigarette Regulations

Beginning with New York in 2004, all states and the District of Columbia require or will require each cigarette manufacturer to certify that its cigarettes comply with the testing and performance standards of American Society for Testing and Materials Standard E21S7-04b. The paper technologies typically used by the industry to achieve low ignition propensity (LIP) compliance typically slowed the burn rate of the cigarette, increased the number of puffs, and increased tar and nicotine deliveries. To maintain consumer acceptance and smoke deliveries consistent with pre-LIP cigarettes, companies employed cigarette design changes, including adjusting the levels of some additives and adjusting cigarette filter efficiency and ventilation. In some cases, these design changes required an increase in the amount of menthol applied to the cigarettes due to, among other things, increased filtration or increased filter ventilation (also called air dilution). Because menthol is filtered at roughly the same rate as tar and nicotine, increased filter efficiency or ventilation causes the menthol delivered in the smoke to be reduced. To ensure that products were delivering the same menthol taste preferred by the consumers of those brands, the amount of menthol in the cigarette was increased to the level necessary to approximate the menthol delivery in the smoke of those brands prior to the design changes. In other cases, the amount of menthol applied to the cigarette was not changed, but the level of filter ventilation was increased to maintain consistent smoke

[2] See Lorillard's submission and presentation on "Characterization of Menthol" to TPSAC on July 15-16, 2010, for a detailed discussion of the levels of menthol in Lorillard cigarettes.

delivery (i.e., 'tar') according to pre-regulation design criteria. In these cases, the actual smoke delivery of menthol decreased as the result of compliance with FSC regulations.

In addition, the TPSAC discussions at the March 30-31, 2010 meeting referred to the belief that cigarette brands reportedly preferred by younger smokers have lower levels of menthol than do brands reportedly preferred by older smokers, and that cigarette manufacturers had lowered menthol levels as a general strategy to attract youthful smokers in recent years. This notion has arisen largely from a single paper published in 2008 by Kreslake et al. The methodology employed in this study (a two point trend analysis based on incompatible analyses performed years apart by different methods in different laboratories) is not scientifically sound, as it does not provide a statistically representative characterization of the menthol levels for products having annual production volumes of billions of units. The data discussed above and the detailed documents supplied to FDA by the industry for a case study of the current most popular menthol brand unequivocally refute the assertion that menthol levels in products have been lowered to attract youth.

HYPOTHESIS: MANUFACTURERS MARKET MENTHOL CIGARETTES DIFFERENTLY THAN NONMENTHOL CIGARETTES

Cigarette marketing practices is a difficult topic to discuss from a single industry perspective. There are many cigarette manufacturers with each company independently deciding how to market its products.

At the July 15, 2010 TPSAC meeting, the three largest cigarette manufacturers (Altria on behalf of Philip Morris USA, R.J. Reynolds Tobacco, and Lorillard Tobacco Company) provided TPSAC with written submissions and presentations about their particular marketing practices for their menthol cigarette brands. Each company independently emphasized that the marketing of menthol cigarettes involves the same activities used for the marketing of nonmenthol cigarettes.

At that meeting, the submissions and presentations of the three largest cigarette manufacturers noted the following common practices for the marketing of menthol cigarette brands:

- The same practices are used to market both menthol and nonmenthol cigarettes.
- All marketing efforts are directed to adult smokers with the intent of maintaining brand loyalty or attracting smokers of competitive brands. Cigarettes are not marketed to non-smokers.
- No marketing activities are directed to youth. Smoking is an adult choice. Underage persons should not smoke.
- The commonly used marketing activities included:
    - Retail merchandising and point-of-sale advertising,
    - Direct mail, electronic mail, and branded websites directed to age-verified adults, and
    - Retail price promotions, which account for the vast majority of all marketing expenditures (TPSAC 2010b p.295).

For decades, cigarette brand marketing has been subject to ever-increasing and substantial prohibitions, restrictions and requirements imposed by Congress, federal agencies, and state and local authorities. Over the last ten to fifteen years, there have been additional dramatic and substantial changes in how the tobacco industry markets cigarettes. Today, no other legal consumer product is subject to more restrictive marketing requirements than cigarettes. All cigarette brand marketing, both menthol and nonmenthol cigarettes, must comply with the extensive restrictions set forth in the Tobacco Settlement Agreements (TSAs)[3] and the Act.

The TSAs include a number of restrictions on the marketing of all cigarette brands. First and foremost, the TSAs prohibited the direct or indirect targeting of youth through advertising, promotion or marketing or any action the primary purpose of which is to initiate, maintain or increase the incidence of youth smoking. The TSAs also included, among other things, prohibitions on (1) the use of cartoons in advertising, promotion or packaging of cigarettes, (2) most outdoor advertising, including billboards, transit and stadium/arena advertising, (3) placement of tobacco products in movies or television shows, (4) brand name sponsored concerts, and (5) distribution of merchandise with cigarette brand names and logos.

In addition to the TSA restrictions, the Act contains additional prohibitions on (1) self-service displays except in adult-only facilities, (2) free cigarette sampling, (3) providing gifts (other than cigarettes) in consideration of the purchase of tobacco products, (4) brand name sponsorships, and (5) co-marketing of tobacco products with other FDA-regulated products.

The Act also limits nearly all cigarette advertising and labeling to black text on white background[4] and requires larger warnings[5], including graphic warnings for all cigarette packaging and advertising. FDA has also announced that it is considering additional restrictions on outdoor advertising (FDA 2010a).

The TSAs of the late 1990s and the Act's passage in 2009 fundamentally changed the way cigarettes are marketed and sold in the United States. It serves no meaningful regulatory purpose for FDA or other forward-looking regulatory bodies to continue to revisit industry marketing practices or industry documents from decades ago, as those practices are no longer relevant in a post-TSA and post-Act environment. Further, most of marketing restrictions in the Act took effect in June 2010. The effectiveness of these restrictions should be measured before determining if other actions are required.

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[3] In 1998, the Major Manufacturers, including Lorillard, RJRT and Philip Morris U.S.A. and other Original Participating Manufacturers, signed an agreement with the Attorneys General of 46 states, five U.S. territories and the District of Columbia (Master Settlement Agreement or MSA). The MSA, along with similar agreements entered into with the States of Florida, Mississippi, Texas and Minnesota, are referred to as the Tobacco Settlement Agreements (TSAs).

[4] FDA announced it would be exercising enforcement discretion and not commence enforcement of this requirement while the injunction against enforcement issued in Commonwealth Brands, Inc. v. United States, No. 1:09-CV-117-M (W.D. Ky. Jan. 4, 2010) is pending appeal.

[5] New warning requirements for cigarettes under the Act have not yet taken effect. According to the Act, new warning requirements must take effect by September 22, 2012.

