

**The Role of Menthol Flavoring in Smoking Initiation, Cessation,
and other Smoking Behaviors: A Search and Methodological
Evaluation of the Literature**

Prepared for Lorillard Inc.

**FINAL STUDY REPORT
Version 1.0**

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STUDY GLOSSARY

Abbreviation/Acronym	Definition
3HC/COT	3 hydroxycotinine/cotinine ratio
ACASI	Audio Computer-assisted Self Interviewing
AHRQ	Agency for Healthcare Research and Quality
BA	Biological Abstracts [®]
BA/RRM	Biological Abstracts/Reports, Reviews, and Meetings [®]
BRFSS	Behavioral Risk Factor Surveillance System
CAI	Computer-assisted Interviewing
CAPI	Computer-assisted Personal Interviewing System
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CO	Carbon Monoxide
COMMIT	Community Intervention Trial for Smoking Cessation
COT/CPD	Cotinine/cigarettes per day
CPD	Cigarettes per Day
CPS	Current Population Survey
DANDY	Development and Assessment of Nicotine Dependence in Youth
e.g.	for example
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
HONC	Hooked on Nicotine Checklist
HRQoL	Health-Related Quality of Life
i.e.	that is
LHS	Lung Health Study
LTD	Literature Tracking Database
MEC	Mobile Examination Center
MeSH	Medical Subject Headings
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NDSA	Nicotine Dependence Scale for Adolescents
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHIS-CCS	NHIS-Cancer Control Supplement
NHSDA	National Household Survey on Drug Abuse
NLM	National Library of Medicine
NSDUH	National Survey on Drug Use and Health
NYTS	National Youth Tobacco Survey
OR	Odds Ratio
QoL	Quality of Life
RCT	Randomized Controlled Trial
RFA	Request for Application
SAMHSA	Substance Abuse and Mental Health Services Administration
TAPS	Teenage Attitudes and Practices Survey
TPSAC	Tobacco Products Scientific Advisory Committee
TTF	Time to First
TUS	Tobacco Use Supplement

Abbreviation/Acronym	Definition
TUSCS	Tobacco Use Special Cessation Supplement
US	United States
VA	Veterans' Affairs

EXECUTIVE SUMMARY

Background: The potential impact of menthol flavoring in cigarettes on smoking initiation, dependency, and cessation has been the topic of much debate. In an effort to understand the disparate findings of studies that have investigated these relationships, Covance conducted a methodological quality assessment of the literature, as well as the content of four national surveys routinely used by researchers to investigate smoking behavior.

Objectives: The primary objective of this quality assessment was to evaluate the appropriateness and rigor of the methodologies of studies reported in the published literature as they relate to the relationships between menthol flavoring and smoking initiation or cessation behaviors. A secondary objective was to review the smoking-related survey items contained in four national surveys and evaluate the extent to which the survey items can be used to investigate the relationship between menthol flavoring and smoking initiation and cessation behaviors.

Methodology: As a first step in this quality assessment, Covance conducted a systematic search and review of the literature to confirm inclusion of all published studies that examine the relationship between menthol flavoring and smoking initiation or cessation behaviors, or studies from which inferences about these relationships have been made. Two reviewers independently evaluated the methodological quality of each study reported in the articles using criteria developed by the Agency for Healthcare Research and Quality (AHRQ) for their report on tobacco prevention, cessation and control. For each study, reviewers provided both an overall quality rating, as well as a quality rating specific to the study's ability to yield inferences or conclusions about the relationship between menthol flavoring and smoking behaviors. Reviewers rated the quality of each study from "Good" to "Poor" ("Good", "Good to Fair", "Fair", "Fair to Poor", and "Poor").

Additionally, Covance conducted an assessment of the conclusions, discussion and/or interpretations of results reported in each article that received a "Fair" rating or better in the methodological quality assessment. This assessment focused on: 1) whether the authors presented conclusions regarding the impact of menthol on smoking behavior; 2) whether the authors' conclusions are supported by the study findings; and 3) whether the authors' conclusions reflect the totality of the study findings.

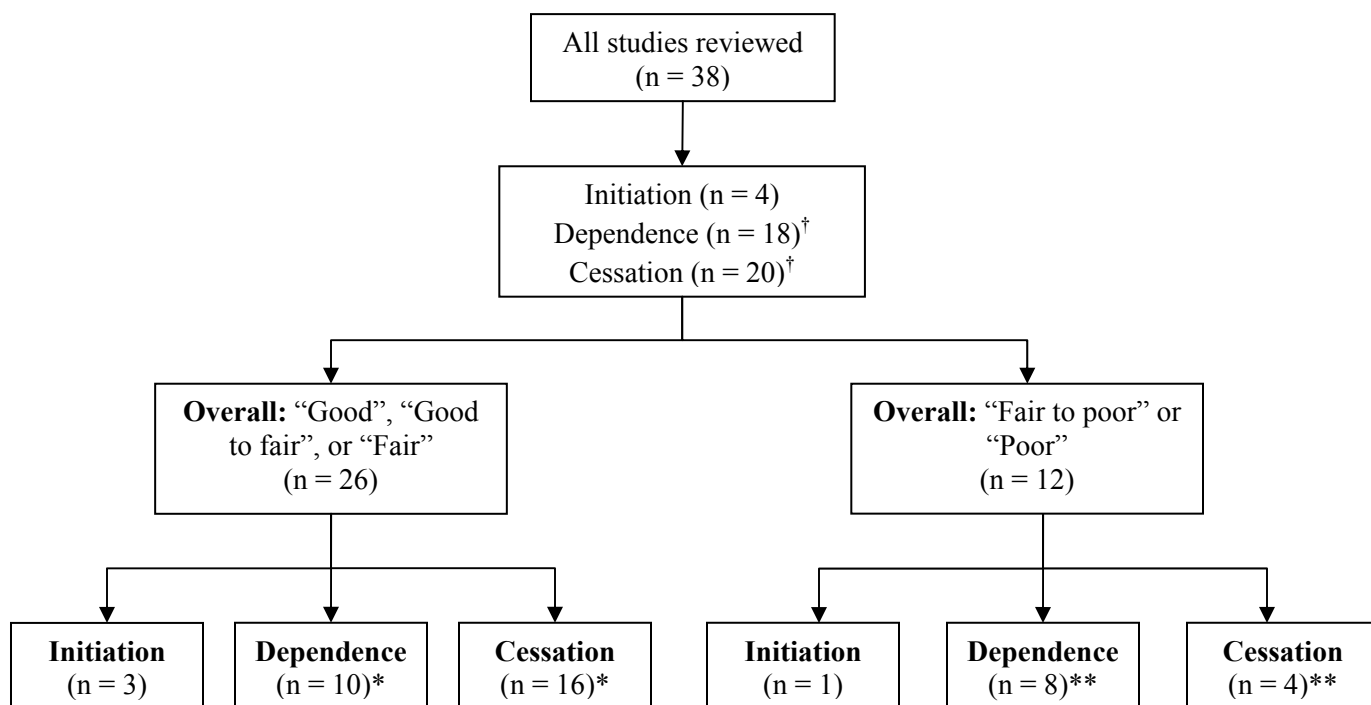
Finally, Covance conducted a review of the smoking-related items contained in four national surveys that are routinely used to investigate smoking behavior: the National Survey on Drug Use and Health (NSDUH), the National Youth Tobacco Survey (NYTS), the National Health and Nutrition Examination Survey (NHANES), and the National Health Interview Survey (NHIS). Each survey was reviewed to: 1) determine which concepts were evaluated in each survey; 2) assess the clarity of the survey questions and response options from the viewpoint of the intended respondents; and 3) assess whether conclusions about the relationship between menthol flavoring and smoking initiation and/or cessation behaviors could be made based on an analysis of the items contained in the surveys.

Results: Thirty-eight articles met the article inclusion criteria and were reviewed in the quality assessment; four articles on smoking initiation, 18 articles on smoking or nicotine dependence,

and 20 articles on smoking cessation. Four of the reviewed studies examined multiple smoking behaviors (e.g., both dependence and cessation behaviors) and were considered under each relevant section.

