Tobacco Products Scientific Advisory Committee

Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations

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PREFACE

This report was written by the Tobacco Products Scientific Advisory Committee (TPSAC) of the Center for Tobacco Products of the Food and Drug Administration (FDA). TPSAC was mandated by the Family Smoking Prevention and Tobacco Control Act to deliver a report to FDA on the public health impact of menthol in cigarettes within a year of the committee's formation establishment. The report was written within the requirements of the Federal Advisory Committee Act, which governs the committee's meetings. During 10 meetings, from March 30–31, 2010 through March 17–18, 2011 (see Appendix B for dates and topics covered), TPSAC and its Menthol Report Subcommittee developed an approach to the task of writing the report, wrote and reviewed draft chapters, reached conclusions and drafted recommendations. Chapters were discussed in meetings of the full committee and there was opportunity for comment.

During this process, TPSAC received valuable input from many public commenters, including researchers, tobacco industry, consultants to the tobacco industry, representatives of the public health sector, and others. The tobacco industry also responded to requests from TPSAC for specific materials. The voting members of TPSAC received useful comments from the non-voting members of the committee; TPSAC acknowledges their collegial input.

Many others provided materials that were considered by TPSAC in writing the report. TPSAC is grateful to contractors to FDA from the University of California, San Francisco, and RTI International who reviewed various sources and prepared reports for TPSAC on a very timely basis. David Mendez, PhD, from the University of Michigan School of Public Health, executed modeling to assist TPSAC in characterizing the public health impact of menthol cigarettes. Lisa Henriksen, PhD, from Stanford University School of Medicine, made a strong and timely contribution to the development of Chapter 5. TPSAC appreciates the efforts of these two scientists, which were made on a very demanding schedule. TPSAC also thanks Denise Gellene, who edited this report and met the challenges posed by the deadline.

In submitting this report, TPSAC has met the requirement of the Family Smoking Prevention and Tobacco Control Act with regard to developing this report and making recommendations on the public health impact of menthol in cigarettes. Of course, TPSAC would be pleased to offer further guidance to FDA on this topic in the future, if needed.

CHAPTER 1: OVERVIEW: WHAT THIS REPORT IS ABOUT

INTRODUCTION

Menthol is an organic compound, either derived from natural sources or synthesized, that is widely used in consumer and medicinal products. It has cooling, analgesic, and irritative properties, reflecting its interactions with specific neuronal receptors that can modulate pain and communicate to areas of the brain concerned with taste and other sensations. It has long been used in cigarettes and for some cigarettes it is a flavor-characterizing additive. Menthol is also an active pharmaceutical ingredient in many products. In medical products, whether menthol is the sole pharmaceutical ingredient, as in throat lozenges or one among many such ingredients as in a cold or cough medicine, menthol is regulated as a drug with restrictions on allowable doses and uses, and requirements with respect to instructions for use and warnings. When used in cigarettes, menthol—like most other ingredients in tobacco products—is not regulated according to the safety standards applied to food and drugs.

The Family Smoking Prevention and Tobacco Control Act (the "Act") charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "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." The Act has the overall purpose of protecting "…the public health by providing the Food and Drug Administration with certain authority..." The issue of menthol in cigarettes was the first brought to TPSAC by the Food and Drug Administration (FDA); under section 907(e) TPSAC is to complete its report and recommendations on menthol in cigarettes within one year of its establishment, that is, by March 23, 2011.

This report addresses the use of menthol in cigarettes as called for by the Act. The goal is to cover the evidence related to the public health impact of the use of menthol in cigarettes and to offer evidence-based recommendations to FDA. As this is the first report prepared by TPSAC, it also describes the principles and practices by which TPSAC has developed this report, offering a precedent that will be followed, as appropriate, for future reports. This chapter and Chapter 2 introduce the methods that TPSAC has used and the basis for their selection.

THE CHARGE TO TPSAC FROM THE FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT

The Act gives TPSAC a specific but broad charge with regard to the use of menthol in cigarettes. The report is to address the public health impact and to make recommendations on menthol in cigarettes. Under section 907 (a)(3)(B)(i),TPSAC is requested to address the following with regard to menthol:

- The risks and benefits to the population as a whole, including users and nonusers of tobacco products;
- The increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- The increased or decreased likelihood that those who do not use tobacco products will start using such products.

If a standard were to be implemented in regard to menthol, under section 907 (b), the Secretary needs to consider additional matters, including technical achievability of the standard and any countervailing effects on the health of adolescent and adult users and non-tobacco users. Such effects could include the creation of a significant demand for contraband.

WHAT IS A MENTHOL CIGARETTE?

Under the Act, menthol is an additive, as defined in Section 900 (1). Menthol is reported to be present in most cigarettes in the United States (Henningfield et al. 2003; Giovino et al. 2004). However, TPSAC did not identify any systematic and recent data on menthol content in cigarettes. Those cigarettes marketed as menthol have sufficient menthol content for menthol to become a "characterizing flavor." A submission to TPSAC from the Lorillard Tobacco Company identified menthol levels of around 1000 ppm (wt/wt) of cigarette tobacco or higher as providing a characterizing flavor (Lorillard 2010). R.J. Reynolds Tobacco Company "...typically characterizes a cigarette as a menthol cigarette when the cigarette's menthol level is 0.3 percent or greater" by weight (R. J. Reynolds Tobacco Company 2010, p.1). Heck (2010) in a literature review noted that the menthol content of some cigarette tobaccos reaches two percent by weight. Celebucki et al. (2005) analyzed 48 menthol brands, finding an average value of 2.64 mg per cigarette. For the purpose of this report, TPSAC has not adopted a quantitative definition for a menthol cigarette, but instead relies on the brand designation.

In the brands not marketed as menthol, the amount of menthol is much lower—about 0.03 percent of the tobacco weight (Giovino et al. 2004). In response to questions from TPSAC, the R.J. Reynolds Tobacco Company submitted written comments, which included the statements below (R.J. Reynolds Tobacco Co. 2010, p.3).

> "When menthol is found in non-menthol cigarettes, the levels are extremely low —usually at a level of 50 ppm (0.005 percent) or less."
>
> "Menthol might be detected at trace levels in a non-menthol cigarette as an incidental byproduct of various tobacco processes, such as the manufacture of reconstituted tobacco."
>
> "Non-menthol cigarettes sometimes use small amounts of commercial flavorings, and these flavorings as prepared by the suppliers may use incidental amounts of menthol as a flavor component."
>
> "Some non-menthol cigarettes are made with extremely small quantities of menthol added to provide a fresh taste without imparting a characterizing menthol taste, or to brighten the tobacco flavor."

In response to the same questions from TPSAC, Altria Client Services commented in its June 30, 2010 submission for Philip Morris USA Inc. that: "PM USA does not include menthol as part of the flavor recipes used in non-menthol cigarettes," (Altria Client Services 2010, p.14). While TPSAC has been given the charge of addressing menthol in cigarettes generally, it has focused this report on menthol cigarettes. This focus is consistent with the language of the Act which refers to menthol in Section 907 (a)(1)(A) in discussing constituents or additives that are "…a characterizing flavor of the tobacco product or tobacco smoke."

THE TPSAC FRAMEWORK FOR ASSESSING THE IMPACT OF MENTHOL CIGARETTES ON PUBLIC HEALTH

In general, determining the public health impact or population harm of a tobacco product involves assessment of multiple factors. As described in the 2001 Institute of Medicine report, *Clearing the Smoke*, based on a harm reduction conceptual framework described by MacCoun and Reuter (2001), population harm is associated with the toxicity of the product (per use), the intensity of its use (per user) and the prevalence of use (Stratton et al. 2001). With regard to population impact, prevalence needs particular emphasis as it defines the size of the population at risk from a product. Menthol cigarettes could increase prevalence by increasing the rate of initiation and subsequent addiction and by more strongly maintaining addiction and reducing successful cessation.

TPSAC has formulated a framework that is specific to its charge related to the public health impact of menthol cigarettes. As TPSAC evaluates the available information on menthol cigarettes, it will do so within an overall conceptual framework or "model" for cigarette smoking that defines points at which the presence of menthol cigarettes could harm either the health of the individual smoker or of the public generally (Figure 1). TPSAC is charged with addressing "...the issue of the impact of the use of menthol in cigarettes on the public health..." and with further considerations related to population impact and users and non-users under section 907 (a)(3)(B)(i). The framework in Figure 1 is useful for both levels—individual and population. The model set out in Figure 1 begins with experimentation with cigarette smoking on the part of children, adolescents, and young adults and ends with the development of disease and death caused by smoking cigarettes. The model is not inclusive in showing all factors that contribute to this sequence from experimentation to disease incidence, but it does include those who might be affected by menthol cigarettes.

The model implies various potential indicators of the consequences of menthol cigarettes: (1) rates of experimentation and initiation; (2) the prevalence of nicotine addiction; (3) rates of quit attempts and successful cessation; (4) population smoking prevalence, the summative consequence of initiation and cessation; and (5) incidence and mortality rates of smoking-caused diseases. These same indicators are of interest within particular subpopulations, reflecting TPSAC's charge in the Act. It is important to note that disease is not the primary or sole outcome that determines the public health impact of menthol cigarettes. The availability of menthol cigarettes could have no significant effect on risk for disease outcomes, yet have a significant effect on increasing initiation or reducing the success of cessation. The resultant increase in the prevalence of smoking would represent a negative public health impact.

QUESTIONS TO BE ADDRESSED WITH REGARD TO MENTHOL CIGARETTES

The framework (Figure 1) highlights issues for which focused reviews need to be carried out to address critical questions related to the charge to TPSAC. The following questions are addressed in the reviews included in this report and answered according to a standardized terminology for strength of evidence. Each is relevant to the assessment of public health impact and the recommendations to be made by TPSAC to FDA.

Related to Individual Smokers

1. Does availability of menthol cigarettes increase the likelihood of experimentation?
2. Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?
3. Does inclusion of menthol in cigarettes increase the likelihood of the smoker becoming addicted?

4. Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?
5. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?
6. Do biomarker studies indicate that smokers of menthol cigarettes receive greater doses of harmful agents per cigarette smoked compared with smokers of non-menthol cigarettes?
7. Do smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes?

Smoking at the Population Level

1. Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?
2. Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

ORGANIZATION OF THE TPSAC REPORT

This report contains seven additional chapters. They cover TPSAC's approach to identifying and weighing the scientific evidence; physiological responses to menthol and to menthol and nicotine; the prevalence and patterns of smoking among the population as a whole and in subpopulations such as by race/ethnicity and gender; marketing of menthol cigarettes; the effects of menthol cigarettes versus non-menthol cigarettes on initiation, dependence and cessation; and biomarkers of exposure and risks for health outcomes. The last chapter integrates the information from the preceding chapters. It offers TPSAC's answers to the questions above based on the weight of evidence. It also provides results of modeling that are informative as to public health impact. The report concludes with TPSAC's recommendations to FDA.

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Chapter 2: TPSAC'S APPROACH TO ITS CHARGE

INTRODUCTION

This report was developed by the Menthol Subcommittee of the TPSAC. The Menthol Subcommittee developed the chapter outline and general approach during open meetings. The initial draft chapters were written by subgroups of the subcommittee and then reviewed by all of its members. The completed report was then considered by the full TPSAC. The remainder of this chapter describes how TPSAC approached its charge.

PRINCIPLES UNDERLYING TPSAC'S APPROACH

TPSAC is charged with reviewing and evaluating evidence, reaching conclusions based on the evidence and making recommendations to the FDA on the public health impact of menthol in cigarettes. In assuming this task, TPSAC adopted core principles to guide its approach and report, including being transparent and evidence-based, and reflecting consensus among TPSAC members.

First among these principles is that the fact finding, evidence gathering and synthesis, and deliberations about the evidence are conducted in a transparent manner. By transparency, TPSAC refers to using open and replicable processes that make the basis of its findings and recommendations completely accessible. In following the FDA's processes and meeting the requirements of the Federal Advisory Committee Act, TPSAC carried out its work in open meetings, unless a closed meeting was needed because of commercial, confidential information. Evidence evaluation and TPSAC deliberations were conducted in a transparent manner.

Second, the recommendations of the TPSAC are evidenced-based, meaning that TPSAC identified and relied on scientific and other information relevant to the topic of menthol cigarettes to develop its recommendations. The range of information considered by TPSAC was extremely broad, including survey data, the findings of laboratory studies of pharmacological activity and toxicity, epidemiological evidence, results of marketing research, and reviews of industry documents. Evidence gaps were anticipated and are identified in this report as specifically as possible. Where evidence was lacking or insufficient, TPSAC made its recommendations with acknowledgement of the gap. In cases where there was not enough evidence to make a recommendation, TPSAC identified the research to be done to address the gap. This strategy has been key to maintaining transparency.

While TPSAC made an effort to identify all relevant evidence on menthol in cigarettes, this was impracticable, given the timeframe for this report and the extent of the materials available. TPSAC has provided a clear statement and listing of what materials it did consider. Because there were too many tobacco industry documents to be systematically reviewed, these non-peer reviewed information sources were selectively reviewed and treated as evidence when appropriate. Reviews of these documents were carried out by FDA consultants and there are plans for publication of the summaries in the peer-reviewed literature. The internal documents were a source for understanding the menthol marketing practices of the tobacco industry targeting children, adolescents and ethnic minorities.

Third, the TPSAC used a consensus-based approach to develop this report. The draft report was developed by the Menthol Subcommittee of TPSAC for consideration and approval by the members of TPSAC. While individual TPSAC members and other Special Government Employees have authored various portions of the report, it is a product of the committee and its findings represent a consensus of TPSAC members. In complex and uncertain matters, such as the subject of this report, experts may not share precisely the same views of the scope and quality of the evidence and of its implications. This report captures a range of views, as appropriate, to characterize uncertainty in the evidence considered. After the evidence was collected and reviewed, TPSAC employed a consensus-based approach to develop the recommendations for this report.

PROCESSES FOR EVIDENCE-BASED DECISION MAKING

Overview

Processes for decision making in public health are grounded in an understanding of what is known and not known about the problem of concern. In making evidence-based decisions with regard to public health, there is a long history of using comprehensive reviews as the foundation for evaluating the state of evidence and for selecting among policy options. The reviews are generally systematic and often carried out by multidisciplinary expert panels, following protocols. Findings present the strength of evidence for a particular factor with regard to the outcome of interest, e.g., the strength of evidence for causation or for a beneficial effect of an intervention. The findings are followed by a decision-making process that might result in promulgation of a guideline, policy, or regulation.

The landmark 1964 Report of the US Surgeon General on tobacco and disease and the consequences of its findings are exemplary (US DHEW 1964). That report, which reached the momentous conclusion that smoking causes lung cancer in men, stands as one of the first comprehensive evidence-based reviews. It used a transparent methodology, involving a critical survey of all relevant literature by an expert panel whose members did not have committed viewpoints at the outset, and applied an explicit framework for assessing the strength of evidence for causation. The causal criteria applied, now often referred to as the "Surgeon General's criteria," are still in use today, and include: temporality, consistency, coherence, specificity, and strength (US DHHS 2004). The causal conclusions of the 1964 report triggered a wide range of individual and governmental actions, including the Federal Cigarette Labeling and Advertising Act of 1965 and a Congressional mandate that a health warning appear on all cigarette packages. In 1967, the Federal Communications Commission (FCC) ruled that the Fairness Doctrine in advertising applied to cigarette ads on television and radio and required broadcasters who aired cigarette commercials to provide air time for information about the health hazards of smoking. Policy actions have similarly followed findings of subsequent reports, e.g., the 1986 report on involuntary smoking (US DHHS 1986).

These same evidence-based approaches have become fundamental in many other areas in clinical medicine and public health. The current paradigm of "evidence-based medicine" involves the systematic review of evidence as the basis for formulating guidelines for clinical and public health practice. Standardized approaches have been developed for carrying out such reviews and the international Cochrane Collaboration engages thousands of researchers and clinicians throughout the world to carry out reviews. In the United States, the Agency for Health Care Research and Policy supports 14 Evidence-based Practice Centers to carry out reviews related to health care. There are also numerous reports from committees of the National Research Council and the Institute of Medicine that

exemplify the use of systematic reviews in evaluating evidence as a guide to policy formulation. Examples include reviews carried out on Agent Orange and the Gulf War, vaccines, asbestos and cancer, arsenic in drinking water, and secondhand smoke and cardiovascular disease risk. A 2008 report of the Institute of Medicine on presumptive disability decision making for veterans proposed a comprehensive scheme for evaluating evidence on whether an exposure sustained in military service had contributed to disease causation (IOM 2008).

Risk assessment is widely used within the government (including FDA) and by other entities in the management of risks from environmental and other factors (National Research Council 1983; 2009). It is an evidence-based decision-making tool that has four elements: (a) hazard identification (is there a risk?);(b) exposure assessment (what is the distribution of exposure to the agent?); (c) dose-response (how does risk vary with dose or exposure?); (d) risk characterization (what is the burden of risk associated with the agent of concern and how is that risk distributed?). The conduct of a risk assessment results in a clear documentation of what is known about a particular agent, and correspondingly what is not known, i.e., the sources of uncertainty. In applying risk assessment to environmental agents, there is also interest in whether particular groups are at higher risk to be exposed (vulnerability) or at heightened risk for the adverse effect(s) (susceptibility). These well worked-out concepts of risk assessment—uncertainty, vulnerability, and susceptibility—are applicable to TPSAC's consideration of menthol cigarettes.

This brief and necessarily selective examination of approaches to evidence review and evaluation documents that models are available for consideration by TPSAC that have proved successful in practice. They have several common elements: transparent and explicitly documented methods; consistent and critical evaluation of all relevant literature; application of a standardized approach for grading the strength of evidence; and clear and consistent phrasing of conclusions.

Systematic reviews

Systematic reviews have become the foundation for evidence-based policy in public health. A systematic review involves the identification of all relevant literature to a particular topic via a transparent and replicable search strategy; the culling of the identified publications for those meeting predetermined criteria for inclusion; a comprehensive and standardized assessment of the selected studies for strengths and weaknesses; the assembly of the findings into tables and figures; and the summarization of the findings and the statement of a conclusion on the strength of evidence. Protocols for carrying out such reviews are available.

A systematic review may also involve a quantitative analysis of the evidence, often referred to as a meta-analysis. Such meta-analyses are based on the summary findings of studies, generally as gleaned from papers, but sometimes from authors. The data from individual studies may be combined to yield a single point estimate for an association; by combining the findings of multiple studies, a more precise estimate can be made and the heterogeneity (variation) in the findings of studies formally assessed. If there is variation, the data might be explored for explanations of the variation, using stratification or meta-regression. Conducting a meta-analysis is beyond the scope of this report, but could be conducted for future consideration.

Causal inference and classification of strength of evidence

After gathering evidence through a defined process, e.g., a systematic review, the next step is the determination of what the evidence shows. In public health, a critical determination is whether there is sufficient evidence to show a causal association, i.e., whether some factor is either harming or benefiting human health. This process of assessing evidence and determining whether there is a causal relationship is referred to as causal inference.

There is an extensive literature on causal inference, both on its philosophical underpinnings and on the methodology for evaluating the strength of evidence for causation. These approaches have in common a systematic identification of all relevant evidence, i.e., a systematic review, criteria for evaluating the strength of evidence, and language for describing the strength of evidence for causation. The topic of causal inference and its role in decision-making has been recently covered in the 2004 report of the Surgeon General (US DHHS 2004) and in the 2008 report of the Institute of Medicine's Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (IOM 2008).

The 2004 Report of the US Surgeon General on smoking and health (US DHHS 2004) provides an updated review of the methods used in that series of reports, which began with the 1964 report (US DHEW 1964). The review approach embodies the common elements described in the preceding paragraph and uses evidence evaluation criteria that originated with the 1964 report and the writings of Sir Austin Bradford Hill (the "Hill criteria") (Hill 1965) (Table 1). The use of these criteria has now been refined through decades of application. These criteria are not rigid and are not applied in a "check list" manner. In fact, only one—temporality—is required for inferring a causal relationship, since exposure to the causal agent must precede the associated effect. Consistency refers to replication of the finding of an association between cause and effect in multiple studies carried out in different populations by different study types and by different investigators. Consistency of findings weighs against non-causal explanations for an association. Coherence refers to the meshing of different lines of evidence, including experimental findings and understanding of biological mechanisms. For many human diseases, other than the infectious diseases, specificity is not useful, since the non-communicable diseases, such as cancer and coronary heart disease, have multiple causes. In general, stronger associations and the presence of a dose-response relationship provide evidence against non-causal explanations for association. Stronger associations are less likely to be due to bias or confounding as is the presence of a dose-response relationship. The magnitude of an effect reflects underlying biological processes and, depending on these processes, might be appropriately small or large. An effect may not necessarily increase progressively with dose, depending on the underlying process.

The "bottom line" from causal inference is a clear statement on the strength of evidence for causation. Such statements should follow a standardized classification to avoid ambiguity and to assure comparability across different agents and outcomes.

TPSAC reviewed the above approach, which involves the systematic evaluation of evidence to reach a conclusion with regard to disease causation. TPSAC's charge for menthol cigarettes extends beyond disease causation, however, and TPSAC needs to reach conclusions on diverse issues, including, for example, the consequences of marketing. In reviewing evidence, TPSAC has adopted the general approach described in the causal inference literature. This involves the compilation and review of relevant information to reach a judgment as to the strength of the available evidence in a structured and transparent fashion.

TPSAC'S APPROACH

Sources of evidence and identification of evidence to be reviewed

In writing this report, TPSAC had multiple sources of evidence to consider, including:

- The peer-reviewed literature: In using this term, TPSAC refers to the studies published in journals or other formats that undergo a process of peer review and editorial evaluation prior to publication. Peer review provides a filter, albeit imperfect, to assure quality prior to publication. Such publications can generally be identified by searching major data bases, such as PubMed.

- Reports written and commissioned by the FDA: TPSAC was provided with multiple reviews of the literature and other reports that were developed by FDA staff or contractors to the FDA. These reports included overviews of the evidence on menthol that were presented at the March 30–31, 2010 meeting and compilations of industry documents from the Legacy data base that were presented at the October 7–8, 2010 meeting. These reports also included the secondary analysis of existing datasets which were made available to TPSAC members and public for the January 10–11, 2011 meeting. Some of these reports have been submitted to the peer-reviewed literature and will become available through that route as well. The reviews of the Legacy documents will be published in a supplement to the journal *Tobacco Control.* FDA also arranged for secondary analyses of various studies and data bases that provided relevant data.

- Tobacco company submissions: The tobacco companies made various submissions to TPSAC under Section 904, some classified as commercial/confidential. These submissions were made on multiple occasions during TPSAC meetings and were directed at the general topic of the meetings. During its initial meeting on March 30–31, TPSAC developed 17 questions for documents to be provided under Section 904 and asked the industry to develop responses, which were offered at the July 15–16, 2010 meeting.

- Public comments: TPSAC received comments from a wide range of public stakeholders. The scope of such presentations was broad.

In developing this report, TPSAC considered evidence from these diverse sources, recognizing the potential strengths and weaknesses of each type of information. The peer-reviewed literature can be systematically accessed through various search engines and TPSAC has attempted to identify all relevant literature, using searches carried out by FDA and its contractors, and also carrying out its own searches. TPSAC used the bibliography assembled by FDA as one resource to identify the most relevant literature. The members of the Menthol Subcommittee also reviewed submissions by the tobacco industry and the public generally to identify other, relevant articles. For other sources, TPSAC did not have resources or sufficient time to carry out its own searches of the Legacy data base nor did it independently review the industry documents that were submitted. Instead, it relied on the reviews of those documents by FDA contractors.

Selection and evaluation of evidence

The report approached diverse topics, each drawing on somewhat disparate lines of evidence. For example, in describing patterns of menthol cigarette use, TPSAC relied in part on updated analyses of recent survey data, even though it had not been reported in the peer-reviewed literature. For such analyses, the methods are well standardized and TPSAC could use the results with confidence based on its review of the approach. In contrast, the research on whether smokers of menthol cigarettes have risks for smoking-caused diseases different from those of smokers of non-menthol cigarettes is based on reports of epidemiological studies that have been published in the peer-reviewed literature. TPSAC did not consider abstracts or meeting presentations for which additional documentation was not available.

TPSAC evaluated all studies considered using evaluation criteria appropriate to the particular type of evidence. For example, assessments of survey findings considered response rate and representativeness, the potential for information bias, and sample size. In considering epidemiological studies, the chapter authors assessed population selection and the external validity of findings, bias and confounding, sample size, and appropriateness of data analysis methods. For surveys, response rates and the potential for misclassification were considered. In considering the literature on marketing, attention was directed at the rigor of study design, the limitations of the data collected, analytical methods, and generalizability (external validity) of findings. These reviews were conducted by the various chapter authors, with referral to the Menthol Subcommittee as needed. Particular attention was given to those studies with findings that were more critical in evidence classification. Given the constraint of time, TPSAC did not establish a formal review process with a review template and multiple reviewers per study.

Classification of the strength of evidence

In this report, TPSAC addresses nine questions, seven at the individual level and two at the population level. Its reviews are the basis for the answers to these questions, which cover a wide range of factors and outcomes (Figure 1). To assure consistency and transparency, TPSAC provides its summary statements on the strength of evidence in a uniform fashion, offering a classification intended to be useful for decision making.

TPSAC used the following hierarchical classification for the strength of evidence providing its summary judgments:

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

This classification was discussed extensively by TPSAC and its members were unanimous in accepting it for use in this report. This classification is based around the concept of "equipoise," i.e., the point of strength of evidence at which the "weight of evidence" is in balance, equally for or against the presence of a relationship. This point reflects an approximate matching of the strength of evidence for a relationship with the evidence against, constituting findings pointing away from or toward a

relationship, taking uncertainty into account. In basing this classification around the point of equipoise, TPSAC plans to use an identifiable point, albeit via judgment, as the anchor for its four-level classification. Additionally, strength of evidence above the point of equipoise might be interpreted as offering a basis for considering a policy action.

In classifying the weight of evidence, TPSAC relied on the judgment of its members as they evaluated the systematically assembled evidence. In this regard, TPSAC followed standard professional practice in public health and regulatory decision making. Strength of evidence was considered to increase with (1) the number of studies providing consistent findings, and (2) the general proportion of studies providing consistent findings. Greater emphasis was given to larger, better executed studies that had been published in the peer-reviewed literature. The coherence of the evidence was also given weight. Because of the variable nature of the evidence considered from chapter to chapter, TPSAC did not propose specific criteria that would be applied uniformly.

These assessments were carried out by the individual chapter authors and then further discussed by the writing subgroup for the chapter. Conclusions were then reviewed and discussed by the Menthol Subcommittee and subsequently by all members of the TPSAC. Consistent with the principles set out by TPSAC, the conclusions reflect a consensus of its members.

USE OF MODELS TO ASSESS IMPACT

The TPSAC has the overall charge of addressing the "...impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, and other racial and ethnic minorities." The framework for considering the consequences of menthol cigarettes (Figure 1) identifies a series of indicators of impact under this charge: rates of experimentation, initiation, and progression or regular use or addiction among youths and young adults; rate of successful cessation; and risk for cigarette-caused morbidity and premature mortality. In approaching the assessment of the impact of menthol cigarettes, TPSAC intends to rely, in part, on models that are mathematical representations of the conceptual framework embodied in Figure 1. A model is constructed to reflect understanding of the mechanistic pathways that determine outcome(s) and how causal factors act through these pathways to produce outcome(s) in the "real world." Models can be used to quantify the impact of menthol cigarettes on the various indicators, providing estimates of impact that reflect the potential consequences of menthol cigarettes at the various, linked points in the framework.

Models are an element of a "systems approach" to characterizing the factors that drive the tobacco epidemic and resultant disease burden, and to assessing the potential consequences of tobacco control measures. Systems approaches based in "systems science" are an emerging paradigm for addressing public health problems (Best et al. 2007; Hammond 2009; Mabry et al. 2010). Systems science approaches are valuable for tobacco control and other complex public health problems because they involve comprehensive consideration of the set of determining factors and of the relationships among these factors. This broad-based understanding leads to the development of models that represent the actions of these factors in the "real world." While necessarily simplifying, models can be useful for exploring how different factors drive public health problems, and for exploring the utility of various control strategies.

Models have long been used to assess the impact of smoking on disease occurrence. In 1953, shortly after the publication of the first major studies that showed the strong association of smoking with lung cancer, Levin published a paper setting out a still-used method for calculating the burden of lung cancer attributable to smoking (Levin 1953). He proposed a parameter, now often referred to as the population attributable risk or population attributable fraction (PAF). This parameter is estimated as:

$$PAF = P_E(RR - 1)/(1 + P_E(RR - 1))$$

where P_E is the prevalence of exposure and RR is the relative risk of mortality associated with the risk factor. This parameter is estimated in the widely used Smoking Attributable Mortality, Morbidity and Economic Costs (SAMMEC) program developed by the Office on Smoking and Health of the Centers for Disease Control. One key concept embedded in this parameter is the comparison scenario for P_E, assumed to be a value of zero. This comparison state, which does not exist, is referred to as "the counterfactual," i.e., a scenario that is counter to the actual facts. For the purposes of the present report, TPSAC is concerned generally with counterfactual scenarios in which menthol cigarettes never existed.

This simple formula for estimating the PAF also indicates the two broad ways that menthol cigarettes could adversely impact public health: by increasing P_E or by increasing RR. An increase in either parameter results in an increase in PAF. Thus, if menthol cigarettes increased P_E but not RR, PAF would increase; if menthol cigarettes increased RR but not P_E, PAF would increase.

The utility of general models for tobacco control has gained increasing traction over the last decade, as the broad range of factors determining initiation and persistence of smoking and of disease risks within a population has been recognized (Best et al. 2007; Mendez 2010). The determinants range from the individual level, where genetics and education have a role, to the global level, where the actions of a small number of multinational companies affect the health of populations. A variety of models have been developed for use in the United States and other countries; they have been used to project consequences of various tobacco control approaches on smoking onset and prevalence and on disease burden (Levy et al. 2002; Best et al. 2007; Mabry et al. 2010).

For assessing the public health impact of menthol in cigarettes, a systems approach is warranted, given the diverse factors driving the smoking of menthol cigarettes. TPSAC cannot satisfactorily address its charge without taking a holistic approach that acknowledges the multiplicity of relevant factors and the potential for them to interact in complex ways. The relevant factors range from the biological impacts of tobacco and smoking on human cells to the influence of marketing on the population. There are well-defined interactions related to race and marketing. Evaluating menthol in isolation of social (ethnic, cultural and community), biologic (nicotine metabolism and receptor affinity), engineered (menthol-nicotine-tobacco matrix) and economic (price and marketing) influences may not easily be achieved and may lead to distorted conclusions about the major influences of menthol cigarettes on the public health. Consequently, TPSAC used models wherever appropriate to address its charge related to public health impact. The basic models might be extended to further explore specific issues, such as negative consequences of removing menthol from cigarettes in which it is a characterizing flavor.

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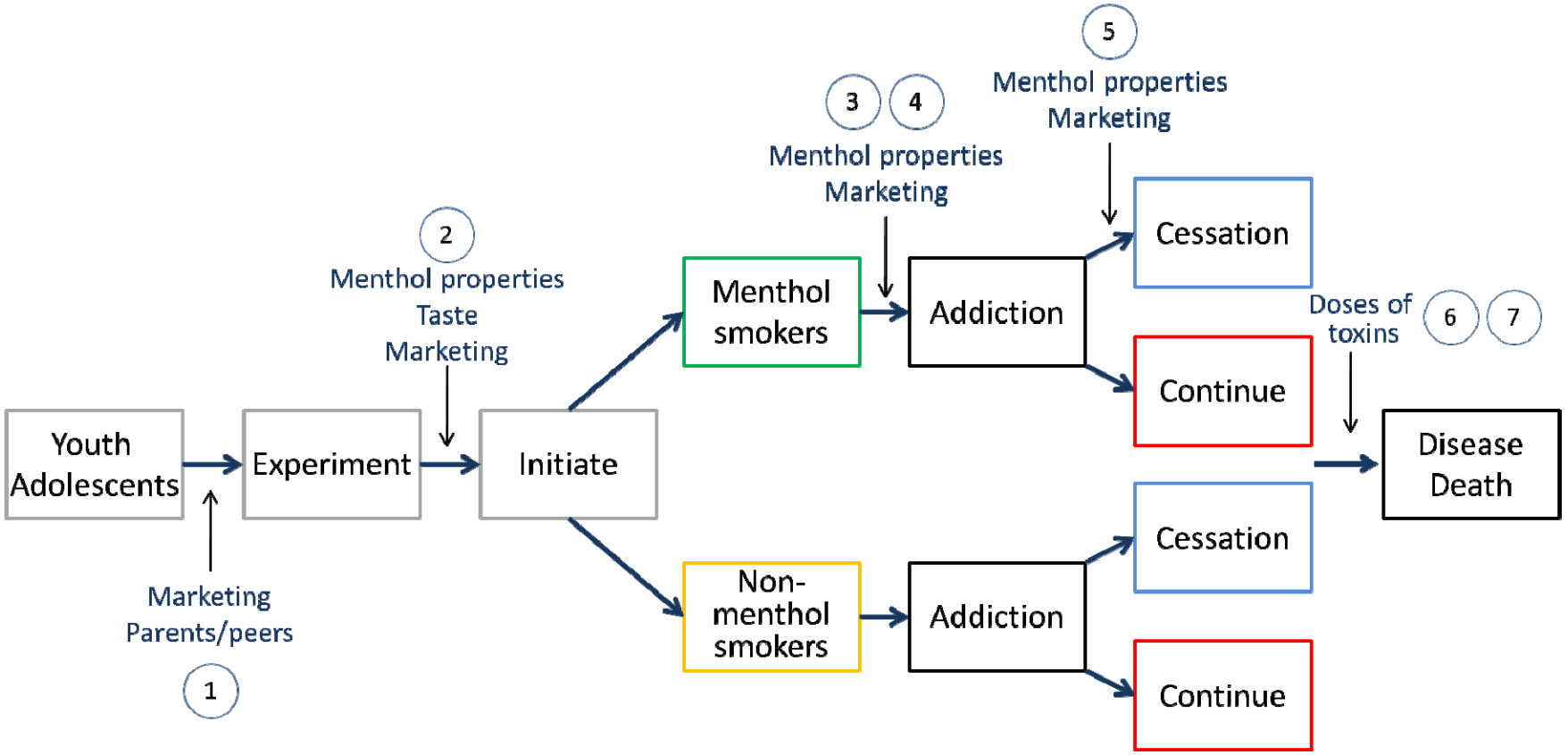
Footnote: Numbers refer to TPSAC questions related to individuals. Marketing refers to marketing of menthol cigarettes.



CHAPTER 3: THE PHYSIOLOGICAL EFFECTS OF MENTHOL CIGARETTES

INTRODUCTION

Menthol is a flavor additive widely used in consumer and medicinal products. It can be natural or synthetic, has a minty taste and aroma, and may have cooling, analgesic or irritating properties. As noted in Chapter 1, menthol is an active ingredient in certain medicinal products, such as cough drops, and when used in medicinal products, it is regulated as a drug. The use of menthol in tobacco products is not regulated. Menthol is present in varying concentrations in 90 percent of tobacco products, including cigarettes that are not marketed as menthol cigarettes.

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "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." Chapter 3 reviews the physiological effects of menthol in cigarettes. It reviews menthol's chemical structure, its mechanism of action, its interaction with key constituents of tobacco and tobacco smoke, and its affect on the sensory experience of smoking.

Specifically, Chapter 3 will address the following questions:

- Does menthol have cooling and/or anesthetic properties that moderate the harshness of cigarette smoke?
- Does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers?
- Does menthol have an effect on nicotine or nicotine-derived nitrosamine metabolism?
- Is it biologically plausible that menthol increases the addictiveness of cigarette smoking?

The answers will assist TPSAC in addressing the nine overarching questions listed and discussed in Chapter 1 that are the subject of this report. While the information in Chapter 3 is relevant to all nine questions, it is of particular importance to those examining the impact of menthol cigarettes on individual smokers.

METHODS

Chapter 2 provided the general framework for this report and the Tobacco Products Scientific Advisory Committee's approach to gathering, reviewing and weighing the evidence. Using this framework, Chapter 3 draws on sources that provide information about the physiological effects of menthol or necessary background information. The sources of information includes papers published in peer-reviewed literature, documents supplied to the committee by tobacco companies, FDA white papers and unpublished, internal tobacco company documents. Chapter 3 relies in part on animal and human studies that biochemically and/or behaviorally assess the physiological effects of exposure to menthol.

WHAT IS MENTHOL?

Chemically, menthol is a monocyclic terpene alcohol. It is a naturally occurring chemical chiefly derived from the peppermint plant (*Mentha piperita*) or the corn mint (*Mentha arvensis*), but it can also be synthetically produced. The chemical structure of menthol is shown in Figure 1. Menthol can exist as one of eight stereoisomers—molecules with identical formulas but different three-dimensional shapes. These isomers include menthol, isomenthol, neomenthol and neoisomenthol, each of which can exist as l, also called (-), or d, also called (+). Each of the stereoisomers has distinct pharmacologic characteristics. The l, or (-), isomer of menthol is the natural isomer and conveys the typical taste and sensory characteristics of menthol. The d, or (+), isomer is active but less so than l-menthol (Eccles 1994).

Tobacco companies use both natural and synthetic menthol in cigarettes. The natural menthol found in cigarettes (l isomer) is typically crystallized from steam-distilled oil of the corn mint plant (R.J. Reynolds 2010, p.6). Synthetic menthol (dl - menthol) is racemic, meaning it contains both the d and l isomers and has different taste characteristics from natural menthol (Lorillard Tobacco Company 2010, p.11, Heck 2010). Some cigarette manufacturers use natural menthol only; others use a mixture of natural and synthetic menthol. Natural menthol has been reported to impart greater cooling and mintness and less sharpness, perhaps due to trace chemicals in the natural extract (Wayne and Connolly 2004). Peppermint and spearmint oils may also be added along with menthol to some cigarettes to modify the taste and other sensory characteristics of the smoke (Wayne and Connolly 2004).

Menthol is volatile and has a relatively low boiling point (212 degrees C) (Heck 2010). Consequently, menthol readily vaporizes during cigarette smoking and easily transfers from the cigarette smoke to the smoker, with little pyrolysis, or decomposition. (Jenkins et al. 1970). In mainstream smoke, the vast majority of menthol is in the particulate phase (Jenkins et al. 1970).

Menthol is added to cigarettes in numerous ways: (1) spraying the cut tobacco during blending; (2) application to the pack foil; (3) injection into the tobacco stream in the cigarette maker; (4) injection into the filter on the filter maker; (5) insertion of crushable capsule in the filter; (6) placement of a menthol thread in the filter; and (7) a combination of the above (R.J. Reynolds 2010, p.7, Altria Client Services 2010). Over time, menthol diffuses throughout the cigarette irrespective of where it was applied. Menthol cigarettes are typically blended using more flue-cured and less burley tobacco (Wayne and Connolly 2004). This is because some of the chemicals in burley tobaccos create an incompatible taste character with menthol.

Menthol in cigarettes can be measured either by weight or yield. When measured by weight, menthol content is expressed either as the ratio of the weight of menthol to the weight of the tobacco in the cigarette (mg menthol/gm tobacco), or the weight of menthol in the entire cigarette (mg menthol/ cigarette). Ratios also can be expressed as parts per million (ppm), where 1000 ppm is equivalent to 0.1 percent. Yield per cigarette measures menthol in cigarette smoke and is expressed in mg. Though the menthol-in-smoke measurement is more biologically relevant, it is important to note that menthol yield is generated using standard smoking machine test methods and may not reflect how individual smokers consume menthol cigarettes. Smokers on average take in larger amount of smoke that the machine predicts, particularly when smoking lower yield cigarettes. Thus smokers of menthol cigarettes are likely to be exposed to more than the machine determined menthol yield per cigarette.

Menthol produces a minty taste and aroma and elicits cooling sensations. At low concentrations menthol has a soothing effect, but at high concentrations menthol is irritating. Menthol is reportedly

added to cigarettes both as a characterizing flavor (higher levels) and for other taste reasons (lower levels). These other taste reasons include brightening the flavor of tobacco blends and/or smoothing or balancing the taste of the blend (R.J. Reynolds 2010, p.15). The lowest detectable concentration identified by smokers as menthol characterizing is about 0.12 percent (Lorillard Tobacco Company 2010, p.13). Most menthol cigarettes contain 0.30 percent or higher. Menthol concentrations in non-menthol cigarettes average about 0.01 to 0.03 percent (Wayne et al. 2004). (b) (4) (b) (4) In addition to taste, menthol also contributes to smoke impact and to modulation of the irritation from nicotine.

In a recent survey of 48 U.S. menthol cigarette brands and sub-brands, the average menthol content in cigarettes by weight was 2.64 mg/ cigarette, with a range from 1.61 to 4.38 mg (Celebucki et al. 2005). The average menthol content in tobacco by weight was 3.89 mg/ gm tobacco, with a range from 2.35 to 7.76. Menthol concentrations tended to be highest in cigarettes with the lowest machined-measured tar deliveries, for reasons discussed below. Thus ultralight cigarettes typically had the most menthol, followed by light cigarettes and full flavor cigarettes. Altria presented data on menthol concentration in tobacco and in smoke for U.S. menthol cigarettes marketed in 2008 and 2009 (Altria Client Services 2010, p.25). The median menthol in tobacco was about 0.6 percent (6 mg/gm tobacco) and the median menthol in smoke was about 0.6 mg/cigarette. The lowest menthol in smoke was 0.35 mg/cigarette and the highest 1.29 mg/cigarette. The latter was in Camel LT KS Men HP cigarettes in which a menthol capsule is crushed prior to machine smoking. Menthol is also present in many non-menthol cigarettes at lower concentrations.

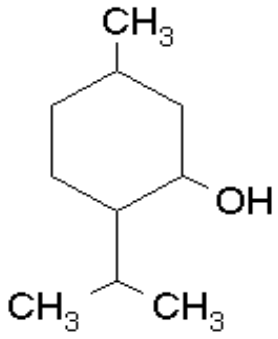
Examples of the menthol contained in the cigarettes and delivered in the smoke (as tested by standard condition machine smoking) for common full flavor menthol cigarette sub-brands are as follows (units are mg): Marlboro FF DS Men HP – 4.1, 0.71; Camel Crush KS HP, breaking capsule – 5.3, 0.87; Camel FF KS Men HP – 3.6, 0.71; Kool FF 100 HP/SP – 4.4, 0.74; Salem FF KS HP Green Label – 3.3, 0.61; Newport FF LS Men HP – 2.3, 0.46 (Altria Client Services 2010).

Low yield cigarettes – light and ultralight brands – are low yield primarily due to increased ventilation or air dilution. Compared to full flavor menthol cigarettes, light and ultralight menthol cigarettes have lower transfer efficiency—the percentage of menthol in the smoke compared to the menthol in the cigarette. The increased filtration and ventilation of lower tar delivery products decreases transfer efficiency. In full flavor menthol cigarettes, the transfer efficiency of menthol averages 10–20 percent, while the transfer efficiency in ultralight menthol cigarettes can be as low as 5 percent (Altria Client Services 2010, p.22–24; Cook et al. 1999). To cite a specific example, menthol transfer from the Newport cigarette is 20 percent, while transfer from Newport Light is 12 percent (Lorillard Tobacco Company 2010, p.6). The higher menthol content in light and ultralight cigarettes compensates for the lower transfer efficiency. The transfer efficiency can change with storage of cigarettes as menthol moves from the tobacco to the filter, from which it may be less available for elution (Altria Client Services 2010).

Tobacco companies have explored adding chemicals with menthol-like cooling effects to cigarettes. A number of cooling agents were developed by Wilkinson Sword Ltd in the 1970s and are identified as WS compounds (Leffingwell & Associates 2010). Several of these chemicals including WS-3, WS-5, WS-12, WS-14 and WS-23, act on the same receptors as menthol and have similar cooling effects, but lack menthol's minty taste and aroma (Ma et al. 2008). Other cooling chemicals have been developed by other companies. (b) (4) but to TPSAC's knowledge, they were never

added to mass marketed cigarettes. (b) (4) In any case, when considering regulation of menthol in cigarette, the presence of menthol analogs or alternative should also be considered.

Figure 1. Chemical Structure of Menthol



MENTHOL'S MECHANISMS OF ACTION

Menthol acts on receptors expressed primarily on sensory nerves, including in the trigeminal nerves that innervate the nose, mouth and airways (Abe et al. 2005). Specifically, menthol acts on Transient Receptor Potential (TRP) channels that contribute to the detection of physical stimuli, including temperature and chemical irritation (Levine et al. 2007; Macpherson et al. 2006). Menthol has been reported to act on three of these receptors: the TRPM8 (transient receptor potential melastatin 8), TRPA1 (transient receptor potential ankyrin1) and TRPV3 (transient receptor potential, vanilloid family, member 3). (b) (4) The TRPM8 receptor, which is responsive to cold, and the TRPA1 receptor, which is a chemosensory receptor, are expressed in the sensory neurons of the trigeminal and dorsal root ganglia. The TRPV3 and TRPV1 receptors are responsive to heat and capsaicin. The TRPV3 receptors are expressed in skin cells, and TRPV1 in trigeminal nerve and dorsal root ganglia cells. All of these receptors have roles in mediating sensations of pain or irritation (Eid et al. 2009).

The TRPM8 receptor is activated by both cold and by menthol (Voets et al. 2004; Maccpherson et al. 2006; Bautista et al. 2007), explaining why menthol elicits sensations of cooling. Menthol decreases cold pain thresholds and enhances pain responses to noxious cold stimuli (Hatem et al. 2006; Wasner et al. 2004). TRPM8 receptors are located on sensory, or afferent, nerves. At low doses menthol produces cooling and analgesia and at high doses menthol can cause irritation and pain via effects on these receptors. With prolonged stimulation menthol desensitizes TRPM8 receptors (Kuhn et al. 2009).

The TRPA1 receptor chiefly mediates the pain response to irritant chemicals, including the unsaturated aldehydes in cigarettes smoke (Andre et al. 2008; Bessac and Jordt 2008). This receptor also transmits responses to noxious cold (Karashima et al. 2009), and inflammatory pain (Bautista et al. 2006). Chemicals interact with TRPA1 to produce cough and airway inflammation (Geppetti et al. 2010). Menthol activates and inhibits the TRPA1 receptor, through which menthol can produce or reduce the

irritation from tobacco smoke (Bressac and Jordt 2008; Talavera et al. 2009; Xiao et al. 2008; Karashima et al. 2007). Nicotine, a known irritant, also activates TRPA1 receptors (Karashima et al. 2007; Xiao et al. 2008). Menthol activates TRPV3 receptors to induce cooling in skin (Macpherson et al. 2006).

TRPV1 receptors, found in airway sensory fibers as well as the nasal mucosa, respond to chemical stimuli including capsaicin and many other irritant chemicals (Bessac and Jordt 2008). Nicotine induces irritation by effects both on nicotinic cholinergic receptors and on TRPA1 and TRPV1 receptors (Talavera et al. 2009; Dussor at el. 2003; Simons et al. 2003; Lee et al. 2009).

Menthol acts on olfactory nerves to produce a minty aroma and pungency, effects that decrease as people age (Murphy 1983). When applied to skin, menthol has cooling and antipruritic effects (Bromm et al. 1995). These anti-itching effects have been attributed to menthol's interaction with cold receptors and possibly with kappa opioid receptors (Galeotti et al. 2002).

In addition to its ability to relieve itching, menthol is a topical analgesic. Menthol desensitizes nociceptive C receptors, which are responsible for sending pain signals to the brain; this activity may contribute to analgesia (Cliff and Green 1994). Given in high doses orally (10 mg/kg) or in smaller doses into the brain (10 mcg intracerebroventricularly) menthol has potent analgesic effects in rodents, effects that depend on activation of the endogeneous opioid system, acting on kappa opioid receptors (Galeotti et al. 2002). Thus in high concentrations, menthol acts on the brain. However, the concentration threshold for effects on the brain is not known. Menthol increases skin blood flow at the site of application, which may also contribute to local analgesia (Harris et al. 2006). Menthol's other attributes include antibacterial and antifungal properties and the ability to enhance of penetration of topical drugs and chemicals (Iscan et al. 2002).

MENTHOL DESENSITIZATION AND INTERACTION WITH NICOTINE

With repeated or prolonged administration, menthol is known to cause desensitization to its own cooling and irritant effects. Menthol is also reported to reduce sensitivity to noxious chemicals, including nicotine. The irritating effects of nicotine on the airway are mediated by activation of nicotinic cholinergic receptors and TRPA1. In cellular electrophysiology studies and in a rodent model of nicotine-induced airway constriction reflex response, menthol inhibits effects of nicotine (Talavera et al. 2009). Other in vitro studies have reported that menthol results in desensitization of nicotine-induced neuronal activation (Hans et al. 2006; Reeh et al. 2006). Altria studies using single cell recordings in cultured rat trigeminal ganglia (b) (4) The half-effective concentration of menthol to inhibit nicotine-evoked responses was 265 uM. Philip Morris studies also found that menthol reduces nicotine-mediated calcium flux in cultured trigeminal neurons and nicotine-mediated calcitonin gene-related peptide (CGRP) release from isolated mouse trachea preparations (Hans 2006; Reeh and Kichko 2006, cited in Altria Client Services 2010). The mouse trachea preparation contains TRPA1, TRPV1 and nicotinic cholinergic receptors. (b) (4)

In an experimental study, people whose tongues were repetitively dosed with menthol in solution became less sensitive to menthol's irritating and cooling effects (Dessirier et al. 2001). Menthol also reduced irritation from nicotine when applied to the tongues of people (Dessirier et al. 2001). Philip Morris research showed that intranasal menthol did not reduce the sensation of stinging pain produced by intranasal nicotine in people (Renner et al. 2008, cited in Altria Client Services 2010). Menthol did however reduce burning pain both in baseline and nicotine conditions. Higher levels of nicotine reduced the subjects' ability to discriminate dose-related odor and cooling effects of menthol compared to lower nicotine levels. While both menthol and nicotine have the potential to desensitize responses with repeated exposure, a study comparing olfactory thresholds for menthol and nicotine in smokers and non-smokers found the smokers had a much higher olfactory threshold for nicotine but no difference in threshold for menthol (Rosenblatt et al. 1998). The same was seen in both menthol and non-menthol smokers. Thus the effects of menthol are persistent in smokers.

MENTHOL KINETICS, METABOLISM AND METABOLIC INTERACTIONS WITH NICOTINE AND TOBACCO-SPECIFIC NITROSAMINES

Menthol moves from cigarette smoke into the lungs and then into the bloodstream. Smokers systemically absorb an average of 5–20 percent of the menthol in a menthol cigarette, depending on the extent of ventilation (Altria Client Services 2010, Benowitz et al. 2004). For a cigarette containing 3 mg of menthol (0.3 percent), a smoker of 20 cigarettes per day is exposed to an average systemic dose of 12.5 mg menthol per day.

Once it enters the general circulation, menthol is rapidly metabolized, making it difficult to measure free menthol in the blood or urine. Menthol is metabolized primarily through glucuronidation, a process that takes place in the liver to detoxify substances, and through oxidation, which also takes place in the liver. Glururonidation primarily is driven by the liver enzyme UDP-glucuronosyl transferase 1A4 (Green and Tephly 1998). The result of this process is a compound called menthol glucuronide. Oxidation of menthol to hydroxylated metabolites has been observed in studies in rats (Yamaguchi et al. 1994; Madyastha and Srivatsan 1988). In humans, approximately 50 percent of an oral dose of menthol is excreted in the urine as menthol glucuronide (Gelal et al. 1999). The half-life of menthol glucuronide after oral menthol dosing is about 50 minutes in plasma and 74 minutes in urine, although there appears to be a longer terminal half-life, most likely due to the slow release of the highly lipid-soluble menthol from body tissues and/or due to enterohepatic recirculation (Gelal et al. 1999). It is difficult to do pharmacokinetic studies with inhaled menthol because the dose absorbed cannot be known with certainty. Urine menthol glucuronide concentrations have been measured in a cross-sectional study of smokers of menthol and non-menthol cigarettes (Benowitz et al. 2010). On average, menthol levels are higher in menthol smokers, but many non-menthol smokers also have high menthol levels due to consumption of menthol-containing foods.

While free menthol concentrations are quite low in blood, they are high in tobacco smoke. As a result, menthol concentrations will be high in the mouth, throat and lungs. Estimating concentrations in smoke is important to assess the plausibility that menthol has effects on sensory nerves and possible drug metabolism in the upper and lower airways in relation to concentrations that have effects in animals or cell preparations. Assuming that a menthol cigarette delivers 0.8 mg of menthol in smoke and that a smoker takes 8 puffs on a cigarette, the menthol per puff is 0.1 mg. Assuming that all of the menthol in a puff is absorbed and that the inhalation volume associated with one puff (puff volume plus air) is 800 ml, the concentration of menthol would be 1250 mcg/L, which would be 8.0 uM/L. There is uncertainty about the partition of menthol between smoke and lung tissue, but this gives some rough approximation about what levels might act in the lungs, where there are drug metabolizing enzymes.

Concentrations could be considerably higher in the mouth and throat, before the inhaled smoke is fully diluted with the fresh air inhaled with the smoke. These high concentrations are in contrast with the low concentrations of free menthol in the blood stream and presumably in the liver, as discussed in more detail below.

Interactions with nicotine

Menthol may alter the metabolism of constituents of tobacco smoke, including nicotine. Menthol inhibits the metabolism of nicotine in liver microsomal test systems (MacDougall et al. 2003). (b) (4) The IC 50 (concentration that inhibits metabolism by 50%) was 70.5 uM for l menthol and 37.8 uM for d menthol in the MacDougall study. This concentration is higher than the concentrations typically detected in the blood of smokers, raising the question of whether circulating menthol levels in smokers would be adequate to inhibit liver metabolism of nicotine. However, nicotine is also metabolized in the lungs (Turner et al. 1975), where, as described previously, menthol levels in smoke are likely to be high enough to inhibit nicotine metabolism. In an experimental study of smokers, Benowitz et al. (2004) found that smoking menthol cigarettes inhibits nicotine metabolism in smokers. This was a two-week crossover study in which 14 smokers smoked menthol or non-menthol cigarettes on alternating weeks. After smoking a particular type of cigarette for several days, each subject was given an intravenous infusion of deuterium-labeled nicotine and cotinine to determine the effects of menthol cigarette smoking on the disposition kinetics of nicotine and cotinine. Nicotine clearance was on average 10 percent slower while smoking menthol cigarettes. Menthol inhibited both oxidative metabolism of nicotine to cotinine, and glucuronidation of nicotine. Menthol had no effect on cotinine metabolism. Potential limitations of this study include its small sample size, that its subjects were all heavy smokers and that its subjects were predominantly men.

Studies that used a different measure of nicotine oxidative metabolism found that menthol had no statistically significant effect on the breakdown of nicotine. These studies measured the ratio of the nicotine metabolites trans-3' hydroxycotinine to cotinine (Dempsey et al. 2004), which result from the activity of the enzyme CYP2A6, the major enzyme involved in the oxidation of nicotine. The ratio of trans-3' hydroxycotinine to cotinine, which can be measured in blood, saliva or urine, is highly correlated with the clearance of nicotine. Using this ratio, three studies found no difference in nicotine metabolism between menthol and non-menthol smokers. One was a cross-sectional multi-site study of 1044 menthol and 2297 non-menthol smokers conducted by Altria (Total Exposure Study, Wang et al. 2010). Another was a study of 755 African American smokers participating in a clinical trial of smoking cessation (Ho et al. 2009). The third was a study of 89 smokers with schizophrenia and 53 controls (Williams et al. 2007). The lack of a menthol effect is consistent with either no effect or a small effect of menthol on oxidative metabolism. The ratio would not be sensitive to an effect of menthol on nicotine conjugation. The Altria Total Exposure Study did look at urine ratios of nicotine glucuronide to nicotine, and found no effect of menthol cigarette smoking, arguing against an effect of menthol on nicotine conjugation (Altria Client Services 2010).

Interaction with tobacco-specific nitrosamines

Menthol may also inhibit the detoxification of the tobacco-specific carcinogen 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL). NNAL is formed as a major metabolite of the potent tobacco-specific nitrosamine and carcinogen 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

NNK (Hecht 2008). NNK is present in cigarette tobacco, and is formed primarily by nitrosation of nicotine in the curing process. A major pathway of detoxification of NNAL is by glucuronidation, considered to be mediated by the isoenzymes UGT2B7 (Ren et al. 2000) UGT2B10 (Chen et al. 2007) and UGT2B17 (Lazarus et al. 2005). A substance that inhibits the detoxification of NNAL could potentially increase the risk of cancer. Richie et al. (1997) found in a study of 34 African American smokers and 27 Caucasian smokers that the ratio of NNAL glucuronide / NNAL in urine was significantly lower in African Americans. This finding suggested slower glucuronidation detoxification of NNAL in African American smokers. Since African Americans predominantly smoke menthol and Caucasians predominantly non-menthol cigarettes, Ritchie et al. hypothesized that menthol inhibits NNAL glucuronidation. Muscat (2009) specifically compared 67 menthol smokers to 80 non-menthol smokers, and found that the glucuronidation ratio was significantly lower in white menthol smokers and menthol smokers overall, with a non-significant trend in the same direction for African American smokers. Muscat et al. also found that menthol inhibited NNAL glucuronidation in vitro using human liver microsomes. In the latter study, the IC 50 values for inhibition of N-glucuronidation and O-glucuronidation of NNAL were 0.26 and 0.41 mM, respectively. These levels are higher than those found in the blood and presumably liver of menthol cigarette smokers. Whether such glucuronidation can occur in the lung is not clear. The Altria-sponsored Total Exposure Study, which included 1044 menthol and 2297 non-menthol cigarette smokers, mentioned previously, found no effect of menthol cigarette smoking within racial groups on the ratio (Altria Client Services 2010).

MENTHOL AND SENSORY RESPONSE TO CIGARETTE SMOKING

Effects on smoke smoothness and impact

Sensory attributes of tobacco smoke can be considered as a combination of taste, smell and chemesthesis (the latter referring to the feel, such as cooling, biting and burning) (Carpenter et al. 2007). These occur in the context of stimulation of physiological responses in olfactory and trigeminal nerves. These responses have been described by Philip Morris as tobacco smoke flavor, which includes attributes derived from aromatic volatile substances, tastes and feeling qualities such as dryness and cooling (Philip Morris 1999). Sensory attributes overall include resistance to draw, throat response (such as smooth, stinging, peppery, cool), mouth response, mouth fullness, dryness and harshness, tobacco taste, aftertaste strength and cooling effect.

As noted above, menthol produces a variety of sensory effects, including a minty taste and aroma, cooling/ soothing effects, anesthetic effects and irritant effects. Menthol contributes to many of the sensory effects of cigarette smoke, including strength, taste, harshness, smoothness, mildness, coolness taste, and aftertaste. (R.J. Reynolds 1984). The effects of menthol are related to concentration. Lower menthol concentrations produce cooling and anesthetic effects, while higher menthol concentrations produce burning and irritation.

At the very low menthol concentrations used in non-menthol cigarettes, menthol is likely to make smoke smoother and less harsh even though the distinctive minty tasted and aroma is not detectable (Wayne and Connolly 2004). At the concentrations found in menthol cigarettes, smokers report that menthol reduces irritation and that menthol cigarettes are less harsh and smoother than non-menthol cigarettes. Smokers of high menthol cigarettes appear to particularly like the taste and aroma of menthol.

Menthol also has irritant effects, as noted above. Throat irritation is an important contributor to smoke impact, which is a key component of the perceived strength and satisfaction of the cigarette. Both

nicotine and menthol stimulate the trigeminal nerve in the mouth and throat to jointly produce the sensory effect of "bite," or "throat grab." Reviews of tobacco company documents and a submission from Altria describe the interaction between menthol, nicotine and tar in producing impact and other sensory effects (Wayne et al. 2004; Kreslake et al. 2008; Altria Client Services 2010; RJ Reynolds 1985). In cigarettes with low levels of tar and nicotine, the addition of menthol can enhance the "bite" or "throat grab" of the smoke, making such cigarettes more acceptable to consumers. Conversely, the addition of menthol to cigarettes high in tar and nicotine can reduce the irritating effect of nicotine, perhaps by cross desensitization, making these cigarettes more palatable. Among menthol cigarette smokers, perception of strength and impact correlate better with menthol delivery than with nicotine delivery (Perfetti 1982).

Thus menthol is not simply a flavoring agent but has drug-like characteristics that modulate the effects of nicotine on the smoker. The consequences of these effects for menthol cigarette smokers are twofold: the sensory stimulation from the "throat grab" of menthol could provide greater reinforcement for smoking behavior, and the reduced irritation provided by lower levels of menthol could lessen aversion to initial self-administration of nicotine among novice smokers, thereby facilitating continued smoking that leads to addiction. Additionally RJR documents (Carpenter et al. 2007) found a relationship between sensory preferences and smoking topography. Smokers who desired a strong cigarette took larger puffs compared to individuals who desired less strength. Since menthol is a determinant of perceived strength, this could be another reason for a relationship between menthol and greater intake of cigarette smoke.

McLernon et al. (2007) examined the interactions of food or beverages with the taste of cigarettes in 209 smokers. Subjects were asked whether foods or beverages worsened or enhanced the taste of their cigarettes. In some people food worsened and in others food enhanced the taste of cigarette smoke. This degree of worsening or enhancement was in general less pronounced in those who smoked menthol compared to non-menthol cigarettes. Insofar as smokers are more likely to smoke cigarettes when the taste of the smoke is consistent and predictable, menthol may enhance dependence by reducing potential interactions with foods and beverages.

Genetic interactions

Individual differences in taste perception, such as the ability to taste bitter chemicals, are well known. These differences are at least in part genetically determined. There has been much research on genetic differences in response to the bitter chemicals phenylthiocarbamate (PTC) and 6-n-propylthiouracil (PROP). Some people can taste bitter taste ("tasters") and some cannot ("non-tasters"). Tasters are less likely to become a smoker, suggesting that bitter taste makes smoking more aversive (Enoch et al. 2001; Cannon et al. 2005; Snedecor et al. 2006). The family of bitter receptors, TAS2R (taste receptor type 2) contribute substantially to the ability to taste bitter. One of the genes, TAS2R38, accounts for 85% of individual variability in response to bitter (Wooding 2004). The two most common genetic variants (haplotypes) of TAS2R38 are PAV and AVI. PAV homozygotes are most sensitive and AVI homozygotes are least sensitive to PTC/PROP. Among people of European descent, smokers with the AVI genotype rate higher taste/sensory and cue exposure-related motivations for smoking compared to smokers with the PAV genotype (Cannon et al. 2005). Thus the ability to perceive bitter taste seems to decrease taste-related motivations for smoking. This study found however that an intermediate taste sensitivity genotype, AAV, was protective against smoking, which seems inconsistent with earlier studies based on the taste sensitivity phenotype. Among African Americans the taster PAV genotype was inversely associated with smoking quantity, whereas the non taster AVI genotype was positively associated with smoking quantity (Mangold et al. 2008). Furthermore, in women, the non-taster

genotype was associated with the level of nicotine dependence. Neither the Cannon nor the Mangold study examined interactions between genotype and menthol cigarette smoking. However, since nicotine contributes to the bitterness of cigarette smoke, and menthol reduces the harshness and other unpleasant taste effects of nicotine, and since reduced bitterness is associated with smoking more, the genetic data support the idea that menthol may affect smoking behavior and associated dependence. These studies also raise the possibility that menthol might interact with genetically determined taste sensitivity to facilitate smoking. That is, menthol could mask bitterness to allow smokers who are genetically more sensitive to bitterness to better tolerate tobacco smoke and therefore to become a smoker.

Respiratory effects

Menthol is used medicinally in decongestant products. Menthol produces a sensation of increased nasal patency, although nasal congestion is unaffected (Eccles 1990; Nishino et al. 1997; Kenia et al. 2008). Menthol inhibits ventilation (Harris 2006) and increases breath-hold time in humans (Sloan 1993). Menthol also acts as a cough suppressant (Laude et al. 1994; Morice et al. 1994). The respiratory effects of menthol—a sensation of cooling, increased breath-hold time and cough suppression—could promote deeper inhalation and/or longer retention of smoke in the lungs while smoking menthol cigarettes. In animal studies, menthol promotes bronchodilation (Wright et al. 1997) and the clearance of mucous from the lungs (Nishino 1997).

Other effects

Orally dosed menthol can cause vasodilation and relaxation of intestinal smooth muscle (Hawthorne et al. 1988). These effects, which are believed to be related to inhibition of calcium currents in smooth muscle (Hawthorne et al. 1988; Taylor et al. 1984), may explain the medical utility of menthol as a treatment for gastrointestinal disturbances. The relevance to the pharmacology of inhaled menthol is unclear. Oral menthol also has been found to increase heart rate, possibly a reflex response to menthol-induced vasodilation (Gelal et al. 1999). However, studies comparing menthol and non-menthol cigarettes have not found any cardiovascular effects of menthol (Pritchard et al. 1999; Pickworth et al. 2002). Studies of electroencephalographic responses to smoking found that response correlated with perceived impact and liking, which may be determined in part by menthol (Gullotta et al. 1989a, 1990, cited in Wayne, 2004). However menthol added to cigarettes had no direct effect on the electroencephalogram (Pritchard et al. 1999).

EVIDENCE SYNTHESIS

Chapter 3 set out to answer four questions relating to the physiological effects of menthol pursuant to TPSAC's charge. The responses to those questions are given below. TPSAC considered this information, along with other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

Does menthol have cooling or anesthetic properties that moderate the harshness of cigarette smoke?

The evidence is sufficient to conclude that menthol has cooling and anesthetic effects that reduce the harshness of cigarette smoke. Research indicates that menthol acts on both thermal and nociceptive receptors. This dual action results in both cooling and counter-irritant effects. Menthol desensitizes receptors by which nicotine produces irritant effects, thereby, reducing the irritation from nicotine in tobacco smoke.

The implications of these findings are that by reducing the harshness of tobacco smoke menthol could facilitate initiation or early persistence of smoking by youth. Also, by reducing the harshness of smoke, it is biologically plausible that menthol would facilitate deeper and more prolonged inhalation of tobacco smoke, resulting in greater smoke intake per cigarette**.**

Does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers?

The evidence is sufficient to conclude that menthol makes low-tar, low-nicotine cigarettes more acceptable to smokers. Like nicotine, menthol has irritant effects that contribute to the impact or "throat grab," of tobacco smoke. In light or ultralight cigarettes with lower nicotine delivery, menthol can be used to provide impact.

The implications of these findings are that menthol is likely to make low-yield cigarettes more satisfying, and smokers who switch to low-yield cigarettes for health concerns may be more likely to continue to smoke rather than quit.

Does menthol have an effect on the metabolism of nicotine or tobacco-specific nitrosamines?

The evidence is sufficient to conclude that it is at least as likely as not that menthol inhibits the metabolism of nicotine in smokers. The evidence in not sufficient to conclude that it is at least as likely as not that menthol inhibits the glucuronidation of NNAL in smokers. Studies using liver micosomes demonstrate that menthol can inhibit the metabolism of nicotine. One experimental within-subject human study, using a state-of-art method of measuring the rate of nicotine metabolism, indicates that menthol cigarette smoking inhibits the metabolism of nicotine by about 10 percent. Menthol could be affecting nicotine metabolism in the lungs, where some nicotine metabolism is known to occur and where menthol concentrations are likely quite high in menthol cigarette smokers. Several cross-sectional studies show menthol has no effect on the nicotine metabolite ratio, a biomarker of the rate of nicotine oxidation. However cross-sectional studies may not have adequate power to detect a 10 percent difference in the metabolite ratio. Given the small magnitude of the menthol effect on nicotine metabolism in the positive human experimental study, it is unlikely that such a metabolic difference would have much, if any, effect on smoking behavior.

Menthol in high concentrations has been shown to inhibit the metabolism of the tobacco-specific nitrosamine, NNAL, in isolated liver preparations. One cross-sectional study found lower ratios of NNAL glucuronide to NNAL in menthol cigarette smokers, but another larger study did not find such an effect. On balance the evidence to date is not sufficient to demonstrate a significant effect. However if menthol does inhibit NNAL metabolism, this could be a basis for higher cancer risk in menthol cigarette smokers.

Menthol is known to enhance the dermal penetration of a variety of drugs, and might in theory enhance the pulmonary absorption of nicotine and/or tobacco carcinogens. The data on menthol and exposure to tobacco toxins is reviewed in Chapter 6.

Is it biologically plausible that menthol enhances the addictiveness of cigarette smoking?

The evidence is sufficient to conclude that it is biologically plausible that menthol makes cigarette smoking more addictive. The evidence reviewed suggests several mechanisms by which menthol could contribute to the initiation and persistence of cigarette smoking.

- Nicotine is required for the acquisition and maintenance of addiction to cigarette smoking. But as described previously, menthol can modulate nicotine effects and may act directly on nicotinic cholinergic receptors to alter nicotine response.

- While nicotine is required for nicotine addiction, the addictiveness of cigarettes is also influenced by sensory factors (Rose 2006; Henningfield et al. 2011 in press). Menthol provides an unmistakable sensory experience—the minty taste, cooling sensation and throat irritation or impact. The taste and odor are pleasurable for menthol cigarette smokers and may reinforce smoking behavior. Animal studies have shown that taste and/or smell can enhance self-administration of drugs, even when those drugs are at concentrations so low that pharmacologically reinforcing effects are not necessarily produced (Meisch 2001; Carroll and Meisch 2011). Sensory factors can also contribute to self-administration because they mask the undesirable properties of the drug alone; at some levels in cigarette smoke, menthol reduces the harshness of nicotine.

- Sensory experiences can contribute to conditioned aspects of smoking behavior. Once drug self-administration has been established, taste and other sensory factors can function as stimuli that can substantially enhance the strength and persistence of drug self-administration (Carroll and Meisch 2011; Panlilio et al. 2005).

- Stimuli associated with drug intake and/or withdrawal can come to evoke craving that promotes resumption of self-administration of the drug after a period of abstinence. Thus, menthol from food or toothpaste could serve as a sensory cue to prompt relapse to smoking. These mechanisms have been demonstrated in a variety of animal and human studies with a variety of addictive drugs (Wilson et al. 2004; Sayette and Griffin 2010).

- Another potentially relevant issue is the relationship between menthol and genetic differences in perception of taste. As noted above, various studies raise the possibility that menthol might interact with genetically determined taste sensitivity to facilitate smoking. Thus, there may be a genetically susceptible population for whom menthol cigarettes facilitate smoking.

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CHAPTER 4: PATTERNS OF MENTHOL CIGARETTE SMOKING

INTRODUCTION

Chapter 4 summarizes recent national survey findings on patterns and trends of menthol cigarette use, providing a background for subsequent chapters on marketing (Chapter 5) and initiation, dependence and cessation (Chapter 6). In keeping with TPSAC's charge, this chapter gives particular attention to menthol cigarette use in special populations including adolescents, African Americans, Hispanics and other racial or ethnic minorities. This chapter also addresses the prevalence of menthol cigarette use in the generally population of smokers and provides some historical context to help understand the current demographics of menthol cigarette use. The trajectories of brands and use patterns over time are relevant to understanding current consumption patterns.

In order for the TPSAC to reach conclusions about the public health impact of menthol cigarettes and to make evidence-based recommendations to the FDA, TPSAC carefully considered the patterns and trends of menthol cigarette smoking. The first chapter of this report presented nine questions relevant to the TPSAC discussion of the public health impact of menthol cigarettes; seven questions are related to individual smokers and two are related to the population effects of smoking. The information and analysis presented in this chapter are particularly relevant to the following population-level questions:

- Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

EARLY MENTHOL CIGARETTE USE

The invention of menthol cigarettes is generally credited to Lloyd "Spud" Hughes. In the 1920s, the Ohio smoker stored his tobacco in a tin with the menthol crystals he used to treat a persistent cold. He discovered that the tobacco absorbed the menthol flavor, which made the cigarettes easier to smoke. He started a menthol cigarette company, and his product spurred imitators. In the decades since, menthol cigarettes have grown to become an important product in the U.S. cigarette market. Today, menthol smokers account for 28 percent to 34 percent of U.S. cigarette smokers.

The development and use of menthol cigarettes in the U.S. is well-documented in scholarly articles and books, such as "Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris" (Alfred A. Knopf 1997) by Richard Kluger and "The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America" (Basic Books 2007) by Allan M. Brandt. In preparing this chapter, TPSAC relied on "The Growth of Menthols 1933–1977," a 1978 report produced for Brown & Williamson by Market Science Associates (MSA), and "Menthol Review and Product Implications" (bates # 2044123054), which covers the period 1985–89. These two tobacco industry documents provide

information on menthol cigarette use before 2000, a period not covered by the data sets and surveys discussed in the methods section of this chapter.

The “Growth of Menthols” report describes the salient trends in menthol cigarette development and use during four distinct time periods from 1933–1977. A summary of each period follows, based on this report.

The first period, from 1933–1955, begins with Hughes’ accidental invention of menthol cigarettes. The company he founded started selling Spud brand cigarettes. By 1932, Spud, which no longer exists, was the fifth best-selling cigarette brand in the country, behind non-menthol brands Lucky Strike, Camels, Chesterfield and Old Gold. In 1933, Brown & Williamson introduced Kool, and by 1935, the brand captured 2.2 percent of the U.S. cigarette market. From the beginning, Kool had a therapeutic image. The brand was promoted as an alternative to the heavy, harsh-tasting experience of some non-menthol cigarettes, or for use during the winter months when lower indoor humidity was thought to contribute to dry throats. Kool marketing campaigns included, “For occasional use—Kool for a change,” “In between the others, rest your throat with Kools,” and “Switch to Kools from Hots.”

In 1942, the Federal Trade Commission filed a suit and won a judgment against Brown & Williamson for false advertising related to the purported “health benefits” of Kool. By 1943, the brand’s market share had fallen to 1.55 percent. To address this decline, Brown & Williamson brought out Willie the Penguin in 1947 as a “spokesanimal” for the ice-cool nature of the brand and by 1949 Kool’s market share had climbed to 2.2 percent. In June, 1950, the landmark Reader’s Digest article, “How Harmful Are Cigarettes?” reported on the potential health hazards of cigarettes. Nonetheless, Kool’s market share rose to 2.6 percent. By 1952, Kool claimed approximately a 3 percent market share. With introduction of a king-size version in 1954, Kool’s share edged up to 3.4 percent. The MSA report summarized Kool’s early history as follows:

> “This quasi-medical appeal, and the increased advertising, while effective in increasing its market share, also retained and reinforced the Kools' image as a specialty product appealing to that special segment that wished to avoid "throat dryness" or wished to "rest their throat "from "hot" cigarettes.” (MSA).

The second period, from 1956–1962, is described as “The Rise of Salem.” R.J. Reynolds Tobacco Co. introduced Salem, the first menthol cigarette with a filter, in 1956. Salem had less menthol taste but more tobacco taste and tar delivery than Kool. According to the MSA report, reaction was phenomenal and within the year, Salem’s share of market had caught up to Kool’s. Salem’s advertising positioned the brand as “a new idea in smoking,” with a rich tobacco taste and menthol-fresh comfort. Salem had more burley tobacco but was only slightly flavored with menthol so the tobacco taste would not be masked. Its advertising was keyed to light, refreshing springtime smoking— “*refreshing as all outdoors*” was the slogan. Newport cigarettes also were introduced during this period but did not garner a noticeable market share. A 1956 product comparison found that Newport was a “very light” product. It lacked tobacco taste and had much less tar and nicotine compared to Salem and Kool.