No Health Claims in Menthol Advertising

Similarly, it serves no purpose to assert that menthol ads contain health claims based on ads that have not been published for several decades. The Cigarette Advertising Guides, promulgated by the Federal Trade Commission (FTC) in 1955, prohibited both explicit and implicit health claims in cigarette ads (FTC 1955). Furthermore, all health-related claims in advertising are prohibited by both the TSAs and the Act.

Terms such as "cool," "smooth," "fresh," "refreshing," and "mild," as well as images of water, springtime and other refreshing imagery are deemed by some to be used in menthol cigarette advertising in an effort to implicitly communicate that menthol cigarettes are less hazardous than nonmenthol cigarettes. First, as shown earlier in this chapter, menthol smokers do not perceive smoking as less risky. Second, cigarettes are marketed as having "cool" and "fresh" tastes and sensations consistent with what adult smokers seek in menthol brands and consistent with the flavor characteristics of the particular brand. Interestingly, some of these terms, particularly "smooth," "fresh," "refreshing," and "mild" have been or are also used in advertising for nonmenthol cigarettes. But more importantly, such terms are only intended to communicate taste, flavor and satisfaction. In fact, these terms are the same terms that smokers, themselves, use to describe preferred cigarette taste characteristics.

Menthol Cigarettes Are More Expensive Than Nonmenthol Cigarettes

For at least the last ten years, the great majority of Industry marketing expenditures have gone toward retail price promotions. The reason for this is straightforward: the cost of cigarettes has risen dramatically. Much of the increased cost is due to substantially higher local, state and federal cigarette taxes. For example, due to changes in the federal excise tax in 2009 and the most recent New York state excise tax increase in 2010, New York City smokers pay more than $7 per pack in federal, state, and local excise and sales taxes. Retail price promotions are only legally available to adult purchasers of cigarettes.

At the July TPSAC meeting, the three largest manufacturers discussed pricing of menthol cigarettes compared to nonmenthol cigarettes as part of their marketing presentations. The prices for menthol cigarettes, after all promotional discount, were slightly higher than nonmenthol cigarettes (TPSAC 2010b p.295). At the November 18, 2010 TPSAC meeting, RTI International (RTI) presented background information for TPSAC about pricing and promotion of menthol cigarettes and confirmed that the prices of menthol cigarettes were slightly higher than nonmenthol cigarettes (RTI 2010). RTI also noted that promoted cigarettes accounted for a greater percentage of sales for menthol cigarettes than for nonmenthol cigarettes (RTI 2010). However, a comparison of the values of the promotions was not provided. Most importantly, prices at retail reflect prices <u>after</u> promotions (TPSAC 2010b p.295). The fact that menthol cigarettes may be promoted more than nonmenthol cigarettes does not change the simple fact that consumers pay higher prices for menthol cigarettes.

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CHAPTER 7.
A BAN ON MENTHOL CIGARETTES WILL RESULT IN SIGNIFICANT COUNTERVAILING EFFECTS

The previous chapters demonstrated that smoking menthol cigarettes do not disproportionately impact the public health compared to smoking nonmenthol cigarettes. However, in order to fully assess countervailing effects as required by the Act, this chapter considers the consequences if a ban on the sale of menthol cigarettes were imposed.

BANNING MENTHOL CIGARETTES WOULD INCREASE BLACK MARKET CIGARETTE SALES AND PRODUCE A RANGE OF PUBLIC HEALTH PROBLEMS

Section 907(b)(2) of the Act requires FDA and TPSAC to:

> "…consider all other information submitted in connection with a proposed [tobacco product] 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 and the significance of such demand."

If the United States government were to ban menthol cigarettes, nearly 30 percent of all cigarettes consumed in the United States would be outlawed. History has shown that when consumer preferences are blocked by government policy, black markets will emerge and criminal enterprises will flourish.

Under a menthol ban, contraband menthol cigarettes would inevitably be sold through an expansion of the sophisticated black market that currently exists. There would be no way to monitor the quality and safety of the cigarettes or their ingredients – or whether they are sold to underage individuals. Furthermore, there is no evidence that overall smoking rates would decline significantly.

This chapter demonstrates the unintended and negative impacts on public health that would result from efforts to ban menthol cigarettes. Congress' purpose of granting FDA with authority to regulate tobacco was to create order and supervision of the industry – not create chaos the likes of which have not been seen since Prohibition[1] (Altria Client Services 2010). In addition to the scientific information presented elsewhere, FDA must carefully consider the countervailing effects of a menthol ban as demonstrated here.

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[1] A report submitted by Altria Client Services Inc. on behalf of Philip Morris USA, Inc. for the January 10, 2011 TPSAC meeting ("Countervailing Effects of a Ban on Menthol Cigarettes"), notes that, from 1920 to 1933, the sale, manufacture and transportation of alcohol were banned during Prohibition in the United States. During this time the federal government devoted nearly half its law enforcement resources to enforcing Prohibition, as millions of otherwise honest citizens routinely flouted the law. Research showed that per capita consumption of alcohol actually increased during Prohibition.

A Large-Scale Illegal Market in Cigarettes Has Been Well Documented

One fact is without dispute: a significant and troubling illicit market in counterfeit and contraband cigarettes currently exists in the United States.

With the infrastructure of the black market already in place, some federal agencies expect the sale of contraband cigarettes to expand even *without* the added stimulus of a ban of menthol cigarettes. A U.S. Department of Treasury report (2010) to Congress said: "The scope of this problem will certainly multiply, based upon the tax increases imposed under CHIPRA [the Children's Health Insurance Program Reauthorization Act of 2009] and similar tax increases at the state level in recent years." It added: "Tax evasion schemes function in a variety of ways and continuously evolve in efforts to outpace enforcement and operate beyond its reach."

Experts at the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) describe, in a report for the Department of Justice Inspector General (USDOJ 2009), the diversion of tobacco as a global problem and say that illegal cigarettes are the No. 1 black market commodity in the world. ATF officials told the Department of Justice Inspector General that individuals and organized crime groups have been involved for decades. These groups are now running larger scale diversion schemes that are more complicated with the enterprises having all the characteristics of a structured business model that mirrors legitimate tobacco manufacturers – a source, a warehousing system, a shipping network and finally a retail outlet. ATF's diversion program "has not kept pace with the level of diversion activity and increasingly complex diversion schemes," the report concluded.