Methodological Quality: Sixty eight percent (n = 26) of the studies reviewed received overall quality ratings of “Fair” or better, as shown in Figure E.1.

Figure E.1 Summary of All Studies Reviewed: Overall Quality



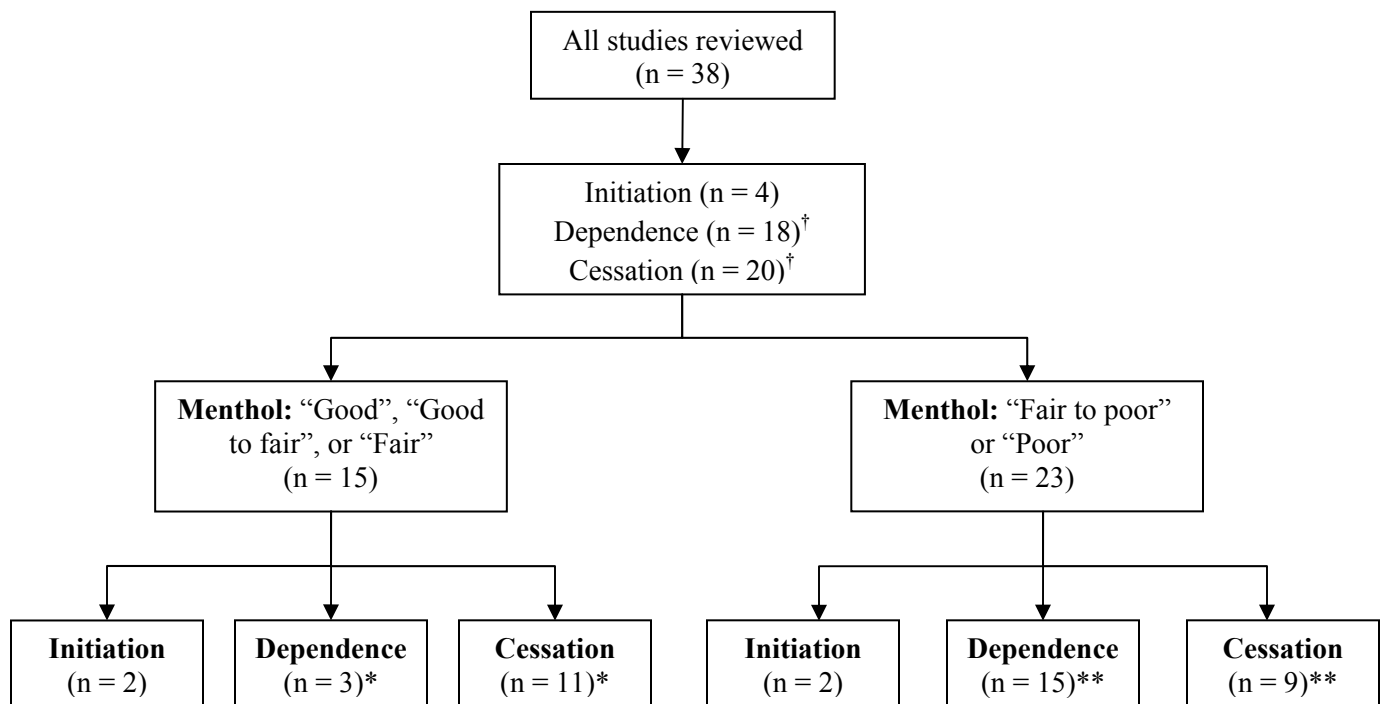
† Four studies discuss both dependence and cessation, and are counted in both totals

* Three studies evaluated under dependence and cessation

** One study evaluated under dependence and cessation

Forty percent of the 38 studies (n = 15) were rated as “Fair” or better with respect to their ability to support inferences regarding the relationship between menthol cigarette use and smoking behaviors. Sixty one percent (n = 23) of the studies reviewed received a “Fair to poor” or “Poor” quality rating with respect to their ability to support inferences regarding the relationship between menthol cigarette use and smoking behaviors (Figure E.2).

Figure E.2 Summary of All Studies Reviewed: Menthol Inferences Quality



† Four studies discuss both dependence and cessation, and are counted in both totals

* One study evaluated under dependence and cessation

** Three studies evaluated under dependence and cessation

Summary of Article Findings: In general, articles that were rated as “Fair” or better with respect to their ability to support inferences regarding the relationship between menthol cigarette use and smoking behaviors used a rigorous study design and appropriate measures for data capture. Their statistical methodology was appropriate for the study and clearly defined in these articles. In contrast, studies rated “Fair to Poor” or “Poor” often failed to use valid measures and/or explain their rationale for the measures used. The design of these studies generally also limited the ability to assess the relationship between menthol and initiation, dependence, or cessation. In addition, they often lacked appropriate statistical rigor and/or clear explanations of the statistical process used. Finally, because of their study design and/or study population (study sample), these studies often lacked generalizability.

Of the two studies assessing **initiation** that were rated “Fair” or better regarding their ability to support inferences related to menthol, neither found any difference in initiation behaviors between menthol and non-menthol smokers.^{1, 2}

Of the three studies assessing **dependence** that were rated “Fair” or better regarding their ability to support inferences related to menthol, two (66%) found no difference,^{3, 4} while the third study (also included in the cessation section) reported that menthol cigarette smokers exhibit signs of greater dependence than non-menthol smokers at six weeks.⁵

Finally, four of 11 studies assessing **cessation** that were rated “Fair” or better regarding their ability to support inferences related to menthol found no differences in cessation rates between

menthol⁶⁻⁹ and non-menthol smokers, while the remaining seven studies found that menthol cigarette smokers were less successful in quitting than non-menthol smokers.

In summary, considering the results of all the studies, among those rated “Fair” or better, eight found no difference while seven found a difference. Among those studies rated as “Fair to Poor” or “Poor”, 10 found no difference while eight found difference, as shown below.

Summary of All Studies Reviewed: Study Outcomes by Menthol Quality Rating

Overall	No Difference*	Difference*
“Good”, “Good to Fair”, or “Fair” Studies (n = 15)		
Overall	Eight studies	Seven studies
Initiation	Two studies ^{1, 2}	None
Dependence/Other Behavior	Two studies ^{3, 4}	N/A
Both Dependence and Cessation	N/A	One study ⁵
Cessation	Four studies ⁶⁻⁹	Six studies ¹⁰⁻¹⁵
“Fair to Poor” or “Poor” Studies (n = 18)		
Overall	Ten studies	Eight studies
Initiation	None	One study ¹⁶
Dependence/Other Behavior	Four studies ¹⁷⁻²⁰	Six studies ²¹⁻²⁶
Both Dependence and Cessation	Two studies ^{27, 28}	N/A
Cessation	Four studies ²⁹⁻³²	One study ³³

NOTE: Five studies are not included in this table. One initiation study (Kreslake, 2008) was more of an editorial. Two dependence studies (Ahijevych, 1993; Moolchan, 2004) and one study in both dependence and cessation (Hymowitz, 1995) only reported the baseline characteristics (no outcomes) by menthol/non-menthol. Finally, once cessation study (Pollack, 2002) reported cessation advice given by menthol status, but not outcomes.