In four years, annual sales of Salem rose to $35 billion in 1960 from $4 billion in 1956, giving the brand 7.5 percent of the cigarette market, far exceeding the market share of Kool. Thanks largely to Salem, menthol cigarette sales grew to account for 11 percent of the total U.S.

cigarette market. With the success of Salem, menthol cigarettes evolved from a specialty product into a large, successful category.

During third period covered by the MSA report, from 1963–1974, Kool overtook Salem to re-establish itself as the menthol market leader, in part by capitalizing on its existing popularity with young adults and African Americans. In 1963, Kool already was the preferred cigarette of young smokers. Brown & Williamson saw the increasing number of marijuana users aged 12–17 (who seemed to prefer menthol cigarettes) as a potential market, according to the report. At the same time, Kool, already popular with African Americans, rapidly became the most popular cigarette within that racial group, in part due to advertising and promotions aimed at them. Data on African American smokers age 16 and over in 10 metropolitan areas showed that menthol cigarette use went from 14 percent in 1968 to 38 percent in 1975 before dropping slightly to 33 percent in 1977. Kool accounted for 60 percent of the menthol cigarette market among African Americans under age 35. The report estimates that 70 percent of the Kool's total 4-point share gain between 1968 and 1974 came from the gains among African Americans. Other surveys cited in the report indicated that Kool was making inroads with younger smokers. Kool's share of 16–25 year old smokers advanced from 3 percent in 1966 to about 16 percent in 1974. The report stated:

> "Kool is facing new risks at both ends of the age spectrum. It is attempting to stem the outflow to low tars (among older users) by offering lower tar line extensions. Simultaneously, programs capable of strengthening Kool's image among the new generation of starters, particularly blacks, are critical to maintaining Kool's overall market position."

Between 1964 and 1971, the number of menthol brands and sub-brands more than doubled from nine to 23. Newport's growth trend got underway in 1973, driven by its "Alive With Pleasure" campaign, which continued into the 1980s. The final period covered in the MSA report marks the growth of low-tar menthol cigarettes from 1975–1977.

By 1976 and through 1988, menthol cigarettes accounted for 28–29 percent of the overall cigarette market, according to Federal Trade Commission reports. Newport emerged as the best-selling menthol cigarette brand in 1993. Although Marlboro menthols were introduced in 1965, they did not become popular until the mid-1990s. In 2003, Marlboro menthols were the second-leading menthol brand behind Newport, with 5.4 percent of the total cigarette market.

"Menthol Review and New Product Implications," a Feb. 6, 1990 report produced for Philip Morris by the Leo Burnett Company (bates # 2044123055), examined menthol cigarette use patterns from 1985 to 1989. The report documents that menthol smoking among certain populations was well-established. It provided this description of menthol cigarette smokers in 1989: "Compared to non-menthol smokers, menthol smokers are likely to be female, black, younger and city dwellers." Reviewing the five-year trend from 1985 to 1989, the report noted that menthol cigarette smokers had become more African American, Spanish-speaking, older, wealthier, and more rural. The following chart summarized menthol smoking among different populations using the industry method of "indexing" menthol use to a standard of 100. A number under 90 indicates less menthol use among the identified group while a number over 120 signals more menthol cigarette use among the identified group.

Table 1. Index of Menthol Smokers 1988-89

Demographic	Index Menthol Vs. Non-Menthol 12 Months Ending 6/89
Male	77
Female	126
White	82
Black	633
Spanish - speaking	150
18-34	115
35+	90
Under $30	102
$30+	100
No College	95
Any College	88

Source: Menthol Review and New Product Implications, 1990

In 1989, the three top menthols have strikingly different profiles. Salem smokers were more female, older, educated and rural; Kool smokers were more male, and Newport smokers were black, young, urban, and less affluent and less educated than smokers of competing brands

METHODS

TPSAC searched PubMed for studies that quantitatively assessed patterns of menthol cigarette use within and among U.S. demographic groups. The search terms were "menthol cigarettes" [MeSH Terms] OR "cigarettes"[All Fields] OR "menthol" [All Fields] and "patterns "[All Fields]. The search yielded 11 potentially relevant references. TPSAC reviewed key information from each report, including the year of data collection, study methods, population sampled, the geographic region studied, smoking behavior, demographic variables and a summary of the methods. Reports were selected for inclusion if they directly compared patterns of menthol cigarette smoking among U.S. demographic groups. Manuscripts were excluded if they did not include patterns of menthol cigarettes in the U.S. population. Articles were also excluded if they were opinion pieces, policy statements, or review articles. Only articles from peer-reviewed journals were considered.

Evidence evaluation

Primary sources

TPSAC selected reports based on one or more of three primary data sources: the National Survey on Drug Use and Health (NSDUH), the Tobacco Use Supplements to the Current Population Survey (TUS-CPS), and the National Youth Tobacco Survey (NYTS). These three primary sources are described below.

NSDUH is a household survey which collects information on the U.S. civilian, non-institutionalized population aged 12 years and older. NSDUH had more than 68,000 respondents in 2008. NSDUH includes two questions that are relevant to cigarette use. The two

questions read: *On the one day you smoked cigarettes during the past 30 days, how many cigarettes did you smoke? Were the cigarettes you smoked during the past 30 days menthol*? Prior to 2004, this question was worded differently. Thus TPSAC reviewed NSDUH data from 2004 to 2008 only. The NSDUH survey also asked about the specific brand that respondents smoked in the past 30 days. However, the responses to that question cannot be used to accurately track menthol cigarette use; many brands have menthol and non-menthol sub-brands but details about sub-brands are not collected in the survey. A description of menthol definitions for NSDUH and other surveys are described in Table 2 below.

TUS CPS is cross-sectional data from 2003 and 2006/07. The data includes adult smokers (at least 18 years old) (*n* = 69,193). The CPS, administered by the U.S .Census Bureau, uses a multistage probability design to collect data from about 50,000 families monthly. This data, obtained in person or through computer-assisted telephone interviews, are used to produce reliable national and state estimates on labor force characteristics among the civilian, non-institutionalized U.S. population. The TUS is a supplement conducted with the CPS every two to three years to collect data on tobacco use, quitting behaviors, nicotine addiction and related attitudes and practices. The 2003 and 2006/2007 TUS CPS included one question that is relevant to cigarette use. The question reads*, Is your usual cigarette brand menthol or non-menthol?*

NYTS is an anonymous school-based survey that used a three-stage cluster sample design that oversampled African American, Hispanic, and Asian students. NYTS was administered to 27,038 students Grades 6–12 in spring 2006. This survey was conducted among youth who had smoked in the past 30 days, had a usual cigarette brand, and could identify their usual brand as menthol or non-menthol. TPSAC's analysis was conducted among likely menthol smokers—those who said they smoked menthol cigarettes and identified a menthol brand (e.g., Kool) as their usual product.

Table 2. Measurement of Menthol Cigarette Smoking

Study	Survey	Definition of menthol cigarette smoking	Related survey question(s)
Lawrence et al. 2010	TUS CPS	Respondents reported the status of their usual cigarette smoked as menthol or non-menthol	Is your usual cigarette brand menthol or non-menthol?
Rock et al. 2010	NSDUH	Respondents reported smoking part or all of a menthol cigarette in the past 30 days	Were the cigarettes you smoked during the past 30 days menthol?
FDA presentation on March 30, 2010 (Ralph S. Caraballo)	NSDUH	Cigarettes smoked in the past 30 days were menthol	Were the cigarettes you smoked during the past 30 days menthol?
Hersey et al. 2010	NYTS	Based on consistency between smokers' report of the brand and the menthol status of the cigarettes they usually smoked.	Is the brand of cigarettes that you usually smoked during the past 30 days, menthol or non-menthol?

Selected reports

Based on the above criteria, TPSAC selected four data sets and the associated reports for inclusion in this chapter. They are NSDUH itself; Hersey et al. 2010; Lawrence et al. 2010; and Giovino et al. 2004; 2009. TPSAC also drew from a presentation given by Ralph S. Caraballo (Office of Smoking and Health, CDC) at the FDA Tobacco Products Scientific Advisory Committee meeting on March 30, 2010. This presentation included an in-depth analysis of NSDUH. All journal articles and the presentation selected for review included nationally representative data**.** These publications provide a national picture of demographic patterns of menthol cigarette use Table 4 provides more detail on the selected reports.

Limitations of the data

One methodological concern is the possibility that both youth and adult smokers may misreport menthol cigarette use. This issue has been discussed in the scientific literature; the Giovino et al. (2004), for example, found that 7.9 percent of smokers age 12 and older who said they mostly smoked Kool, Newport or another menthol brand also reported they did not smoke menthol cigarettes. Conversely, Giovino et al. found that 4.2 percent of those who smoked brands that are only available in non-menthol form (e.g., Winston) said they smoked menthol cigarettes. According to Giovino et al., discrepancies in self-reported menthol cigarette use were higher for adolescent smokers aged 12 to 17 years than for adult smokers, although the 2004 paper does not provide specific data on this issue. TPSAC concludes that these discrepancies, over the time span considered, do not affect its trend analysis.

A second limitation is that TPSAC's primary sources—NSDUH, TUS CPS and NYTS—are cross-sectional annual surveys, i.e., data are collected at only a single point in time from the respondents. We have limited longitudinal data that track how smoking changes in specific individuals over time. Thus, our analyses of trends are at the population level.

Curtin et al. (submission to the FDA, June 2010) from R.J. Reynolds criticized the NSDUH data. They said the NSDUH question— *Were the cigarettes you smoked during the past 30 days menthol*?—was not specific enough to identify smokers whose usual cigarette was menthol (i.e., the question could capture non-menthol cigarette smokers who smoked one menthol cigarette). To address this, Curtain et al. reanalyzed data from a number of different surveys: National Health and Nutrition Surveys (NHANES; 2005/06, 2007/08), National Health Interview Survey (NHIS; 2005); NSDUH (2007); National Youth Tobacco Survey (NYTS, 2006). These surveys defined current smokers as those who had smoked on 10 or more of the last 30 days. Menthol use among current smokers was defined as usual cigarettes, usual brand, or usual brand smoked during the last 30 days for NHANES, NHIS, NYTS respectively. Based on these definitions, no differences were found in the rate of menthol cigarette use across the different age spectrum for the NHANES and NHIS surveys. The NYTS and NSDUH surveys showed a trend toward decreasing menthol cigarette use with increasing age.

Giovino (unpublished FDA submission 2010) presented data as a public comment that provided clarification on the NSDUH question regarding whether menthol cigarettes were smoked during the past 30 days. He noted that the question that eventually assessed menthol vs. non-menthol cigarette use status was preceded by a question regarding the brand of cigarettes that was smoked most often in the last 30 days. Once this inquiry was made, the subjects were asked if

the brand of cigarettes smoked during the past 30 days was menthol. Using cross-sectional NSDUH data from 2004 to 2008 and based on the definition of use of menthol in the past 30 days, and making corrections for misclassifications (e.g., reporting Newport cigarettes as non-menthol cigarettes), he observed a statistically significant age gradient across smokers 12–17 years old (49.3 percent), 18–25 years old (37.5 percent) and 26–34 years old (29.9 percent), replicating the main findings from Rock et al. (2010). (See Tables 2 and 4; also Chapter 6).

PREVALENCE OF MENTHOL CIGARETTE SMOKING

There are approximately 19.2 million menthol cigarette smokers in the U.S. (Caraballo 2010). Of this group, 18.1 million are adults ages 18 years or older. The remaining 1.1 million menthol smokers—nearly 6 percent of the total—are adolescents ages 12 to 17 (see Figures 1 & 2).

As noted above, menthol smokers as a group account for between 28 percent and 34 percent of all U.S. cigarette smokers, depending on the data used (Lawrence et al. 2010; NSDUH 2009). Detailed demographic information about menthol cigarette smokers is presented below. In keeping with TPSAC's charge, this information focuses on children, adolescents, African Americans, Hispanics and other racial and/or ethnic minorities.

Adolescents

Adolescents 12 to 17 years of age smoke menthol cigarettes at a higher rate than any other age group (NSDUH 2009). Among adolescent smokers, 49.9 percent of those in middle school and 44.9 percent of those in high school report that they usually smoke a menthol cigarette brand (Caraballo and Asman, white paper).

Rates of menthol cigarette smoking are higher among established middle school smokers—those who have smoked cigarettes for at least one year—than among novice middle school smokers. According to Hersey et al., where they analyzed the NYTS 54.7 percent of established middle school smokers and 42.2 percent of novice middle school smokers usually smoke menthol cigarettes.

With regard to high school smokers, experienced and novice smokers use menthol cigarettes in roughly the same proportion; 43.1 percent of established high school smokers and 42.8 percent of new high school smokers say they usually smoke menthol cigarettes (Hersey et al. 2010).

Data from the TUS CPS, which does not survey people under 18, show that menthol smoking prevalence is highest among 18–24 year olds—an additional indication that menthol cigarettes are particularly popular among younger smokers (Lawrence et al. 2010).

Race and ethnicity

The prevalence of menthol cigarette smoking is highest among African Americans across all socio-demographic and smoking-related categories, whether stratified by income, age, gender, marital status, region, education, age of initiation, and length of time smoking (NSDUH 2009; Lawrence et al. 2010).

Menthol cigarette use is particularly high among minority youth ages 12 to 17, according to an analysis of NYTS data by Hersey et al. The NYTS classifies smokers as "likely menthol cigarette

smokers" based on their answers to questions that ask them to identify their brand and to state whether they usually smoke menthol.

Figure 1. Percent of Menthol Cigarette Use Among Past-month Cigarette Smokers: 2004-2008, NSDUH

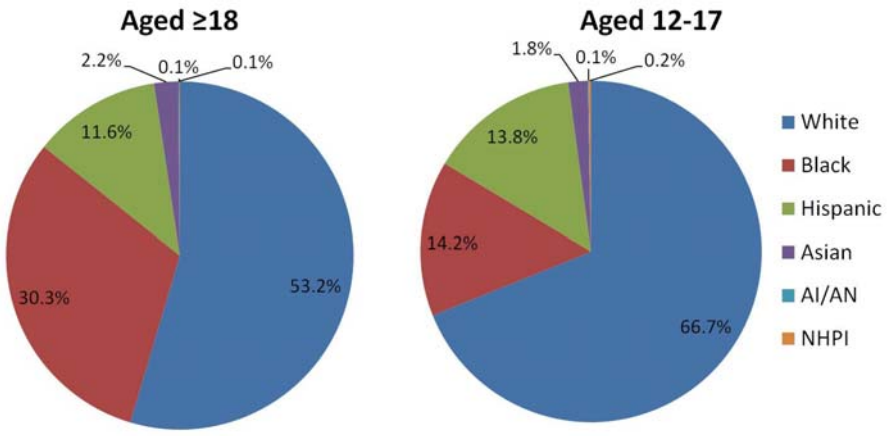
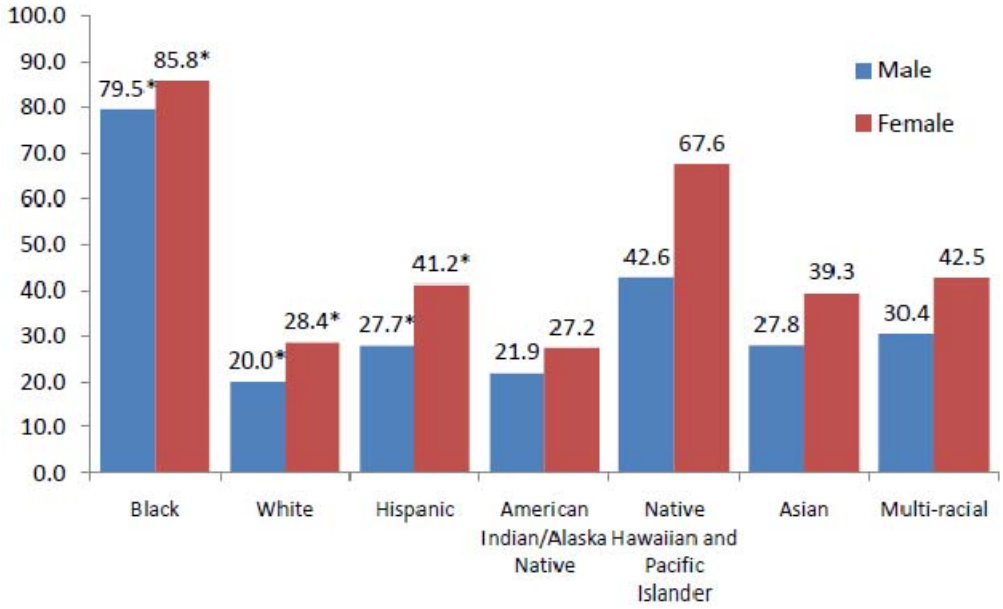


Figure 2. Percent Menthol Cigarette Use Among Past-month Cigarette Smokers Ages 12 and Older by Race/Ethnicity: 2004-2008, NSDUH



The respondents in this survey are identified as menthol smokers if they report that they smoke menthol cigarettes and they also report using a specific menthol brand (e.g., Newport). The answers to these two questions must be consistent in order for respondents to be classified correctly with certainty.

According to this definition, 80.6 percent of African American middle school smokers and 84.8 percent of African American high school smokers regularly smoke menthol cigarettes. Among

Hispanics, 57.9 percent of middle school smokers and 56.4 percent of high school smokers reported smoking menthol cigarettes. In Asian Americans a menthol brand is used by 57.4 percent of middle school smokers and 43.6 percent of high school smokers (Hersey et al. 2010; see Table 3). Menthol cigarettes were used less among non-Hispanic white youths; in this demographic, 43.1 percent of middle school smokers and 37.6 percent of high school smokers said they regularly smoked menthol cigarettes (Hersey et al. 2010).

The prevalence of menthol cigarette smoking varied for each racial/ethnic group by region (Lawrence et al. 2010). Rates of menthol cigarette use among white, Hispanic and American Indian/Alaska Native smokers are highest in the Northeast. For African American smokers, the rate of menthol smoking is highest in the Midwest. For Asian and Pacific Islander smokers, the prevalence of menthol cigarette smoking is highest in the West. Menthol cigarette smoking is significantly higher in metropolitan areas for all racial and ethnic groups except American Indians/Alaska Natives and Asian and Pacific Islanders.

Table 3. Percentage of Youth Smokers Who Used a Menthol Brand of Cigarettes in Middle School and High School

Subgroup	**All current smokers**	
	Middle school (*n* = 771)	**High school (*n* = 2,510)**
All youth smokers	51.7 (45.8–57.5)	43.1 (37.0–49.1)
Male	55.1 (43.9–54.7)	39.4 (33.6–45.2)
Female	48.1 (28.1–51.6)	46.9 (38.9–54.9)
Less than 1 year	42.2 (29.8–54.7)	42.8 (34.5–51.2)
1 year or more	54.7 (48.2–61.3)	43.1 (36.6–49.6)
African American	80.6 (72.0–89.3)	84.8 (77.3–92.3)
Asian American	57.4 (27.7–87.1)	43.6 (24.3–63.0)
Hispanic	57.9 (48.8–67.0)	56.4 (48.7–64.2)
White (non-Hispanic)	43.1 (36.2–50.0)	37.6 (31.0–44.3)

Source: NYTS 2006

Gender

Women are more likely to smoke menthol cigarettes than men (NSDUH 2009). This pattern is seen across all racial/ethnic groups except among American Indians/Alaskan Natives; in that group, men are more likely to smoke menthol cigarettes (NSDUH 2009; Lawrence et al. 2010).

People with mental illness

While smoking prevalence is high among people with mental illness (Lasser et al. 2000), there are no peer-reviewed journal articles on menthol cigarette in this vulnerable group.

TRENDS IN MENTHOL CIGARETTE USE

Trends by age

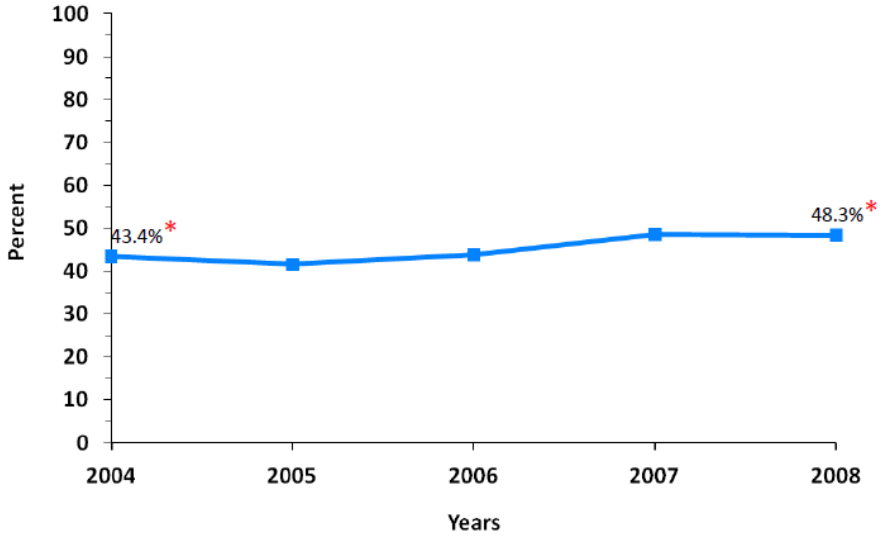
Adolescent smokers

According to the NSDUH data, among all past month smokers 12 to 17 years of age, the proportion of menthol cigarette smokers rose to 48.3 percent in 2008 from 43.4 percent in 2004—a statistically significant 11 percent increase over four years (see Figure 3). Driving this increase was a jump in menthol cigarette use among white adolescent smokers, the only racial/ethnic group to show a statistically significant increase over this period.

Adult smokers

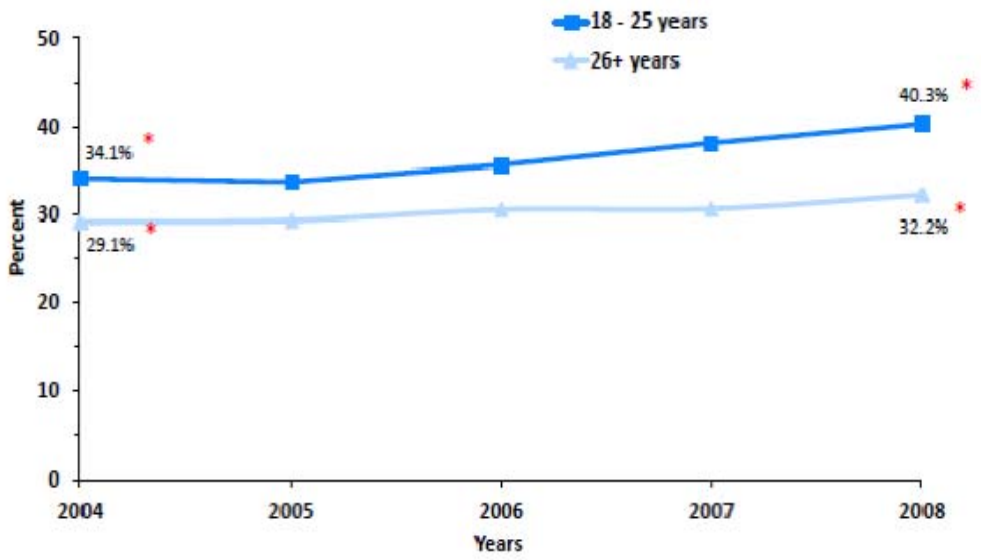
Among all past month adult smokers, the proportion of menthol cigarette smokers rose to 33.8 percent in 2008 from 30.2 percent in 2004—a 13 percent increase over four years (NSDUH 2009; see Figure 4). The increase was particularly sharp among young adults. The proportion of smokers aged 18 to 25 years who smoked menthol cigarettes rose to 40.3 percent in 2008 from 34.1 percent in 2004—a statistically significant 17 percent jump. Among smokers aged 26 years and older, the proportion who smoked menthol cigarettes rose to 32.2 percent in 2008 from 29.1 percent in 2004—an increase of 10 percent.

Figure 3. Trends in Menthol Cigarette Use Among Past-month Smokers Ages 12–17, 2004–2008



Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

Figure 4. Trends in Menthol Cigarette Use Among Past-month Adult Smokers by Age Group, 2004–2008



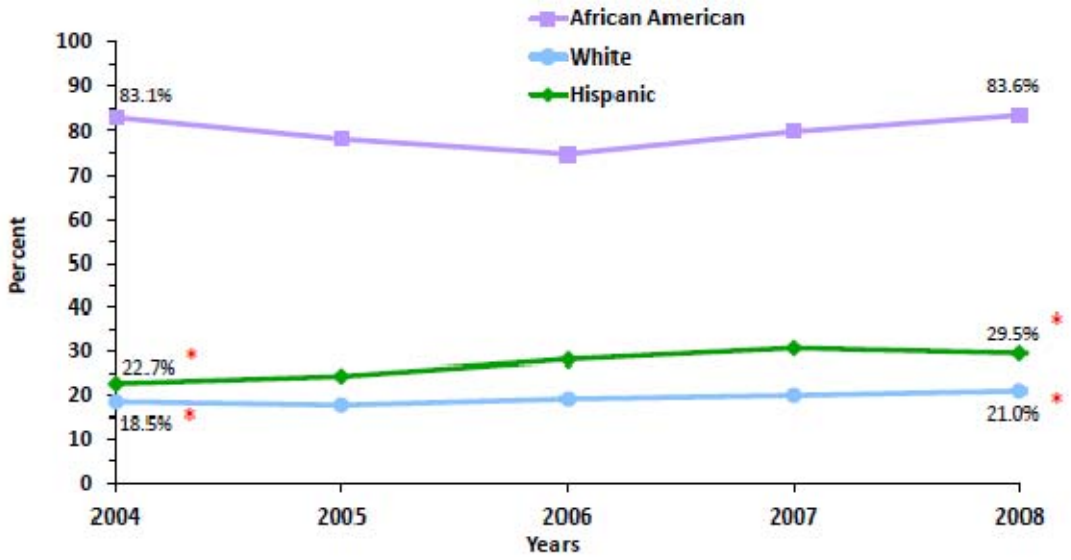
Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

Trends by gender

Men

The proportion of male cigarette smokers aged 12 years or older who smoked menthol cigarettes increased to 30.8 percent in 2008 from 26.9 percent in 2004, a statistically significant gain (NSDUH 2009). Statistically significant increases in past-month menthol cigarette use were observed among white and Hispanic male smokers aged 18 and older, according to NSDUH data. The proportion of white adult male past-month cigarette smokers who smoked menthol cigarettes increased to 21 percent in 2008 from 18.5 percent in 2004. The proportion of Hispanic adult male past-month cigarette smokers who smoked menthol cigarettes increased to 29.5 percent in 2008 from 22.7 percent in 2004.The proportion of African American adult male past-month cigarette smokers who smoked menthol cigarettes did not change, standing at 83 percent in both 2004 and 2008 (see Figure 5).

Figure 5.Trends in Menthol Cigarette Use Among African American, White, and Hispanic Men Age ≥ 18, 2004-2008

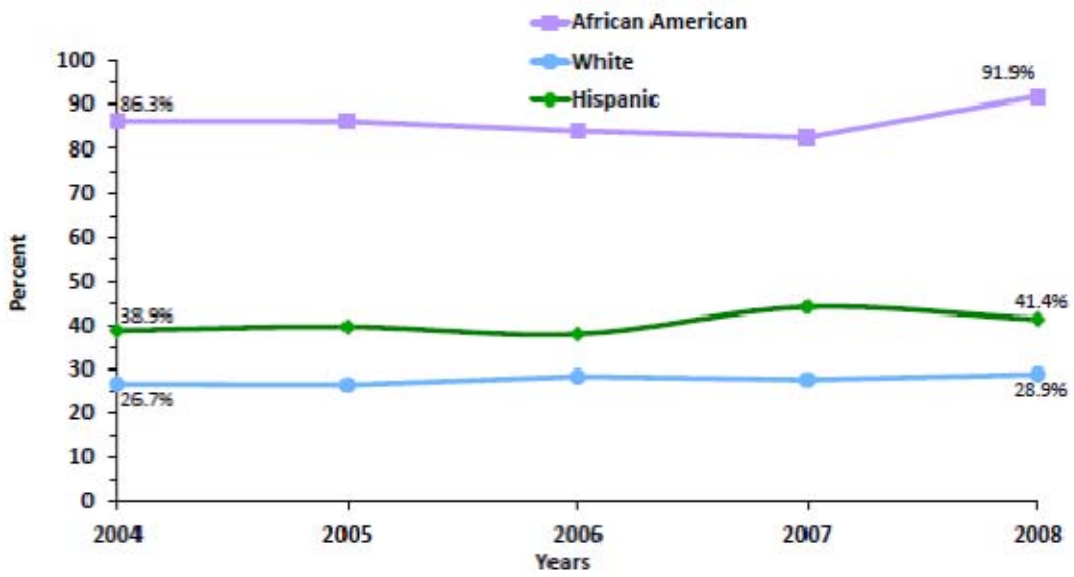


Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

Women

Although the proportion of adolescent and adult female smokers who smoked menthol cigarettes increased between 2004 and 2008, the changes were not statistically significant in any age or racial/ethnic category examined (NSDUH 2009; Caraballo 2010). The proportion of female cigarette smokers age 12 and older who smoked menthol cigarettes rose to 37.5 percent in 2008 from 35.9 percent in 2004. Among adult female African American smokers, the proportion of menthol smokers rose to 91.9 percent in 2008 from 86.3 percent in 2004. Among adult female white and Hispanic smokers, the proportion who smoked menthol cigarettes rose to 28.9 percent from 26.7 percent and to 41.4 percent from 38.9 percent, respectively, over the same period (Figure 6).

Figure 6. Trends in Menthol Cigarette Use Among African American, White, and Hispanic Women ages ≥ 18 years, 2004–2008

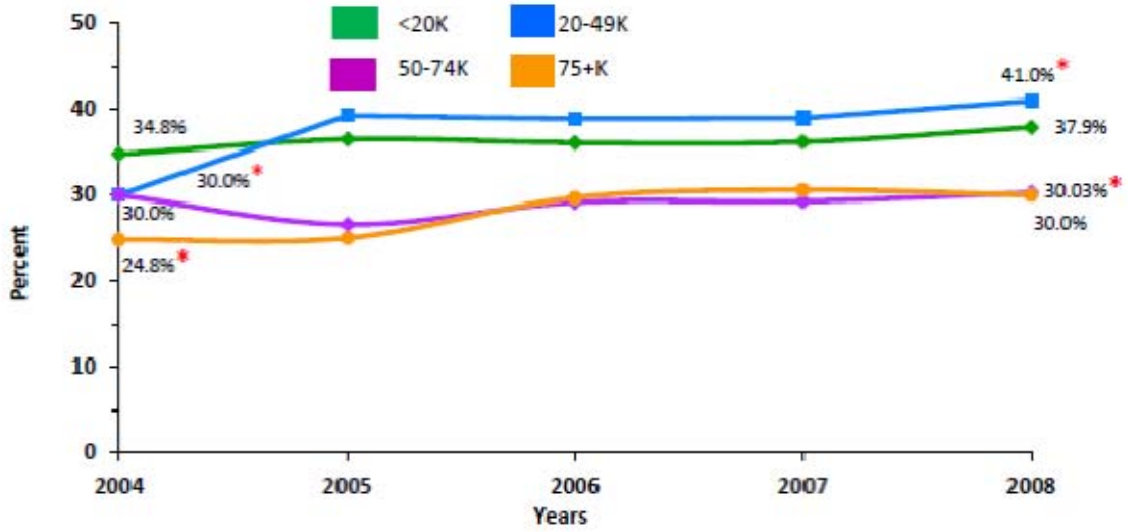


Source: National Surveys on Drug Use & Health, 2004-2008

Trends by income

Between 2004 and 2008, there were increases in the proportion of adult smokers who smoked menthol cigarettes among families with smokers and incomes between $20,000 and $49,999 and of $75,000 or more (see Figure 7).

Figure 7. Trends in Menthol Cigarette Use Among Past-month Smokers Ages ≥ 18, by Family Income, 2004–2008



Source: National Surveys on Drug Use & Health, 2004-2008
*Statistically significant

SUMMARY

Based primarily on three national data sets on smoking, the review in this chapter demonstrates that menthol cigarette use is high among women and the special populations relevant to TPSAC's charge—ethnic/racial minorities, including African Americans and Hispanics, and adolescents. Specifically, TPSAC finds:

- Menthol cigarette use is very high among minority youth. More than 80 percent of adolescent African American smokers and more than half of adolescent Hispanic smokers use menthol cigarettes. Menthol cigarettes are used by more than half of Asian American middle-school smokers.

- Use of menthol cigarettes is rising among adolescents, driven by a significant increase in the number of white youth ages 12–17 who are smoking menthol cigarettes. Trend data also shows a significant increase in menthol cigarette use among young adult smokers and white and Hispanic men.

- The review of these national data sets also shows that menthol use is prevalent among the unemployed, people with an annual family income of less than $10,000 and people who never married.

Table 4: Studies of Patterns of Menthol Cigarette Smoking				
	Study Periods	**Population**	**Key Results**	**Limitations**
Lawrence et al. 2010	2003 and 2006/07 TUS CPS	Adult current smokers (*n* = 63,193)	African American smokers were 10–11 ti mes more likely to smoke mentholated cigarettes than white smokers men: odds ratio (OR): 11.59, 99% confidence interval (CI): 9.79–13.72; women: OR: 10.12, 99% CI: 8.45–12.11). With the exception of American Indian / Aleut/ Eskimo smokers, non-white smokers were significantly more likely to smoke mentholated cigarettes than were white smokers. Additional significant factors associated with mentholated cigarette smoking included being unmarried (never married: OR: 1.21, 99% CI: 1.09–1.34; divorced/separated: OR: 1.13, 99% CI: 1.03–1.23), being born in a US territory (OR: 2.01, 99% CI: 1.35–3.01), living in a non-metropolitan area (OR: 0.87, 99% CI: 0.80–0.96), being unemployed (OR: 1.24, 99% CI: 1.06–1.44) and lower levels of education. Race/ethnicity-stratified analyses showed that women were more likely than men to smoke mentholated cigarettes. Among African American smokers, young adults (aged 18–24 years) were four times more likely to smoke mentholated cigarettes compared with individuals aged 65+	Cross-sectional study Small sample sizes for the AI/AN and API
National Survey on Drug Use and Health	2004 to 2008	Persons aged 12 or older (n =68,736)	Among past month smokers, the rate of smoking menthol cigarettes increased from 31.0 percent in 2004 to 33.9 percent in 2008; increases were most pronounced for adolescents aged 12 to 17 (43.5 percent in 2004 vs. 47.7 percent in 2008), young adults aged 18 to 25 (34.1 vs. 40.8 percent), and males (26.9 vs. 30.8 percent). Past month smoking of menthol cigarettes was more likely among those who were recent smoking initiates (i.e., began smoking in the past year) than among those who were longer term smokers (i.e., initiated use more than a year ago) (44.6 vs. 1.8 percent, respectively); this pattern was consistent for persons aged 12 to 17 and those aged 18 to 25, for both genders, and for whites and Hispanics. For African Americans, past month use of menthol cigarettes was less likely among past month smokers who were recent smoking initiates than among their counterparts who were longer term smokers (73.9 vs. 82.8 percent).	Cross-sectional study

Table 4: Studies of Patterns of Menthol Cigarette Smoking

Study	Study Periods	Population	Key Results	Limitations
Giovino et al. 2003	1999 National Household Survey (NHS)	12 and older (n= 71,764)	NHS and NYTS both confirm that Newport is the far leading brand among African American adolescents. Among African American smokers more than three-fourths of the adolescents ages (12-17 yrs) and young adults (18-25 yrs old) used Newport Baseline data from the ITCPES indicated that among adult smokers, females were more likely than males to use mentholated brands in the US (31.8% vs 22.1%)	Misclassification of self reported menthol status Cross-sectional study
	1998,99, 2000 Monitoring the Future (MtF)	8th, 10th, and 12th graders (n= 136,000)		
	2000 National Youth Tobacco Survey (NYTS)	middle and high school students (n= 35,838)		
	2002 International Tobacco Control Policy Evaluation Survey (ITCPES)	18 and older ever smokers (n=2500)		
FDA Presentation on March 30, 2010 (Ralph S. Caraballo)	2004-2008 NSDUH Survey	12 years old and older (n=68,000)	Total of 19.2 million menthol cigarette smokers Among smokers aged 12-17 years, 1.1 million menthol smokers Among smokers aged 18 and older. 18.1 million menthol smokers African American smokers are far more likely to smoke menthol cigarettes than smokers of other US racial and ethnic groups 7 of 10 African American adolescent smokers reported smoking menthol cigarettes followed by about half of multirace and Asian smokers. 8 of 10 African American adult smokers reported smoking menthol cigarettes followed by about half Native Hawaiian and other Pacific Islander adult smokers. Female smokers more likely to smoke menthol cigarettes than male smokers.	Cross-sectional study Accuracy for self-reporting smoking methanol cigarettes
Hersey et al. 2010	2006 National Youth Tobacco Survey	Grades 6th- 12th N= 27,038	51.7% (95% *CI*: 45.8–57.5) of middle school smokers and 43.1% (95% C.I.: 37.0, 49.1) of high school smokers reported that they usually smoked a menthol brand of cigarettes,	Misclassification of self reported menthol status Cross-sectional study

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CHAPTER 5: MARKETING AND CONSUMER PERCEPTION

INTRODUCTION

This chapter is concerned with addressing the question as to whether tobacco company marketing of menthol cigarettes increases the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available, and if this is the case in subgroups within the population. Accordingly, Chapter 5 reviews menthol cigarette marketing strategies, against the background of broader tobacco marketing strategies and with reference to general marketing principles. In addition, this chapter examines consumer beliefs relevant to menthol cigarettes.

Specifically, Chapter 5 will address the following questions:

- How is menthol marketing different from and similar to non-menthol marketing, in terms of product, place, price, promotion and packaging?
- What health reassurance messages were/are used in menthol marketing messages?
- What other messages were/are conveyed to potential consumers by menthol marketing messages?
- Who are the target populations for menthol marketing? Is there evidence to show that youth, women, and specific racial/ethnic groups were targeted?
- Does menthol marketing influence the perceived taste and/or sensory experience of menthol cigarettes?
- Do consumers perceive menthol cigarettes as safer or less harmful than non-menthol cigarettes?

Chapter 4 contains additional information on the history of menthol cigarette marketing.

METHODS

Chapters 1 and 2 provided the general framework for the report and the Tobacco Products Scientific Advisory Committee's (TPSAC) approach to gathering, reviewing and weighing evidence. Using this approach, Chapter 5 drew on peer-reviewed papers and government reports; white papers and analyses either written or commissioned by the FDA; tobacco company presentations and written submissions; and public presentations and comments to TPSAC that provided data relevant to the topic at hand.

HOW IS MENTHOL MARKETING DIFFERENT FROM AND SIMILAR TO NON-MENTHOL MARKETING, IN TERMS OF PRODUCT, PLACE, PRICE, PROMOTION AND PACKAGING?

This section addresses similarities and differences between menthol and non-menthol marketing. The studies and reports were organized according to the elements that make up the tobacco marketing mix. Like the marketing of other products, cigarette marketing strategy typically involves specifying a target audience and establishing an appropriate marketing mix known as the "4P's," involving product, place, price, and promotion (NCI 2008). *Product* refers to brand name and variety, as well as more tangible physical aspects of functionality. *Place* refers to where tobacco products are sold and their availability to consumers. *Price* includes wholesale and retail pricing, and other discount strategies. *Promotion* includes advertising in traditional and non-traditional media, as well as sponsorship, sampling, direct marketing and other strategies. A fifth "P" – packaging – is sometimes added in more recent formulations of the 4P's model, although packaging can also be included either as part of Product or Promotion.

Product

Menthol cigarettes accounted for 27 percent of all cigarettes sold in the U.S. in 2009 (Altria Client Services, July, 2010; Graves/R.J. Reynolds Tobacco Co., July, 2010). According to the Federal Trade Commission's Cigarette Report for 2006 (the most recent available), menthol market share increased from 16 percent in 1963 to 27 percent in 2005 of all cigarette sales, then decreased to 20 percent in 2006 (Federal Trade Commission 2009). However, this drop in market share in 2006 was not reflected in the data that tobacco companies provided to FDA. Menthol market share has been increasing since 2005, and the current share is as high as it has been since the 1980s. These patterns were reported in submissions in July 2010 from the three major tobacco companies, Altria (manufacturer of Marlboro), R.J. Reynolds Tobacco Company (manufacturer of Kool, Salem, and Camel), and Lorillard (manufacturer of Newport). The prevalence surveys reviewed in Chapter 4 also reflect increasing preference for menthol cigarettes among smokers.

Loomis (Oct 2010) described cigarette sales trends using AC Nielsen scanner data that were collected between August 2008 and July 2010 from convenience stores and a combination of food retailers, drug stores, and mass merchandisers. Consistent with the industry's reports, the percent of total sales for menthol cigarettes increased slightly, to 27.0 percent from 25.1 percent in convenience stores and to 25.7 percent from 24.5 percent in the combined channel. Approximately 80 percent of 195 different brand families featured at least one menthol variety. Menthol varieties accounted for 36.5 percent of the 1,401 varieties of cigarettes sold.

There are more than 350 different varieties of menthol cigarettes (R.J. Reynolds Tobacco Company, July, 2010), but five brand families accounted for 20.6 percent of total market share in 2009 (Altria Client Services, July 2010, Figure 2.2). As shown in the graph provided by Altria (Figure 1), market share was 9.8 percent for Newport, 5.4 percent for Marlboro menthol, 2.5 percent for Kool, and 1.6 percent for Salem. In addition, a 1.3 percent market share for Camel Menthol was reported separately by Altria. The pattern for market share is reflected in the brand preferences of adult smokers aged 20 or older: 11.6 percent smoked Newport; 5.9 percent, Marlboro menthol; 2.7 percent, Kool; 1.2 percent, Salem; and 8.9 percent smoked other menthol brands (National Health and Nutrition Survey (NHANES) 2007-08, see Caraballo & Asman 2010). Additional comparisons of brand preference by race/ethnicity, gender, and age group are summarized in Chapter 6.

Figure 1. Key Menthol Brand Share History

SOURCE: Maxwell Reports 1925-1973; Management Science Associates, Inc. Shipment History 1974-2008; 72 Month Shipment Database 2009

popular cigarette brand among African American smokers, preferred by 49.5 percent of African American smokers aged 12 or older (National Survey on Drug Use and Health (NSDUH) 2005, see NSDUH Report 2007). Newport is distinctly more popular with younger smokers: 23.2 percent of adolescent smokers (ages 12–17) and 17.8 percent of young adult smokers (ages 18–25) smoked Newport, but only 8.7 percent of older smokers used the brand (NSDUH 2005, see NSDUH Report 2007). The brand's popularity with younger smokers is evident in all three racial/ethnic subgroups that were examined in the analysis of the NSDUH 2000 data by Giovino et al. (2004). Among African Americans, Newport was the most frequently used brand. Of African Americans who smoked in the past 30 days, 79.2 percent of 12–17 year olds, 76.7 percent of 18–25 year olds, and 31.5 percent of adults aged 26 or older smoked Newport. Among Hispanic smokers, Newport was the second most popular cigarette brand, preferred by 31.4 percent of 12–17 year olds, 16.7 percent of 18–25 year olds, and 7.1 percent of adults aged 26 or older. Newport was less popular among non-Hispanic white smokers, but used by 18.0 percent of 12–17 year olds, 9.3 percent of 18–25 year olds, and 2.9 percent of adult smokers aged 26 or older. From its introduction in 1957, Newport was an exclusively menthol brand, but non-menthol varieties were test marketed in the 1980s (Stein 1982) and Newport Red, a non-menthol variety, was introduced in 2010.

Kool and Salem (both manufactured by R.J. Reynolds Tobacco Company) have been exclusively menthol brands since their introduction and gained the largest market share in the 1960s. Kool is the second most popular cigarette brand among African American smokers, preferred by 11.4 percent of African American smokers aged 12 or older (NSDUH 2005, see NSDUH Report 2007). The brand is more popular with older smokers: Among African Americans, Kool was the cigarette brand used most often by 14.1 percent of adults aged 26 or older, 4.6 percent of 18–25 year olds, and 2.1 percent of 12–17 year olds who smoked during the past 30 days (NSDUH 2000, see Giovino et al. 2004). Salem is also preferred by older smokers and is the fourth most popular cigarette brand among African American smokers: 6.9 percent of adults aged 26 or older, and 1.9 percent of 18–25 year olds and of 12–17 year olds used Salem most often (NSDUH 2000, see Giovino et al. 2004). Among Hispanic smokers aged 26 or older, 3.6 percent smoked Kool and 3.4 percent smoked Salem. Salem was slightly more popular than Kool among non-Hispanic white smokers aged 26 or older (3.0 percent vs. 1.8 percent). Among Hispanics and non-Hispanic whites, less than 1 percent of younger smokers reported smoking these brands. Salem is also favored primarily by female smokers (Giovino et al. 2004).

Introduced in 1965, Marlboro menthol (manufactured by Altria/Philip Morris USA) is now the second leading brand of menthol cigarettes in the U.S.; it surpassed Kool and Salem in popularity after the introduction of Marlboro Milds in 2000 (Altria July, 2010). Its increase in market share is reflected in

the Caraballo & Asman (2010) analysis of the NSDUH data: The proportion of smokers aged 20 or older for whom menthol Marlboro was the brand used most often increased from 3.9 percent in 2003–2004, to 4.2 percent in 2005–2006, and to 5.9 percent in 2007–2008 (Table 5 in Caraballo & Asman 2010).

Tobacco companies manipulate the concentration of menthol to achieve a desired taste, aroma, and cooling sensation based on anticipated consumer preference and demand. As discussed in Chapter 3, many cigarettes contain menthol in quantities insufficient to be considered a characterizing flavor. Lorillard described this use of menthol as analogous "to the use of a few grains of salt in a sweet dish" (Lorillard, July, 2010, p. 19). Lower concentrations of menthol are known to appeal to younger smokers and women (Kreslake et al. 2008 NTR; Lee & Glantz, in press). A survey of products purchased and tested in 2003 observed lower concentrations of menthol in cigarettes labeled "light" and "ultralight" (Celebucki, Wayne, Connolly, et al. 2005). In the full flavor, 100 mm varieties, menthol concentration (measured in milligrams per gram of tobacco weight) was 2.44 mg/g for Newport, 2.64 mg/g for Marlboro menthol, 2.78 mg/g for Salem, and 3.56 mg/g for Kool (Celebucki et al. 2005). A different rank order of brands was observed in Altria's summary of products that were tested in 2008–2009: 2.9 mg/g for Newport, 3.3 mg/g for Salem, 4.4 mg/g for Kool, and 4.5 mg/g for Marlboro menthol (also full-flavor,100mm varieties) (July, 2010, Table 1.3). Kreslake et al. (2008, AJPH) compared menthol concentration for eight products tested in 2007 with values reported in tobacco industry documents for the same brands. The authors observed that the concentration of menthol had decreased in Newport, Kool, and Salem brands between 2000 and 2007, and increased by 25 percent in Marlboro menthol. They concluded that increasing menthol content was intended to reposition Marlboro menthol for older smokers and to distinguish it from Marlboro Milds, a variety with a lower menthol content that appealed to younger smokers. Lorillard presented data indicating that the menthol concentration of its Newport brand did not decrease during this time period (July 2010, Figure 1). Additional research about consumer perceptions of menthol content is addressed later in this chapter and in Chapter 6.

Place

Menthol and non-menthol cigarettes are distributed in identical channels. The primary venues are retail outlets: convenience stores, small grocery or "corner" stores, gas stations, liquor stores, supermarkets, mass merchants, pharmacies, and tobacco stores. The total number of U.S. stores that sell cigarettes is unknown. The 2007 Economic Census identified at least 100 different types of businesses that sell tobacco and estimated sales for approximately 235,000 retailers in the U.S. (http://www.census.gov/econ/census07/). However, that figure likely underestimates the total number of retailers because the survey is limited to payroll establishments. A larger estimate of 543,000 retailers was obtained by extrapolating from the subset of states that maintained licensing records (DiFranza, Peck et al. 2001).

The retail channel is ideally positioned to target the lower income and racial/ethnic minority populations who smoke menthol cigarettes. Indeed, inequities in the concentration of tobacco retailers by neighborhood demographics are well documented. For example, the tobacco retailer density (outlets per roadway kilometer) was almost four times greater in Erie County census tracts with the lowest income residents than in tracts with the highest income residents; tobacco retailer density was two times greater in tracts with the highest proportions of African American residents than in tracts with the lowest proportions (Hyland, Travers, et al. 2003). Similar disparities in tobacco outlet density by income, race/ethnicity or both were observed in census tracts in New Jersey (Yu, Peterson, Sheffer et al. 2010), Iowa (Schneider, Reid, Peterson et al. 2005), and Chicago (Novak, Reardon et al. 2006). In addition, more tobacco retailers were located near California high schools with larger proportions of low-income and Hispanic students (Henriksen, Feighery et al. 2008). Such

disparities in tobacco retailer density contribute to the greater availability of cigarettes, both menthol and non-menthol, in areas of social and economic disadvantage.

Price

Price is a critical feature of tobacco marketing and influences myriad aspects of smoking behavior. Higher prices discourage initiation, reduce consumption, promote quitting, prevent relapse, and may lead smokers to substitute cheaper brands (Chaloupka et al. 2010). According to the Federal Trade Commission's Cigarette Report, the tobacco industry spends the largest share of its annual marketing budget—74 percent of $12.5 billion in 2006—on price discounts (Federal Trade Commission 2009). This section uses the term "price promotions" to refer to discounts and other strategies that reduce the price of cigarettes at the point of sale, such as retailer promotional allowances, multi-pack offers and gifts with purchase. Additional data about expenditures for sales promotions in relation to other marketing activities is provided in the section on Promotion.

Information about price and price promotions was obtained from multiple sources, including submissions to FDA by tobacco companies and other presentations to TPSAC, as well as peer-reviewed articles that analyzed data from retail scanners, or receipts from single-pack purchases, or audits of advertised prices at point of sale, or purchase prices reported by smokers themselves. Most studies examined reported data from nationally representative samples of stores or smokers. The studies below are grouped by data source.

Industry submissions

In its submission to FDA, R.J. Reynolds Tobacco Co. reported that the average price paid per carton of cigarettes was slightly higher for menthol than for non-menthol cigarettes for each year from 2000 to 2009, with more discrepant prices observed in more recent years (e.g., an average $49 for menthol and $46 for non-menthol in 2009) (presentation by Graves/RJ Reynolds, July, 2010). Data on the average price paid per pack (which constitutes the way that the majority of smokers buy their cigarettes) was not provided, but in response to a question, Monica Graves from R.J. Reynolds indicated the same trends held for pack prices. These data were presented in an aggregated form for the entire industry, and no data were presented by company or by individual brand, precluding determination of the use of different pricing approaches for individual brands. In addition, the data did not address whether there was a differential price paid for menthol and non-menthol cigarettes in geographic areas with different proportional representations of race/ethnicity, or during focal time periods (e.g., when tobacco taxes were increased).

From 2000 to 2009, the proportion of sales volume with a price promotion nearly doubled for non-menthol cigarettes (to 71 percent from 36 percent) and it more than doubled for menthol cigarettes (to 67 percent from 26 percent). However, these data were similarly aggregated over brands and companies, and by geographic location, and were not provided for more fine-grained time periods in relation to tobacco tax increases. In addition, these particular data only indicate whether or not some kind of price promotion was applied to menthol and non-menthol, and not the relative value of the price promotion. R.J. Reynolds drew attention to the menthol share of shipments being flat from 2000 to 2004 during a period when the percentage of volume promoted for menthol increased, and also that the menthol share of shipments grew from 2005 to 2009 when menthol promotional levels were relatively stable. This interpretation overlooks the alternative that the percentage of volume promoted may have reached a critical threshold by 2005, which acted to increase the share of menthol shipments thereafter.

Retail scanner data

Cigarette pack prices and sales volume derived from ACNielsen scanner data are designed to represent national markets for different types of retail outlets (Loomis Oct 2010). Loomis (2010) compared price and promotions for menthol and non-menthol sales in two retail channels: convenience stores and food retailers (supermarkets, drug stores and mass merchants combined) from 2008 to 2010. The average pack price was higher for menthol than non-menthol cigarettes in both retail channels, and 13 cents more (3 percent higher) in convenience stores, which is the retail channel that sells the largest volume of cigarettes. Over time, the use of multi-pack discounts was replaced by the use of "cents off" discounts for both menthol and non-menthol sales. In both retail channels, promoted sales accounted for a greater proportion of total sales for menthol than for non-menthol cigarettes. In convenience stores, 8.31 percent of menthol sales involved a promotion, compared with 5.11 percent of non-menthol sales. These figures cannot be compared with those reported by R.J. Reynolds because the two describe different types of promotions (retail vs. what appears to be wholesale) and different denominators (total pack sales in convenience stores vs. volume of shipments).

Using ACNielsen scanner data from supermarkets for the period 1994–2004, Farrelly et al. (2007) compared estimated change in pack price as well as tar and nicotine per cigarette for menthol and non-menthol brands (Farrelly, Loomis, & Mann 2007). Slightly higher average prices were observed for menthol than for non-menthol packs, and the discrepancy increased after the 1998 Master Settlement Agreement (MSA), in which tobacco companies agreed to restrict certain advertising practices. Over time, price increases were associated with increases in sales of cigarettes that contained more tar and nicotine, but this trend was more pronounced for menthol than for non-menthol cigarette sales. The authors concluded that menthol smokers are more likely than non-menthol smokers to compensate for price increases by smoking cigarettes with higher levels of tar and nicotine.

One limitation of studying retail scanner data is the potential for under-reporting of promoted sales due to missing information for some transactions. In addition, the scanner data are derived from a proprietary method of projecting to the population and are not a representative sample of stores. This proprietary sampling method also precludes researchers from determining whether promoted sales were higher in regions or neighborhoods with different race and ethnic group distributions.

Store audits

Store audits typically used trained coders to record advertised prices and sales promotions for particular cigarette brands or flavor categories in a random sample of tobacco retailers. For example, Ruel et al. (2004) conducted annual observations (1999–2002) in a geographically stratified sample of 11,703 stores in the U.S. (Ruel, Mani, Sandoval et al. 2004). They recorded the lowest advertised pack price for the leading menthol (Newport) and leading non-menthol (Marlboro) brand. Over the three years, the average price for Newport increased 78 cents (25 percent change) compared to 85 cents (29 percent change) for Marlboro. Increases in Newport prices were observed for all regions (West, Midwest, South, Northeast) and locales (urban, suburban, town, rural). The proportion of stores that advertised a price promotion for Newport increased by 19 percentage points, but the proportion of stores with a promotion for Marlboro increased by only 7 percentage points. In urban areas, a linear increase was observed for Newport promotions but not for Marlboro promotions. One shortcoming of these comparisons is that the two brands represent different corporate marketing strategies. According to Lorillard, Newport maintains the highest average price of major U.S. cigarette brands (Lorillard July 2010).

Toomey et al. (2009) observed the same pattern of differential pricing for menthol and non-menthol

varieties of the same brand family. In a random sample of 214 Minneapolis convenience stores, the average difference between the single-pack price for the menthol and non-menthol varieties of the same (unidentified) brand was 37 cents (11 percent more for menthol). Menthol price was not correlated with the proportion of non-white residents or youth in the census tracts where the stores were located; non-menthol price was positively correlated with the proportion of non-white residents and negatively correlated with the proportion of youth. However, the study did not examine the availability of discounts or other price promotions.

Population surveys

Three surveys illustrated differences between menthol and non-menthol smokers in response to pricing. A 2002 survey of 4,618 California smokers found relatively more of those who smoked menthol brands reported taking advantage of price promotions than those who smoked non-menthol brands: percentages were 57.1 percent for those who smoked menthol-only brands (Newport or Kool), compared to 49.1 percent for Camel and 34.8 percent for Marlboro (given menthol variants were a small percentage of the market for both these brands) (White et al., 2006). This finding is consistent with the results of the scanner data showing that a larger proportion of menthol compared to non-menthol cigarette sales involved price promotions (Loomis, 2010). Among African American smokers in the California survey, 65.4 percent of menthol smokers compared to 28.7percent of non-menthol smokers reported using promotional offers. Young adults, women, and daily smokers were also more likely to use promotional offers, but the difference between menthol and non-menthol smokers in these subgroups was not reported.

Fernander et al. (2010) undertook an analysis of the data from the 2003 and 2006-2007 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) in order to compare the demographic traits and purchase behaviors of menthol and non-menthol smokers (Fernander et al. 2010). A larger proportion of menthol smokers (68.8 percent) than non-menthol smokers (59.2 percent) reported buying cigarettes by the pack. Adjusting for other factors, such as gender, race/ethnicity, age group, education level, income, smoking frequency and age of initiation, the odds of being a menthol smoker were significantly lower for smokers who reported buying cigarettes by the carton exclusively. The authors concluded that the finding is consistent with other studies suggesting that menthol smokers smoke fewer cigarettes.

In a separate analysis of the TUS-CPS, Tauras et al. (2010) examined questions about the type of cigarette smoked and the price that smokers last paid for either a pack or carton. Using data aggregated over multiple survey waves (2003 and 2006-2007), Tauras et al. (2010) estimated state-specific prices for menthol and non-menthol packs. Adjusted to 2010 dollars, the average menthol price was $3.88, which was 9 cents more than the average non-menthol price.

Tauras et al. (2010) also estimated the probability of being a menthol smoker, based on different state-specific prices for menthol and non-menthol cigarettes and adjusting for other characteristics of smokers. Holding these variables constant, a 10 percent increase in the price of menthol cigarettes was associated with a 2.3 percent decrease in the probability of being a menthol smoker. A 10 percent increase in the price of non-menthol cigarettes was associated with a 4.7 percent increase in the probability of being a menthol smoker. These different price elasticities suggest that menthol and non-menthol cigarettes are not close substitutes for each other. The authors concluded that, holding other factors constant, menthol smokers would be much less likely to switch to non-menthol cigarettes than non-menthol smokers would be likely to switch to menthol cigarettes. The pattern of results did not differ by gender or income. However, younger smokers (aged 18–24) and African American smokers were even less likely to substitute non-menthol cigarettes for menthol cigarettes, indicating stronger preference for menthol cigarettes among the population subgroups of smokers with a higher prevalence of smoking menthol. A limitation of this cross-sectional study is

that it could not model change in smoker behavior (switching or quitting) over time. In addition, the analysis excluded smokers who indicated no preference for menthol or non-menthol cigarettes. However, this comprised only 2.3 percent of the sample, indicating that the vast majority of adult smokers had a definite preference.

Summary. Prices for both menthol and non-menthol cigarettes are increasing and the average price for menthol cigarettes is slightly higher than for non-menthol cigarettes. These patterns emerged regardless of the different data sources used to study price. There was limited information available on menthol pricing and price promotion by neighborhood race/ethnicity characteristics, in relation to tobacco tax increases, and in relation to brand. The retail scanner data indicates that a larger proportion of menthol than non-menthol sales is promoted. More menthol smokers take advantage of price promotions than non-menthol smokers, and this is particularly true for African Americans. Menthol smokers have a stronger cigarette preference and are less sensitive to price fluctuations than non-menthol smokers.

Promotion

As explained in a recent National Cancer Institute review of tobacco marketing and its effects on tobacco use, the main goals of the *Promotion* part of the marketing mix are to inform, persuade and remind (NCI 2008). Informing is generally considered important for newly developed products in order to tell consumers something about the product. Promotions aimed at reminding are typically aimed at consumers who already have positive attitudes towards a brand. Promotions that persuade tend to focus on the advantages of one brand over another. Branding is the use of a name, term, symbol or design to identify a product. The creation of a 'brand image' is key to a successful promotional strategy. As explained further in a later section on menthol marketing messages, cigarette advertising is short on factual information and rich in imagery designed to establish and reinforce branding.

The aim of branding is to create a set of associations or perceptions about a brand in the mind of consumers, so that they will want to buy the product and keep buying it (NCI 2008). Branding is a key aspect of product marketing in general, whereby marketers create an image for the brand they promote, a brand image that promises the target market something they value. This has also been referred to as "consumer appeal," "product appeal," and "product attractiveness" (Henningfield, Hatsukami, Zeller and Peters 2011; European Union Scientific Committee on New and Emerging Health Risks, 2010). In the case of tobacco products, such efforts contribute to the risk that non-tobacco users will be exposed to the addictive effects of nicotine, and also contributes to the risk that tobacco users will persist in their use (Henningfield, Hatsukami, Zeller and Peters 2011; Scientific Committee on New and Emerging Health Risks 2010). The effects of nicotine exposure that contribute to the development and maintenance of dependence and persistent tobacco use are discussed further in Chapters 3 and 6.

Branding often incorporates persuasion-based promotions often link products with desirable images (such as lifestyle or healthful imagery) and identities (such as slogans or brand symbols), in order that consumers associate the brand with positive emotions or reduced negative emotions (NCI 2008). In a comprehensive review of the evidence, the NCI review concluded that "*tobacco advertising has been dominated by three broad themes: providing satisfaction (taste, freshness, mildness etc.), assuaging anxieties about the dangers of smoking, and creating associations between smoking and desirable outcomes (independence, social success, sexual attraction, thinness etc.)*" (NCI 2008, p170).

Later sections about messaging and targeting describe the message themes that distinguish menthol from non-menthol marketing. This section describes similar types of marketing activities used to promote both menthol and non-menthol cigarettes, noting some differences in practice. Price

promotions that were discussed in the price section are included here because these are reflected in various marketing activities, such as retail advertising and direct mail, and are essential to understand the context of tobacco marketing practices.

As reported to the Federal Trade Commission, current promotional activities for cigarettes include advertising (print media and point-of-sale), direct marketing (direct mail, coupons, distribution of free cigarettes and specialty items, company website, other internet and telephone), sponsorship, public entertainment, promotional allowances for wholesalers and retailers, and retail price promotions (as described in the section on price). After the MSA eliminated billboard and transit advertising and curtailed sponsored events by tobacco companies, annual spending on retail marketing more than doubled to $10.7 billion in 2006 from $4.7 billion in 1998 (Federal Trade Commission 2009). Over the same period, retail marketing expenditures increased to 86 percent from 70 percent of the industry's total annual marketing dollars. These figures include retail advertising, promotional allowances, and price promotions (discounts, bonus cigarettes, and gifts with purchase). While total marketing expenditures decreased every year since 2003, proportional expenditures on point-of-sale advertising nearly doubled to 1.9 percent in 2006 from 1.1 percent in 2003. Proportional expenditures on price promotions increased to 80.4 percent in 2006 from 76.0 percent in 2003.

Tobacco companies exercise strict control over the retail outlet, using contractual obligations with store merchants to maximize the visibility of products and advertising for selected brands (Pollay 2007; Feighery, Ribisl, Clark et al. 2003; John, Cheney, & Azad 2009). The shift toward retail marketing is apparent to consumers; the average number of cigarette marketing materials per store and the proportion of stores with price promotions have increased since the MSA (Celebucki & Diskin 2002; Feighery, Schleicher, Cruz & Unger 2008; Wakefield et al. 2002). As described in the previous section about price, a larger increase was observed in the proportion of stores that promoted Newport than in the proportion of stores that promoted Marlboro (Ruel et al. 2004).

Lorillard (July, 2010) described its marketing plan in terms of four components: retail price promotions, retail advertising, print advertising, and direct marketing. The latter category includes a direct mail list for distributing coupons and its "P.S. Pleasure Scene" magazine that was started in 2003. The company reported that coupons represented the largest proportion of its direct mailing expenditures, but did not disclose the amounts. In 2008, Lorillard spent $19.7 million on magazine advertising, a category that represented less than 1 percent of its annual marketing budget in 2009. Retail price promotions comprise more than 90 percent of the company's annual marketing expenditures. In 2006, magazine advertising represented 0.4 percent of annual tobacco industry marketing expenditures and price promotions (discounts and retail value-added) represented 80.4 percent of total expenditures (Federal Trade Commission 2009).

R.J. Reynolds Tobacco Co. (July, 2010) reported using price promotion, direct mail, email, website promotion, event promotion, and direct sales in bars and clubs to promote both menthol and non-menthol brands, but did not disclose expenditures or compare them by brand type. The company proposed that a recent shift in preferences toward menthol could not be attributed to marketing activities because these were substantially constrained and because "menthol advertising has changed little in message and medium during this time frame" (Graves/RJ Reynolds, July 2010). In spite of a restricted environment, the industry's total expenditures for cigarette marketing increased every year after the MSA until 2003 (Federal Trade Commission 2009). In addition, even if message and medium remained constant for menthol brands, proportional expenditures to advertise and promote menthol brands could have increased.

The FTC does not publish expenditures separately by manufacturer, brand, or variety of cigarette (menthol vs. non-menthol). However, expenditure data for some marketing channels can be

purchased from commercial sources. Using such data for cigarette advertising in magazines, one study found that spending for non-menthol brands decreased to $39.8 million in 2005 from $309.3 million in 1998, but spending for menthol brands increased to $43.8 million from $36.5 million in the same time period (Kreslake, Wayne, Alpert, et al. 2008). The proportion of expenditures for menthol brands increased to 52.4 percent from 10.6 percent of the total expenditures over this time period, and the spending for menthol exceeded spending for non-menthol brands in 2005. This pattern suggests greater effort to advertise menthol than non-menthol brands in magazines during a period of increased advertising restrictions.

(b) (4)

Summary. In a restricted environment, retail has become the dominant channel for tobacco promotion. Tobacco companies use similar marketing activities to promote menthol and non-menthol brands, but expenditure data suggest some differences in practice. In recent years, the tobacco industry spent as much or more on magazine advertising for menthol as for non-menthol brands, even though menthol brands represent a much smaller share of the market. (b) (4)

Further evidence that speaks to differences in promotional practices for menthol—that the mix of marketing strategies used to promote these brands are determined by neighborhood demographics—is addressed in a later section on targeting.

Packaging

Cigarette packaging plays a key role in the creation and reinforcement of brand imagery (NCI 2008) and tobacco companies conduct considerable consumer research on all elements of packaging (Wakefield et al. 2002; DiFranza et al. 2002). Unlike many other products where the packaging is discarded after opening, smokers generally keep their cigarette pack with them until all the cigarettes in it are smoked. This means that the pack is frequently being taken out and put on display. This high degree of social visibility leads cigarettes to be described by marketers as "badge

products." The use of a badge product associates the user with the brand image, giving the smoker some of the identity of the brand image. As one cigarette package designer, John Digianni, stated: "*A cigarette package is unique because the consumer carries it around with him all day . . .it's a part of a smoker's clothing, and when he saunters into a bar and plunks it down, he makes a statement about himself*." (Koten, cited in Wakefield et al. 2002).

Cigarette packaging becomes more important for overall marketing strategy, as traditional avenues for cigarette advertising are restricted. In a restricted advertising environment, aside from its key role in communicating brand image, cigarette packaging is used to create greater salience for brand families at the retail display (NCI 2008). Reviews of internal tobacco industry documents on cigarette packaging show that that variants within one brand family are designed to be sufficiently similar to indicate membership of the overall parent brand, and different enough for consumers to be able to distinguish between the variants. In this way, the arrangement of packs from the same brand family achieve greater "stand out" from the clutter of competing brands at the point of sale (Wakefield et al. 2002; DiFranza et al. 2002).

For both menthol and non-menthol cigarettes, different shades of the same color and the proportion of white space are commonly used to distinguish between variants of the same brand family. Lighter colors on packs are used to signify 'lower tar' cigarettes (Wakefield et al. 2002; DiFranza et al. 2002) and consumers interpret lighter shades on cigarette packaging to infer that the cigarettes are less harmful (Hammond & Parkinson 2009). In the presence of a ban on terms such as 'light,' 'low tar' and 'mild' which connote reduced harm, tobacco companies use alternative brand descriptors such as 'smooth,' color descriptors such as 'silver,' and 'tar' numbers that are incorporated into brand names, and that consumers also interpret to mean reduced harm (Hammond & Parkinson 2009). The relationship between branding and consumer perceptions of harm and related sensory experience is discussed further in a later section.

Given the central role of packaging in cigarette branding and marketing (NCI 2008), it is somewhat surprising that no study has attempted to quantify and describe changes in cigarette packing over time or differences between packaging for menthol and non-menthol brands. However, historical examples of cigarette packs are available on the internet *http://www.cigarettespedia.com/index.php/Main_Page* (click on brand name) and more recently *http://www.tobaccolabels.ca/cigarettepackagepictures/unitedstates*. In a submission to FDA, R.J. Reynolds Tobacco Co. (June 30, 2010) reported using cool and fresh imagery for menthol products and blue and green colors in package labeling. According to consumer perception studies conducted by Lorillard, smokers generally associate and prefer green packaging with menthol cigarettes (Lorillard July, 2010). However, these studies were not described in the company's report. Color theories suggest that green is commonly associated with "health" and "healing," in addition to "nature," "renewal," "new beginnings," and "harmony" (Frazer & Banks, 2004 in NCI, 2008). Green also connotes positive affective states, such as "calming," "gentle," and "peaceful" (Madden et al., 2000, cited in Anderson, Ling, & Glantz 2007). The following section describes the use of imagery and other messages in menthol marketing in more detail in connoting health reassurance.

WHAT HEALTH REASSURANCE MESSAGES WERE/ARE USED IN MENTHOL MARKETING MESSAGES?

In this section, we distinguish between two main types of messages that may provide health reassurance to consumers. First, messages may be explicit in nature, in that they make an obvious and direct connection between use of the product and a consequent expected health benefit or reduction of health risk. An example of an explicit health claim might be "*a cigarette to soothe a sore throat."* This claim overtly promises that the product confers a medicinal benefit in relieving the symptoms of a specific health condition. Second, messages may be implicit, in that they connote

some kind of benefit related to health or well-being, without expressly saying so. These implicit messages tend to be more indirect and make use of imagery, associations and/or descriptive language. An example of an implicit health claim might be "*a cigarette as fresh as a mountain stream.*" By associating its product with a fresh mountain stream, this phrase invokes imagery of nature and cleanliness and thereby infers healthiness. Implicit messages can be highly effective as communication tools, in covertly shaping consumers expectations about a product. In addition, their ambiguity makes them difficult for consumers to discount.

During the 1950s, growing concern among consumers about the health harms of cigarettes created considerable dissonance within smokers, who were anxious about the fact that they were incurring a health risk, but found themselves unable to quit. This cognitive dissonance made smokers open to messages that might reassure their health concerns (Pollay & Dewhirst 2002). From a marketing point of view, since the health harms of tobacco became widely known, explicit claims that one cigarette brand was healthier, safer or less harmful than another risked being rejected by consumers as not being believable. Furthermore, explicit claims had the undesirable consequence for the tobacco industry of reminding smokers that they were engaging in a behavior that was inherently harmful to their health. Instead, the tobacco industry turned to implicit marketing messages through the use of brand descriptors, slogans, and rich advertising imagery, to offer health reassurance (Pollay & Dewhirst 2002). These implicit messages promoted attributes such as taste, flavor, sensory experience, satisfaction and enjoyment.

In a review of tobacco industry documents and advertising, Sutton and Robinson (2004) identified extensive use of four types of messages in menthol marketing: healthy/medicinal claims, taste sensation (e.g., fresh, refreshing, cool, clean, crisp), youthfulness, and ethnic awareness. The first two categories are the focus of one section because these themes are inextricably linked in marketing messages and in the minds of consumers (see later sections on consumer perceptions).

Healthy/medicinal claims and taste sensation

Until the mid 1950s, marketing messages positioned menthol cigarettes for occasional use as a remedy for myriad ailments (Gardiner 2004; Sutton & Robinson 2004). For example, Samji and Jackler (2008) archived and reviewed several thousands of cigarette ads that were sampled from popular magazines and scholarly journals between 1920 and 1954. Only ads that depicted the throat or a throat doctor were selected for further description and their analysis was not specific to menthol advertising. Brand slogans for Spud, the first menthol cigarette (Ashton-Fisher Tobacco Co.), and for Kool, promoted these products as remedies for nose and throat irritation and for congestion. A 1937 ad featured a prescription from Dr. Kool, a cartoon penguin: "*Tell him to switch to Kools and he'll be all right. Doctors…agree that Kools are soothing to your throat*." The researchers remarked that the introduction of menthol played a central role in positioning tobacco products as a treatment rather than an irritant.

In their overview of research reviews of qualitative tobacco industry documents that were prepared for FDA, Lee and Glantz (in press) also noted that explicit health claims characterized menthol cigarettes as a healthier, less harsh alternative for smokers who required temporary relief from symptoms. To illustrate the extent to which health claims were widely accepted, the authors cited an example of a 1951 case report from the Journal of American Medical Association that referred to menthol cigarettes as "medicated cigarettes" with an "anesthetic and cooling effect" (Highstein & Zeligman 1951, cited in Lee & Glantz in press).

A brief history of tobacco marketing from the Institute of Medicine (2001) noted that explicit health claims persisted in spite of a 1942 agreement between the Federal Trade Commission and Brown & Williamson to end such advertising. The IOM report cited two slogans from 1946 and 1949: "*HEAD*

STOPPED UP? GOT THE SNEEZES? SWITCH TO KOOLS. . . THE FLAVOR PLEASES!" and "*Got a COLD? Smoke KOOLS as your steady smoke for that clean, KOOL taste"* (Table 3-1 in IOM, 2003). These and other examples serve to illustrate that early marketing messages linked claims about the perceived health benefits of menthol with its taste sensation. After the Federal Trade Commission codified the cigarette advertising guidelines in 1955, marketing messages about taste, flavor, aroma, and enjoyment replaced explicit health claims. The IOM report highlighted the industry's use of taste and sensory descriptors such as "mild," "light" and "smooth" to suggest the concept of product safety.

In a review of tobacco industry documents about marketing for "light" and "low-tar" cigarettes, Pollay and Dewhirst (2002) described how the industry repositioned menthol cigarettes from a health remedy for occasional use to a positive smoking experience for regular use. In response to growing concern about the health effects of smoking, motivation researchers and trade analysts advised the industry to adopt subtler tactics, using visual imagery and advertising copy that implied healthfulness (Pollay 1989, cited in Pollay & Dewhirst 2000). A Brown & Williamson document highlighted the important role of menthol in assuaging smokers' concerns about health: "*Menthol in the filter form in the Salem advertising was a 'refreshing' taste experience. It can be very 'reassuring' in a personal concern climate. Undoubtedly, the medicinal menthol connotation carried forward in a therapeutic fashion as positive taste benefit*." (Cunningham & Walsh 1980, cited in Pollay & Dewhirst 2002). The authors concluded the use of menthol was a critical element of the tobacco industry's efforts to convince consumers that particular cigarette brands are relatively healthy. As described by Pollay & Dewhirst, "*cigarette advertising is notoriously uninformative, with characteristic forms using veiled health implications and pictures of health along with vague promises of taste and satisfaction*" (2002, p.i28).