And recently, a submission by the United States to the World Trade Organization (2010), dated November 16, 2010, acknowledges that millions of adults regularly smoke menthol cigarettes and expressed its concern that banning "any type of cigarette favored by a large portion of U.S. smokers" could significantly expand the existing black market and result in harmful consequences. The U.S. government submission, made in connection with a dispute resolution with Indonesia regarding certain flavored cigarettes, including clove cigarettes, added:

> "<u>Banning all cigarettes – or any type of cigarette favored by a large portion of U.S. smokers – could significantly increase the existing black market for cigarettes and all the attendant contraband trafficking and other illegal activity.</u> There is already a sizeable black market for cigarettes in the United States. The Treasury Department's Alcohol and Tobacco Tax and Trade Bureau ("TTB") estimates that around $2 billion dollars in federal excise tax revenue is lost each year due to this black market." [Emphasis added.]

In March 2011, the U.S. Government Accountability Office (GAO) also observed the pervasiveness of the current black market in cigarettes in a report on the illicit trade of tobacco in the United States (GAO 2011). GAO noted the range of schemes used to import both genuine and counterfeit product for distribution on the black market and stated that federal and state law enforcement officials acknowledge that "the patterns of smuggling and diversion are not static, but change in response to many factors, including changes in tobacco taxes, tobacco regulation and law enforcement activity." Further, GAO said that the "illicit trade in tobacco products, according to U.S. law enforcement agencies, is also a source of financing for both domestic and international criminal activities."

In combination, these reports by U.S. agencies – from government experts who are closest to the problem of contraband markets – provide compelling evidence of the extent, dangers and potential growth opportunities of contraband markets that currently exist.

Another perspective of the pervasiveness of contraband markets is provided by Canada. Today, one out of every two packs of cigarettes sold in some areas of Canada is illegal (Bryans D 2011). A special Canadian task force advising Canada's Minister of Public Safety on the sale of contraband tobacco concluded:

> "Persons involved in contraband tobacco, including the end users, are undermining global and domestic health objectives, contributing to the proliferation of organized crime, inviting criminals into their communities, undermining the local legitimate economy, and evading taxes that support Canada's programs" (Task Force 2009).

The task force cited a study (GfK 2008) for cigarette manufacturers that found about 30 percent of tobacco purchased in Canada is bought illegally, and that illegal cigarettes were in one out of five smokers' homes. The study also found that the problem is at its worst in Quebec and Ontario, where rates hover around 40 percent and 50 percent respectively. An estimated 13 billion illegal cigarettes were bought in 2008, up from 10 billion a year earlier. Regular analyses of cigarette butts collected at various locations found that a quarter to a third of the cigarettes smoked at various high schools were contraband.

Estimating the Size of an Expanded Black Market if Menthol is Banned

TPSAC received a variety of submissions and presentations cautioning that any ban or other similar restriction on the sale of menthol cigarettes would lead to an explosion of the black market and the unregulated manufacture and distribution of contraband products lacking the product standards of U.S. manufacturers. They included among others:

- Altria Client Services Inc. (2010)
- Ontario Convenience Store Association (Bryans 2011)
- Center for Regulatory Effectiveness (Levinson 2011)
- Compass Lexecon (2010)
- Law Enforcement Alliance of America (2010)
- Maryland Association of Tobacco and Candy Distributors (2010)
- National Association of Attorneys General (2011)
- National Association of Convenience Stores (2010)
- National Organization of Black Law Enforcement Executives (2010)
- National Troopers Coalition (2010)
- National Black Chamber of Commerce (2011)
- American Wholesale Marketers Association (2011)

Using various methodologies and assumptions, three studies attempted to estimate the impact of a menthol ban on the U.S. contraband market. Each study used a different approach to provide a range of estimates on the size of an expected illegal tobacco market. It is difficult to estimate the size of the current illegal tobacco market with absolute certainty. Such studies are constrained

because black market participants – buyers and sellers alike – do not report information as they do for legal cigarette sales.

All three studies uniformly agreed that banning menthol cigarettes would lead to the manufacture, sale and purchase of menthol contraband cigarettes and the creation of a significantly expanded black market. The studies:

Compass Lexecon (2010). In a study commissioned by Lorillard, economists concluded that a ban on the sale of menthol cigarettes would not lead to a significant reduction in aggregate smoking. "Following a ban," it said, "menthol smokers are likely to turn to the black market and to non-menthol cigarettes, thereby substantially mitigating the decline in cigarette smoking."

The study found that a 10 percent increase in the effective price of illegal menthol cigarettes would lead to an initial decline in overall smoking of only about one percent and black market sales would be about 87 percent of current menthol sales. Prices 25 percent higher would lead to menthol sales of about 72 percent of the current size of the current sales, and total smoking would initially fall by about two percent.

It is important to note that the "effective price" cited in the study is not just the money paid. It is an economic price, which includes not only the money paid but also the effort required and the reluctance consumers must overcome to purchase on the black market. Said another way, if prices for illegal menthol cigarettes stay the same as the prices before a ban, effective prices would increase because consumers would have to expend additional time and effort to overcome the illegality and potential inconvenience to acquire contraband cigarettes.

It is also worth noting here, however, that bootleggers have substantial incentives to reduce pre-ban monetary prices, which would result in consumers actually spending less money to purchase menthol cigarettes. This incentive is provided by the amount of taxes that are not collected in black market transactions. A large amount of the sales price, if purchased legally, is related to taxes (e.g., total taxes in New York City are more than $7 per pack and more than $5 per pack in Chicago). Bootleggers could reduce the monetary sales price and yet still enjoy very high profits, providing lucrative incentives for both dealers and consumers to engage in the black market sale of menthol cigarettes.

Altria Client Services Inc. (2010). Altria Client Services Inc., on behalf of Philip Morris USA Inc., noted that criminal organizations already distribute large volumes of illicit cigarettes and make significant profits in the United States. The report added: "A ban on menthol would be an irresistible opportunity to dramatically expand those criminal operations, the volumes of illicit cigarettes they distribute, and their profits."

Altria's study assessed the impact of varying levels of contraband sales. If only 20 percent of the current taxed menthol volume migrated to the illicit market, it said, it would double the size of the existing illicit cigarette market and represent 10 percent of cigarettes sold in the United States – about 33 billion sticks and $8 billion in untaxed annual sales – roughly equivalent to the revenues of Campbell's Soup© or eBay©. The report provided the potential impacts of menthol smoker migration to illicit cigarette markets, see Table 7-1 below.

Table 7-1. Potential impacts of menthol cigarette volume moving to the U.S. illicit cigarette market

Migration of additional menthol cigarette volume to illicit market	0%	10%	20%	30%	40%	100%
Resulting illicit market (billions of sticks)	16	25	33	42	50	102
Share of U.S. cigarette market	5%	8%	10%	13%	16%	32%
Approximate illicit sales ($ billion)	4	6	8	10	12	25
Of which approximate tax losses ($ billion)	2	3	4	5	6	12

Source data: Total U.S. total volume of 317.7 billion sticks, $77 billion in retail sales, 27% menthol share, and $37.5 billion in total tax revenue.
Table reproduced from Altria Report, Table 1.2

Center for Regulatory Effectiveness (Levinson 2011). From a practical perspective, the Center for Regulatory Effectiveness (CRE) said, "there is no reason to assume that a menthol ban would have much long-term impact on U.S. consumption of menthol-flavored cigarettes. The evidence clearly demonstrates that there is essentially limitless cigarette manufacturing capacity overseas and domestically."