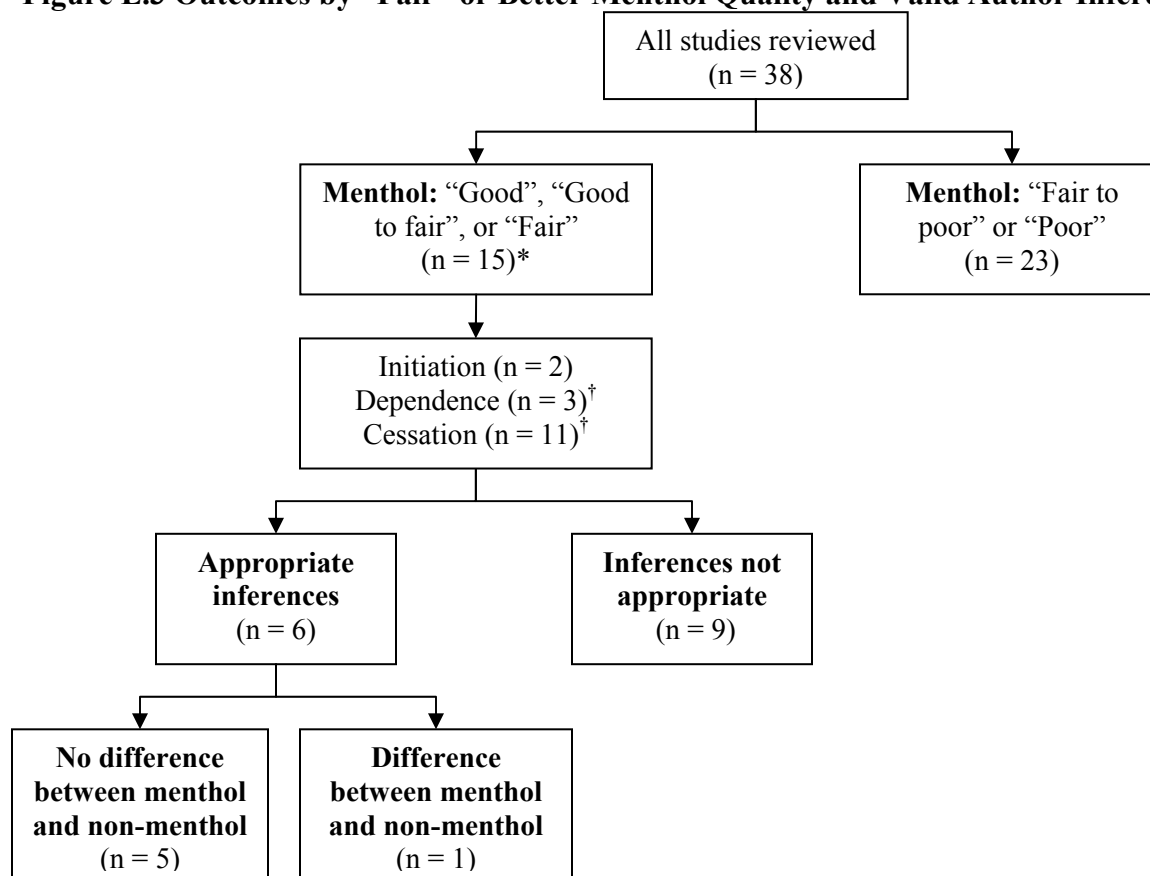
* Between menthol and non-menthol cigarette smokers.

Validity of Authors’ Interpretations: Covance conducted an assessment of the conclusions, discussion and/or interpretations of results reported in each article that received a “Fair” rating or better in the menthol methodological quality assessment. Fifteen of the 38 studies were “Fair” or better (one study was reviewed in both the dependence and cessation section, but was only counted once in the total above).

Of the two studies on initiation that received a “Fair” rating or better in the menthol methodological quality assessment, neither (n = 0) were able to address “true” initiation behaviors and preference for menthol vs. non-menthol together. Of the three studies on dependence that received a “Fair” rating or better in the menthol methodological quality assessment, reviewers agreed two utilized appropriate methods and made the appropriate conclusions based on the study data. Of the 11 studies on cessation that received a “Fair” rating or better in the overall methodological quality assessment, reviewers agreed four utilized appropriate methods and made the appropriate conclusions based on the study data.

Overall, we found that only six out of 38 studies^{3, 4, 6-8, 11} were rated as “Fair” or better based on a methodological review and made appropriate conclusions based on the data. Five of these six studies found no difference in outcomes between those smoking menthol and non-menthol cigarettes (Figure E.3).

Figure E.3 Outcomes by “Fair” or Better Menthol Quality and Valid Author Inferences



† One study discusses both dependence and cessation, and is counted in both totals

* Five studies did not evaluate how menthol smoking impacted outcomes

Review of Items in Four National Surveys: While each of the four national surveys contained items assessing smoking initiation and cessation behaviors or experiences, none of the surveys contained an item asking respondents to indicate the type of cigarette smoked during initial smoking experiences and only one of the surveys (the NHIS Cancer Supplement) contained an item asking respondents to indicate the type of cigarette smoked during quit attempts. Without such items, relationships between cigarette type or menthol flavoring and smoking initiation and cessation cannot be ascertained.

Conclusions: Based on our evaluations, the extent to which data reported in the reviewed articles may be used to develop inferences regarding the relationship between menthol and smoking behaviors is quite limited. The results of our assessments indicate that while the studies were not necessarily poorly designed overall, most were not designed to test the impact of menthol on smoking behaviors thereby limiting inference related to these behaviors. Across those that were well designed, only a handful of studies made appropriate conclusions regarding the impact of menthol flavoring on smoking outcomes. Overall, only six of the 38 studies reviewed used appropriate methods and made appropriate conclusions based on the study data. Results from these studies, while mixed, suggest that menthol has no significant impact on initiation, cessation, and/or dependence and other behavioral outcomes. However, given the

small number of these studies, we recommend that new studies be designed a priori to examine these relationships in order to advance the body of knowledge regarding the impact of menthol flavoring on smoking behaviors.

I. INTRODUCTION AND BACKGROUND

On June 22, 2009 the “*Family Smoking Prevention and Tobacco Control Act*” gave the Food and Drug Administration (FDA) the authority to regulate tobacco products. Section 907 of the legislation (Tobacco Product Standards) bans the use of constituents and additives in cigarettes or any cigarette components that are characterizing flavors. However, menthol was exempted from this ban, and the FDA is conducting an ongoing review and evaluation of the menthol exception.

The act required the FDA to create the Tobacco Products Scientific Advisory Committee (TPSAC). The purpose of this committee is to advise the Commissioner or designee in discharging responsibilities as they relate to the regulation of tobacco products. The committee is responsible for reviewing and evaluating the safety, dependence, and health issues relating to tobacco products in order to provide appropriate advice, information, and recommendations to the Commissioner of Food and Drugs. To do this, the TPSAC is currently tasked with the pursuit of a sound, science-based assessment of published and unpublished information on menthol in cigarettes. By March 23, 2011, the TPSAC will submit a report and recommendations on the impact of the use of menthol in cigarettes on public health, including such use among children, African Americans, Hispanics and other racial and ethnic minorities.³⁴

One of the sources TPSAC will likely review will be a bibliography of over 300 studies related to menthol and tobacco developed by the National Cancer Institute (NCI).³⁵ This bibliography includes studies that purport to evaluate whether menthol flavoring in cigarettes encourages more people to take up smoking (initiation) and/or makes it harder to quit smoking (cessation). However it is not clear how this bibliography was developed and why certain studies were not listed as part of this bibliography, or whether these studies were actually designed a priori to evaluate these relationships. The NCI bibliography provides no interpretation or analysis of published literature beyond the authors’ verbatim published abstracts.

There have been conflicting reports on the effect of menthol on smoking initiation and cessation behaviors. It also is very difficult to separate out the effects of menthol from various cultural and socio-demographic factors that may influence smoking habits and dependency. It has been suggested that menthol in cigarettes may make them more appealing to young people, more addictive, and more difficult to quit than regular cigarettes. Teasing out the direct effects of menthol from indirect effects resulting from the preferences of certain groups for menthol cigarettes can be quite difficult without a rigorous study design and analysis methodology. For example, some studies suggest a lower cessation rate among African American smokers compared to other races^{12,13} and a higher likelihood of reporting nicotine dependence among adolescent menthol smokers than adolescent non-menthol smokers²⁶. This has led to speculation that the disproportionate popularity of menthol cigarettes among these groups may play a role in nicotine addiction and difficulties with cessation. Yet other studies have come to very different conclusions, with reports that African Americans initiate smoking at a lower rate and at an older

age, and consume fewer cigarettes per day (CPD), on average, than other races/ethnicities.^{15, 21, 31} These discrepant findings may be explained in part by differences in study methodologies. For example, differences in key study measures or disproportionate study populations across studies may result in different findings.