Sutton and Robinson (2004) observed that general market magazine and newspaper advertising of the 1950s and 1960s promoted menthol brands with outdoor scenes, such as woodlands, rain forests, rock gardens, and country streams. These images were paired with sensory descriptors, such as "cool," "clean," "fresh"—terms that connote health benefits. For example, advertising for Salem mentioned "perpetual springtime" and "a wonderful world of freshness" (MSA Inc. 1978, cited in Gardiner 2004) and Newport's introduction in 1957 featured the slogan: "*Rich taste – with a touch of refreshing mint*" (Anderson, 2011).

Anderson (2011) examined 953 tobacco industry internal documents gleaned from a string of search terms about menthol marketing and consumer perception. Consistent with other accounts, she reported that menthol cigarettes were first popularized as a remedy to the burn, dryness and throat irritation that accompany smoking. The industry documents included examples of early advertising slogans for menthol cigarettes that promised healthful outcomes, such as "*Breathe easy, smoke clean*," (Brown & Williamson 1978, cited in Anderson, 2011) and "*The beneficial head-clearing qualities of menthol*" (Brown & Williamson undated, cited in Anderson 2011). When overtly health-oriented messages were forbidden, marketing messages exploited consumer perception of the characterizing flavor as both a taste and a sensation. In addition, the messages capitalized on the perception of a cooling sensation as healthful: "*What a wonderful difference when you switch to snow fresh Kools. Your mouth feels clean and cool, your throat feels soothed and fresh. Enjoy the most refreshing experience smoking*" (Brown & Williamson, 1968, cited in Anderson, 2011). Indeed, tobacco companies sought to preserve the connotations of menthol with health. For example, a 1978 Brown & Williamson document described its objective to "*provide product safety reassurance while enhanc[ing] the satisfaction and refreshment perception of the appropriate Kool styles…*" (Brown & Williamson, 1978, cited in Anderson 2011). Anderson concluded that marketing messages served to reassure smokers that menthol cigarettes were healthier than non-menthol cigarettes and that this reassurance continues in contemporary marketing messages that feature more oblique references to health.

A study by Paek et al. (2010) highlighted the contributions of product labeling and visual imagery to communicate implicit health-related claims. Their content analysis examined the prevalence of implicit health-promotion messages for cigarettes in 1,300 magazine ads from 1954 to 2003. Equal numbers of ads for 10 brands were sampled from five time periods. The sample included ads for 10 brands, including Newport and Kool, but the analysis did not compare menthol and non-menthol advertising. The presence of an implicit health claim was coded whenever verbal cues used either factual terms (e.g., low tar, no additives, filter) or impressionistic terms (e.g., mild, natural, gentle calm, soft, smooth) to characterize cigarettes. The presence of an implicit health claim was coded whenever visual cues associated cigarettes with healthful places or objects, such as mountains, fields, an ocean, or a glass of water. Verbal health claims appeared in advertising copy for 49 percent of the ads from the post-MSA era (1999–2003) compared to 45 percent of the ads overall. Visual health claims were found in 50 percent of the post-MSA era ads, compared to 42 percent overall. The researchers concluded that implicit claims about health are as prevalent in contemporary cigarette advertising as they have been previously.

Throughout TPSAC meetings, tobacco industry representatives consistently pointed to taste as being the main driver of preference for menthol cigarettes among menthol cigarette smokers, with cooling sensation being considered to be part of the overall consumer taste experience (July 2010). Lorillard indicated in its submission that terms such as 'smooth,' 'fresh,' 'refreshing' and 'mild' are only intended to communicate taste, flavor and satisfaction (Lorillard, July 2010), and not to implicitly communicate that menthol cigarettes are less hazardous than non-menthol cigarettes.

Summary. Analyses of tobacco industry internal documents and the marketing messages the industry produced provide corroborating evidence of explicit and unwarranted claims that smoking menthol cigarettes would improve smokers' health. Over time, marketing messages increasingly relied on sensory descriptors and imagery to imply that menthol cigarettes are safer than non-menthol cigarettes.

WHAT OTHER MESSAGES WERE/ARE CONVEYED TO POTENTIAL CONSUMERS BY MENTHOL MARKETING MESSAGES?

Marketing messages about health claims and sensory appeals derive from direct references to menthol, but other marketing messages convey the product's appeal without reference to its characterizing flavor. In a 1982 marketing report, R.J. Reynolds characterized menthol smokers (the "Coolness Segment") as the youngest, the most economically disadvantaged, and the most likely to be in minority and ethnic groups, who "*tend, more than average, to desire their brand of cigarettes to symbolize personal qualities such as youth; modern womanhood; romance; career orientation; and success*" (cited in Anderson, 2011). Previous research describes two dominant themes used to appeal to these target audiences and their aspirations. One theme is the exuberance of youth, which Sutton and Robinson (2005) labeled as "youthful, silliness, fun" and Anderson (2011) characterized as "fun-loving, sociable, and youthful." Menthol advertising also associates product use with images of an idealized self and social identity—a theme that Sutton and Robinson (2005) labeled as "ethnic awareness," and Anderson (2011) characterized more broadly as "identity or in group belonging." These themes are not mutually exclusive; the same advertisement may serve to communicate both types of messages (see for example, Figure 3 in Anderson 2011).

Youthfulness and sociability

Newport introduced its "Alive with Pleasure!" campaign in 1972 with advertising that portrayed young people having fun, but engaged in activities that seemed childish or juvenile (Sutton and Robinson, 2005). According to Klausner's (in press) review of tobacco industry documents, the Newport campaign was based on the assumption that peer influence is critical to smoking uptake

and the advertising imagery sought to recreate and reinforce that influence. After the first four years, Newport was still lagging behind Kool and Salem, but its market share increased among youth. "*Newport's SOM [share of market] among smokers 14–17 years old is significantly higher than brand's Total SOM, reflecting strong appeal to young/new smokers*" (Esty 1976, cited in Klausner, in press). Newport's "Pleasure" campaign (the "Alive with…" part of the slogan was later dropped) continues to this day. Newport has been the leading menthol cigarette brand and the second leading cigarette brand among youth since the early 1990s.

Anderson (2011) acknowledged that images of youthfulness and sociability were not unique to marketing messages for menthol. Indeed, a 1981 R.J. Reynolds report observed, *"…The benefit of smoking which has most frequently and most successfully been exploited by brand families appears to be Social Interaction*." After this approach proved effective for Lorillard's Newport brand, R.J. Reynolds Tobacco Co. launched a similar campaign for Salem. "*Advertising must convince younger adult smokers that Salem is smoked by natural, unpretentious but interesting people who are social leaders/catalysts (make things happen) whose sense of humor and wit makes them fun and exciting to be with*" (R.J. Reynolds Tobacco 1981, cited in Anderson 2011). Anderson concluded that it was menthol's younger profile relative to other cigarettes that made the themes of youthfulness and sociability particularly appealing and persuasive.

Two empirical studies addressed consumer perceptions of youthfulness in cigarette marketing messages. In one study, 561 adults viewed and rated the perceived age and level of attractiveness of models in magazine ads for menthol and regular cigarettes (Mazis et al. 1992). Advertisements for menthol brands were judged to have significantly younger models (average 25.7 years) than advertisements for regular cigarette brands (average 31.9 years). Irrespective of their own age group, people rated younger models in the advertisements as being more attractive than older models.

Barbeau et al. (1998) asked 913 sixth- to eighth-grade students from Massachusetts to rate magazine ads for four cigarette brands (Newport, Camel, Marlboro and Virginia Slims) and four non-cigarette products. All the ads were from 1994 and featured human figures or anthropomorphic characters. The majority of students judged each of the four cigarette ads to say that smoking will make people look cool (72 percent to 84 percent), attractive (53 percent to 81 percent), popular (50 percent to 80 percent) and healthy (51 percent to 71 percent). Students' responses indicated that the advertisements communicate ideas that were in violation of the Tobacco Institute Voluntary Advertising and Promotion Code. Like the adults in the previous study (Mazis et al. 1992), the students rated Newport models as looking younger than the models appearing in ads for other cigarette brands. Weaknesses of both studies are that they surveyed convenience samples and could not control for objective differences between models that appeared in ads. Nonetheless, the results suggest that the message that Newport is a brand for younger consumers was apparent to both adults and adolescents.

Identity/In-group belonging

Establishing a sense of belonging is a central task of identity development in adolescence, particularly for racial/ethnic minorities (Castro 2004). Images of the self as a smoker or non-smoker contribute to this identity. As concluded in Chapter 7 of NCI's Monograph 19 (2008), much tobacco advertising creates the perception that smoking will satisfy adolescent psychological needs relating to popularity, peer acceptance and positive self-image. Furthermore, adolescents who believe that smoking can satisfy their psychological needs or whose desired image of themselves is similar to their image of smokers are more likely to experiment with cigarettes (NCI 2008, p280).

Several histories of menthol marketing commented on appeals to racial identity, which coincided with increased market share among African Americans in the 1960s and 1970s (Gardiner 2004; Sutton & Robinson 2005). For example, commenting on Kool brand advertising of this period, Sutton and Robinson (2005) observed a departure from the standard fare of waterfalls, country streams and romantic couples found in white-oriented media to darker-skinned models, slang terms, and more masculine imagery in African American-oriented media. Increasingly, marketing messages for menthol cigarettes appropriated images of athletes, entertainers, hairstyles, clothing, music and other elements of African American popular culture (Gardiner 2004; Giovino et al. 2004; Hafez & Ling 2006; Sutton & Robinson 2004). Several researchers observed that the word "cool," and its significance to the African American community, played a central role in the appeal of the Kool brand as well as the product category (Gardiner 2004; Castro 2004).

Balbach et al. (2003) examined ads for R.J. Reynolds' brands from three magazines aimed at an African American audience. Nearly all of the ads were for menthol brands. Between 1989 and 1990, every ad depicted an escapist or fantasy theme when a setting was visible, 74 percent of the ads featured expensive objects when objects were visible, and 58 percent portrayed nightlife whenever social life was shown. All three themes remained evident in ads that were sampled from the same magazines a decade later, although fewer of the ads featured expensive objects. In combination with evidence gleaned from their review of R.J. Reynolds' internal documents (discussed in the section on targeting), the authors concluded that marketing messages associated menthol cigarettes with luxury objects, a glamorous nightlife, and a fantasy world in order to appeal to the aspirations of young adult African Americans.

Nightlife settings were observed in menthol marketing aimed at a broader audience of young adults. Belstock et al. (2008) examined all cigarette and alcohol advertising that appeared in Maxim, FHM, Cosmopolitan and Ebony in 2003 and 2004. These magazines were selected because of their popularity with young adult readers (ages 18–24). Although none of the 317 alcohol ads referred to cigarettes, 28 percent of the 114 cigarette ads included text or imagery related to alcohol. Cigarette and alcohol advertisements were equally likely to portray a bar or club setting that implied a nighttime or after-hours social gathering. Newport and Kool were two of the four cigarette brands that featured alcohol-related content in their advertising. However, the proportion of total ads for menthol and the proportion of menthol ads with alcohol content were not reported.

Anderson's review of industry documents (2011) noted that menthol marketing appeals to multiple group identities, especially, but not exclusively, to African Americans. She observed that menthol marketing conveys varied images of menthol smokers because the three largest, exclusively menthol brands developed such different identities. Several examples from industry documents characterized Kool as having a more masculine image than other brands, Salem a more feminine image, and Newport as the brand with the youngest demographics in the industry. Anderson concluded that no single unified image of a menthol smoker emerges from marketing messages about the product.

Two empirical studies examined consumer perceptions of menthol smokers, and commented on the degree to which perceptions fit the messages conveyed in menthol marketing. Allen and Unger (2007) examined selected socio-cultural factors associated with menthol smoking in a convenience sample of African Americans from Los Angeles. They interviewed 432 smokers of at least five cigarettes per day (296 menthol and 136 non-menthol) recruited from a campus medical center, shopping malls and other community sites. Differences between groups of smokers were presented as odds ratios (adjusted for age and employment status) and without response frequencies. The results suggested that for both males and females, a significant correlate of menthol use was the belief that most African Americans smoke menthols. Among females (but not males), an additional correlate was a lack of belief that menthol smoking "*is a Black thing*."

Segerstrom et al. (1994) randomly assigned 100 white and 94 African American community college and university students with a short written description of a target smoker that varied by race (African American or white) and cigarette type (menthol or regular). Students then rated the smoker on 15 attributes using semantic differential scales (e.g., rich/poor, unpopular/popular, weak/strong). Overall, the pattern of ratings according to the subject's own race and smoking status was inconsistent and no single unified image of a menthol smoker emerged. Although the small sample size limits conclusions about differences in perceptions between groups, the study finding is consistent with the conclusion of Anderson's document review (2011). However, the study did not examine perceptions of those who smoked different brands of menthol cigarettes, which would likely differ.

Summary. Menthol marketing features youthful imagery and consumers perceive differences between menthol and non-menthol advertising in terms of the relative age of the models. Menthol marketing also uses socially and culturally relevant messages about in-group identity to appeal to different market segments. Different group identities are emphasized in marketing for different brand families, which may explain why consumers do not share a singular impression of a menthol smoker.

The next section considers the role of youthful imagery and other messages about in-group identity in cultivating target markets for menthol brands.

WHO ARE THE TARGET POPULATIONS FOR MENTHOL MARKETING? IS THERE EVIDENCE TO SHOW THAT YOUTH, WOMEN, AND SPECIFIC RACIAL/ETHNIC GROUPS WERE TARGETED?

Few products are promoted to the entire population in an undifferentiated manner. The planning of promotional strategy requires the definition of a clear target market, whereby the population is segmented into defined subgroups. This target market can include people who are potential buyers, current users, those who make the buying decision, or those who influence it. Extensive qualitative and quantitative research is undertaken to identify the salient beliefs, values and preferences of the planned target market, which might be defined on the basis of age, gender, ethnicity, income, and lifestyle, among other attributes (NCI 2008). Promotional strategies are then designed for and directed to this well-defined consumer group (or segment). Typically, many consumer tests are undertaken to pre-test and refine branding elements. The message in a segmented campaign may have broad appeal, but will be most salient to and resonate with the specific targeted segment. The recent National Cancer Institute (NCI) review concluded that "*the tobacco industry has become increasingly sophisticated in applying market research to population segments in order to design products, messages, communication channels and promotions more aligned with the needs and susceptibilities of particular market segments. This research results in more efficiency, greater reach, and increased effectiveness for marketing activities aimed at targeted populations*." (NCI 2008, p171).

This section draws on three types of evidence about target marketing: (1) analyses of tobacco industry documents that described the development, intent, and consequences of marketing menthol brands, (2) analyses of the advertising environment that compared the quantity of menthol advertising either by neighborhood characteristics or by audience demographics, and (3) observational studies that compared advertising recall and recognition by audience demographics.

Targeting: Youth and young adults

In relation to tobacco use, brand image is especially important for adolescents because this is the age during which the vast majority of people take up smoking and brand choices are made. The recent NCI review concluded that "*much tobacco advertising targets the psychological needs of adolescents, such as popularity, peer acceptance and positive self-image. Advertising creates the perception that smoking will satisfy these needs.*"(NCI 2008, p280).

Tobacco companies frame their marketing efforts as being solely aimed at influencing brand switching in current users, and deny their advertising and promotional strategies promote youth smoking uptake. However, there is an abundance of empirical studies to show that the tobacco industry does target its marketing efforts towards youth and young adults and that youth are strategically important for the customer base. As concluded by Pollay et al. (1996), "*the battle of the brands for market share is waged largely among the young, for it is a brand's success among the young that leads to greater brand sales and profit in the long term*"(p.13). Youth notice and are influenced by, tobacco marketing efforts in ways that increase their likelihood of taking up smoking (NCI 2008). The recent NCI review examined research studies linking tobacco advertising and promotion with smoking attitudes and behaviour, including qualitative, cross-sectional, experimental, cohort and time series studies. The review concluded that "*the total weight of evidence from multiple types of studies, conducted by investigators from different disciplines, using data from many countries, demonstrates a causal relationship between tobacco advertising and promotion and increased tobacco use, as manifested by increased smoking initiation and increased per capita tobacco consumption in the population*" (NCI 2008, p281).

Industry documents research

Ling & Glantz (2002), in a review of tobacco industry documents from Philip Morris, RJ. Reynolds and Lorillard, explored tobacco industry strategies for marketing to young adults aged 18 to 24 years. They concluded that tobacco advertising encourages regular smoking and increased consumption by integrating smoking into social activities and places that reflect life changes experienced by young adults, with menthol brands such as Newport being featured in example documents. Kreslake et al. AJPH (2008), in a review of tobacco industry documents, found evidence that younger smokers preferred milder brands with lower menthol levels, with R.J. Reynolds observing that "*the want for less menthol does indeed skew younger adult*"(Etzel 1993, cited in Kreslake AJPH 2008). The success of Newport among younger consumers—Newport has lower menthol levels than Kool and Salem brands—was attributed to this feature, and the authors noted that from the 1980s, all other major menthol brands actively pursued a low-level menthol formulation to attract this market (Kreslake et al. AJPH 2008). In Kreslake et al. (NTR 2008), industry documents indicated a clear acknowledgment of this low-menthol formulation being more attractive for those initiating smoking. For example, one Brown & Williamson document outlined that "*a successful starter cigarette would need to provide a low tobacco taste, low impact and irritation, low tobacco aftertaste, and low menthol content*"(Cantrell, 1987 cited in Kreslake et al., NTR 2008). Kreslake et al. (NTR 2008) refer to several Lorillard documents that detailed studies finding lower satisfaction ratings among younger people in their twenties when given cigarettes with higher menthol levels. By comparison, smokers aged 45 and older had higher satisfaction ratings of cigarettes with higher menthol levels.

Klausner (in press), in her industry document review, concluded that youth were a target of menthol marketing. She notes Philip Morris was concerned in the late 1970s that it lacked a competitive menthol product at a time when menthol cigarette use was increasing among the young, women and African Americans. "*We knew that Blacks, females, and younger smokers were more likely to smoke menthol cigarettes than whites, males and older smokers. …These differences could have a profound effect on the future growth of the menthol share of the market. We know, for example, that males,*

whites and older smokers are more likely to quit smoking than females, Blacks and younger smokers" (cited in Klausner, in press). Anderson's tobacco industry document review (2011) also noted the importance of young people as a primary target group for menthol cigarette marketing. For example, she found documents that indicated that the marketing strategy for Newport through much of the 1990s was to "*continue to improve Newport's appeal as the 'peer' brand among young adult smokers*"(cited in Anderson, 2011). She concluded that menthol is targeted to young people in the U.S. and that although different menthol brands are associated with different "brand identities," menthol in general is perceived to be for females, younger smokers and lighter smokers. She concludes that marketing that emphasizes "*coolness, refreshing sensations, mildness, soothing taste and youth fun-loving imagery*" contributes to these perceptions (Anderson, 2011). As detailed further in a later section on targeting to African Americans, Hafez & Ling (2006) document how the company used music to appeal initially to African Americans with its Kool Jazz concerts and related music efforts, but initially failed in its aim to "*find an idea or symbol that was truly pan racial (universal racial*)." With its 2004 Kool Mixx campaign, which promoted elements of hip-hop culture through colorful cigarette packaging and related giveaways, such as radios, and music compact disks, the brand finally succeeded in reaching beyond its core target group of African Americans to young adults in general.

Empirical studies

Two empirical studies addressed the content and/or appeal of menthol marketing to adolescents or young adults. Unger et al. (1995) had 386 eighth-grade students in southern California rate each of 20 cigarette and alcohol ads that appeared in magazines or on television during early 1993. Brand name information was concealed on each ad. For Newport ads, 63.3 percent of students correctly identified the ad/s as being for cigarettes and 31.4 percent correctly identified the brand. For Kool ads, 10.5 percent correctly identified the ad/s as being for cigarettes and 11.6 percent identified the brand. This compared with correct identification of cigarette ad/s for Marlboro ads (87.8 percent) and correct identification of the brand (71.7 percent). Stage of smoking uptake (non-susceptible nonsmoker; susceptible non-smoker; user) was significantly associated with correct brand name recognition for all seven cigarette brands analyzed together and for Newport specifically, with users recognizing the ads significantly more than non-susceptible nonsmokers. Smoking susceptibility was positively associated with ad liking for the menthol brands Kool and Newport, and non-menthol brands Marlboro, Camel and Capri. These results were noted by the authors as consistent with the notion that cigarette advertising is attractive to susceptible nonsmokers as well and may influence them to experiment with the product.

Arnett & Terhanian (1998) showed 534 sixth- to twelfth-graders one print advertisement for each of five cigarettes brands—Marlboro, Camel, Kool, Benson & Hedges or Lucky Strike—and after each viewing they completed questions about the ad. Overall, 56 percent had seen the Kool ad more than six times, 38 percent liked it, 30 percent said it made smoking look appealing and 9 percent said it made them want to smoke that brand. Responses to these questions were higher for Marlboro and Camel and lower for Benson & Hedges and Lucky Strike. As for other brands, smokers more frequently indicated than non-smokers that they liked the Kool ad, and that the Kool ad made them want to smoke the brand.

Two studies provide ecological evidence that menthol marketing expenditures are related to adolescent cigarette brand preference. In a survey reported by Barker et al. (1994) the three most commonly purchased brands among adolescent smokers in 1993 (Marlboro, Camel and Newport) were the three most heavily advertised brands in 1993. This is despite the fact that Camel and Newport ranked seventh and fifth, respectively, in overall market share. Similarly, the increase from 1989–1993 in adolescents' brand preference for Camel cigarettes and the decrease in preference for Marlboro cigarettes during that period were not explained by changes in overall market share for

these brands. Rather, these changes mirrored the direction of changes in brand-specific advertising expenditures: from 1989–1993, Marlboro advertising decreased to $75 million from $102 million, while Camel advertising increased to $43 million from $27 million. In contrast, the increased preference for Newport menthol cigarettes did not reflect the decrease in Newport menthol advertising expenditures to $35 million from $49 million during the same period. The authors suggest that regional differences in brand preference of adolescents and changes in those preferences during 1989–1993 might be explained by further analysis of the relation between regional advertising expenditures and brand preferences.

Pollay et al. (1996) modeled the relationship between advertising expenditures for nine brands including Newport, Kool and Salem and youth and adult cigarette brand preference between 1974 and 1993. Brand preference data was sourced from population surveys of youth and from Maxwell Report market share data for adults. Using standard techniques to analyze market share involving Koyck-type models, they found that brand choices among teenagers were related to the extent of brand-specific cigarette advertising. Furthermore, the relationship between brand choice and brand advertising was significantly stronger among teenagers than among adults, by a factor of almost three (Pollay et al. 1996). These findings were robust to different assumptions, including the removal from the model of the most popular brand, Marlboro. These findings suggest that advertising for cigarette brands, including menthol cigarette advertising, has a greater impact on the brand preferences of teenagers than on adults.

Summary. Taken together, the section on youthful imagery in menthol marketing and the studies of industry documents described in this section confirm that the industry developed menthol marketing to appeal to youth. This is particularly true of the Newport brand, but the strategy was also adopted by other tobacco companies. Marketing messages positioned menthol cigarettes as an attractive starter product for new smokers who are unaccustomed to intense tobacco taste and/or high levels of menthol. Empirical studies provide further evidence of targeting: youth pay attention to and are attracted to menthol cigarette advertising. Cigarette advertising, including menthol cigarette advertising, has a greater impact on the brand choice of adolescents than it does for adult smokers. Studies of the role of menthol cigarettes in smoking initiation are discussed in Chapter 6.

Targeting: Women

The white paper by Rising & Alexander (2010) points out that neither of two reviews of tobacco use among women included information that was menthol-specific. However, four tobacco industry document reviews included information about menthol marketing to women and one empirical study was focused on menthol marketing to women.

Carpenter et al. (2005) reviewed tobacco industry documents to show that extensive research was conducted by the industry on female smoking patterns, needs and product preferences, including menthol brands. The industry took account of women's social and cosmetic concerns for cleanliness and freshness through menthol cigarette product design and marketing. Lorillard, for example, experimented with a lemon-flavored menthol brand to address female sensitivity to unpleasant odor and aftertaste while capitalizing on their greater willingness to experiment with flavored cigarettes (Carpenter et al. 2005).

In their review of menthol cigarette marketing which includes tobacco industry documents, Sutton & Robinson (2004) point out that female smokers were the first targeted population for menthol cigarettes, when a 1930's advertisement for Spud menthol cigarettes proclaimed that "*to read the advertisements these days, a fellow'd think the pretty girls do all the smoking*" (USDHHS, cited in Sutton & Robinson 2004). These authors also noted that advertisements for menthol cigarettes from

the 1950s onward had a distinctly feminine aura, featuring images of romance, flowering fields and springtime.

Klausner's document review (in press), mentioned above, described examples of marketing efforts directed at young females. For example in 1976, R.J. Reynolds described Lorillard's marketing effort as follows: "*Newport is placing increased emphasis on both young female and young male publications reducing older female publications [magazines]. Trend is toward younger readers and more men although overall female skew continues*" (document cited in Klausner, in press). Anderson's document review (2011) found that the three largest stand alone menthol brands had different brand identities in the mind of both manufacturers and consumers. R.J. Reynolds documents portrayed Salem as a brand for smokers who are "*passive, feminine,*" describing its Salem Slim Lights variant to be positioned for consumers "*who desire a refreshing, low tar cigarette with (a) stylish, unpretentious feminine image*" (cited in Anderson, 2011). Although the menthol segment "*skews female*" (documents cited in Anderson, 2011), the Kool brand has a more masculine image, described by Lorillard as "*a strong tasting, 'tough guy' cigarette*" (documents cited in Anderson, 2011).

Fernandez et al (2005) conducted a descriptive analysis of menthol advertising in women's magazines compared to one men's magazine from 1988 to 2002. They found that the proportion of menthol ads out of all cigarette ads in each issue of magazines for white women did not differ from those for white men. However, as discussed more fully in the next section on ethnicity, there was a higher prevalence in magazines for Hispanic women.

<u>*Summary*</u>. Some menthol brands appear to be more targeted to women than men, while others have more masculine branding. However, there is more evidence that menthol marketing efforts are directed to youth and young adults in general, and to racial/ethnic subgroups of women (see also next section).

Targeting: African Americans

A large body of research has documented a disproportionate volume of cigarette advertising aimed at African Americans (cf. Primack et al. 2007). Only the subset of studies that categorized or quantified advertising for menthol cigarettes were examined for this section.

Industry documents research

The tobacco industry's internal documents illustrate sustained efforts to target African Americans through the development and advertising of menthol products and through corporate involvement in community-based organizations.

Balbach et al. (2003) reviewed 21,000 industry documents from a search string of terms related to R.J. Reynolds' launch of Uptown, a full flavor cigarette with lower levels of menthol than Salem, that was designed to appeal to young African American men. In a 1988 speech, a senior marketing official noted that the company had been using targeted marketing programs for decades: "*Reynolds tobacco has made a special effort to reach Black Smokers since the early 1960s…almost 70 percent of Black smokers choose a menthol brand. That's why special advertising and promotions for Salem cigarettes make a lot of sense in Black media and Black communities*" (Winebrenner 1988, cited in Balbach et al. 2003). The objective of R.J. Reynolds' Black Initiative Program was to regain its share of the African American market with a plan that featured "targeted Black print media (Jet, Essence, Ebony, key newspapers)" and a heavy "outdoor presence" (R.J. Reynolds 1990, cited in Balbach et al. 2003). Special packaging for Uptown reflected the company's beliefs that African American smokers opened cigarettes from the bottom and that a pack containing only 10 cigarettes would address the price sensitivity of the target audience. As a result of intense public pressure that followed R.J.

Reynolds' press release, the company canceled the test marketing in Philadelphia and it abandoned the Uptown brand. A 1990 Philip Morris memorandum attributed this failure to its competitor's miscalculation: *"…marketing cigarettes to minorities was not new, saying so was."* (Philip Morris 1990, cited in Balbach et al., 2003) R.J. Reynolds' continued efforts to build brand share in the African American market were informed by the idea that "a highly visible commitment to social responsibility is fundamental to successful ethnic marketing" (R.J. Reynolds 1994, cited in Balbach et al. 2003). The authors noted that the company's strategy represented a combination of marketing existing menthol brands and building community relationships through support of local events and programs.

Hafez and Ling (2006) examined 210 industry documents related to music sponsorship and the Kool brand. Using music as the unifying element of an integrated marketing campaign aimed at young African American smokers was a proven formula for Brown & Williamson. Beginning with the first Kool Jazz concert in 1975, music promotions were used to maintain and augment market share in the African American community. For example, a 1981 marketing document suggested that Kool's music campaign was originally developed "*on a strategy of more effectively reaching a major segment of our target audience, providing some kind of reward for this same group in the form of shows at bargain prices, and using the events to offset Black media availability deficiencies*." (Broecker 1981, cited in Hafez & Ling 2006). Vans equipped with loudspeakers, such as the "Kool Mobile Music Tour," were used to distribute free Kool cigarette samples in inner-city neighborhoods. Similar promotional techniques were the foundation of a 1981 Kool Market Development Program, which also encouraged the involvement of Brown & Williamson's sales representatives and managers in "*retail and community organizations that will assist in fostering positive relations in the Black community*." (Brown & Williamson, 1982, cited in Hafez & Ling,2006).

Yerger et al. (2007) examined documents from the four companies (Brown & Williamson, Lorillard, Philip Morris, and R.J. Reynolds) whose menthol brands were the most heavily marketed in African American neighborhoods, using search terms related to African American, inner city, and urban. The analysis highlighted four strategies that were common to the industry's marketing programs in the inner cities from 1980 to the late 1990s: collecting psychographic and other data about African American consumers, using mobile vans to maximize the distribution of free cigarettes, developing specialized promotions for inner-city retailers, and engaging with local organizations to improve corporate image in the African American community. For example, Philip Morris sought to resolve problems with product availability and visibility in its "Black accounts," which were smaller liquor, grocery, and convenience stores in inner cities (Philip Morris 1984, cited in Yerger et al. 2007). The company redesigned product displays and paid retailers incentives to expand inventories and maintain visually prominent displays. First tested in Detroit, the program was later expanded nationwide to promote only menthol extensions of the company's most popular brands. Similarly, Brown & Williamson's "Kool Inner City Family Program" targeted the top 20 African American markets with free gifts for retailers and distributors, in-store advertising with African American models, and a variety of consumer offers (Lagreca 1987, cited in Yerger et al. 2007). R.J. Reynolds conducted interviews in inner-city zip codes with at least 50 percent African American residents and yearly household incomes under $20,000 in order to determine the boundaries of target neighborhoods for a "BYAS" (Black Young Adult Smoker) Initiative to increase market share for its Salem brand (Hawkins et al. 1989, cited in Yerger et al. 2007). Additionally, the value of the target audience for increasing brand share was described in the company's marketing report: "*The daring, flamboyant aspect of YA [young adult] Black smokers' personalities are evident in <u>the many trends they start</u>. And the fact that these trends often spread to the general population speaks to the <u>unrecognized power and influence</u> this subgroup yields on society…*" [emphases in original]. (Leferman Associates 1989, cited in Yerger et al. 2007). The authors concluded that geographically specific, aggressive, and intentionally disproportionate levels of marketing contributed to the tobacco-related health disparities that are evident among African Americans.

In their review of 144 industry documents, Johnson et al. (2008) identified similar targeting strategies, including industry-sponsored studies of African American culture, geographic targeting of urban areas, and investments in community, ethnic, and cultural events to enhance the industry's image in the African American community. For example, a 1976 marketing plan for Brown & Williamson reported: "*Kool is to develop programs which ingratiate themselves with the Black community. These programs are to show the makers of Kool as a community citizen, be backfire-proof and pave the way for supporting the brand*." (Brown & Williamson 1976, cited in Johnson et al. 2008).

Cruz, Wright & Crawford (2010) combined data from interviews with a former Brown & Williamson executive with analyses of tobacco industry documents to examine how a mix of marketing strategies was used to promote growth in menthol brand share among new and existing African American smokers in urban areas. According to the executive, Brown & Williamson used the term "focus" to refer to communities or stores in predominately low-income, African American areas that were identified as being critical to increasing market share. For example, a 2002 business plan stated: "*Kool is delivering a premium message to its anticipated audience and concentrating in 22 trend-setting urban cities where the majority of this audience lives. These cities house the 102 focus assignments that Kool has identified to be key to the growth of the brand*" (Kool USA 2002, cited in Cruz et al. 2010). The company placed a greater quantity of interior and exterior signs in focus stores, and installed pack displays that featured more shelf space for menthol than for non-menthol brands. In addition, a 2002 marketing report documented that a multi-pack discount offered in 1,600 stores resulted in a larger market share for menthol than was observed in stores that did not receive the promotion. The authors concluded that menthol is the lynchpin in a tightly integrated series of campaigns aimed at the urban poor, especially African Americans.

Anderson's (2011) analysis of tobacco industry documents highlighted the role of marketing in the growing popularity of menthol cigarettes among African American smokers. According to a history of menthol brands written by an R.J. Reynolds marketing official, Kool led this trend by advertising to African Americans before its competitors did: "*Kool ads were in Ebony consistently from at least 1962, when our records start….Kool became 'cool' and, by the early 1970s, had a 56 percent share among younger adult Blacks – it was the Black Marlboro*" (Burrows 1984, cited in Anderson 2011). This sentiment was echoed in a 1968 document from Philip Morris, which observed that menthol cigarettes were "*especially suited to the needs, desires and tastes of Negro consumers*." (Philip Morris 1968, cited in Anderson 2011). In a "Black Opportunity Analysis" conducted by R. J. Reynolds in 1985, the company's research observed that an "underclass" of African American smokers would remain reliable customers in spite of growing health concerns: "*Blacks simply have more pressing concerns than smoking issues*." (R.J. Reynolds 1985, cited in Anderson 2011). A 1983 industry study of low-income African American smokers observed that recall of advertising for specific menthol brands had improved since 1979 and "*the use of menthol cigarettes among the 18–34 lower income Black segment is almost universal*" (Lorillard estimated 1983, cited in Anderson 2011). The author concluded that heavy targeting of largely African American urban populations is reflected in the nearly exclusive preferences for menthol brands among these smokers. Indeed, survey data described in Chapter 4 confirms that although more menthol smokers are non-Hispanic white than African American, African American smokers disproportionately favor menthol brands.

All types of research methods are subject to limitations, including qualitative documents research. A separate peer-reviewed paper by Anderson et al. (2011) identified several limitations that pertain to the studies reviewed in this section and elsewhere in this chapter. The sheer volume of documents available (more than 60 million pages) makes it impossible for researchers to determine that all relevant data were included for each topic examined. Although researchers aim to identify the most important documents among similar results for combinations of related search terms, this "saturation" was not achieved in all studies. The prevalence of acronyms and evidence of code words

for menthol suggests that researchers' understanding of the documents may be hampered if the context is unknown. In addition, evidence that the industry tried to conceal its findings and to destroy documents increases the chance that relevant documents could be missing and that a researcher's understanding of a topic might be incomplete. Despite these limitations, the studies reviewed here are noteworthy for a consistency of evidence about the tobacco industry's systematic efforts to promote menthol cigarettes to African Americans.

Advertising environment

The white paper by Rising & Alexander (2010) identified six relevant peer-reviewed articles. In addition, this section included one peer-reviewed study that was published after the white paper (Seidenberg et al. 2010). The studies are organized by the type of advertising examined and then reviewed in chronological order.

Magazines

Three studies documented that advertisements for menthol cigarettes were overrepresented in magazines that are popular with African American readers. Cummings et al. (1987) compared ads that appeared in three magazines with a largely African American readership (Jet, Ebony, Essence) and four magazines with a largely non-Hispanic white readership (Newsweek, Time, People and Mademoiselle). Full-page ads appearing between June 1984 and May 1985 were classified according to product, and brand (menthol, non-menthol, or both). Compared to the other magazines, those targeting African Americans contained a larger proportion of cigarette ads (12.0 percent versus 9.9 percent) and larger proportion of these cigarette ads were for menthol cigarettes (65.9 percent vs. 15.4 percent). Both comparisons were statistically significant.

Informed by hypotheses from an analysis of tobacco industry documents about R.J .Reynolds' Uptown brand, one study compared cigarette ads for R.J. Reynolds brands that appeared in the same three magazines targeted at African American readers (Jet, Ebony, and Essence) with those that appeared in People Weekly (Balbach et al. 2003). Ads were sampled from two time periods: the years surrounding the introduction of the Uptown brand (1989–1990) and one decade later (1999–2000). Compared to People Weekly, the magazines targeted to African Americans contained a significantly larger proportion of R.J. Reynolds' ads for menthol brands—100 percent vs. 31.6 percent in 1989-90 and 97.7 percent vs. 0 percent in 1999-2000.

Landrine et al. (2005) examined cigarette ads that appeared in one magazine targeted at African Americans (Ebony), one at Latinos (the Spanish language edition of People) and one at non-Hispanic whites (the English language edition of People). In issues sampled from January 1990 through August 2002, the proportion of ads for menthol cigarettes was 67.2 percent in the African American magazine, 35.3 percent in the Latino magazine, and 17.3 percent in the other magazine. Unadjusted odds ratios suggested that the African American magazine was 9.8 times more likely to contain a menthol ad than the white magazine; the Latino magazine was 2.6 times more likely to contain a menthol ad.

In a submission from Lorillard to FDA, the company stated that "Newport marketing expenditures have not been disproportionately weighted toward African American smokers or any other ethnic group or gender" (p. 44, Lorillard, July 2010). Although the company's advertising expenditures for general market magazines consistently exceeded its expenditures for African American magazines (see Figure 11, Lorillard July 2010), that difference does not preclude a pattern of targeted marketing that was documented in the studies of magazines. Assuming lower rates are paid to advertise in magazines with a smaller circulation, it would be possible to place a larger volume of ads in African American magazines at a substantially lower total cost. Lorillard increased its spending on African

American magazines relative to general market magazines in 1993 (see Figure 11, Lorillard July 2010), but no studies examined the relative impact of that increase on the proportion of ads for menthol brands. Content analyses of magazine advertising for menthol and non-menthol brands after 2002 were not found.

Outdoor and retail advertising

All four studies on this topic found that menthol cigarettes were marketed disproportionately in areas with more African American residents. Altman et al. (1991) compared billboard advertising by the racial/ethnic demographics of census tracts in San Francisco, California. Each of the 901 billboards in the city was photographed between 1985 and 1987. Census tracts were categorized by the predominant racial/ethnic group and without regard to the proportion of non-Hispanic white residents. Thus, African American neighborhoods referred to census tracts where 30 percent of the residents were African American and they were the dominant ethnic/racial minority group, even if a larger proportion of residents were non-Hispanic white. The proportion of all billboards that advertised menthol cigarettes was 22 percent in African American neighborhoods, 17 percent in Hispanic, 11 percent in white and 10 percent in Asian neighborhoods. African American neighborhoods were significantly more likely to contain billboards advertising menthol cigarettes.

Pucci et al. (1998) described outdoor advertising for cigarettes in six Boston neighborhoods—two with the highest median household income, two with the lowest, and two in the middle range. In the two of the neighborhoods, 89.2 percent and 62.3 percent of the residents were African American. All outdoor ads for tobacco, including billboards, placards, posters, stickers, banners, neon and freestanding signs, were counted and categorized by brand. Ads for exclusively menthol brands, Newport, Kool, and Salem, made up 49 percent of the outdoor advertising for cigarettes in the two African American neighborhoods, compared to 38 percent in the Latino neighborhoods, and 22 percent in the non-Hispanic white neighborhoods. The proportion of all ads for menthol, regardless of brand, was not coded.

Laws et al. (2002) visited all stores in 10 demographically contrasting areas of Boston, Massachusetts and compared the proportion of all cigarette ads for menthol brands. To identify predominantly Latino and African American neighborhoods, the researchers selected census tracts of similar per capita income but different ethnic compositions. The comparison areas were predominantly non-Hispanic white and more affluent. Field observations were conducted in all 128 stores that sold cigarettes in 1999. Stores in the area with the highest proportion of African American residents contained the highest concentration of cigarette ads for menthol brands—32 percent in that area compared to 13 percent overall. The difference between the proportion of ads for menthol in predominantly minority areas (29 percent) and non-minority areas (12 percent) was statistically significant.

Similarly, Seidenberg et al. (2010) compared the proportion of all cigarette ads for menthol on storefronts in two Boston neighborhoods, one with predominantly African American residents (50.1 percent) and one with few African American residents (2.7 percent). To eliminate the large discrepancy in the number of retailers that sold tobacco in the two areas, the researchers visited all 59 stores that sold cigarettes in one zip code in the African American neighborhood with all 43 stores that sold tobacco in the comparison community. The proportion of cigarette ads for menthol brands was significantly greater in the African American neighborhood (53.9 percent vs. 17.9 percent). Adjusting for other characteristics of the ads (including size, proximity to school, and the presence of a price), the odds of finding an ad for menthol cigarettes was five times greater on storefronts in the African American neighborhood.

One weakness of the studies about outdoor and retail advertising is that they were limited to small geographic areas. In addition, some of the analyses did not control for neighborhood income, making it difficult to discern whether neighborhoods were targeted because they were predominantly low-income, African American, or both.

Summary. All of the tobacco industry document reviews provide evidence that the tobacco industry developed specialized brands and tailored marketing strategies to promote menthol cigarettes to African Americans. Studies of the advertising environment that have compared menthol and non-menthol advertising provide corroborating evidence of the target marketing strategies that were identified in the industry documents research. In all three empirical studies on the subject, menthol cigarettes were advertised disproportionately more than non-menthol cigarettes in magazines aimed at African American readers, compared to magazines with low African American readership. Both studies of outdoor advertising and both studies of retail store advertising showed a higher proportion of menthol ads out of all cigarette ads, in neighborhoods with more African American residents than neighborhoods with lower proportions of African American residents.

Targeting: Other Race/Ethnicity

Although there are many studies that confirm African Americans to be a particular target audience for menthol marketing efforts, there are fewer industry document reviews and empirical studies that point to the use of menthol advertising targeted towards particular ethnic groups, such as Hispanics, Asian Americans and Hawaiian/Pacific Islanders. Nonetheless, available studies generally show purposeful targeting towards these ethnic groups.

Industry document reviews

A review of tobacco industry documents on targeting of Asian Americans and Pacific Islanders described many tobacco marketing campaigns to reach these population subgroups, but marketing strategies for menthol cigarettes were not specifically mentioned (Muggli et al. 2002). A tobacco industry document review by Anderson (2011) identified menthol marketing campaigns specifically aimed towards Asians and Hawaiians/Pacific Islanders. For example, a study of an R.J. Reynolds' Kool cigarette marketing campaign targeting Hawaiians in 1988 remarked that the use of ethnic models "*could provide an opportunity for Kool to capitalize on being the first to employ ethnic advertising in Hawaii*" and "*display what islanders call the aloha spirit*" (Anderson 2010) Anderson (2011) also documented that Philip Morris' Marlboro promotion plan in 1992 included "*special programs to menthol Hispanic and Asian smokers*" to increase its market share among young adult smokers.

Empirical studies

Altman et al. (1991) conducted a descriptive analysis of billboards by census neighborhood demographic characteristics during 1985-1987 in San Francisco. Overall, 19 percent of billboards featured ads for tobacco (and 13 percent for menthol cigarettes). Menthol cigarette billboards were more likely in African American (22 percent) and Hispanic (17 percent) neighborhoods than in Asian (10 percent) and white (11 percent) neighborhoods. Although no statistical analysis was undertaken, the rates appeared disproportionately lower for non-menthol cigarette billboards in African American (2 percent) neighborhoods, while being around half the rate in Hispanic (8 percent), Asian (4 percent) and white (6 percent) neighborhoods.

Two studies focused on magazine advertising were located. In the same study described above in the section on targeting African Americans, Landrine et al. (2005) examined tobacco advertising in issues of Ebony, People magazine and People in Spanish between 1988 and 2002. In this study, ads

for menthol brands were significantly more likely in the Spanish-language edition of People (35 percent of cigarette ads), compared to 17 percent of ads in the English language version of People magazine. A more recently published study reported on a descriptive analysis of cigarette ads in the English- and Spanish-language versions of Cosmopolitan and Glamour magazines from 1988 to 2002 (Fernandez et al. 2005). Despite these magazines having the same publisher, content, length and advertising policies, there were significantly more ads for menthol brands in the magazines for Spanish-speaking women (51.1 percent of cigarette ads) than in the versions for English-speaking women (28.3 percent of cigarette ads). In fact, magazines targeting Spanish speakers were 2.64 times more likely than the English language magazines to contain ads for menthol cigarettes. Sixty percent of the cigarette ads in the Hispanic versions were for Kool and Newport, compared to only 26 percent of the cigarette ads in the white magazine versions. Although this study was looked at just two women's magazines, it focused on popular titles. These studies both provide evidence of targeting of Hispanics through menthol magazine advertising.

The point of sale advertising study by Laws et al. (2002), described in a previous section, audited stores in Boston neighborhoods for tobacco advertising. The researchers found 32.3 percent of all interior and exterior advertisements for menthol brands were in neighborhoods with the highest percentages of minority (African American and Hispanic) residents while 10 percent of all menthol cigarette ads were in neighborhoods with the lowest minority populations—a statistically significant difference. Another retail-focused study by Glanz et al. (2006) reported on an audit of tobacco advertising in 184 tobacco retail outlets in Hawaii in late 2002. Overall, advertisements for Kool menthol cigarettes were the most common of all tobacco ads identified, irrespective of whether ads were a straight count or were weighted by size. Kool also had the most outdoor ads using both outcomes. It had the largest number of indoor ads when a straight count was used, and was second to Marlboro when adjusted for size of ad. This retail advertising for Kool was thought to reflect the preference among Hawaiian youth for menthol cigarettes (especially Kool), which differs from youth preferences for Marlboro on the mainland (Appleyard et al. 2006; USDHHS USSG report 2004).

Summary. Comparatively fewer reviews and empirical studies examined whether menthol marketing has been targeted to racial/ethnic groups other than African Americans. Although no tobacco industry document reviews were available on the topic, all four empirical studies examining menthol and non-menthol advertising found a higher proportion of menthol ads out of all cigarette ads in Hispanic neighborhoods (2 studies)/magazines (2 studies), than in non-Hispanic white neighborhoods/magazines. A tobacco industry document review provided evidence that Asian Americans and Hawaiian/Pacific Islanders were targeted in menthol marketing. One empirical study showed a high prevalence of retail advertisements for Kool cigarettes in Hawaii.

Does menthol marketing influence perceived taste and/or sensory experience of menthol cigarettes?

Throughout TPSAC meetings, tobacco industry representatives consistently pointed to taste as being the main driver of preference for menthol cigarettes among menthol cigarette smokers (July 2010). However, taste is a complex perception, since it is the product of both flavor and other sensory attributes. Consumers can also be quite unclear as to what they mean by taste, often simply echoing descriptions given to them by tobacco branding, labeling and advertising (Pollay & Dewhirst 2002). Furthermore, there is evidence that consumers use elements of taste to infer the healthiness and other attributes of products. This is likely a natural human tendency, with evolutionary advantages. For example, a key element of unpleasant taste is the perception of bitterness, thought likely to have evolved in animals to help them avoid eating plants and other foods containing toxins and other harmful chemicals.

This section is organized into two parts. First, it summarizes consumer research from other domains related to taste perception to document how branding and labeling can influence consumer taste perception and sensory evaluation. Subsequently, this section summarizes studies specifically pertaining to messages about cigarettes in general and menthol cigarettes in particular.

It should be noted that additional literature on the sensory experience of smoking menthol cigarettes compared to non-menthol cigarettes is summarized in Chapters 3 and 6.

Role of branding and labeling in taste perception and sensory evaluation

Consumers have generally poor ability to discriminate between tastes, due in part to our taste buds' ability to detect only sweet, sour, bitter, salty and umami tastes. Multiple other senses are involved in taste perception, including smell, sound (when bitten or chewed) and touch (texture in the mouth and temperature) (Elder & Krishna 2009). Visual cues also contribute to the sense of taste by generating expectations about flavor. Evidence from the consumer science literature about the degree to which branding and labeling influence perceptions of the taste of food and drinks illustrates that taste perception is subjective and easily manipulated (Deliza & MacFie 1996). Use of branding, including use of color and descriptive names, results in an expectation or sensory halo effect, whereby the expectation halo influences how a person thinks a product might taste as well as taste perceptions and liking when the product is consumed.

There are several ways in which expectations might influence the sensory experience of products and people's liking of the product (Deliza & MacFie 1996; Cardello 2007). One model predicts the existence of a contrast effect (or boomerang effect), which may occur if the consumer holds expectations that are vastly different from the eventual product performance. Under these circumstances, consumers who have very low (or very high) expectations about a product might be pleasantly surprised (or very disappointed) by the contrast when the product is actually consumed. However, contrast effects have rarely been observed in the literature, even when disconfirmation of expectation is arguably quite large (Cardello 2007). Another model, known as the assimilation model, predicts that evaluation of the product will change in the direction of expectations. In other words, an expectation can be a driver of sensory experience and liking. In studies where food and beverages have been used as test products, the vast majority of observed effects have been assimilation effects (Deliza & MacFie 1996; Cardello 2007).

For example, bitter coffee was appraised after sampling as tasting less bitter only among those consumers who were exposed beforehand to three advertisements asserting that the coffee was not bitter (Olson & Dover 1978). An early study found that a slice of turkey was rated more positively after tasting if consumers thought it was a popular brand rather than an unknown brand (Makens 1965). In a more recent study, people who were given an energy bar supposedly containing soy protein were more likely to rate it as 'grainy' and 'tasteless,' compared with identical bars that contained no mention of the word 'soy' (Wansink & Park 2002). In fact, neither bar contained soy. In another study in Illinois, evocative descriptive names of cafeteria meals (such as 'Succulent Italian Seafood Filet') led to meals being rated after consumption as more appealing, tastier and caloric, and eliciting more positive comments, than exactly the same meals with less descriptive names (such as 'Seafood Filet') (Wansink et al. 2005). Color and labeling influenced perceptions of otherwise identical M&M candies: brown M&Ms were rated as more 'chocolatey' than all other colors, and those labeled as *dark chocolate* were rated as more 'chocolatey' than those labeled *milk chocolate* (Shankar et al. 2009). Even children express the effects of branding on taste perception: a study of three to five year olds in California found that identical food products were appraised as tasting better when they were branded with McDonald's than when they were unbranded (Robinson et al 2007).

There is variability in the extent to which brand and label information influence evaluation of different types of products. For example, in another controlled cafeteria study, diet and health labels (e.g., chocolate pudding vs. healthy chocolate pudding; pineapple soy muffins vs. diet pineapple soy muffins) improved the rated taste of desserts but not the rated taste of entrees (Wansink et al. 2004). In interpreting these findings, the investigators suggested that people might expect a dessert labeled as healthy or diet-related to not taste very good. When it tastes better than expected, it prompts an over-evaluation of taste ratings. By contrast, health labels had less ability to influence evaluation of the entrees offered, since they were already relatively healthy. This study suggests that for products that are less healthy, descriptive labels likely have greater capacity to promote positive taste evaluations.

In recent years, much progress has been made in understanding the neural basis of cognitive effects on taste and other sensory experiences. This research has used functional magnetic resonance imaging (fMRI) technology that measures blood flow in various regions of the brain in response to product consumption under varying conditions of expectation. In summary, these studies demonstrate that expectancies can change both the subjective evaluation of the product and the neural response to these products (Cardello 2007; Cardello & Wise 2008). For example, McClure et al. (2004) found that Coke was rated higher in a subjective taste test when consumed from a cup bearing the Coke logo than from an unmarked cup. Consistent with these subjective ratings, the study also found that the image of a Coke can presented prior to Coke tasting resulted in greater brain activity in the dorsolateral prefrontal cortex (DLPFC), hippocampus and midbrain, compared to unbranded Coke delivery (McClure et al 2004). This finding is important because the hippocampus and DLPFC have both been previously implicated in processing emotion and affect as it relates to behavior change. The investigators suggested that branding information biases preference decisions through the DLPFC, with the hippocampus engaged to recall the associated information (McClure et al 2004). In a more recent study, Nitschke et al. (2006) found that when people tasted a highly unpleasant (bitter) fluid, the level of activation in the bilateral taste cortex in the brain was reduced when they were told it would be only mildly unpleasant, compared to when they were told that it would be highly unpleasant. This misleading information also led to people rating the bitter fluid as less unpleasant than that same fluid when it was tasted following the truthful cue. Together, these studies imply that branding and labeling can lead people to hold more favorable expectations about a product, and these expectations influence brain functions in ways that result in an enhanced sensory experience.

The influence of branding on sensed experience when products are consumed is automatic, in that consumers are largely unaware of these processes. In part, this is likely to be because when consuming a product, consumers have limited time to make their evaluation and tend to rely on short-cuts – easily available information which is processed quickly and efficiently to assist their decision-making and guide their evaluation (also known as heuristic processing). Most consumers do not think that awareness of branding or labeling prior to tasting would change their sensed experience of products and are, in fact, unable to correctly predict the results of taste tests in which expectancies are manipulated in the ways described (e.g., Lee et al. 2006).

It is important to note that branding and labeling are not the only information available to form consumer expectations: the shared experiences and recommendations of others and one's own experience with the class of product to be tasted will also influence expectations and therefore one's subjective perceptions of taste. Individuals who have less experience with the class of products to be tasted and low involvement with the product tend to rely more on branding and labeling information (Deliza & McFie 1996; Cardello 2007).

Overall, this body of consumer sensory research suggests that a product that people may find unremarkable or even unpleasant, or that they know may be unhealthy, can be manipulated to be experienced as more pleasant by strengthening consumer's expectations that the product will offer a

positive experience. Branding and labeling have a critical role to play in shaping consumer expectations about a product. As suggested by Cardello (2007), "*the opportunity exists to improve the acceptance of a product and its market share through creative marketing that establishes a positive image and expectation for a product. Here lies the heart of all advertising strategies aimed at improving product image*" (Cardello 2007, p.230). Those who have less experience with a class of products, including young people, may be especially vulnerable to the effects of marketing on product liking and sensory experience, and therefore, on its consequent influence upon product acceptance and use.

Branding and labeling effects on subjective experience of cigarettes

There is good evidence that branding and labeling modify the subjective perception of tobacco when it is consumed. Most of this research has been undertaken using cigarette packaging as the medium for branding. In a review of internal tobacco industry documents on tobacco packaging made public through litigation filed against major U.S. cigarette manufacturers, Wakefield et al. (2002) found that tobacco companies employed the concept of expectancy manipulation or 'sensation transfer' to guide the design of cigarette packaging. In the industry documents, the term 'sensation transfer' is used to refer to the phenomenon whereby brand elements on packaging create expectations of what the cigarette will be like when smoked—also referred to as the 'halo effect' of branding. Numerous tobacco industry studies were found whereby exactly the same cigarettes presented in different packs led consumers to evaluate them differently when they were smoked. Tobacco companies discovered that lighter colors on the pack promoted perceptions of lower cigarette strength. For example, identical cigarettes presented in blue packs were described after being smoked as 'too mild,' 'not easy drawing,' and 'burn too fast,' whereas when presented in a red pack, they were described as 'too strong' and 'harsher' (Wakefield et al. 2002).

A published empirical study randomly assigned 200 male and female smokers to smoke identical cigarettes that were branded either "April" or "Frontiersman" (Friedman & Dipple 1978). Female smokers who smoked the cigarettes with the feminine brand name rated all aspects of taste and enjoyment more favorably than the female smokers who tried the identical cigarettes with the masculine name. Similarly, male smokers favored the masculine brand, but the effect was less pronounced. In their industry document review on marketing imagery, Pollay & Dewhirst (2002) find that market researchers for the tobacco industry and its advertising agencies were not confident consumers knew what they were talking about when referring to 'taste' of a cigarette. As one document from 1975 detailed, *"[I]t is almost impossible to know if the taste smokers talk about is something which they, themselves, attribute to a cigarette or just a 'play-back' of some advertising messages."* (Marketing & Research Counselors Inc., cited in Pollay & Dewhirst 2002).

DiFranza et al. (2002) suggest that tobacco companies understand that the process by which pack design communicates what consumers might expect from the cigarettes is subconscious. An R.J. Reynolds marketing department document indicated that "*on the first level a package serves to reinforce the brand's advertising in establishing a certain brand image or set of connotations, and in doing so it operates on a subconscious level. That is, the fact that it does this is not readily apparent to the consumer*" (Marketing Research Department 1969, cited in DiFranza et al. 2002). DiFranza et al. also note that the influence of pack design on the subjectively experienced qualities of the cigarette is of such a magnitude that when purely objective ratings of the cigarette qualities are desired, the test cigarettes are not branded (DiFranza et al. 2002). At the July 15, 2010 TPSAC meeting, tobacco industry representatives acknowledged that the presence of branding information does influence consumer evaluations of cigarettes when they are smoked (transcript p.183–185.) Thus, consumers' perceived taste and sensory evaluation of cigarettes are influenced not only by the product itself, but by related branding information, including color, pack design, and labeling.

In a review of tobacco industry documents, Wakefield et al. (2002) found that green colors in menthol packaging were predominantly used to influence expectations of menthol taste and sensory experience. For example, after smoking identical menthol cigarettes in a Philip Morris test, panelists consistently ascribed more menthol coolness to those presented in the darker of two shades of green, compared with the standard white paper cigarettes. There was no discernable difference between the lighter shade of green and white (Martin 1969, cited in Wakefield 2002). Another Philip Morris test found that the menthol brand Saratoga was perceived as having more menthol when the cigarette itself was wrapped with green paper than either production Saratoga, which had the same menthol level but was in a white wrapper, or the More brand, which had a higher menthol level but was in a brown wrapper—indicating that the green paper had an effect on the amount of menthol perceived (Howes 1976, cited in Wakefield 2002). A similar review of tobacco packaging by DiFranza et al. (2002) also commented on these sensation transfer tests, giving an example of an R.J. Reynolds pack test in which men strongly preferred the cigarette smoked when taken from an 'ice pack' over a cigarette smoked when taken from a 'green pack,' even though the cigarettes were identical in composition. The test concluded "*the cigarette related to the ice pack seems to be perceived as being a milder cigarette by the respondents. The ice on the ice pack connotes a cool/refreshing cigarette to the respondents*" (Magnus 1969, cited in DiFranza et al. 2002). Thus, manipulating elements of package design is sufficient to change smokers' expectations and evaluations of menthol cigarettes when they are smoked regardless of how much menthol they contain.

Consumer testing of cigarette packs was also undertaken to ensure that expectations of menthol content remained stable when lower tar and nicotine brand extensions were introduced. DiFranza et al. (2002) point to a consumer study by R.J. Reynolds in 1975 for three pack design options for Salem menthol cigarettes. Overall, the report concluded that "*the 'Green Line' design was the most effective in connoting lower tar and nicotine, especially among Salem smokers and female smokers. This package was also the least likely of the three alternatives to connote less menthol*" (Daniel 1975, cited in DiFranza et al 2002).

Summary. There is strong evidence from the general marketing literature that branding and labeling influence consumer expectations about a product and the subjective experience of product consumption. Tobacco company research and empirical studies demonstrate that elements of packaging such as branding, color and use of descriptive labels influence consumer beliefs about cigarettes, as well as the sensory experience when the product is smoked. There have been no peer-reviewed experimental studies specifically on the effects of menthol branding on consumer taste and sensory evaluation. However, consumer testing conducted by tobacco companies demonstrates that manipulation of elements of menthol cigarette packaging influences consumer sensory experiences of perceived coolness, amount of menthol, mildness, and overall preference. Thus, menthol packaging reflects the tobacco industry's knowledge about how color, labeling and other elements of branding will improve the consumer experience of the product's characterizing flavor.

DO CONSUMERS PERCEIVE MENTHOL CIGARETTES AS SAFER OR LESS HARMFUL THAN NON-MENTHOL CIGARETTES?

As indicated in the section on Packaging, for both menthol and non-menthol cigarettes, different shades of the same color and the proportion of white space are commonly used to distinguish between variants of the same brand family. Two studies illustrate that color and other branding features influenced adults' and adolescents' (ages 12–17) expectations about perceived health risk (Hammond & Parkinson 2009); Hammond, Dockrell, Arnott, Lee & McNeill 2009). Using a paired comparison study design with one element of packaging manipulated, adult smokers rated cigarette packs that featured lighter colors, sensory descriptors (smooth, light, mild), and pictures of filters as delivering smoother taste, less tar and reduced health risks (Hammond & Parkinson 2009). In

addition, beliefs about taste were positively correlated with beliefs about tar delivery and health risk. These studies did not include menthol packs, but they illustrate the extent to which branding elements about taste and sensory experience may contribute to beliefs that some cigarettes are less harmful than others. This section examines evidence from qualitative analyses of tobacco industry documents, qualitative focus group research, and survey research that examined consumer perceptions about the health benefits and relative risks of menthol cigarettes.

Industry document reviews

Reviews of tobacco industry internal documents made public as a result of legal proceedings against tobacco companies provide a wealth of information about consumer perceptions of menthol cigarettes. The limitations of industry document reviews have been outlined in a previous section.

Giovino and colleagues (2004) identified tobacco industry documents in the late 1960s and 1970s which suggested that menthol smokers, including African Americans, perceived menthol cigarettes to be less hazardous than non-menthol cigarettes. Giovino et al. refer to a study from R.J. Reynolds called "Project Y" where menthol smokers were classified as 'more concerned' than smokers of non-menthol cigarettes. They point to a Philip Morris report on focus group discussions undertaken to assess the attitudes of African American smokers about menthol cigarettes, which states, "*There are indications that menthols tend to be considered generally better for one's health. That impression refers not only to the health of the respiratory tract, but the whole organism. The majority view is that menthols are 'less strong' than regular cigarettes, and that a cigarette which is 'less strong' is better for a person's health"* (Tibor Koeves, cited in Giovino et al. 2004). It was uncommon for consumers to openly assert that menthol cigarettes conferred an explicit health advantage; rather, that perception was more implicit and described indirectly by the use of terms such as strength, cooling, lower in tar, and less irritating. Consistent with the promises of early menthol marketing campaigns discussed in a prior section, tobacco industry documents indicated that individual sampling of menthol cigarettes often occurred because of a cold or sore throat, and during the winter months (Tibor Koeves, cited in Giovino et al. 2004), reflecting the higher seasonal rates of acute respiratory infection during this time. Another R.J. Reynolds document reported that African Americans were more likely than whites to believe menthol cigarettes were "*better when you have a cold,*" "*less likely to make you cough,*" and "*less irritating to the throat*" (R.J. Reynolds, cited in Giovino et al. 2004).

In their tobacco industry document review, Kreslake et al. (NTR 2008) summarize some of the tobacco industry's extensive research to assess how product design influences consumer ratings of attributes of interest. They find that the way in which consumers describe product attributes differs between menthol and non-menthol smokers. For example, cigarette strength for menthol smokers is defined by menthol intensity, minty flavor and tobacco flavor, whereas for non-menthol smokers, strength is defined by throat impact and throat scratch. Harshness is defined by amount of tobacco flavor for menthol smokers, but by throat impact, presence of a burnt or tarry flavor, and absence of added flavor for non-menthol smokers (Swaim, cited in Kreslake et al. NTR 2008). There was evidence in tobacco industry consumer research that consumers used menthol cigarettes as part of a purposive effort to change their smoking behavior in ways consistent with trying to reduce their exposure to the health harms. Kreslake et al. (NTR 2008) describe qualitative research with consumers undertaken by tobacco companies between 1972 and 1994. These studies suggest that some menthol smokers switched from non-menthols in an effort to maintain their smoking without the negative physical symptoms they attribute to non-menthols. These studies also describe consumers' use of menthols during a respiratory problem such as a cold, sore throat or bronchitis. Switching to menthols to try to cut down on the amount smoked was reported in qualitative interviews. Menthol cigarettes were perceived by consumers as milder than regular cigarettes, but were seen as distinct from 'light' cigarettes because they were viewed as not being compromised by

the higher filter ventilation. A report by Roper (cited in Kreslake NTR 2008) on smokers of 'low tar' cigarettes concluded that "*menthol seems to compensate or make up for both few cigarettes and light cigarettes"* by providing *"an extra something.*" Kreslake et al. (NTR 2008) conclude that smokers who may otherwise quit because of the perceived harshness and health effects of 'higher tar' cigarettes, seek out menthol cigarettes for their 'substitute sensation' as they move to what they perceive is a lower tar cigarette with its associated implicit health reassurance. Tobacco industry document reviews on the role of menthol cigarettes in influencing quitting beliefs and intentions are discussed more fully in Chapter 6 in the section on smoking cessation.

Anderson (2011) also analyzed industry documents on consumer perceptions of menthol cigarettes up to the mid 1990s. Consistent with Kreslake et al. (NTR 2008) and Giovino et al. (2004), Anderson also concluded that consumers view menthol cigarettes as safer, or less harmful, than non-menthol or full-flavor cigarettes. She notes that menthol smokers sometimes identify this perception explicitly (directly) and sometimes implicitly (indirectly), through the use of terms that suggest improved safety or health benefits, such as 'light,' 'mild,' 'cooling' or 'soothing.' For example, she cites an American Tobacco focus group study, which observed that "*there were indications that the menthol smoker subconsciously perceived menthol cigarettes as being healthier. There was somewhat of a 'health image' associated with menthol, related to its masking of the tobacco taste and its association with medicine, colds and sore throats*" (American Tobacco, cited in Anderson 2011). Anderson found that menthol cigarettes have been marketed as, and are often perceived by consumers to be, milder and less irritating than regular cigarettes and therefore less of a health threat, in the same way that light/low tar cigarettes are mistakenly perceived to be safer. She concludes that menthol cigarettes provide psychological reassurance to consumers without providing any real health protection. This is exemplified in an R.J. Reynolds analysis of potential for share growth of menthol in 1977 : *"[t]he health concern was perhaps the primary motive for switching to menthol in the first place. In the hierarchy of product benefits/attributes desired by menthol filter smokers, throat concerns rank just behind generic taste and satisfaction*" (RJR, cited in Anderson 2011).

Klausner's (in press) tobacco industry document review was consistent with the findings of these other reviews in concluding that some young people smoke menthol cigarettes because they perceive them to be less harmful than non-menthol cigarettes, a notion they point out was encouraged through menthol advertising. Documents referred to young smokers choosing menthol cigarettes because they found the menthol "*less harmful*" or "*moving away from the problem [of smoking a harmful product]*" and "*a guilt-reducing mechanism…it manages in some small measure to subtly disguise the sin*" (cited in Klausner, in press). Klausner also notes that some youth use menthols for the first time when they have a sore throat or a cold because they perceive them to be less irritating than non-menthols. For example, a British American Tobacco study from 1982 found some smokers "*ascrib[e] medicinal properties to the mentholation*" and believe that "*menthols are somehow less intrusive or even less harmful than regular cigarettes.*"

Empirical and qualitative studies

The White Paper by Rising & Alexander (2010) found no published empirical studies of youth beliefs about menthol cigarettes. Studies of adults' beliefs about menthol cigarettes are discussed below. After first considering contextual and methodological interpretation issues, this section presents studies grouped by population surveys, clinic surveys, and focus group studies.

Surveys that compared menthol and non-menthol smokers' beliefs about the overall harm of smoking or disease risks of smoking (referred to in Lorillard's submission, July 2010) were not reviewed in this chapter. These surveys assessed the perceived harm or risk from smoking cigarettes in general, but not menthol cigarettes in particular. Over the years, a growing proportion of smokers

agree that cigarette smoking is harmful (e.g., NSDUH surveys), as might be expected from the considerable investment in media campaigns about this important public health concern. Menthol smokers differ from non-menthol smokers on many demographic and psychosocial traits that would influence their beliefs about the harms of smoking. Comparing the beliefs about smoking in general for menthol and non-menthol smokers does not inform the research question about the perceived harm of menthol cigarettes relative to non-menthol cigarettes.

Research about the perceived relative harm of menthol cigarettes must be interpreted within the context of increased mass media education about the risks of smoking. During the 1990s, several states implemented tobacco education campaigns and after the MSA many more state-funded campaigns publicized the serious health harms of smoking and encouraged smokers to quit (NCI 2008). Over the past decade, a national media campaign from the American Legacy Foundation (Legacy) also broadcast messages about the misleading and deceptive practices of tobacco companies. Another Legacy media campaign emphasized the difficulty of quitting smoking and encouraged smokers to seek help. Media coverage about the deceptive marketing of "light" and "low tar" cigarettes is also relevant. A federal court order in 2006 prohibited the defendant tobacco companies from stating or implying any health benefits of a brand of cigarettes through the use of misleading terms such as "light," "mild," and "low tar." The FDA implemented a ban on these terms in the marketing and sale of cigarettes in June 2010. During the past decade, the public has been exposed to ongoing news coverage and media education that refutes tobacco marketing claims that some cigarettes are less harmful than others.

Against this backdrop it is increasingly unlikely that consumers would identify <u>any</u> cigarettes as offering explicit health benefits. In addition, questions that ask respondents about comparative risks are likely to elicit responses that different types of cigarettes are similarly risky. However, even in a population acutely aware of the harms of smoking, some studies reveal consumer perceptions that some cigarettes are safer than others (Hammond & Parkinson 2009; Hammond et al. 2010). When socially desirable responding is likely, studies that require consumers to choose between two or more products that differ on specific dimensions of interest are more sensitive indicators of consumer beliefs. Such studies typically compare two or more products with one element manipulated, or ask respondents to rank order products along particular dimensions. These kinds of comparative assessments are routinely used in consumer research, including in tobacco company consumer product testing, and in cigarette pack testing studies, such as those conducted by Hammond and colleagues (Hammond & Parkinson 2009; Hammond et al. 2010). To date, no published studies have used these methods to compare consumer perceptions of menthol and non-menthol cigarettes. However, reports from qualitative methods that permit more in-depth and indirect assessments of consumer beliefs about menthol cigarettes are included in this review. Assessment of implicit health benefits are particularly revealing, including aspects of taste and sensory experience, such as cooling, soothing, smoothness, mildness, low nicotine, lower strength, easing uncomfortable physical symptoms, or attributes such naturalness. As indicated earlier, smokers interpret these kinds of attributes to imply reduced harm (Pollay & Dewhirst 2002; Wakefield et al. 2002; DiFranza et al. 2002; Hammond & Parkinson 2009; Paek et al. 2010).

Population-based surveys

Two secondary analyses examined adults' perceptions of the explicit benefits or harms/risks of menthol cigarettes. Davis et al. (2010) examined responses of 4,556 adults to questions about menthol cigarettes from the HealthStyles survey that was mailed to a national consumer panel in 2009. The survey asked respondents "*Do you believe menthol cigarettes, such as Newport, Kool, Marlboro Menthol, Camel Menthol have beneficial health effects?*" Excluding 250 respondents who did not know what menthol cigarettes were or provided no answer, 76.8 percent of respondents (and 81.2 percent of smokers) believed menthol cigarettes had no health benefits, 18.9 percent (14.7

percent of smokers) did not know whether they did or did not, and 4.3 percent (4.2 percent of smokers) thought they did have health benefits. African Americans (9.0 percent), those with up to high school education (8.6 percent) and those with annual incomes less than $25,000 (8.0 percent) were more likely to believe that menthol cigarettes had health benefits. However, there were no differences by age group.

The HealthStyles survey also asked whether "*menthol cigarettes such as Newport, Kool, Marlboro Menthol, Camel Menthol are: more harmful to my health than non-menthol/regular cigarettes; just as harmful to my health as non-menthol/regular cigarettes; less harmful to my health than non-menthol cigarettes or; I don't know*." The 248 respondents who did not know what menthol cigarettes were or gave no answer were excluded. Of the remaining respondents, 45.8 percent perceived menthol to be just as harmful as non-menthol cigarettes to their health, 40.9 percent did not know if menthol cigarettes were more or less harmful, 12.6 percent thought menthol cigarettes were more harmful and 0.6 percent, less harmful. Former smokers were more likely than never smokers to state that menthol cigarettes were more harmful (15.9 percent vs. 10.3 percent), but the comparison for current smokers (14.9 percent) was not significant. African Americans were more likely than whites to state that they did not know whether menthol cigarettes are more or less harmful than non-menthol cigarettes, but no interactions with smoking status were tested. Differences by age group were not reported as being significant. Although the survey achieved a 65 percent response rate, which is acceptable for a mailed questionnaire, the study was limited by the fact that the sampling frame was a pre-existing national panel that may not be representative of the national population. Also, no information was available about respondents' past or current use of menthol cigarettes. Odds ratios that compared beliefs by demographics were unadjusted, so the associations could be confounded.

Around 13 percent responded that menthol cigarettes were more harmful to health, but it was difficult to know if a perception of more harm to health might be due to menthol cigarettes being perceived to be more addictive or harder to quit. The survey did ask these two additional questions, and while again a majority (55 percent) responded that it was equally easy to get hooked on menthol and non-menthol cigarettes, or that they didn't know, 24.2 percent thought menthol cigarettes were more addictive. Similarly, while 82 percent thought both types of cigarettes were equally hard to quit, 12.1 percent thought menthols were harder to quit than non-menthols. However, the study did not explore the relationships between perceived harm and these variables.

Wackowski et al. (2010) examined data from a 2005 telephone survey of New Jersey adults, of whom 17.4 percent were smokers and 40.4 percent of smokers were menthol cigarette smokers (Wackowski et al. 2010). Smokers were asked "*compared to regular cigarettes, how risky do you think the following products are? Somewhat less, about the same, or somewhat more risky?"* Menthol cigarettes were included on a list of eight tobacco products (e.g., cigars, kreteks, bidis and light, herbal and flavored cigarettes). Question order was rotated. Overall, 70.1 percent of respondents reported menthol cigarettes posed the same risk as non-menthol cigarettes, 25.9 percent (and 30.2 percent of menthol smokers) reported that menthol cigarettes posed somewhat more risk, and 4 percent reported that menthol cigarettes posed somewhat less risk. Among menthol smokers specifically, 35.2 percent of African Americans and 46.3 percent of young adults (ages 18 to 24) believed menthol cigarettes posed somewhat more risk than non-menthol cigarettes. Independent of other demographics, young adult smokers were significantly more likely than the referent group of older smokers (age 65 or older) to believe that menthol cigarettes were somewhat more risky than regular cigarettes. Among menthol smokers, 46.3 percent of 18–24 year olds indicated menthol cigarettes were somewhat more risky than regular cigarettes, but the comparable responses for older menthol smokers were not reported.

A limitation of this study was that the response rate was 20.7 percent and the sample was sourced from only one US state. The study contained only one item about explicit health benefits of menthol cigarettes, and the authors pointed out that it is unknown how respondents interpreted the meaning of "somewhat less risky" and "somewhat more risky" than regular cigarettes. The authors speculated that the perceived ease of inhalation permitted by menthol may lead smokers to inhale more deeply and although this is interpreted as a benefit, it may also partly explain why menthols are perceived to be more risky. In addition, as for the Davis et al. (2010) survey, interpretation of the meaning of the response is compromised because an alternative interpretation of "more risky" could be that menthol cigarettes were perceived as being more addictive and/or difficult to quit.