Given the uncertainties of contraband markets, CRE said it is possible to "reasonably conclude" that a menthol ban could lead to an increase in consumption of menthol flavored cigarettes. That is because street-level prices (without taxes) are lower, leading to higher consumption; street-level vendors act as an "advertising mechanism," and a contraband market "increases youth access to tobacco." Assessing various scenarios, CRE conservatively estimated that if a menthol ban were imposed, the contraband market that exists today would increase by about 45 percent.

Based on these studies and other available data, it would be speculative and premature to conclude that banning menthol cigarettes will reduce overall smoking prevalence. This factor alone – the continued availability of menthol cigarettes through contraband channels – will undermine any anticipated public health benefit of removing menthol cigarettes from the legitimate marketplace.

Countervailing Effects on the Public Health from an Expanded Black Market

In determining the regulation of tobacco products, Congress applied a standard based on the net effect on public health. The creation of a significant black market for menthol cigarettes – in addition to enabling the circumvention of the policy decision to prevent individuals from obtaining menthol cigarettes – would have adverse public health consequences. The countervailing effects on public health would be manifested in several ways:

<u>Negative impact on public health with unregulated contraband cigarettes</u>

Two purposes of the Act were to provide FDA with the authority:

- "to set national standards controlling the manufacture of tobacco products and the identity, public disclosure, and amount of ingredients used in such products."

- "to regulate the levels of tar, nicotine, and other harmful components of tobacco products…"

Any policies that result in an increased supply of cigarettes not manufactured according to legal requirements demands analysis because such policies would be contrary to the purposes and intents of the Act. Illegal cigarettes evade quality control standards of cigarettes regulated by FDA under the Act, and likely contain more harmful constituents. Because illicit manufacturers cannot be effectively regulated, Americans will be deprived of the significant benefits of the Act.

Counterfeit cigarettes pose serious health risks over and above the normal health risks posed by smoking. As noted in the U.S. submission to the World Trade Organization, black market cigarettes "may be even less safe than those that are currently being sold in the U.S. market" (First Submission 2010). The ATF states in a fact sheet (2010) that:

> "The trade of counterfeit tobacco products is also a rapidly growing global problem. Smokers who are tricked into buying fake cigarettes don't get the product they're expecting. While all cigarettes are dangerous and cause disease, it has been reported that counterfeit cigarettes had 75 percent more tar, 28 percent more nicotine and about 63 percent more carbon monoxide than genuine cigarettes. Furthermore, many are even contaminated with sand and other packaging materials such as bits of plastic."
>
> "…Since these are illegally manufactured and imported cigarettes, consumers do not know what ingredients are used to manufacturer these cigarettes. <u>Counterfeit cigarettes pose a significant health risk to consumers because of this reason."</u> [Emphasis added]

Moreover, researchers from the National Center for Environmental Health at the Centers for Disease Control and Prevention have found that levels of cadmium, thallium and lead in mainstream smoke "were far greater for counterfeit than the authentic brands, in some cases by an order of magnitude" (Pappas et al. 2007).

The CRE monograph lists published literature and research findings, reported by governments in some instances, that have detailed levels of metals and miscellaneous contaminants found in illegally manufactured cigarettes (Levinson 2011). It cites studies that illustrate the heightened levels of substances like cadmium, thallium and lead in counterfeit cigarettes. For example, the CRE monograph references research conducted by the New York State Department of Health that found levels of many metals "were significantly higher in counterfeit cigarette samples than in genuine-brand cigarette samples." See Figure 7-1.

Figure 7-1. Many Toxic Metals are in Higher Concentrations in Counterfeit Cigarettes (NY)

Metal Concentrations in Counterfeit Cigarettes as a Percentage of their Concentration In Legal Product (µg per cigarette)

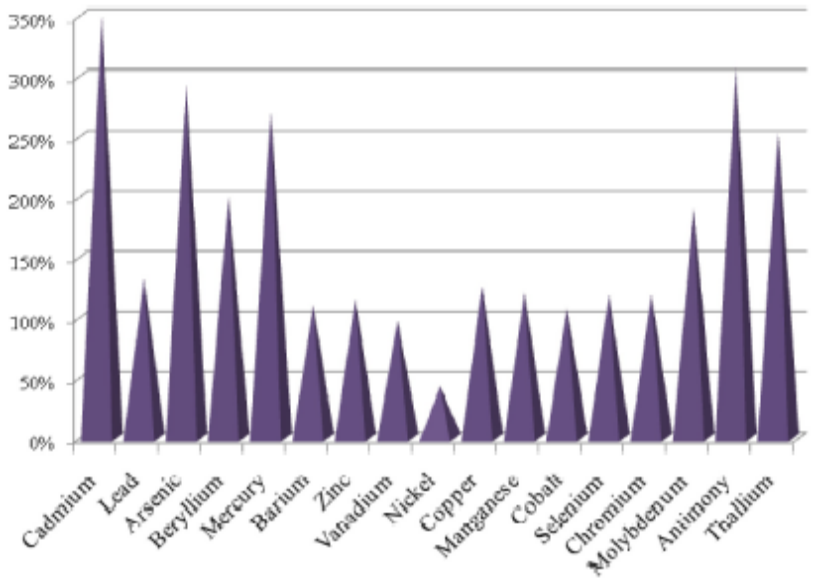

Figure reproduced from CRE monograph, Figure 5 (Levinson 2011); original source: Swami et al. 2009, Table 8B

Another study included in CRE's report, conducted in Australia in 2007, addressed the health impact of illicit tobacco (Aitken et al. 2009). The study compared the health of past and current smokers of illicit tobacco with that of smokers of licit tobacco. It found that current users of illicit tobacco had significantly greater odds of beginning smoking at a younger age than the legal age. The results also implied a relationship between illicit tobacco smoking and decreased physical health. The report said, "The public health message that emerges from our data is that people who smoke or have smoked illicit tobacco report significantly worse health than smokers of licit tobacco."

In addition, there is little evidence before TPSAC that banning menthol would significantly reduce overall smoking. Not only will greater numbers of smokers buy illicit menthol cigarettes, but other smokers undoubtedly will make their own through self-mentholation, buy cigarettes illegally over the Internet or through the mail, or roll their own cigarettes. At the January TPSAC meeting, a National Association of Attorneys General presentation showed that loose menthol tobacco (roll-your-own and pipe tobacco) are already available in the market as are menthol little cigars, which often look and smoke similar to cigarettes.