In addition to a review of the public literature, TPSAC will also likely review studies published from the following four surveys that include questions on self-reported smoking behaviors by adolescents and others to determine whether menthol affects smoking initiation:³⁶

- National Survey on Drug Use and Health (NSDUH),
- National Youth Tobacco Survey (NYTS),
- National Health and Nutrition Examination Survey (NHANES), and
- National Health Interview Survey (NHIS).

*NSDUH*³⁷

The NSDUH, formerly called the National Household Survey on Drug Abuse (NHSDA), among other names, was initiated in 1971 as a result of legislation enacted in 1970 that created the Commission on Marijuana and Drug Abuse. This survey has grown in size and complexity from its initial sample size of about 3,000 to its current multistage area probability sample of nearly 70,000 persons. Participants of the survey represent the United States (US) civilian, non-institutionalized population, aged ≥ 12 years, including residents of non-institutional group quarters such as college dormitories, group homes, shelters, rooming houses and civilians dwelling on military installations. The survey is currently conducted via computer-assisted interviewing (CAI) mode, which utilizes audio computer-assisted self-interviewing (ACASI) for the more sensitive sections of the questionnaire.

In 2002, further design changes were introduced, including the adoption of the current name, in order to enhance the likelihood of participation and improve the accuracy of the data. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) under a contract by RTI International (a trade name of Research Triangle Institute).

*NYTS*³⁸

In collaboration with the Centers for Disease Control and Prevention (CDC), the American Legacy Foundation developed the NYTS to measure the tobacco-related beliefs, attitudes and behavior of youth, and the pro- and anti-tobacco influences to which they are exposed. NYTS is an anonymous, self-administered school-based survey that targets students in grades 6 through 12 (aged 9-21 years). Surveys are completed anonymously, in a group setting, during the school day and on school property. The 1996, 1998, 2000 surveys used passive parental consent, while the 2002 and 2004 surveys used active parental consent. In contrast, the 2006 and 2008 surveys used a mixed parental consent procedure.¹ The NYTS uses a multi-stage sampling design to produce a nationally representative sample of students.

¹ Youth smoking. California Department of Public Health, California Tobacco Control Program: [cdph.ca.gov/programs/Tobacco](http://www.cdph.ca.gov/programs/Tobacco). Accessed December 14, 2010 at http://www.cdph.ca.gov/programs/tobacco/Documents/CTCPYouthSmoking_10.pdf

NHANES³⁹

The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the US. The NHANES provides stratified multistage probability samples of the US civilian, non-institutionalized population, completed in two-year cycles; construction of this survey allows data from multiple cycles to be combined and weighted to generate valid national estimates. The survey combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS). The survey examines a nationally representative sample of about 5,000 persons each year (the combined NHANES 2005/06 and 2007/08 databases provided a sample size of 19,712, with 10,343 respondents completing the smoking survey). Fifteen counties across the country are visited each year.

Smoking information for adult respondents (aged ≥ 20 years), is collected by interviews completed prior to the physical examination, in the home, using the CAPI system. For respondents aged 12-19 years, smoking information is obtained during the physical examination, at the Mobile Examination Center (MEC) using ACASI.

NHIS⁴⁰

The NHIS is a cross-sectional survey that collects information on a variety of health indicators. It uses a multi-stage area probability sampling design to produce nationally representative estimates of the civilian non-institutionalized population of the US and is one of the major data collection programs of the NCHS. The NHIS is a continuing nationwide sample survey that collects data using personal household interviews with individuals aged ≥ 18 years through an interviewer-administered CAPI system. The NHIS includes an Adult Health Behavior section that contains questions related to cigarette smoking.

All adults who indicate that they currently or formerly smoked were asked whether they had ever used menthol cigarettes, whether they had ever tried to quit smoking, and the method(s) they used the last time they tried to stop smoking in the Tobacco section of the Cancer Control Module. The Tobacco section of the 2005 Cancer Control Module collected smoking/tobacco-related information from all adults in the NHIS interviewed sample.

II. OBJECTIVES

In an effort to understand both the positive and negative results in published findings regarding the relationships between menthol and smoking initiation and cessation behaviors, Covance conducted a critical review of the related literature, as well as the content of four national surveys that are routinely used by researchers to investigate smoking behavior. Variation in the quality and rigor of studies within this body of literature may lead to conflicting results that could affect decision makers' confidence about findings from systematic reviews. Therefore, our goal was to evaluate the extent to which sound conclusions can be drawn from the methods employed by these studies and the four surveys regarding the relationships between menthol and smoking initiation and cessation behaviors. This effort will facilitate a scientifically-sound evidence base that may be used by the FDA and others to make informed objective decisions regarding the regulation of menthol cigarettes.

The objectives of this study were twofold:

1. to evaluate the appropriateness and rigor of the methodology used in each study as they relate to the relationships between menthol flavoring and smoking initiation or cessation behaviors, and
2. to evaluate the appropriateness of the survey questions in the four national surveys of interest (NSDUH, NYTS, NHANES, and NHIS) as they relate to the relationship between menthol flavoring and smoking initiation or cessation behaviors.

Our review and evaluation focused on whether reasonable inferences about menthol flavoring and smoking initiation or cessation can be made based on the content of each article or survey.

III. METHODS

The methodology developed for this evaluation was guided by the following key question:

Are published data sufficiently rigorous with regard to the evidence on initiation, dependence, and cessation for the TPSAC/FDA to create policy recommendations about the regulation of menthol cigarettes?

Covance first developed a protocol (approved on September 17, 2010) which outlined the steps required to complete this review. Using the search terms and search limits identified in the protocol, we conducted a literature search and review to confirm inclusion of all published studies that examine the relationship between menthol flavoring and smoking initiation or cessation behaviors, or studies from which inferences about these relationships have been made, even if the initial study was designed for another purpose. Next, we reviewed the abstracts from all studies identified in the literature search to confirm inclusion of content relevant to our evaluation. Following the review of all abstracts (and full text articles when required) two reviewers independently evaluated the methodological quality of each article using the criteria provided in the protocol. In the subsections that follow, we describe in detail each component of our study methodology.

A. Literature Search

1. Databases and Search Strategy

MEDLINE[®], EMBASE[®], BIOSIS[®], and PsycINFO[®] were used to conduct a systematic search for relevant articles (see Appendix 1 for a description of these databases). The search was conducted through Dialog. Dialog is an online information service that is capable of searching multiple databases and removing duplicates during the search. Terms related to menthol cigarette smoking were crossed with initiation or cessation behavior concepts, as appropriate.

Medical Subject Heading (MeSH) terms were used to search categorized topic areas in MEDLINE[®], BIOSIS[®], and PsycINFO[®]; EMTREEⁱⁱ terms were used to search categorized topic areas in EMBASE[®]; and key titles and abstract terms were used to search for relevant articles (Exhibit 1). Duplicate articles were removed following the search.

ⁱⁱ Elsevier's life science thesaurus - An extensive thesaurus covering 55,000 preferred terms.