Given the aforementioned contextual factors, it is unsurprising that the vast majority of respondents attributed no explicit health benefits to menthol cigarettes and a small minority thought that menthol cigarettes were different than non-menthol cigarettes in explicit harms to health.

Two studies examined data from the same survey about perceptions of menthol cigarettes among African American smokers. Allen et al. (2010) developed a questionnaire based on focus groups with African Americans. Items were also informed by the Castro (2004) literature review of biological, social, and cultural influences on the use of menthol cigarettes among African Americans and Hispanics. She cited examples of culturally relevant beliefs about the medicinal properties of menthol, including ingesting a menthol product (Vicks VapoRub) to treat congestion and colds. Castro concluded that health-related beliefs about menthol shared by lower-income African Americans and Hispanics are consistent with a view of menthol cigarettes as less toxic and addictive than regular cigarettes. The questionnaire developed and used in the Allen et al. study contained five multi-item scales, two of which assessed medicinal benefits and relative harm. The Medicinal Effects scale included statements that menthols are better than non-menthols for a sore throat, help to loosen up a stuffed up nose, help to cool a fever, and ease asthma problems; the Less Harmful scale included statements that menthol cigarettes contain fewer chemical additives, less nicotine, are less harmful and more natural than non-menthols. In other words, the Less Harmful scale was mostly comprised of items that assessed implicit harm. Another scale measured positive evaluations about the taste, cooling sensation and smell of menthols (Taste/Sensation). The remaining two scales measured the extent to which respondents endorsed beliefs that menthol cigarettes present an African American or stylish image (Image) and beliefs about menthol being frequently smoked by African Americans now and in the past (Tradition).

Allen et al (2010) surveyed 720 smokers in Los Angeles County who were recruited via street intercept methods from regions with high percentages of African Americans and interviewed between late 2006 and early 2007. Respondents were categorized as exclusively menthol smokers (57 percent), exclusively non-menthol smokers (15 percent), or smokers of both cigarette types (28 percent). Scale scores were derived from item responses to a 4-point scale with higher numbers indicating stronger agreement. Analyses compared scale scores for the three groups of smokers, adjusting for age, gender, education, and cigarettes per day. The three groups of smokers were equally likely to endorse the Image and Tradition scales. On the Taste/Sensation scale, menthol-only smokers scored higher than smokers of both types, who scored higher than non-menthol smokers. It was noteworthy that the scale scores for Taste/Sensation were positively correlated with scores for Medicinal Effects and Less Harmful. This finding is consistent with consumer research undertaken by tobacco companies, and with the findings of Hammond & Parkinson (2009), indicating that the concepts of taste, sensory experience and harm are related in the minds of consumers.

Compared to those who smoked exclusively non-menthols, menthol-only smokers and those who smoked both cigarette types had significantly higher scores on the Medicinal Effects and Less Harmful scales. Older participants and those with less education were also more likely to hold these beliefs. Compared to those who smoked exclusively non-menthols, smokers of both cigarette types

had higher scores on the Medicinal Effects but not on the Less Harmful scale. The pattern of results suggests that menthol smokers were more likely than non-menthol smokers to perceive that menthol cigarettes provide medicinal benefits and reduced implicit health harms. Smokers ages 40 and older and less educated smokers were more likely to endorse these beliefs.

Unger and colleagues (2010) undertook a more detailed analysis of these data, including a larger set of covariates, such as perceived discrimination, depressive symptoms, anxiety symptoms, sensation-seeking, stress and reported frequency of exposure to menthol marketing. This ancillary analysis found Taste/Sensation to account for just over half the variance between menthol and non-menthol smoker subgroups. When excluded in order to evaluate the influence of other variables, it was found that compared with non-menthol smokers and adjusting for many covariates, those who smoked any menthol cigarettes were more likely to perceive medicinal benefits than others. Additional subgroup analysis showed that this was particularly the case among males ages 40 and older, although it should be noted that this subgroup analysis had low power to detect effects, with an approximate sample size of only 25 people who were regular smokers in each age/gender subgroup.

Surveys of smokers seeking cessation treatment

Hymowitz et al. (1995) administered a questionnaire to menthol cigarette smokers attending a smoking cessation program in New Jersey. Of 213 menthol smokers, 97 percent indicated menthol cigarettes "taste better", 61 percent thought they were "more soothing to my throat" than non-menthol cigarettes, and 51 percent indicated that "I can inhale menthol cigarettes more easily than regular cigarettes." Although menthol smokers endorsed these implicit health benefits, few of them (8 percent) reported that menthol cigarettes "are better for you than regular non-menthol cigarettes." There were few significant differences between African Americans and whites, and the small sample size limited these subgroup comparisons. Another limitation is that a convenience sample of smokers who are sufficiently motivated to quit to seek formal smoking cessation treatment likely differs from the general population of smokers. Despite the study limitations, it is notable that its findings are consistent with conclusions from reviews of tobacco company internal documents that consumers hold beliefs that menthol cigarettes offer a form of implicit or apparent health protection. This especially applies to menthol's throat-soothing qualities when inhaled in tobacco smoke, and the reduction of sensory barriers to inhaling the smoke. By comparison, few menthol smokers endorsed the statement that menthol cigarettes were explicitly healthier/safer than non-menthols.

Bansal et al. (2004) assessed smokers' beliefs about menthol cigarettes as part of an educational intervention about cigarette products. Of the 982 smokers who agreed to enroll in a cessation trial, 34.2 percent smoked menthol cigarettes and the sample was predominantly non-Hispanic white (72.8 percent). Prior to randomization to different educational conditions, participants rated their agreement with six statements about menthol cigarettes: "give you less tar than regular cigarettes;" "are cleaner than regular cigarettes;" "are safer than regular cigarettes;" "are easier to quit smoking than regular cigarettes;" "are smoother on your throat than regular cigarettes" and "feel easier on your chest than regular cigarettes." Respondents who agreed or disagreed also indicated the strength of their belief (somewhat or strongly). Respondents who were uncertain were assigned a value of 2 on a scale that ranged from 0 to 4. Higher scores reflected greater disagreement with beliefs that menthol cigarettes are less harmful than regular cigarettes. A mean of 3.28 out of 4 (standard deviation was not reported) suggests that on average, smokers enrolled in a cessation trial disagreed that menthol cigarettes were less harmful than regular cigarettes. The high level of internal consistency of the scale suggests that ratings about sensory experience (smoother and easier on the chest) were positively correlated with other items about relative harm. In addition, lower scores were observed for the two items about sensory experience, indicating more agreement with these items than others. In this respect, the pattern of findings was consistent with other studies

(Allen et al. 2010; Hymowitz et al. 1995). However, differences between item responses were not tested and separate scores for menthol and non-menthol smokers were not reported. As noted previously, a convenience sample of smokers seeking cessation treatment likely holds different perceptions of menthol cigarettes than the larger population of smokers.

Focus groups

Richter and her colleagues undertook two studies of health risk perceptions of menthol cigarettes. In 2002, Richter et al. (2006) conducted 16 focus groups in Dallas and Chattanooga with young adult smokers (ages 18–22 years) who had tried or currently used non-traditional tobacco products (NTPs), such as bidis, shisha, and herbal cigarettes. All participants rated light, regular and menthol cigarettes against each other and against each of the NTPs on a six-point scale from 'much safer' to 'much more harmful.' Non-Hispanic whites (the largest participant group), perceived menthol cigarettes as less harmful than regular cigarettes and more harmful than light cigarettes. Among Hispanics, light cigarettes were consistently rated as safer than regular cigarettes, but there was inconsistency in comparative menthol ratings. Among African Americans, light cigarettes were rated as either the same or safer than regular and menthol cigarettes, whereas menthol and regular cigarettes were perceived to pose the same risk. A strength of this study was repeated use of the rating exercise in all groups. A limitation was that results were not presented overall, but rather by race/ethnicity and college/non-college attendance, which limited the stability of estimates. It was noteworthy that the group with the largest sample size (non-Hispanic whites) more clearly rated menthol cigarettes as being in between light and regular cigarettes on the harmfulness scale.

In 2005, Richter et al. (2008) conducted six focus groups with African American menthol smokers aged 45 to 64 years old in Atlanta. Among the main discussion themes was a belief that smoking menthol cigarettes leads to fewer negative health effects. Taste was described as a prime reason for smoking menthol cigarettes, although this appeared to be closely linked to perceptions of harm. Menthol cigarettes were commonly described as being 'refreshing,' 'soothing' or 'smooth,' while non-menthols were 'strong' or 'harsh.' As one participant explained: "*A regular cigarette is too strong. If I smoke that, I mean, I just start coughing because it's too strong. Menthol is lighter*." Some participants described unpleasant reactions to smoking non-menthol cigarettes in comparison with menthol cigarettes. "*I can't smoke non-menthol cigarettes because I wind up with a headache and a dry mouth. It dries my tongue out. And a menthol cigarette doesn't. I can enjoy it, especially after I eat,*" one said. Another person commented: "*It'll hurt your head and hurt your chest if you try to smoke a non-menthol.*" Participants in a group asked to rank brands from most to least dangerous placed full flavor menthol brands in an intermediate position between brands described as 'light' or 'slim,' which were perceived to be least dangerous, and full flavor non-menthol brands, perceived to be most dangerous. Two additional themes that were related to each other were that non-menthol smokers were considered to be hard-core smokers with less interest in quitting, and that switching to non-menthol cigarettes was perceived as a strategy that menthol smokers used to try to quit smoking. Participants' preference for menthol cigarettes were strong and non-menthol cigarettes were viewed as a cessation aid. Some described switching to non-menthols as a strategy to help them quit, whereas others indicated that switching to menthol delayed quitting. "*The reason I started smoking menthol was because the regulars were so strong and instead of me quitting, I was trying to find some means to get around that, so I went to menthol*," one participant said.

Limitations of focus groups are that individuals may be influenced by other group participants, and skilled group moderation is required to ensure that dominant views do not skew responses of other participants. Focus groups are unlikely to be representative of the population from which participants are drawn, but are designed to capture a range of views and permit in-depth discussion of concepts, which requires synthesis using careful qualitative analysis. Conducting focus groups in multiple cities is a strength of the research reported here. In addition, the results from the

comparative ranking task and the qualitative findings are consistent with tobacco industry consumer research on perceptions of menthol cigarettes.

Summary. Taking the tobacco industry's document research and empirical studies into account, the evidence suggests that consumers perceive that menthol cigarettes offer some form of implicit health protection or medicinal benefit that non-menthol cigarettes do not provide. This was reported in all four reviews of industry documents. These reviews also pointed to consumer beliefs about explicit health benefits of menthol cigarettes, reflecting early advertising messages that more explicitly promoted the health benefits of menthol cigarettes (see messaging section). Evidence from focus groups and several surveys also suggested that consumers perceive implicit health benefits of menthol cigarettes (Hymowitz et al. 1995; Richter et al. 2006; Richter et al. 2008; Allen et al. 2010; Unger et al. 2010). Two studies that used multi-item scales (Allen et al. 2010; Bansal et al. 2004) also found positive correlations between beliefs about taste/sensation, medicinal benefits, and relative harm, as was found or suggested in other studies (Pollay & Dewhirst 2002; Wakefield et al. 2002; DiFranza et al. 2002; Hammond & Parkinson 2009).

In studies that addressed both implicit and explicit health benefits, smokers were more likely to endorse the former than the latter (Hymowitz et al. 1995; Bansal et al. 2004). Indeed, few smokers endorsed any statement that menthol cigarettes are explicitly safer or less harmful than non-menthol cigarettes (Bansal et al. 2004; Davis et al. 2010; Hymowitz et al. 1994; Wackowski et al. 2010). In the large population-based surveys, some smokers reported that menthol cigarettes were more harmful/risky than non-menthol cigarettes (Davis et al. 2010; Wackowski et al. 2010), but the meaning of this response is difficult to interpret.

Notably, much of this research focused predominantly or exclusively on African American smokers (Allen et al. 2010; Unger et al. 2010; Richter et al. 2008, Hymowitz et al. 1995), which raises the question of whether these consumers are substantially more likely than others to endorse implicit health benefits of menthol cigarettes. The two survey studies of African Americans (Allen et al. 2010; Unger et al. 2010), together with the focus group study of older African Americans (Richter et al. 2008), and the earlier clinic population survey of Hymowitz et al. (1995) which included a large proportion of African Americans, all found the respondents to hold beliefs about the medicinal benefits of menthol cigarettes and other implicit health benefits pertaining to menthol cigarette strength, constituents, smoothness and ease of inhalation. These studies asked about implicit health benefits in addition to explicit health harms or risks, and employed research methods that entailed the completion of multi-item scales, required respondents to make comparative rather than absolute judgments about products, or used qualitative techniques. The studies that included sample sizes large enough to compare African Americans with other racial/ethnic groups did not use these methods.

EVIDENCE SYNTHESIS

Chapter 5 set out to answer six questions relating to the marketing and consumer perception of menthol cigarettes. The responses to those questions are provided below. These answers assisted TPSAC in addressing the nine overarching questions listed and discussed in Chapter 1 that are the subject of this report. Specifically, these responses address TPSAC's population-based questions: *Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?* TPSAC considered this information, along with the other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

How is menthol marketing different from and similar to non-menthol marketing, in terms of product, place, price, promotion and packaging?

The evidence is sufficient to conclude that menthol cigarettes are marketed in similar ways to non-menthol cigarettes, in that the same general marketing principles are employed.

However, there may be an important difference in practice in relation to retail marketing and pricing. Overall, menthol cigarettes are slightly more expensive than non-menthol cigarettes, although a larger proportion of retail sales for menthol than non-menthol cigarettes are promoted. More menthol smokers than non-menthol smokers take advantage of such promotions and this difference was greater for African American smokers. There was limited information available on pricing and promotions by neighborhood demographics, in relation to tobacco tax increases, and in relation to brands. This precluded a more detailed understanding of the extent to which the tobacco industry and consumers may use price promotions for menthol versus non-menthol brands to undermine the potential benefits of tobacco tax increases and other tobacco control policies on quitting, particularly among key population subgroups. While the prevalence of smoking has declined in the past several years, the proportion of smokers who prefer menthol cigarettes has increased. Thus, the rate of decline in smoking prevalence is slower for menthol than for non-menthol smokers. This phenomenon has coincided with a substantially increased emphasis on tobacco marketing and price promotions at the point of sale. Existing evidence is insufficient to conclude that retail marketing practices may be responsible for recent increases in the proportion of smokers who smoke menthol cigarettes. Research is needed to examine the relationship between the move towards retail-based marketing, especially price promotions, and the increase in the proportion of smokers who smoke menthol cigarettes.

What health reassurance messages were/are used in menthol marketing messages?

The evidence is sufficient to conclude that menthol cigarettes have been and continue to be marketed with a set of associated branding elements and labels that connote health benefits. These originally included claims of explicit medicinal benefits such as soothing a sore throat or clearing a blocked nose, but moved over time towards more implied health benefits, with the use of powerful images of coolness and refreshment, the use of phrases and labels stressing sensory experience such as ‘refreshing’ and ‘smooth,’ and the use of the color green which is associated with nature and healthiness. While contemporary tobacco marketing efforts have been constrained by legislation that restricts advertising in traditional media, the powerful advertising messages used in the past are reinforced and continued by the ongoing use of menthol brand names and menthol marketing messages such as ‘smooth’ and ‘fresh’ that are implicitly linked to health benefits.

What other messages were/are conveyed to potential consumers by menthol marketing messages?

The evidence is sufficient to conclude that other menthol marketing messages feature youthful imagery and themes to appeal to youthful audiences, as well as socially and culturally relevant messages about in-group identity to appeal to different market segments. Different in-group identities are emphasized in marketing for different brand families, so there is no single brand image that signifies a menthol smoker.

Who are the target populations for menthol marketing? Is there evidence to show that youth, women, and specific racial/ethnic groups were targeted?

Identification of primary target groups for marketing is basic marketing practice. NCI's Monograph 19 provides abundant evidence of targeting of youth, young adults, racial/ethnic groups, women and other population subgroups in cigarette marketing (NCI 2008).

Evidence presented in this chapter and Chapters 4 and 6 indicates that menthol use is higher among youth and young adult smokers, compared with older adult smokers. There is sufficient evidence to conclude that menthol cigarettes are marketed disproportionately to younger people. There is evidence from tobacco industry documents that the tobacco industry designed menthol cigarettes with lower menthol yields, with an awareness that, at these lower menthol levels, the sensory effects of menthol reduce the harshness of cigarettes for new smokers. In addition to messages that implied health reassurance, menthol cigarette marketing has promoted a more youthful brand image than for non-menthol cigarettes, and has emphasized the role of menthol cigarettes in peer group acceptance.

Chapter 4 demonstrates that menthol use is higher among female than male smokers. While there is evidence from industry document reviews and empirical studies that women have been targets of tailored menthol marketing efforts, there is insufficient evidence that menthol marketing was targeted proportionately more to women per se than non-menthol marketing.

The evidence is sufficient to conclude that menthol cigarettes are disproportionately marketed per capita to African Americans. African Americans have been the subjects of specifically tailored menthol marketing strategies and messages. Billboard advertising and point-of-sale advertising for menthol cigarettes has been over-represented in neighborhoods with a high percentage of African Americans and in magazines with high African American readership, and more so than non-menthol cigarette advertising. Consistent with these targeted marketing efforts, menthol cigarettes are disproportionately smoked by African American smokers. The evidence is sufficient to conclude that it is at least as likely as not that menthol cigarettes have also been disproportionately marketed to Hispanics. Menthol use is higher in Hispanic smokers than in non-Hispanic white smokers. Although Asian Americans, Hawaiian/Pacific Islanders and females have been the subjects of tailored menthol marketing messages and menthol use is higher in all these population subgroups of smokers, there is insufficient evidence to conclude that they have been proportionately more targeted by menthol than non-menthol marketing.

Does menthol marketing influence perceived taste and/or sensory experience of menthol cigarettes?

The evidence is sufficient to conclude that menthol branding and messaging influences the perceived sensory experience of menthol cigarettes, contributing to consumer's overall subjective evaluation and liking of the product.

Do consumers perceive menthol cigarettes as safer or less harmful than non-menthol cigarettes?

The evidence is sufficient to conclude that, consistent with marketing themes, consumers hold beliefs about the medicinal benefits of menthol and beliefs about other implicit health benefits, and that this is especially the case among African Americans. However, in the context of widespread public education about the health harms of tobacco use, it is uncommon to state an explicit belief that menthol cigarettes are safer or less harmful than non-menthol cigarettes.

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CHAPTER 6: EFFECTS OF MENTHOL CIGARETTES ON INITIATION, ADDICTION AND CESSATION

INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "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." This chapter is concerned with the effects of menthol cigarettes on smoking initiation, addiction and cessation. Put another way, does smoking menthol cigarettes—when compared to non-menthol cigarettes—make it more or less likely that someone will start smoking, become addicted, or quit?

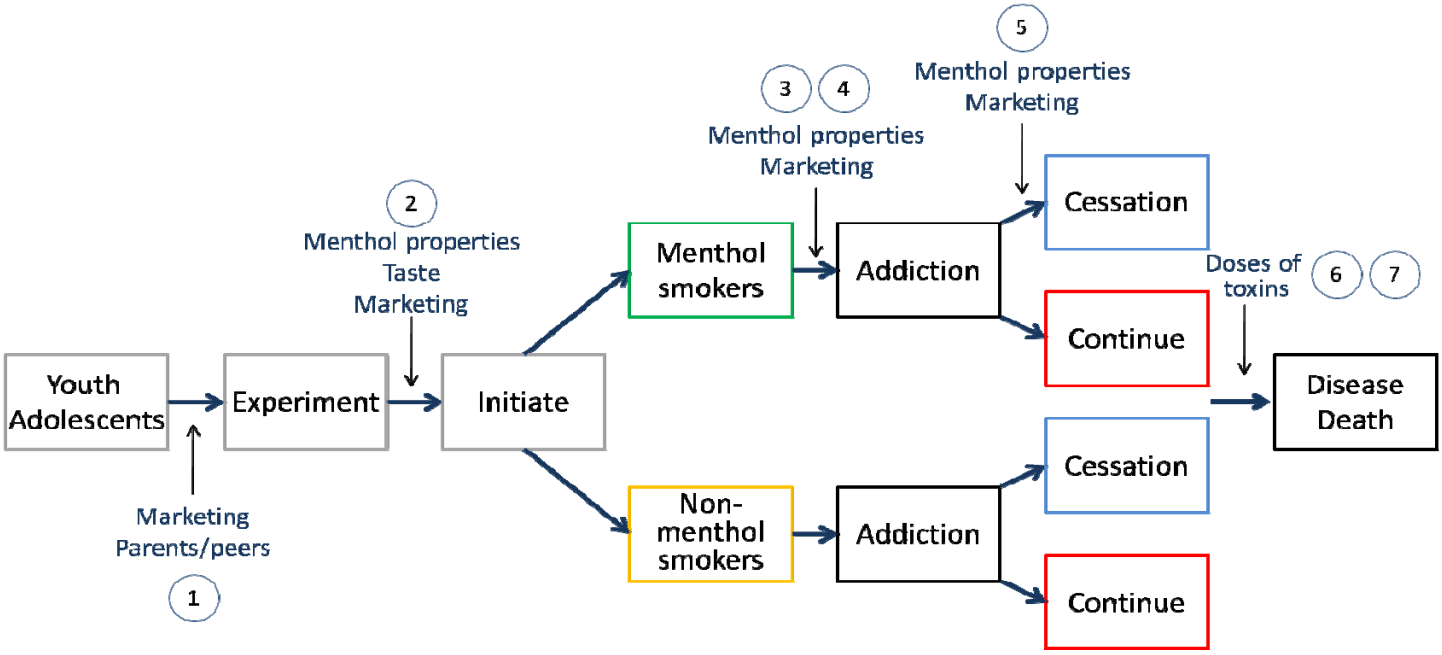
This chapter builds on information presented in previous chapters about the influence of menthol cigarette marketing (Chapter 5) and the physiological effects of menthol cigarette smoking, including the cooling sensation that menthol imparts and the ability of menthol to counter the harshness of nicotine (Chapter 3). Chapter 4 explored the broad patterns and trends of menthol cigarette use by age, race, gender and income. In order for TPSAC to execute its charge, it also addresses the impact of menthol cigarettes on smoking initiation, addiction and cessation.

The first chapter of this report presented nine questions relevant to TPSAC's consideration of the public health impact of menthol cigarettes; seven are related to individual cigarette smokers and two are related to the population effects of availability of menthol cigarettes. The information and analysis provided in this chapter are relevant to five of the seven questions that relate to individual cigarette smokers. They are:

- Does availability of menthol cigarettes increase the likelihood of experimentation?
- Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?
- Does inclusion of menthol in cigarette increase the likelihood of the smoker becoming addicted?
- Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?
- Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?

In accordance with the public health model presented in Chapter 1 (see Figure 1, below), this chapter is divided into three sections: (1) experimentation and initiation, (2) addiction, and (3) cessation. As indicated in Figure 1, several factors may have a role in each stage within this model. The marketing of menthol cigarettes and their availability from peers or family members may influence experimentation with menthol cigarettes. Experimentation—and the continued influences of peers and marketing, coupled with the sensory effects of menthol cigarette smoking—may lead to smoking initiation. Nicotine pharmacokinetics, the sensory properties of menthol cigarettes (e.g., a cooling sensation) and beliefs transmitted by marketing messages or social groups about menthol cigarettes (e.g., relative safety), may promote regular smoking and eventually addiction. The same biological, social and commercial factors that lead to initiation and addiction may also affect the increased or decreased likelihood of smoking cessation for menthol cigarette smokers compared to non-menthol cigarette smokers.

Figure 1. Model of Smoking and Health: From Experimentation to Disease



METHODS

Chapter 2 provided the general framework for this report and the TPSAC's approach to gathering, reviewing and weighing the evidence. Using this framework, Chapter 6 draws on sources that provide information about menthol cigarette smoking experimentation, initiation, addiction and cessation, or provide necessary background information. Four sources of documents were examined: (a) peer-reviewed articles obtained from the search conducted by the FDA and from additional studies identified from these articles; (b) white papers and secondary analysis of existing datasets either written or commissioned by the FDA; (c) tobacco company presentations and written submissions; and (d) public comments that provided relevant evidence. Much of this evidence is summarized in Tables 1-7.

EXPERIMENTATION AND INITIATION

The experimentation and initiation section covers five topics: (1) the rates of menthol vs. non-menthol cigarette use among youth and young adults compared to older adults; (2) the rates of menthol vs. non-menthol cigarette use in recent initiators and established smokers; (3) the age of cigarette initiation of menthol vs. non-menthol cigarette smokers; (4) switching between and among menthol and non-menthol cigarette smokers; and (5) the characteristics of menthol cigarettes that may enhance the abuse liability or appeal of the product (sensory experience, reduction of harshness, cooling sensation, beliefs about relative safety). This chapter draws on population-level information in Chapter 4 in addition to multiple datasets, surveys and analyses that provide in-depth information about

experimentation and initiation with menthol cigarettes. This chapter also draws on information about the sensory experience of smoking menthol cigarettes presented in Chapter 3.

Patterns of smoking menthol cigarettes in adolescents and young adult smokers

Age gradient of proportion of menthol cigarette use across the age spectrum

Table 1 provides the key studies related to the age gradient of menthol cigarette smoking. Most smokers start smoking during adolescence before the legal age for purchasing cigarettes or during their young adult years (Institute of Medicine 1994; Substance Abuse and Mental Health Services Administration 2009; U. S. Department of Health and Human Services 1994). Thus, examining patterns of menthol cigarette smoking among adolescents and young adults is informative to understanding the role of menthol cigarettes in initiation.

In data collected in 2008, almost half of adolescent smokers between 12–17 years old (47.7 percent) reported past 30-day use of menthol cigarettes and 40.8 percent of young adults aged 18–25 years smoked menthol cigarettes (http://www.oas.samhsa.gov/2k9/134/134MentholCigarette.htm; Substance Abuse and Mental Health Services Administration, 2009). The rate of initiation with menthol cigarettes compared to non-menthol cigarettes is not well characterized. However, a pattern of greater menthol smoking has been observed among youth and younger adults compared to older adult smokers in most population of smokers (Hymowitz et al. 1995; Substance Abuse and Mental Health Services Administration 2009; Sidney, Tekawa, & Friedman 1989; Fernander et al. 2010; see Chapter 4). For example, based on analysis of pooled cross-sectional 2004-2008 NSDUH data, the proportion of menthol smokers among adolescent smokers ages 12–17 (44.7 percent) was higher than among young adult smokers ages 18–25 (36.1 percent) or adult smokers 26 years old or older (30.2 percent) (Rock, Davis, Thorne, Asman, & Caraballo 2010). When considered by age and racial/ethnic group, the proportion of menthol smokers was higher in adolescent smokers 12–17 years old compared to smokers 18–25 years or 26 years and older among whites (41.0 percent vs. 28.8 percent vs. 21.9 percent, respectively), Hispanics (47.0 percent vs. 38.2 percent vs. 29.5 percent), Asians (51.5 percent vs. 35.8 percent vs. 28.6 percent) and American Indian/Alaska Natives (34.7 percent vs. 27.4 percent vs. 23.0 percent). By contrast in the African American population, 71.9 percent of adolescent smokers smoke menthol cigarettes compared to 82.2 percent of adult menthol smokers.

Giovino (2010, unpublished submission to FDA) conducted a fine grain analysis of NSDUH data to determine if an age gradient existed when smokers were divided into two categories: those who smoked fewer than 10 cigarettes a month (less established smoking) and those who smoked 10 or more cigarettes a month (more established smoking). He observed a statistically significant age gradient among those menthol smokers aged 12–34, with the highest proportion observed among the 12–17 year olds for both categories of smokers.

As discussed in detail in Chapter 4, TPSAC received public submissions that criticized and clarified findings in the NSDUH survey data. TPSAC reviewed these submissions and concludes that the issues raised in Curtin et al. (2010c, R.J. Reynolds Tobacco Co. submission to the FDA, June 2010) are addressed in Giovino et al. (2010, unpublished submission) and do not affect TPSAC's interpretation of analyses of the NSDUH data.

Age gradient of proportion of menthol cigarette use within youth

Studies have also been conducted examining age gradients within adolescents. According to an analyses of the 2004, 2006 and 2009 National Youth Tobacco Survey (NYTS), a slightly higher portion of current

middle school smokers than current high school smokers used menthol cigarettes within the past 30 days (49.4 percent vs. 44.9 percent; Caraballo & Asman 2010). These results are concordant with the Appleyard et al. study (2001) using the 2000 NYTS and the study of Hersey et al. (2006), using the 2000 and 2002 NYTS among whites and Hispanics, but not among Blacks/African Americans (Appleyard, et al., 2001; Hersey et al., 2006), and among Asian and Native Hawaiians/ Pacific Islanders (Appleyard, et al., 2001). Giovino (2010, unpublished submission), analyzing the 2003 National Youth Smoking Cessation Survey, observed that menthol cigarette use was highest among smokers ages 12–15 years (53.5 percent), followed by ages 16–17 years (47.0 percent), ages 18–21 years (40.5 percent) and ages 22–25 years (34.6 percent). A statistically significant age gradient was observed overall and within males, females and whites. In an analysis of the 2006 NYTS, Curtin et al. (2010b) found a statistically significant higher percentage for "current smokers aged 9–13 years (59.3 percent) and lower percentage for current smokers aged 17–21 years (38.3 percent) reporting menthol vs. non-menthol cigarette smoking." The smoking rate among 14–16 year olds was 45.8 percent.

In an analysis of 2004–2008 pooled NSDUH data, (February 10, 2011 presentation, *Comparative Rates of Initiation of Menthol and Non-menthol Cigarette*s), Hersey observed that younger adolescent smokers were more likely to smoke menthol cigarettes than older adolescent smokers. The percentages of menthol smokers in each gradient, with confidence intervals, were: 12–13 years old, 48.6 percent (42.4, 54.8); 14–15 years old, 46.3 percent (43.6, 49.0); 16–17 years old, 43.9 percent (42.1, 45.6); 18–25 years old, 36.3 percent (35.5, 37.1). Age gradients were observed regardless of whether the groups analyzed were all current smokers or smokers who identified their menthol or non-menthol status. Similar age gradients were observed among whites (12–14 years old, 42.7 percent [39.0, 46.3]; 15–17 years old, 38.1 percent [36.4, 39.8]) and Hispanics (12–14 years old, 47.1 percent [37.3, 57.0]; 15–17 years old, 42.2 percent [37.5, 46.9]). The age gradients were reversed among African American adolescents (12–14 years old, 50.9 percent [40.8, 61.0]; 15–17 years old, 70.4 percent [65.3, 75.4]) and other racial/ethnic groups (12–14 years old, 37.2 percent [24.7, 49.7]; 15–17 years old, 46.4 percent [39.9, 53.0].

Brand preference among youth: age gradient and trends

The most popular menthol brand smoked by youth is Newport, which is manufactured by Lorillard. Along with the non-menthol brands Marlboro and Camel, Newport ranks among the top three brands purchased by adolescents. These three brands are used by 81.3 percent of smokers aged 12–17 years old and 82.4 percent of smokers aged 18–25 years old (SAMSHA 2005, see Caraballo & Asman 2010) . Internal tobacco documents show that as early as 1976, Lorillard had noted that Newport had a strong appeal among young or new smokers (Klausner, 2011 in press, page 16).

The findings from the product preference studies are congruent with the age gradients found in the proportion of menthol cigarette users among adolescent smokers. In the 1993 Teenage Attitudes and Practice Survey (TAPS), 70 percent of current smokers reported that they usually bought their own cigarettes and younger smokers (aged 12–15 years) were more likely than older smokers (aged 16–18) to purchase Newport cigarettes (19.4 percent vs. 10.6 percent) and less likely to buy Marlboro cigarettes (49.5 percent vs. 63.1 percent, Barker 1994). Similarly, the 1999 Monitoring the Future Survey found fewer adolescents in higher grades compared to lower grades reporting preference for Newport cigarettes (eighth grade, 22.5 percent; tenth grade, 17.7 percent; twelfth grade, 13.3 percent) (Johnston, O'Malley, Backhan, & Schulenberg, 1999).

Giovino et al. (2004), in an analysis of 2000 NSDUH data by racial/ethnic group, found the age gradient was dependent on the brand of menthol cigarettes. Among African Americans, more than three-fourths of adolescent smokers (79.2 percent, ages 12–17) and young adult smokers (76.7 percent, ages 18–25

years) but less than one-third of smokers age 26 and older (31.5 percent) smoked Newport. African American smokers age 26 and older smoked Kool (14.1 percent) and Salem (6.9 percent) more than African American smokers ages 12–17 (2.1 percent and 1.6 percent for Kool and Salem, respectively) and African American smokers ages 18–25 (4.6 percent and 1.6 percent for Kool and Salem, respectively). Among white smokers ages 12–17, nearly one of five (18 percent) smoked Newport but less than one of 10 older smokers smoked Newport (9.3 percent of 18–25 year olds and 2.9 percent of 26 years and older). White smokers ages 26 and older, smoked Kool (1.8 percent) and Salem (3.0 percent) more than white adolescent smokers ages 12–17 (0.7 percent and 0.3 percent for Kool and Salem, respectively). Among Hispanics, nearly one of three adolescent smokers age 12–17 (31.4 percent), one of six young adult smokers ages 18–25 (16.7 percent) and less than one of fourteen adult smokers ages 26 years and older (7.1 percent) smoked Newport cigarettes. The age gradient for Kool (0.3 percent vs. 0.9 percent vs.3.6 percent among adolescent, young adult and older adult smokers, respectively) and Salem (no data vs. 0.2 percent vs. 3.4 percent for adolescent, young adult and older adult smokers, respectively) were the inverse of the gradient for Newport.

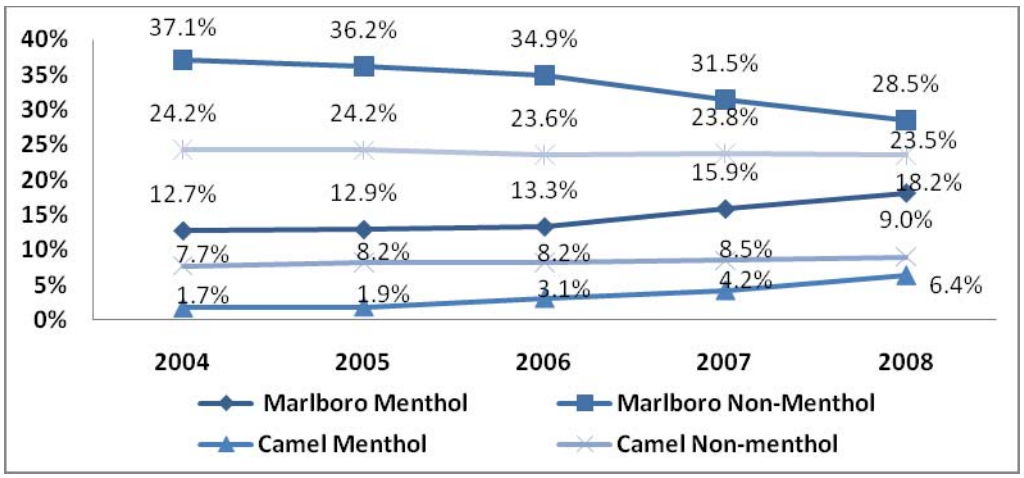
Hersey et al. detected an age gradient in an analysis of novice smokers based on 2000 to 2008 NSDUH survey data. The analysis compared the percentage of novice smokers by age, brand and menthol status (Presentation to TPSAC February 11 2011, *Comparative Rates of Initiation for Menthol and Non-Menthol Cigarettes*). Novice smokers were defined as those who smoked fewer than 100 cigarettes in their lifetime. The researchers found that Marlboro menthol smokers ages 12–17 had a higher percentage of novice smokers than Marlboro menthol smokers ages 18–25 (51.7 percent [CI: 48.0, 55.5] vs. 48.3 percent [CI: 44.5, 52.0], respectively). The picture was reversed for non-menthol Marlboro, with a lower percentage of novices among Marlboro smokers ages 12–17 than among ages 18–25 (38.1 percent [CI: 35.5, 40.8] vs. 61.9 percent [59.2, 64.5], respectively). As with Marlboro menthol, there was a higher percentage of novices among Camel Menthol smokers ages 12–17 than ages 18–25 (62.1 percent [CI: 55,4, 68.9] vs. 37.9 percent [CI: 31.1, 44.6], respectively.) Camel non-menthol smokers followed the same pattern as Marlboro non-menthol smokers, with a lower percentage of novices among Camel smokers ages 12–17 than ages 18–25 (40.3 percent [CI: 35.2, 45.4] vs. 59.7 percent [CI: 34.6, 64.8], respectively). Newport did not follow the same pattern as the two other menthol brands. Newport smokers ages 12–17 had a lower percentage of novice smokers than Newport smokers ages 18–25 (46.8 percent [CI: 44.2, 49.3] vs. 53.2 percent [CI: 50.7, 55.8], respectively).

Studies suggest an increasing trend in menthol use among youth both historically and in recent years, depending on the menthol brand (see Table 2 for findings of studies on trends in menthol smoking among youth). TAPS showed a substantial change in brand preferences among the adolescents from 1989 to 1993, with a 55 percent increase in the purchasing of Newport cigarettes (4.5 percentage points) in spite of the unchanged market share for Newport and a decrease in Newport advertising expenditures to $35 million from $49 million during this time (Barker 1994). Similarly, Kaufman et al. (2004), analyzing data from three nationally representative cross-sectional surveys of adolescents (1996 National Survey of Tobacco Price Sensitivity, Behavior, and Attitudes Among Teenagers and Young Adults; and the 1989 and 1993 TAPS), found that percentages of white and Hispanic adolescents who usually bought Newport doubled between 1989 and 1996. The percentage of white adolescent Newport buyers grew to 10.4 percent from 5.3 percent and the percentage of Hispanic adolescents who usually bought Newport increased to 25.9 percent from 12.8 percent, with dramatic increases among those ages 12–14 (from 4.8 percent to 19.2 percent). Increases in Newport purchases were observed among both males and females. More recent data show that the percent of past month Newport (one of the top selling brands among youth) smokers among students in grades 8, 10 and 12 has remained stable from 1998 to 2008 (see Caraballo & Asman, 2010, FDA white paper), although a decreasing trend has

been observed with Marlboro (another top selling brand among youth) cigarettes (see Figures 3–5 in paper).

Similarly, Hersey et al.'s analysis of current smokers ages 12–17 found that the percentage that smoked Newport was flat between 2000 and 2008 (23.4 percent and 23.5 percent, respectively). However, the researchers found the percentage that smoked Marlboro menthol increased to 18.2 percent from 12.7 percent and the percentage that smoked Camel Menthol increased to 6.4 percent from 1.7 percent. On the other hand, the percentage of adolescent smokers who smoked non-menthol Marlboro cigarettes decreased to 28.5 percent from 37.1 percent (presentation to TPSAC February 11 2011; see Figure 2).

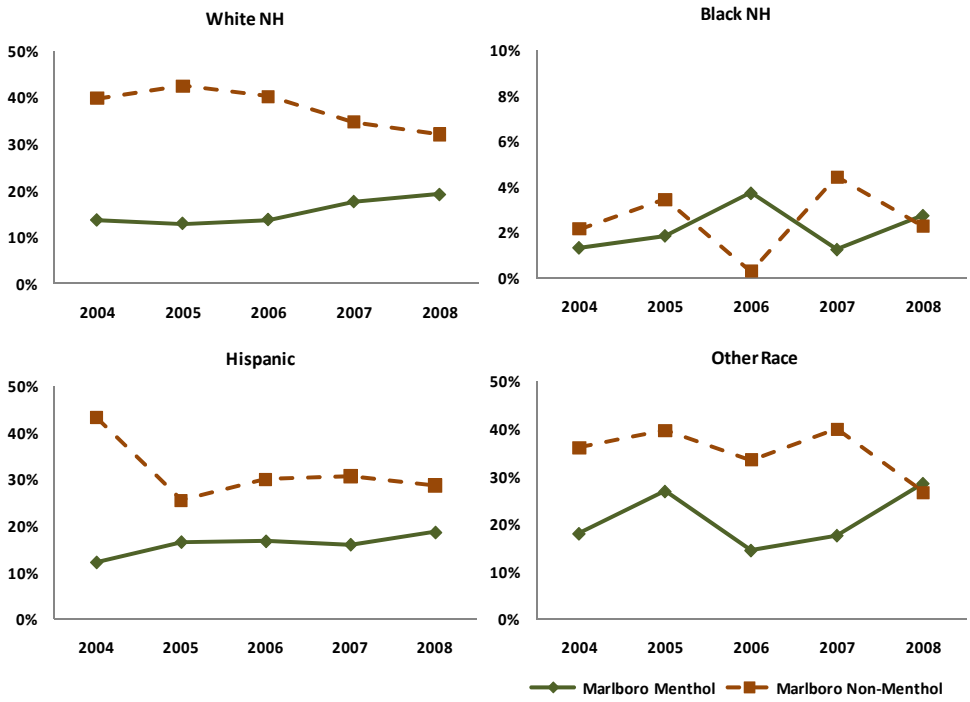
Figure 2. Trends in the Percentage of Brand Use Among 12–17 Year-Old Current Smokers in the National Household Survey of Drug Use and Health (NSDUH): 2004–2008



Note: This figure shows percentage of current smokers aged 12 – 17 who smokeda particular brand and type of cigarettes. Data were analyzed by RTI from the National Household Survey on Drug Use and Health (NSDUH). The number of current smokers aged 12-17 in this analysis by year was 2004: 2,225; 2005: 2,221; 2006: 1,996; 2007: 1,907; and 2008: 1,759. Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008

Hersey et al. observed an increase in Marlboro menthol use and a decrease in non-menthol Marlboro use among whites, Hispanics and the other race category, but not among African Americans ages 12–17 (Presentation to TPSAC February 11 2011, see Figure 3).

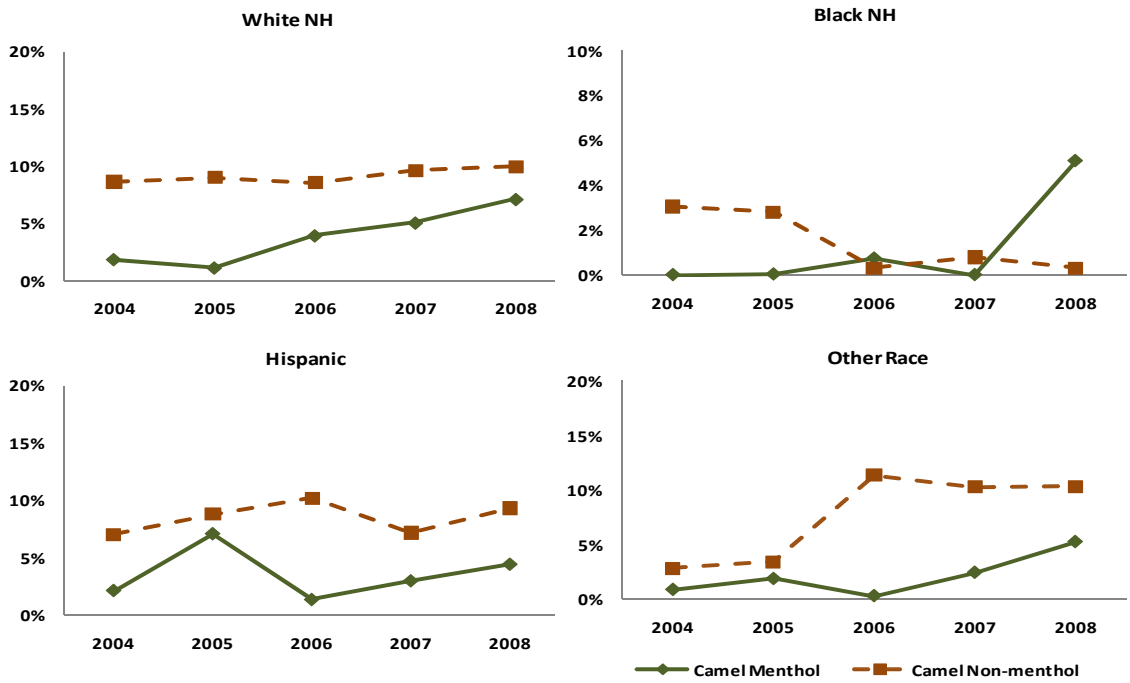
Figure 3. Percent of Smokers, Ages 12–17, Smoking Menthol vs. Non-Menthol Marlboro from 2004 to 2008 by Race/Ethnicity



Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008

For Camel Menthol, increases were seen for all racial/ethnic groups, whereas non-menthol Camel use decreased among African Americans, did not change among whites and Hispanics, and increased among smokers in the other race category (see Figure 4).

Figure 4. Percent of Smokers Ages 12–17 Smoking Camel Menthol and Camel from 2004 to 2008 by Race/Ethnicity



Source: RTI analysis of the National Survey on Drug Use and Health (NSDUH) 2004 -- 2008

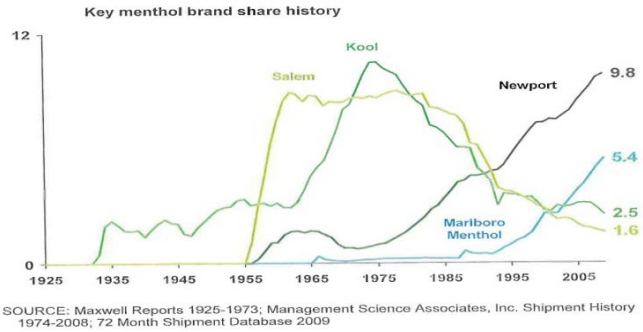
The data were also examined by age and level of experience with smoking, as assessed by those who had smoked less than 100 cigarettes (novice smokers) and those who had smoked 100 cigarettes or more (experienced smokers). The percentage of Marlboro menthol smokers increased among novice and experienced smokers ages 12–17 (+6.1 percentage points and +4.3 percentage points, respectively) and among novice and experienced smokers ages 18–25 year olds (+5.6 percentage points and +3.3 percentage points). Greater increases were observed in the youngest group.

Altria Client Services provided information intended to counter the hypothesis that the availability of menthol cigarettes increases cigarette initiation. In a June 30, 2010 submission (Page 100), Altria said the rate of cigarette purchases among underage adolescents had decreased dramatically since 1995. According to the Youth Risk Behavior Survey, in 1995, 54.5 percent either purchased (38.7 percent) or had someone else purchase cigarettes (15.8 percent) whereas in 2009, 42.1 percent who either purchased (14.0 percent) or had someone else purchase cigarettes (28.1 percent). This document also refers to studies indicating that most adolescents obtain their cigarettes from peers and potentially family members, rather than purchasing the cigarettes themselves (articles cited include: Croghan, Aveyard, Griffin, & Cheng 2003; Emery, Gilpin, White, & Pierce 1999; Forster, Chen, Blaine, Perry, & Toomey 2003; Harrison, Fulkerson, & Park 2000; Ma, Shive, Legos, & Tan 2003; Substance Abuse and Mental Health Services Administration 2007; S. S. Williams & Mulhall 2005). Concordant with these findings, Allen and Unger (2007) examined factors associated with menthol and non-menthol cigarette use among a convenience sample of 432 adult African American smokers in lower income neighborhoods in Los Angeles in 2001. After controlling for age and employment, significant correlates

of menthol use included parents' menthol cigarette smoking (among females) and among both men and women, the belief that most African American smokers smoke menthol, suggesting that social and cultural norms contribute to menthol cigarette smoking. As noted in Chapter 5, "Menthol marketing…uses socially and culturally relevant messages about in-group identity to appeal to different market segments." This finding would suggest that marketing messages play an important role in the availability and uptake of menthol cigarettes among certain social networks.

A submission by Altria (June 30, 2010, page 30) showed a significant increase in the market share of Marlboro menthol cigarettes from 1975 to 2005 (5.4 percent share of US market in 2005, see Figure 5) as well as Newport cigarettes (9.8 percent of market share in 2005). It was noted that this increase in market share could not be explained by any change in levels of menthol yield in cigarettes (Lorillard Tobacco Company, submission, June 30, 2010 for Newport Full Flavor, Lights and Mavericks). Although the menthol content in cigarettes has increased, the yield has stayed the same through increased ventilation of cigarettes.

Figure 5. Trends in Market Share of Menthol Cigarettes

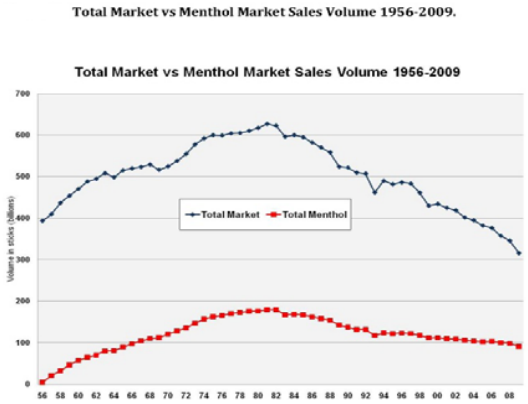


In order to examine the association between market share and youth smoking rates, the June 30, 2010 submission from Lorillard correlated menthol market share with youth smoking rates by state (2009 data of youth smoking rates obtained from Campaign for Tobacco Free Kids, Key State-Specific Tobacco-Data and Rankings). The data show an inverse association of menthol market share with youth smoking rates (see page 49 and 50, Figures 13 and 14). This analysis did not explore potential ecological confounding by such factors as race.

To further support the lack of relationship between youth smoking and the availability of menthol cigarettes, the June 30, 2010 document submitted by Altria points to the significant declines in under-age smoking since peak levels in the late 1990s. However, by contrast, Giovino (2010 unpublished submission) showed that the rate of decrease is less among menthol cigarette smokers compared to non-menthol cigarette smokers. Among all 12–17 year olds, 5.3 percent of adolescents smoked mentholated cigarettes in 2004 and 4.6 percent in 2008, whereas 6.0 percent smoked non-mentholated cigarettes in 2004 compared to 3.9 percent in 2008. The slopes of the regression lines were -0.14 for menthol smoking and -0.53 for non-menthol (p=0.0028). Among all young adults (18–25 year olds), no change in the rate of menthol use has been observed from 2004 to 2009 (14.0 percent vs. 14.5 percent) compared to a decrease in non-menthol use (25.7 percent vs. 20.4 percent). The slopes of the regression lines were 0.17 for menthol smoking and -1.49 for non-menthol (p=0.002). This finding

follows the market share pattern observed for menthol vs. non-menthol cigarettes (see Figure 6, [Figure 9 from Lorillard June 2010 submission]). Furthermore, while the rate of smoking has been declining among adolescents (although the most recent Monitoring the Future report shows that smoking rates have stopped declining, with a slight increase in eighth and tenth graders from 2009 to 2010, www.monitoringthefuture.org), the proportion of adolescent cigarette smokers who report using menthol cigarettes increased significantly from 2004 to 2008 (Rock, et al. 2010), as noted in Chapter 4. Specifically, Rock et al. (2010) noted that the 2004 to 2008 NSDUH data showed that menthol cigarette use increased significantly among white smokers aged 12–17 (from 40.3 percent in 2004 to 46.0 percent in 2008, $p < 0.01$) and among menthol smokers aged 18–25 years old for both Hispanics (from 33.9 percent in 2004 to 42.4 percent in 2008) and in whites (from 26.7 percent to 32.5 percent, $p < 0.01$).

Figure 6. Total Market Vs. Menthol Cigarette Sales Volume 1956–2009



Finally, the suggestion has been made that menthol cigarettes are not likely to contribute to the initiation of smoking because African American youth have a higher proportion of menthol smokers compared to whites, yet they experience a lower rate of smoking and a later age of onset compared to whites (presentation by Hunter, July 15–16, Altria). Hunter did not address other factors such as the role of cultural norms and ethnicity and race, which need to be taken into consideration. Menthol cigarettes may still facilitate initiation of smoking in the African American culture even if they experience different patterns of initiation than whites.

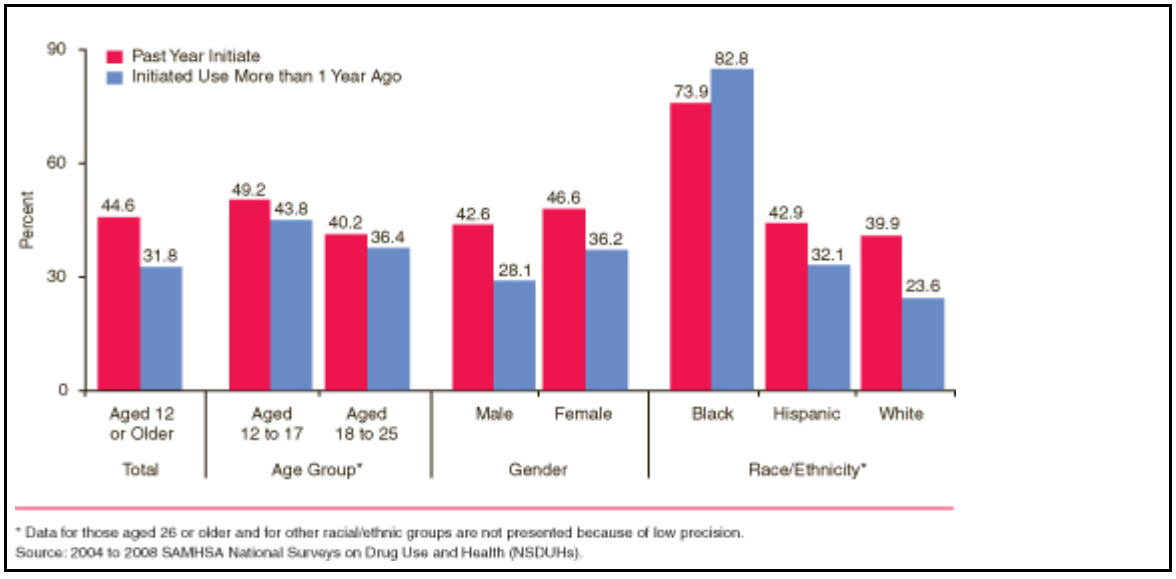
Summary: The evidence strongly suggests a higher proportion of menthol cigarette use among adolescent smokers compared to adult smokers, except among African Americans. This finding is concordant with the trend and prevalence data presented in Chapter 4. The discrepant results observed in some studies using national surveys, particularly in the analysis presented by Curtin et al. (2010a) (see Chapter 4), may reflect the small subject sample (e.g., NHANES had only 20 menthol smokers in the 12–17 year old category) or subjects less than 18 years and older were not interviewed (e.g., NHIS). The results also show that a higher proportion of younger adolescent smokers tend to smoke and prefer menthol cigarettes compared to older adolescent smokers. The data show that while adolescent smoking has been declining among menthol and non-menthol smokers, the rate of decline is greater among non-menthol smokers and the proportion of adolescent smokers smoking menthol cigarettes, particularly Camel and Marlboro menthol cigarettes, has been increasing among both experimenting smokers (<100 cigarettes in a lifetime) and more established smokers (smoking 100 or more cigarettes in a lifetime). It is unclear whether a greater proportion of younger adolescents initiate and experiment with cigarette smoking with menthol cigarettes compared with older adolescents.

Pattern of menthol smoking in recent smokers versus established smokers

Two peer-reviewed articles, two white papers and three public or tobacco industry comments were identified and reviewed by TPSAC. Table 3 shows the rates of menthol cigarette smoking among novice vs. established smokers.

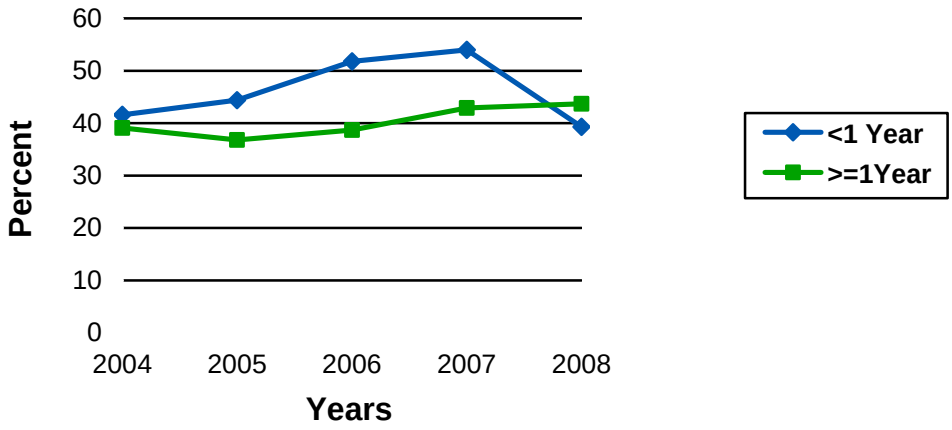
Peer-reviewed studies of national survey data show that recent adolescent smokers are more likely to smoke menthol cigarettes than more established adolescent smokers (Hersey et al. 2006; Substance Abuse and Mental Health Services Administration 2009), although the trend was reversed in 2008 among smokers aged 12–21 (Rising & Wasson-Blader 2010). Hersey et al. (2006) analyzed data from the 2002 NYTS that examined middle and high school students who smoked one or more times in the past 30 days and who described the brand and/or the menthol status of the cigarettes they usually smoked. A significantly higher percent of menthol smokers was found among middle school students who had been smoking for less that 1 year compared with middle school students who had been smoking for more than 1 year (62.4 percent vs. 53.3 percent, $p < 0.002$). This same pattern was observed for high school students, but the difference was not statistically significant (45.9 percent vs. 41.9 percent, respectively). In an analysis of the 2004 to 2009 NSDUH data, the proportion who smoked menthol cigarettes compared to non-menthol cigarettes among those who had been smoking less than 1 year was higher among smokers aged 12–17 years (49.2 percent vs. 43.3 percent) and among smokers aged 18–25 years (40.2 percent vs. 36.4 percent) as well as among whites (39.9 percent vs. 23.0 percent), Hispanics (42.9 percent vs. 32.1 percent), but not among African Americans, although no statistical analysis was provided (See Figure 7, NSDUH Report Menthol Cigarettes,2009).

Figure 7. Past-Month Menthol Cigarette Use Among Past-Month Cigarette Smokers Ages 12 or Older, by Recency of Cigarette Initiation and Demographic Characteristics: 2004 to 2008



In the white paper submitted by Rising and Wasson-Blader (2010), unpublished data on the use of menthol cigarettes by young smokers (aged 12–21 years) from the 2004 to 2008 NSDUH was described that showed a higher percent of menthol use among smokers who smoked less than one year compared to smokers who smoked for more than one year, but this pattern was reversed in 2008 (see Figure 8).

Figure 8. Menthol Cigarette Use by New Smokers Ages 12–21

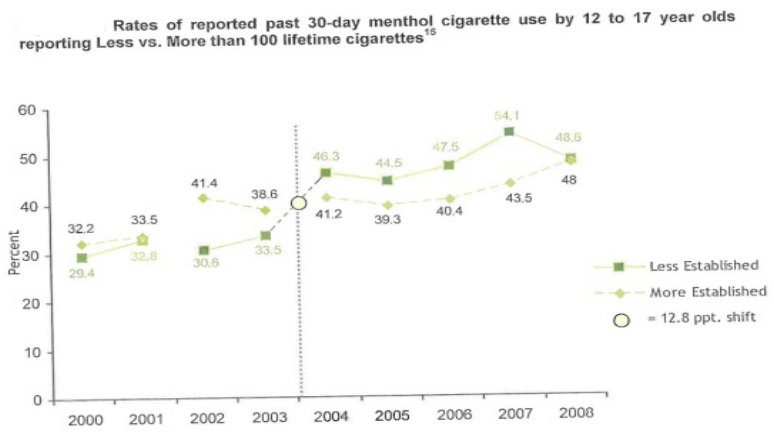


National Survey on Drug Use & Health
Substance Abuse and Mental Health Services Administration

In the submission dated June 30, 2010 (page 110), Altria raised the issue that the findings from the 2004 to 2008 NSDUH might reflect how the question was phrased. It pointed out that prior to 2004, the question was phrased as: *During the past 30 days, did you smoke (insert brand name if identified) menthol or regular cigarettes* ***most often***. After 2003, the question was phrased: *Were the (insert brand name if identified) cigarettes smoked during the past 30 days menthol* (which thereby assessed any use of menthol cigarette smoking). Altria contended that few differences were observed in the percent of menthol smokers among current initiates (current smokers who had indicated that they had smoked for the first time in the past year) vs. prior initiates (current smokers who said that they initiated smoking in prior years) prior to 2004, but after the change in phrasing, higher rates of recent smokers were observed to smoke menthol compared to more established smokers. TPSAC found it difficult to attribute the differences in the data after 2003 to changes in the survey question. Even before the change, menthol smokers were beginning to account for a larger percentage of recent smokers. However, Altria (June 2010) pointed out that the jump in percentage was more than expected after the change in how the question was framed (see Figure 6.6, page 109). On the other hand, as pointed out by Giovino (2010, unpublished submission), Altria failed to note that the survey after 2003 included a question prior to the menthol cigarette inquiry which asked for the brand ***most often used*** and then an inquiry was made as to whether this brand of cigarettes (most often) smoked during the past 30 days was menthol. Relatively few smokers do not answer the question about the cigarettes most often smoked. For example, in 2008, only 4 percent of the sample responded to the question of whether they smoked menthol cigarettes in the past month without naming a usual brand of cigarette.

Altria (June 2010 submission) conducted another analysis in which adolescent subjects were divided into those who had smoked less than 100 cigarettes cumulatively (novice smokers) and those who had smoked more than 100 cigarettes cumulatively (experienced smokers) (see Figure 9). The results showed a lower percentage of menthol smokers vs. non-menthol smokers in the novice smoker category during the earlier time period. However, it is important to note that the more recent survey data showed a higher percentage of menthol smokers in the novice smoker category, except in 2008.

Figure 9. Menthol Cigarette Use by Novice vs. Experienced Adolescent Smokers



In a study combining data from the 2004, 2006 and 2009 NYTS, differences were not observed in potential stages and the proportion of smoking menthol cigarettes (Caraballo & Asman, 2010). Among adolescents who smoked <1 cigarette per day (CPD) on 1–5 days of the past 30 days, 30.9 percent reported smoking menthol cigarettes, a rate similar to or slightly lower than the range among adolescents who smoked 1–5 CPD on 1–5 days, 6–9 days, 20–29 days, and all 30 days (from 45.3 percent to 49.7 percent). These data suggest that adolescents are not more likely to initiate smoking with menthol cigarettes. Similarly, using the NSDUH 2004-2008 surveys, Giovino (2010, unpublished submission) also found no differences in proportions of use of menthol cigarettes among smokers of all ages who smoked 1–5 days in the past 30 days (36.1 percent), 6 to 9 days (38.3 percent) or 10 days of more (31.9 percent). Among those aged 12–17 years, the proportions were 52.8 percent, 54.5 percent and 46.3 percent, respectively.

Another way to examine whether or not greater initiation in smoking occurs with menthol smokers is to compare the rates of menthol cigarette use vs. non-menthol cigarette use among less established smokers. As noted above, Hersey et al. found a higher percentage of novice smokers among adolescent menthol vs. non-menthol smokers. For example, 51.7 percent of Marlboro menthol smokers aged 12–17 reported smoking fewer than 100 cigarettes in their life vs. 38.1 percent of Marlboro non-menthol smokers. Similarly, 62.1 percent of Camel Menthol smokers were novices versus 40.3 percent of Camel non-menthol smokers. Among Newport smokers in the same age range, 46.8 percent were novices. Because of the cross-sectional nature of the study, the causal direction is hard to interpret (e.g., smokers who smoke fewer cigarettes reflect initiation on menthol cigarettes vs. smokers of menthol cigarettes tend to smoke fewer cigarettes).

Summary: These studies are limited by being cross-sectional and we can only infer that novice users as opposed to more established users are representative of those who initiated smoking with menthol cigarettes. Nonetheless, there is some evidence to show that among more recent smokers, a higher percentage smoke menthol cigarettes than among established smokers in studies of adolescents that examined duration of smoking. However, there is mixed evidence to show that smokers of a few cigarettes (who might represent experimenters) tend to smoke more menthol cigarettes than smokers of a higher number of cigarettes.

Age of initiation for menthol vs. non-menthol cigarettes

Eight peer-reviewed articles, two unpublished submissions, and one white paper on the internal tobacco documents were identified. Eight peer-reviewed studies and one unpublished secondary analysis showed no differences in age at which the first cigarette was smoked (Allen & Unger, 2007; Okuyemi, Ebersole-Robinson, Nazir, & Ahluwalia 2004; Pletcher et al. 2006), age of initiation (Cubbin, Soobader, & LeClere 2010) or started smoking (Hyland, Garten, Giovino, & Cummings 2002; Hyland & Rivard 2010 b November submission to FDA; Hymowitz, et al. 1995) or age of regular smoking (Lawrence et al., 2010; Okuyemi et al. 2004; Okuyemi, Faseru, Sanderson Cox, Bronars, & Ahluwalia 2007), comparing smokers of menthol and non-menthol cigarettes. The types of studies examined ranged from cross-sectional surveys (Allen & Unger 2007; Cubbin et al. 2010; Lawrence, Rose, et al. 2010; Okuyemi et al. 2004), multicenter cohort studies (Hyland et al. 2002; HYland & Rivard 2010; Hymowitz et al. 1995; Pletcher et al. 2006) to a treatment study (Okuyemi et al. 2007). Two studies specifically examined African American populations (Okuyemi et al. 2004; Okuyemi et al. 2007). Three of the studies used the COMMIT database but with analyses of different time periods (Hyland et al. 2002; Hyland & Rivard 2010 b; Hymowitz et al. 1995). One study that examined risk factors for menthol status showed marginal statistical significance for age of regular smoking, with delayed initiation associated with menthol status (Fernander, Rayens, Zhang, & Adkins 2010). Tobacco industry documents also do not provide any evidence to show the menthol smokers start earlier than non-menthol smokers (Klausner, 2011 in press).

In a submission from R.J. Reynolds, Curtin et al. (2010b) examined self-reported age of initiation in four national surveys: first whole cigarette smoked (NHANES <20 years old; NYTS), age started smoking regularly (NHANES, age < 20 years; NHIS), age first began smoking cigarettes (NSDUH) or age at first cigarette (NSDUH). The authors concluded that in general, based on NHANES, NHIS and NSDUH data, older age of initiation was observed among current menthol compared to non-menthol smokers, especially among females and individuals 30 years or older. However, significant differences were not observed with control for race, age and gender. On the other hand, the NYTS showed the age of first whole cigarette smoked was younger among the menthol compared to the non-menthol cigarette smokers, even when controlling for race, age and gender. The average initiation age was 0.52 years younger in current menthol smokers vs. non-menthol cigarette smokers ($p<0.05$).

Summary: The preponderance of evidence shows that menthol cigarette smokers do not report an earlier age of initiation of cigarette use (age of onset of first cigarette or regular smoking). However, the one study that examined an adolescent sample observed an earlier age of first smoking a whole cigarette among menthol vs. non-menthol smokers.

Rate of switching from menthol to non-menthol cigarettes and from non-menthol to menthol

Switching rate was considered important to consider because greater switching from menthol to non-menthol compared to non-menthol to menthol suggests that menthol may serve as a starter product. Table 4 summarizes the key studies. In the following description of studies, most of the switching rates were calculated among menthol smokers and among non-menthol smokers, unless noted otherwise. (It should be noted that some studies did not clearly indicate the denominator.) Two peer-reviewed articles, four unpublished secondary analysis (one of which was a public comment and submission) and one presentation of industry documents were identified for this topic. In the 15-year CARDIA cohort study that enrolled 1,535 healthy African American and European white men and women aged 18–30 years old in 1985, no differences were observed in the percent of young adult smokers (18–30 years old at the time of enrollment) who switched types of products (12 percent menthol to non-menthol

switchers, 11 percent non-menthol to menthol switchers; Pletcher, et al., 2006). In another study of 29,037 current smokers and members of the Kaiser Permanente Medical Care Program followed for 4.5 years, more African American smokers under the age of 40 years switched from non-menthol to menthol cigarettes (14.6 percent) than from menthol to non-menthol cigarettes (3.6 percent), even when adjusting for age and sex (Sidney, et al., 1989); however, this study was conducted in the early 1980s and the follow-up rate was quite low (28 percent to 32 percent).

Hyland and Rivard (2010 b November submission to FDA) explored the characteristics of menthol smokers and rates and correlates of switching to and from mentholated products using data from the COMMIT (Community Intervention Trial for Smoking Cessation) study. They calculated the percentage of 2,095 smokers using menthol tobacco in 1988 through 2001 by different demographic and smoking-related characteristics. As in other studies, they found that switching between menthol and non-menthol cigarettes is uncommon for all smokers, regardless of race. About 6.4 percent (out of 2,095) switched from menthol to non-menthol and 4.2 percent switched from non-menthol to menthol. Logistic regression was used to examine the correlates of switching from menthol to non-menthol cigarettes and vice versa in 1993 and in 2001. Smokers age 55 and older, as well as those who started smoking at 15 years or younger, were most likely to switch from menthol to non-menthol cigarette in 1993 or 2001. Smokers who report smoking fewer than 25 cigarettes per day were most likely to switch from a non-menthol to a menthol cigarette in 1993 or in 2001.

Hyland and Kasza (2010 b November submission to the FDA) conducted another secondary analysis of epidemiological studies using the International Tobacco Control Four Country Survey (ITC-4), which collected information from 7,532 subjects 18 years and older between 2002 and 2008 (annual assessments) from four different countries. Current smokers were defined as having smoked at least 100 cigarettes during their lifetime, and currently smoking at least monthly, and menthol cigarette status was determined by the brand that they presently smoked. Among whites, the probability of switching from menthol to non-menthol cigarettes (7.63 percent) was higher than switching from non-menthol to menthol (1.74 percent). Similarly, among Hispanics, the probability of switching from menthol to non-menthol cigarettes was higher (17.39 percent) than switching from non-menthol to menthol (6.72 percent). Among African Americans, the probability of switching from menthol to non-menthol (7.8 percent) was lower than non-menthol to menthol (14.78 percent).

In a document presented by Dr. Eric Johnson to TPSAC on February 2011 based on information from the Switching Book, Altria 1991 (34,117 cigarette smokers 18 and older participating in a 1990-1991 telephone survey), the best estimate of percentages among past year non-menthol and menthol switchers, respectively, was the following: non-menthol to menthol: 7-8 percent; menthol to non-menthol: 20-25 percent. Best estimate of percentages among all past year switchers: non-menthol to menthol: 5.7 percent; menthol to non-menthol 6.9 percent.

(b) (4)

Two studies addressed data for adolescents or young adults. One report analyzed the 2003 National Youth Smoking Cessation Survey. This survey examined 2,582 16–24 year olds who had ever smoked 20 lifetime cigarettes and had smoked at least once during the previous 30 days. After 24 months, 1,045 out of the 2,582 initially enrolled participants were still smoking. Menthol status was determined at baseline and at follow-up. Results showed that more 16–24 year old smokers switched from smoking menthol cigarettes to non-menthol cigarettes than vice versa after a two-year assessment period (15.0 percent vs. 6.9 percent, Giovino, 2010 unpublished submission). Nonnemaker et al. (November 2010 submission to the FDA) analyzed a three-year longitudinal cohort school-based study of 12–18 year olds using the American Legacy Longitudinal Tobacco Use Reduction Study. This school-based survey of 47,237 middle school and high school youth was conducted in three waves from 2000 through 2003 in 83 schools in seven communities and five states. The analyses were restricted to youth who participated in all three waves of the survey (N=16,396 out of 35,352 interviewed at baseline). Youth who initiated smoking prior to baseline or who were older than 18 were dropped from the study. Analyses were estimated using weights that account for baseline characteristics as well as attrition. Data was analyzed excluding and then including youth who initiated smoking in Wave 3. Including Wave 3 initiates because of the larger sample size, the results showed that 5.9 percent switched from menthol to non-menthol and 8.0 percent from non-menthol to menthol among all smokers, a direction opposite that observed by Giovino (2010 unpublished submission).

Summary: There is some evidence to suggest that more menthol smokers switch to non-menthol cigarettes within certain populations of smokers. This switching pattern may in part explain some of the age trends in menthol smoking (lower proportion among older adults), where more subjects are switching from menthol to non-menthol. It is notable that relatively few smokers switch brands, thereby demonstrating brand loyalty.

Sensory experience of menthol cigarettes

Several articles have described characterizing menthol as facilitating the initiation of smoking because it reduces the harshness of tobacco and provides a cooling sensation, thereby increasing the appeal of the product (Henningfield et al., 2003; Lawrence, Cadman, & Hoffman, 2010). As described in chapter 3, these effects from menthol make it biologically plausible that menthol enhances the addictiveness of cigarettes.

Because of the limited research in this area, internal tobacco industry documents were a useful source on the industry's thinking about menthol cigarettes as a product for initiators or non-established smokers. In research that assesses relevant documents from 1965 to 2000, two types of menthol smokers emerge—those who cannot tolerate the harshness and irritation of non-menthol cigarettes, and those who seek out the flavor and physical sensation of menthol (Kreslake, Wayne, & Connolly 2008).

For the first type of smoker, menthol reduces the negative sensory characteristics associated with smoking. This type includes a large proportion of occasional smokers or young smokers, or smokers who switched to menthol cigarettes because of the harshness or perceived negative health effects of their non-menthol cigarettes. The tobacco industry documents show that the companies were aware of how to manipulate menthol levels to appeal to cigarette smoking initiates. Kreslake stated that an author (Cantrell 1987 in Kreslake et al. 2008, page 710) of an internal Brown & Williamson memo noted that a "successful starter cigarette would need to provide a low tobacco taste, low impact and irritation, low tobacco aftertaste and low menthol content." A Lorillard document noted that among younger subjects (aged 21–29), ratings of overall satisfaction were lower when the levels of menthol increased.

Thus, Newport Lights, which contained lower levels of menthol in the cigarette, were more appealing to younger respondents than cigarettes, such as Salem Lights, which contained higher levels of menthol (Coggins 2000a; Kreslake et al. 2008, page 711). The second type of smoke includes individuals who seek out specific menthol flavors associated with physical sensation. These established menthol smokers appear to be tolerant of or seek out stronger sensory characteristics and tend to be African American and male.

A search of internal tobacco industry documents commissioned by the FDA using the Legacy Tobacco Document Library addressed properties of menthol and the smoking experience. The review found that "menthol has cooling and anesthetic properties that are dose-sensitive and that can moderate the harshness and irritation of tobacco." (conclusion from R.J.Reynolds Tobacco Co. study, page 8, Yerger, in press). This finding is congruent with a search conducted by Wayne and Connolly (2004) who reviewed the archival database maintained at Tobacco Documents Online, ranging in date from 1920s through 1990s. These authors reported that documents indicate that tobacco companies thought that mentholation led to "altered perception of tobacco smoke and its constituents via cooling, smoothing and anesthetic effects; increased impact through stimulation of trigeminal receptors and interaction with nicotine controlling its perception, delivery and uptake." The FDA commissioned report (Yerger, in press page 7) further observed, "In addition to making cigarettes smoother and less harsh, menthol's cooling effect alleviates nicotine's irritating effect. The tobacco companies were well aware that younger, inexperienced smokers have low tolerance for irritation and tobacco taste."