Illicit tobacco markets undermine efforts to prevent underage smoking

As illicit tobacco markets grow, the effectiveness of policies to prevent underage smoking diminishes. A robust black market with lower prices leads to sales unprotected by regulation and standard age checks by retailers. These new sales avenues create greater availability of cigarettes for adolescents and can increase adolescent smoking (Levinson 2011, Compass Lexecon 2010). If this

occurs, it would hinder the progress the United States has made toward reducing access to cigarettes for minors.

Underage individuals gain greater access to cigarettes in black markets because smugglers, "white van" salesmen and street corner vendors do not worry about age verification. Canadian studies of cigarette butts collected at high schools confirm this conclusion. They show that an increasing number of teens are acquiring contraband tobacco as that country's black market expands. A 2007 study showed that roughly 35 percent of cigarette butts collected near Quebec high schools were contraband (CCSA 2009). TPSAC was presented with evidence from Canada that the burgeoning black market there had the effect of increasing youth access to cigarettes:

> "Provinces that suffered the greatest increase in black market sales – specifically Ontario and Quebec – saw teen smoking increase relative to the rest of Canada. Between 1991 and 1994 – the period during which black market sales peaked, as discussed above – smoking prevalence among 15- to 19-year-olds rose by 35 percent in Ontario and by 14 percent in Quebec. By contrast, in the rest of Canada, smoking prevalence among 15- and 19-year-olds rose by only 10 percent between 1991 and 1994. This result suggests that substantial growth in black market sales can affect youth smoking." (Compass Lexecon).

For underage smokers, a contraband market not only serves as a major tobacco source but also provides them cigarettes that contain ingredients and constituents potentially even more dangerous than lawful cigarettes.

Expansion of criminal enterprises, requiring increased spending by law enforcement

As the Department of Treasury notes, enforcement measures aimed today at black market tobacco operations are "insufficient to countervail the lure of high profit potential" (Dept. of Treasury 2010). This same report to Congress says that "illicit trade has been linked to organized crime and violent crime, and poses a serious risk to our national security." The ATF also recently noted, "Organized criminal groups, including those with ties to terrorist organizations, have increasingly engaged in the illegal trafficking of tobacco products, particularly counterfeit and lawfully manufactured cigarettes (2010).

The associated increases in crime, given a larger black market, will undoubtedly require more government spending on law enforcement, courts and prisons if government chooses to combat the problem.

To our knowledge there is no estimate for added expenditures necessary to ensure effective enforcement of *today's* contraband problem, much less the additional costs to enforce a significantly expanded contraband market if menthol cigarettes are banned. Nonetheless, effective enforcement would almost certainly include several initiatives, such as:

- Increased coordination with domestic and international law enforcement partners to identify and target criminal organizations
- Development and support of innovative law enforcement models to target and disrupt smuggling and distribution networks
- Coordination with judicial officials to ensure appropriate application of federal mandates

- Mechanisms to deter organized crime's involvement in the trade of illicit tobacco
- Intelligence assessments on contraband tobacco
- Adding more law enforcement personnel

Initiatives like these would be expensive and would be difficult to fund in an era of limited federal and state resources. Properly funding enforcement efforts might require diverting resources from fighting other crime issues, a step that federal agencies have not been willing to take so far. For example, the 2009 Inspector General Report (USDOJ 2009) commented:

> "ATF has placed a lower priority on its alcohol and tobacco diversion mission area compared with its other mission areas involving firearms, arson, and explosives. Proportionately, ATF commits few resources to its diversion mission.…"
>
> "We recognize that the number of investigations does not always reflect the amount of work conducted because diversion cases can be large, include numerous targets, and can take a long time to develop. However, we found other indications of ATF's lack of emphasis on its diversion mission, including minimal resources and staffing levels for the diversion mission, and field structures that do not include diversion groups. Consequently, ATF's diversion program has neither adequate resources nor an adequate structure for addressing the significant tax revenue losses to state and federal governments caused by tobacco diversion and its potential links to other criminal activities."

Impact on urban communities

In testimony and statements to TPSAC, representatives of groups who regularly work in urban communities voiced concern about the practical impact of a menthol ban on urban communities. The National Organization of Black Law Enforcement Executives (NOBLE), for example, expressed concern about the ramifications of a contraband market in which counterfeit and smuggled cigarettes are sold on the streets and neighborhoods (NOBLE 2010). In their statement NOBLE noted, "If unregulated sales to minors spike through street sales in African American communities, it would create a problem for law enforcement – potentially even leading to wrongful and selective prosecutions, and to what end?"

Mark Little, former chair of The National Black Chamber of Commerce and director of Maryland Chamber of Commerce, testified that a ban would cause the current illicit market to expand (Little 2010):

> "It is not a stretch to believe that it would be controlled by organized crime, or that street sales would increase in black communities, or that unregulated sales to minors would increase. Is this how the FDA wants our police, prosecutors and judges spending their time – by policing unregulated sales to minors of cigarettes, and an upsurge in contraband sales, all due to a decision that lacks scientific credibility? When it comes to menthol, it is this committee's job to present a credible decision to Americans in general, and specifically to black Americans."

Similar sentiments were expressed at a TPSAC meeting by a representative of the Congress of Racial Equality (CORE).

> "Your study is highly significant and symbolic for the African-American community for the simple reason that menthol cigarettes are indeed popular with blacks. It's no secret that menthol cigarettes provide a taste and flavor that is preferred by many African-Americans, some even call it in my community the black man's cigarette."
>
> "…there are significant indications that a ban on menthol would boomerang and create a bad situation in our community. It is CORE's hope that the advisory panel will fulfill its requirement of considering the unintended consequences of a ban on menthol cigarettes. Any recommendation must be grounded in a real world understanding of the devastating impact that illegal counterfeiting, smuggling, distribution and consumption of cigarettes has on our lives and on our streets."
>
> "If smokers were a captive population and tobacco products a captive industry, you might be able to make a case that banning menthol could work. But because there would be a strong demand fed by many alternative sources of cigarettes, banning menthol would be a self-defeating and indeed a very harmful step for my community. It would drive more smokers to unlicensed, unregulated, side of the street, and more troubling, it would give underage access to kids making it easy for them to smoke unregulated cigarettes. And we have to ask ourselves, is that really what we want to do."
>
> "If menthol is banned, history shows that a large underground market would be created and many questions should follow. They involve questions of how effective contraband tobacco enforcement has been to date and the cost of additional law enforcement." (CORE 2011)

Foregone government revenue

A substantially expanded black market means that federal, state and local governments would experience significant reductions in cigarette excise tax collections. According to the Altria report (2010), previously mentioned, the sale of cigarettes generated approximately $37.7 billion in federal, state and local government revenues in fiscal year 2009. Menthol cigarettes accounted for approximately 27 percent of the U.S. taxed cigarette base that year. As a result, if all menthol cigarettes were removed from the taxed cigarette market, up to $10.2 billion in government revenues, including Tobacco Settlement Agreement (TSA) monies, would be lost. See Table 7-2. A significant part of these taxes and TSA funds are earmarked for specific purposes, including education and children's health care programs.