Exhibit 1. Literature Terms Searched with “Menthol”

MeSH Terms	EMTREE Terms	Title/Abstract Terms
<ul style="list-style-type: none"> Smoking 	<ul style="list-style-type: none"> Adolescent smoking Cigarette smoking Smoking Smoking and smoking related phenomena Tobacco smoke 	<ul style="list-style-type: none"> Cigarette Smoke Smoker Smoking Tobacco
<i>AND</i>		
<ul style="list-style-type: none"> Adolescent Behavior Behavior, Addictive Cultural Ethnic group Habits Health survey Interview Maintenance Mental health Patient satisfaction Personal satisfaction Qualitative research Quality of life Questionnaires Smoking Cessation 	<ul style="list-style-type: none"> Addiction Adolescent Behavior Cultural factor Drug dependence Ethnic group Ethnic, racial and religious group Habit Health survey Health care survey Interview Juvenile Maintenance Mental health Panel study Qualitative research Quality of life Questionnaire Race Reduction Satisfaction Smoking cessation Smoking-habit Reinforcement Withdrawal syndrome 	<ul style="list-style-type: none"> Addict Behavior Cessation Dependence First Focus group Habit/habits HRQoL Global impression Initiate/initiation Interview Maintain/maintenance Patient reported/patient-reported Predict/predictive Predictor Prefer/preference Qualitative Quality of life/QoL Questionnaire Quit/quitting Reduce/reduction Start Survey Tool

NOTE: The BIOSIS® databases began using MeSH® terms in 1999. QoL = Quality of life, HRQoL = Health-related quality of life.

2. Search Parameters and Limits

The literature search was restricted to the parameters and limits presented in Exhibit 2.

Exhibit 2. Literature Search Parameters and Limits

Search Parameters	Limit (Exclusions)	
<ul style="list-style-type: none"> • January 1, 1993 to present • Humans only • English • US only • Original research studies 	<ul style="list-style-type: none"> • Editorials • Letters • Case reports • Lectures • News • Comments/commentaries 	<ul style="list-style-type: none"> • Legal cases • Newspaper articles • Technical reports • Review articles • Animal studies • Studies outside of the US

B. Literature Selection

Article selection occurred in two stages. First, two independent reviewers reviewed each downloaded title and abstract to determine relevance. Next, articles meeting the inclusion and exclusion criteria were reviewed and critically evaluated.

1. Article Inclusion and Exclusion Criteria

Upon completion of the literature search, all abstracts were downloaded into a Literature Tracking Database (LTD). The article abstracts were reviewed to determine relevance to menthol smoking initiation, cessation, or other similar behavior. In addition, article abstracts from the NCI menthol bibliography were saved into a separate spreadsheet and reviewed to determine their relevance. Finally, any articles identified by Lorillard were added to the bottom of the “Literature Search” spreadsheet and reviewed to determine relevance. An “Articles Evaluated” spreadsheet was created to list the articles selected for evaluation. Appendix 2 summarizes the contents of the LTD spreadsheets.

Each abstract downloaded into the LTD was reviewed individually by two team members to determine relevance and if the full-text article should be retrieved. Articles that were clearly not relevant based on information provided in the abstract were not retrieved for review. Articles that clearly met the inclusion/exclusion criteria (Exhibit 3) based on reviewing the abstract were categorized as “Evaluate” to identify those appropriate for review and methodological evaluation.

Articles that required evaluation of the full text to determine if the article should be reviewed were categorized as “Article Review Required”. All articles identified for evaluation or further review were retrieved by Lorillard and sent to Covance for evaluation. The same criteria were applied to these articles to determine their relevance. Any disparities in recommendations to review were discussed between the reviewers and, if necessary, resolved with the help of a third reviewer. Studies ultimately excluded from the review are reported in the LTD along with the reasons for exclusion.

Exhibit 3. Article Inclusion and Exclusion Criteria

Inclusion	Exclusion
Includes an evaluation of menthol cigarette smokers	Review articles, meta-analyses, editorials, letters, lectures, case reports, news, commentaries, legal cases, newspaper articles, technical reports and conference abstracts ⁱⁱⁱ
Study location(s) in the US	Articles exclusively on smokeless tobacco products
Evaluates smoking initiation and/or smoking cessation	Articles outside the realm of menthol cigarette smoking initiation or cessation behaviors
Published during or after 1993	Articles that do not report menthol findings
	Animal studies

C. Article Summary and Assessment of Methodological Quality

There were two assessments of each article meeting the inclusion criteria.

1. Article Summary

Key elements of each study were extracted from each of the articles meeting the inclusion and exclusion criteria and summarized via data extraction tables. These tables were constructed independently of the methodological quality assessment and were not formally evaluated. The purpose of the data extraction tables is to provide the audience of this report with an understanding of the key elements of each article, such as details about the authors, study design, population, interventions, outcomes, and findings and limitations. Three unique data extraction tables were created; one to summarize articles related to initiation, one to summarize articles related to cessation, and one to summarize articles related to other smoking behaviors (i.e., dependence).

2. Assessment of Methodological Quality

Critical to this discussion and our review effort is the definition of quality. The methodological quality of each article was evaluated in parallel by at least two independent, trained researchers. These independent reviews were conducted in a “blinded” fashion such that each reviewer entered/completed their findings in a separate spreadsheet. This procedure served to minimize bias and maximize the likelihood of objective reviews.

The evaluation criteria used for the Agency for Healthcare Research and Quality’s evidence report on tobacco prevention, cessation and control were used in this study to evaluate the methodological rigor of each article.⁴¹ As such, two Methodological Review Criteria Checklists were created; one checklist for randomized controlled trial (RCT) studies (Appendix 3) and one for non-RCT studies (Appendix 4). Researchers on the study team agreed that comparing and contrasting study quality systems without differentiating among study types was likely to be less revealing or productive than assessing quality for RCTs and non-RCT studies independently.

Using the Methodological Review Criteria Checklists, each reviewer entered their findings into a separate spreadsheet. Each article received two quality ratings, as follows:

ⁱⁱⁱ Conference abstracts do not contain enough information for an appropriate evaluation. However, conference posters and/or PowerPoint presentations were considered.

1. An “Overall Methodological Quality” of the study as described in the article, and
2. A “Menthol Inferences” rating of the study, which was based on the ability to make inferences about smoking behaviors by menthol smoking status.

Reviewers rated the quality of each study from “Good” to “Poor” (“Good”, “Good to Fair”, “Fair”, “Fair to Poor”, and “Poor”).

Upon completion of the study review, the researchers compared results to identify any differences in findings. Disagreements between the reviewers were resolved through discussions among the team members and additional review of the article. Arbitration by another senior-level researcher was used to resolve any disagreements that remained following discussion by the quality assessment review team members.

D. Validity of Authors’ Discussion/Conclusions Based on Reported Findings with Respect to Menthol

In order to provide additional value to this report and additional information regarding the best available science with respect to the effects of menthol flavoring in cigarettes on smoking behaviors, researchers also evaluated the validity of the authors’ conclusions and/or interpretations of the study results. To do this, the researchers evaluated the following:

- whether the authors’ conclusions (or discussion points) regarding the impact of menthol on smoking behavior could reasonably be supported by the study findings, and
- whether the authors’ conclusions regarding the impact of menthol on smoking behavior reflect the totality of the study findings (i.e., were any findings under or over represented in the authors’ conclusions).

Researchers initiated this additional evaluation only for studies rated “Fair” or better based on the assessment of methodological quality. Researchers did not review studies receiving a “Fair to Poor” or “Poor” menthol quality rating, because, based on these ratings, no valid conclusions should be drawn from the data, especially as they related to menthol. This assessment was completed in a group working session, and group consensus was required before moving onto the next study. For each of these articles, the group determined whether any meaningful conclusions could be drawn. Section IX (Summary of Next Steps and Recommendations) elaborates on the suggested approaches to address information gaps.

E. Quality Review of Commonly Used Secondary Data Sources

Data from a number of population-based national (US) surveys have been used to explore initiation, cessation, and smoking dependency. In particular, several publications from the following four surveys have purported to evaluate self-reported smoking behaviors by adolescents and others to determine whether menthol affects smoking initiation and cessation:

- NSDUH,
- NYTS,
- NHANES, and

- NHIS.

It is important to ascertain whether these surveys contain items that allow for the investigation of the relationships between menthol and initiation or cessation behaviors. Furthermore, it is important to understand the differences in the questions asked between the different surveys to determine the impact that these differences could have on estimates related to menthol versus non-menthol smokers. Therefore, as part of our evaluation of the quality of information related to menthol flavoring and smoking initiation and cessation behaviors, we reviewed these surveys to evaluate whether these questions adequately address whether menthol in cigarettes affects smoking behaviors. We critically reviewed the survey items related to smoking and menthol cigarettes, including:

- smoking initiation behavior,
- smoking status,
- smoking “flavor” and brand preferences,
- smoking dependency, and
- smoking cessation behavior.