The white paper commissioned by the FDA (Klausner, 2011 in press) on menthol initiation concluded that their analyses indicate that youth and experimenters choose menthol cigarettes because they are easier to smoke; are more soothing on the throat; and cooler, milder and less harsh or burning. Further, the author describes an early study that was conducted by Philip Morris, which showed that what menthol smokers report they like about menthol is due to effect rather than taste. The key effects that appear to appeal to menthol smokers include "cooling effects; clean, antiseptic effects; slightly numbing, anesthetic effects; and heady, lifting effects (page 6)." The author points to a Brown & Williamson document that surmised the beginning smoker's familiarity with mint-flavored candies contributed to the acceptance of menthol. Similar to the Kreslake et al. (2008) study, the author describes the tobacco companies' knowledge that initiators of smoking prefer cigarettes with a hint of menthol but as the smokers age, they prefer cigarettes with more menthol. In addition, the documents also showed that some youth smoke menthol cigarettes because they perceive them to be less harmful than non-menthol cigarettes. The tobacco companies also found family and peer influences to be important in determining use of menthol cigarettes by young and new smokers. Other tobacco manufacturers believed that "the decision to smoke menthols as a random or unconsidered event" (page 9). Industry presentations and associated documents suggest that individuals have different taste preferences and taste is what drives them to smoking menthol cigarettes (July 2010 TPSAC meeting).

Summary: Based on review of internal tobacco industry documents, the evidence suggests that youth choose menthol cigarettes, particularly at lower menthol yields, mainly because of the relative ease of smoking a menthol cigarette for the naive smoker and because they perceive menthol cigarettes to be less harmful than non-menthol cigarettes. These internal industry document findings are coherent with the studies on the physiological effects of menthol conducted both internally and externally to the tobacco companies and possibly the finding that adolescent smokers prefer Newport cigarettes, which tend to have lower menthol in cigarette as percent of tobacco weight and lower menthol in smoke than brands like Kool or Salem (June 30, 2010 Altria submission, Table 1.3). Taken together, the various lines of evidence support an appeal of menthol cigarettes to youth and starting smokers because of their sensory effects.

REGULAR SMOKING AND ADDICTION

This section examines whether menthol cigarette use is more likely to lead to regular smoking or nicotine addiction compared to non-menthol cigarette use. TPSAC looked at evidence in three relevant areas: abuse liability, the trajectory of addiction, and the degree of addiction. Abuse liability addresses whether menthol interacts with nicotine or enhances the experience of smoking to make menthol cigarettes more addictive than non-menthol cigarettes. Trajectory of addiction characterizes the likelihood and speed with which menthol cigarette smokers become addicted to nicotine compared to non-menthol cigarette smokers. Degree of addiction assesses whether menthol cigarette users are more or less dependent on nicotine or cigarette smoking than non-menthol cigarette users.

Abuse liability assessment

Menthol's effects on the nicotine pharmacokinetics

Nicotine pharmacokinetics are important because the reinforcing strength of cigarettes is based on the amount and speed of nicotine delivery as well as the rate of nicotine clearance (U. S. Department of Health and Human Services 1988, 2010). As noted in Chapter 3, the preponderance of evidence shows no differences in the amount of nicotine acutely delivered by a single cigarette to menthol vs. non-menthol cigarette smokers. Although evidence presented in Chapter 3 suggests menthol may slow the clearance of nicotine from the bloodstream, the effect is small and not likely to affect pharmacokinetics significantly. Therefore, most likely, menthol does not alter the pharmacokinetics of nicotine in a way that would enhance the development addiction beyond that of a non-menthol cigarette. Chapter 3 reports that menthol may act on nicotinic receptors and may modulate pharmacologic effects of nicotine, but the functional consequence of such effects with respect to addiction is unknown.

Abuse Liability Laboratory Studies

To date no formal animal or human abuse liability assessment has been conducted with menthol cigarettes. In the absence of such research, TPSAC examined four peer-reviewed studies on smoker responses to menthol and non-menthol cigarettes; one peer-reviewed analysis of internal tobacco company documents, and two peer-reviewed studies on behavioral economic analysis of menthol and non-menthol cigarette smokers.

<u>Smoker responses to menthol and non-menthol cigarettes</u>

Several studies have examined the effects of menthol containing cigarette substitutes and cigarettes on subjective responses, which may provide insight into whether a product containing menthol may be more rewarding. The within-subject, laboratory studies and their findings are summarized below.

Levin et al. (1990) used cigarette substitutes to examine smokers' taste reactions to five flavors, three tobacco flavors and two menthol-like flavors. Each flavored cigarette substitute was rated on several dimensions and compared to placebo. Cigarette substitutes with menthol-like flavors received statistically significantly higher ratings on liking and satisfaction than placebo and were among the highest ranked in both menthol and non-menthol smokers.

Pickworth et al. (2002) examined smokers' reactions to high-nicotine yield (2.5 mg nicotine yield) and low-nicotine yield (.2 mg nicotine yield) menthol and non-menthol laboratory cigarettes and two menthol (Kool, Newport) and two non-menthol (Winston, Marlboro) commercial cigarette brands. Menthol cigarette smokers used menthols in the study; non-menthol cigarette smokers used non-

menthols. No statistically significant differences in most subjective responses (strength, satisfaction, psychological reward, negative effects) were observed between the menthol and non-menthol smokers. Nicotine yield, not menthol, had effects on subjective measures.

Pritchard et al. (1999) compared responses of smokers to "denicotinized" (0.06 mg nicotine yield) menthol (4.1 mg menthol/cigarette) and non-menthol cigarettes. In this study, menthol and non-menthol smokers tested both types of cigarettes. As in the study by Pickworth et al. (2002), no significant differences in subjective responses (mental alertness, anxiety/nervousness, muscular relaxation) were observed between menthol and non-menthol cigarettes. In addition, little evidence of pharmacological effect, as assessed by EEG and heart rate, were observed between menthol and non-menthol cigarettes.

These laboratory studies are limited by their small sample sizes, unbalanced distribution of race/ethnicity among menthol and non-menthol smokers, and focus on established smokers and other inclusion criteria, limiting the generalization of these finding.

Only one study has examined reactions associated with smoking menthol vs. non-menthol cigarettes during the first smoking experience. No differences in subjective reaction to the first inhaled cigarettes by mentholation were observed (DiFranza et al., 2004). The DiFranza et al. study is limited due to the small sample size and retrospective recall of their experiences with their first inhaled cigarette. Furthermore, just over half could recall the brand of their first inhaled cigarette.

Analyses of internal tobacco company documents

One recent peer-reviewed study of internal tobacco industry documents reveals experiments that indicate menthol has a significant impact on low-nicotine and denicotinized cigarettes.

Yerger (in press) writes that during the late 1980s, Philip Morris scientists conducted tests on various prototypes of "alkaloid (nicotine) reduced tobacco" (ART). The non-mentholated ART prototypes were described as lacking impact (e.g., "kick" or "grab" in the back of the mouth and throat when inhaling a cigarette, a sensory experience believed to contribute to immediate smoking satisfaction). Yerger writes (page 8): "Philip Morris found the mentholated prototypes of ART to be 'subjectively superior' to non-mentholated versions because they were the only ART prototypes that provided any impact." She further states, "When further testing the mentholated ART prototypes, Philip Morris scientists found menthol provided this perceived impact because it produced some nicotine-like effects."

Yerger (in press) additionally writes that Philip Morris conducted a study that combined four levels of menthol with three levels of nicotine. The results showed that cigarettes without nicotine were preferred more when menthol was added; low or intermediate menthol levels were preferred over high menthol levels in cigarettes. Yerger describes other Philip Morris studies that confirmed the observation that "menthol increased impact for the low-nicotine delivery cigarettes…The effect of menthol was most pronounced for the cigarette with the lowest nicotine delivery" (page 11, quote by Gerry Nixon from Philip Morris).

Yerger (in press) further describes tobacco industry studies conducted by Philip Morris and Brown & Williamson in the 1970s of different menthol concentrations on low-tar delivery cigarettes to maximize customer appeal and increase market demand for these cigarettes. During that time, these low-tar/nicotine brands were believed to address concerns about the health effects of smoking and were considered to represent a growth area for the market.

Yerger (in press) also writes of human studies conducted by Philip Morris that found menthol produces some nicotine-like central nervous system and subjective effects (e.g., mental alertness, muscular relaxation), making menthol a "partial replacement" for nicotine (page 15). This observation is likely to be due the stimulation of the trigeminal nerve or nerve fibers, which are considered "essential to eliciting 'liking' response to tobacco products" (page 15). Yerger writes that because of the nature of the documents, no information was provided on the specifics of study designs or who comprised the subjects for this study.

Behavioral economic models

The relative abuse liability of a product can be determined by the extent to which another product can be substituted for it. Tauras et al. (2010) observed that smokers do not find menthol and non-menthol cigarettes to be close substitutes. Using data from the 2003 and 2006/07 Tobacco Use Supplements to the Current Population Survey (n=57,387, aged 18 and older), they developed a regression model that estimated the probability of being a menthol smoker, conditional on being a current smoker who reported a preference for menthol or non-menthol cigarettes. Cigarette prices, smoke-free air laws and socioeconomic and demographic characteristics were examined as covariates. The results showed that non-menthol cigarettes were less of a substitute for menthol cigarettes than vice versa. A 10 percent increase in menthol cigarette prices would cause 2.36 percent of menthol smokers to switch to non-menthol cigarettes. By contrast, a 10 percent jump in non-menthol cigarette prices would cause 4.75 percent of non-menthol cigarette smokers to switch to menthol cigarettes. This difference was more pronounced among African Americans and young adults. Furthermore, these investigators found relatively greater use of menthol cigarettes in states that have stronger laws restricting smoking. Both these findings suggest that menthol cigarettes may be more reinforcing or addicting than non-menthol cigarettes.

Farrelly et al. (2007) examined the effect of price increases on the purchase of stronger cigarette types (cigarettes with higher tar and nicotine yields). Scanner data (ScanTrack licensed from ACNielsen) on cigarette prices and sales were obtained from supermarkets (with at least $2 million in annual sales) across the United States from 1994 to 2004. Using multivariate regression models, price elasticities suggest that the average inflation-adjusted price increase of 55.8 percent for menthol cigarettes was associated with an increase of 1.73 percent in sales-weighted tar yields and 1.28 percent increase in sales-weighted average nicotine yields. A 50.5 percent price increase of non-menthol types of cigarettes over the same period produced an estimated increase of 1 percent in tar per cigarette purchased but no statistically significant increase in nicotine yields. Thus, these findings show an increased probability that stronger cigarettes are smoked as the price of cigarettes is increased, and this effect is larger among menthol than non-menthol smokers. Concordant with the prior study, these results also suggest that addiction to cigarettes may be stronger among menthol smokers, although the study results do not show if more exposure to tar and nicotine occurs as a result of smoking higher tar and nicotine yield cigarettes. However, one of the strengths of these studies is that they involve nationally representative samples and examine actual behavior of consumers.

Summary: No animal and relatively few human studies have been conducted directly examining the relative abuse liability of menthol vs. non-menthol cigarettes. Reviews of internal tobacco industry documents identified studies conducted by the tobacco industry that demonstrate that menthol is associated with greater impact or "throat grab" when added to denicotinized or lower nicotine yield cigarettes. As suggested in chapter 3, abuse liability of menthol cigarettes may be higher because of potentially strong conditioned cue response with menthol cigarettes. Finally, studies using behavioral

economic models, which have been used to assess the abuse liability of other drugs, suggest greater reinforcing effects from menthol cigarettes.

Trajectory from initiation to regular smoking or dependence

To date, only the study by Nonnemaker et al. (2010 November submission to FDA) has examined if early menthol cigarette use was more likely to be associated with regular smoking or dependence than early non-menthol cigarette use. As previously described, this unpublished research analyzed data from the American Legacy Longitudinal Tobacco Use Reduction Study, a three-year longitudinal cohort school-based study of 12–18 year olds. Progression to greater smoking was determined in three ways: (1) a transition from smoking less than 100 cigarettes to smoking more than 100 cigarettes; (2) a transition from smoking on less than 20 days per month to smoking 20 or more days per month; and (3) a transition from non-daily smoking to daily smoking. Nicotine dependence was measured in response to the following questions: (a) *How soon after you wake up do you usually smoke your first cigarette on weekdays? during the weekend?* (b) *If you are sick with bad cold or sore throat, do you smoke cigarettes?* (c) *How true is this statement for you? When I go without a smoke for a few hours, I experience cravings*; (d) *How true is this statement for you? I sometimes have strong cravings for cigarettes where it feels like I'm in the grip of a force that I can't control*. The higher the score on this dependence measure, the greater the extent of dependence. Key explanatory variables included an indicator for reporting the first cigarette smoked was menthol (n=1100), and indicators for pattern of menthol use: menthol to menthol (n=3930): menthol to non-menthol (n=55); non-menthol to menthol (n=82); and non-menthol to non-menthol (n=459). Analysis includes adolescents who initiated in Wave 3 to provide a larger sample size and also because some ethnic/racial groups do not start smoking until a later age. All regression analysis was controlled for gender, age, and race/ethnicity. Key findings follow.

> Among Wave 3 smokers, 43.0 percent reported menthol use at initiation. A large majority of current smokers at Wave 3 maintained a preference for the type of cigarette they started on across survey waves—36.8 percent began smoking menthols and still smoked menthols at Wave 3, and 49.3 percent began smoking non-menthols and still smoked non-menthols in Wave 3. As previously noted, only a small percentage reported going from menthol to non-menthol (5.9 percent) and from non-menthol to menthol (8.0 percent).
>
> Initiation to menthol is positively associated with smoking daily (OR: 1.99, 95% CI: 1.42–2.80), established smoking (OR: 1.94, 95% CI 1.41–2.66) and lifetime cigarette smoking (OR:1.94, 95% CI: 1.40–2.68) at Wave 3 compared to non-menthol reference group initiators.
>
> Respondents who switched from menthol cigarettes to non-menthol cigarettes were significantly more likely to meet the definition for smoking daily (OR: 3.30, 95% CI 1.59–6.87), established smoking (OR:3.25, 95% CI: 1.58–6.66) and lifetime cigarette smoking (OR: 3.41, 95% CI: 1.59–7.31) compared with the non-menthol reference group initiators. The greater likelihood of smoking regularly or of lifetime smoking may be related to switching rather than menthol status. For example, respondents who switched from the non-menthol to menthol group were also significantly more likely to qualify for established smoking (OR: 2.05, 95% CI: 1.08–3.87) and Lifetime Cigarette Smoker (OR:1.98 95% CI: 1.03–3.78). However, menthol to menthol respondents were also more likely to qualify for daily smoking (OR: 2.09, 95% CI: 1.45–3.03), established smoking (OR: 2.07, 95% CI: 1.47–2.93) and lifetime cigarette smoking (OR: 2.08, 95% CI:

1.47–2.94) than for the non-menthol reference group.

Most importantly, for all three outcomes—daily smoking, established smoking and lifetime cigarette smoking—the models that include Wave 3 initiators reveal a positive and statistically significant association between menthol at initiation and transitions to higher levels of smoking (smoking daily, OR: 2.11, 95% CI: 1.47–3.03; established smoking, OR: 2.02, 95% CI: 1.44–2.84; and lifetime cigarette smoking, OR: 2.32, 95% CI: 1.64–3.28)

Respondents who switched from menthol cigarettes to non-menthol cigarettes were statistically significantly more likely to transition to increased smoking for each transition outcome compared with the non-menthol reference group (smoking daily, OR: 3.65, 95% CI: 1.46–9.16; established smoking, OR: 4.72, 95% CI: 1.86–11.99; lifetime cigarette smoking; OR: 7.42, 95% CI: 2.73–20.22). Transitions for each outcome were also more likely for menthol-to-menthol respondents (smoking daily, OR: 2.12, 95% CI: 1.44–3.12; established smoking, OR: 2.09, 95% CI: 1.45–3.00; lifetime cigarette smoking, OR: 2.27, 95% CI: 1.57–3.28). Respondents who switched from non-menthol to menthol were not more likely to transition to increased smoking for any of the transition outcomes.

Menthol cigarette use at initiation is positively and statistically significantly associated with nicotine dependence, according to the results of the ordinary least square regressions for the nicotine dependence (B:1.04, 95% CI: 0.26–1.82). Menthol to non-menthol smokers were significantly more likely to have higher dependence scale scores (B: 2.33, 95% CI: 1.08–3.59) than non-menthol to non-menthol smokers. However, menthol to menthol smokers have significantly lower scale scores (B: 0.96, 95% CI: 0.08–1.83) than the non-menthol reference group. This latter finding is not robust. No statistically significant results were found in the non-menthol to menthol group.

Klausner (2011 in press) found no evidence in internal tobacco company documents to indicate that people who start smoking menthol compared to non-menthol cigarettes progress more quickly toward established smoking. No study has primarily examined the rapidity with which people initiate smoking and become regular smokers. Okuyemi et al. (2004), in a study of African American treatment seekers, found that menthol smokers report three years between their first cigarette and the start of regular smoking compared to two years for non-menthol smokers. The generalizability of this data is limited.

Summary: In order to specifically determine if menthol cigarettes play a significant role in the initiation of smoking, the optimal study would examine the rates of continued or established smoking and dependence among those who initiated smoking with menthol vs. non-menthol cigarettes. There are limitations to the Nonnemaker et al. (2010) study including: (a) a small sample size of ethnic/racial minority groups, (b) inclusion of subjects who only completed all three waves of the study, (c) the lack of national representativeness of the sample, and (d) long intervals between assessments. While replication of these results would be important and an establishment of a longitudinal cohort study would be valuable, the currently presented evidence is persuasive in demonstrating that initiating with menthol cigarettes is associated with increased risk for transitioning to more established smoking**.**

Degree of addiction

There are several ways to assess the degree of addiction to a tobacco product. These include examining: (1) the number of cigarettes smoked, with higher levels of smoking denoting greater dependence,(2) biomarkers of exposure (e.g., urinary total nicotine equivalents (NE), plasma or saliva cotinine, total NE/cigarette, cotinine/cigarette), (3) alterations in the 3 hydroxycotinine (3OH) to cotinine ratio, with higher ratio potentially indicating greater risk for dependence, and (4) self-report measures of dependence which include the Fagerstrom Test for Nicotine Dependence (FTND), a component of the FTND (time to first cigarette or TTF), other measures of dependence, waking up in the middle of the night to smoke, and severity of withdrawal symptoms. The majority of these measures have been validated with each other or other indicators of addiction (U. S. Department of Health and Human Services 2010). The section reviews studies using these indices of addiction to assess whether adults and adolescents who smoke menthol cigarettes are more addicted to nicotine than those who smoke non-menthol cigarettes.

Adults

Cigarettes per day

The number of cigarettes smoked per day (CPD) has been found to be a strong indicator of nicotine dependence (U. S. Department of Health and Human Services, 2010). TPSAC identified 28 studies that measured CPD by cigarette type. Of these studies, one was excluded because of its small sample size (Ahijevych, Tyndale, Dhatt, Weed, & Browning 2002). Of the remaining 27 studies, 16 found no CPD differences between menthol and non-menthol cigarette smokers. The studies are summarized below.

Ten peer-reviewed studies and one tobacco company submission found that menthol cigarette users reported smoking fewer cigarettes per day. The statistical significance of the results varied by race/ethnicity in some of the studies. A limitation of many of the studies is that they did not control for age, race/ethnicity, or income. Results of the 11 studies follow.

- Wang et al. (2010), analyzing a cross-sectional, multi-site, observational study, reported 15.0 vs. 16.8 CPD for menthol vs. non-menthol cigarette users, respectively (unadjusted $p < 0.01$). Although CPD was statistically significantly higher in white menthol vs. non-menthol cigarette smokers (18.1 vs. 17.2 CPD), there was no difference in African Americans (10.9 menthol vs. 12.1 non-menthol CPD).

- Giovino et al. (2004), analyzing the U.S. component of the International Tobacco Control Policy Evaluation survey, found a statistically significant difference of 18.1 vs. 19.8 CPD ($p<0.01$) in white menthol vs. non-menthol smokers, respectively. No difference was observed in African Americans.

- Curtin et al. (2010 c June submission to FDA) analyzing 2003 NHIS, found borderline significance for lower intensity of smoking among menthol vs. non-menthol cigarette smokers overall ($p=0.06$), a statistically significant difference in white menthol vs. non-menthol cigarette smokers (15.5 vs. 16.98 CPD, respectively, $p < 0.05$), but not among African Americans or the “other” ethnic group. In an analysis of 2007 NSDUH, white menthol cigarette smokers also showed a lower smoking intensity than white non-menthol cigarette smokers ($p < 0.01$), but this difference was not seen among African Americans or other racial/ethnic groups.

- Stahre et al. (2010), analyzing the 2005 National Health Interview Survey, found 14.6 vs. 17.5 CPD ($p < 0.0001$) in menthol vs. non-menthol cigarette smokers, respectively.

- Analyzing data from the 2002 and 2006/07 Tobacco Use Supplement-Current Population Survey (TUS-CPS), Fagan et al. (2010) found 13.1 vs. 15.0 CPD ($p < 0.001$) in menthol vs. non-menthol cigarette smokers, respectively; Lawrence et al. (2010) found that 51.9 percent of menthol cigarette smokers consumed fewer than 10 cigarettes per day compared to 42.3 percent of non-menthol cigarette smokers.

- Pletcher et al. (2006), examining a longitudinal cohort study with young adults examining risk in cardiovascular disease (CARDIA), reported 10 vs. 15 CPD ($p < 0.001$) for menthol and non-menthol cigarette smokers, respectively.

- Hyland et al. (2002), examining a national community-based intervention trial, found menthol smoking was associated with smoking five cigarettes or less a day compared to smoking more than this amount at baseline after controlling for covariates.

- Gandhi et al. (2009), examining a large sample of treatment seekers, reported 19.0 vs. 23.1 ($p< 0.001$) overall, 15.7 vs. 20.3 CPD ($p<0.001$) in African American menthol vs. non-menthol cigarette smokers, respectively, and 17.0 vs. 22.1 CPD ($p=0.017$) in Hispanic menthol vs. non-menthol cigarette smokers, respectively. No differences were observed in whites ($p=0.09$) or "other" ethnic group.

- Fu et al. (2008), in a multi-site study of Veterans Administration multi-ethic treatment seekers, observed 20 vs. 30 CPD ($p < 0.001$) in menthol vs. non-menthol cigarette smokers, respectively. Subjects were asked to recall CPD for the two years prior to study entry.

- Muscat et al. (2002), in a cross-sectional analysis of a case-control study on smoking and lung cancer, found 28.1 vs. 28.9 CPD in white menthol vs. non-menthol cigarette smokers, respectively (prevalence odd ratio, POR, for smoking $\geq$ 21 CPD vs. smoking $\leq$ 20 CPD= 0.9, 95% CI=0.8-1.0), and 18.2 vs. 20.9 CPD in African American menthol vs. non-menthol cigarette smokers, respectively (POR for smoking $\geq$ 21 CPD vs. smoking $\leq$ 20 CPD= 0.7, 95% CI=0.5-0.9).

Ten peer-reviewed studies showed no differences in CPD between menthol and non-menthol cigarettes. These studies included:

- Treatment studies (Fu, et al., 2008; Mustonen, Spencer, Hoskinson, Sachs, & Garvey 2005; Okuyemi et al. 2003; Okuyemi et al. 2007). Okuyemi et al. (2003; 2007) were conducted only in African Americans.

- Community based, cross-sectional studies (Hyland, et al., 2002 at follow-up; Muscat et al., 2009; Okuyemi, et al., 2004). Okuyemi et al. (2004) was conducted only in African Americans.

- A cross-sectional analysis of longitudinal cohort and intervention study for smoking and lung health (Murray, Connett, Skeans, & Tashkin 2007).

- National surveys, including a secondary analyses of the 2005 NHIS and Cancer Control Supplement (Cubbin et al. 2010) and the 2006/07 TUS-CPS (Ahijevych & Ford, 2010). The latter study found no differences in CPD by menthol status among daily and non-daily cigarette smokers.

Two non-peer-reviewed secondary analyses of cross-sectional surveys also found no CPD differences in menthol vs. non-menthol cigarette smokers.

- Hyland et al. (2010 a November submission to FDA) examined the International Tobacco Control Four

Country Survey (ITC-4) involving data collection from 7532 individuals between 2002 and 2008. No differences were observed in number of cigarettes within racial/ethnic and gender strata.

- Curtin et al. (2010 c June submission to FDA) conducted cross-sectional secondary analyses of 2005/06, 2007/08 NHANES and 2007 NSDUH. After controlling for sex, race/ethnicity and age, no overall differences in smoking intensity between menthol and non-menthol smokers were observed with NHANES and no differences were seen with NSDUH. When examining the NHANES data within racial/ethnic groups, no CPD differences were found among whites, African Americans or the "other" ethnic group.

  Four non-peer-reviewed treatment-related studies also found no differences in CPD between menthol and non-menthol cigarette smokers. The first study examined the response to pharmacological treatments for nicotine addiction (King, Cao, & Matthews, 2010 November submission to FDA); the second study assessed the efficacy of a motivational treatment for smoking-relapse prevention in pregnant mothers; the third study examined the efficacy of palmtop computers for smoking cessation; and the fourth study probed the social determinants of smoking cessation. The latter three studies involved both unadjusted and adjusted analyses (Reitzel, 2010 a, 2010 b, 2010 c November submissions to FDA).

Summary: The evidence for differences in number of cigarettes smoked between menthol and non-menthol smokers is mixed. There is some evidence showing that menthol cigarette smokers consume fewer cigarettes per day than non-menthol cigarette smokers, particularly in some race/ethnicity groups compared to others, but the evidence within races is also mixed.

Biomarkers of exposure

Cigarettes per day may not be the most precise measure of actual exposure to nicotine (Caraballo et al., 1998). Determining actual nicotine exposure requires measurement of either total nicotine equivalents or cotinine (a metabolite of nicotine). These biomarkers of nicotine exposure can be examined in two ways: overall levels or per cigarette smoked.

Biomarkers of exposure overall

As described in Chapter 3, TPSAC identified 14 peer-reviewed studies that measured and compared overall levels of biomarkers of nicotine exposure in menthol and non-menthol cigarette smokers. Results of these studies are summarized below.

Four studies found that menthol cigarette smokers had statistically significantly higher levels of cotinine compared to non-menthol smokers. These studies were primarily experimental laboratory studies conducted with African American and white female smokers (342 vs. 230 ng/ml, p=0.019, Ahijevych et al. 2002; 239 vs. 180 ng/ml, p=0.02, Ahijevych & Parsley 1999), smokers with schizophrenia as well as normal smokers (294 vs. 240 ng/ml, p=0.041, Williams et al., 2007) or African American and white smokers (478.2 vs. 249.1 ng/ml, significant even after adjusting for race, cigarettes per day and mean amount of each cigarette smoked, p=0.03, Clark, Gautam, & Gerson, 1996).

One study (Benowitz, Herrera, & Jacob 2004) found higher cotinine levels in African Americans when they smoked menthol compared to non-menthol cigarettes, and lower cotinine levels in white smokers when they smoked menthol vs. non-menthol cigarettes. Cigarettes smokers who had experience in smoking both menthol and non-menthol cigarettes smoked menthol or non-menthol cigarettes with same machine-determined yield and nicotine content for one week before crossing over to smoke the

other cigarette type for the second week. Subjects were confined to a residential unit 3 days out of each week. During this stay, subjects were instructed to smoke 20 CPD, with one cigarette smoked every 45 minutes, blood levels of nicotine were measured throughout the day and an intravenous infusion of deuterium labeled nicotine and cotinine was administered to determine rate and pathways of nicotine clearance. Systemic intake of nicotine was not affected by menthol cigarettes. Plasma cotinine averaged over 24 hours was not significantly different between menthol and non-menthol smokers overall. However, there was a condition x race interaction, where $AUC_{nicotine}$ and average cotinine concentrations were higher in African Americans when smoking menthol cigarettes compared to non-menthol cigarettes and the opposite was observed for whites. Although the sample size in this study was very small (n=14), the results emphasize the importance of examining race x menthol interactions.

Two studies detected a trend toward higher cotinine levels in menthol cigarette smokers compared to non-menthol cigarette smokers. Mustonen et al. (2005) found that African American and white menthol smokers had higher levels of cotinine compared to respective non-menthol smokers in a treatment study, but the differences were not significant (p=0.18). Muscat et al. (2009), in a cross-sectional, community-based study, observed slightly higher plasma cotinine in African American menthol vs. non-menthol smokers, but results were not statistically significant (p=0.09).

Seven studies found no differences in levels of cotinine and total nicotine equivalents (NE) between menthol and non-menthol smokers. These studies are:

- Wang et al. (2010), a cross-sectional, observational multi-site study, involving 24-hour urine collection and adjusted for covariates (lower NE levels were found in unadjusted analysis, 12.8 mg/24 hr vs. 13.5 mg/24hr, $p < 0.05$);
- Heck (2009), a parallel-arm study with subjects matched for machine-measured tar and balanced for sex, age and race, involving 24-hour urine collection;
- Signorello et al. (2009), a community-based cohort study on cancer occurrence;
- Murray et al. (2007), a community-based cohort intervention study among smokers at risk for COPD;
- Allen and Unger et al. (2007), a cross-sectional survey of African Americans living in an urban area (stratified by gender and controlled for age and employment status);
- Okuyemi et al. (2003; 2007), treatment studies with African American smokers; and
- Ahijevych et al. (1996) ,a laboratory smoke-exposure study with female African Americans and whites, balanced for menthol status and race.

Biomarkers of exposure as measured per cigarette

The above studies measure overall levels of nicotine exposure; it is also possible to measure nicotine exposure per cigarette. Higher cotinine or nicotine equivalent levels per cigarette may be associated with greater reinforcing effects from each cigarette and subsequently a higher potential for addiction. TPSAC identified six peer-reviewed studies that measured and compared either plasma or saliva cotinine per cigarette (cotinine/cigarette) or urinary nicotine equivalents per cigarette (NE/cigarette) in menthol and non-menthol smokers.

Four studies showed higher levels of nicotine exposure per cigarette in menthol cigarette smokers compared to non-menthol cigarette smokers.

- Mustonen et al. (2005) found higher cotinine/cigarette in a treatment study of 307 white and African American smokers (23.3 ng/ml vs. 19.4 ng/ml, p=0.004), particularly black male menthol vs. non-menthol smokers.

- Ahijevych et al. (2002) reported cotinine/cigarette levels of 20.7 ng/ml vs. 12.4 ng/ml (p=0.05) in an experimental laboratory study of a small number of African American and white female smokers. In a similar sample stratified for race and menthol status, Ahijevych et al. (1999) reported cotinine/cigarette levels of 17.8 ng/ml vs. 13.1 ng/ml, but found no race x menthol interaction.

- Wang et al. (2010), using unadjusted statistical analysis, found higher NE/cigarette overall (0.96 vs. 0.90 mg/cigarette, $p < 0.05$) and within the African American (1.10 vs. 1.00 mg/cigarette, $p<0.05$) but not white (0.86 vs. 0.89 mg/cigarette) menthol cigarette smokers compared to non-menthol cigarette smokers, in a large cross-sectional, observational, ambulatory, multi-site study. When data was adjusted for covariates, no significant differences were observed.

Two studies found no differences in cotinine/cigarette in menthol vs. non-menthol cigarette smokers. One of these studies examined African American and white female smokers enrolled in smoke-exposure laboratory study (Ahijevych, et al., 1996). The other study included smokers with schizophrenia and smokers without mental illness. These subjects were participants in either a treatment or experimental study in which cotinine/cigarette was adjusted for cigarettes per day, group (with and without mental illness) and ethnicity (Williams et al. 2007).

Summary: There is conflicting evidence regarding the effects of menthol on nicotine exposure levels as measured by cotinine or 24-hour nicotine equivalents. Four studies found menthol cigarette smokers had statistically significantly higher cotinine levels; one study found higher cotinine levels in African American but not white menthol smokers; two studies detected a trend toward higher cotinine levels in menthol smokers; and seven studies found no difference in nicotine exposure between menthol and non-menthol smokers. The results are also mixed for the effects of menthol cigarette smokers on nicotine levels per cigarette (four of six studies supportive of higher levels, with one study finding effects in unadjusted analysis). Unfortunately, the majority of these studies did not control for race, income or gender, factors that may the affect number of cigarettes smoked or extent of nicotine exposure. In addition, as described in Chapter 7, smokers who smoke fewer than 10 cigarettes per day may be a group where menthol effects may be observed.

Subjective measures of dependence

Fagerstrom Test for Nicotine Dependence (FTND)

The Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom 1991) is the most widely used dependence measure (U. S. Department of Health and Human Services, 2010). TPSAC identified seven studies with FTND measures—five peer-reviewed, one unpublished secondary analysis, one unpublished submission by Altria. Six found no differences in FTND scores between menthol and non-menthol cigarette smokers. These studies were a cross-sectional survey of African American smokers seen at an inner-city health center generally serving a low income population (Okuyemi, et al., 2004), a cross-sectional survey of African Americans living in an urban area (Allen & Unger, 2007), a community-based, cross-sectional study aimed at studying smoke exposure and nicotine dependence, adjusted for age, race, sex and education (Muscat, et al. 2009), a community-based, cohort

study examining interventions for smoking cessation and lung health in smokers with mild and moderate airflow obstruction (Murray et al. 2007), a cross-sectional , observational, multisite study (findings after adjusting for age, race, gender, education and tar yields; Altria Client Services on behalf of Philip Morris USA 2010, June 2010 submission, p. 135) and a treatment study of African American smokers (Okuyemi, et al. 2003).

One study found statistically significantly higher FTND scores in menthol versus non-menthol smokers participating in a treatment study (5.56 ± 1.83 vs. 4.97 ± 1.81 years, *p = 0.007*). This study also found a greater smoking urge at baseline (first study visit) using the Brief Questionnaire of Smoking Urge in menthol vs. non-menthol cigarette smokers (total 33.32 ± 13.79 vs. 30.17 ± 12.63, *p = 0.043*) (King, et al., 2010 November submission to FDA). This study was limited by its small sample of African American non-menthol cigarette smokers and white menthol cigarette smokers.

Time to first cigarette (TTFC)

A potentially better measure of dependence than the FTND is time to first cigarette (TTFC)—the amount of time that lapses between waking and smoking the first cigarette of the day. This item has been found to be highly associated with physical dependence measures such as withdrawal symptoms and relapse to smoking after a cessation attempt (Piper, McCarthy, & Baker 2006; U. S. Department of Health and Human Services 2010). Sixteen studies were identified with TTFC measures. Seven of them—six peer-reviewed studies and one unpublished secondary analysis—showed a shorter TTFC with menthol cigarettes. Eight studies—four peer-reviewed and four unpublished secondary analysis—showed no difference in TTFC between menthol and non-menthol cigarette smokers. One unpublished secondary analysis showed menthol cigarette smokers had a longer TTFC than non-menthol smokers.

The seven studies showing a shorter TTFC among menthol vs. non-menthol cigarette smokers follow.

- Ahijevych et al. (1999), in an experimental, laboratory smoke-exposure study in African American and white females, found TTFC of 19.9 vs. 37.4 minutes for menthol vs. non-menthol cigarette smokers, respectively, (p=0.02). The sample was stratified for race and menthol status.

- Okuyemi et al. (2003), in a smoking cessation treatment study in African Americans, found 81.7 percent of menthol vs. 69.8 percent of non-menthol cigarette smokers endorsed smoking $\leq$ 30 minutes after waking.

- Gandhi et al. (2009), in a smoking cessation treatment study in African American and white smokers, found 24.3 percent of menthol vs.19.9 percent of non-menthol cigarette users smoked within five minutes of waking.

- Muscat et al. (2009) measured TTFC in a community-based, cross-sectional study of smoke exposure and nicotine dependence in African American and white volunteers. Menthol cigarette smokers were more likely than non-menthol cigarette smokers to have a first cigarette 30 minutes or less after waking (OR: 2.1, 95% CI: .96-3.8). The results were adjusted for age, sex, race and education.

- Fagan et al. (2010), in a secondary analysis of pooled 2003 and 2006/07 TUS-CPS data on smokers of six to 10 cigarettes per day, found menthol cigarette smokers were more likely than non-menthol cigarette smokers to have a first cigarette within 5 minutes of waking (OR: 1.22, 95% CI: 1.05, 1.43 after controlling for a number of covariates such as gender, age, race/ethnicity and income).

- Ahijevych and Ford (2010), in a secondary analysis of the 2006/07 TUS-CPS among young adult, non-daily smokers using random effects model, found first cigarette within 30 minutes of waking associated with menthol smoking ($p<0.05$). Non-daily smokers were defined as those who smoked between one and 29 days in the last 30 days.

- Hyland and Kasza (2010 a November submission to FDA), in a non-peer-reviewed secondary, multivariate analysis of adult smokers who were interviewed as part of the International Tobacco Control Four Country Survey (ITC-4), found that when considering all respondents, menthol smokers reported fewer minutes to first cigarette compared to non-menthol smokers ($p < 0.01$). The analysis was adjusted for age, education, income, and quitting indicators. The strength of this relationship differed between racial/ethnic groups, with Hispanic respondents (particularly men), experiencing the greatest difference between menthol and non-menthol smokers (significance for menthol X white/Hispanic interaction term <0.05).

No differences were observed in eight studies:

- A secondary analysis of the 2006/07 TUS-CPS among daily, young adult smokers (using random effects model, Ahijevych & Ford, 2010); a secondary analysis of pooled 2003 and 2006/07 TUS-CPS among smokers who smoked fewer than six cigarettes per day or more than 10 cigarettes per day (after controlling for a number of covariates such as gender, age, race/ethnicity and income; Fagan, et al., 2010); and a secondary analysis of the pooled 2003 and 2006/07 TUS-CPS when using multivariate logistic regression model (Lawrence, Rose, et al. 2010).

- A cross-sectional, multi-site observational study (first cigarette < 5 minutes or within 30 minutes, after adjusting for gender, age, race, income, tar yield, smoking amount, etc., Altria Client Services on behalf of Philip Morris USA, 2010 June submission to FDA).

- A large multi-site clinical trial comprised of a multi-ethnic sample to test a repeat tobacco cessation treatment found no differences between menthol and non-menthol cigarette smokers who had their first cigarette 30 minutes or less after waking. The study used retrospective recall of both menthol status and TTFC two years prior to study enrollment (Fu et al. 2008).

- Three studies conducted by Reitzel (2010 a, 2010 b; 2010 c November submissions to FDA) also showed no difference by menthol status in time to the first cigarette of the day $\leq$ 5 minutes using adjusted analysis. These studies include research on the efficacy of a motivationally-based treatment for smoking relapse prevention in racially diverse pregnant mothers (Reitzel 2010 c) and palmtop computers used for smoking cessation among African American smokers (Reitzel 2010 b). The third study examined social determinants of smoking cessation in a racially diverse population (Reitzel, 2010 a). In the randomized pregnant female smokers of diverse race, menthol was nearly statistically significantly associated with the time to the first cigarette of the day $\leq$ 5 minutes in unadjusted analyses (OR : 0.73, 95% CI: .54-1.00, p=0.05; (Reitzel 2010 c).

Conversely, in a secondary analysis of the 1988 telephone use surveys from COMMIT (Hyland, et al. 2002), increased menthol use was associated with greater than 60 minutes compared to less than 10 minutes to the first cigarette in the morning (OR: 1.16, 95% CI: 1.00–1.35 after adjusting for such covariates as for sex, age, race/ethnicity, education, amount smoked). Menthol users were slightly less likely to report smoking within 10 minutes after waking (RR: 0.90, 95% CI: 0.81–0.99).

Waking up in the middle of the night

A recently validated measure of dependence is whether a smoker wakes up in the middle of the night. This measure has been related to smoking within 30 minutes of awakening, number of cigarettes per day and has been shown to be a predictor of treatment outcome (Bover, Foulds, Steinberg, Richardson, & Marcella 2008; Foulds et al. 2006). Two studies have shown an association between menthol smoking and this measure. Gandhi et al. (2009) examined smokers who attended a specialist smoking cessation service and found a higher percent of menthol cigarette smokers vs. non-menthol cigarette smokers endorsed waking up in the middle of night to smoke (55.3 percent vs. 44.9 percent, p<0.001). Bover et al. (2008) also examined cigarette smokers who sought treatment as a specialist smoking cessation clinic. In multivariate analysis, night smoking was associated with smoking menthol cigarettes (AOR: 1.50; 95% CI: 1.20–1.87, p=0.0004).

Other dependence measures

Five treatment studies (two peer-reviewed studies and three unpublished secondary analyses) use two other dependence measures to analyze nicotine addiction by menthol status: Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). None of these studies showed a consistent menthol effect.

The Nicotine Dependence Syndrome Scale is multidimensional validated measure for nicotine dependence that provides a total score and score for several factors: Drive (craving and withdrawal and compulsion to smoke), Priority (behavioral preference of smoking over other reinforcers), Tolerance (reduced sensitivity to the effects of smoking); Continuity (regularity of smoking) and Stereotypy (invariance of smoking) (Shiffman, Waters, & Hickcox 2004). Okuyemi et al. (2007) used NDSS to assess dependence in a treatment study of African American light smokers. No significant difference was observed between menthol vs. non-menthol cigarette smokers. In another survey (Florida Behavioral Risk Factor Surveillance System), using six items from the NDSS, non-menthol cigarette smokers reported greater dependence compared to menthol cigarette smokers, but multivariate analysis showed that the odds of menthol smoking were not related to nicotine dependence (Hooper et al., 2011).

The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) is a comprehensive, multi-dimensional measure of dependence that yields an overall smoking dependence score (WISDM-68 total score) as well as subscale scores for critical dimensions of dependence, including non-physical indices of dependence e.g., affiliative attachment, automaticity, social/environmental goals (Piper et al., 2004). Higher scores on the WISDM-68 are indicative of greater tobacco dependence. Three non-peer-reviewed secondary analysis of treatment studies using WISDM-68 were conducted by Rietzel (2010 a, 2010 b; 2010 c November submissions).

In the first study, Reitzel (2010 b November submission to FDA) used WISDM-68 to measure dependence in a smoking cessation trial designed to determine the efficacy of using palmtop computers for cessation in African American smokers. Menthol cigarette use was not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, sex, partner status, income, employment status, and educational achievement. When examining each of the 13 subscales of the WISDM-68, in unadjusted analyses, menthol cigarette use was significantly associated with WISDM-68 Craving (β= .46, SE = .21; p = .03) and marginally associated with Taste/Sensory Processes (β= .41, SE = .22; p = .06). Specifically, menthol cigarette use was associated with more craving and taste/sensory-related dependence than non-menthol use. In adjusted analyses,

the only significant association was between menthol cigarette use and WISDM-68 Taste/Sensory Processes (β= .52, SE = .24; p = .03).

Reitzel (2010 c November submission to FDA) also examined dependence with the WISDM-68 in a study that randomized racially diverse pregnant female smokers of diverse race in clinical trial designed to test the efficacy of a motivationally based treatment for smoking relapse prevention. Menthol cigarette use was not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, race/ethnicity, partner status, income, and educational achievement. When the association between menthol use and each of the 13 subscales of the WISDM-68 was examined, in an unadjusted analyses, menthol cigarette use was significantly associated with WISDM-68 Cue Exposure/Associative Processes (β= -.52, SE = .21; p = .01) and Tolerance (β= .38, SE = .20; p = .05). Specifically, menthol cigarette use was associated with less dependence in response to cue exposures/associative processes, but more tolerance-related dependence relative to non-menthol use. However, these significant associations were not maintained in adjusted analyses.

In the third study that utilized the WISDM-68, Reitzel (2010 a November submission to FDA) conducted a longitudinal cohort study designed to examine the social determinants of smoking cessation in 424 racially/ethnically diverse adult smokers. Menthol cigarette use was again not statistically significantly associated with the WISDM-68 total score in unadjusted analyses or in analyses adjusted for age, sex, race/ethnicity, partner status, income, employment status, and educational achievement. None of the 13 subscales of showed any significant relationships in unadjusted or adjusted analyses.

Withdrawal symptoms

Another measure of physical dependence is the extent to which menthol vs. non-menthol cigarette smoking leads to more severe withdrawal symptoms. Only one study examined this topic. Okuyemi et al. (2007), in a treatment study of African American smokers, found no differences in reported withdrawal symptoms between menthol and non-menthol cigarette smokers.

Summary: The evidence is conflicting regarding the effects of menthol on subjective measures of dependence in adult smokers. This conflicting evidence is observed whether they studies are population-based surveys, longitudinal cohort studies or treatment studies.

Adolescents

TPSAC identified six peer-reviewed articles and three unpublished secondary analyses that examined indications of nicotine dependence in adolescent menthol and non-menthol smokers (see Table 5 for descriptions). Five peer-reviewed studies and the three unpublished secondary analyses showed higher indicators of dependence.

Hersey et al. (2006) examined data from 2000 and 2002 NYTS, providing one of the most informative adolescent studies. This study controlled for demographic background (i.e., age, gender and race/ethnicity) and smoking behavior (i.e., length, frequency, and level of smoking) and used the validated Nicotine Dependence Scale for Adolescents (NDSA). Smokers were classified as menthol or non-menthol cigarette smokers based on their usual brand. The study found that adolescent menthol cigarette smokers were 45 percent more likely to score above the median on the NDSA than adolescent non-menthol cigarette smokers (p=0.006).

In another recent study, Hersey, Nonnemaker and Homsi (2010) examined the 2006 NYTS, using a logistic regression model that controlled for background (i.e., school level, gender, race/ethnicity) and

smoking behavior (i.e., length, frequency, and level of smoking). Smokers whose usual brand was menthol had a significantly greater likelihood of endorsing needing a cigarette within 1 hour than among non-menthol smokers (OR=1.86, p=0.003). This relationship was also observed among established smokers (smoking > 100 cigarettes in a lifetime; OR=2.06, p=0.001). Among established smokers, smoking a menthol brand was significantly associated with feeling restless and irritable without smoking (OR=1.39, p=0.049) and with experiencing craving after going without smoking for a few hours (OR=1.35, p=0.035).

Wackowski and Delnevo (2007) also analyzed data from 1345 "established" adolescent smokers (smoked in the past 30 days and smoked at least 100 cigarettes in a lifetime) from the 2004 NYTS. Those who usually smoked menthol cigarettes had higher odds of endorsing two of four dependence related statements, even after controlling for demographic characteristics and smoking pattern. Compared to non-menthol cigarette smokers, menthol cigarette smokers were 2.6 times more likely to go less than an hour before needing a cigarette and 1.6 times more likely to experience cravings after not smoking for a while ($p<.05$). No significant differences were found for items inquiring as to the extent to which they feel restless or irritable after not smoking for a while and their perception about their ability to quit smoking now if they wanted to.

Muilenburg and Legge (2008) surveyed middle and high school students in six public institutions in a large metropolitan area in southeastern U.S. Respondents included 2068 adolescents who had used or at least experimented with smoking. Compared to non-menthol cigarette users, menthol cigarette users smoked significantly more cigarettes based on various indicators of amount (total cigarettes smoked ever, days smoked in month, cigarettes smoked in month and ever smoked daily, OR: 3.41 to 5.35, $p \leq 0.01$), irrespective of race. Menthol cigarette smokers were statistically significantly more likely to report a shorter length of time since their last cigarette (OR=3.22, $p \leq 0.01$). It was important to note that only 18.6 percent of respondents reported smoking menthol cigarettes, though the population was predominantly African American. African American adolescent smokers have a much higher proportion of menthol cigarette smoking (see Chapter 4).

Collins and Moolchan (2006) assessed adolescent smokers (531 menthol and 41 non-menthol smokers) who were being recruited for a smoking cessation study. A higher percentage of menthol cigarette smokers endorsed smoking within the first 5 minutes of awakening compared to non-menthol smokers (45 percent vs. 29 percent). No differences were observed for FTND scores or smoking rate. This study did not describe the racial/ethnic composition of the menthol and non-menthol groups, which could be a potential confounding factor.

In a non-peer-reviewed study, Nonnemaker et al. (2010 November submission to FDA) analyzed a three-year longitudinal cohort, school-based study of 12–18 year olds using the American Legacy Longitudinal Tobacco Use Reduction Study. As noted above (see *Trajectory from initiation to regular smoking or dependence*), this study demonstrated that initiation to menthol cigarettes was positively associated with smoking daily (OR: 1.99, 95% CI: 1.42-2.80), established smoking (OR: 1.94, 95% CI 1.41-266) and lifetime cigarette smoking (OR: 1.94, 95% CI: 1.40-2.68). Menthol use at initiation was also positively and statistically significantly associated with nicotine dependence (B: 1.04, 95% CI: 0.26-1.82).

Hersey, Nonnemaker, Homsi and Allen (2010 November submission to FDA) examined a 2002 survey of 5,511 youth in 48 U.S. schools sponsored by Legacy for Health. Analyses were conducted with 587 youth who had smoked cigarettes over the past three days and had a cotinine level of 5 ng/ml or higher. The study provided descriptive analysis and used multiple regression to model cotinine levels, or score on the Nicotine Dependence Scale for Adolescents controlling for age, sex; race/ethnicity, and the length,

frequency, and level of smoking. Some of the more interesting results were the following: (1) Over all youth, in models that included cigarettes per day smoked, smoking menthol cigarettes did not have greater association with cotinine levels than smoking non-menthol cigarettes. (2) Among youth who smoked for less than one year, there was a statistically significant interaction between menthol use and the mean number of cigarettes smoked per day—menthol cigarette use was associated with increased cotinine levels among youth who smoked more heavily ($p=0.048$ to $p<0.001$). (3) Among youth who smoked for less than one year, smoking menthol cigarettes rather than non-menthol cigarettes was associated with statistically significantly higher levels of nicotine dependence ($p=0.049$). (4) Findings were similar for whites and non-whites, although samples sizes were quite small in some ethnic/racial groups.

Curtin et al. (2010c June submission to FDA) conducted cross-sectional secondary analyses of the NYTS data. With regard to smoking intensity, current menthol cigarette smokers compared to non-menthol cigarette smokers were significantly ($p < 0.001$) more likely to be overrepresented in the higher use categories (>20 cigarettes, 13.1 percent vs. 5.1 percent) and less represented in the lower use categories ($\leq$ 10 cigarettes per day, 73.3 percent vs. 82.9 percent). This observation was statistically significant in both genders and among whites and other racial/ethnic groups, but not African Americans. When controlling for age, gender and race/ethnicity, current menthol cigarette smokers were more likely to smoke 11–20 cigarettes (OR: 1.43, 95 percent CI: 0.97-2.10) and >20 cigarettes (OR: 2.25. 95 percent CI: 1.32-3.85) compared to non-menthol smokers.

DiFranza et al. (2004) found no differences in dependence measures between menthol and non-menthol smokers in a study that followed 267 seventh graders in the Boston area for 30 months. Students were asked at the end of the study if the first cigarette they had smoked was menthol or non-menthol. There were no differences in responses to the Hooked on Nicotine Checklist between menthol and non-menthol smokers. It is important to note that about 50 percent of this population did not know if the first cigarette they smoked was menthol or non-menthol. It was not known what cigarette type subjects continued to smoke.

Summary: There is strong evidence indicating that adolescent menthol cigarette smokers are more dependent on nicotine than adolescent non-menthol cigarette smokers. Seven of the nine studies reviewed by TPSAC incorporated multivariate analyses that controlled for demographic characteristics and smoking history. Differences were found on a dependence measure (Hersey et al. 2006; Nonnemaker et al, 2010; Hersey et al. 2010 November submission to FDA) and on items related to smoking urgency (e.g., needing a cigarette within 1 hour, shorter time to needing a cigarette, inability to go for less than one hour before feeling like they need a cigarette, shorter length of time since last cigarette), and craving or feeling irritable/restless for a cigarette after not smoking for a while (among established smokers) (Hersey, Nonnemaker, & Homsi, 2010; Muilenburg & Legge, 2008; Wackowski & Delnevo, 2007). Furthermore, studies showed greater cigarette use among menthol smokers (Curtin, et al., 2010c; Muilenburg & Legge 2008; Nonnemaker et al. 2010). Hersey et al. (2010 November submission to FDA) observed greater cigarette use among specific populations of menthol smokers, but less cigarette use among menthol smokers overall. A study that did not conduct a multivariate analysis found that more menthol cigarette users smoked within five minutes of waking than non-menthol cigarette users—a measure of smoking urgency (Collins & Moolchan, 2006). Only one small study did not find significant differences on a dependence measure, but this study was limited by problems of recall and small sample size (DiFranza et al. 2004).

CESSATION

This section examines whether menthol cigarette smokers are more or less likely to successfully quit than non-menthol cigarette smokers. Three types of research were reviewed: cross-sectional population surveys, longitudinal cohort studies (e.g., community tobacco intervention studies and epidemiological studies of health effects) and clinical trials of cessation treatments. See Table 6 for a summary of the population survey studies and Table 7 for a summary of the longitudinal cohort and treatment studies.

TPSAC also assessed the effectiveness of approved pharmacologic treatments in menthol cigarette smokers compared to non-menthol cigarette smokers. This section first presents the evidence on cessation in adults, followed by the evidence on cessation in adolescents.

Cessation in adults

Twenty-seven studies were identified and considering mainly the findings for studies that adjusted for confounding factors, 13 showed no effect of menthol cigarette smoking on cessation rates, two studies showed a better outcome among menthol smokers, and 12 studies showed a detrimental effect of smoking menthol cigarettes. These studies are summarized below.

Studies showing no significant differences in cessation between menthol vs. non-menthol smokers

Population surveys

Alexander et al. (2010) used the 2006 TUS-CPS (n=30,176 current everyday or some day smokers 18 years or older) to determine differences in quitting behaviors between menthol and non-menthol cigarette smokers among groups with different occupational status. The results showed a trend toward a greater number of menthol cigarette smokers ever quitting smoking for one day or longer (70.9 percent vs. 69.5 percent, p=0.09), a statistically significantly higher number of menthol smokers quitting smoking for one day or longer *in the past 12 months* (55.0 percent vs. 50.3 percent, p<0.001). No differences between menthol and non-menthol cigarette smokers were seen in number of quit attempts in the past 12 months (mean=4.0, SE=0.2 vs. mean=3.8, SE=0.1) or longest length of time (months) they stopped smoking (mean=2.0, SE=0.2 vs. mean=2.2, SE=0.2). For blue-collar workers, menthol smokers were more likely to ever stop smoking for one day or longer compared to non-menthol smokers (71 percent vs. 65 percent, p=0.0008) and to stop smoking for one day or longer *in the past 12 months* (56 percent vs. 49 percent, p=0.002). Among service workers, menthol smokers were less likely to ever stop smoking for one day or longer compared to non-menthol cigarette smokers (65 percent vs. 71 percent, p=0.007). Using logistic regression to control for occupational status and workplace policies, no significant difference was seen in the likelihood of menthol vs. non-menthol cigarette smokers ever to quit smoking for one day or longer (OR: 0.98, 95% CI: 0.83-1.15).

Fagan et al. (2002) conducted a secondary analysis of the 2003 TUS-CPS to identify factors associated with quit attempts and serious intention to quit among young adult smokers ages 18–30 (n=7,912). Subjects were divided into daily (everyday) and non-daily (some day) smokers. Multivariate logistic regression for the outcome of making 1 or more quit attempts (stopping smoking for 1 day or longer) during the past 12 months among menthol vs. non-menthol smokers showed an OR (95% CI) of 1.00 (0.89-1.16) for current smokers, 1.00 (0.85-1.18) for daily smokers and 0.99 (0.62-1.41) for nondaily smokers. Multivariate logistic regression of 1 or more quit attempts during the past 12 months among smokers who reported serious intention to quit within the next 6 months showed non-significant effects

of menthol among current smokers and daily smokers. However among non-daily smokers, the OR (95% CI) was 1.35 (0.60-3.03) but non-significant.

Fagan et al. (2010) conducted a secondary analysis with the pooled 2003 and 2006/07 TUS-CPS. Data was analyzed among current daily smokers (n=46,273, 18 years or older). Statistically significant differences were observed for number of quit attempts made for one day or longer among those who made quit attempts in the past 12 months, with the higher number observed for the menthol cigarette smokers (mean=2.23, SE=0.04 vs. mean=2.14, SE=0.02, $p < 0.05$). There were no differences in the length of abstinence in the past 12 months between menthol and non-menthol cigarette smokers who tried to quit (mean=0.32, SE= 0.01 for both groups). Bivariate and multivariate models did not show any significant association between usual cigarette brand (either menthol vs. non-menthol) and quit attempts in past 12 months (OR: 0.92, 95% CI: 0.83-1.02 to OR: 1.10, 95% CI: 0.91-1.34) or duration of quit attempts > 2 weeks in the past 12 months across various number of cigarettes categories (OR: 0.93, 95% CI: 0.79-1.12 to OR: 1.05, 95% CI: 0.82-1.36).

Longitudinal cohort studies

Murray et al. (2007) examined smokers (n=5,887 smokers aged 35-60 years) with evidence of mild to moderate airflow obstruction who enrolled in the Lung Health Study from 1986 to 1989. Menthol status was determined by inquiring whether the type of cigarettes they smoked was plain or menthol. Participants were randomly assigned to one of three intervention groups to determine their effects in preventing COPD: (a) smoking cessation and ipratropium, an inhaled bronchodilator, (b) smoking intervention and placebo inhaler and (c) usual care. For the smoking cessation analysis, data for the five years after enrollment was examined. At annual follow-up visits, an inquiry was made on whether participants had smoked cigarettes in the past 12 months. Menthol vs. non-menthol differences were examined for three classifications: (a) sustained quitters (participants who were biochemically confirmed as quitters at the five annual visits and could recall no month with mean smoking greater than one cigarette/day at any annual visit; (b) intermittent smokers (participants who were biochemically confirmed as quitters at some annual visits and as smoking at other annual visits, (c) continuing smokers (participants who were identified as smoking at all annual visits). No significant differences between menthol vs. plain cigarette smokers were observed in the percentages of participants who were sustained quitters (male: 16.6 percent vs. 17.2 percent; females: 13.8 percent vs. 15.4 percent) intermittent (male: 26.0 percent vs. 26.9 percent; females: 30.4 percent vs. 28.7 percent) or continuous smokers (male: 57.3 percent vs. 55.9 percent; female: 55.9 percent vs. 55.9 percent) by use of menthol cigarettes.

Hyland et al. (2002) examined smokers (n=13,268 smokers 25-64 years old) enrolled in the Community Intervention Trial for Smoking Cessation (COMMIT), which involved selecting a random sample of smokers from a representative sample. COMMIT was a randomized community-based intervention trial for smoking cessation in 11 matched pairs of communities. These smokers completed a telephone tobacco use survey in 1988 and were re-interviewed in 1993. Use of menthol cigarettes (determined by participants' report of whether their cigarette brand was menthol or plain) was analyzed at baseline and in 1993 when six-month cessation was assessed. Successful cessation was measured by negative responses to the questions, *Do you smoke now?* and *Have you smoked any cigarettes in the past 6 months?* Multivariate regression was used to assess association of menthol cigarette use with outcomes controlling for other factors related to dependence (e.g., age, sex, education, cigarettes per day, time to first cigarette, history of past serious quit attempts). No association was observed between menthol cigarette smoking and cessation both overall (RR: 1.00, 95% CI: 0.90-1.11) and in race-specific analysis (whites RR: 0.94, 95 percent CI: 0.83-1.05; African Americans RR: 1.04, 95 percent CI: 0.73-1.47; Hispanic

RR: 1.22, 95 percent CI: 0.80-1.87). However, the data showed a greater likelihood of more than two quit attempts among menthol smokers (OR: 1.16, 95% CI: 1.03-1.30).

In a non-peer-reviewed study, Hyland and Rivard (2010 b November submission to FDA) conducted another analysis of the COMMIT data set. A total of 2,095 cohort members were included in the analysis. The association between cessation as determined in 2005 and use of menthol cigarettes in 1988 through 2001 was examined using logistic regression models which controlled for gender, age, race, education, frequency of alcohol consumption, age started smoking, amount smoked, time to first cigarette, number of past quit attempts, other smokers in the household, and desire to quit smoking. There were three key cessation indicators.

> (a) Quit Attempts in 2005: *Since 2001, how many times have you made a serious attempt to quit smoking?* A response of 1 or greater was considered a quit attempt.
>
> (b) Cessation in 2005*: Have you smoked any cigarettes in the last six months?* A current smoker was defined as a person who smoked in the six months before the survey; a quitter was defined as a person who was a current smoker in 2001 and a former smoker in 2005.
>
> (c) Cessation in 2005 among those who attempted.

Menthol smokers were equally as likely as non-menthol smokers to try to quit smoking in the overall population (OR: 0.91, 95% CI: 0.72–1.15, 57.5 percent vs. 60.3 percent), among African Americans (OR: 1.24, 95% CI: 0.27–5.67, 55.3 percent vs. 62.5 percent) and among whites (OR: 0.91, 95% CI: 0.71–1.17, 58.8 percent vs. 61.0 percent). Menthol smokers were equally likely to be successful in quitting in the overall population (OR: 0.84, 95% CI: 0.61–1.15, success rates 14.7 percent vs. 18.5 percent) and in whites (OR: 0.79, 95 percent CI: 0.56–1.11, 14.7 percent vs. 19.1 percent). The odds ratio for successful quitting could not be calculated for African Americans because of the small sample size. For African Americans, success rates were 17.0 percent for menthol and 9.4 percent for non-menthol. Menthol smokers were also equally likely as non-menthol smokers to be successful in quitting among those who had made a quit attempt as observed in the overall population (OR: 1.03, 95% CI 0.71–1.48, success rates 22.1 percent vs. 24.5 percent) and among whites (OR: 0.96, 95% CI: 0.65–1.41, success rates 22.0 percent vs. 25.2 percent). Among African Americans, the success rate was 26.9 percent for menthol vs. 10.0 percent for non-menthol smokers. Unfortunately, in this study, the number of blacks was quite low (n=91 total, and lower when examining the effects of menthol).

Muscat et al. (2002) examined adult smokers (19,545 current and ex-smokers, 16,540 non-menthol smokers and 3,005 menthol smokers) enrolled in a case-control study on smoking tobacco-related cancers between 1981 and 1999. Ever smokers were defined as having smoked at least one cigarette each day for one year. Current smokers smoked at least one cigarette each day for the preceding year. Ex-smokers were smokers who did not smoke at least one cigarette each day for the preceding year. Menthol status was based on whether the subject reported the last brand smoked as menthol. Unconditioned logistic regression analysis was used to estimate the prevalence odds ratio (POR) of current vs. ex-smoker by menthol status. The models adjusted for sex, education, case-control status, years of smoking and cigarettes per day. Menthol was not associated with continued smoking. The POR was not significant among African American (POR: 1.1; 95% CI: 0.8–1.4) or white (POR: 1.1, 95% CI: 1.0-1.3) smokers. The main weakness of this study was the use of a hospital-based control series rather than a random population-based sample. In addition, the sample was mostly older adults. Furthermore, the criterion for ex-smokers was quite unusual (not smoking each day for the past year).

In an in-press article, Blot et al. (Blot et al., in press) analyzed data from the Southern Community Cohort Study (SCCS), a prospective study of 85,806 racially diverse adults to examine racial disparities in cancer and other chronic diseases. Adults ages 40–70 years residing in 12 southern states were predominantly recruited through mailings to stratified random samples of the general population and at a community health center. Subjects were followed from March 2002 to September 2009. Subjects were classified as smokers (defined as those who smoked 100 cigarettes in their lifetime) or former smokers. Menthol status was determined by whether or not they usually smoked menthol cigarettes. During follow-up, subjects were classified as quitting or continuing to smoke. Results from data collected at the time of enrollment showed that African American, menthol and non-menthol cigarette smokers had equal odds of quitting after adjustments for age, income, education, recruitment source, pack years smoked, BMI) (OR=1.03; 95% CI: 0.96–1.11). White menthol cigarette smokers were statistically significantly more likely to quit than non-menthol cigarette smokers (OR=1.55, 95% CI: 1.41–1.70). Among smokers who were followed for an average of 4.3 years (7,886 and 4,487 current smokers of menthol and non-menthol during baseline, respectively), the odds (adjusted for the same variables above plus race) of quitting were similar among menthol and non-menthol smokers (OR=1.02, 95% CI: 0.89–1.16). This is a large study, but interpretation of the findings needs to consider the older age of this population, which limits the generalizability of results.

Treatment studies

Cropsey et al. (2009) examined differences in treatment outcome among white and African American female prisoners (N=233; white=109, 38.1 percent menthol while in prison; African American=124, 81.3 percent menthol while in prison) who underwent a 10-week nicotine replacement and group psychotherapy intervention. Some were randomized to a wait list for six months before entering the cessation component. Smoking cessation was assessed across the 12-month follow-up period (weeks 1-10 and 1 week and 3, 6 and 12 months post-treatment). Seven-day point prevalence abstinence (not smoking in the past seven days) was determined at each assessment period. Although whites had statistically significantly higher overall smoking cessation rates across time compared to African American women, menthol cigarettes were not associated with these differences in quit rates and the Interaction between race and smoking menthol was not significant. This study was limited by the relatively young age of participants (mean age was early to mid-thirties) and the select population of smokers.

Fu et al. (2008) examined the effects of menthol cigarette smoking on cessation among a multi-ethnic sample of smokers (N=1,343, white=76%, African American=14%, other=10%, 342 menthol users, 19 years and older) enrolled in a multi-site, randomized controlled trial of an intervention designed to facilitate repeat tobacco cessation treatment. Subjects who had received a prescription for NRT or bupropion for smoking cessation from one of five Veterans Administration Medical Centers were assigned to usual care or intervention. The intervention consisted of phone calls to patients with the aid of a computerized provider-prompt to assess smoking status, interest in making another quit attempt and preferences for tobacco treatment. The primary outcome was seven-day point prevalence abstinence at six months post-randomization. Menthol status was assessed with a follow-up survey by inquiring if subjects smoked menthol cigarettes two years ago (one year prior to the index quit attempt). Analysis on the effect of menthol was adjusted for covariates including predictors of abstinence as well as ethnicity, gender, site and time to first cigarettes. No significant effects of menthol on smoking cessation rates were observed, using multivariate analysis (OR: 1.31, 95% CI: 0.95–1.82) and unadjusted logistic regression analysis (OR: 1.14, 95% CI:0.85–1.53). Although a significant interaction between the intervention and menthol cigarettes was observed (p=0.02), with greater success among menthol smokers in the treatment condition (OR: 1.80, 95% CI: 1.18–2.76), this interaction was no longer

statistically significant after Bonferroni correction for multiple comparisons. Therefore, this study found that menthol did not decrease smoking cessation among older smokers during a quit attempt aided by pharmacotherapy. No differences were found in number of 24-hour quit attempts in the past month. The primary weaknesses of this study was the two-year recall for the assessment of menthol cigarettes with no brand switching information during this period, and the older age of the smoking population (mean age=56 years old).

Harris et al. (2004) examined predictors for successful quitting among 600 African Americans participating in a smoking cessation trial. This cessation study involved a double-blind, placebo-control randomized trial examining bupropion vs. placebo prescribed for seven weeks. The outcome variable was seven-day biochemically confirmed abstinence among 535 participants who completed the seven-week medication phase. Although the univariate analysis showed that not smoking menthol cigarettes was a predictor of cessation success (p=0.0062; 41.53 percent vs. 28.3 percent), menthol cigarette use was not a predictor in the logistic regression analysis. It should be noted that this is the same population of smokers used in the Okuyemi et al. (2003) study described below.

In a non-peer-reviewed secondary analysis of data, Reitzel, in her November submissions to FDA, examined the menthol cigarette effects in three treatment studies, two of which found no differences in treatment outcome. One study (Reitzel, 2010 a), Project CARE, was a longitudinal cohort study designed to examine the social determinants of smoking cessation and included 424 adult (21 years or older) treatment-seeking smokers (34 percent non-Latino African Americans, 33 percent Latino, and 33 percent non-Latino white) recruited from the Houston, TX area and enrolled from 2005–2007. Menthol cigarette smoking status was determined by asking participants if their regular brand of cigarettes was menthol or non-menthol. All subjects received six weeks of nicotine patch treatment, six brief smoking cessation counseling sessions and self-help materials. Treatment success was defined as biochemically verified continuous abstinence from smoking since the quit date through week 26 post-quit. Both unadjusted and adjusted analyses were conducted. Menthol cigarette users had lower rates of continuous abstinence than non-menthol cigarette users at all follow-up points. However, menthol cigarette use did not statistically significantly predict continuous abstinence from smoking in analyses adjusted for time (p =0 .73; n =680), or in analyses adjusted for age, sex, race/ethnicity, partner status, income, employment status, educational achievement, time, cigarettes smoked per day, and time to the first cigarette of the day (p = 0.84; n = 607). Continuous abstinence rates within each racial/ethnic group did not differ by menthol cigarette use status in unadjusted or adjusted analysis.

In the other non-peer-reviewed paper, Reitzel (2010 b) conducted a secondary analysis of Project BREAK FREE, a randomized clinical trial that examined the efficacy of smoking cessation treatment delivered on palmtop computers. This trial recruited 399 treatment seeking, African American smokers from 2005–2007 from the Houston, TX area. Menthol status was determined by asking participants if their regular brand of cigarettes was menthol or non-menthol. Outcome variable and analysis was similar to the previously described study (Reitzel, 2010 a). Menthol users had higher rates of continuous abstinence than non-menthol users at all follow-up points. However, menthol cigarette use did not significantly predict continuous abstinence from smoking in analyses adjusted for time and treatment group (p = .40; n = 573), or in analyses adjusted for age, sex, partner status, income, employment status, educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day (p = .30; n = 457).

Studies showing a higher rate of cessation among menthol smokers

Population surveys

Cubbin et al. (2010) conducted a secondary data analysis using the 2005 NHIS and Cancer Control Supplement of current smokers (those who smoked at least 100 cigarettes and currently smoke some days or everyday) and former smokers (those who smoked at least 100 cigarettes but did not smoke right now) (n=31,428, ages 25–65). Menthol status was determined by asking whether the usual cigarette brand was menthol (in the 12 months before quitting for former smokers). All analyses were weighted for income and education. No statistically significant differences were observed for quit attempts in the past year by cigarette type among current everyday smokers by gender and racial/ethnicity. There was, however, a trend for menthol smokers for both genders and all racial/ethnic groups to have higher levels of quit attempts than similar subgroups of non-menthol smokers (e.g., as great as 10–20 percent difference). When examining quit duration among former smokers, statistical significance was observed only in white female menthol smokers. They had abstained about 2.5 years longer than white female non-menthol smokers (15.0 vs.12.5 years, $p<0.01$).

In a non-peer-reviewed study, Hyland and Kasza (2010 a November submission to FDA) conducted a secondary analysis of a nationally representative sample of adult smokers (N=7532) who were interviewed as part of the International Tobacco Control Four Country Survey (ITC-4) between 2002 and 2008. ITC-4 is an ongoing prospective cohort survey conducted with nationally representative respondents from four countries, including the United States. Current smokers were defined as persons who reported having smoked at least 100 cigarettes in their lifetime and who currently smoked on at least a monthly basis. Menthol cigarette use status was determined by the brand of cigarettes smoked. Cessation behaviors were defined as:

> (a) Making a quit attempt. Respondents were asked: *Have you made any attempts to stop smoking since we last talked with you?*
>
> b) Successful smoking cessation, defined as no longer smoking on at least a monthly basis; and
>
> c) Successful cessation among those making a quit attempt.

Adjusted associations between menthol cigarette use and cessation behaviors were estimated for respondents overall, as well as for separate racial/ethnic groups and genders. The menthol x race/ethnicity and menthol x gender interaction terms were specifically tested in the overall models. Multivariate analyses included an adjustment for respondent gender and race/ethnicity (unless stratified on these variables), age, education, income, ever made a quit attempt before baseline, and intention to quit. Additionally, outcomes were also adjusted for the heaviness of smoking index. Results showed white respondents (particularly women) who smoked menthols were less likely than those who smoked non-menthols to report making quit attempts (OR: 0.84, 33.5 percent vs. 38.4 percent in both sexes and OR: 0.81, 34.3 percent vs. 40.1 percent in females, $p<0.05$), while African American women who smoked menthols were more likely to report successful cessation (OR:3.58, 12.8 percent vs. 8.5 percent, $p<0.05$) and successful cessation among those who attempt to quit (OR:3.96, 24.6 percent vs. 15.8 percent, $p <0.05$) than non-menthol cigarette smokers.

Studies showing a lower rate of cessation among menthol smokers

Population surveys

Gundersen, Delnevo and Wackowski (2009) analyzed data from the 2005 U.S. National Health Interview Survey (NHIS) to determine the relationship between race/ethnicity, menthol smoking and cessation in a nationally representative sample. The sample included 7,815 white, African American and Hispanic current and former cigarette smokers who did not use other tobacco products and who had made a quit attempt. Menthol cigarette smoking status was determined by whether or not the usual brand of cigarettes in the past 12 months or the 12 months prior to quitting were menthols. The outcome variable was being a current smoker (having smoked 100 cigarettes in a lifetime and now smoking everyday or some days) vs. being a former smoker (having smoked 100 cigarettes in a lifetime but not currently smoking). Multiple logistic regression analysis was used to test the relationship of menthol smoking with cessation, controlling for various demographic, smoking behavior and risk perception factors (e.g., sex, age, cigarettes per day, education, perceived likelihood of getting cancer). Overall, menthol smokers were less likely than non-menthol smokers to be former smokers (56.9 percent vs. 61.5 percent, $p < 0.01$). This relationship was statistically significant among African Americans (43.7 percent vs. 62.1 percent, $p < 0.01$) and Hispanics (48.5 percent vs. 61.2 percent, $p < 0.01$), but not among whites (62.8 percent vs. 61.6 percent, $p=0.44$). In the multiple logistic regression analysis, when African Americans and Hispanics were collapsed into non-whites, non-white menthol smokers were statistically significantly less likely to have quit smoking compared to non-menthol smokers (AOR: 0.55, 95% CI: 0.43–0.71, $p<0.01$). This result was largely driven by the Hispanic group (AOR; 0.61, 95% CI: 0.39–0.97, $p=0.04$) and not by African Americans (AOR; 0.78, 95% CI: 9.56–1.00, $p=0.15$). Among white smokers, menthol cigarette smokers were more likely to be former smokers than non-menthol smokers (AOR; 1.17, 95% CI: 1.00–1.36, $p<0.05$).

Similarly, Stahre et al. (2010) conducted a secondary analysis of cross-sectional data from the 2005 National Health Interview Survey Cancer Control Supplement examining current smokers (n=6055, 1,700 menthol; 4,355 non-menthol) and former smokers (n=5949, 1,515 menthol smokers; 4,434 non-menthol smokers). Univariate analysis of the data was conducted to determine variables that differed significantly by menthol status. Menthol status was determined by whether or not the respondent's usual brand of cigarettes was menthol. Multiple logistic regression analysis was used to model the associations of menthol smoking status, demographic characteristics and smoking-related characteristics with the population quit ratio and utilization of quit aids. In the univariate analysis, the quit ratio was significantly higher among non-menthol vs. menthol smokers (50 percent vs. 47 percent, $p=0.014$). When examining quit ratios within races, no significant differences in quit ratios for menthol vs. non-menthol smokers were observed for whites (52 percent vs. 50 percent), Asian Americans (38 percent vs. 42 percent), American Indian/Alaska Native (52 percent vs. 35 percent) or Hispanics (40 percent vs. 45 percent). However, quit ratios were significantly lower for African American menthol vs. non-menthol smokers (34 percent vs. 49 percent, $p < 0.001$). In multiple logistic regression analysis, there was a significant interaction between race and menthol smoking status. African American menthol smokers were significantly less likely to quit smoking than white non-menthol smokers (OR: 0.72, 95% CI: 0.53–0.97). No analysis was done with menthol status alone. Menthol cigarette smoking was not associated with utilization of quit aids.