Table 7-2. Estimated fiscal 2009 cigarette revenue by category, based on the assumption that menthol cigarettes made up 27% of the U.S. taxed cigarette market that year ($ billion)

Revenues	Total[1]	Menthol[2]
Federal excise tax	8.5	2.3
State excise tax	15.8	4.3
State sales tax	4.1	1.1
Local excise tax	0.5	0.1
[T]SA	8.8	2.4
Total	**$37.7 billion**	**$10.2 billion**

[1] Orzechowski and Walker (2009), *The Tax Burden on Tobacco* (44). Prepared with the financial support of Altria Client Services, the Lorillard Tobacco Company, and Reynolds American.
[2] Menthol revenue calculations are estimated based upon a 27% market share assumption; state figures do not represent a weighted-average calculation.
Table reproduced from Altria Report, Table 4.1

Because the illegal movement of tobacco is an international problem that crosses porous borders, lost government revenue is likewise an international problem (Lencucha and Callard 2011). A study of 12 diverse countries (excluding the United States) found that the lost excise tax revenue between 2003 and 2008 for the most-sold brand ranged from more than $23 million a year in Ecuador to almost $5 billion a year in the UK. Along with the lost revenue, it added: "Illicit trade compromises health outcomes to the extent that it undermines price strategies, labeling requirements or other policies aimed at reducing the demand for tobacco products… For the countries we studied, lost revenue due to the illicit trade of cigarettes is higher than government investments in tobacco control."

Loss of jobs dependent in whole or part on the legal sale of menthol cigarettes

Many thousands of working Americans rely upon menthol sales beyond the factory workers who manufacture them. According to the Altria study, nearly 500,000 American jobs depend in whole or part on the legal sale of menthol cigarettes (2010).

Job losses would vary along the stage of the tobacco value chain, but are likely to have a disproportionate impact on small, independent convenience store owners, tobacco growers and independent distributors to convenience stores. See Table 7-3 below. The sad truth is that a ban of menthol cigarettes would cost jobs in the United States, only to replace them with jobs overseas at contraband manufacturers.

Table 7-3. Summary of employment across the tobacco value chain

	Growers	Processors & Manufacturers	Distributors & Transportation	Selling Organizations
Primary activities	Farm, harvest, cure, grade and wholesale tobacco leaf	Procure, process, pack and supply tobacco for the manufacture of cigarettes	Warehousing and transport of cigarettes to retail outlets	Retail outlets such as convenience stores that sell cigarettes to adults
Estimated total employment	62,000	19,000	40,000	Convenience only: 1-1.5 million. Other outlets: 4-5 million
Jobs at risk if all menthol cigarette volume were eliminated	25,000	3,500	3,000	475,000

Table reproduced from Altria Report, Table 5.1

Building the Knowledge Base

After passage of the Act, the Center for Tobacco Products at FDA noted the importance of building a "knowledge base required for meaningful regulation of tobacco products…" (Deyton et al. 2010). However, TPSAC has not developed the knowledge base sufficient to assess the countervailing health impacts of a ban, including the effects of contraband. In fact, TPSAC received only one one-hour background briefing on the topic. Industry and other interested groups provided substantial information regarding the unintended consequences of a menthol ban, but that was limited to written public submissions and oral comments during the public session of meetings in which speakers were provided 5-10 minutes to speak.

Congress explicitly asked TPSAC to address the issue of contraband. From the day TPSAC convened its first meeting on March 30, 2010, it had the opportunity and the responsibility to help build a knowledge base in the countervailing impact of menthol regulation, including the adverse public health impact of creating an expanded contraband market.

Such steps should have included engaging various components of the federal government that deal with tobacco diversion on a daily basis, such as the Bureau of Alcohol, Tobacco, Firearms and Explosives, and the Alcohol and Tobacco Tax and Trade Bureau (TTB); commissioning studies and white papers; seeking advice from law enforcement agencies and experts who deal with these issues on a daily basis; commissioning studies on the adverse health impact of ingredients in contraband cigarettes from expert scientists and researchers at the U.S. Centers from Disease Control and Prevention; consulting with other federal and state experts; seeking testimony from international experts about the capacity to produce illicit cigarettes in China, Eastern Europe and elsewhere; and assessing the experience of other countries in determining the impact of unregulated contraband sales on youth smoking rates.

TPSAC, however, eschewed all of these avenues. It is too late now to remedy the unmistakable omissions in TPSAC's public record. It is hoped that TPSAC's final report – underway at this writing – acknowledges these deficiencies and its incomplete effort to study the "countervailing effects" as Congress mandated. FDA, nonetheless, must rigorously assess the countervailing effects of any potential regulation of menthol cigarettes.

A rigorous assessment must include:

1. Economic studies assessing the likely size and impact of an expanded contraband market if menthol cigarettes are restricted or banned: Assess the size of today's contraband market in the United States and provide a range of estimates on the size of an expanded contraband market if menthol cigarettes are restricted or banned.

2. Public health assessments of contaminants in illicit cigarettes and their impact on public health: Assess the ingredients and constituents found in samples of counterfeit cigarettes now sold in the United States, such as toxic metals like lead, along with the tar, nicotine and carbon monoxide levels; assess the increased health risks posed by the prevalence of contraband cigarettes in other countries that might be diverted to the United States.

3. Research regarding the adverse health consequences caused by undermining youth anti-smoking efforts: Assess how the expected increased illicit cigarette trade jeopardizes progress on reducing underage initiation and thus runs contrary to the Act's goals of further helping prevent underage access.

4. Research regarding the impact of increased black market cigarette activity on criminal activity, and the added cost burdens to law enforcement: Evaluate the entirety of the tobacco products diversion problem -- whether additional controls are needed, the likelihood of associated criminal activity, and an assessment of efforts and resources needed, including their costs, to enforce any regulation or ban of menthol cigarettes.

These topics demand conscientious study because of the possibilities of unintended consequences of any action to restrict or ban menthol cigarettes. Economic and political history shows that any regulatory intervention in complex social and economic systems can create unintended consequences. When regulatory actions impose a new set of circumstances upon consumers, governments cannot always predict how the market – people – will react (Scanlon 2011). Often the unintended consequences are more harmful than the problem they intended to solve.