We developed a checklist, similar to those used for the reviews of the published literature to focus our survey review and identify any relevant survey questions prior to reviewing the content of any survey. When reviewing each survey, our goal was to determine what content was included, as well as the wording of the question and response options for these questions (Exhibit 4), as follows:

- determine which concepts were evaluated in each survey;
- for each concept identified, determine all relevant questions;
- for each question evaluated, evaluate whether the wording of the question and response options are clear or ambiguous from the viewpoint of the target responding audience (e.g., school-aged children, adults, across all age groups, ethnic groups, etc); and
- consider whether appropriate conclusions about menthol cigarette smoking initiation and/or cessation trends could be extrapolated by analysis of findings from these questions.

Exhibit 4. Survey Items Considered

Category	Items Gauged by Covance
Initiation	Initiation age
	Type first tried
	Regular smoking vs. experimentation
	More than 1 type tried when began "experimenting"
	Type of cigarette tried (i.e., menthol/non-menthol) at initiation
	Time smoking 1st type prior to trying another type
	How was first cigarette obtained?
	Number of cigarettes smoked within 30 days of initiation
	Cigarette types smoked within 30 days of initiation (% menthol vs. % non-menthol)
Smoking Status	Ever smoked
	Current smoker
	Former smoker

Category	Items Gauged by Covance
Smoking Flavor and Brand Preference	Cigarette type used when started smoking regularly
	More than 1 type ever smoked
	More than 1 type currently used
	Current cigarette type preferred
	Age when started smoking current cigarette type
	Cigarette types smoked (% menthol vs. % non-menthol)
Smoking Dependency	Age when started smoking regularly
	Number of cigarettes smoked daily
	Time of first cigarette smoked each day
Cessation	Quitting/cessation attempts
	Number of quit attempts
	Age during each quit attempt
	Cigarette type smoked prior to quitting identifiable?
	Quit method(s) used (e.g., nicotine replacement, pharmaceuticals, counseling, etc.)

These items were reviewed for clarity and the suitability of the item to draw inferences regarding menthol cigarette smoking initiation and cessation behaviors.

IV. RESULTS: ARTICLES REVIEWED

We screened a total of 473 article titles and abstracts obtained from the NCI bibliography (n = 341), the independent literature search (n = 124), and recommendations from Lorillard (n = 8). Fifty-two full text publications were obtained, and we reviewed the methodological quality of 38 articles (Appendix 5). Seven of the 38 studies were RCTs; however, four of these seven included study design components of both a RCT and non-RCT. The vast majority of studies we evaluated were non-randomized and were comprised of convenience samples. Appendix 6 summarizes how each article was classified (initiation, dependence, and/or cessation study).

The sections below present the breakdown of these 38 studies as they relate to initiation, other smoking behaviors, and cessation. Please see Appendix 7 for a summary of each article and additional details.

A. Smoking Status Definitions Used

Table 4.1 summarizes the definitions used for subject recruitment and/or to identify individuals as smokers in the studies reviewed and evaluated. Among those studies that provide definitions for the smoking variables, “Current smoker” or “Smoker” (including current established smoker), were the most commonly defined terms. A current smoker was most often defined as someone smoking at least one cigarette per day.

Table 4.1. Definitions of “Smoker” Used in Reviewed Studies

Definition	Number of Studies	First Author
Smoked \geq 1 CPD	8 studies	Ahijevych, K. 1993 Appleyard, J. 2001* Hersey, J. 2006* Muilenburg, J. 2008* Muscat, J. 2002 [†] Okuyemi, K. 2004* Pollak, K. 2002 [‡] Muhammad-Kah, R. 2010 [†]
Smoked \geq 5 CPD	4 studies	Ahijevych, K. 2002 [†] Allen, B. 2007 [†] Cropsey, K. 2009 Muscat, J. 2009
Smoked \geq 10 CPD	2 studies	Okuyemi, K. 2003 Moolchan, E. 2006
Smoked average of \geq 20 CPD	1 study	Rose, J. 2004
Smoked \geq 100 cigarettes in life	4 studies	Fagan, P. 2007 Gundersen, D. 2009 Hooper, M. 2011 Wackowski, O. 2007*
Smoked on at least 1 day in past 30 days	2 studies	Kaufman, N. 2004 DiFranza, J. 2004 [§]

NOTE: In some cases, the authors used smoking status as part of the study inclusion/exclusion criteria.

CPD = Cigarettes per day

* in past 30 days (NYTS definition)

[†] in past year

[‡] in past 7 days

[§] termed “monthly smoker”

Fifteen of the 38 studies reviewed did not specify the smoking status of study participants. Of the studies providing a smoking status, most only provided one definition.¹⁰⁻²⁴ Other definitions related to smoking status, such as continuing smoker, heavy smoker, light smoker, and ever smoker are summarized in Appendix 7a. Former and ex-smokers did not have as consistent a definition as smokers. Ex-smokers were defined as not having smoked in a set time period (both six months and one year were used). Former smokers were defined as those not currently smoking at all. Three of the studies used carbon monoxide (CO) assessment to confirm smoking abstinence, however only two of the three provided a level to indicate abstinence.

B. Use of Menthol Cigarettes: Independent, Control or Dependent Variable

For any study to adequately assess the impact of menthol cigarette smoking on smoking behaviors, including initiation, cessation, and other dependence behaviors, it must be designed with that objective in mind. In order to draw conclusions regarding the impact of menthol cigarette smoking, menthol smoking status must be an independent (or control) variable. Ideally, menthol smoking status would be the primary independent variable in the study.

Table 4.2 below, as well as Appendix 7b, summarizes how menthol smoking status was utilized, that is as the independent, control, or dependent variable, in each of the reviewed studies. Of the 38 studies reviewed, eight included menthol cigarette smoking status as a dependent variable, and two studies did not include menthol status as a variable at all. One of these two studies (Ahijevych, 1993) summarized menthol and non-menthol smoking status at baseline, but the authors did not use this as a variable in the data analysis.⁴² The other study (Kreslake, 2008) attended toward editorializing, and no primary analyses were conducted using menthol status.²⁵ Given the design of these 10 studies, no conclusions can be drawn regarding the impact that menthol smoking status may have on smoking behaviors.

Less than 70 percent of the studies reviewed (26/38) included menthol smoking status as an independent variable. We also identified eight studies where menthol cigarette smoking was analyzed either as a control variable or factor held constant to test the relative impact of another independent variable, and two studies analyzed menthol as both an independent and a control variable.

Results of analyses where menthol smoking status is the control variable are more useful than those in which menthol cigarette smoking status is a dependent variable; however, they cannot necessarily be used to draw conclusions regarding causality.