Trinidad et al. (2010) conducted a secondary data analysis of the 2003 and 2006-07 TUS-CPS that examined current smokers and their interest in seriously quitting in the next six months and former smokers (ever smokers) who had successfully quit for at least 6 months at the time of the survey.

Among African Americans (OR: 1.62, 95% CI: 1.35–1.95) and Hispanics/Latinos (OR: 1.21, 95% CI: 1.00–1.47), those who currently smoked menthol cigarettes were more likely to be seriously considering quitting in the next six months than non-menthol smokers, after adjusting for socio-demographic variables. Among former smokers, those who smoked menthol compared to non-menthol cigarettes were less likely to have successfully quit for at least six months within various racial/ethnic groups: African Americans (AOR: 0.23, 95% CI: 0.17–0.13); Asian Americans/PI (AOR:0.22, 95% CI: 0.11–0.45); Hispanics/Latinos (AOR:0.48, 95% CI: 0.34–0.69) and non-Hispanic whites (AOR:0.28, 95% CI: 0.25–0.33).

In a non-peer-reviewed submission, Delnevo et al. (2010 November submission to FDA) conducted a secondary analysis of the 2003 and 2006/7 TUS-CPS. In this analysis, they attempted to address the limitations of Gundersen et al. (2009), that is, the inadequate control of socioeconomic variables, and the potential lack of statistical power among the African American population. The sample consisted of white, African American and Hispanic current smokers and former smokers who quit in the past five years. In addition this study examined two subpopulations of Hispanics: Mexican vs. Puerto Rican in origin. Current smoker was defined as meeting two conditions: having smoked 100 cigarettes in a lifetime and now smoking "everyday" or "some days." Former smoker was defined as meeting two conditions: having smoked 100 cigarettes in a lifetime and now smoking not at all. With regard to assessing menthol status, current smokers self-reported whether or not their usual brand of cigarettes in the past 12 months was menthol. Former smokers, who quit in the past five years, reported whether or not their usual brand 12 months prior to quitting was menthol. Because the relationship between menthol and cessation may be impacted by sample restriction decisions, the authors examined five sample restrictions:

1. Current and former smokers who quit within the past five years, regardless of past quit attempts or current other tobacco product (OTP) use;

2. Current and former smokers who quit within the past five years who did not report current OTP use;

3. Current and former smokers who quit within the past five years who reported ever having made a quit attempt;

4. Current and former smokers who quit within the past five years who did not report current OTP use and have ever made a quit attempt (replicates Gundersen, et al., 2009); and

5. Past 12-month cigarette smokers who made a quit attempt or had quit.

Multiple logistic regression was used to estimate the odds ratio of being a former smoker for menthol smokers relative to non-menthol smokers while controlling for other independent variables (education, household income, gender, age, seasonality and for restriction 5, exposure in the past 12 months to cigarette excise tax increase. Using sample restriction 1, menthol smokers were less likely to be former smokers than were non-menthol smokers (AOR=0.914, 95% CI: 0.868–0.961) overall. This relationship held among whites (AOR: 0.928, 95% CI: 0.877–0.982) and African Americans (AOR: 0.810, 95% CI: 0.670–0.979). The magnitude of the relationship among Hispanics was similar to whites, but was not statistically significant (AOR=0.936, 95% CI:0.793–1.105). Statistically significant findings were observed across various sample restrictions, with overall AOR ranging from 0.902 for sample restriction 3 to 0.932 for sample restriction 2. Only in sample restriction 5 was the finding not statistically significant. Similarly, the relationship between menthol smoking and cessation was statistically significant across sample restrictions among whites except in sample restriction 5. Among African Americans, the

relationship was statistically significant across all restrictions, with an AOR ranging from 0.684 in sample restriction 4 to 0.810 in sample restriction 1. Among Hispanics, the relationship was statistically significant in sample restriction 5 only. However, when examining Hispanics by origin, menthol smokers of Mexican origin are substantially more likely to have quit smoking, though this was statistically significant only in sample restrictions 2 (AOR=1.338, 95% CI: 1.039–1.722) and 4 (1.349, 95% CI: 1.016–1.790). In contrast, menthol smokers of Puerto Rican origin were substantially *less* likely to have quit relative to non-menthol smokers across all categories, with adjusted odds ratios ranging from 0.421 in sample restriction 5 to 0.63 in sample restriction 2. Because of the number of analyses, the data is provided in at the end of this chapter. This study offers evidence that smoking menthol cigarettes leads to less cessation among smokers, in particular among African Americans and Puerto Rican Hispanics.

In an in-press embargoed article, Levy et al.(2011 in press) analyzed the 2003 and 2006-07 waves of the TUS-CPS with state-level tobacco control spending, prices and smoke-free air laws. The sample was comprised of individuals who are 18 years and older (34,260 in the 2003 wave and 31,250 in the 2007 wave). Current smokers were defined as having met two conditions: smoked at least 100 times in a lifetime and were currently smoking. Those not currently smoking were defined as former smokers. Former smokers were categorized a recent quitters (quit in the last year and for at least three months) and long-term quitters (quit in the last five years and for at least three months). Socio-demographic characteristics (race/ethnicity, age, income, education, marital status, state tobacco control policies, and survey year) that influence cessation behavior were controlled in the data analysis. The results showed menthol smokers have a greater likelihood of making quit attempts in the last year than non-menthol smokers (4.3 percent higher in 2003 and 8.8 percent higher in 2007-08). However, the likelihood of quitting was 4 percent lower for quit in the past year in 2003 and 12 percent less likely in 2007. The likelihood of quitting was 11 percent lower for quit in the past five years in 2003 and 14 percent lower in 2007 among menthol compared to non-menthol smokers. Using logistic regression analysis, those who smoked menthol are more likely to make a quit attempt than non-menthol cigarette smokers. Quit rates were lower among menthol vs. non-menthol cigarette smokers with 3.5 percent lower likelihood of quitting in the last year (AOR: 0.92 95% CI: 0.91-0.92 to AOR: 0.97, 95% CI: 0.96-0.97) and about 6 percent for those who quit within the last five years (AOR: 0.94, 95% CI: 0.94-0.94 to AOR: 0.95, 95% CI: 0.95-0.95) using models that do or do not control for degree of dependence. Quit success in the past five years was even lower among African Americans who smoked menthol cigarettes (AOR: 0.97, 95% CI: 0.97-0.97) and young adults (AOR: 0.94 95% CI: 0.94-0.94), although the likelihood of success was higher among African American menthol smokers (AOR: 1.24 95% CI: 1.23-1.25) and younger menthol smokers (AOR: 1.14 95% CI: 1.13-1.15) who quit in the past year.

Longitudinal cohort studies

Pletcher et al. (2006) used the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a longitudinal study of risk factors for coronary artery disease, to determine the effects of menthol cigarettes on smoking cessation and health outcome measures. Using this dataset, 1,535 smokers (952 menthol and 563 non-menthol) ages 18–30 and healthy were identified in 1985. Participants underwent baseline examination and then follow-up at years 2, 5, 7, 10 and 15 with 74 percent retention at year 15. At each examination, participants were questioned on four items: recent quit attempts, success in recent quit attempts, no current smoking since the past two times they were examined, and any relapses. After adjusting for ethnicity, sex, age, demographic and social factors, a trend toward menthol smokers experiencing lower cessation (OR: 0.71, 95% CI 0.49–1.02, p=0.06) and a lower likelihood of recent quit attempts (p=0.11) compared to non-menthol smokers was found. The results were not statistically significant. However, a statistically significant increase in the risk of relapse, that is, non-sustained quitting, was observed in menthol vs. non-menthol cigarette smokers (OR: 1.89, 95% CI, 1.17–

3.05, p=0.009). Results were similar among African Americans and whites, after additional adjustment for cigarettes smoked daily at baseline. Baseline menthol cigarette smokers were more likely to still be smoking during follow-up examinations compared to baseline non-menthol cigarette smokers (69 percent vs. 54 percent, p <0.001), but stratification by ethnicity attenuated this association. The main weakness of this study was that it was difficult to tease apart the effects of ethnicity and menthol preference due to the limited number of white menthol smokers (N=189) and African American non-menthol smokers (N=95). The authors pointed out that differences in nicotine levels in cigarettes may confound results.

Treatment studies

Foulds et al. (2006) conducted a retrospective cohort analysis of 1,021 patients (670 white, 219 African American, 80 Hispanics, 52 other) who attempted to quit tobacco at a specialist tobacco dependence treatment outpatient clinic in New Jersey during 2001–2003. Treatment was comprehensive and multidisciplinary; it included assessment of the smoker, an individualized treatment plan that recommended medication and group treatment (six weekly 90-min. sessions), and establishment of a target quit date. A four-week follow-up was conducted in person (39 percent) or on the telephone (61 percent). Biochemical verification was obtained among those who attended in-person follow-up. Six-month follow-up was collected by telephone contact or by mail. The outcome measure was abstinence from tobacco over the past seven days. Although univariate analysis demonstrated that menthol compared to non-menthol cigarette smoking had a significant effect on abstinence success (lower rates at four weeks, 35.4 percent vs. 42.3 percent and at 26 weeks, 24.9 percent vs. 35.8 percent), multivariate analysis (which took into account various demographic and tobacco history variables) showed a trend toward a significant effect of menthol, p=0.053). Similarly, Gandhi et al. (2009) conducted a retrospective cohort analysis of 1,688 participants (778 smoked menthol cigarette smokers: 302 African American, 348 white, 99 Latino, 20 other; and 910 non-menthol cigarette smokers: 72 African American, 738 white, 50 Latino, 50 other) who attended the same specialist smoking cessation service in New Jersey during 2001–2005 and who set a quit date and attempted to quit smoking. This study extended the sample size of the Foulds et al. (2006) study. The outcome measure was self-reported seven-day point prevalence abstinence from tobacco products. Biochemical verification was available on some people, but accuracy of self-reported abstinence ranged from 99.4 percent to 100 percent. Unadjusted abstinence rates were lower with menthol vs. non-menthol cigarette smokers at the four-week follow-up overall (no values given) and among whites (43 percent vs. 50 percent, p=0.031), African Americans (30 percent vs. 54 percent, p <0.001) and Latinos (23 percent vs. 50 percent, p=0.001). At the six-month follow-up, similar observations were made overall (no values given), and among African Americans (18 percent vs. 36 percent, p=0.001) and Latinos (11 percent vs. 28 percent, p=0.009), but not whites. At four-week follow up, African Americans, Latino and white non-menthol smokers had similar quit rates (54 percent, 50 percent and 50 percent, respectively). In contrast, among menthol smokers African Americans and Latinos (30 percent and 23 percent, respectively) had lower quit rates compared to whites (43 percent p< 0.001). Logistic regression analyses showed a significant two-way interaction between race/ethnicity and menthol cigarette smoking status (p=0.04) at four weeks. African American and Latino menthol smokers had significantly lower unadjusted (OR: 0.34, 95% CI: 0.17–0.69 and OR: 0.30, 95% CI: 0.14–0.62, respectively) and adjusted odds (OR: 0.32, 95% CI: 0.16–0.62 and OR: 0.43 95% CI: 0.1–0.9, respectively) of quitting than their non-menthol counterparts. For whites this finding was evident only for the unadjusted analysis (OR: 0.75, 95% CI: 0.58–0.97). At the six month follow-up, African American menthol smokers had half the odds of being abstinent compared to non-menthol smokers, for unadjusted (OR: 0.40, 95% CI: 0.23–0.70) and adjusted (OR: 0.48, 95% CI: 0.25–0.9) analysis which controlled for specific covariates (e.g.,

gender, education and employment status). Statistically significant differences were observed in Latinos only for unadjusted analysis (OR: 0.32, 95% CI.13-0.70). The difference between four-week quit rates among menthol and non-menthol cigarette smokers was greater among those who were unemployed vs. employed, especially among African Americans (16 percent vs. 43 percent, p=0.03) whereas no differences were observed among the employed African Americans (42 percent vs. 56 percent, p=0.20).

Two treatment studies were conducted among African American smokers. Okuyemi et al. (2007) examined 615 menthol and 138 non-menthol light smokers (10 cigarettes a day or less) in a 2 x 2 treatment study (nicotine replacement vs. placebo for eight weeks; motivational interviewing vs. health education for six sessions). Participants reported use of menthol or non-menthol cigarettes. Using logistic regression, no significant differences were observed for seven-day verified abstinence rates at eight weeks for non-menthol vs. menthol (26.8 percent vs. 22.6 percent). However, at 26 weeks post-randomization, seven-day verified abstinence rates were significantly lower for menthol smokers (11.2 percent vs. 18.8 percent, p=0.015). Using logistic regression, at 26 weeks non-menthol cigarette smokers who received nicotine gum had statistically significantly higher abstinence rates than menthol cigarette smokers who had received nicotine gum (p=0.013). There were no statistically significant differences in abstinence rates between menthol vs. non-menthol cigarette smokers who were assigned placebo. Similar findings were observed for those who received Health Education: menthol smokers had lower abstinent rate compared to non-menthol smokers (p=0.037).

In another study, Okuyemi et al. (2003) recruited African American smokers from an inner-city health center for a double-blind, placebo-controlled randomized trial examining bupropion vs. placebo prescribed for seven weeks. Subjects were 471 menthol and 129 non-menthol African American cigarette smokers who smoked at least 10 cigarettes per day. Menthol cigarette use was ascertained by the question, *Do you usually smoke menthol cigarettes?* Outcome variable was seven-day biochemically confirmed abstinence among 535 participants who completed the seven-week medication phase. Logistic regression was used to determine the effects of menthol cigarettes on smoking cessation. Seven-day point prevalence abstinence from smoking at six weeks was statistically significantly lower for menthol vs. non-menthol cigarette smokers (28.3 percent vs. 41.5 percent, p=0.006), but no differences were found at the six-month follow-up (21.4 percent vs. 27.0 percent). When separated by treatment, among those who received bupropion, the seven-day point-prevalence abstinence rate at six weeks was higher for non-menthol compared to menthol cigarette smokers (60.3 percent vs. 36.2 percent, $p < 0.01$), but no there were no differences within the placebo group (23.3 percent vs.20.5 percent). Statistically significant menthol effects were observed for those under the age of 50 at six-week follow-up, with lower cessation rates among menthol vs. non-menthol smokers (24.9 percent vs. 44.4 percent, $p<0.01$). No differences were observed among smokers 50 and older. In a stepwise logistic regression analysis, among smokers < 50 years old, non-menthol cigarette smokers were twice as likely to quit smoking at the end of six weeks compared to menthol smokers (OR: 2.02, 95% CI: 1.03–3.95).

In non-peer-reviewed submission, King et al. (2010 November submission to FDA) conducted a secondary analysis of data collected from a double-blind, randomized placebo-controlled trial of the efficacy of the oral opioid antagonist, naltrexone, in combination with nicotine patch and individual behavioral counseling. Participants were equally randomized to one of two medication groups: patch + counseling (PC) or patch + counseling + naltrexone (PCN). Study participants included 110 African Americans and 181 whites. Among whites, 45 were menthol cigarette users, and 136 were non-menthol cigarette users, but among African Americans, 91 were menthol cigarette users and 19 were non-menthol cigarette users. Subjects were recruited from 2006 to 2009. In a univariate analysis on baseline smoking characteristics, menthol and non-menthol cigarette smokers were comparable in terms of number of prior quit attempts and longest time quit in the past. For week four quitting, the multivariate analysis

(controlling for sex, socioeconomic status, and education) indicated a statistically significant three-way interaction [medication x race x menthol, OR(se) = 22.80 (34.47), *p = 0.039*]. Separate analysis indicated a statistically significant interaction between medication and menthol use only in African Americans [OR(se) = 16.19(21.90), p = 0.039]. For quitting at week 12, the multivariate analysis revealed the three-way interaction had a p-value of 0.10 [medication x race x menthol, OR(se) = 16.84 (28.92), *p = 0.10*]. A further examination indicated a statistically significant medication x menthol interaction in African Americans [OR(se) = 31.22(49.16), *p = 0.029*], but not in whites. It appears that naltrexone may mitigate the poorer treatment response among African American menthol cigarette smokers to nicotine replacement treatment. The major weakness of this study is the small sample size, particularly the African American non-menthol group.

In another non-peer-reviewed article, Reitzel (2010 c November submission to FDA) conducted a secondary analysis of a randomized clinical trial to test the efficacy of motivationally based treatment for smoking relapse prevention among pregnant mothers who were in their 30^{th}-33^{rd} week of pregnancy at the time of enrollment. Participants (n=251, 32 percent African American, 30 percent Latina, 36 percent white, 2 percent other) who had quit smoking and were interested in remaining quit postpartum were recruited into the study from 2005–2007. Menthol cigarette smoking status was determined by asking participants if their usual brand of cigarettes was menthol or non-menthol. The outcome was continuous abstinence from smoking, defined as self-report of no smoking (not even a puff) since the delivery date and biochemical verification at eight and 26 weeks. Unadjusted continuous abstinence rates by menthol cigarette use status showed that menthol users had lower rates of continuous abstinence than non-menthol users at both follow-up points. However, menthol cigarette use did not significantly predict continuous abstinence from smoking in analyses adjusted for time and treatment group (*p* = .46; *n* = 338), or in analyses adjusted for age, race/ethnicity, partner status, income, and educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day (*p* = .52; *n* = 304). In a post-hoc racial/ethnic group subgroup analyses, menthol cigarette use predicted continuous smoking abstinence among white women in unadjusted analyses [*p* = .01; *n* = 120, OR = .15 (.05 - .40)] and in analyses adjusted for age, partner status, income, and educational achievement, time, treatment group, cigarettes smoked per day, and time to the first cigarette of the day [*p* = .03; *n* = 108, OR = .19 (.04 - .89)]. White menthol users were less likely to maintain continuous abstinence through post-quit week 26 than white non-menthol users. In this analysis, the sample size of white menthol cigarette smokers was quite low (n=20).

Note: Descriptions of the results of some cessation studies use text directly from the referenced material.

Summary: Delnevo et al. (2010 November submission to FDA) astutely point out that many cessation studies rely on convenience samples, secondary analyses of clinical trial data or case control designs. Some study samples are not representative of the general population of smokers who quit. Other studies fail to examine subpopulations of smokers, which is critical in determining the public health effects of menthol. The characterization of cessation outcomes is inconsistent across studies. As a result, TPSAC used specific criteria to select studies that would be considered to be of sufficient quality to make an informative decision on the effects of menthol cigarettes compared to non-menthol cigarettes on cessation.

First, the most weight was placed on population survey studies. Population studies were weighed more heavily because most smokers quit on their own, rather than through cessation programs (Chapman & MacKenzie, 2010), and because of the large sample sizes of most studies and the representativeness of the

samples. We also believed that studies that focus on comparing cessation rates between menthol and non-menthol smokers among racial/ethnic groups are important because of potential racial/ethnic differences in response to menthol. Furthermore, the charge for TPSAC included the examination of the effects of menthol on specific racial/ethnic groups. We also selected studies that focused on broad age ranges. Limitations of these population surveys include the cross-sectional nature of the study and for some studies, the uncertainty of duration of the quitting attempt.

Using these selection criteria three studies were given less weight because they did not focus on examining cessation rates among racial/ethnic groups (Alexander, et al., 2010; Fagan, et al., 2010; Fagan et al., 2002). Five of the seven studies that met TPSAC criteria for inclusion by specifically examining the effects of menthol status on quit ratios and quit success among different racial/ethnic groups showed lower cessation success among menthol cigarette smokers. Two of these studies used the 2005 NHIS (Gundersen et al. 2009; Stahre et al. 2010) and the other three used the 2003/2006-7 TUS-CPS (Delnevo, et al. 2010; Levy et al. 2011 in press; Trinidad, Gilpin, Lee, & Pierce 2004). The types of analysis differed, but the results were consistent across the studies using similar surveys, that is, less quitting with menthol use in African American populations when analyzing data in the NHIS and less quitting with menthol use among almost all racial/ethnic groups when analyzing data in the TUS-CPS. The Delnevo et al. (2010) study was particularly strong because different subject inclusion criteria were used to examine quitting.

Four national/international surveys (two of which are listed above) found greater quitting success among subgroups of menthol smokers. Two of the studies analyzed the 2005 NHIS (Cubbin, et al., 2010; Gundersen, et al., 2009) in which white smokers were observed to have higher quit rates or duration of quitting. Another study based in the ITC-4 (Hyland & Kasza, 2010 a) found that African American women menthol smokers were more likely to succeed in quitting than African American non-menthol cigarette smokers. The fourth study (Delnevo, et al., 2010) found that although most other racial/ethnic menthol smokers experienced lower quitting than non-menthol smokers, Mexican American Hispanic menthol smokers as compared to Puerto Rican Hispanic menthol smokers experienced greater success than the respective non-menthol smokers.

To summarize, when focusing on population survey studies that examined difference by menthol status within racial/ethnic groups, in general, most studies support the finding that non-whites, particularly African Americans, who smoke menthol cigarettes have lower quit rates than non-whites who smoke non-menthol cigarettes, but the results for whites are mixed. A few studies showed that white menthol smokers may possibly have higher quit rates compared with non-menthol smokers.

With regards to longitudinal, cohort studies, TPSAC also focused on studies that examined ethnic/racial groups, had sufficient sample sizes at least among whites and blacks (number of subjects that is at least 100), was broadly representative of a general population of smokers, and had appropriate criteria for cessation (not smoking even a puff on a cigarette). TPSAC also considered studies that focused primarily on African Americans. Of the six reports on longitudinal cohort studies, two used the same COMMIT database, both finding no effect of menthol cigarette smoking (Hyland, et al., 2002; Hyland & Rivard, 2010 b). Although both data analyses were well-executed, one of the studies examined smokers prior to the 1990s (Hyland, et al., 2002) and the other study had a very small sample size of black smokers who had attempted to quit, which may have reduced the power to detect any differences (Hyland & Rivard, 2010 b). Two other studies also found no association with menthol cigarette smoking (Murray, et al., 2007; Muscat, et al., 2002). One of these studies had an unusual definition of cessation (e.g., not smoking each day for the past year), undertook cross-sectional analysis, enrolled a convenience sample,

and enrolled an older population of adults, thereby limiting generalizability (Muscat, et al., 2002). The other study, which had a small number of participants in racial/ethnic subgroups, did not examine potential racial ethnic differences, and also enrolled subjects with mild to moderate chronic airflow obstruction (Murray, et al., 2007). The fifth study that found no association focused on a diverse group of smokers and included a large sample size; however it primarily recruited older adults (Blot, in press). One study found a greater risk of relapse or non-sustained quitting among both African American and European American menthol smokers (Pletcher et al. 2006). This study had a small sample size of African American non-menthol smokers. The major limitations of all these studies include the secondary analysis of studies not intended to primarily focus on menthol, but more importantly, the limited number of racial/ethnic groups that allow an examination of racial/ethnic effects. Because of their limitations, none of these studies were considered to be sufficiently informative to be considered in TPSAC's evidence review.

With regards to clinical trials, TPSAC used the criteria that was used to evaluate longitudinal, cohort populations and studies, with the additional requirement that follow-up had to be at least six months. TPSAC also considered studies that focused primarily on African Americans. Five of the eleven clinical trials did not find a menthol effect and three were not considered to meet criteria. Some of these studies tended to have a non-representative population of treatment seekers, were not focused on effects of menthol per se or only observed significant menthol effects in the unadjusted analysis. One of these trials examined female prisoners (Cropsey et al. 2009), a very selected population. Another trial recruited from five Veterans Administration Medical Centers (Fu et al. 2008) , therefore enrolling smokers who were older, and based on the study by Okuyemi et al. (2003), menthol cigarette effects may be found predominantly among a younger population of treatment seekers. Harris et al. (2004) analyzed the same sample of African Americans as Okuyemi et al. (2003) and this study was mostly focused on examining ethnic racial differences. It should be noted that univariate analysis of the data did show poorer abstinence among menthol smokers, which is concordant with Okuyemi and associates (2003) findings. Reitzel (2010b) examined a more broadly representative ethnic/racial population of smokers (Reitzel, 2010 a) or of African American smokers (Reitzel, 2010 b) and found no associations with menthol cigarette smoking. One of the studies conducted by Reitzel (2010 a) observed lower cessation rate using unadjusted analysis but not adjusted analysis. Both these studies were considered to be of sufficient quality to be considered as part of TPSAC's evidence review.

With regard to the six clinical trial studies that showed poorer treatment outcomes among menthol smokers, four did not meet the selection criteria. Two studies did not meet criteria because they examined pregnant women (Rietzel et al. 2010 c) or had small sample sizes in subgroups of smokers (King et al. 2010). Another study found effects at the end of treatment, but not at the sixth-month follow-up (Okuyemi et al. 2003). Two other studies used a similar population of treatment seekers (Foulds et al. 2006; Gandhi et al. 2009). Setting aside the Foulds et al. (2006) study with a smaller population of treatment seekers, then treatment outcome is poorer in menthol compared to non-menthol cigarette smokers particularly among a non-white population (Gandhi, et al., 2009), which is concordant with the NHIS data results (Gundersen, et al., 2009; Stahre, et al., 2010). The other study that was considered to meet criteria included that of Okuyemi et al. 2007 which found that African American menthol cigarette smokers experienced a lower cessation rate than non-menthol smokers.

After excluding clinical studies with small sample sizes, no six month follow-up and no analysis of racial/ethnic minorities, the evidence from clinical trials (Gandhi et al. 2009; Okuyemi et al. 2007 vs. Rietzel 2101a, b) was mixed.

Studies also show that the association of menthol with cessation is more prominent among smokers who are prescribed medications (Okuyemi et al. 2003). In the Okuyemi et al. (2003; 2007) studies, an association with menthol cigarette smoking status was evident only in the active treatment conditions (NRT and bupropion) and not in the placebo condition. Similarly, King et al. (2010) conducted a study using NRT vs. NRT + Naltrexone. They observed that an effect of menthol cigarette smoking was found among the NRT only group, leading to the hypothesis that naltrexone, an opioid antagonist, has a mitigating effect. The King et al. (2010) study had a very small sample size of African American smokers. Finally, it should be noted that in the Gandhi et al. (2009) and Foulds et al. (2006) studies, treatment seekers were recommended to use medications. Thus, the evidence points towards a detrimental effect of menthol cigarettes on the efficacy of medications. It is possible that the lack of response to treatment may be most evident for NRT. In the study that examined bupropion SR (Okuyemi et al. 2003), menthol effects were only observed at the end of treatment and not at follow-up.

In conclusion, based on the various studies that TPSAC considered informative, the evidence is sufficient to indicate that menthol is associated with a lower level of cessation among African Americans, while the evidence in white is mixed. Menthol cigarette smoking may also affect response to medications.

Adolescents

No studies have been conducted in adolescent smokers that examined the effect of menthol cigarettes on cessation. Moolchan (2004) examined adolescents living in the Baltimore area who responded via telephone to advertisements or community outreach for an outpatient, teenage smoking-cessation study. Moolchan (2004) observed that about 90 percent of the 622 adolescents who responded and provided data were smoking menthol cigarettes.

Mediators of cessation attempts among menthol smokers

To date, no studies have systematically examined factors that may or may not make it difficult for menthol cigarette smokers to quit smoking. A potentially informative report by Anderson et al. (2011 in press) was comissioned by the FDA. The report examined internal tobacco industry documents to assess menthol's potential role in quit attempts and success in quit attempts. In this qualitative research study of the digitized repository of previously internal tobacco industry documents, a snowball sampling design was used to search the Legacy Tobacco Documents Library. Based on this search and analysis of these documents, Anderson et al. (2011 in press and 2010 November submission to FDA) came to the following conclusions.

> "Menthol smokers perceive the ….soothing, cooling, anesthetic sensations with menthol cigarettes. These perceptions appear to discourage quitting in menthol smokers" (Anderson 2010 November submission, page 9).
>
> "Two main motivations for smokers to quit are health concerns and the social unacceptability of smoking. Menthol's cooling, soothing, and anesthetic effects mask superficial health effects such as throat irritation and cough in menthol smokers, which lessen their concern about health effects [and provide an alternative to giving up smoking altogether (page 14, Anderson, 2011 in press)]. Menthol smokers also believe menthol smoke to smell better and be less offensive to others, which lessens menthol smokers' sense of the social unacceptability of smoking. These aspects of menthol appear to discourage motivation or desire to quit among menthol smokers."

> "Menthol appeals to some socio-demographic groups who are also known to have difficulty initiating quitting or staying quit, including women, lower income smokers, and African Americans. Although it is not clear why there is substantial overlap between the overall menthol profile (younger, non-white, female, and low income) and socio-demographic variables that predict difficulty in quitting or staying quit, it appears that tobacco companies took an interest in this overlap" (Anderson, 2010, November submission, page 10).
>
> "The evidence demonstrating smokers' switching fro non-menthol to menthol cigarettes when they have a cold or sore throat points to a presumption of therapeutic or health protective effects of menthol, effects that lead smokers to believe it is unnecessary to quit smoking in order to protect one's health. Tobacco industry executives acknowledged the health reassurances such beliefs about menthol imply and have marketed menthol with both explicit and implicit health messages" (Anderson, 2011 in press, page 22).

Philip Morris observed that African Americans, females and younger smokers were more likely to smoke menthol cigarettes than whites, males and older smokers, according to an analysis of internal company documents by Klausner (2011 in press). A Philip Morris document dated 1978 said: "These differences could have a profound effect on the future growth of the menthol share of the market. We know, for example, that males, whites, and older smokers are more likely to quit smoking than females, blacks and younger smokers."

EVIDENCE SYNTHESIS

The goal of chapter 6 was to gather and review evidence on the effects of menthol cigarettes on smoking experimentation and initiation, the transition to regular smoking and addiction, and the success of smoking cessation. The evidence in these areas is summarized below. TPSAC considered this information, along with other evidence gathered, reviewed and synthesized in this report, to assess the overall public health impact of menthol cigarettes and to make its recommendations to the FDA.

Initiation and Experimentation

Is there evidence to indicate that the availability of menthol cigarettes increases the likelihood of experimentation and initiation?

- The evidence is sufficient to conclude that there is a higher proportion of menthol cigarette use among younger smokers compared to older smokers (except in African Americans among whom high rates were observed in both adolescents and adults). Within the population of youth, the evidence is sufficient to conclude that the rate of menthol cigarette use is highest among the youngest users and then decreases with age.

- The evidence is sufficient to conclude that there is an increasing trend of menthol cigarette smoking and a decreasing trend of non-menthol cigarette smoking among adolescent smokers, including novice smokers (those who have smoked less than 100 cigarettes). Although cigarette smoking is becoming less prevalent, the evidence is sufficient to conclude that menthol cigarette smoking is declining at slower rate than is non-menthol cigarette smoking.

- The evidence is sufficient to conclude that less established smokers (less than one year smoking) are more likely to smoke menthol cigarettes than more established smokers (greater than one year smoking).

- Although most studies showed that the age of initiation was similar comparing menthol and non-menthol cigarette smokers, one national survey of adolescents showed that menthol smokers experienced an earlier age of initiation. This finding was observed even after controlling for age, race and gender.

- The evidence shows, based on concordant findings of the studies of internal tobacco industry documents, that tobacco companies were aware of the appeal of menthol cigarettes to younger, novice smokers because these cigarettes are easier to smoke. Chapter 3 documents the biological plausibility of an increased appeal of menthol cigarettes because of the pharmacological effects of menthol.

Addiction

Does the availability of menthol cigarettes increase the likelihood of becoming addicted?

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

Does inclusion of menthol in cigarettes increase the degree of addiction to the smoker compared to non-menthol cigarettes?

- Among adults there is little evidence to support the conclusion that menthol cigarettes increase addiction to smoking based on the mixed findings on differences between menthol and non-menthol for pharmacokinetics of nicotine, cigarettes smoked per day, exposure to nicotine in general and per cigarette (although little is known about differences in those who smoke less than 10 cigarettes per day or those who are in the early stages of smoking acquisition), and subjective measures of dependence.

- Among youth, there is sufficient evidence to indicate that those who smoke menthol cigarettes tend to be more dependent than those who smoke non-menthol cigarettes as reflected by the number of cigarettes smoked and dependence measures. Thus, this population seems to be particularly vulnerable to the effects of menthol cigarette smoking.

Cessation

Is there evidence to indicate that smokers of menthol cigarettes are less likely to quit successfully than smokers of non-menthol cigarettes?

- Although the number of studies that are considered to be of adequate quality is limited, there is sufficient evidence based on national surveys to show that the non-white smokers, particularly

African American, of menthol cigarettes compared to non-menthol cigarettes experience more difficulty with cessation. The data in whites is mixed.

- The literature also suggests that menthol cigarette smoking leads to less responsiveness to medications. This is an area that requires further exploration.
- No studies on cessation have been conducted with adolescent smokers.
- Menthol cigarettes are marketed (see Chapter 5) toward African Americans and the young. Both groups are at high risk for poor cessation outcomes.

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Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Appleyard. Smoking among Asian American and Hawaiian/Pacific Islander youth: data from the 2000 National Youth Tobacco Survey. 2001 American Legacy Foundation and CDC	Cross-sectional survey, secondary analysis of the 2000 National Youth Tobacco Survey	N=35,828 US middle school (MS) and high school (HS) students Overall response rate was 84%. Number of subjects: Asian American: 1742 Hawaiian/Pacific Islander: 487 African American: 5913 Hispanic: 6565 White: 19,884 American Indian/Alaskan Native: 666	Independent Variables: MS and HS by Race/ethnicity Outcome variable. Proportion reporting menthol smoking among current smokers; proportion of menthol smoking initiation among every smokers Current smokers defined as reporting smoking a cig on ≥1 day of last 30 days Menthol use defined as usually smoking menthol brand	Percentage of youth who usually smoke menthol brand of cigarettes by Middle and High School Middle School / High School Asian American 50.9% / 59.9% Hawaiian/PI 38.9% / 51.2% African American 70.9% / 75.0% Hispanics 56.9% / 48.7% Whites 42.4% / 29.6% Smoking initiation with menthol cigarettes by grade level Middle School / High School Asian American 39.5% / 42.5% Hawaiian/PI 44.0% / 24.9% African American 47.6% / 31.5% Hispanics 45.8% / 33.9% Whites 47.2% / 33.2%	
Barker D. Changes in the Cigarette Brand Preferences of Adolescent Smokers — United States, 1989–1993. 1994. Centers for Disease Control and Prevention	Cross-sectional national survey; secondary analysis 1989 and 1993 Teen Age Attitudes and Practices Survey (TAPS): national household sample of adolescents (aged 12–18 years)	Of the 9135 respondents to the 1989 TAPS, 7960 (87.1%) participated in TAPS-II (age 15-22) In addition, 4992 (89.3%) persons from a new probability sample participated in TAPS-II. Data for the 12–18-year-olds in each survey were analyzed (n=9135 for TAPS; n=7311 for TAPS-II).	Independent variable: Age group of adolescent Outcome Variable: Adolescent current smokers were asked if they usually bought their own cigarettes, and if so, which brand they usually bought. Current smoking defined as smoking on 1 or more of the 30 days preceding the survey Menthol cigarettes defined as brand usually bought	Younger smokers (aged 12–15 years) were more likely than older smokers (aged 16–18 years) to buy Newport (19.4% vs. 10.6%) and less likely to buy Marlboro (49.5% vs. 63.1%)	Weaknesses: • Small number of Black and Hispanic respondents in TAPS II, • Study conducted in early 90s although provides historical perspective
Caraballo, Asman. Epidemiology of menthol cigarette use in the United	Literature review and data analyses using the National Survey on Drug Use and Health,	NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 high school from years '04, '06,	Independent Variables: Middle School vs. High School Outcome variable:	Almost half of smokers age 12-17 reported smoking menthol (~ n=1 million) (NSUDH).	

* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions.

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States. 2010. Funding source not explicitly stated	the National Youth Tobacco Survey, the Monitoring the Future Survey, and the National Health and Nutrition Examination Survey	'09 who smoked in past 30 days and have a usual brand. N=2,580 adol. smokers from 35 states	Proportion of current adolescent menthol smokers Current smoking defined as smoking at least 1 day of past 30 days NYTS: Menthol use defined as usually smoking menthol cigarettes	Proportion of menthol use among Middle and High School students (NYTS) Middle School: 49.4% High School: 44.9%	
Curtin et al. Descriptive Epidemiological Analysis of Menthol Use from Four National US Surveys: I. Demographics. 2010 (FDA Submission) RJReynolds	Cross-sectional survey; secondary analyses of 2006 NYTS	N=27,038 students enrolled in US public and private schools, grades 6 through12 (aged 9-21 years) Response rate information not provided in the article N in analysis: Menthol smokers=745 Non-menthol smokers =758	Independent Variables: Age group of smoker Outcome variable: Proportion current menthol smoker Current smokers defined as smoking any cigarettes on 10 or more of the last 30 days Menthol use defined by usual cigarettes being menthol	Proportion of menthol use by age group 9-13 year olds: 59.3% 14-16 years old: 45.8% 17-18 years old: 38.3%	
Fernander, A., Rayens, M.K., Zhang, M., Adkins, S. Are age of smoking initiation and purchasing patterns associated with menthol smoking? 2010 Funding source not explicitly stated	Cross-sectional survey data; secondary analysis of in 2003 and 2006/2007 TUS-CPS	N=66,145 current smokers Menthol smokers = 16, 294 Non-menthol smokers = 46,899 [2,952 smokers were unresponsive]	Independent variable Age at which first started smoking cigarettes fairly regularly Outcome variable: Proportion of menthol smoking and non-menthol smoking Outcome variable: Current smoking defined as smoking at least 100 cigarettes in life-time and currently smoking every day or some days (including at least once in the last 30 days)	Current smokers who were younger were more likely to smoke menthol cigarettes (e.g., OR: 1.66, 95% CI: 1.47-1.88 for 18-24 y/o relative to those aged 65 and above). Of the menthol smokers: 53.2% (95% CI +/-.9) started smoking before age 18 and 46.8% (95% CI +/-.9) started smoking at age 18 or older. Of non-menthol smokers: 56.2% (95% CI +/-.6) started smoking before age 18 and 43.8% (95% CI +/-.6) started smoking at age 18 or older.	Commentary: • Reference group was those aged 65 and above

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			Menthol smoking status was determined with the item: 'Is your usual cigarette band menthol or non-menthol?' with responses of 'menthol', 'nonmenthol' and 'no usual type'. Those who stated that they had no usual type were treated as missing values for the cigarette type variable.		
Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States American Legacy Foundation	Cross-sectional survey; secondary analysis of 2004-2008 NSDUH	179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >=12 years old to report on patterns of methol use. Response rate – 66.2% (2008 survey)	Independent variable: Age Outcome variable: Proportion of menthol use among all smokers Current cigarette smoking defined as smoking cigarettes in the past month Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol	Proportion of menthol cigarettes us by age - 12-17 years old: 49.3% - 18-25 years old: 37.5% - 26-34 years old: 29.9% A statistically significant age gradient in these age categories also was observed among males, females, whites, and Hispanics. Among African Americans, a ceiling effect likely occurred, with menthol use rates of at least 91.9% observed in all of the 12-34 year old age categories examined. Proportion of menthol cigarette use by age and race/ethnicity 12-15 y/o 16-17 y/o 18-21 y/o 22-25 y/o Total 53.5% 47.0% 40.5% 34.6% White 47.6% 40.1% 32.6% 25.7% Black 95.6% 93.9% 94.1% 92.5% Hispanic 56.2% 50.5% 44.7% 34.9% Asian 70.7% 50.7% 32.8% 39.6%	Strengths: • Data were weighted to produce estimates that were representative of the population being sampled.
Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology	Cross-section national survey, secondary analysis of 2000 National Household Survey on Drug Abuse (NHSDA)	N in analysis=18,359 current smokers	Independent variable: Age of smoker by race/ethnicity Outcome variable: Proportion of current smoker	Percentage of current smokers who most often smoked menthol by age and race/ethnicity: 2000 NHSDA 12-17 y/o 18-25 y/o 26 + y/o Total 31.6% 25.8% 28.6% White 28.4% 20.1% 22.5%	Strength: • All data were weighted to provide nationally representative estimates, and

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of menthol cigarette use. 2004 National Institute on Drug Abuse			smoking menthol cigarettes Current smoking defined as smoking during the past 30 days Menthol status defined as response to: ''During the past 30 days, what brand of cigarettes did you smoke most often?'' and ''During the past 30 days, did you smoke (name of brand) menthol or regular cigarettes most often?''	Black 55.7% 68.6% 69.5% Hispanic 35.7% 25.9% 29.7% Newport cigarettes use by race/ethnicity and age 12-17 y/o 18-25 y/o 26 + y/o White 18.0% 9.3% 2.9% Black 79.2% 76.7% 31.5% Hispanic 31.4% 16.7% 7.1% Marlboro cigarette use by race/ethnicity and age 12-17 y/o 18-25 y/o 26 + y/o White 58.8% 61.4% 37.9% Black 5.3% 7.3% 6.6% Hispanic 52.5% 67.7% 54.0%	standard errors for 95% confidence intervals were calculated in a way that reflected the complex survey design.
Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006 American Legacy Foundation	Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS	2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002. Response rate: 84% in 2000, 75% in 2002. N in analysis=5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS).	Independent variable: School grade by race/ethnicity Outcome variable: Proportion of smoking menthol cigarettes among youth smokers Current smoking defined as 'smoking cigarettes on one or more of the past 30 days' Menthol use: defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol (''During the past 30 days, what brand of cigarettes did you usually smoke?'' and ''Is the brand of cigarettes that you usually smoked during the past 30 days mentholated?'')	Proportion of Menthol Use Middle School High School Total 59.6% 43.6% White 53.1% 37.4% Black 87.5% 86.8% Hispanic 62.9% 52.4%	Strengths: • Controlled for demographic background and the length, frequency, and level of smoking; • Takes into account misclassification; used standardized scale to measure dependence.
Hersey et al., 2010	Cross-sectional survey;	2006 NYTS: Administered to	Independent variable:	Percent menthol smokers among past 30 day smokers	

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Menthol cigarettes contribute to the appeal and addiction potential of smoking for youth, NTR Dec 2010 supplement	secondary analysis of 2006 NYTS	27,038 students enrolled in US public and private schools, grades 6 through 12 (aged 9-21 years) Response rate – 80.2% N in analysis=4,738 youth who smoked in the past 30 days, had a regular brand and could identify whether the brand was menthol or non-menthol	School grade by racial/ethnic groups Outcome variable: Proportion of smoking menthol cigarettes among youth smokers Current smoking defined as 'smoking cigarettes on one or more of the past 30 days' and smoking 100 plus cigaettes in a lifetime Menthol use defined as usual brand of cigarette smoked ("usual brand is menthol or nonmenthol")	Middle School / High School White 43.1% / 37.6% Black 80.6% / 84.8% Hispanic 57.9% / 56.4% Proportion of menthol smokers among smokers who smoked 100 plus cigarettes in a lifetime High School White 38.1% Black 84.4% Hispanic 66.1%	
Hymowitz N, Corle D, Royce J, Hartwell T, Corbett K, Orlandi M, Piland N. Smokers' Baseline Characteristics in the COMMIT Trial 1995. National Cancer Institute	Baseline telephone survey data from 10 of 22 COMMIT sites, COMMIT is a collaborative prospective clinical trial of community-based intervention. It is a community-level, multi-channel, 4-year intervention designed to increase quit rates among cigarette smokers.	Smokers ages 25-64 years from intervention and matched comparison communities in CA, NJ, NY, NM, and NC. N=16,857 White: 11,128 Black: 3,322 Puerto Rican: 537 Mexican: 1,870	Independent Variables: Age Outcome Variables: Menthol cigarette use Current smoking defined as smoking cigarettes now Menthol use definition not provided in the article	Preference for menthol was greatest among the youngest smokers (OR: 0.71 (0.68-0.74).	Commentary: • Studies conducted in 90s but provides historical perspective • Results are not clearly described (e.g., referent group)

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Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Rock V.J., Davis S.P., Thorne S.L., Asman K.J., Caraballo R.S. Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. 2010 Funding source not explicitly stated	Cross-sectional data: secondary analysis of 2004–2008 NSDUH	2004-2008 NSDUH: Menthol smokers: 25,579 Non-menthol smokers: 46,026 See Table 1 and 2 (p S119 and S120) for more details.	Independent Variables: Age by race/ethnicity. Outcome Variables: Proportion of menthol use among current smokers A current cigarette smoker defined as anyone who answered "yes" to the question, "During the past 30 days, have you smoked part or all of a cigarette?" Menthol use defined by response to "Were the cigarettes you smoked during the past 30 days menthol?"	Higher proportion of menthol smokers vs. non-menthol smokers among those aged 12-17 years old (5.8% [5.5,6.1] vs. 3.4% [3.3,3.5]) Higher proportion of cig smokers smoked menthol among adolescents than young or older adults 12-17 y/o: 44.7% 18-25 y/o: 36.1% 26+: 30.2% Proportion of menthol cigarette use among current smokers aged 12 years or older by race/ethnicity 12-17 y/o 18-25 y/o 26+ y/o Total 44.7% 36.1% 30.2% White 41.0% 28.8% 21.9% Black 71.9% 85.0% 82.2% Hispanic 47.0% 38.2% 29.5% Asian 51.5% 35.8% 28.6% AI/AN 34.7% 27.4% 23.0% .	Commentary: • The precision of smoking prevalence estimates for certain racial/ethnic populations was low due to small sample size (i.e., Asians and Native Americans/Alaska Natives), especially when stratified by age.

* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 1: Age Gradient for Menthol Cigarette Use

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Sidney S., Tekawa I., Friedman G. Mentholated cigarette use among multiphasic examinees, 1979–86. 1989 NCI	Prospective cohort	Starting in July 1979, patients at Kaiser Permanente Medical Care Program medical centers in Oakland and San Francisco were asked to complete a supplementary questionnaire that explored their smoking habits in detail. Between 1979 – 1986, the questionnaire had been completed by 114,934 examinees (approximately 86 percent of the examinees), of whom 31,428 (27.3 percent) were current smokers. Mentholated cigarette use habits were examined in the 29,037 current smokers ages 15-79 years of Black, White, or Asian race.	Independent variable: age Outcome variable: percent menthol users No definition provided for current smoking or menthol use	There was a marked inverse relationship between age and mentholated cigarette use in Blacks and in Asians, while there was relatively little difference in mentholated cigarette use with age in Whites (see Figure 1, page 1416)..	

Note: See Hersey presentation (February 2011, Comparative rates of initiation of menthol and non-menthol cigarettes) in text.

* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 2: Trends in menthol use among youth

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study and Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Barker D. Changes in the Cigarette Brand Preferences of Adolescent Smokers — United States, 1989–1993. 1994. Centers for Disease Control and Prevention	Cross-sectional national survey; secondary analysis of 1989 and 1993 Teen Age Attitudes and Practices Survey (TAPS): national household sample of adolescents (aged 12–18 years)	Of the 9135 respondents to the 1989 TAPS, 7960 (87.1%) participated in 1993 TAPS-II (age 15-22) In addition, 4992 (89.3%) persons from a new probability sample participated in TAPS-II. Data for the 12–18-year-olds in each survey were analyzed (n=9135 for TAPS; n=7311 for TAPS-II). N for analysis=702 smokers who usually bought their own cigarettes	Independent variable: Brand of cigarettes Outcome Variables: Changes in brand preferences of teenage smokers over time Current smoking defined as smoking cigarettes on 1 or more of the past 30 days Menthol cigarettes defined as brand usually bought	Between 1989 and 1993, the percentage of adolescents purchasing Newport cigarettes increased 4.5 percentage points (55% increase). Increases for Newport cigarettes were greatest among younger smokers and adolescents residing in the Northeast. Change in self-reported cigarette brand preference among adolescents aged 12-18 years TAPS 1989 TAPS 1993 Change Newport 8.2% 12.7% +4.5 Marlboro 68.7% 60.0 -8.7 Camel 8.1% 13.3% +5.2 Increase in Newport cigarette preference in youth exceed market share increase of +0.1	Weaknesses: • Small number of Black and Hispanic respondents in TAPS II, • Study conducted in early 90s, but provides historical perspective
Caraballo, Asman. Epidemiology of menthol cigarette use in the United States. 2010. Funding source not explicitly stated	Literature review and data analyses using the National Survey on Drug Use and Health, the National Youth Tobacco Survey, the Monitoring the Future Survey, and the National Health and Nutrition Examination Survey	NSDUH: ages 12-17 who smoked in past month (9,595) and 18+ who smoked in past month (62,010) from surveys conducted 2004-2008 NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 high school from years '04, '06, '09 who smoked in past 30 days and have a usual brand. Analysis on 2,580 adol. smokers from 35 states	Independent Variables: Menthol status; brand of cigarettes Outcome variable: Proportion of current adolescent menthol smokers over time Current smoking defined: smoking at least 1 day of past 30 days	According to NSDUH, menthol cig use increased from 04-08 (see below, Rock et al. 2010) According to the MTFS data from 1998 to 2008, no consistent or significant change was observed during the period for Newport among 8th, 10th and 12th graders, however, a significant increase was observed for Kool. According to the data from the 2004, 2006, and 2009 NYTS survey, a slight non-significant decrease in smoking Newport was observed among middle school smokers and no change among high school smokers.	

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Table 2: Trends in menthol use among youth

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study and Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
		MTFS: US Students in 8th (n=20,863), 10th (n=30,722), 12th (n=40,914) grades for years '98-'08			
Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology of menthol cigarette use. 2004 National Institute on Drug Abuse	Cross-section national survey, secondary analysis of 1998, 1999, 2000 Monitoring the Future	136,000 participants surveyed 16,313 students analyzed	Independent variable: Brand of cigarettes Outcome measure: Proportion of current smoker who smoked Newport, Kool or Salem between 1998 and 2000 by grade Current and menthol status defined as response to what brand usually smoked in the past 30 days.	No significant change was observed in percent smoking menthol cigarettes (Newport, Kool or Salem) across time within each grade.	Weakness: Brands not examined separately. For example, Kool cigarette smoking may have decreased but Newport smoking may have increased.
Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States American Legacy Foundation	Cross-sectional survey; analysis of 2004-2008 NSDUH	2004-2008 NSDUH: 179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >12 years old I Response rate for 2008 survey was 66.2%	Independent variable: Menthol status Outcome variable: Proportion of menthol smokers in all youth over time Current smoker defined as smoking cigarettes in the past month Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol	Trends in prevalence of menthol and non-menthol cigarettes among all youth 2004 2008 12-17 y/o Menthol 5.3% 4.6% Non-menthol 6.0% 3.9% Slopes of regression liens are -0.14 for menthol and -0.53 for non-menthol and statistically different (p=0.003). 18-25 y/o Menthol 14.0% 14.5% Non-menthol 25.7% 20.4% Slopes of regression liens are 0.17 for menthol and -1.49 non-menthol and statistically different (p=0.0002).	Strengths: Data were weighted to produce estimates that were representative of the population being sampled.

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Table 2: Trends in menthol use among youth

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study and Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006 American Legacy Foundation	Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS	2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002. Response rate: 84% in 2000, 75% in 2002. Data analyzed on 5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS).	Independent variable: Menthol use Outcome variable: Proportion smoking menthol cigarettes among MS and HS smokers by year Current smoking defined as smoking cigarettes on one or more of the past 30 days' Menthol use defined as the brand of cigarettes usually smoked and if the brand of cigarettes usually smoked during the past 30 days is menthol	Menthol cigarette use among youth smokers between 2000 and 2002 2000 2002 Total * 40.0% 47.4% Middle School* 51.6% 59.6% High School 36.9% 43.6% *Significant difference $p < 0.05$	Strengths: • Controlled for demographic background and the length, frequency, and level of smoking; • Takes into account misclassification; standardized scale to measure dependence.
Hersey et al., 2011 Trends in brand and type of cigarette smoking by 12-17 year olds from 2004 to 2008, presentation to TPSAC, February 2011	Cross-sectional survey; secondary analysis of 2004 to 2008 NSDUH	NSDUH samples of 12-17 year olds range from 17,727 to 18,678 for each of the years; number of smokers range from 1,759 to 2,255	Independent variable: Brand of cigarettes Outcome variable: Proportion smoking menthol cigarettes among youth smokers over time Current cigarette defined as smoking menthol cigarettes in the past month Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol	Percentage of brand use among 12-17 year old smokers in the NSDUH: 2004 to 2008 2004 2008 Marlboro Menthol 12.7% 18.2% Marlboro Non-menthol 37.1% 28.5% Camel Menthol 1.7% 6.4% Camel Non-menthol 7.7% 9.0% Newport 24.2% 23.5%	

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Table 2: Trends in menthol use among youth

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study and Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Kaufman, N.J., Castrucci, B.C., Mowrey, P., Gerlach, K.K., Emont, S., Orlean, T. Changes in Adolescent Cigarette-Brand Preference, 1989 to 1996. 2004 Funding source not explicitly stated	Cross-sectional national survey; secondary analysis of the Robert Wood Johnson Foundation 1996 National Survey of Tobacco Price Sensitivity, Behavior, and Attitudes Among Teenagers and Young Adults (RWJF survey) used to make national estimates of brand preference in 1996. These estimates were compared with similar estimates derived from the Centers for Disease Control and Prevention (CDC) Teenage Attitudes and Practices Surveys (TAPS) conducted in 1989 (TAPS I) and 1993 (TAPS II) surveys	RWJ survey N=17,287 TAPS-I N=9,315 TAPS-II N=12,952 (7,960 from TAPS-I plus 4,992 new respondents)	Independent variable: Brand preference Outcome variable: Trends over time by age Current smoking and menthol use defined as: In TAPS, adolescents who had smoked on at least one day during the past 30 and who usually bought their own cigarettes were asked, "What brand do you usually buy?" RWJF survey respondents who had smoked on at least one day during the past 30 and who had ever bought cigarettes were asked, "When you buy cigarettes, what brand do you usually buy?" The possible cigarette brand choices differed slightly among the 3 surveys. More brands were listed in the RWJF survey than in TAPS. Both the RWJF survey and TAPS-II included "no usual brand" as a possible response. On the RWJF survey, respondents were queried as to the brand they usually smoked. Respondents were asked, "What *one* brand of cigarettes do you *usually* smoke?"	Between 1989 and 1996, Marlboro, Camel, and Newport were the brands respondents most often reported as the "brand usually bought." These 3 brands combined accounted for slightly over 84% in 1989 and 1993 and over 90% in 1996 of all brands respondents reported that they usually bought. Of the 3 brands, Newport was the only one to increase significantly in each of 3 age-groups from 1989 to 1996. The percent reporting usually buying Newport increased 347% among 13 to 14 year olds, 189% among 15 year olds, and 69% among 16 to 18 year olds. Percentage distribution of cigarette brand usually bought by adolescents by age 1989 1996 Marlboro 13-14 y/o 69.6% 66.9% 15 y/o 77.4% 64.1% 16-18 66.9% 68.1% Total 68.5% 67.2% Camel 13-14 y/o 13.7% 3.3% 15 y/o 13.9% 7.6% 16-18 3.6% 8.4% Total 8.1% 8.1% Newport 13-14 y/o 4.8% 19.2% 15 y/o 7.4% 21.4% 16-18 8.8% 14.9 % Total 8.3% 16.4% When brand preferences by race and ethnicity are examined, only slight fluctuations were found in market share for Marlboro and Camel when comparing 1989 to 1996. However, the percentage of white and Hispanic adolescents who reported Newport as the brand they usually buy doubled (for whites, 5.3% to 10.4%, for Hispanics, 12.8% vs. 25.9%). No significant change was observed in Blacks. Kool also had a significant portion of the African American adolescent market, ranging from 9.4% in 1989 to 7.7% in	Weaknesses: • This is not generalizable to children who obtained cigarettes from nonretail sources or who had not smoked during the 30 days prior to survey. • Old data set , but provides historical perspective

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Table 2: Trends in menthol use among youth

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study and Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
				1996. Although almost 6% of Hispanic adolescents usually bought Kool in 1989, by 1996 Kool had less than a one-percent preference among any ethnic group or race other than African American.	
Rock V.J., Davis S.P., Thorne S.L., Asman K.J., Caraballo R.S. Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. 2010 Funding source not explicitly stated	Cross-sectional data; secondary analysis of 2004–2008 NSDUH	2004-2008 NSDUH: Menthol smokers: 25,579 Non-menthol smokers: 46,026 See Table 1 and 2 (p S119 and S120) for more details.	Independent variable: Menthol smoking Outcome Variables: Prevalence of menthol smoking from 2004 to 2008 by age and race/ethnicity A current cigarette smoker was defined as anyone who answered "yes" to the question, "During the past 30 days, have you smoked part or all of a cigarette?" To estimate menthol cigarette use, current smokers (*n* = 71,605) were asked, "Were the cigarettes you smoked during the past 30 days menthol?" Anyone who answered "yes" was considered to be a current menthol cigarette smoker.	Trends is proportion of menthol cigarette use among current smokers of different ages 2004 2008 12- 17 y/o --White* 40.3% 46.0% --Black 72.5% 66.6% --Hispanic 40.4% 46.7% 18-25 y/o --White* 26.7% 32.5% --Black 86.6% 87.4% --Hispanic* 33.9% 42.4% Significant changes from 2004 to 2008 in white 12-17 y/o smokers Significant changes from 2004 to 2008 in white and Hispanic 18-25 y/o smokers No significant changes from 2004 to 2008 among 26 plus year old among all ethnic/racial groups.	Weakness: . • The precision of smoking prevalence estimates for certain racial/ethnic populations was low due to small sample size (i.e., Asians and Native Americans/Alaska Natives), especially when stratified by age.

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* Note: Some of these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 3: Rate of menthol smoking in novice vs. established smokers

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study/Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Results/Conclusion(s) related to Menthol*	Comments
Caraballo, Asman. Epidemiology of menthol cigarette use in the United States. 2010. Funding source not explicitly stated	Literature review and data analyses using the 2004, 2006 and 2009 National Survey on National Youth Tobacco Survey (NYTS)	NYTS: US students grades 6-12; n=1,978 middle school students and 6,163 high school from years '04, '06, '09 who had information on smoking history Data analyzed on 2,580 adol. smokers from 35 states	Independent Variables: Amount of cigarette smoking Outcome variable: Percent current adolescent menthol smokers in adolescents who started smoking less than 2 years ago Current smoking defined as smoking at least 1 day of past 30 days Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol ("During the past 30 days, what brand of cigarettes did you smoke most often?" and "During the past 30 days, did you smoke (name of brand) menthol or regular cigarettes most often?")	# cigarettes by days smoking in the past 30 days / % menthol smoker ≤ 1 cigarette on 1-5 days: 39.9% 1-5 cigs on 1-5 days: 45.3% 1-5 cigs on 6-9 days: 47.5% 1-5 cigs on 10-19 days: 44.2% 1-5 cigs on 20-29 days: 49.7% 1-5 cigs on all 30 days: 46.6%	
Giovino 2010, Patterns of and Recent Trends in the Use of Mentholated Cigarettes in the United States American Legacy Foundation	Cross-sectional survey; secondary analysis of 2004-2008 NSDUH	2004-2008 NSDUH: 179,242 respondents in the U.S. population who were 12-25 years old. Also used data on 69,322 smokers who were >12 years old Response rate for 2008 survey was 66.2%	Independent variable: Amount of cigarette smoking Outcome variable: Proportion of menthol smokers based on amount of smoking Current smoker described as smoking menthol cigarettes in	Proportion of menthol smoking by number of days per month 1-5 days / 6-9 days / ≥10 days >12 y/o: 36.1% / 38.3% / 31.9% 12-17 y/o: 52.8% / 54.5% / 46.3%	Strength: • Data were weighted to produce estimates that were representative of the population being sampled.

* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions.

Author Name(s), Article Title and year	Type of Study/Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Results/Conclusion(s) related to Menthol*	Comments
			the past month Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol		
Hersey JC, Ng SW, et al: Are menthol cigarettes a starter product for youth? 2006 American Legacy Foundation	Cross-sectional survey; secondary analysis of 2000 and 2002 NYTS	2000 NYTS: 35,828 students in grades 6 through 12 in spring 2000 and to 26,149 students in spring 2002. Response rate: 84% in 2000, 75% in 2002. Data analyzed on N=5,512 youth (2000 NYTS) and 3,202 youth (2002 NYTS).	Independent variable: Duration of smoking Outcome variable: Proportion smoking menthol cigarettes among MS and HS smokers Current smoking defined as smoking cigarettes on one or more of the past 30 days' Menthol use defined as the brand of cigarettes usually smoked and if the brand of cigarettes usually smoked during the past 30 days is menthol	Proportion of menthol smoking and length of smoking by grade level, 2002 NYTS Less than year / More than a year Middle school * 62.4% / 53.3% High School 45.9% / 41.9% * $p < 0.002$	• Takes into account misclassification; uses standardized scale to measure dependence. .
Hersey et al., 2010 Menthol cigarettes contribute to the appeal and addiction potential of smoking for youth, NTR Dec 2010 supplement	Cross-sectional survey; secondary analysis of 2006 NYTS	2006 NYTS: 27,038 students enrolled in US public and private schools, grades 6 through 12 Response rate: 80.2% Data analyzed on 4,738 youth who smoked in the past 30 days, had a regular brand and could identify whether the brand was menthol or non-menthol	Independent variable: Duration of smoking Outcome variable: Proportion smoking menthol cigarettes among MS and HS smokers Current smoking defined as 'smoking cigarettes on one or more of the past 30 days' and smoking 100 plus cigarettes in a lifetime	Proportion of menthol smoking and length of smoking by grade level, 2006 NYTS Less than year / More than a year Middle school 42.2% / 54.7% High School 42.8%% / 43.1%% No significant differences in rate of menthol smoking among less established vs. more established smokers No differences were found in rate of menthol smoking across different amounts of smoking	

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Table 3: Rate of menthol smoking in novice vs. established smokers

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study/Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Results/Conclusion(s) related to Menthol*	Comments
			Menthol use defined as usual brand of cigarette smoked ("usual brand is menthol or nonmenthol")		
Footnote Rising & Blader 2010 Altria June 2010 submission				In a white paper written by the FDA, unpublished data from 2004 to 2008 NSDUH of menthol cigarette use among young smokes (aged 12-21 years) was presented. The data showed that rate of menthol smoking was higher among new smokers (smoking fore less than 1 year) than among experienced smokers (smoking for more than a year). The pattern, however, was reversed in 2008. Using the same data, in the June 2010 submission by Altria, an analysis was presented in which menthol smokers were divided into smoking less than 100 cigarettes in a lifetime and smoking 100 cigarettes or more in a lifetime. The results again showed greater menthol cigarette smoking among the initiates as opposed to the more established smokers with the rates converging in 2008.	Data beyond 2008 should be examined to determine whether this data point is unusual.

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Table 3: Rate of menthol smoking in novice vs. established smokers

Version Date: 3-20-11

Author Name(s), Article Title and year	Type of Study/Study Design	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Results/Conclusion(s) related to Menthol*	Comments
Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *The NSDUH Report: Use of Menthol Cigarettes*. 2009 SAMHSA	Cross-sectional survey; secondary analysis of 2004 to 2008 National Survey on Drug Use and Health (NSDUH) survey includes individuals ages 12 and older.	2004 to 2008 NSDUH survey of subjects 12 or older	Independent variable: Duration of smoking by age and race/ethnicity Outcome Variable: Proportion of menthol smokers Current smoker defined as smoking menthol cigarettes in the past month Menthol use defined by most often smoked usual brand and whether this brand smoked in past 30 days was menthol	Past month use of menthol cigarettes among past month cigarette smokers 12 and older, by recency of cigarette initiation and demographic characteristics Past year initiate / > 1 year use Age 12 and older: 44.6% / 31.8% 12 to 17 y/o: 49.2% / 43.8% 18-25 y/o: 40.2% / 36.4% Black: 73.9% / 82.8% Hispanic: 42.9% / 32.1% White: 39.9% / 23.6% .	

Note: See Hersey presentation (February 2011, Comparative rates of initiation of menthol and non-menthol cigarettes) in text.

* Note: some of these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 4. Rates of switching: menthol to non-menthol vs non-menthol to menthol*

Author	Survey/Study	Menthol to Non-menthol	Non-menthol to menthol
Pletcher 2006	CARDIA 1535 current smokers	Among menthol smokers:12%	Among non-menthol smokers: 11%
Hyland 2010	COMMIT Smokers defined as N=2095 completing 3 waves of surveys	Among all smokers: 6.4%	Among all smokers: 4.2%
Hyland & Karza2010	ITC-4 Smokers defined as smoking at least 100 cigarettes in a lifetime and currently smoking monthly N=7532	Among menthol smokers Total: 8.11% Whites: 7.6% Blacks: 7.8% Hispanics: 17.4%	Among non-menthol smokers Total: 2.2% Whites: 1.74% Blacks: 14.8% Hispanics: 6.7%
Switching Book. 1991, Phillip Morris		Among all past year switchers: 6.9%	Among all past year switchers: 5.7%
Eric Johnson presentation January 10, 2010 Switching Book	% among 34,117 cigarette smokers 18 year of age and older participating in a national telephone survey (1990-1991).	Among all current smokers: 0.6% Among past year menthol switchers: 26.1%	Among all current smoker's 0.5% Among past year non-menthol switchers: 7.7%
Giovino (2010)	2003 Youth Smoking Cessation Survey 16-24 y/o N=1045	Among menthol smokers: 15%	Among non-menthol smokers: 6.9%
Nonnemaker 2010	American Legacy Longitudinal Tobacco Reduction Study Middle and high school youth N=1100 for total N=757 whites N=92 blacks N=100 Hispanics N=151 other	Among smokers Total: 5.9% Whites: 6.1% Blacks: 3.9% Hispanics: 9.2% Other: 4.2%	Among smokers Total: 8.0% Whites: 7.5% Blacks: 5.1% Hispanics: 7.6% Other: 12.0%

* Sidney et al. (1989) study was excluded because of the low follow-up rate

Table 5. Studies of Menthol Smoking and Dependence Among Youth (updated Table from Hersey et al., 2010)

Study	Population	Operational definition of menthol	Findings
Initial smokers			
DiFranza et al. (2004)	237 seventh-grade students in two small Massachusetts cities who had inhaled a cigarette sometime during the study (68% White and 20% Hispanic in initial cohort) followed every 4 months for 30 months	Analysis based on the 50.6% of smokers (n=121) who recalled that their first cigarette was menthol (42%) or nonmenthol	10-item Hooked on Nicotine Checklist scores not related to reported menthol of first cigarette Menthol / Nonmenthol Median 6.5 / 7.0 Mean 6.0 / 6.0 *SD* 3.3 / 3.4
Nonnemaker et al., 2010	1,100 out of 47,237 middle and high school youth in the 2000 through 2003 American Legacy Longitudinal Tobacco Use Reduction Study	First cigarette smoked is reported to be menthol	Menthol initiates higher than nonmenthol initiates on the following: Smoking daily *OR:* 1.99** Established (smoking 20 or more days in past 30 days) *OR:* 1.94** Lifetime smoking (100+ cigs** In lifetime) *OR*: 1.94 Nicotine dependence *B*: 1.04**
Earlier smoker			
Hersey, et al. (2006)	26,149 6th - to 12th-grade students in the 2002 NYTS (for the subset who smoked in last month and had a usual brand of cigarettes)	Youth who identified their usual brand as menthol (excluding nonmenthol brands)	Menthol higher than nonmenthol smokers on a six-item Nicotine Dependence Scale for Adolescents: *OR*: 1.45** (*p*=.006)
Hersey, Nonnemaker et al., (2010)	3,281 out of 27,038 6th-to-12th grade students in the 2006 NYTS who smoked in the last month and had a usual brand of cigarettes	Youth who identified their usual brand as menthol (excluding nonmenthol brands)	Menthol higher than nonmenthol on reduced time for needing a cigarette among smokers with regular brand: OR: 1.86**
Hersey et al., (November 2010 submission)	5,511 youth in 48 schools around the country in a national biochemical validation survey; 1,215 students smoked in the past 30 days, 441 reported usual brand of cigarettes was menthol, 587 smoked in the prior 3 days and had positive cotinine (≥ 5 ng/ml)	Youth who identified their usual brand as menthol	No main effect for menthol on cotinine levels Menthol higher than nonmenthol on levels of dependence among smokers who smoked less than one year (P< 0.05). No differences in those who smoked 1 year or longer.

Muilenburg and Legge (2008)	2,061 9th- to 12th-grade students in six southern schools (48% male; 73% Black)	Answered "yes" to usually smoking menthol cigarettes	Menthol higher than nonmenthol smokers on the following: Shorter time since last smoke *OR*: 3.22*** Total cigarettes/lifetime *OR*: 4.35*** Smoke more days per month *OR*: 5.35** Ever a daily smoker *OR*: 3.41***
Established youth smokers			
Collins and Moolchan (2006)	572 adolescent smokers recruited for a cessation study (55% female, 46.9% Black; mean age: 15.1 years)	Usual brand was menthol	Menthol 45%* Nonmenthol 29% Smoke within <5 min after waking
Hersey, Nonnemaker et al., (2010)	1,457 out of 27,038 6th-to-12th grade students in the 2006 NYTS who smoked in the last month and had a usual brand of cigarettes and smoked at least a 100 times in their lifetime	Youth who identified their usual brand as menthol (excluding nonmenthol brands)	Menthol higher than nonmenthol on reduced time for needing a cigarette among smokers with regular brand: OR: 2.06**; feeling restless and irritable without smoking: OR1.39*; experiencing craving after going without smoking for a few hours: OR 1.35*.
Wackowski and Delnevo (2007)	1,345 current established smokers (30 days smoking and 100 cigarettes lifetime) in Grades 9 to 12 in the 2004 NYTS	Answered "yes" to usually smoking menthol cigarettes	Menthol vs. nonmenthol smokers more likely to need a cigarette within 1 hr after smoking: 16.3% vs. 7.4%; *AOR*: 2.6* Menthol vs. nonmenthol smokers more likely to experience cravings after not smoking for a few hours: 35.9% vs. 25.4%; *AOR*: 1.6*

Note. *AOR* = adjusted odds ratio; *OR* = odds ratio; NYTS = National Youth Tobacco Survey.
*p<.05; **p<.01; ***p<.001.

Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Alexander et al. Occupational status, work-site cessation programs and policies and menthol smoking on quitting behaviors of US smokers. 2010 Funding source not explicitly stated	Cross-sectional study; analysis of 2006/07 TUS CPS	In the 2006/07 TUS CPS data set, there was a total of 172 023 self-respondents. Respondents eligible for inclusion in this analysis were TUS CPS current smokers (every day or some days) aged 18 years or older. There was a total of 31 501 eligible self-respondents. Of these, 1325 were excluded due to missing information on cigarette brand type (non-menthol or menthol). Total sample size for current study = 30,176 (Menthol=7718; Non-menthol=22,458) Percent in each ethnic group: Menthol smokers--30.2% Black, 69.8% white/other Non-menthol smokers--Black: 4.4%, white/other: 95.6%	Independent variable: Menthol status Outcome Variable: Ever stopped smoking for one day or longer because trying to quit smoking	Controlling for occupational status and work-place policies and demographics, there were no differences for menthol versus non-menthol smokers on quitting behaviors OR = 0.98 (95% CI: 0.83-1.15)	Weaknesses: • Menthol use, whether or not survey participants switched brands during or after any quit attempts • Measure of quitting (measure is same for quit attempts no matter length of time without smoking) • Did not examine menthol effects in different racial/ethnic groups
Cubbin C, Mah-Jabeen S, LeClere FB. The intersection of gender and race/ethnicity in smoking behaviors among menthol and non-menthol smokers in the United States. 2010 Funding source not explicitly stated	Cross-sectional survey; analysis of 2005 NHIS and Cancer Control Supplement	Total sample= 31 428; analytical sample = 21,196 (included women and men 25–64); sample analyzed for quitting = 3902 (current every day smokers) 3786 (former smokers) Response rate: 90% of eligible households. Percent cigarette type and each racial/ethnic group: See attachment A	Independent variable: Menthol status Outcome Variables: (i)proportion of quit attempt in the past year (ii) time since quitting Current smokers: smoked at least 100 cigs and smoke some or every day Former smokers: smoked at least 100 cigs and currently do not smoke	Menthol smokers had higher levels of quit attempts compared with non-menthol smokers; differences were as great as 10–20% Among white women menthol smokers had abstained about 2.5 years longer than non-menthol smokers ($p < 0.01$)	Weakness: • No data if respondents started and remained smoking menthol or non-menthol cigarettes

* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Delnevo et al. Examining the relationship between menthol smoking and cessation using data from the 2003 and 2006/7 Tobacco Use Supplement 2010 submission. NCI and CDC	Cross-sectional survey; analysis of 2003 and 2006/07 Tobacco Use Supplements to the Current Population Survey: multistage clustered probability sampling	Sample size ranged from 71,193 to 24,465 (depending on criteria used for inclusion) Response rate: The individual level self response rates for the 2003 TUSCS were 65.8%, 63.6%, and 61.4% for February, June, and November, respectively, and for the 2006/07 TUS the response rates were 60.7%, 61%, and 64.3% for May, August, and January respectively N in each ethnic/racial group: See attachment B	Independent Variables: Menthol status Outcome Variables: Cessation operationalized as current and former smokes who quit within the past 5 years who did not report current other tobacco products. Former smoker deified as having smoked 100+ cigs in lifetime and now smokes 'not at all.' Current smoker defined as having smoked 100+ cigs in lifetime and now smoke 'everyday' or 'some days' Menthol use defined as self-report if usual brand in past 12 months (or 12 months prior to quitting) was mentholated	Current smokers who quit in the past 5 years, menthol vs. non-menthol cigarettes AOR (95% CI) Total 0.92 (0.88-0.97) White 0.94 (0.89-0.999) Black 0.78 (0.64-0.95) Hispanics 0.96 (0.81-1.13) If Hispanics are divided by country of origin, AORs are 1.34 (1.04- 1.73) for Mexicans and 0.63 (0.40-098) for Puerto Ricans. Additional details on the covariates and AORs by the 5 sample restrictions available in Appendix A.	• Examined different ways to define subject sample.
Fagan P, Augustson E, Backinger CL, O'Connell ME, Vollinger RE Jr, Kaufman A, Gibson JT. Quit attempts and intention to quit cigarette smoking among young adults in the United States. 2007 National Cancer Institute	Cross-sectional survey; analysis of 2003 Tobacco Use Special Cessation Supplement (TUSCS) to the Current Population	Total N=33983 smokers and nonsmokers (Table 1 in article). Analysis included young adult current smokers aged 18 to 30 years old: N=7912 Response rate: 82.8%:, 76% were self-respondents and were eligible for the entire TUSCS Percent ethnic in each group Hispanic: 19% 2 or more races: 2% Non-Hispanic White: 61% Non-Hispanic Black: 13% Non-Hispanic Asian/ Pacific	Independent variable: Menthol status Outcome Variables: Number of quit attempts and a serious intention to quit - *Quitting behaviors.* Quit attempts were assessed by asking current smokers, "How many times during the past 12 months have you stopped smoking for 1 day or longer because you were trying to quit smoking?" Responses were categorized into 1 or more quit attempts and zero quit attempts. The intention to quit was assessed by asking smokers, "Are you	Multivariate logistic regression of 1 or more quit attempts during the past 12 months among menthol vs. non-menthol smokers showed OR (95% CI) was 1.00 (0.89-1.16) for current smokers, 1.00 (0.85-1.18) for daily smokers and 0.99 (0.62-1.41) for nondaily smokers. Multivariate logistic regression of 1 or more quit attempts during the past 12 months among smokers who reported serious intention to quit within the next 6 months showed non-significant effects of menthol among current smokers and daily smokers. However among non-daily smokers, the OR (95% CI) was 1.35 (0.60-3.03) but non-significant..	• Small sample sizes for racial/ethnic among nondaily smokers • Menthol use, whether or not survey participants switched brands during or after any quit attempts • Measure of quitting (measure is same for quit attempts no matter length of time without smoking) • Did not examine menthol effects in racial/ethnic groups

* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions.