Two recent examples of unintended consequences in other arenas are instructive. One involves online gambling. Even though online gambling was effectively made illegal in 2006, several sources forecast that the industry has actually expanded in size since then. Another example is the result of laws enacting electronic systems to track the sales of cold medicine used to make methamphetamine. After reviewing Drug Enforcement Agency data from 2000 to 2009, the Associated Press reported that the "lure of such easy money has drawn thousands of new people into the methamphetamine underworld over the last few years." Further, the Associated Press noted the tracking system "failed to curb the drug trade and instead created a highly lucrative market for profiteers..." (USA Today 2011)

CONCLUSION

A comprehensive public health assessment and recommendation on the impact of the use of menthol cigarettes must include a thorough inquiry into the illegal tobacco problem in the United States. It is a fundamental and indispensable piece of the public health puzzle and is required to be considered under the Act.

As this chapter shows, today's illegal tobacco market already poses daunting challenges for government, retailers, and the public health community in the United States. Banning menthol cigarettes would fuel a larger illegal cigarette market and result in negative impacts on public health. The negative impacts on public health would be:

- Thousands upon thousands of Americans, both young and old, will be exposed to more harmful ingredients and constituents and thus deprived of the significant benefits of the Act. A ban would lead to the increased availability of illegal cigarettes that do not comply with regulations that apply to the rest of the tobacco industry, such as ingredient and constituent reporting and disclosures.
- The expanded sales of contraband cigarettes will increase youth access to tobacco. For decades, successive governments have worked to keep cigarettes out of the hands of youth. Sellers of illicit cigarettes, however, flout the law. They do not care about age verification, undermining tobacco control programs.
- Criminal networks that traffic in illegal cigarettes will expand. Tobacco trafficking and organized crime often go hand in hand. As official U.S. government reports cite, these criminal networks today also traffic in drugs, firearms and alcohol. Lured by additional and large profits from selling illicit menthol cigarettes, criminal organizations will expand their operations, distribution, and sales. The increased profits will fund other criminal activities, such as drug and gun trafficking.
- The increased crime that results from more smuggling will require greater government spending on law enforcement, courts and corrections. At a time when federal and state governments are entering an era of budget deficits, a menthol ban would place a significant "unfunded mandate" on governments. Governments will be forced to devote more resources, including financial resources, to law enforcement efforts to combat the black market and other illegal activities.
- At the same time, an increase in contraband tobacco sales – and a resulting decrease in licit, regulated sales – will mean lost revenues for federal and state governments. Menthol cigarettes generated more than $10 billion in federal, state and local government revenues in 2009.
- Thousands of jobs will be at risk. Up to 500,000 jobs depend wholly or in part on menthol cigarette sales. With a shift of sales from legal to illegal markets, banning menthol cigarettes will affect thousands of jobs.

By passing the Family Smoking Prevention and Tobacco Control Act, Congress specifically granted FDA the authority to regulate tobacco products in order to regulate the manufacture and sale of cigarettes. However, if FDA were to impose a ban on the sale of menthol cigarettes, it would result in severe unintended consequences including exacerbating an already troubling illicit tobacco trade, creating an unregulated contraband market and undermining the precise public health safeguards that Congress intended.

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CHAPTER 8.
CONCLUSIONS

TPSAC has been charged with issuing a report and recommendation to FDA on the impact of menthol in cigarettes on public health, including such use among children, African Americans, Hispanics, and other racial and ethnic minorities. This Industry Menthol Report is respectfully submitted to aid FDA in making a science-based regulatory decision regarding whether menthol cigarettes affect public health disproportionately compared to nonmenthol cigarettes.

The Industry's review was conducted with an emphasis on sound science. The relevant literature was identified through a comprehensive literature search and literature on each topic was evaluated in a rigorous manner. Conclusions related to each relevant topic were based on the most methodologically sound studies and those that were best able to support inferences related to menthol. Weight-of-the-evidence conclusions about causal inferences were developed according to the framework developed by the Surgeon General's Reports. This framework has been applied for decades to understand relationships between smoking and health. Importantly, for most of the endpoints of interest, there are sufficient data available to draw conclusions with confidence. The conclusions of the Industry Menthol Report are provided, topic by topic, with justification, below.

MAJOR CONCLUSIONS OF THE REPORT

The conclusions of the Industry Menthol Report comply with FDA's mandate to "follow the science."

Using the Surgeon General's framework for assessing causality, a synthesis of the reliable data on the use of menthol in cigarettes, including data relating to its impact on disease and smoking behavior, leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol cigarettes and any disproportionate impact on the public health as a whole or for any demographic group when compared to nonmenthol cigarettes. As a result, there is no scientific basis to support the regulation of menthol cigarettes any differently than nonmenthol cigarettes.

Demographics of Menthol Cigarette Preference and Current Trends in Smoking Prevalence

Smoking prevalence refers to estimates of cigarette use among the overall population, whereas smoking preference refers to the percentage of smokers who smoke a particular type of cigarette (e.g., menthol versus nonmenthol). An increase in smoking prevalence in the population could represent an adverse population-level effect, while higher preference for a particular cigarette type that does not provide any increased risk for disease or adversely impact smoking behavior among a declining smoking population would not. Cigarette smoking in the overall population (prevalence) has steadily declined during the last two decades, irrespective of race/ethnicity, sex and age category. Menthol cigarettes are used by only a quarter of the smoking population (preference). The majority of all menthol smokers are White. The vast majority of African American smokers prefer menthol cigarettes, and it is reported that female smokers prefer menthol more than male smokers. Some studies appear to suggest that menthol cigarette preference is also higher among younger as

compared to older smokers. During the last two decades, declines in smoking prevalence have generally been more pronounced for minorities (including African Americans), females and adolescents, despite their preference for menthol. Also, prevalence of African American adolescent smoking is far below that of White adolescent smoking.

Menthol in Cigarettes Does Not Change the Inherent Health Risks of Cigarette Smoking

The available epidemiologic studies clearly demonstrate that smokers of menthol cigarettes are at no greater risk of developing chronic smoking-related diseases than are nonmenthol smokers. The number of studies and their consistency make it possible to draw this conclusion with confidence. While all epidemiology studies have limitations, the available studies are well-designed and well-analyzed. The diseases studied include lung cancer (the most common smoking-related cancer), cancers of the upper aerodigestive tract (esophagus, larynx, oropharynx), and other cardiac and lung outcomes. The studies provide data on risks specific to both sexes and to both Whites and African Americans, and do not find that there is any subpopulation of menthol smokers who incur increased risks compared to nonmenthol smokers. Thus, it can be concluded that, according to the Surgeon General's framework for assessing causality, the **"evidence is suggestive of no causal relationship"** between the use of menthol cigarettes and increased smoking-related disease risk above that caused by use of nonmenthol cigarettes.