**Table 4.2 Evaluation of Menthol vs. Non-Menthol Cigarette Smokers:
 Number of Studies and First Authors**

Smoking Behavior	Menthol Independent Variable	Menthol Control Variable	Menthol Dependent Variable
Initiation [†]	Two: Hersey, 2006; DiFranza, 2004	Zero	One: Appleyard, 2001
Dependence or Other Behavior*	Nine: Ahijevych, 1999 [‡] ; Ahijevych, 2002; Bover, 2008; Collins, 2006; Muilenburg, 2008; Muhammad-Kah, R. 2010; Muscat, 2009; Okuyemi, 2003; Wackowski, 2007	Three: Ahijevych, 1999 [‡] ; Li, 2005; Moolchan, 2006	Six: Allen, 2007; Hooper, 2011; Hymowitz, 1995; Kaufman, 2004; Kreslake, 2008; Moolchan, 2004
Cessation	Fifteen: Bover, 2008; Cropsey, 2009 [‡] ; Fagan, 2007; Foulds, 2006; Fu, 2008; Gandhi, 2009; Gundersen, 2009; Harris, 2004; Hyland, 2002; Murray, 2007; Muscat, 2002; Okuyemi, 2003; Okuyemi, 2004; Okuyemi, 2007; Pletcher, 2006	Five: Berg, 2010; Cropsey, 2009 [‡] ; Li, 2005; Pollak, 2002; Rose, 2004	One: Hymowitz, 1995

[†] Kreslake, 2008 was more of an editorial

[‡] Menthol both an independent and control variable

* Ahijevych, 1993 only used menthol to describe baseline characteristics

C. Quality of Articles Reviewed

As shown in Figures 4.1a - 4.1c, 68 percent of the studies reviewed received overall quality ratings of “Good”, “Good to Fair”, or “Fair”. However, when evaluating the methodological quality of the studies with regard to the ability to make inferences about the impact of menthol cigarette use on smoking behaviors, the quality ratings were quite different. Only 40 percent of the studies were rated as “Good”, “Good to Fair”, or “Fair”, while 58 percent of the studies reviewed received a “Poor” rating. The figure suggests that while the studies are not necessarily

poorly designed to assess the primary study questions, they are poorly designed with regard to secondary objectives or subsequent secondary analysis of the impact of menthol on smoking behaviors. Appendices 8a – 8c and 9a – 9d provide additional details on the quality ratings for each article. In addition, Appendix 10 provides a summary of inconsistencies inadvertently noted when reviewing studies.

Figure 4.1a Rating on Overall Study Quality and Ability to Make Menthol Inferences

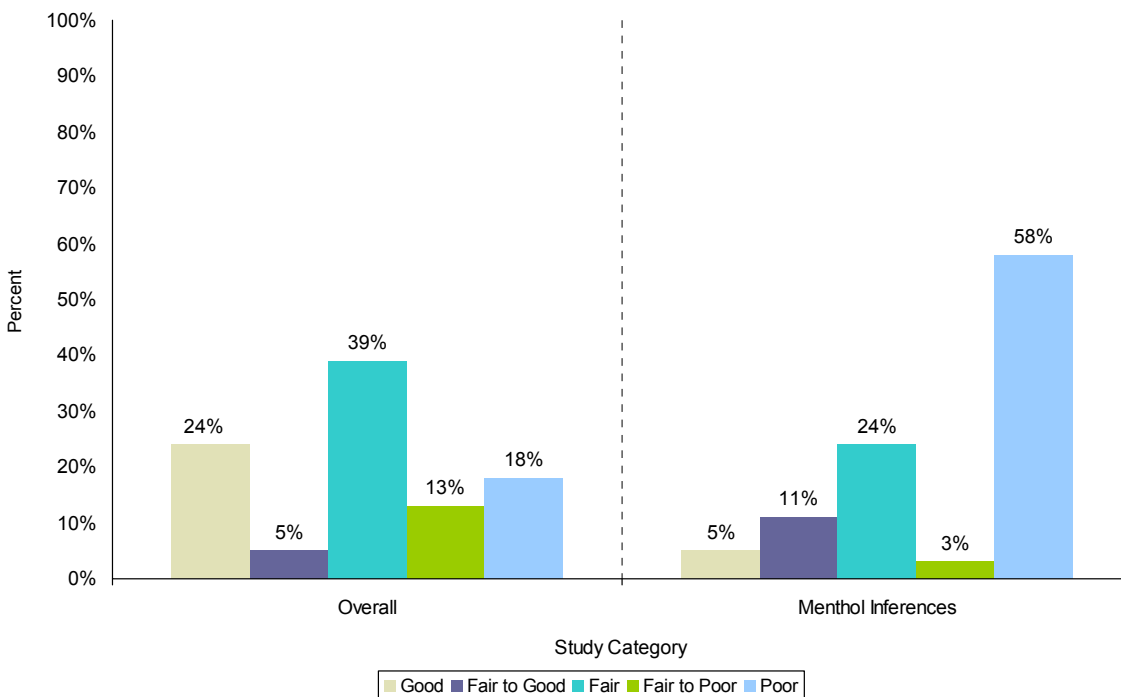
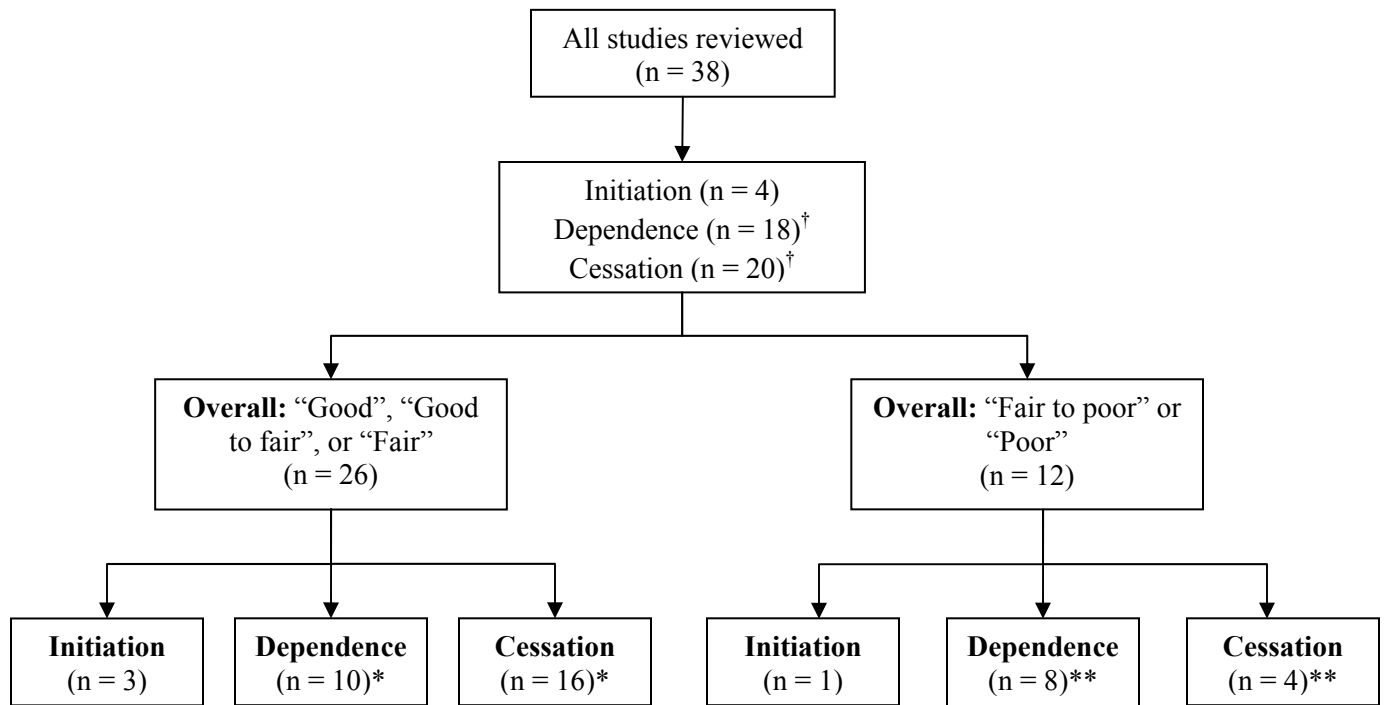