Table 6: Quitting Success in National Surveys

Version Date: 3-12-11

Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
		Islander: 5% Non-Hispanic American Indian/Alaska Native: 0.7%	seriously considering quitting smoking within the next 6 months?" and included the responses yes or no. Current smokers defined as smoked every day (daily smokers) or some days (nondaily smokers). Menthol status defined as menthol or non-menthol as usual cigarette type or no usual type.		
Fagan et al. Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns. 2010 National Cancer Institute.	Cross-sectional survey; analysis of 2003 and 2006/07 Tobacco Use Supplements to the Current Population Surveys	Daily current smokers aged 18+ (*n* = 46 273) Response rate: 82.9% and 82.6% Menthol=11,671; NM=33, 644 For the number of individuals in each ethnic group by usual cigarette brand smoked, refer to Attachment C.	Independent Variable: Menthol status Outcome Variable: --Number of times during the past 12 months quit for one day or longer because trying to quit --Longest period of abstinence in last 12 months because trying to quit smoking --Intention to quit (planning to quit in next 30 days) Current daily smoking defined as smoked at least 100 cigarettes and smoking every day Menthol status defined as usual brand of cigarettes as being menthol or non-menthol	Multivariate models did not show sig. associations between usual brand of cigs and quit attempts 1 day or longer in past 12 months: OR (95% CI) ranged from 0.92 (0.83-1.02) to1.10 (0.91-1.34) depending upon cigarettes smoked per day Multivariate models did not show sig. associations between usual cig brand and duration of smoking abstinence ⍰weeks vs. ≤ 2 weeks in the past 12 months: OR (95% CI) ranged from 0.93 (0.79-1.12) to1.05 (0.82-1.36) depending upon cigarettes smoked per day	• Did not examine menthol effects in racial/ethnic groups
Gundersen DA, Delnevo CD, Wackowski O. Exploring the relationship between race/ethnicity,	Cross-sectional survey; analysis of 2005 U.S. National Health Interview Survey —Cancer Control Supplement (NHIS-CCS).	N=7815 white, black, and Hispanic current and former cigarette smokers who indicated that they do not currently use other tobacco products and have made a quit attempt.	Independent Variable: Menthol status Outcome Variable: Cessation operationalized as current vs. former smoker	Menthol smokers were less likely than nonmenthol smokers to be former smokers (56.9% vs. 61.5%; p<0.01). This relationship was found among blacks (43.7% vs. 62.1%; p<0.01) and Hispanics (48.5% vs. 61.2%; p<0.001), but was not statistically significant among whites	

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Table 6: Quitting Success in National Surveys

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Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
menthol smoking, and cessation, in a nationally representative sample of adults. 2009 Funding source not explicitly stated		Response rate: NA Menthol smokers : 26.5% Non-menthol smokers: 73.5% Percent ethnic in each group White: 82.7% Black: 8.9% Hispanic: 8.4%	Former smoker is defined as having smoked 100 cigarettes in a lifetime and now smoking "not at all." Current smoker is defined as having smoked 100 cigarettes in a lifetime and now smoking "everyday" or "some days." Menthol use defined as whether or not their usual brand of cigarettes in the past 12 months or in the 12 months prior to quitting was mentholated.	(62.8% vs. 61.6%, p=0.44). The odds of being a former smoker does not differ statistically or substantially relative to nonmenthol smokers (AOR=1.05, p=.47; Model 1) after controlling for demographics, smoking behavior, and perceived risk of cancer. White menthol smokers are more likely to be former smokers than their nonmenthol smoking counterparts, while black and Hispanic menthol smokers are less likely to have quit relative to black and Hispanic nonmenthol smokers respectively. Among non-whites (i.e. blacks and Hispanics collapsed) menthol smokers are less likely to have quit relative to nonmenthol smokers (AOR=0.55, p<0.01). AOR (95% CI) White: 1.17 (1.00-1.36) Blacks: 0.78 (0.56-1.09) Hispanic: 0.61 (0.39-0.97) Non-white: 0.55 (0.43-0.71)	
Hyland & Kasza. A Longitudinal Study of the Association Between Menthol Cigarettes and Indicators of Dependence: Findings from the International Tobacco Control Project 2010. National Cancer Institute Canadian Institutes for Health Research, Australian National Health and Medical Research Council, Australian Commonwealth Department of	Cohort survey; analysis of International Tobacco Control Four Country Survey ITC-4, which is an ongoing prospective cohort survey conducted with nationally representative respondents from four countries, including the United States.	Data were collected from 7532 adult smokers (18 years +) between 2002 and 2008. Random digit dialing was initially used to recruit current smokers within strata defined by geographic region and community size. Respondents who agreed to participate (cooperation rate ~80%) were typically contacted and completed a 35-minute survey designed to evaluate the psychosocial and behavioral impact of various national-level tobacco control policies.	Independent variable: Menthol status Outcome variables: -Making a quit attempt – respondents were asked: "Have you made any attempts to stop smoking since we last talked with you?" -Successful smoking cessation defined as no longer smoking on at least a monthly basis -Successful cessation among those making a quit attempt	In terms of quit attempts and quit outcomes, white respondents who smoked menthol cigarettes were significantly less likely to report making a quit attempt compared to white respondents who smoked non-menthol brands (0.84). No differences were seen in African Americans and Hispanics. No significant differences were observed in successful smoking cessation across all races, except African American women who smoked menthols were more likely to report successful cessation (3.58) and cessation among attempters at quitting (OR 3.96) than African American non-menthol smokers.	• Sample sizes were relatively small among minority racial/ethnic groups.

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Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Health and Aging Cancer Research UK, Canadian Tobacco Control Research Initiative, Centre for Behavioural Research and Program Evaluation of the National Cancer Institute of Canada/Canadian Cancer Society		Menthol smokers: 27% Non-menthol smokers: 73% Percent/number in each ethnic group White: 79% African American: 11% Hispanic 5% Asian: 1% Native American:4%			
Stahre M., Okuyemi K.S., Joseph A.M., Fu S.S. Racial/ethnic differences in menthol cigarette smoking, population quit ratios and utilization of evidence-based tobacco cessation treatments. 2010 Funding source not explicitly stated	Cross-sectional survey; analysis of 2005 National Health Interview Survey (NHIS).	6055 current adult smokers. Of these; 3068 male, 4932 White, 861 African American, 54 AI/AN, 119 Asian, average # cpd = 16.8, 1700 menthol smokers, 4355 non-menthol smokers 5949 former smokers. Of these; 3058 male, 5147 White, 573 African American, 45 AI/AN, 98 Asian, average # cpd = 18.6, 1515 menthol smokers, 4434 non-menthol smokers	Independent variable: Menthol status by racial/ethnic groups Outcome Variables: Population quit ratio: dividing the total number of former smokers by the total number of individuals who had reported smoking during their life-time (i.e. both former and current smokers). Current smokers not defined Former smokers defined as individuals who had reported quitting smoking within the previous 12 months. Current smokers were also asked whether they had attempted to quit smoking within the past year. Menthol cigarette status defined as whether or not respondent's usual brand of cigarettes was mentholated.	Of current menthol smokers, 49% reported a quit attempt in the past year, while 41% of non-menthol smokers reported a quit attempt. In addition, the quit ratios were significantly higher for non-menthol versus menthol smokers (50% versus 47%, $P = 0.014$). No significant difference in the quit ratios for menthol versus non-menthol smokers for whites (52% versus 50%), Asian Americans (38% versus 42%), AI/AN (52% versus 35%) or Hispanics (40% versus 45%). However, significant differences in the quit ratio for menthol versus non-menthol among African American smokers (34% versus 49%, $P < 0.001$). African American menthol smokers were significantly less likely than white nonmenthol smokers to have quit smoking (AOR: 0.72, 95% CI: 0.53, 0.97, *P*-value 0.031) after controlling for age group, sex, region, marital status and average number of cigarettes smoked per day	:

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Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Independent & Outcome Variables	Authors' Results/Conclusion(s) related to Menthol* (excerpted directly from article)	Comments
Trinidad D, Perez-Stable EJ, Messer K, White M, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. 2010 Funding source not specified	Cross-sectional survey; analysis of 2003 and 2006-2007 Tobacco Use Supplements to the Current Population Survey (TUS CPS).	Respondents ages 20-65 years at the time of the survey. Total N=283,441; 25,758 (Af-Am), 10,853 (Asian), 28,720 (Hispanic), 2,616 (Native American), 212,693 (White) Among current smokers – 14,791 were menthol smokers vs 42,352 non-menthol smokers. Among former smokers who had quit less than 6 months ago; 2,876 were menthol smokers, 9,707 were non-menthol smokers Among smokers who had quit smoking for 6+ months prior to the survey; 950 were menthol smokers, 3,015 were non-menthol smokers Response rate: CPS response rate 92%. Survey includes proxy and self-response data. Response rate for self-response data (only self-response data was used in this article) – 61%	Independent Variables: Menthol status by racial/ethnic group Outcome Variables: -Quit attempts: Current smokers were asked if they made an attempt to quit in the past 12 months, and, if so, the length of their longest quit attempt and the length of their last quit attempt. -Quitting intentions: Current smokers were asked if they were seriously considering quitting smoking within the next 6months (yes/ no). Current smokers were also asked to assess how likely they thought they would succeed in quitting smoking altogether in the next 6 months. -Quitting success: Among former smokers, successful smoking cessation/ long-term quitting was defined as being quit for at least 6 months at the time of the survey. Menthol status defined as response to question on their brand preferences (menthol, non-menthol or no usual brand). Former smokers were asked to think to the year before they quit and identify their brand preference. Those who reported having no usual brand were excluded from statistical modeling analyses. Current and former smoker defined as lifetime cigarette use (Have you ever smoked 100 cigarettes?')	African Americans and Hispanics/Latinos who smoked mentholated cigarettes were significantly more likely to be seriously considering quitting in the next 6 months compared to those who smoked nonmentholated cigarettes [African Americans: odds ratio (OR) = 1.62, 95% CI: 1.35–1.95; Hispanics/Latinos: OR = 1.21, 95% CI: 1.00–1.47]. No suggestion of a similar relationship was found among Asian Americans/ Pacific Islanders, Native Americans/Alaska Natives or non-Hispanic whites, African Americans and Hispanics/Latinos who smoked mentholated cigarettes were significantly more likely to have a positive estimation of quitting successfully in the next 6 months compared to those who smoked nonmentholated cigarettes (African Americans: OR = 1.87, 95% CI: 1.60–2.19; Hispanics/Latinos: OR = 1.34, 95% CI: 1.11–1.62). This was not found among Asian Americans/Pacific Islanders, Native Americans/Alaska Natives and non-Hispanic whites. Those who smoked mentholated cigarettes were significantly less likely to have quit successfully for at least 6months, for all racial/ethnic groups except Native Americans/Alaska Natives (African Americans: OR = 0.23, 95% CI: 0.17–0.31; Asian Americans/ Pacific Islanders: OR = 0.22, 95% CI: 0.11–0.45; Hispanics/Latinos: OR = 0.48, 95% CI: 0.34–0.69; Native Americans/Alaska Natives: OR = 0.49, 95% CI: 0.14–1.71; non-Hispanic whites: OR = 0.28, 95% CI: 0.25–0.33).	.

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			Current cig use defined as smoking every day or some days; former smoker as not smoking at all.		

Note: Please see text for information on embargoed study by Levy et al., in press

* Note: some these statements are taken directly from articles and may not include all relevant results/conclusions.

Attachments to Quitting Success in National Survey

A:

Predicted* prevalence of menthol cigarette type among current every day and former smokers by gender and race/ethnicity, National Health Interview Survey, 2005, *n* = 7688.

	Menthol			Non-menthol		
	Black	Hispanic	White	Black	Hispanic	White
Women	77.9	35.6	24.5	72.7	34.9	30.4
Men	69.7	16.5	14.6	66.0	14.5	15.2

Cubbin C, Mah-Jabeen S, LeClere FB. The intersection of gender and race/ethnicity in smoking behaviors among menthol and non-menthol smokers in the United States. 2010

B:

Sample counts by sample restriction and outcome, 2003 and 2006/7 Tobacco Use Supplement to Current Population Survey

	Overall	Whites	Blacks	Hispanics	Mexicans	Puerto Ricans
Current and former smokers who quit within the past 5 years, regardless of past quit attempts or current OTP use						
Total sample size	7 1,193	60,525	5,827	4,841	2,769	735
Current and former smokers who quit within the past 5 years who did not report current OTP use						
Total sample size	6 5,316	55,347	5,448	4,521	2,577	691
Current and former smokers who quit within the past 5 years who reported ever having made a quit attempt						
Total sample size	5 5,322	47,672	4,178	3,472	1,939	563
Current and former smokers who quit within the past 5 years who did not report current OTP use and have ever made a quit attempt (replicates Gundersen et al.)						
Total sample size	5 0,761	43,618	3,898	3,245	1,805	527
Past 12 month cigarette smokers who made a quit attempt or quit						
Total sample size	2 4,465	20,640	2,135	1,690	962	282

Delnevo et al. Examining the relationship between menthol smoking and cessation using data from the 2003 and 2006/7 Tobacco Use Supplement 2010 submission

C:

Socio-demographic characteristics of daily smokers by usual cigarette brand, aged 18+: Tobacco Use Supplements to the Current Population Surveys (TUS CPS), 2003, 2006/07

Race/ethnicity	Menthol	Non-menthol	No usual type	Total
Non-Hispanic white	7 823	29 415	704	37 942
Non-Hispanic black/African American	2 509	883	95	3 487
Hispanic	688	1 643	93	2 424
Non-Hispanic American Indian/Alaska Native	109	500	13	622
Non-Hispanic Asian American/Pacific Islander	271	519	37	827
Non-Hispanic two or more races	271	684	16	971

Fagan et al. Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns. 2010

Table 7 Main Characteristics and Findings of Longitudinal Cohort and Clinical Trial Studies Comparing Smoking Cessation Outcomes in Menthol and Nonmenthol Cigarette Smokers (additional information added to Table in Foulds et al., 2010)

Author (publication year)/study years	Location	N M/NM	*N*—W/AA/ Hisp/Other	Cigarettes/ day (M/NM)	Design	Intervention?	Definition (of a quitter)	Evidence of M effect?	Comments
Fu et al. (2008)/2006	United States—VA pharmacy databases	Total = 1,343 M = 342 (25%)/ NM = 1,001 (75%) *M* age = 56 (10.3)	All smokers: Caucasian: 76% AA: 14% Other: 10%	Total: 25 M: 20 NM: 30	Cross-sectional analysis at end of interventional trial	Intervention aimed to stimulate repeat quit attempts All participants had previously failed using NRT or bupropion	Seven-day point prevalence, self-reported	No overall effect of M on abstinence. Some evidence of increased quitting among menthol smokers, restricted to intervention group, with lower menthol quitting in controls.	Older sample. One significant interaction between menthol status and treatment group only, not significant after Bonferroni correction
Cropsey et al. (2009)/ 2004–2006	Women's prison in Virginia	N=233 M=159 NM=74 *M* age = 34	W = 109 (49% M) AA = 124 (95% M) (all female)	W = 20 AA = 14	Retrospective analysis of trial cohort.	Randomized trial of NRT plus group, versus wait list control	Seven-day point prevalence by self-report (and exhaled CO < 3 ppm) at 6 weeks and 12 months.	No effect of menthol	Relatively small sample of incarcerated women (only six AA nonmenthol smokers)
Gandhi et al. (2009)/ 2001–2005	Outpatient Smokers' Clinic Central New Jersey	Total = 1688 M = 778 (46%)/ NM = 910 (54%) *M* age = 42 (13.3)	1086/374/149/79 64%/22%/9%/5 %	Total sample: 21 M: 19 NM: 23	Clinic cohort, followed up at 4 weeks and 6 months.	Tailored Smoking cessation treatment with meds and counseling	Self-report of not smoking in previous 7 days at 4 weeks and 6 -month follow-up. Biochemical verification in those attending at 4 weeks.	Yes, but restricted to non-whites. Also related to *SES*. For AAs at 6 months, Adj. OR = 0.48 (0.25–0.9)	Cigarettes/day lower in AA and H menthol smokers. Follow-up rate= 74% at 4 weeks and 58% at 6 months.
Okuyemi et al. (2007)/ 2003–2004	Kansas	755 light smokers (<11 cigarettes/day) *M* age = 45.1 (*SD* = 10.7)	0/755/0/0	M: 7.5 NM: 7.8	Clinical trial cohort followed up at 6m.	Nicotine gum × motivational interviewing trial (factorial)	Seven-day point prevalence, verified by CO/salivary cotinine at 6-month follow-up	Yes, unadjusted: 11.2% vs. 18.8%	M not significant in fully adjusted model (overadjusted by using number of appointments attended?) (Nollen et al. 2006); M effect stronger in age < 50

Author (publication year) / study years	Location	N M / NM	*N*—W / AA / Hisp / Other	Cigarettes / day (M / NM)	Design	Intervention?	Definition (of a quitter)	Evidence of M effect?	Comments
Okuyemi et al. (2003)/ 1999–2000	Kansas	600 smokers (471/129) *M* age = 44	0/600/0/0	M: 18 NM: 18	Clinical trial cohort followed up at 6m.	Bupropion versus placebo randomized controlled trial	Seven-day point prevalence, verified by CO/salivary cotinine	Yes, in subgroup. At 6 weeks in age < 50: OR (NM) 2.02 (1.03–3.95)	No significant effect at 6 months and or in smokers > 50 y/o
Murray et al. (2007)/ 1986–2001	United States	Total = 5,887 M = 1,216 (21%)/ NM = 4,671 (79%) *M* age = 48.4 (*SD* = 6.8)	White:95.2% AA: 3.8% H: 0.6%	Overall average 26 cigarettes/ day Pack-years: M: 38.18 NM: 40.1	Clinical trial cohort followed up 5 and 14 years after enrollment	12-week group intervention plus nicotine gum (repeatable for 5 years) or usual care	Smoking at all in past 12 months	Three categories: sustained quitter, intermittent smoker, continuing smokers; no menthol effect	Only 114 AA menthol smokers in the study.
Pletcher et al. (2006)/ 1985–2000	Birmingham, Chicago, Minneapolis, and Oakland	1535 smokers (972/563) *M* age= 25.1 (3.6)	657/878/0/0	M: 10 NM: 15	Prospective cohort study	No	*Sustained cessation*: not current smoker at last 2 visits *Relapse*: smoker → nonsmoke → smoker at last exam	No *Sustained cessation*: Adj. OR = 0.71(0.49-1.02) Yes *Relapse*: Adj. OR = 1.89 (1.17–3.05)	Long-term study, not in context of a quit attempt
Muscat et al. (2002)/ 1981–1999	Hospitals in New York, Washington DC, and Pennsylvania	Total = 19545 NM = 16540 (85%) M = 3005 (15%) 56%–72% aged > 54	W = 17,639 (89%) AA = 1906 (11%)	W: NM = 29 M = 28 AA NM = 21 M = 18	Cross-sectional case-control study based on convenience sample of cases (lung cancer) and controls (other medical patients)	No intervention	Ever smoked daily for a year and not smoked daily in past year.	No effect on quitting OR = 1.1	Older and relatively affluent sample, with unusually low menthol rate in AAs (34%). Definition of abstinence relatively lenient. Possible effect of illness on quitting.
Hyland et al. (2002)/ 1988–1993	22 communities in North America	*N* = 13,268 (age 25–64) M = 3,184 (24%)/ NM = 10,084 (76%) 23% Whites smoke M, 57% AAs smoke M. 51% ages < 45	All smokers: Caucasian: 10,004 (75%) AA: 878 (7%) Hispanic: 693 (5%) Other: 294 (2%) Canadian: 1,382 (10%)	Total sample: 23.2/day	Prospective population cohort survey, followed up after 5 years.	Randomized community intervention trial	Self-report of no cigarette use in past 6 months at 5-year follow-up.	No. (e.g., adjusted RR for quitting by AA menthol smokers = 1.04.)	M smokers more likely to have 2+ prior quit attempts. No data on whether participants tried to quit.

Author (publication year) / study years	Location	N M / NM	*N*—W / AA / Hisp / Other	Cigarettes / day (M / NM)	Design	Intervention?	Definition (of a quitter)	Evidence of M effect?	Comments
Unpublished November 2010 submissions to FDA									
Hyland, Rivard et al. (2010a)	22 communities in North America	N=2095 M=409 NM=1464 Other=222	W=1866 AA=91		Prospective population cohort survey, assessed in 2005; Menthol status 1988-2001.	Randomized community intervention trial	Self-report of no cigarette use in past 6 months in 2005	No effect on quitting OR: 0.84	Sample size too small for AA analysis
King et al. 2010	Outpatient smokers clinic Chicago	N=291 M=136 NM=155	W=181 B=110		Clinical trial cohort followed up at 4 and 12 weeks	NRT vs. NRT plus naltrexone	CO verified prolonged abstinence	Significant med x menthol interaction in AA (OR=31.22, p=0.029)	AA menthol vs. nonmenthol smokers who used NRT only did worse
Reitzel 2010a	Outpatient clinic Houston TX	N=420 M=175 NM=245	W=138 B=143 Latino=139	M=20.7 NM=21.5	Clinical trial cohort followed up to 26 weeks	NRT plus counseling	CO verified no smoking since quit date	Menthol did not predict abstinence	
Reitzel 2010b	Outpatient clinic Houston, TX	N=391 M=321 NM=70	B=391	M=20.6 NM=21.0	Clinical trial cohort followed up to 26 weeks	Treatment with palm pilot computers	CO verified no smoking since quit date	Menthol did not predict abstinence	
Reitzel 2010c	Outpatient clinic Houston, TX	N=249 M=125 NM=124	W=88 B=81 Latina=75 Other=5	M=9.2 NM=11.1	Clinical trial cohort followed up to 26 weeks	Motivation based treatment for pregnant women	CO verified no smoking since quit date	Menthol did not predict abstinence	Post-hoc analysis showed White menthol vs. non-menthol smokers did worse (small n)

- *Note.* M = menthol; NM = nonmenthol; OR= odds ratio; RR= relative risk; adj. = adjusted for other baseline variables; CO = exhaled carbon monoxide concentration; AA= African American; W = white (non-Hispanic); H = Hispanic/Latino; *M* age = mean age of sample; SES = Socioeconomic status; NRT = Nicotine Replacement Therapy; VA=Veteran's Affair; SES=SocioEconomic Status.
- ***Note:*** **Please see text for embargoed study by Blot et al., in press.**

4. Adjusted Odds of Smoking Cessation for Menthol Use by Race/Ethicity for Various Cigarette Smoking Subgroups, 2003-2006/7 Tobacco Use Suppement Current Population Survey

	Overall			White			Black			Hispanic			Mexican			Puerto Rican		
Sample Restriction	**AOR**	**95 % CI**		**AOR**	**95 % CI**		**AOR**	**95 % CI**		**AOR**	**95 % CI**		**AOR**	**95 % CI**		**AOR**	**95 % CI**	
Cigarette smokers and former smokers who quit in the past 5 years*	0.914	0.868	0.961	0.928	0.877	0.982	0.810	0.670	0.979	0.936	0.793	1.105	1.288	0.999	1.661	0.569	0.371	0.874
Cigarette smokers and former smokers who quit in the past 5 years who do not currently use other tobacco products*	0.923	0.876	0.973	0.943	0.891	0.999	0.781	0.640	0.952	0.958	0.810	1.133	1.338	1.039	1.722	0.630	0.403	0.984
Cigarette smokers and former smokers who quit in the past 5 years who have made a quit attempt*	0.902	0.855	0.953	0.937	0.882	0.994	0.716	0.585	0.875	0.881	0.733	1.059	1.302	0.978	1.733	0.541	0.344	0.849
Cigarette smokers and former smokers who quit in the past 5 years who have made a quit attempt and do not currently use other tobacco products*	0.911	0.862	0.964	0.952	0.897	1.011	0.684	0.555	0.844	0.901	0.749	1.084	1.349	1.016	1.790	0.590	0.368	0.947
Past year smokers #	0.922	0.847	1.004	0.982	0.894	1.079	0.740	0.558	0.981	0.725	0.543	0.969	1.200	0.778	1.852	0.421	0.209	0.851

* controlling for gender, age, income, education, race/ethnicity (overall only), year, and month

controlling for gender, age, income, education, race/ethnicity (overall only), year, month, and past year cigarette tax increase

CHAPTER 7: EFFECTS OF MENTHOL ON THE DISEASE RISKS OF SMOKING

INTRODUCTION

This chapter addresses the specific question of the comparative risk of menthol compared with non-menthol cigarettes: Do smokers of menthol cigarettes have increased risk for diseases caused by smoking in comparison with smokers of non-menthol cigarettes? It does not address the broader public health impact of menthol cigarettes, which is covered in Chapter 8. In the TPSAC conceptual framework, this question is directed at the relative risks for development of the various diseases caused by smoking with the comparison being between users of non-menthol cigarettes as the reference. Risks could be greater or lesser for smokers of menthol cigarettes if the various toxins and carcinogens in smoke differ by type of cigarette; if smoking patterns differ by type of cigarettes in ways that affect the doses of disease causing-agents reaching target sites; if menthol affects the kinetics and metabolism of disease-causing tobacco smoke components; and if menthol itself contributes to disease risk.

Multiple lines of research are relevant to the overall question that is the focus of this chapter. These include: (1) studies directed at the topography of smoking; (2) studies comparing levels of biomarkers of tobacco smoke in smokers of menthol and non-menthol cigarettes; (3) studies on the toxicology of menthol; and (4) epidemiological studies that directly compare disease risks in smokers of menthol compared with non-menthol cigarettes.

STUDIES OF SMOKING TOPOGRAPHY

An important question in assessing risks of smoking menthol cigarettes is whether menthol cigarette smokers inhale more smoke and are exposed to more tobacco smoke toxins than smokers of non-menthol cigarettes. This question has been examined in two types of studies. The first type involves laboratory studies that compare puffing behaviors (called topography studies) or the increase (boost) of nicotine and/or carbon monoxide levels from smoking a cigarette in individual menthol and non-menthol smokers. This section reviews such studies. The second consists of cross-sectional studies in which tobacco smoke exposure biomarkers are measured in people smoking cigarettes, typically their usual brand of cigarette, and menthol and non-menthol smokers are compared. A subsequent section considers these studies.

Before describing the various studies, it is important to mention important potential confounding factors and other methodologic problems that are relevant to a number of studies. Since most African American smokers smoke menthol cigarettes and most whites smoke non-menthol cigarettes, any comparison of menthol vs. non-menthol without considering race is problematic. African American and white smokers differ in several relevant ways. On average African Americans smoke fewer cigarettes per day, take in more smoke per cigarette and metabolize nicotine and cotinine differently than white smokers (Perez-Stable et al. 1998). Some studies statistically control for race, but "control" may not be possible, given the high proportion of African Americans who smoke menthol cigarettes. The optimal study design compares menthol vs. non-menthol smokers within a racial group, but few studies have adequate numbers to do this. Also, a number of the published studies, particularly the topography studies, are quite small and predominantly include adult heavy smokers recruited by advertisements for experimental studies. This

approach to identifying participants limits the generalizability of findings. Furthermore, topography studies generally measure puffing behavior while smoking one cigarette via a cigarette holder, to which monitoring equipment is attached. Smoking a single cigarette through a cigarette holder is not representative of how a person normally smokes their cigarettes throughout the day. Several studies have involved rapid smoking of cigarettes or smoking with fixed puff sizes or fixed numbers of puffs, also experimental scenarios that are not representative of usual smoking.

Eleven laboratory studies of topography were identified (Table 1). These studies varied considerably in design, but included at least some measurement of smoking behavior: number of puffs per cigarette, average puff volume, total puff volume, time to smoke the cigarette and/or biomarker measurements: increase in nicotine and/or carbon monoxide levels before and after smoking a cigarette.

Nine studies reported effects of menthol smoking on number of puffs or puff volume (Nil and Battig 1989; Caskey et al. 1993; Miller et al. 1994; Ahijevych et al. 1996; Jarvik et al. 1994; McCarthy et al. 1995; Ahijevych and Parsley 1999; Pickworth et al. 2002; Strasser et al. 2007). Some studies compared smokers smoking their preferred type of cigarette while some were crossover studies. Some studies reported a decrease, one reported an increase, and others saw no change in puffing behavior comparing menthol to non-menthol cigarette smoking. Jarvik et al. (1994) also compared inhaled volume and lung retention time and found no effect of menthol cigarettes. St Charles et al. (2009) similarly reported no effect of smoking menthol cigarettes on inhalation volume or total lung exposure times, although the inhalational tidal ratio (the inhalation volume as a proportion of resting tidal volume) was borderline lower in menthol (1.52, SD 0.47) compared to non-menthol (1.79, 0.60) smokers ($p = 0.054$).

Six studies reported carbon monoxide (CO) boost in relation to type of cigarette smoked (Nil and Battig, 1989; Miller et al. 1994; McCarthy et al. 1995; Jarvik et al. 1994; Ahijecych et al. 1996; and Pickworth et al. 2002). In general there were small or no differences between the CO boost by type of cigarette. Miller et al. (1994) found that CO boost was higher from smoking cigarettes into which 8 mg menthol had been injected compared to lower levels, despite no change in puff volume. Two other studies also found that the increase in CO in relation to puff volume or number of puffs was higher in smokers of menthol cigarettes compared with non-menthol cigarettes.

Patterson et al. 2003 measured the plasma nicotine boost in treatment-seeking smokers and in a multivariate analysis found no effect of menthol cigarette smoking.

Overall, there is little evidence from laboratory studies that the presence of menthol in a menthol cigarette increases the extent of inhalation of smoke from a cigarette. Some studies suggest that menthol might selectively enhance absorption of CO. However, the generalizability of this finding is uncertain since the subjects in these studies were all experienced adult daily smokers. There are no data on the effect of menthol cigarettes on inhalation parameters in novice smokers, and or in light and intermittent smokers. The latter group is important because there is strong evidence that people who smoke fewer cigarettes per day inhale more smoke per cigarette. Additionally, African Americans are more likely to be light smokers. Since African Americans predominantly smoke menthol cigarettes, it is important to determine whether menthol facilitates inhalation of large volumes of smoke in those who are smoking few cigarettes per day.

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
1. Ahijevych ., Gillespie J, Demirci M, Jagadeesh J, 1996. Menthol and non-menthol cigarettes and smoke exposure in African American and white women. Pharmacology Biochemistry and Behavior 53, 355–360.	Two-factorial design	N = 37 women stratified by race and menthol or non-menthol cigarettes 18 AA/8 menthol 19 white/10 menthol	Blood nicotine and cotinine and expired air carbon monoxide was measured before and after smoking one of her usual cigarettes. Subjects' smoking and respiratory topography were measured.	Nicotine and expired CO boost; number of puffs, puff volume and total puff duration.	There were significant main and interaction effects of race and menthol/non-menthol cigarette use on CO boost. African American women had a mean CO boost of 10.1 ppm vs. 7.2 ppm for white women, while women using nonmenthol cigarettes had a higher CO boost (mean = 10.6 ppm) compared to those regularly using menthol cigarettes (mean = 6.5 ppm). African American women had non-significantly higher puff volumes compared to white women (mean – 48.4 vs. 43.5 ml), while non-menthol smokers had nosignificantly higher puff volumes than menthol smokers (mean = 48.5 vs. 42.7 ml). Lower CO boost with mentholated cigarettes suggests factors beyond mentholation may affect elevated smoke constituent exposure among African American women.	Strengths include groups balanced by race and menthol. Weaknesses include small N, research volunteers all heavy smokers, women only, limiting generalizability.
2. Ahijevych K, Parsley LA, 1999. Smoke constituent exposure and stage of change in African American and white women cigarette smokers. Addictive Behaviors 24, 115–120.	Two-factorial design	N = 95 women stratified by ethnicity and menthol/non-menthol preference 48 AA/27 menthol 47 White/22 menthol	Respiratory and puffing topography were measured during the cigarette smoking bout.	Puff volume	Menthol smokers had significantly larger puff volumes compared to non-menthol smokers	Strengths include groups fairly well balanced by race and menthol. Weaknesses include women only.
3. Caskey NH, Jarvik ME, McCarthy WJ, Rosenblatt MR, Gross TM, Carpenter CL, 1993. Rapid smoking of menthol and non-menthol cigarettes by African American and white smokers. Pharmacology Biochemistry and Behavior 46, 259–263.	Repeated-measures cross-over design	Two independent groups of male cigarettes smokers. One group (N = 12) characterized themselves as predominantly menthol cigarette smokers and other as non-menthol smokers (N = 16). 25 AA/9 menthol 11 white/3 menthol	Subjects participated in a modified rapid smoking procedure in two sessions, 1 week apart. In one session, subjects smoked regular cigarettes and in the other, they smoked menthol cigarettes. Subjects puffed	Number of puffs Expired CO boost	No difference was observed for the number of puffs taken or CO boost from regular compared to menthol cigarettes.	Weaknesses include small N, imbalance of race and menthol; rapid smoking differs from usual way of smoking.

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
			cigarettes every 15 seconds until they were unable to continue.			
4. Clark PI, Gautam S, Gerson LW, 1996. Effect of menthol cigarettes on biochemical markers of smoke exposure among African American and white smokers. Chest 110, 1194–1198.	Cross-sectional	N = 65 AA and N = 96 white adult smokers 65 AA/54 menthol 96 white/22 menthol	Subjects were asked to smoke one cigarette and carbon monoxide levels were measured.	Expired carbon monoxide	The mean unadjusted expired-air carbon monoxide levels were not significantly higher in menthol smokers (40.3 ppm) compared to nonmenthol smokers (35.8 ppm; p=0.09). However, menthol was a significant contributor to expired-air carbon monoxide levels after adjusting for cigarettes per day and amount of each cigarette smoked	Weaknesses include imbalance or race and menthol
5. Jarvik ME, Tashkin DP, Caskey NH, McCarthy WJ, Rosenblatt MR, 1994. Mentholated cigarettes decrease puff volume of smoke and increase carbon monoxide absorption. Physiology and Behavior 56, 563–570.	Crossover	N = 20 smokers 10 AA/5 menthol 10 white/5 menthol	All subjects smoked both types of cigarettes, one on each of two days, through puff monitoring device..	Carbon monoxide boost; Number of puffs; Average puff volume; Total puff volume; Mean puff flow	Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide, despite the fact that mentholated cigarettes decreased average and total cumulative puff volumes and increased mean puff flow rates of inhaled smoke. These chemical and topographic differences were independent of race. No significant differences in depth of inhalation of the smoke or the amount of insoluble smoke particulates delivered to or retained in the respiratory tract were noted between the two types of cigarettes. Mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide.	Strengths include balanced race and menthol. Weaknesses include small N and subjects randomized to smoke non-preferred cigarettes.
6. McCarthy WJ, Caskey NH, Jarvik ME, Gross TM, Rosenblatt MR, Carpenter C, 1995. Menthol vs. non-	Crossover	N = 29 male smokers	Smokers smoked either a regular or a mentholated cigarette in two	Number of puffs	When smoking the non-mentholated brand of cigarettes, participants smoked 22% more puffs and had 13% higher mean volumes per puff than they did when smoking the mentholated brand of cigarettes. The aggregate 39%	Weaknesses: small N, race and menthol imbalance,

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
menthol cigarettes: effects on smoking behavior. American Journal of Public Health 85, 67–72.		16 AA/ 8 menthol 13 white/3 menthol	separate sessions 1 week apart. Commercial brands with comparable tar, nicotine, and CO content were used. Smoking behavior was constrained by fixed 15-second inter-puff intervals but puff volume and number of puffs were unconstrained.	Puff volume	excess exposure of cigarette smoke in the regular-cigarette conditions was not accompanied by commensurate excesses in expired carbon monoxide or in physiological measures normally correlated with nicotine exposure.	artificial smoking procedure, used one brand of cigarettes, poor generalizabilty because of sample characteristics
7. Miller GE, Jarvik, ME, Caskey NH, Segerstrom SC, Rosenblatt MR, McCarthy WJ, 1994. Cigarette mentholation increases smokers' exhaled carbon monoxide levels. Experimental and Clinical Psychopharmacology 2, 154–160.	Crossover	N = 12 male smokers Recruited from drug treatment program All were AA/6 menthol	3 smoking sessions spaced 1 week apart. In each session, subjects inhaled cigarette through smoking apparatus, one puff every 30 sec until 1200 cc of cigarette smoke was inhaled. Menthol dosage varied across sessions, such that subjects smoked experimental cigarettes that had been injected with 0 mg, 4 mg, or 8 mg of menthol.	Exhaled carbon monoxide boost No puffs, puff volume	No effect of menthol on number or volume of puffs. The CO boost was 5.6, 6.1 and 8.1 ppm for 0, 4 and 8 mg menthol cigarettes ($p < 0,004$).	Weaknesses include small N, use of subjects with drug abuse history, artificial smoking procedure, resulting in poor generalizability.

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
8. Nil R, Battig K. Separate effects of cigarette smoke yield and smoke taste on smoking behavior. *Psychopharmacology (Berl)* 1989, 99(1):54–59.	Crossover	N = 15; no data on usual brand menthol preference or race	Subjects came to laboratory weekly for 7 weeks. Each week a test cigarette or own brand was smoked. The test cigarettes include 2 menthol brands, one high and one low tar. During each session the first cigarette was smoked naturally through a cigarette holder, the second was puffed every 30 seconds.	No puffs, average puff volume, puff volume per cigarette, expired CO boost	Significantly fewer puffs and smaller total puff volume in high tar menthol vs. other brands during natural smoking; smaller total puff volume for high tar menthol vs. other brands for 30 second-puff smoking	Weaknesses include small N, smokers not smoking preferred cigarettes, artificial smoking procedure
9. Patterson F, Benowitz N, Shields P, Kaufmann V, Jepson C, Wileyto P, Kucharski S, Lerman C, 2003 Individual differences in nicotine intake per cigarette. Cancer Epidemiology Biomarkers and Prevention 12, 468- 471.	Clinical trial of nicotine replacement therapy for smoking cessation	N = 190 treatment-seeking smokers 120 white, 47 AA and 23 other race 55 menthol (no data by race)	Plasma nicotine levels measured before and after participants smoked one of their own brand cigarettes *ad libitum*.	Plasma Nicotine boost	Nicotine boost not significantly different in menthol vs. non-menthol cigarettes smokers.	Weaknesses: sample was treatment seekers, generalizability, only studied nicotine boost after smoking one cigarette in the middle of the day
10. Pickworth WB, Moolchan ET, Berlin I. Murty R. 2002. Sensory and physiologic effects of menthol and non-menthol cigarettes with	Double blind experimental study	N = 18 menthol smokers (17 AA) N = 18 non-menthol smokers (3 AA)	Menthol and non-menthol cigarette smokers participated in a single session during which three	Number of puffs CO boost	No differences between menthol and non-menthol cigarettes on number of puffs or CO boost were observed.	Weaknesses include small number of subjects; race by menthol

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
differing nicotine delivery. Pharmacology, Biochemistry and Behavior 71, 55–61.			cigarettes were smoked 45 minutes apart, in random order. Cigarettes were research nicotine low yield (0.2 mg), commercial cigarettes (1.2 mg) and research high nicotine yield (2.5 mg). Subjects smoked menthol or non-menthol on the basis of their usual brand.			imbalance; smokers smoked research cigarettes or commercial cigarettes but not their own brand.
11. St.Charles FK, Krautter GR, Dixon M, Mariner DC, 2006. A comparison of nicotine dose estimates in smokers between filter analysis, salivary cotinine, and urinary excretion of nicotine metabolites. Psychopharmacology 189, 345–354.	Observational study	N = 74 smokers selected according to machine determined yield of usual cigarettes. 18 menthol smokers, race not specified.	A 5-day clinical study was conducted. Filters were analyzed to estimate the daily mouth exposure of nicotine. Twenty-four-hour urine samples for nicotine equivalents. Saliva samples were collected daily for cotinine analysis. Respiratory pattern recording during smoking of selected cigarettes	Inhalation tidal ratio (ratio of inhalation volume / resting tidal volume)	Inhalation tidal ratio borderline higher in non-menthol (1.79) compared to menthol (1.52) smokers (p = 0.054)	No Strengths or Weaknesses specifically noted by authors.

Chapter 7 Table 1. Menthol Smoking and Topography						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
12. Strasser AA, Malaiyandi V, Hoffmann E, Tyndale RF, Lerman C, 2007. An association of CYP2A6 genotype and smoking topography. Nicotine and Tobacco Research 9 (4), 511–518.	Observational study	N = 119 participants enrolled in smoking cessation clinical	Subjects smoked a cigarette through in a cigarette holder attached to a puffing monitoring device.	Number of puffs Mean puff volume Total puff volume	Smoking topography variables did not differ significantly by level of nicotine dependence or cigarette mentholation (p values >0.2).	Weaknesses: subjects seeking smoking cessation treatment, smoking a single cigarette through cigarette holder, generalizability
13. Williams JM, Gandhi KK, Steinberg ML, Foulds J, Ziedonis DM, Benowitz, NL. Higher nicotine and carbon monoxide levels in menthol cigarette smokers with and without schizophrenia. *Nicotine and Tobacco Research* 2007, 9(8):873–881.	Observational study	N = 89 smokers with schizophrenia N = 53 control smokers ….	All subjects attended on the afternoon of a normal smoking day and provided a measure of exhaled CO and a blood sample approximately 2 min after smoking one of their usual cigarettes.	Expired carbon monoxide Serum nicotine Serum cotinine	Serum nicotine levels (27 vs. 22 ng/ml, p=.010), serum cotinine levels (294 vs. 240 ng/ml, p=.041), and expired CO (25 vs. 21 ppm, p=.029) were higher in smokers of menthol compared with non-menthol cigarettes	Weaknesses: mixed psychiatric and health study groups, race by menthol imbalance, generalizability

BIOMARKER STUDIES

This section reviews studies that have compared biomarkers of exposure to tobacco smoke constituents in smokers of menthol and non-menthol cigarettes. Biomarker measurements provide a quantitative assessment of systemic exposure to cigarette constituents. Exposure biomarkers include measurement of nicotine intake (nicotine, cotinine and other nicotine metabolites), gas phase exposure (carbon monoxide and various volatile organic compounds) and particulate phase (the tobacco-specific nitrosamine NNAL and metabolites of polycyclic aromatic hydrocarbons). The biomarkers may be measured in blood, urine or saliva. Carbon monoxide (CO) is measured either as carboxyhemoglobin in blood or as CO in exhaled air. Most biomarker studies are cross-sectional in design, involving comparisons of biomarker levels in menthol vs non-menthol cigarette smokers at a single point in time. Some studies have measured biomarkers immediately before or after smoking a cigarette in a laboratory. Some additional, general methodologic issues warrant mention. All studies included adult daily smokers and the protocols for most studies required subjects to have smoked five or more cigarettes per day. Some urine samples were collected as spot urine samples and some as 24-hour collections. The latter are more accurate reflectors of daily exposure, but it is difficult to collect a full specimen from people in naturalistic settings. Correction for urine creatinine to deal with dilutional differences is useful. Many researchers do not report time from last cigarette to time of biomarker collection. Information on this interval may be needed as some biomarkers, like nicotine, have relatively short half-lives.

As previously discussed, there is the potential for confounding or modification of results by race in studies of menthol cigarettes. Racial factors are important in relation to interpreting cotinine levels. African Americans on average metabolize cotinine more slowly than whites (Perez-Stable et al 1998). Many studies show that cotinine levels are higher when normalized for cigarettes smoked per day in African Americans vs. whites (for example, Caraballo et al. 1998; Benowitz et al. 2009). Therefore higher cotinine levels in menthol smokers overall could result from a predominance of African Americans among the menthol cigarette smokers. Urine nicotine equivalents is a term used to describe the sum of nicotine and its metabolites, nicotine glucuronide, cotinine, cotinine glucuronide, trans-3' hydroxycotinine and its glucuronide, in urine. The sum of metabolites accounts for 85–90 percent of the nicotine doses and is a useful surrogate for nicotine intake that is not affected by racial differences (Hukkanen et al. 2005).

We have identified thirteen published cross-sectional studies and one unpublished tobacco company analysis of a cross-sectional study that compared biomarker levels in smokers of menthol and non-menthol cigarettes. We also describe one experimental study in which biomarkers of exposure were measured in smokers while smoking menthol or non-menthol cigarettes. Study design and results are summarized in Table 2. Brief descriptions of the studies follow.

Wagenknecht et al. (1990) measured serum cotinine in 822 African American and 602 white smokers who were participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. In a multiple linear regression model which included race, age, sex, education, cigarettes per day, inhalation pattern, secondhand smoke exposure and machine-determined nicotine yield, African-American race

was associated with substantially and highly statistically significantly greater cotinine levels compared to whites. Higher serum levels in African-Americans compared to whites were seen both in menthol and non-menthol cigarette smokers. The beta coefficient for race in the regression model was higher for menthol smokers (89.0 ng/ml) compared to non-menthol smokers (51.5 ng/ml), but no statistical comparison of these coefficients was presented by the authors.

Ahijevych et al. (1996) measured plasma cotinine in 37 women stratified by race and menthol cigarette smoking. Plasma cotinine tended to be higher in menthol (254 ng/ml) compared to non-menthol (204 ng/ml) smokers, but this difference was not significant. The ratio of plasma cotinine to cigarettes per day was higher in menthol (18.1 ng/ml/cig) compared to non-menthol (15.3 ng/ml/cig) smokers, but this difference also was not statistically significant.

Clark et al. (1996) measured serum cotininine in 65 African American and 96 white smokers who smoked at least five cigarettes per day. Serum cotinine levels overall in menthol (478 ng/ml) vs. non-menthol (349 ng/ml)smokers, and the difference (84 ng/ml) remained statistically significant in a linear regression analysis after controlling for race, cigarettes per day and amount of each cigarette smoked.

Mustonen et al. (2005) measured saliva cotinine in 51 African American and 256 white smokers of at least 10 cigarettes per day. Cotinine levels were higher overall in menthol vs. non-menthol smokers (476 ng/ml vs. 442 ng/ml), but the difference was not statistically significant. The cotinine per cigarette per day ratio was statistically significantly higher in menthol smokers, but this could be due at least in part to racial confounding. Analysis of covariance found several race x sex x menthol subgroup differences, but these cannot be readily interpreted as a general effect of menthol cigarettes.

Williams et al. (2007) measured serum nicotine and cotinine in 155 smokers, of which 89 had schizophrenia or schizoaffective disorder and 53 were healthy controls. Blood samples were collected two minutes after smoking one of their usual cigarettes. After adjustment for psychiatric diagnostic group, race and cigarettes per day, serum nicotine, serum cotinine and expired CO were statistically significantly higher in menthol cigarette smokers.

Signorello et al. (2009) reported serum cotinine levels in 130 African American and 125 white smokers. In a linear regression analysis adjusted for cigarettes per day, age, race and sex no significant effect of menthol brand was observed.

Muscat et al. (2009) measured plasma cotinine, urine cotinine, plasma thiocyanate (a biomarker of cyanide exposure) and urine NNAL (a metabolite of the tobacco-specific nitrosamine and carcinogen NNK) in 237 African American and 288 white smokers of at least 5 cigarettes per day. In a multiple regression analysis adjusted for cigarettes per day, age and sex and performed separately by race, there was no effect of smoking menthol cigarettes on these biomarkers. However, when NNAL was analyzed as the ratio of NNAL glucuronide / NNAL, the ratio was lower in menthol cigarette smokers. This finding was statistically significant, and along with the in vitro data presented in the paper, suggests that menthol may inhibit the glucuronidation of NNAL, which represents a detoxification pathway for this known carcinogen.

In a study conducted by Lorillard Tobacco Company, Heck et al. (2009) measured blood carboxyhemoglobin, urine nicotine and metabolites and urine total NNAL (24-hour urine collection) in 28 African American and 84 white smokers of at least 15 cigarettes per day. The menthol smokers appear to have been switched to a specified menthol brand for 3 weeks prior to sample collection. Statistically significant differences in biomarker levels comparing menthol and non-menthol cigarette smokers were not observed.

Ho et al. (2009) studied 755 African American light smokers (ten or fewer cigarettes per day) who were enrolled in a smoking cessation trial. This group included 569 menthol and 131 non-menthol cigarette smokers. Menthol smokers smoked fewer cigarettes per day compared to non-menthol smokers (7.07 vs 7.53, $p = 0.05$). However levels of expired CO and plasma cotinine were quite similar for the groups. This suggests that the intake of CO and nicotine may be higher per cigarette for menthol compared to non-menthol cigarettes, although that specific analysis was not presented by the authors.

In the Total Exposure Study supported by Altria Client Services, Wang et al. (2010) reported data from a large multi-center study involving 1,044 menthol cigarette smokers (448 African American and 596 white) and 2,299 non-menthol smokers (161 African American and 2,031 white). All had smoked at least one cigarette per day for a year, with a mean of 15.0 for menthol cigarette smokers and 16.8 for non-menthol smokers. Blood was collected for serum cotinine and blood carboxyhemoglobin and a 24-hour urine for nicotine equivalents was also obtained. In unadjusted analyses, urine nicotine equivalents per 24 hours and carboxyhemoglobin were significantly lower in menthol smokers. As seen in most other studies, African Americans smoked on average fewer cigarettes per day than whites, and the level of nicotine equivalents per cigarette smoked was on average higher in menthol cigarette smokers. Analysis of covariance that adjusted for race found no statistically significant difference. Smoking menthol cigarettes was not associated with serum cotinine level or carboxyhemoglobin level.

Additional unpublished data from the Wang et al. study were provided to the TPSAC by (Altria Client Services 2010). Analyses were presented on particulate phase markers, urine total NNAL and 1-hydroxypyrene, and 4-aminophenol adducts; and gaseous phase markers (metabolites of acrolein and 1,3 butadiene). No statistically significant differences in biomarker levels were found, comparing the two groups of smokers.

Benowitz et al. (2011) examined the menthol cigarette biomarker question from a different perspective. The question was asked: Does smoking menthol cigarettes increase exposure to toxins in tobacco smoke in a dose-related way? As described earlier, different brands of menthol cigarettes contain different amounts of menthol. Benowitz et al. analyzed the relationship between urine menthol concentration (a quantitative indicator of menthol exposure) and various exposure biomarkers. In a group of 60 menthol cigarette smokers (70 percent African American) there were strong positive correlations between urine menthol concentration and plasma nicotine, plasma cotinine, urine nicotine equivalents, urine total NNAL and urine total PAH metabolites. However, in a multiple regression model, when both menthol and a measure of nicotine intake (nicotine equivalents or plasma cotinine) were included, only the nicotine intake effect remained statistically significant. Thus, while urine menthol is highly correlated with biomarkers of exposure, it is not an independent predictor of carcinogen

exposure. This study also reported average levels of various biomarkers in menthol vs. regular smokers (not controlled for race) and found no differences in plasma cotinine or urine NNAL. Urine nicotine equivalents and urine PAHs were lower in menthol cigarette smokers, and although this difference was statistically significant, it may be partly due to a longer interval from last cigarette to time of urine collection for the menthol smokers.

Finally, Benowitz et al. (2004) conducted a crossover study involving 14 subjects, half regular menthol and half non-menthol cigarette smokers. All subjects smoked a non-menthol cigarette for the first week, then they were randomized to smoke a menthol or non-menthol for the second week, after which they were switched to other type of cigarette for the third week. From days 3 to 6 subjects were confined to a research ward, where they smoked 20 cigarettes per day and had frequent blood and urine sampling. Findings with respect to rates and pathways of nicotine metabolism are discussed in chapter 3. While nicotine metabolism was on average slower in menthol cigarette smokers, based on similar levels of plasma nicotine and blood carboxyhemoglobin levels through the day while smoking menthol compared to non-menthol cigarettes, there was no significant effect of menthol on nicotine or CO exposure.

In summary, some cross-sectional studies of biomarkers, particularly smaller studies, have found higher blood nicotine or cotinine levels per cigarette smoked in menthol cigarette smokers, consistent with greater inhalation. This increment persisted after controlling for race in some of the studies. Larger studies have generally not found independent effects of menthol cigarette smoking on exposure biomarkers. However, the findings of the study by Muscat et al. suggest that menthol may impair detoxification of NNAL, which is a pulmonary carcinogen. As mentioned previously, there has been no analysis of menthol effects on biomarkers of exposure at very low levels of cigarette consumption. At such levels of consumption, menthol could have its greatest effects in facilitating greater inhalation and hence exposure to tobacco smoke toxins.

Chapter 7 Table 2. Biomarkers of Exposure						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
1. Ahijevych K, Gillespie J, Demirci M, Jagadeesh J. Menthol and nonmenthol cigarettes and smoke exposure in African American and white women. Pharmacol Biochem Behav. 1996 Feb;53(2):355-60.	Laboratory Two-factorial design	N = 37 women stratified by race and menthol or nonmenthol cigarettes 18AA/8menthol 19 white/10menthol	A blood sample for nicotine and baseline cotinine analysis was obtained before and after smoking a cigarette.	Plasma cotinine	Plasma cotinine was Plasma cotinine was nonsignificantly higher in non-menthol smokers compared to menthol smokers (254 ng/ml and 204 ng/ml, respectively). Cotinine per cigarette ratios were non-significantly higher in non-menthol smokers as well (18.1 vs. 15.3 ng/ml cotinine/cigarette).	Strengths include groups balanced by race and menthol. Weaknesses include small N, heavy smokers, women only.
2. Ahijevych K, Parsley LA. Smoke constituent exposure and stage of change in African American and white women cigarette smokers**.** Addictive Behaviors 1999, 24(1):115–120.	Laboratory Two factorial design	N = 95 women stratified by ethnicity and menthol/non-menthol preference N = 48 African American/ 27M N = 47 white / 22M	A blood sample for nicotine and cotinine analysis was obtained 1 min before smoking.	Plasma nicotine and cotinine	. Menthol smokers)had significantly, higher cotinine levels compared to non-menthol smokers	Strengths – race and menthol balanced. Weaknesses include small N, women only
3. Altria Total Exposure Study (Altria 7/15/10; chapter 4)	Cross-sectional multi-center study	Total Exposure Study (TES): 3341 smokers of one or more cpd, recruited from 39 investigative sites from 31 states, selected by 4 categories of machine yields. 1044 menthol /	Blood and 24-hour urine samples. Smokers were asked to return all cigarette butts smoked over the 24-hour period.	COHb Urine 3-HPMA MHBMA and DHBMA 4-aminobiphenyl adducts Nicotine Cotinine Trans-3'-hydroxycotinine Total NNAL	No statistically significant differences in biomarkers of exposure were observed between menthol and non-menthol smokers, stratified by race. No statistically significant difference in the nicotine metabolite ratio between menthol and non-menthol smokers.	Strengths include the large study size and the multi-center recruitment of smokers; weakness if race by menthol imbalance.

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Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
		448 AA 2297 non-menthol / 166 AA		Total 1-hydroxypyrene		
4. Benowitz N, Dains K, Dempsey D, et al. Urine menthol as a biomarker of mentholated cigarette smoking. Cancer Epidemiology Biomarkers and Prevention. 2010, 19: 3013-3019.	Cross-sectional study	N = 127 cigarette smokers 60 menthol / 42 AA 67 non-menthol / 19 AA	Concentrations of menthol glucuronide, nicotine equivalents, NE), NNAL and polycyclic aromatic hydrocarbon (PAH) metabolites were measured in the urine.	Urine menthol, nicotine equivalents, NNAL, PAH metabolites; plasma cotinine	Urine menthol was measurable in 82% of menthol and 54% in regular cigarette smokers. Among menthol smokers, urine menthol was highly correlated with NE, NNAL, and PAHs. In a multiple regression model NE but not menthol was significantly associated with NNAL and PAHs. Plasma cotinine similar in menthol and non-menthol smokers.	Strengths include quantification of menthol exposure; Weaknesses include race by menthol imbalance.
5. Clark PI, Gautam S, Gerson LW. Effect of menthol cigarettes on biochemical markers of smoke exposure among African American and white smokers. Chest. 1996 Nov; 110(5):1194-8.	Laboratory cross-sectional	N = 65 African American and N = 96 white smokers 65 AA / 54 menthol 96 W / 22 menthol	Serum samples for cotinine analyses	Serum Cotinine	After adjusting for race, cigarettes per day, and mean amount of each cigarette smoked, menthol was associated with higher cotinine levels (p=0.03) and expired carbon monoxide concentrations (p=0.02).	Weaknesses include race and menthol imbalance.
6. Heck JD. Smokers of menthol and non-menthol cigarettes exhibit similar levels of biomarkers of smoke exposure. Cancer Epidemiol Biomarkers Prev. 2009 Feb;	Parallel arm study	N = 112 male and female heavy smokers 28 AA / 23 menthol 84 white / 31 menthol	The study subjects were provided with specified brands of cigarettes according to their menthol or non-menthol preference for 3 weeks. On the third	Blood carboxyhemoglobin Urine nicotine equivalents; urine NNAL	There were no significant differences in carboxyhemoglobin, urine nicotine equivalents or total urinary NNAL comparing the menthol and non-menthol cigarette smokers	Weaknesses include smoking brands other than usual brand; race by menthol imbalance; subjects smoked at least 15 cigarettes per day

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Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
18(2):622-9. Epub 2009 Feb. 3. Erratum in Cancer Epidemiol Biomarkers Prev. 2009 Jul;18(7):2155.			week two 24-hour urine samples spaced one week apart, were collected.			
7. Ho MK, Mwenifumbo JC, Al Koudsi N, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. *Clinical Pharmacology and Therapeutics* 2009 Jun, 85(6):635-43.	Smoking cessation clinical trial	N = 755 African American smokers of 10 or fewer cigarettes per day; 569 smoked menthol cigarettes	Blood and expired CO samples obtained prior to randomization	Plasma cotinine; expired CO	Menthol cigarette smokers tended to smoke fewer cigarettes per day (7.07 vs 7.53, p = 0.05). Expired CO and plasma cotinine were not significantly different in menthol vs non-menthol smokers (13.49 vs 14.74 ppm; 243 vs 247 ng/ml, respectively). Suggests that CO and/or nicotine intake may be higher per cigarette for menthol smokers.	Strengths include large number of African American smokers with considerable numbers of menthol and non-menthol smokers; includes light smokers
8. Muscat JE, Chen G, Knipe A, Stellman SD, Lazarus P, Richie JP Jr. Effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL glucuronidation. Cancer Epidemiol Biomarkers Prev. 2009 Jan; 18(1):35-41.	Cross-sectional	N = 525 male and female smokers of at least 5 cpd. 237 AA / 204 menthol 288 white / 80 menthol	Plasma and urine collection.	Urinary and plasma cotinine; Plasma thiocyanate; Urinary NNAL and NNAL-Gluc	In regression models that adjusted for daily cigarette intake, no significant differences were observed in the concentration of these biomarkers by menthol status in both races. The ratio of NNAL-Gluc to NNAL, was significantly lower in menthol versus non-menthol smokers. The NNAL Gluc/NNAL ratio was 34% lower in whites (P < 0.01) and 22%	Strengths include relatively large sample size; Weaknesses include race by menthol imbalance;

Chapter 7 Table 2. Biomarkers of Exposure						
Author Name(s), Article Title and Year	Type of Study	Subject Recruitment, Description (Including Special population(s)) and Sample Size	Study Design	Outcome Variables	Results related to Menthol	Strengths / Weaknesses
					lower in African Americans	
9. Mustonen TK, Spencer SM, Hoskinson RA, Sachs DP, Garvey AJ. The influence of gender, race, and menthol content on tobacco exposure measures. Nicotine Tob Res. 2005 Aug;7(4):581-90.	Cross-sectional study	N = 307 male and female smokers participating in cessation clinic 51 AA / 33 menthol 256 white / 54 menthol	Saliva cotinine obtained prior to cessation treatment	Salivary cotinine Expired carbon monoxide	Cotinine and CPD correlations varied by gender and race among menthol cigarette smokers. Significant genderxracexmenthol interaction on salivary cotinine level as well as cotinine/CPD ratio.	Weaknesses included race by menthol imbalance; small N for subgroup analyses; treatment seeking smokers of at least 10 cigarettes per day
10. Signorello LB, Cai Q, Tarone RE, McLaughlin JK, Blot WJ. Racial differences in serum cotinine levels of smokers. Dis Markers. 2009;27(5):187-92.	Cohort Study;	Southern Community Cohort Study. 130 AA and 125 white smokers; no data on number of menthol smokers	Blood samples taken at time of baseline evaluation	Serum cotinine measured by radioimmunoassay	After adjustment for race and sex and cigarettes smoked per day, no significant difference in cotinine levels comparing menthol vs. non-menthol smokers	Weaknesses include race by menthol imbalance; cotinine assay is non-specific with some cross-reactivity with cotinine metabolite
11. Wagenknecht LE, Cutter GR, Haley NJ, Sidney S, Manolio TA, Hughes GH, Jacobs DR. Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults Study. Am J Public Health. 1990 Sept;80(9):1053-6.	Prospec-tive cohort study	N = 142418-30 year old smokers of at least five cigarettes per week, African American and white, men and women participating in the Coronary Artery Risk Development in (Young) Adults Study	Blood same at initial examination.	Serum cotinine	. Serum cotinine level was significantly higher in African American than White smokers. The race difference persisted for African Americans who smoked menthol or non-menthol cigarettes (no details of this analysis were presented)	Strengths include the large study size and the multi-center recruitment of smokers; weaknesses include race by menthol imbalance

Author Name(s), Article Title and Year	Type of Study					
12. Wang J, Roethig HJ, Appleton S, Werley M, Muhammad-Kah R, Mendes P. The effect of menthol containing cigarettes on adult smokers' exposure to nicotine and carbon monoxide. Regulatory Toxicology and Pharmacology. 2010; 57: 24-30.	Cross sectional multi-center study					
13. Williams JM, Gandhi KK, Steinberg ML, Foulds J, Ziedonis DM, Benowitz, NL. Higher nicotine and carbon monoxide levels in menthol cigarette smokers with and without schizophrenia. *Nicotine and Tobacco Research* 2007, 9(8):873–881.	Laboratory study					

TOXICOLOGY STUDIES

Additional understanding of the differential risks posed by menthol versus non-menthol cigarettes comes from toxicological studies. The relevant studies include in vitro and in vivo approaches using menthol or smoke from cigarettes. As for toxicologic studies in general, there are questions about the relevance of animal and cell toxicology studies with respect to the potential toxic effects of menthol in cigarette smokers.

Various studies have addressed the toxicity of menthol using in vitro cellular assays that assess whether menthol damages or kills cells. One general issue in interpreting such studies is the relevance of the concentrations used and the endpoints investigated to toxicity in smokers. Bernson and Pettersson (1983) investigated the toxicity of menthol in four different bioassays. They summarize the findings as suggesting that menthol may lead to "...a deterioration of biological membranes." Other studies have shown that menthol affects cell membrane properties. Azzi et al. (2006) used a system that measures diffusion of carcinogens across porcine esophageal tissue to assess the effect of menthol on permeation and reservoir formation in the tissue for NNK and B[a]P. Menthol slowed the diffusion of these two carcinogens but increased the size of the tissue reservoir for NNK. In another cell system, menthol decreased the transepithelial electrical resistance, but the decrease was not different from that observed with non-menthol cigarettes (Alakayak and Knall 2008).

Several studies have addressed interactions of menthol with membrane receptors. Sidell et al. (1990) used a human neuroblastoma cell line and identified a calcium channel that was blocked by menthol. More recent studies have focused on the TRPM8 Ca^{2+}-permeable channel. Results from various cellular systems show that activation of the TRPM8 channel by menthol induces cell death (Yamamura et al. 2008; li et al. 2009), although one study using prostate cancer cells found that TRPM8 activation was not the mechanism of menthol-induced cell death in that system (Kim et al. 2009).

(b) (4)

(b) (4)

Another inhalation study was reported in the peer-reviewed literature in 1997 (Gaworski et al. 1997). In this study, Fischer 344 rats were exposed to mainstream smoke from a reference cigarette and a similar cigarette containing 5000 ppm synthetic *l*-menthol. The only difference noted between the two exposure groups was a dose-response trend with level of particulate matter for nasal discharge in the reference cigarette group but not in the menthol cigarette group.

R.J. Reynolds Tobacco Co. conducted a 90-day inhalation study comparing menthol vs no menthol in heated tobacco vs. conventional cigarettes (ref 26 cited in Salgado and Glantz 2011). Menthol inhalation from heated tobacco produced more severe histopathological changes in the lungs compared to conventional cigarettes.

Several studies have shown that high levels of menthol increase the amount of tar and fine particles in cigarette smoke (Carmines 2002; Baker 2004; Rustemeier 2001, reviewed in Lee and Glantz 2011). The mechanism of increased particle formation was speculated to increase the transfer of the additive materials to the particle phase of the smoke relative to most other tobacco constituents (Rustemeier 2001, as cited in Lee and Glantz 2011). Increased particulate matter in smoke is of concern because particulates are associated with greater morbidity and mortality from cardiovascular disease and are suspected to increase the risk of sudden cardiac death (Brook 2010; Pope 2009; IOM 2010; also see Lee and Glantz 2011). The smoke generated from cigarettes to which menthol was added also delivered higher levels of formaldehyde and lead, both tobacco smoke toxicants, compared to smoke from the control cigarettes (Rustemeier 2001, as cited in Lee and Glantz 2011).

Several short-term human studies also supply relevant information. A group of investigators in Turkey reported findings of a series of studies involving measurements of cardiovascular parameters after smoking menthol cigarettes versus non-menthol cigarettes (Ciftci et al. 2008a, Ciftci et al. 2008b; Ciftci et al. 2009). They describe differing patterns of short-term response using echocardiography and measures of vascular response. The participants were healthy young volunteers. These findings have uncertain implications with regard to the comparative cardiovascular disease risks of smokers of menthol cigarettes versus non-menthol cigarettes. Pritchard et al. (1999) investigated the effects of menthol in cigarettes by having volunteers smoke "denicotinized" cigarettes, with and without menthol. Using electroencephalogram and heart rate as outcome measures, they did not identify differences in response to the menthol-containing and non-menthol-containing cigarettes.

The Altria-supported Total Exposure Study mentioned above also examined biomarkers of potential harm, including markers of oxidative stress (i-epi-prostaglandin-F2 alpha, 8-isoprostaglandin F2 alpha-V1), inflammation (white blood cell count, fibrinogen, C-reactive protein, monocyte chemotactic protein and interleukin-6), endothelial function (von Willebrand factor, microalbumin, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1), coagulation (platelets, fibrinogen, von Willebrand factor, 11-dehydrothroboxane-B2), lipids (triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, oxidized LDL, lipoprotein-associated phospholipase A2) and metabolism (glucose, adiponectin, leptin) (Altria Client Services 2010). No significant effects of menthol smoking on these biomarkers were observed.

EPIDEMIOLOGICAL STUDIES

The comparative risks of menthol cigarette smokers versus non-menthol cigarette smokers have been assessed for several cancer sites, and selected cardiovascular and respiratory outcomes. The evidence comes primarily from case-control studies but also from three cohort studies. A variety of indicators were used for classifying the extent of exposure to menthol cigarettes. None of the studies were designed to specifically address risks of menthol cigarettes and consequently the investigators constructed indices that used the available information with acknowledgement of the potential for misclassification. For example, the cohort study of Northern California Kaiser Permanente participants used the type of cigarette smoked on enrollment to classify menthol cigarette status (Sidney et al. 1995). In the four-city case-control study of lung cancer, Kabat and Hebert (1991) determined mentholation for each brand smoked.

For cancer, the evidence is most abundant for lung cancer (Table 3). Findings are available from three case-control studies and three cohort studies, the Northern California Kaiser Permanente Study, the Lung Health Study, and the Southern Community Cohort Study. The analyses took account of other smoking-related determinants of lung cancer risk, e.g., amount smoked. Most of the studies found no significant differences in risk for lung cancer in smokers of menthol compared with non-menthol cigarettes. In fact, most of the point estimates were around unity, indicating no difference in risk, and measures of the extent of menthol smoking were not associated with lung cancer risk. The most recent study, the Southern Community Cohort Study, found a statistically significantly reduced risk of lung cancer in smokers of menthol cigarettes vs. the comparison of non-menthol cigarette smokers (Blot et al., in press). Only one study, the Kaiser Permanente Study, found a statistically significantly increased risk for menthol cigarette smokers. In males, the relative risk for menthol smokers was 1.45 (95 percent confidence interval 1.03–2.02). In females, the relative risk was 0.75 (95 percent confidence interval 0.52–1.11).

More limited findings are available for other cancers, including esophageal and oral cancers and all smoking-related cancers other than lung cancer. For each of these outcomes, findings are available from only a single study (Table 3). As for lung cancer, the evidence does not show a difference in risk for menthol smokers compared with non-menthol cigarette smokers.

For cardiovascular disease, two cohort studies provide findings: the Coronary Artery Risk Development in Young Adults (CARDIA) Study (Pletcher et al. 2006) and the Lung Health Study (Murray et al. 2007). In the CARDIA Study, a long-term cohort study, coronary calcification was measured in 2000, 15 years after participants were enrolled (Pletcher et al. 2006). Using the periodically collected smoking information, the numbers of pack-years of smoking menthol and non-menthol cigarettes were estimated. Risk for the prevalence of calcification increased similarly with pack-years of menthol and non-menthol cigarettes. In the Lung Health Study, participants were classified as menthol smokers based on the type of cigarette smoked at enrollment (Murray et al. 2007). Risks of death from coronary heart disease death or cardiovascular disease were not increased for menthol cigarette smokers; similarly, all-cause mortality was not higher.

The same two cohort studies provide information on several respiratory outcome measures. In the Lung Health Study, the frequencies of participant reports for "...having seen or talked to a physician for the following conditions: any respiratory condition, emphysema, asthma, pneumonia, head cold, chest cold, or sore throat..." were similar in menthol and non-menthol cigarette smokers (Murray et al. 2007). In the CARDIA Study, the 10-year rates of lung function decline (the forced expiratory volume in one second or the FEV_1) were similar in the two groups (Pletcher et al. 2006).

Overall, the epidemiological studies indicate comparable risks for a number of cigarette-caused diseases in smokers of menthol compared to non-menthol cigarettes. The point estimates are largely centered around unity. Several limitations of these studies need to be noted in interpreting the findings. The extent of information on smoking of menthol cigarettes was variable and complete across the full smoking history only in one of the case-control studies. Random misclassification of menthol smoking would tend to bias estimates of the comparative risk of smoking menthol cigarettes towards unity, regardless of whether there was a "true" increase or decrease in risk for menthol cigarette smokers. Additionally, many of the studies, particularly those on cancer risk, were carried out several decades previously. Consequently, given historical patterns of menthol cigarette use, there would be few participants in these studies who had smoked menthol cigarettes across their full smoking history. Finally, the studies generally have relatively small numbers of participants. However, even with the relatively modest sample sizes of some of the studies, the point estimates do not provide any consistent indication of increased risk.

Table 3. Cancer Risk for Smokers of Menthol Versus Non-Menthol Cigarettes

Author (Publication year)	Study design, study period, location	Sample size	Menthol exposure	Findings
Lung cancer				
Kabat and Hebert (1991)	Case-control study 1985-1990 Four U.S. cities	1044 cases 1324 controls	Non-menthol smokers Menthol 1-14 years Menthol ≥15 years	No significant difference in risk overall, or by histological type
Sidney et al. (1995)	Cohort study 1979-1991 Northern California Kaiser enrollees	9761 participants Current smokers 318 cases	Current cigarette brand Menthol or non-menthol	Increased risk for males, but not for females
Carpenter et al. (1999)	Case-control study 1990-1994 Los Angeles county	337 cases 478 controls	Proportion of cigarettes smoked that were menthol	No increase in risk with extent of menthol smoking
Brooks et al. (2003)	Case-control study 1981-2000 Multi-hospital, eastern U.S.	643 cases 4110 controls	Years smoked menthol cigarettes based on current brand and brand smoked the longest	No indication of increased risk for ever smoking menthol or with extent of menthol smoking
Murray et al. (2007)	Randomized trial in observational phase 1986-2001 Multi-site	5887 participants 240 deaths	Baseline cigarette type	No increase in risk for menthol smokers
Blot et al. (2011)	Nested case-control study 2002-2009 Twelve southern U.S. states	440 cases 2213 controls	Menthol or non-menthol, adjusted for pack-years smoked	Significantly lower risk of lung cancer incidence and mortality among menthol compared to non-menthol smokers, with the deficit holding among both African Americans and whites.
Oropharyngeal cancer				
Kabat and Hebert (1994)	Case-control study 1985-1990 Four U.S. cities	276 cases 1256 controls	Ever menthol use Duration of menthol use	No significant difference in risk overall, or by subsite
Esophageal cancer				
Hebert and Kabat (1989)	Case-control study 1969-1984 Nine U.S. cities	312 cases 462 controls	Menthol based on brand Ever menthol use Duration of menthol use	No clear pattern of significantly different risk
Non-lung smoking-related cancers				
Friedman et al. (1998)	Cohort study 1979-1994 Northern California Kaiser enrollees	11760 participants 281 cases	Current brand of mentholated cigarettes	No indication of increased risk

EVIDENCE SYNTHESIS

This chapter reviews diverse lines of evidence with regard to potential differential risks to health of smoking menthol versus non-menthol cigarettes. The evidence reviewed includes studies on differences in the ways that menthol cigarettes are smoked versus non-menthol cigarettes; studies on levels of biomarkers of dose of tobacco smoke components in smokers; studies on the toxicity of menthol and smoke from menthol cigarettes; and studies on the comparative risks of smoking menthol and non-menthol cigarettes in human populations. For some of these topics, the number of studies is limited for some of these major lines of evidence. For example, only six epidemiological studies address lung cancer and lesser numbers were identified for other health outcomes.

The in vitro studies show that menthol has activity in various systems. Chapter 3 addresses the pharmacologic actions of menthol which may lead to some of these effects. The very limited bioassay data does not indicate that smoke from menthol cigarettes has greater toxicity than smoke from non-menthol cigarettes. The epidemiological literature, albeit limited in scope, suggests that there is not greater risk for disease development for smokers of menthol versus non-menthol cigarettes. For lung cancer, the studies are consistent in this regard.