Menthol in Cigarettes Has No Meaningful Effect on Smoking Biomarkers

The vast majority of studies of biomarkers of exposure to smoke constituents and biomarkers of potential harm have found no meaningful differences between menthol and nonmenthol smokers. The body of available scientific evidence from biomarker studies leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between the use of menthol cigarettes and increases in biomarkers of exposure and potential harm over and above those caused by the smoking of nonmenthol cigarettes.

Evidence on Menthol and Smoking Topography is Inadequate to Support a Conclusion that Menthol Cigarettes are Smoked More Intensely

The available studies on menthol cigarettes and smoking topography differ in the ways that they attempt to measure smoking variables such as puffing, depth, volume and frequency; and many have weaknesses (e.g., small numbers of subjects, use of cigarettes differing in yield and menthol content, etc.). This makes it difficult to compare the studies and to reach definitive overall conclusions regarding these aspects of smoking topography. Although the findings are somewhat inconsistent, the majority of studies find no significant differences between menthol and nonmenthol smokers in smoking topography variables. These data provide no support for the presence of a clear and consistent association between menthol smoking and an adverse impact on smoking topography and provide no convincing support for the suggestion that menthol increases the exposure to smoke constituents through effects on smoking behavior. However, given the inconsistencies that exist, the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between use of menthol cigarettes and adverse impacts on smoking topography. When placed in the context of the epidemiology and biomarker evidence referenced above, there is no reason to

conclude that smoking topography differences, if any, lead to any increased health risks over those of nonmenthol cigarettes.

Menthol in Cigarettes Does Not Adversely Impact the Toxicologic Properties of Mainstream Smoke

Toxicology studies show that menthol has no notable effects at exposures spanning the ranges typical for its flavor application in cigarettes. Additionally, the weight of the evidence on the toxicologic properties of the mainstream smoke from menthol cigarettes compared with nonmenthol cigarettes provides no indications of increased toxicity, consistent with a broader conclusion that menthol has no causal relationship to adverse impacts on public health. This leads to the conclusion that the **"evidence is suggestive of no causal relationship"** between menthol added to cigarettes and increases in the toxicity of cigarette smoke.

Menthol in Cigarettes Does Not Meaningfully Alter the Chemical Composition of Mainstream Smoke

The weight of the evidence clearly shows that the chemical compositions of the mainstream smoke from menthol and nonmenthol cigarettes are very similar, apart from the presence of menthol itself. Thus, the **"evidence is suggestive of no causal relationship"** between the use of menthol in cigarettes and potentially harmful changes in mainstream smoke chemistry.

Evidence is Inadequate to Conclude that Menthol in Cigarettes Influences Smoking Initiation

Smoking initiation rates have not changed significantly over the past decade. In addition, menthol smokers report later onset of initiation as compared to nonmenthol smokers. While some studies report that younger smokers have a higher preference for menthol cigarettes than older smokers, there are no studies that directly examine cigarette type (menthol versus nonmenthol) at the time of initiation. Although these data are suggestive of no causal relationship between menthol cigarette use and adverse smoking initiation behaviors, they do not directly address the cigarette type used to initiate smoking. Thus, using the Surgeon General's framework for assessing causality, it must be concluded that the **"evidence is inadequate to infer the presence or absence of a causal relationship"** between menthol cigarette use and adverse smoking initiation behaviors, including higher or earlier smoking initiation by the general population or by subpopulations.

Menthol in Cigarettes Has No Meaningful Impact on Smoking Cessation

Review of the methodologically sound literature on menthol smoking and cessation demonstrates that the most relevant studies – those that address successful long-term quitting – do not indicate that smokers of menthol cigarettes are less likely to quit than smokers of nonmenthol cigarettes. There are a sufficient number of high-quality studies that consistently find that menthol has no meaningful impact on smoking cessation. A few studies (three cross-sectional studies and one of a smoking cessation clinic) reported some lower cessation rates among non-White menthol smokers only. However, if menthol is a factor that affects the ability to quit smoking, one would expect to see consistency among White and non-White subjects. This race-associated inconsistency suggests that some other factor, possibly related to socioeconomic status or genetics, affects the ability to quit, rather than menthol itself. Given the number of high-quality studies that consistently find that

menthol cigarette use has no meaningful impact on smoking cessation, using the Surgeon General's framework for assessing causality leads to the conclusion that the **"evidence is suggestive of no causal relationship."**

Menthol in Cigarettes Has No Meaningful Impact on Nicotine Dependence

Review of the methodologically sound literature on menthol smoking and measures of nicotine dependence demonstrates that menthol smokers are not any more dependent on nicotine than nonmenthol smokers, as assessed by a variety of measures including cigarettes per day (CPD), time to first cigarette (TTFC), and Fagerström Test for Nicotine Dependence (FTND). There are a sufficient number of studies, and they are consistent in their results. Menthol smokers do not smoke significantly more CPD than nonmenthol smokers; in fact, half of the studies reported that menthol cigarette smokers report significantly fewer CPD than nonmenthol smokers. Similarly, menthol and nonmenthol smokers do not differ significantly on composite measures of dependence. With respect to the studies that evaluated TTFC, half found no difference between menthol and nonmenthol smokers and about half found that menthol smokers had significantly shorter TTFC than nonmenthol smokers, but this was true only among limited subgroups of subjects. Given both the number of high-quality studies and their overall consistent findings, it is reasonable to conclude that the **"evidence is suggestive of no causal relationship"** between smoking menthol cigarettes and significantly increased levels of nicotine dependence.

Numerous Hypotheses Put Forth by TPSAC are Speculative and Cannot Serve as the Basis for Regulatory Policy

From review of meeting transcripts and presentations given at TPSAC meetings, it is apparent that committee members are concerned about a number of unfounded hypotheses. For example, TPSAC has addressed whether menthol cigarettes are perceived by menthol smokers as less harmful than nonmenthol cigarettes. The data show that this is not true. This and other speculative hypotheses are addressed in Chapter 6.

A Ban on Menthol Cigarettes Will Result in Significant Countervailing Effects

If a ban were imposed on menthol cigarettes, despite the scientific evidence that does not support regulating menthol cigarettes differently than nonmenthol cigarettes, the evidence unequivocally shows that the result would be a dramatically larger illegal cigarette market than currently exists. As a result, there also would be severe negative impacts on public health, including exposure of smokers to more harmful contraband cigarettes, increased access of youth to tobacco, increased criminal activity particularly in urban communities, reduced government revenues and loss of jobs.