TPSAC concludes, based on the evidence reviewed in this chapter, that:

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers inhale more smoke than non-menthol cigarette smokers. Because of methodologic issues in studying smoking topography, the generalizability of these findings to the smoking of menthol cigarettes in daily life is questionable.

- The evidence is insufficient to conclude that it is more likely than not that menthol cigarette smokers are exposed to higher levels of nicotine and other tobacco smoke toxins, at least in regular daily smokers of more than 5 or 10 cigarettes per day. There are insufficient data to know if menthol cigarettes result in greater smoke intake and more exposure to tobacco smoke toxins among smokers of relatively few cigarettes per day.

- The evidence is insufficient to conclude that smokers of menthol cigarettes face a different risk of tobacco-caused diseases than smokers of non-menthol cigarettes. Some toxicology studies raise concern, particularly the finding that the addition of menthol is associated with greater fine particles which are suspected to contribute to cardiovascular disease. Available epidemiologic data do not demonstrate increased disease risk in people, but the data are largely limited to lung cancer. The hypothesis that menthol cigarette smoking increases the risk of cardiovascular disease is biologically plausible and needs to be investigated.

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CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

INTRODUCTION

In this chapter, TPSAC synthesizes the evidence included in Chapters 3–7 to address the charge given to it in the Act. Using the methodology described in Chapter 2, TPSAC has systematically identified and evaluated relevant studies and other evidence, including papers published in the peer-reviewed literature, documents supplied to the committee by tobacco companies, FDA white papers and secondary analysis of data sets provided to the FDA, and tobacco industry documents in the Legacy Tobacco Documents Library. Here, TPSAC provides its conclusions to the seven key questions in Chapter 1 related to individual smokers and the two key questions related to effects at the population level. These conclusions are expressed in the classification set out in Chapter 2 that is based around the anchoring point of "equipoise" in the strength of evidence for and against a relationship. Answers to these questions underlie TPSAC's qualitative judgment as to whether there is an adverse impact on public health from menthol cigarettes; the results of models are used to provide a quantitative picture of the adverse impact. Because the answers to questions 1 and 2 utilize the same evidence, these closely related questions are answered together. For the same reason, questions 3 and 4, which also are closely related, are answered together. Chapter 8 concludes with recommendations to the FDA and a discussion of contraband, as called for under section 907 (b).

EVIDENCE SYNTHESIS FOR KEY QUESTIONS

Related to Individual Smokers

1. Does availability of menthol cigarettes increase the likelihood of experimentation?

2. Does availability of menthol cigarettes increase the likelihood of becoming a regular smoker?

Regular cigarette smoking begins with experimentation, typically during adolescence, as noted in Chapter 6. To understand the role of menthol cigarettes in the continuum that ends with regular smoking, TPSAC closely examined data presented in Chapters 4 and 6 on the prevalence and patterns of menthol cigarette smoking in youths ages 12–17. TPSAC considered studies, summarized in Chapters 3 and 6, about the sensory impacts of menthol cigarette smoke and reviewed evidence from internal tobacco company documents and consumer research, presented in Chapter 5, on the influences of menthol cigarette advertising and marketing on smoking of menthol cigarettes.

TPSAC's review in these chapters led to key findings related to the above two questions. (1) There is a higher proportion of menthol cigarette smokers among youth smokers than adult smokers. (2) Younger adolescent smokers have a higher proportion of menthol cigarette smokers than older adolescent smokers. African Americans, who tend to begin smoking later, are an exception. (3) There is some evidence that new smokers—those who have been smoking for less than a year—have a greater prevalence of menthol cigarette use than established smokers. (4) The proportion of menthol cigarette use among youth smokers is trending upward while non-menthol cigarette use is trending downward or is flat. (5) Menthol's cooling and anesthetic properties reduce the harshness of cigarette smoke for new smokers. Menthol cigarettes produce sensory cues, such as a minty taste and odor, a cooling sensation and throat irritation or impact—all of which may provide strong cigarette-associated cues that reinforce smoking behavior. Thus, it is biologically plausible that menthol cigarettes lead to increased

experimentation and higher risk for continued regular smoking among youth. (6) Menthol cigarette marketing influences the anticipated sensory experience of smoking menthol cigarettes, thereby enhancing consumers' subjective sensory experience and liking. (7) Initiating with menthol cigarettes is more likely to lead to established smoking than initiating with non-menthol cigarettes, according to one key cohort study of youth initiators. (8) These findings, coming from multiple lines of investigation, are coherent in supporting a role for menthol cigarettes in increasing experimentation and progression to regular smoking.

TPSAC finds, based on its review, that:

The evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes increases experimentation and regular smoking. (Above Equipoise)

3. Does inclusion of menthol in cigarettes increase the likelihood of the smoker becoming addicted?

4. Does inclusion of menthol in cigarettes increase the degree of addiction of the smoker?

TPSAC considered these two questions separately for adults and adolescents. Due to a lack of relevant evidence, TPSAC was unable to reach a conclusion about the relationship between menthol cigarettes and nicotine addiction in adults. Evidence about the severity of addiction in adult menthol cigarette smokers compared to adult non-menthol smokers was mixed.

TPSAC found clear evidence of a relationship between menthol cigarettes and nicotine addiction in youth. This evidence, presented in Chapters 3 and 6, produced three key findings. (1) Youth who initiated with menthol cigarettes were more likely to become daily, regular, or established smokers than youth who initiated with non-menthol cigarettes. (2) Adolescent menthol cigarette smokers have a higher prevalence of nicotine dependence and more severe nicotine addiction than those who smoke non-menthol cigarettes. (3) Studies of sensory cues and self-administration of addicting drugs in animals show that sensory factors enhance and sustain self-administration of addictive drugs. These animal studies provide biological plausibility for a role of menthol in cigarettes in increasing the likelihood of addiction in youth and increasing the degree of addiction of the young smoker. TPSAC finds, based on its review, that:

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

There is insufficient evidence to conclude that menthol cigarettes increase the likelihood of addiction and the severity of addiction in adults. (Below Equipoise)

5. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes?

TPSAC examined data from national population surveys and other studies to determine the comparative success of quit attempts among smokers of menthol compared with non-menthol cigarettes. The national surveys measure quitting success using quit ratios (the ratio of former to ever smokers) or rates of quitting among menthol smokers and non-menthol smokers. In addition, TPSAC reviewed other types of research, including secondary analyses of data from cohort and treatment studies, both of which have limitations that were discussed in Chapter 6. Across the most informative national surveys, the

preponderance of evidence for non-white adults showed lower success rates for quitting among menthol smokers compared to non-menthol smokers, particularly among African Americans. The evidence for whites was mixed. Of the other studies found to be informative and of sufficient quality by TPSAC, the evidence was mixed. Considering all of the evidence, TPSAC concluded that non-white—and particularly African American—menthol smokers are less likely to quit successfully than non-menthol smokers.

TPSAC reviewed experimental and pharmacological evidence, presented in Chapter 3, that provided a plausible biological explanation for lower cessation success among menthol smokers. Several animal studies showed that once drug self-administration is established, taste and other sensory factors can function as stimuli that substantially enhance the strength and persistence of drug self-administration. Stimuli associated with drug intake can come to evoke craving that promotes resumption of drug self-administration after a period of abstinence. As discussed in Chapters 5 and 6, empirical and qualitative research—including consumer research conducted by tobacco companies— showed consumers hold beliefs about the implicit health benefits of menthol cigarettes, which could undermine quitting intentions and attempts. As discussed in Chapter 5, these beliefs about the implicit benefits of menthol cigarettes are especially apparent among African Americans.

TPSAC finds, based on evidence reviewed in Chapters 3, 5 and 6, that:

The evidence is sufficient to conclude that a relationship is more likely than not that the availability of menthol cigarettes results in lower likelihood of smoking cessation success in African Americans, compared to smoking non-menthol cigarettes. (Above Equipoise)

The evidence is sufficient to conclude that a relationship is as likely as not that the availability of menthol cigarettes results in lower likelihood of smoking cessation success in other racial/ethnic groups. (At Equipoise)

6. Do biomarker studies indicate that smokers of menthol cigarettes receive greater doses of harmful agents per cigarette smoked compared with smokers of non-menthol cigarettes?

To examine the question of whether menthol cigarette smokers are exposed to higher levels of harmful agents, TPSAC reviewed studies directed at the topography of smoking (puffing behavior and exposure to nicotine and carbon monoxide from single cigarettes) and studies comparing levels of biomarkers of tobacco smoke exposure in smokers of menthol and non-menthol cigarettes. This evidence was presented in chapter 7. Because of methodologic issues in studying smoking topography, including small numbers of subjects, imbalance between race and menthol use, smoking through cigarette holders and/or artificial patterns of smoking, the generalizability of the topography findings to the smoking of menthol cigarettes in daily life is questionable. The biomarker studies are more generalizable in that they typically include larger numbers of smokers smoking their own cigarettes in a naturalistic way, and the studies involve larger numbers of smokers than the topography studies. There is some evidence from one large study that while daily exposure is not different, the intake of nicotine per cigarette is higher for menthol compared to non-menthol smokers. There are insufficient data to know if smoking menthol cigarettes is associated with greater smoke intake and more exposure to tobacco smoke toxicants among smokers of relatively few cigarettes per day.

TPSAC finds, based on the evidence reviewed, that:

> **The evidence is insufficient to conclude that it is more likely than not that menthol smokers inhale more smoke per cigarette or that they are exposed to higher levels of nicotine and other tobacco toxins. (Below Equipoise)**

7. Do smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes?

Chapter 7 summarizes the diverse lines of evidence relevant to this question, including the findings of toxicological and epidemiological studies. The findings pertaining to biomarkers and smoking topography, leading to the conclusion for Question 6 related to individual smokers, are also relevant. That conclusion does not give support to increased risk for diseases in smokers of menthol compared to non-menthol cigarettes.

The toxicological studies considered in Chapter 6 use diverse in vivo and in vitro systems. The evidence is mixed. The in vitro studies show that menthol has activity in various systems. Chapter 3 addresses the pharmacologic actions of menthol which may lead to some of these effects. The very limited bioassay data does not indicate that smoke from menthol cigarettes has greater toxicity than smoke from non-menthol cigarettes. The epidemiological literature, albeit limited in scope, suggests that there is not greater risk for disease development for smokers of menthol versus non-menthol cigarettes. For most of the diseases caused by smoking, the evidence is extremely limited. For lung cancer, the most studied disease, there are only six epidemiological studies and lesser numbers were identified for other health outcomes.

TPSAC finds, based on the evidence reviewed in this chapter, that:

> **The evidence is insufficient to conclude that it is more likely than not that smokers of menthol cigarettes have increased risk for diseases caused by smoking compared with smokers of non-menthol cigarettes. (Below Equipoise)**

Smoking at the Population Level

1. Does the availability of menthol cigarettes increase the prevalence of smoking in the population, beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

The prevalence of adult smoking is substantially driven by the experimentation and subsequent regular smoking by youth and adolescents. As noted in Chapter 6, the proportion of menthol cigarette smoking is highest in the 12–15 year age group and decreases progressively within every older age group to age 25. The early use of menthol cigarettes by between one-half to one-third of youth smokers most likely contributes to nicotine dependence in at least the 30 percent of adult smokers who use menthol cigarettes. The evidence for Question 5 above, which indicates that menthol cigarette smokers are less likely to quit smoking than non-menthol cigarette smokers in some populations of smokers, is also relevant.

In addition, some smokers who initiate with menthol cigarettes later switch to non-menthol cigarettes. Thus, menthol initiation also contributes to the prevalence of non-menthol cigarette smoking in the general population. Because of the high prevalence of smoking menthol cigarettes in these early ages

and because of the likelihood that smoking menthol cigarettes increases their dependence on smoking and makes quitting less likely, TPSAC concludes that the availability of menthol cigarettes increases the prevalence of smoking in the general population and particularly in African Americans, beyond the anticipated prevalence if such cigarettes were not available.
TPSAC finds, based on the evidence reviewed, that:

> **The evidence is sufficient to conclude that it is more likely than not that the availability of menthol cigarettes increases the likelihood of experimentation and regular smoking beyond the anticipated prevalence if such cigarettes were not available, in the general population and particularly in African Americans. The evidence is sufficient to conclude that it is more likely than not there is a causal relationship between the availability of menthol cigarettes and regular smoking among youth. (Above Equipoise)**

2. Does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available? In subgroups within the population?

Chapter 4 provided an introduction to the history of marketing of menthol cigarettes. Chapter 5 summarized strategies for marketing of menthol cigarettes, menthol marketing messages, target groups for menthol marketing and consumer perceptions of menthol cigarettes. The findings pertaining to patterns of menthol smoking for the population overall, and for population subgroups, as reviewed in Chapter 4 and 6 are also relevant. In addition, Chapter 3 provided information on the sensory properties of menthol cigarettes which are relevant for considering consumer perception issues.

TPSAC found there to be sufficient evidence that marketing messages for menthol cigarettes have been different from those used in non-menthol cigarette marketing. Menthol cigarettes have been and continue to be marketed with a set of associated branding elements and labels that connote health benefits. Early messages featured explicit references to health benefits through medicinal assistance (such as soothing a sore throat or clearing a blocked nose) and later messages emphasized implicit health benefits, through the promotion of the particular features of menthol cigarettes that refer to their 'freshness' and sensory cooling properties. Studies show consumer perceptions of the taste/sensory experience of cigarettes are correlated with perceptions of harm, including for menthol cigarettes. Against a background of consumer research studies demonstrating that taste perception is subjective and highly amenable to suggestion from product advertising, branding and labeling, menthol cigarette marketing influences the anticipated sensory experience of menthol cigarettes, thereby enhancing consumers' subjective sensory experience and liking. There is sufficient evidence from tobacco industry document reviews and empirical studies to conclude that consumers hold beliefs about the implicit health benefits of menthol cigarettes and this is particularly the case among African Americans.

In addition to messages that implied health reassurance, menthol marketing messages emphasized the role of menthol cigarettes in peer group acceptance and promoted a more youthful brand image than messages for non-menthol cigarettes. There is substantial evidence that menthol marketing has been especially targeted to youth and African Americans, with youthful imagery, messages promoting an appealing sensory experience, and peer group acceptance. There is also evidence from tobacco industry documents that the tobacco industry designed menthol cigarettes with lower menthol levels, with an awareness that, at these lower levels, the sensory effects of menthol reduce the harshness of cigarettes for new smokers. Menthol smoking is higher in more youthful smoker population groups and among African American smokers.

The evidence is sufficient to conclude that Hispanics have been a target of marketing of menthol cigarettes. Menthol cigarette smoking is also higher among Hispanic smokers. Although menthol cigarette smokers comprise a higher proportion of Asian American and Hawaiian/Pacific Islander smokers, there is insufficient evidence to conclude that these population groups have been targeted for marketing of menthol cigarettes. Finally, although female smokers have higher menthol smoking rates than male smokers, there is insufficient evidence to conclude that they have been disproportionately more targeted by menthol than non-menthol marketing.

TPSAC finds, based on the evidence reviewed, that:

The evidence is sufficient to conclude that it is more likely than not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for the whole population, and for youth and African Americans.(Above Equipoise)

The evidence is sufficient to conclude that it is as likely as not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for Hispanics. (At Equipoise)

The evidence is insufficient to conclude that it is more likely than not that menthol cigarette marketing increases prevalence of smoking beyond anticipated prevalence if such cigarettes were not available for Asian Americans, Hawaiians/Pacific Islanders and women. (Below Equipoise)

OVERALL CONCLUSIONS

Based on the conclusions to the nine questions, TPSAC provides the following general conclusions:

- Menthol cigarettes have an adverse impact on public health in the United States.
- There are no public health benefits of menthol compared to non-menthol cigarettes.

PUBLIC HEALTH IMPACT

The Family Smoking Prevention and Tobacco Control Act charges the Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "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." The availability of menthol cigarettes in the marketplace could adversely affect public health through two consequences: (1) increasing the risk for the diseases caused by smoking cigarettes; and (2) increasing the number of people who smoke. These two consequences are captured in the population attributable risk statistic, used to calculate the disease burden attributable to a causal factor, such as cigarette smoking.

The committee finds that the evidence does not indicate increased disease risks in smokers of menthol cigarettes compared to non-menthol cigarettes. TPSAC does conclude that the availability of menthol cigarettes has led to an increase in the number of smokers and that this increase does have adverse public health impact in the United States. TPSAC found evidence that the availability of menthol cigarettes increases initiation; of particular concern was the high rate of menthol cigarette smoking among youth and the trend over the last decade of increasing menthol cigarette smoking among 12–17 year olds, even as smoking of non-menthol cigarettes declines. TPSAC also concluded that cessation is less likely to be successful among smokers of menthol cigarettes. Thus, the availability of menthol

cigarettes increases initiation and reduces cessation, thereby increasing the number of people who are smoking. This increase in the number of smokers represents an adverse impact of the availability of menthol cigarettes on public health.

To gain an understanding of the quantitative impact of menthol cigarettes on public health, TPSAC turned to the results of models of smoking in the United States, one developed for the entire population and the other for the African American population (Appendix A). Details of the models developed by Mendez are provided in Appendix A. Mendez expanded a previously developed compartmental model of smoking in the population of the United States to incorporate smoking of menthol and non-menthol cigarettes (see references in Appendix A for background). Based on the review provided in this report, TPSAC provided specifications for model parameters, including a central or "best" estimate and plausible lower and upper bounds. For parameters not covered in the TPSAC review, parameter values were based on documents available to TPSAC. Table 1 below (Table 3 in Appendix A) documents these choices.

The model compares two scenarios: a scenario based on the current pattern of smoking of menthol and non-menthol cigarette smoking and a counterfactual or comparison scenario representing smoking in the United States, but without the availability of menthol cigarettes. These two scenarios match at the outset in every way except for the availability of menthol cigarettes. Over time, the patterns of experimentation, initiation, and cessation differ as described in Table 1 and switching occurs between the two types of cigarettes in the menthol cigarette scenario. Models were implemented for the boundary conditions defined by the lower and upper bounds for the model parameters. The results provide insight into the sensitivity of findings to values of model parameters.

The model results indicate that the availability of menthol cigarettes increases the numbers of people who initiate smoking, as well as leading to premature death from smoking caused diseases. Table 1 provides the numbers of excess initiators and of premature deaths. The first row of the table provides the results based on TPSAC's best estimates of the model parameters. The findings provide an approximate indication of the magnitude of the public health impact of the availability of menthol cigarettes. For example, assuming the best estimates, by 2020 about 17,000 premature deaths will occur and about 2.3 million people will have started smoking, beyond what would have occurred absent availability of menthol cigarettes. The cumulative figures mount over time. The remaining rows of the table provide similar results for the additional scenarios. All show excess mortality and numbers of smoking initiators as associated with the availability of menthol cigarettes.

Table 1. Results – General Population

Scenario	Description	Cumulative Excess Deaths				Cumulative Excess Smoking Initiation			
		2020	2030	2040	2050	2020	2030	2040	2050
1	TPSAC Estimates	17,182	67,817	164,590	327,565	2,288,534	4,429,326	6,710,101	9,124,867
2	Low Menthol Initiation	17,181	67,812	164,555	327,396	2,288,534	4,429,326	6,710,101	9,124,867
3	High Menthol Initiation	17,182	67,822	164,625	327,733	2,288,534	4,429,326	6,710,101	9,124,867
4	Low Menthol Experimentation	15,411	61,041	147,794	292,601	2,019,295	3,908,229	5,920,677	8,051,353
5	High Menthol Experimentation	20,723	81,367	198,181	397,489	2,827,013	5,471,520	8,288,948	11,271,894
6	Low Yield from Experimenter to Smoker	2,127	10,220	21,810	30,346	0	0	0	0
7	High Yield from Experimenter to Smoker	19,838	77,980	189,784	380,008	2,692,393	5,210,972	7,894,236	10,735,137
8	Low Menthol Cessation	18,495	74,138	178,061	346,122	2,288,534	4,429,326	6,710,101	9,124,867
9	High Menthol Cessation	11,023	38,336	101,964	241,409	2,288,534	4,429,326	6,710,101	9,124,867
10	Low Menthol Mortality Risk	-239,508	-293,535	-220,657	-41,279	2,288,534	4,429,326	6,710,101	9,124,867
11	High Menthol Mortality Risk	238,551	378,451	494,892	644,022	2,288,534	4,429,326	6,710,101	9,124,867
12	Low Switch Rate Menthol to Non-menthol	17,227	68,265	166,070	330,538	2,288,534	4,429,326	6,710,101	9,124,867
13	High Switch Rate Menthol to Non-Menthol	17,138	67,397	163,252	324,972	2,288,534	4,429,326	6,710,101	9,124,867
14	Low Switch Rate Non-menthol to Menthol	17,139	67,399	163,249	324,993	2,288,534	4,429,326	6,710,101	9,124,867
15	High Switch Rate Non-menthol to Menthol	17,224	68,223	165,874	329,989	2,288,534	4,429,326	6,710,101	9,124,867

Mendez also explored the public health impact of the high proportion of menthol cigarette smoking among African American smokers. He compared two scenarios: one reflecting the current proportion of menthol use among experiments and initiators (80 percent for both) compared with a counterfactual identical to that for the general population (40 percent of experiments using menthol cigarettes and 45 percent experimenters). Table 2 below (Table 6 in Appendix A) provides the findings for the current situation and for the counterfactual, respectively. The difference between the estimates in any cell of the two tables reflects the difference in menthol cigarette use. For example, in 2020, there are an additional 2,025 (4,716–2,691) excess deaths because of the higher menthol prevalence in the scenario labeled TPSAC estimates. Similarly, there are about 150,000 additional smokers in 2020 attributable to the higher menthol prevalence.

Table 2. Results—African American Population

Description	Cumulative Excess Deaths				Cumulative Excess Smoking Initiation			
	2020	2030	2040	2050	2020	2030	2040	2050
African American Population – TPSAC Estimates	4,716	16,381	35,250	66,524	461,273	859,101	1,262,086	1,656,005
Low Menthol Prevalence Hypothetical African American Population	2,691	10,244	23,218	44,771	307,515	572,734	841,391	1,104,003

The results of all models are subject to uncertainty, reflecting incomplete knowledge about underlying relationships and the values of the parameters in the model. Mendez used previously developed and well-characterized models as the starting point for developing the menthol models. The values for parameters were based on the literature reviews carried out by TPSAC. The consequences of assuming particular values for key parameters were explored through sensitivity analyses. As the parameters used as input of the model are subject to the statistical uncertainty inherent to their individual estimation process, a Monte Carlo analysis would be required to capture the combined effect of such uncertainty or the results of the analysis. This analysis would not likely change the magnitude of the results, as the model is linear, and the simulation settings and parameters chosen were conservative.

TPSAC also considered the findings of modeling carried out by Levy et al. (2011) on the future effects of a menthol cigarette ban in the total U.S. population and among African Americans. While TPSAC is not proposing specific policy actions that should be taken by FDA, the modeling of the consequences of a ban provides further insight into the impact of menthol cigarettes on public health. The scenarios considered involved the consequences of implementing a ban in 2011, using the distribution of smoking in the U.S. population as of 2003. Table 3 (below) provides the principal findings for changes in the numbers of smokers and the avoided premature deaths. The comparison scenarios to the status quo involve changes of 10 percent, 20 percent, and 30 percent in the rates of initiation (reduced) and cessation (increased). The authors do not propose that any of these scenarios is most probable. Regardless of scenario, a ban is associated with avoidance of premature mortality for a substantial

number of deaths. The figure for a 10 percent change is similar to the estimate based on TPSAC's best estimates.

The results from Mendez and Levy et al., while based on different models and assumptions, provide comparable insights into the quantitative magnitude of the public health impact of the availability of menthol cigarettes. The burden is substantial; for example, the cumulative excess deaths estimated by Mendez for the 40-year period, 2010–2050, is about 80 percent of the number of deaths annually currently attributed to cigarette smoking in the United States (US DHHS 2004). Over that same time period, an estimated 9 million people will initiate smoking because of the availability of menthol cigarettes. The models for African Americans show that the high prevalence of menthol cigarette smoking adds to the burden of premature death experienced by this population.

While subject to uncertainty, the results of the models confirm TPSAC's qualitative judgment on the adverse impact of menthol cigarettes on public health. They do not capture the considerable excess burden of morbidity, coming from chronic diseases, infectious diseases, and diminished well-being that is attributable to smoking.

Table 3. **Smoking-attributable Deaths (SADs) and Deaths Averted if Menthol is Banned**

	2010	2020	2030	2040	2050	Total SADs	Total Deaths Averted
Total Population							
Status quo	386,732	410,809	399,028	342,472	272,424	1,811,465	
10% change	386,732	406,046	388,347	331,117	262,574	1,488,358	323,107
20% change	386,732	402,568	382,621	326,799	259,002	1,333,311	478,154
30% change	386,732	399,091	376,893	322,478	255,424	1,178,214	633,252
African Americans							
Status quo	53,836	57,056	53,382	45,022	37,475	246,771	
10% change	53,836	55,234	50,086	42,175	35,320	155,027	91,744
20% change	53,836	53,706	47,562	40,044	33,340	82,306	164,465
30% change	53,836	52,177	45,036	37,908	31,347	9,454	237,317

Table 3 presents three scenarios (10%, 20% and 30% change in initiation and cessation), projected from 2010-2050 for total population and African American population. (Levy et al. 2011)

RECOMMENDATIONS

Mentholation of cigarettes was discovered by accident in the 1920s. Even then, the sensory and medicinal properties of menthol were known and these properties, along with cigarette design and marketing, have made menthol cigarettes a substantial component of the cigarette market in the United States. In the decades since the first menthol cigarettes were made, there have been substantial advances in the understanding of the pharmacology of menthol, of how to use menthol to manipulate flavor and the sensory perception of cigarette smoke, and of the interplay between menthol and nicotine. Marketing of menthol cigarettes has been successful. Menthol cigarettes are now smoked by most African American smokers and there is a concerning rise of menthol cigarette smoking among youth. Menthol cannot be considered merely a flavoring additive to tobacco. Its pharmacological actions reduce the harshness of smoke and the irritation from nicotine, and may increase the likelihood of nicotine addiction in adolescents and young adults who experiment with smoking. Furthermore, the distinct sensory characteristics of menthol may enhance the addictiveness of menthol cigarettes, which appears to be the case among youth. TPSAC has found that the availability of menthol cigarettes has an adverse impact on public health by increasing the numbers of smokers with resulting premature death and avoidable morbidity.

Consequently, TPSAC makes the following overall recommendation to FDA:

Removal of menthol cigarettes from the marketplace would benefit public health in the United States.

The Act offers a variety of mechanisms for FDA to consider, if it concludes that it should pursue this recommendation. At this time, TPSAC has no specific suggestions for follow-up by FDA to this recommendation.

CONTRABAND

With regard to any proposed standard, the Act states under section 907(b) that: "The Secretary shall consider all other information submitted in connection with a proposed standard, including information concerning the countervailing effects of the tobacco product standard on the health of adolescent tobacco users, adult tobacco users, or non-tobacco 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."

Several presentations in public hearings and written submissions to TPSAC speculated on the potential for contraband as a consequence of a ban on menthol cigarettes. TPSAC was not constituted to carry out analyses of the potential for and impact of a black market for menthol cigarettes. Lacking knowledge of FDA's intent on receipt of this report, TPSAC concluded that FDA would need to assess the potential for contraband menthol cigarettes as required by the Act. A summary of relevant comments that TPSAC received on the subject is presented here.

The concerns expressed originated with experience gained from black market activity involving non-menthol cigarettes. The general concern about contraband following a potential ban on menthol cigarettes can be summarized as follows: a black market for menthol cigarettes could be created, criminal activity could ensue, and different methods might be used to supply such a black market. The demand for contraband menthol cigarettes might be met through evasion, illegal production and importation of menthol cigarettes, and after-market mentholation (Hering 2011).

Evasion

TPSAC recognizes that the current laws governing the sale and taxation of cigarettes can be evaded. According to Michael Hering's January 2011 presentation to TPSAC, examples of evasion that might not violate a menthol ban include the use of menthol cigars, roll your own menthol cigarettes, menthol pipe tobacco, menthol tubes, rolling papers and filters, and the emergence and use of aftermarket mentholation kits. The response of some marketers to the FDA's recent tobacco flavoring ban may offer additional insight into possible marketplace reactions to a menthol cigarette ban. The flavoring ban currently pertains only to cigarettes and not to cigars. Shortly after the FDA flavor ban was implemented, Djarum introduced clove cigars into the market. Other cigars with cherry, peach, strawberry, grape and pina colada and appletini flavors were also introduced, effectively evading the FDA ban on flavored tobacco.

Illegal production and importation of menthol cigarettes

Based on public testimony, TPSAC identified a number of likely sources of menthol cigarettes that would be illegal under a ban. The sources of imported contraband could include foreign manufacturers, domestic manufacturing for foreign markets, and unlicensed domestic manufacturers.

Aftermarket mentholation

As described above, roll your own (RYO) menthol tobacco, menthol pipe tobacco, menthol tubes or rolling paper, or menthol filter tips could potentially allow consumers to prepare their own menthol cigarettes and evade a ban. Whether these aftermarket products could provide the taste or sensory experience of the current branded products or whether the millions of menthol cigarette smokers would make the effort to mentholate their own cigarettes remains unknown.

Potential black market for menthol cigarettes

TPSAC recognizes that the potential size of a menthol black market cannot be readily estimated, due to the need to make uncertain assumptions as to the nature and functioning of such a black market. For example, how would large volumes of contraband menthol cigarettes move through illegal channels to the public on a daily basis? If the precisely engineered menthol levels in currently available menthol brands cannot be reproduced, is it likely that a substantial black market would develop, particularly since non-menthol cigarettes would be available?

TPSAC did receive industry-supported testimony from Compass Lexecon that attempted to estimate the size of a potential menthol cigarette black market. Based on marketing data provided by Lorillard Inc., Compass Lexecon undertook an analysis that modeled the effect of a menthol cigarette ban. It concluded that a ban would not eliminate menthol cigarette consumption in the U.S. because a sizable black market would quickly emerge to illegally supply menthol cigarettes. Compass Lexecon also speculated on the possible unintended consequences of increased criminal activity as well as concerns about the possibility that youth might have greater access to unregulated cigarettes associated with a black market.

The Compass Lexecon report described the dynamics of a black market, which is expected to drive menthol cigarette prices up while reducing sales volume. It estimated that a 10 percent increase in the cost of menthol cigarettes would lower unit sales to 87 percent of current volumes. A 50 percent price increase would reduce unit sales to about 56 percent of current legal menthol sales. (Compass Lexecon 2010). This same analysis predicted, based on the black market price increases noted above, that a 10

percent price increase would reduce overall smoking rates by 1 percent and a 50 percent black market price increase would result in a 3.5 percent reduction in the overall smoking rates. The authors concluded, based on the above predictions, that a reduction in smoking prevalence of less than 30 percent would be achieved by a ban on menthol cigarettes.

TPSAC noted that this economic analysis did not address the question of a menthol ban's effects on youth smoking initiation or the cumulative effect of a ban after several years. The analysis does not address whether African American smokers who prefer menthol cigarettes and are not yet addicted to nicotine would choose to continue smoking. Because the analysis did not incorporate these possibilities, the results may have underestimated the percentage and number of people who would stop smoking as well as the number of youth who would never begin smoking if menthol cigarettes were not available. Consequently, the model may have overestimated the size of any potential black market.

TPSAC, whose charge includes issues related to youth smoking, also recognizes that an analysis of the impact of a menthol ban on the overall smoking rates over time should include the effect of price increases on youth. The hypothesis that cigarette smoking by younger persons will be relatively more responsive to price than smoking among older persons is confirmed by studies of cigarette demand based on cross-sectional surveys of youths and young adults. Recent estimates indicate that youths are up to three times more sensitive to price than adults, with a 10-percent price increase estimated to reduce youth smoking prevalence by 5 percent or more and also to reduce cigarette consumption among continuing young smokers (Chaloupka and Grossman 1996; Evans and Huang 1998; Lewit et al. 1997; NCI 2010, p.193). The greater price sensitivity of youth and young adults, compared to adults 25 years and older, indicates that price increases produced by a black market would reduce initiation and encourage cessation among the youth and young adults.

TPSAC acknowledges that the potential for contraband menthol cigarettes exists, should FDA choose to implement a ban or take some other policy action that restricts availability of menthol cigarettes. Consistent with the requirements of the Act, TPSAC recommends that FDA consult with appropriate experts and carry out relevant analyses depending on the actions taken in response to this report from TPSAC.

Other Considerations

The removal of menthol cigarettes from the market could result in a substantial reduction in cigarette smoking, according to data from the May 2010 TUS-CPS survey. The survey asked menthol smokers (N=2877)*, "If menthol cigarettes were no longer sold, which of the following would you most likely do?"* According to analysis of their responses presented to TPSAC by Anne M. Hartman of the National Cancer Institute (January 2011), 39 percent of menthol smokers would quit, followed by those would switch to non-menthol cigarettes (36.2 percent) or switch to another tobacco product (7.7 percent). Based on their survey responses, she estimated the percentage of menthol cigarette smokers who would potentially quit smoking by race/ethnicity, age and gender: African Americans,(47 percent), non-Hispanic whites (34 percent), ages 18–44 years (41 percent), age 45 years and over (37 percent), female menthol smokers (42 percent), and male menthol smokers (36 percent).

In her presentation, Hartman noted that behavioral intention is associated with actual behavior. She concluded that the results suggest a potential substantial reduction in tobacco use if menthol cigarettes were no longer sold. Should FDA take any action that would remove menthol cigarettes from the marketplace, planning should address the potential demand for cessation services.

TOPICS FOR RESEARCH

In the course of reviewing the evidence related to its charge, TPSAC noted gaps in understanding of menthol cigarettes and public health that should be addressed with further research. Here, TPSAC makes brief recommendations with acknowledgement that the priority given to particular recommendations may depend on any policy action taken by the FDA.

- **Subliminal menthol**: TPSAC was given the charge of addressing "menthol in cigarettes," but, as set out in Chapter 1, focused this report on menthol cigarettes. Several studies suggested that menthol may be present in some cigarettes in which it is not a flavor characterizing additive. TPSAC suggests that further research should be carried out to characterize the menthol content of cigarettes in general and to assess whether menthol has pharmacologic effects at these concentrations that might affect initiation, dependence or cessation.

- **Susceptible and vulnerable populations**: TPSAC found little data on use of menthol cigarettes by the severely mentally ill, a population with a high prevalence of cigarette smoking. This gap should be addressed, as should data gaps for other potentially vulnerable populations. There is now substantial research on genetic determinants of addiction to nicotine; studies on this topic should incorporate consideration of menthol cigarette smoking into their protocols. In addition, more research is required to assess whether menthol interacts with genetically determined bitterness taste sensitivity (sensitivity to phenylthiocarbamate (PTC) and 6-n-propylthiouracil (PROP)) to facilitate smoking.

- **Strengthen the evidence foundation on the public health impact of menthol cigarettes:**
    - Cohort studies of adolescents and young adults should be carried out that follow participants from experimentation to initiation to dependence. These studies would provide an improved understanding of the risk for moving across this sequence that is associated with menthol cigarette availability.
    - The consequences of menthol cigarette smoking for likelihood of successful cessation need further investigation in the general population. Additionally, the implications of menthol cigarettes for sustained quitting should be addressed in clinical trials of cessation therapy and other databases.
    - Develop surveillance protocols to track industry marketing practices including price promotions and their impact on smoking patterns with attention to menthol cigarettes. The protocols should be sufficiently fine-grained with regard to populations and places and focus on critical periods of policy implementation.

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Appendix A

Results from a Population Dynamics Model of the Consequences of Menthol Cigarettes for Smoking Prevalence and Disease Risks[1]

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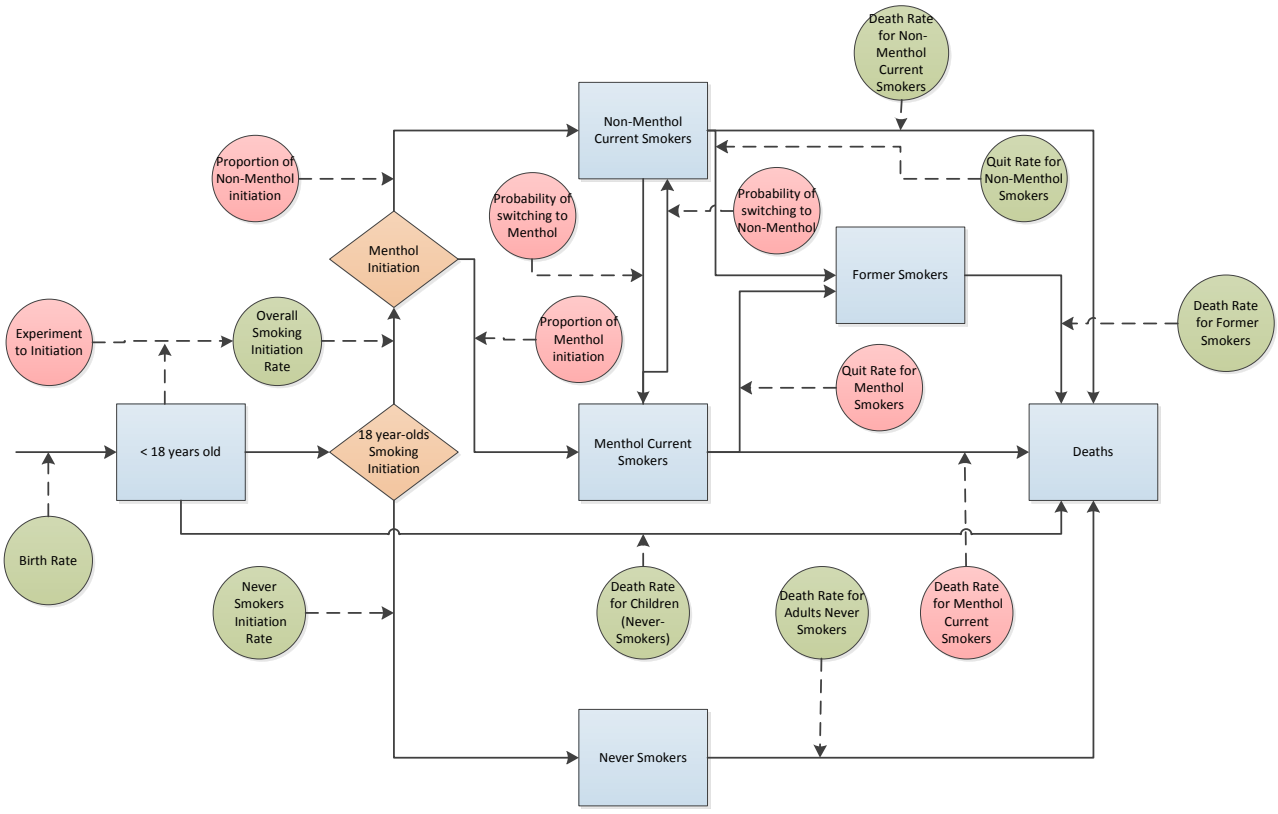
University of Michigan
March 2011

[1] The work reported was done under contract with the Center for Tobacco Products at FDA. The content and conclusions of this report are solely the author's

Results from a Population Dynamics Model of the Consequences of Menthol Cigarettes for Smoking Prevalence and Disease Risks

This document describes the constructs of, and results from, the model commissioned by the Tobacco Products Scientific Advisory Committee (TPSAC) to estimate the consequences of menthol cigarette smoking on the U.S. population. The model is an extension and modification of a population dynamics model previously developed to track smoking prevalence and smoking related risks, which has been extensively discussed in the literature.[1-7] The following figure shows the general organization of the model, as modified to address menthol cigarettes:

Menthol Model Block Simulation Diagram



The boxes (compartments) represent the stock of individuals in different categories at a given time; the arrows represent the flow between compartments; and the circles represent parameters that modify the flow. Red circles refer to parameters related to menthol smoking while green circles refer to the other parameters. Diamonds represent the event of smoking initiation, concentrated at a single age.

Following is a mathematical description of the constructs of the model:

Definition of dynamic (time-dependent) variables:

$P(a,t)$ = US population of age a in year t

$N(a,t)$ = Population of never – smokers of age a in year t

$F(a,t,q)$ = Population of former – smokers of age a, in year t, that quit q years ago

$C(a,t)$ = Population of current – smokers of age a in year t

$C_m(a,t)$ = Population of current menthol – smokers of age a in year t

$C_n(a,t)$ = Population of current non – menthol – smokers of age a in year t

$\pi_N(a,t)$ = Prevalence of never – smokers of age a in year t

$\pi'_N(t)$ = Adult prevalence of never – smokers in year t

$\pi_F(a,t)$ = Prevalence of former – smokers of age a in year t

$\pi'_F(t)$ = Adult prevalence of former – smokers in year t

$\pi_C(a,t)$ = Prevalence of current – smokers of age a in year t

$\pi'_C(t)$ = Adult prevalence of curent – smokers in year t

$\pi_{C_m}(a,t)$ = Prevalence of current menthol – smokers of age a in year t

$\pi'_{C_m}(t)$ = Adult prevalence of current menthol – smokers in year t

$\pi_{C_n}(a,t)$ = Prevalence of current non – menthol – smokers of age a in year t

$\pi'_{C_n}(t)$ = Adult prevalence of current non menthol smokers in year t

$D(t)$ = Total deaths in year t

Definition of Non-dynamic variables and parameters:

$\mu(a)$ = Overall death rate for individuals of age a

$\mu_N(a)$ = Death rate among non – smokers of age a

$\mu_F(a,q)$ = Death rate among former – smokers of age a who quit q years ago

$\mu_C(a)$ = Death rate among current – smokers of age a

$\mu_{C_m}(a)$ = Death rate among current menthol – smokers of age a

$\mu_{C_n}(a)$ = Death rate among current non – menthol – smokers of age a

$\rho(a)$ = Overall smoking quit rate for individuals of age a

$\rho_{C_m}(a)$ = Smoking quit rate for menthol smokers of age a

$\rho_{C_n}(a)$ = Smoking quit rate for non – menthol smokers of age a

S_{mnn} = Switching rate from menthol to non – menthol among current menthol smokers

S_{nnm} = Switching rate from non – menthol to menthol among current menthol smokers

I = Smoking initiation age

γ = Overall smoking initiation rate

γ_{C_m} = Smoking initiation rate for menthol smokers

γ_{C_n} = Smoking initiation rate for non – menthol smokers

$RR(a,q)$ = Relative risk of death for a former smoker of age a who quit q years ago – $q = 0$ implie

K_1 = Mortality risk ratio $\left(\frac{Menthol}{Non - Menthol}\right)$

K_2 = Quit rates ratio $\left(\frac{Menthol}{Non - Menthol}\right)$

K_3 = Proportion of Menthol among Initiators

K_4 = Proportion of Menthol among Experimenters

K_E = *Ratio of Yields from Experimenter to Established Smoker* $\left(\frac{Menthol}{Non-Menthol}\right)$

Dynamic (time-dependent) relationships:

$$N(0,t) = P(0,t)$$

$$N(a,t) = N(a-1,t-1) \times (1 - \mu_N(a)) \quad for\ a \neq 1$$

$$N(a,t) = N(a-1,t-1) \times (1 - \mu_N(a)) \times (1 - \gamma_{C_m} - \gamma_{C_n}) \quad for\ a = 1$$

$$F(a,t,q) = 0 \quad for\ a - q \leq 1$$

$$F(a,t,1) = C_m(a-1,t-1) \times (1 - \mu_{C_m}(a-1)) \times \rho_{C_m}(a-1) + C_n(a-1,t-1) \times (1 - \mu_{C_n}(a-1)) \times \rho_{C_n}(a-1)$$

$$F(a,t,q) = F(a-1,t-1,q-1) \times (1 - \mu_{C_F}(a-1,q-1)) \quad for\ a - q > 1\ and\ q > 1$$

$$C_m(a,t) = 0\ for\ a < 1$$

$$C_m(a,t) = \gamma_{C_m} \times N(a-1,t-1) \times (1 - \mu_N(a-1)) \quad for\ a = 1$$

$$C_m(a,t) = C_m(a-1,t-1) \times (1 - \mu_{C_m}(a-1)) \times (1 - \rho_{C_m}(a-1)) \times (1 - S_{msn}(a-1)) + C_n(a-1,t-1) \times (1$$

$$C_n(a,t) = 0\ for\ a < 1$$

$$C_n(a,t) = \gamma_{C_n} \times N(a-1,t-1) \times (1 - \mu_N(a-1)) \quad for\ a = 1$$

$$C_n(a,t) = C_n(a-1,t-1) \times (1 - \mu_{C_n}(a-1)) \times (1 - \rho_{C_n}(a-1)) \times (1 - S_{nsm}(a-1)) + C_m(a-1,t-1) \times (1 -$$

$$P(a,t) = N(a,t) + \sum_{q=1}^{q=80+} F(a,t,q) + C_m(a,t) + C_n(a,t)$$

$$\pi_N(a,t) = \frac{N(a,t)}{P(a,t)}$$

$$\pi'_N(t) = \frac{\sum_{a=18}^{a=100} N(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_F(a,t) = \frac{\sum_{q=1}^{q=80+} F(a,t,q)}{P(a,t)}$$

$$\pi'_F(t) = \frac{\sum_{a=18}^{a=100} \sum_{q=1}^{q=80+} F(a,t,q)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_{C_m}(a,t) = \frac{C_m(a,t)}{P(a,t)}$$

$$\pi'_{C_m}(t) = \frac{\sum_{a=18}^{a=100} C_m(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$\pi_{C_n}(a,t) = \frac{C_n(a,t)}{P(a,t)}$$

$$\pi'_{C_n}(t) = \frac{\sum_{a=18}^{a=100} C_n(a,t)}{\sum_{a=18}^{a=100} P(a,t)}$$

$$D(t) = \sum_{a=0}^{a=100} N(a,t) \times \mu_N(a) + \sum_{a=0}^{a=100} \sum_{q=1}^{q=80+} F(a,t,q) \times \mu_F(a,q) + \sum_{a=0}^{a=100} C_m(a,t) \times \mu_{C_m}(a) + \sum_{a=0}^{a=100} C_n(a,t) \times \mu_{C_n}$$

Non-dynamic relationships:

- Expressions related to mortality risks and derivation of death rates for current, former and never smokers given overall death rates $\mu(a)$ in 2010.

$$K_1 = \frac{\mu_{C_m}(a)}{\mu_{C_n}(a)}$$

$$\mu_F(a,q) = \mu_N(a) \times RR(a,q)$$

$$\mu_{C_m}(a) = K_1 \times \mu_N(a) \times RR(a,0)$$

$$\mu_{C_n}(a) = \mu_N(a) \times RR(a,0)$$

$$\mu(a) = \mu_N(a) \times \pi_N(a,2010) + \left(\sum_{q=1}^{q=80+} \mu_N(a) \times RR(a,q) \times \pi_F(a,2010,q) \right) + K_1 \times \mu_N(a) \times RR(a,0) \times \pi_{C_m}(a,201$$

$$\mu_N(a) = \frac{\mu(a)}{\pi_N(a,2010) + \sum_{q=1}^{q=80+} (RR(a,q) \times \pi_F(a,2010,q)) + K_1 \times RR(a,0) \times \pi_{C_m}(a,2010) + RR(a,0) \times \pi_{C_n}(a,2010)}$$

Expressions related to quit rates and derivation of quit rates for menthol and non-menthol cigarette smokers given overall quit rates $\rho(a)$ in 2010.

$$K_g = \frac{\rho_{C_m}(a)}{\rho_{C_n}(a)}$$

$$\rho_{C_m}(a) = K_g \times \rho_{C_n}(a)$$

$$\rho(a) = K_g \times \rho_{C_n}(a) \times \pi_{C_m}(a, 2010) + \rho_{C_n}(a) \times \pi_{C_n}(a, 2010) \rightarrow$$

$$\rho_{C_n} = \frac{\rho(a)}{K_g \times \pi_{C_m}(a, 2010) + \pi_{C_n}(a, 2010)}$$

- Expressions related to the initiation rate and derivation of initiation rate under the counterfactual scenario (in which menthol cigarettes do not exist) given overall smoking initiation rate γ in 2010.

$$\gamma = \gamma_{C_m} + \gamma_{C_n}$$

$$\gamma_{C_m} = K_g \times \gamma$$

$$\gamma_{C_n} = (1 - K_g \times \gamma)$$

Let W be the size of a cohort of potential experimenters, E the proportion of experimenters in that cohort, Y_m the proportion of menthol cigarette experimenters that become established smokers, and Y_n the proportion of non − menthol experimenters that become established smokers; then, $W \times E \times K_s$ is the number of menthol cigarette *experimenters and $W \times E \times (1 - K_s)$ is the number of non − menthol experimenters.*

It follows that:

$$W \times E \times K_s \times Y_m + W \times E \times (1 - K_s) \times Y_n = W \times \gamma$$

Given that $\frac{Y_m}{Y_n} = K_g$, *then*

$$W \times E \times K_s \times K_g \times Y_n + W \times E \times (1 - K_s) \times Y_n = W \times \gamma \quad or$$

$$Y_n = \frac{\gamma}{E \times (K_A \times K_B + (1 - K_A))}$$

Let γ' be the initiation rate under the counterfactual, then, assuming the same proportion of experimenters as in the status – quo scenario:

$$W \times E \times Y_n = W \times \gamma' \text{ or}$$

$$\gamma' = E \times Y_n = \frac{E \times \gamma}{E \times (K_A \times K_B + (1 - K_A))} = \frac{\gamma}{K_A \times K_B + (1 - K_A)}$$

Description of the Model

The model projects the US population, distinguished by age (0 to 100) and smoking status, over the period 2010–2050. Smoking status is categorized by current smokers of menthol cigarettes, current smokers of non-menthol cigarettes, never smokers and former smokers. The latter group is further divided by years quit. The model tracks former smokers from 1 to 30 years after quitting.

Each year, for the next 40 years (2010 to 2050) and for every year of age (from 0 to 100), the model follows the number of individuals in each category. Each simulated year the model introduces a birth cohort obtained from the U.S. Census Bureau projections for the period 2010–2050 and ages the population using age- and smoking status- specific death rates. Individuals younger than 18 are consider non-smokers. At age 18 (age 20 for African Americans), a proportion of individuals become menthol smokers, another fraction become non-menthol smokers and the rest remain non-smokers for their remaining life span. After age 18, smokers are given the chance to quit smoking or switch between menthol and non-menthol cigarettes. Those who quit become former smokers and are tracked not just by age but also by years since quit.

The age-specific background cessation rates used in the simulations are those estimated by Mendez and Warner (1998)[1]. Those quit rates have been validated since.[5] The quit rates were adjusted to reflect differences between menthol and non-menthol smoking according to the expressions derived on page 6. Age-specific death rates were computed for current (menthol and non-menthol), never, and former smokers by years quit, employing smoking relative risks derived from the American Cancer Society's Cancer Prevention Study II (CPS II) data[8] and the procedure described on pages 5 and 6. Relative risks for current and former smokers specific to the US African American population were derived from CPS II data and supplied by the American Cancer Society (Michael Thun, American Cancer Society, personal communication, March 2011). Background death rates for the general population were obtained from the US Census Bureau. Initial (2010) estimates for overall smoking prevalence for the general and African American populations were obtained from the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS), respectively. The initiation rate for the general population was taken to be 21.8 percent, the smoking prevalence among 18 year olds reported by the NHIS in 2009. For African Americans, the initiation rate was taken to be 19.8 percent, consistent with the smoking prevalence at age 20 reported by the BRFSS 2005 for African Americans. Initial (2010) estimates of menthol prevalence were obtained from the National Survey on Drug Use and Health (NSDUH). All data used to produce this report are publicly available.

Simulation Experiments Settings and Results

The model was used to evaluate the impact of menthol cigarettes on the entire US population and the U.S. African American population. To do this, a simulation covering the period from 2010 to 2050 was performed assuming that current (2010) initiation and cessation

rates will remain constant through that period (status-quo scenario). Then the simulation was repeated, now assuming as the counterfactual that menthol cigarettes have never existed in the U.S. The actual 2010 U.S. smoking prevalence was assumed as the 2010 smoking prevalence under the counterfactual, now produced only by non-menthol smoking. For quit rates under the counterfactual, the same non-menthol age-specific quit rates employed in the comparing status-quo scenario were used; the initiation rate on the counterfactual (γ') was computed according to the expression derived on page 6 and 7. The difference in cumulative deaths and cumulative initiation between the status-quo and counterfactual scenarios is reported.

Status quo parameters related to menthol were provided by TPSAC based on literature review findings. An extensive sensitivity analysis of those parameters on the results for the general population was conducted employing parameter ranges also supplied by TPSAC. The results of the analysis for the general population are shown in Tables 1–3.

A sensitivity analysis on the African American model was not conducted because of lack of specific data on some parameters and because the rest of the parameters did not show to be sensitive in the general population model. Instead, the results of the African American model were compared to those of a hypothetical population identical to the US African American population in all aspects except menthol cigarette smoking prevalence. This hypothetical population was given the same menthol cigarette smoking prevalence as the general US population. This comparison highlights the disproportional burden that availability of menthol cigarettes imposes on the African American population. The results of the analysis for the African American population are shown on Tables 4–6.

As the parameters used as input of both models (overall and African American populations) are subject to the statistical uncertainty inherent to their individual estimation process, a Monte Carlo analysis would be required to capture the combined effect of such uncertainty or the results of the analysis. This analysis would not likely change the magnitude and significance of the results, as the model is linear and the simulation settings and parameters chosen were conservative.

Table 1. Input Parameters – General Population:

Parameter	Min	TPSAC Estimate	Max
Proportion of Menthol among Initiators[2] (K_a)	0.35	0.40	0.45
Proportion of Menthol among Experimenters[3] ($K_1 4$)	0.38	0.45	0.60
Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[4] ($K_1 5$)	1.00	1.68	1.85
Cessation Rates Ratio (Menthol/Non-menthol)[5] ($K_1 2$)	0.92	0.95	1.10
Mortality Risk Ratio (Menthol/Non-menthol)[6] (K_1)	0.80	1.00	1.20
Switching Rate from Menthol to Non-menthol (among Menthol smokers) ($S_1 m2n$)	0.9%	1.8%	2.7%
Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[7] ($S_1 n2m$)	0.4%	0.8%	1.2%

[2] Proportion of menthol among those aged 18 to 25. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. (November 19, 2009). The NSDUH Report: Use of Menthol Cigarettes. Rockville, MD.

[3] Provided by TPSAC. 45% was based on the proportion of 12-17 or 14-16 yeor old smokers (from Rock, V. J., Davis, S. P., Thorne, S. L., Asman, K. J., & Caraballo, R. S. (2010). Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. *Nicotine Tob Res, 12 Suppl 2*, S117-124. doi: ntq204 [pii]10.1093/ntr/ntq204 and Curtin, G. M., Sulsky, S. I., Fuller, W. G., Van Landingham, C., Ogden, M. W., & Swauger, J. E. (2010a). Descriptive epidemiological analysis of menthol use from four national US surveys: I.., respectively); 38% was based on 18-25 year and 17-18 old smokers (from Giovino, G. A. (2010). Patterns and recent trends in the use of mentholated cigarettes in the United States *Submission to the Food and Drug Administration's Tobacco Products Scientific Advisory Committee,*. Rock, V. J., Davis, S. P., Thorne, S. L., Asman, K. J., & Caraballo, R. S. (2010). Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. *Nicotine Tob Res, 12 Suppl 2*, S117-124. doi: ntq204 [pii]10.1093/ntr/ntq204; Curtin, G. M., Sulsky, S. I., Fuller, W. G., Van Landingham, C., Ogden, M. W., & Swauger, J. E. (2010a). Descriptive epidemiological analysis of menthol use from four national US surveys: I.) and the 60% is based on smoking among middle schoolers or 9-12 yearo olds (from Curtin, G. M., Sulsky, S. I., Fuller, W. G., Van Landingham, C., Ogden, M. W., & Swauger, J. E. (2010a). Descriptive epidemiological analysis of menthol use from four national US surveys: I..; Hersey, J. C., Ng, S. W., Nonnemaker, J. M., Mowery, P., Thomas, K. Y., Vilsaint, M. C.,Haviland, M. L. (2006). Are menthol cigarettes a starter product for youth? *Nicotine Tob Res, 8*(3), 403-413. doi: R32206802V873N68 [pii]10.1080/14622200600670389

[4] Provided by TPSAC. Nonnemaker, J., Hersey, J., Homsi, G., Busey, A., & Vallone, D. (2010). Menthol cigarettes and youth smoking uptake Submission to the Food and Drug Administration's Tobacco Products Scientific Advisory Committee.

[5] Provided by TPSAC. 95 was based on looking at the range of Ors for cessation across a variety of population survey studies and using a conservative estimate (Alexander, L. A., Crawford, T., & Mendiondo, M. S. (2010). Occupational status, work-site cessation programs and policies and menthol smoking on quitting behaviors of US smokers. *Addiction, 105 Suppl 1*, 95-104. doi: 10.1111/j.1360-0443.2010.03227.x; Delnevo, C. D., Gundersen, D. A., & Hrwyna, M. (2010). Examining the relationship between menthol smoking and cessation using data from the 2003 and 2006/7 Tobacco use Supplement: U S Food and Drug Administration commissioned secondary analysis; Fagan, P., Moolchan, E. T., Hart, A., Jr., Rose, A., Lawrence, D., Shavers, V. L., & Gibson, J. T. (2010). Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns. *Addiction, 105 Suppl 1*, 55-74. doi: 10.1111/j.1360-0443.2010.03190.x; Fagan P, Augustson E, Backinger CL, O'Connell ME, Vollinger RE Jr, Kaufman A, Gibson JT (2007). Quit attempts and intention to quit cigarette smoking among young adults in the United States. American Journal of Public Health, 97, 1412-1420; Gundersen, D. A., Delnevo, C. D., & Wackowski, O. (2009). Exploring the relationship between race/ethnicity, menthol smoking, and cessation, in a nationally representative sample of adults. *Prev Med, 49*(6), 553-557. doi: S0091-7435(09)00478-2 [pii]10.1016/j.ypmed.2009.10.003; Trinidad, D. R., Gilpin, E. A., Lee, L., & Pierce, J. P. (2004). Do the majority of Asian-American and African-American smokers start as adults? *Am J Prev Med, 26*(2), 156-158. doi: S0749379703003180 [pii] ; OR 0.92 was obatined from Delnevo, C. D., Gundersen, D. A., & Hrwyna, M. (2010). Examining the relationship between menthol smoking and cessation using data from the 2003 and 2006/7 Tobacco use Supplement: U S Food and Drug Administration commissioned secondary analysis; OR of 1.10 was dervived from Fagan, P., Moolchan, E. T., Hart, A., Jr., Rose, A., Lawrence, D., Shavers, V. L., & Gibson, J. T. (2010). Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns. *Addiction, 105 Suppl 1*, 55-74. doi: 10.1111/j.1360-0443.2010.03190.x

[6] Provided by TPSAC

[7] Switching Book, 1991 – Philip Morris 2500136466-2500137049. 0.5% of all smokers switched from non-menthol to menthol / 0.67- proportion of non-menthol smokers among smokers. Range +/-50%

Table 2. Scenario Analysis – General Population

Scenario	Description	Prop of Menthol Initiation	Proportion of Menthol Experimentation	Experimentation to Initiation Yield Ratio Menthol/Non-Menthol	Initiation Rate under Counterfactual	Cessation Ratio Menthol/Non-Menthol	Mortality Ratio Menthol/Non-Menthol	Switching Rate Menthol to Non-Menthol	Switching Rate Non-Menthol to Menthol
1	TPSAC Estimates	0.40	0.45	1.68	16.7%	0.95	1.00	1.8%	0.8%
2	Low Menthol Initiation	0.35	0.45	1.68	16.7%	0.95	1.00	1.8%	0.8%
3	High Menthol Initiation	0.45	0.45	1.68	16.7%	0.95	1.00	1.8%	0.8%
4	Low Menthol Experimentation	0.40	0.38	1.68	17.3%	0.95	1.00	1.8%	0.8%
5	High Menthol Experimentation	0.40	0.60	1.68	15.5%	0.95	1.00	1.8%	0.8%
6	Low Yield from Experimenter to Smoker	0.40	0.45	1.00	21.8%	0.95	1.00	1.8%	0.8%
7	High Yield from Experimenter to Smoker	0.40	0.45	1.85	15.8%	0.95	1.00	1.8%	0.8%
8	Low Menthol Cessation	0.40	0.45	1.68	16.7%	0.92	1.00	1.8%	0.8%
9	High Menthol Cessation	0.40	0.45	1.68	16.7%	1.10	1.00	1.8%	0.8%
10	Low Menthol Mortality Risk	0.40	0.45	1.68	16.7%	0.95	0.80	1.8%	0.8%
11	High Menthol Mortality Risk	0.40	0.45	1.68	16.7%	0.95	1.20	1.8%	0.8%
12	Low Switch Rate Menthol to Non-menthol	0.40	0.45	1.68	16.7%	0.95	1.00	0.9%	0.8%
13	High Switch Rate Menthol to Non-Menthol	0.40	0.45	1.68	16.7%	0.95	1.00	2.7%	0.8%
14	Low Switch Rate Non-menthol to Menthol	0.40	0.45	1.68	16.7%	0.95	1.00	1.8%	0.4%
15	High Switch Rate Non-menthol to Menthol	0.40	0.45	1.68	16.7%	0.95	1.00	1.8%	1.2%

Table 3. Results – General Population

Scenario	Description	Cumulative Excess Deaths				Cumulative Excess Smoking Initiation			
		2020	2030	2040	2050	2020	2030	2040	2050
1	TPSAC Estimates	17,182	67,817	164,590	327,565	2,288,534	4,429,326	6,710,101	9,124,867
2	Low Menthol Initiation	17,181	67,812	164,555	327,396	2,288,534	4,429,326	6,710,101	9,124,867
3	High Menthol Initiation	17,182	67,822	164,625	327,733	2,288,534	4,429,326	6,710,101	9,124,867
4	Low Menthol Experimentation	15,411	61,041	147,794	292,601	2,019,295	3,908,229	5,920,677	8,051,353
5	High Menthol Experimentation	20,723	81,367	198,181	397,489	2,827,013	5,471,520	8,288,948	11,271,894
6	Low Yield from Experimenter to Smoker	2,127	10,220	21,810	30,346	0	0	0	0
7	High Yield from Experimenter to Smoker	19,838	77,980	189,784	380,008	2,692,393	5,210,972	7,894,236	10,735,137
8	Low Menthol Cessation	18,495	74,138	178,061	346,122	2,288,534	4,429,326	6,710,101	9,124,867
9	High Menthol Cessation	11,023	38,336	101,964	241,409	2,288,534	4,429,326	6,710,101	9,124,867
10	Low Menthol Mortality Risk	-239,508	-293,535	-220,657	-41,279	2,288,534	4,429,326	6,710,101	9,124,867
11	High Menthol Mortality Risk	238,551	378,451	494,892	644,022	2,288,534	4,429,326	6,710,101	9,124,867
12	Low Switch Rate Menthol to Non-menthol	17,227	68,265	166,070	330,538	2,288,534	4,429,326	6,710,101	9,124,867
13	High Switch Rate Menthol to Non-Menthol	17,138	67,397	163,252	324,972	2,288,534	4,429,326	6,710,101	9,124,867
14	Low Switch Rate Non-menthol to Menthol	17,139	67,399	163,249	324,993	2,288,534	4,429,326	6,710,101	9,124,867
15	High Switch Rate Non-menthol to Menthol	17,224	68,223	165,874	329,989	2,288,534	4,429,326	6,710,101	9,124,867

Table 4. Input Parameters – African American Population:

Parameter	TPSAC Estimate
Proportion of Menthol among Initiators[8] (K_2)	.80
Proportion of Menthol among Experimenters[9] (K_14)	.80
Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[10] (K_15)	1.68
Cessation Rates Ratio (Menthol/Non-menthol)[11] (K_12)	0.95
Mortality Risk Ratio (Menthol/Non-menthol)[11] (K_1)	1
Switching Rate from Menthol to Non-menthol (among Menthol smokers)[11] (S_1m2n)	0.9%
Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[12] (S_1n2m)	4%
Initiation Rate under Counterfactual (Y')[13]	12.7%

[8] Same as experimenters

[9] Provided by TPSAC. 80% was based on the proportion of 12-17 or 14-16 yeor old smokers (from Appleyard, J., Messeri, P., & Haviland, M. L. (2001). Smoking among Asian American and Hawaiian/Pacific Islander youth: data from the 2000 National Youth Tobacco Survey. *Asian Am Pac Isl J Health, 9*(1), 5-14.; Giovino, G. A. (2010). Patterns and recent trends in the use of mentholated cigarettes in the United States *Submission to the Food and Drug Administration's Tobacco Products Scientific Advisory Committee*; Giovino, G. A., Sidney, S., Gfroerer, J. C., O'Malley, P. M., Allen, J. A., Richter, P. A., & Cummings, K. M. (2004). Epidemiology of menthol cigarette use. *Nicotine Tob Res, 6 Suppl 1*, S67-81. doi: 10.1080/14622203710001649696 14AH8W576MJQ7MCN [pii]; Hersey, J. C., Ng, S. W., Nonnemaker, J. M., et al. (2006). Are menthol cigarettes a starter product for youth? *Nicotine Tob Res, 8*(3), 403-413. doi: R32206802V873N68 [pii]10.1080/14622200600670389; Hersey, J. C., Nonnemaker, J. M., & Homsi, G. (2010). Menthol cigarettes contribute to the appeal and addiction potential of smoking for youth. *Nicotine Tob Res, 12 Suppl 2*, S136-146. doi: ntq173 [pii]10.1093/ntr/ntq173; Rock, V. J., Davis, S. P., Thorne, S. L., Asman, K. J., & Caraballo, R. S. (2010). Menthol cigarette use among racial and ethnic groups in the United States, 2004-2008. *Nicotine Tob Res, 12 Suppl 2*, S117-124. doi: ntq204 [pii]10.1093/ntr/ntq204

[10] Same values as in the general population.

[11] Switching Book, 1991 – Philip Morris 2500136466-2500137049 – 0.7% of all African American smokers switched from menthol to non-menthol / 0.8 – proportion of menthol smokers among African American smokers.

[12] Switching Book, 1991 – Philip Morris 2500136466-2500137049 – 0.8% for all African American smokers switched from non-menthol to menthol / 0.2 – proportion of non-menthol smokers among African American smokers.

[13] Computed using the procedure described on page 7.

Table 5. Input Parameters – Hypothetical Low Menthol African American Population:

Parameter	Estimate
Proportion of Menthol among Initiators[14] (K_3)	.40
Proportion of Menthol among Experimenters[15] (K_14)	.45
Ratio of "Proportion of Menthol Experimenters that become Established Smokers" / "….Non-menthol….."[15] (K_15)	1.68
Cessation Rates Ratio (Menthol/Non-menthol)[16] (K_12)	0.95
Mortality Risk Ratio (Menthol/Non-menthol)[16] (K_1)	1
Switching Rate from Menthol to Non-menthol (among Menthol smokers)[16] (S_1m2n)	0.9%
Switching Rate from Non-menthol to Menthol (among Non-menthol smokers)[16] (S_1n2m)	4%
Initiation Rate under Counterfactual (I')[16]	15.0%

[14] Same value as in the general population

[15] Same value as in the African American population

[16] Computed using the procedure described on page 7

Table 6. Results – African American Population

Description	Cumulative Excess Deaths				Cumulative Excess Smoking Initiation			
	2020	2030	2040	2050	2020	2030	2040	2050
African American Population – TPSAC Estimates	4,716	16,381	35,250	66,524	461,273	859,101	1,262,086	1,656,005
Low Menthol Prevalence Hypothetical African American Population	2,691	10,244	23,218	44,771	307,515	572,734	841,391	1,104,003

References:

1. Mendez D, Warner KE and Courant PN. "Has Smoking Cessation Ceased? Expected Trends in the Prevalence of Smoking in the United States." *American Journal of Epidemiology*, 1998;148(3):249-58.

2. Mendez D and Warner KE. "Smoking Prevalence in the Year 2010: Why the Healthy People Goal is Unattainable." *American Journal of Public Health*, 2000;90(3):401-403.

3. Mendez D, Warner KE and Courant PN. "Expected Trends in the Prevalence of Cigarette Smoking." Chapter in Lu R, Mackay J, Niu S and Peto R, eds. *The Growing Epidemic*, Singapore: Springer-Verlag, 2000:49-52.

4. Warner KE, Mendez D and Smith DG. "Cost Effectiveness of Smoking Cessation Programs in Managed Care Organizations." *Inquiry*, 2004;41(1):57-69.

5. Mendez D and Warner KE. "Smoking Trends in the US: Declining as Expected if not as Desired." *American Journal of Public Health*, 2004;94:251:252.

6. Mendez D and Warner KE. "Commissioned Simulation Modeling of Smoking Prevalence as an Outcome of Selected Tobacco Control Measures." Chapter in The Institute of Medicine's Committee on Reducing Tobacco Use, eds. *Ending the Tobacco Problem: A Blueprint for the Nation The Institute of Medicine*, 2007.

7. Mendez D and Warner KE. "Setting a challenging, yet realistic smoking prevalence target for Healthy People 2020: Learning from the California experience." *American Journal of Public Health*, 2008;98(3):556-9.

8. Mendez D, Warner KE. "The relative risk of death for former smokers: the influence of age and years-quit." *Unpublished research monograph*, 2001. Available at http://www.umich.edu/~dmendez/tobacco/RRiskmonograph.doc. Accessed March 14, 2011.

APPENDIX B

TPSAC MEETING DATES AND TOPICS

- March 30–31, 2010 — Summary presentation of published literature on menthol
    - Invited Presenters: Lawrence Deyton, M.S.P.H., M.D., Catherine Lorraine, J.D., Corinne Husten, M.D., M.P.H., Ralph Caraballo, Ph.D., M.P.H., Deirdre Lawrence, Ph.D., M.P.H., Joshua Rising, M.D., M.P.H., Allison C. Hoffman, Ph.D.

- July 15–16, 2010 — Industry presentations on menthol in cigarettes as it relates to characterization of menthol, clinical effects of menthol, biomarkers of disease risk, marketing data, and population effects
    - Invited Presenters: Corinne Husten, M.D., M.P.H., James E. Dillard III, Jane Y. Lewis, Ph.D., Michael W. Ogden, Ph.D., William R. True, Ph.D., Mohamadi A. Sarkar, Ph.D., Pascal A. Fernandez, Monica J. Graves, Leonard H. Jones, Geoffrey M. Curtin, Ph.D., Jennifer L. Hunter, William R. True, Ph.D., David L. Ashley, Ph.D.

- September 27, 2010 — Menthol Report Subcommittee met to discuss timelines and the structure of the Menthol Report.
    - Invited Presenters: Corinne Husten, M.D., M.P.H., Karen M. Templeton-Somers, Ph.D., Jonathan Samet, M.D., M.S.

- October 7, 2010 —Presentations on publicly available industry documents from the Legacy Tobacco Documents Library
    - Invited Presenters: Corinne Husten, M.D., M.P.H., Allison C. Hoffman, Ph.D., Jonathan Samet, M.D., M.S., Stacey J. Anderson, Ph.D., Valerie B. Yerger, N.D.

- November 18, 2010 —Updates from the Menthol Report Subcommittee and presentation on secondary analysis of the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Presenters: Corinne Husten, M.D., M.P.H., Jonathan Samet, M.D., M.S., James C. Hersey, Ph.D., Brett R. Loomis

- January 10–11, 2011 —Updates from the Menthol Report Subcommittee , presentation regarding contraband and menthol, presentation on modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting.
    - Invited Presenters: Jonathan M. Samet, M.D., M.S., Neal L. Benowitz, M.D., Patricia Nez Henderson, M.P.H., M.D.., Dorothy K. Hatsukami, Ph.D., Mark Stuart Clanton, M.D., M.P.H.

- February 10, 2011 — Updates from the Menthol Report Subcommittee, presentation on updated modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Speakers: Corinne Husten, M.D., M.P.H., David Mendez, Ph.D., Brian F. Thomas, Ph.D., Hernán Navarro, Ph.D., Kenneth H. Davis, Jr., James Hersey, Ph.D., Jonathan Samet, M.D., M.S.

- February 11, 2011 —Menthol Report Subcommittee met to discuss timelines and the structure of the Menthol Report.
    - Invited Speakers: Corinne Husten, M.D., M.P.H., Jonathan M. Samet, M.D., M.S., Neal L. Benowitz, M.D., Patricia Nez Henderson, M.P.H., M.D., Karen L. DeLeeuw, M.S.W. , Dorothy K. Hatsukami, Ph.D., Mark Stuart Clanton, M.D., M.P.H.,

- March 2, 2011 — Updates from the Menthol Report Subcommittee, presentation on updated modeling schema, and presentations regarding the data requested by the committee at the March 30 and 31, 2010 TPSAC meeting
    - Invited Speakers: David L. Ashley, Ph.D., David Mendez, Ph.D., Neal Benowitz, M.D., Jonathan Samet, M.D., M.S., Eric O. Johnson, Ph.D., J. Daniel Heck, Ph.D., DABT

- March 17–18, 2011— Updates from the Menthol Report Subcommittee (including proposed recommendations) and presentation on updated modeling schema
    - Invited Speakers: Corinne Husten, M.D., M.P.H., David Mendez, Ph.D., , Jonathan Samet, M.D., M.S., Neal Benowitz, M.D., Patricia Nez Henderson, M.P.H., M.D., Mark Stuart Clanton, M.D., M.P.H., J. Daniel Heck, Ph.D., DABT, Lawrence Deyton, M.S.P.H., M.D.

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Alphabetical list of all invited speakers (consolidated from agendas)

Stacey J. Anderson, Ph.D.
David L. Ashley, Ph.D.
Neal L. Benowitz, M.D.
Ralph Caraballo, Ph.D., M.P.H.
Mark Stuart Clanton, M.D., M.P.H.
Geoffrey M. Curtin, Ph.D.
Kenneth H. Davis, Jr.
Karen L. DeLeeuw, M.S.W.
Lawrence Deyton, M.S.P.H., M.D.
James E. Dillard III
Pascal A. Fernandez
Monica J. Graves
Dorothy K. Hatsukami, Ph.D.
J. Daniel Heck, Ph.D., DABT
Patricia Nez Henderson, M.P.H., M.D.
James C. Hersey, Ph.D.
Allison C. Hoffman, Ph.D.
Jennifer L. Hunter
Corinne Husten, M.D., M.P.H.
Eric O. Johnson, Ph.D.
Leonard H. Jones
Deirdre Lawrence, Ph.D., M.P.H.
Jane Y. Lewis, Ph.D.
Brett R. Loomis
Catherine Lorraine, J.D.
David Mendez, Ph.D.
Hernán Navarro, Ph.D.
Michael W. Ogden, Ph.D.
Joshua Rising, M.D., M.P.H.
Jonathan Samet, M.D., M.S.
Mohamadi A. Sarkar, Ph.D.
Karen M. Templeton-Somers, Ph.D.
Brian F. Thomas, Ph.D.
William R. True, Ph.D.
Valerie B. Yerger, N.D.
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