Figure 4.1b Summary of All Studies Reviewed: Overall Quality

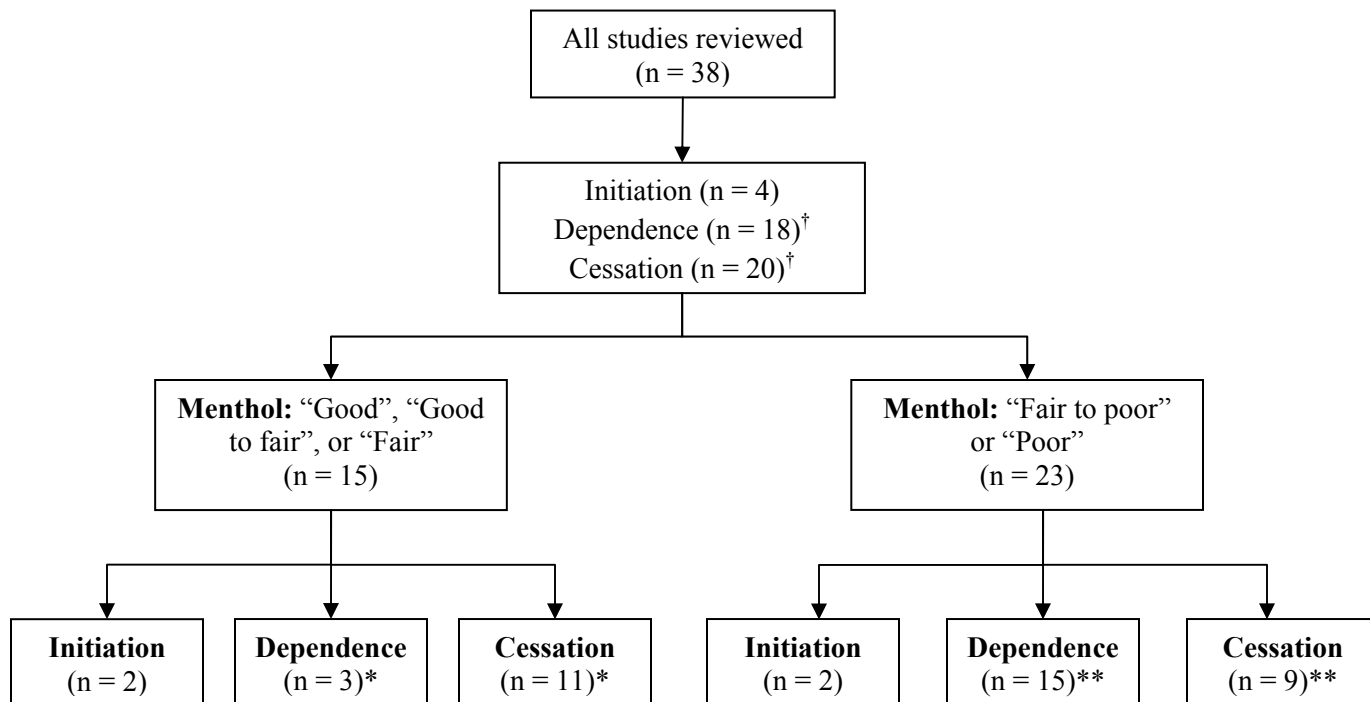


† Four studies discuss both dependence and cessation, and are counted in both totals

* Three studies evaluated under dependence and cessation

** One study evaluated under dependence and cessation

Figure 4.1c Summary of All Studies Reviewed: Menthol Inferences Quality



† Four studies discuss both dependence and cessation, and are counted in both totals

* One study evaluated under dependence and cessation

** Three studies evaluated under dependence and cessation

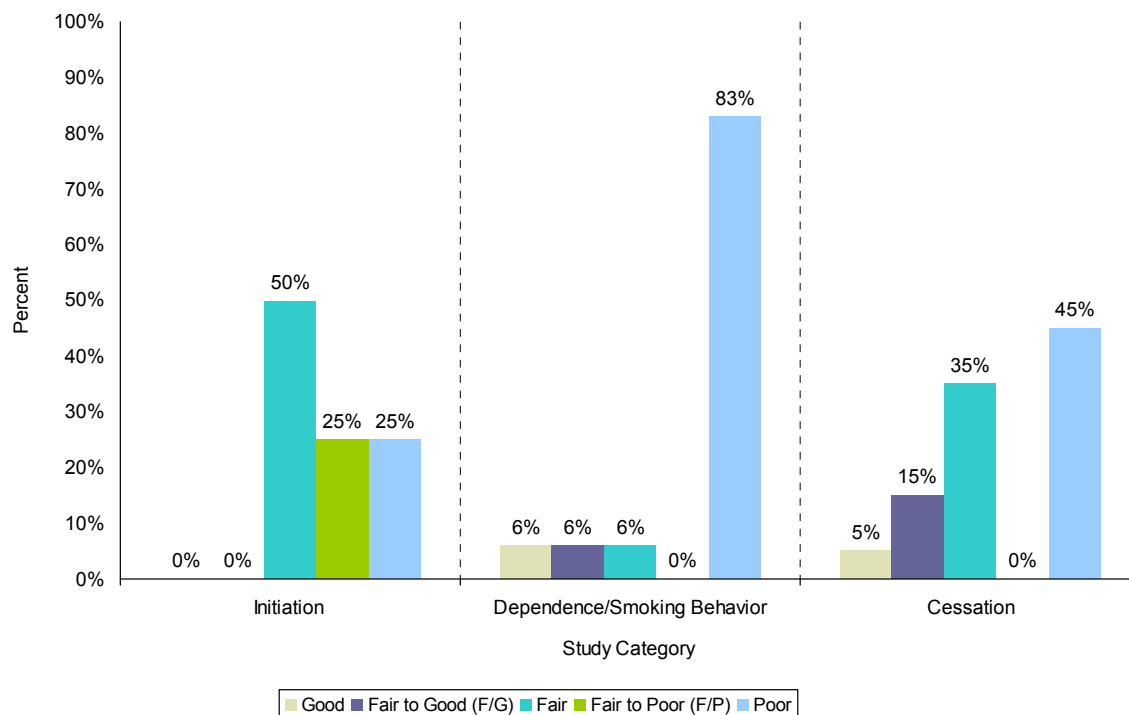
Figure 4.2 provides a summary of the study quality ratings related to the ability to make inferences on specific smoking behaviors: initiation, other (e.g., dependence) behaviors, and cessation.

Of the four studies reviewed on smoking initiation behavior, two (50%) were “Fair” while the other two (50%) were either “Fair to Poor” or “Poor” in terms of the ability to make menthol inferences.

Twelve percent (12%) of the dependence/smoking behavior studies received a “Good” or “Good to Fair” rating, six percent earned a “Fair” rating, while the remaining 83 percent received a “Fair to Poor” or “Poor” rating.

Only five percent of smoking cessation studies earned a rating of “Good”, while 80 percent of the cessation studies reviewed received a “Fair” or “Poor” rating related to ability to make menthol inferences.

Figure 4.2 Rating on Ability to Make Menthol Inferences



Additional details supporting the quality ratings, particularly related to ability to make inferences regarding menthol, are discussed in the following sections. Within each section, studies are presented by their quality rating pertaining to the ability to make inferences regarding menthol based on the study methods.

D. Initiation Studies

Four of the 38 articles contained significant content related to initiation behaviors: Appleyard et al (2001), DiFranza et al (2004), Hersey et al (2006), and Kreslake et al (2008). Two of these articles (Appleyard et al.¹ and Hersey et al.¹⁶) analyzed the NYTS and were thus based on national probability samples of youth in the US. The analyses reported by DiFranza and colleagues were based on a longitudinal cohort study of seventh-grade students.² Finally, Kreslake et al. reported on a content analysis of tobacco industry documents relating to the sensory perceptions, preferences, and attributes of menthol smokers.²⁵ We did not identify any initiation-related articles based on data from a RCT.

1. “Fair” Menthol Rating

Using the 2000 NYTS, Appleyard and colleagues (2001) examined the smoking prevalence, cigarette type preference, and age at smoking initiation of Asian American and Hawaiian/Pacific Islander youth in middle and high school.¹ “Current smokers” were defined by the authors as those who reported smoking at least one cigarette on at least one of the past 30 days, while menthol preference was determined by the item “Is the brand of cigarettes that you usually

smoked during the last 30 days mentholated?” Age at initiation was determined by the item “How old were you when you smoked a whole cigarette for the first time?” Estimates and 95% confidence intervals were provided for current smoking, age at smoking initiation, use of menthol cigarettes, and tobacco brand preferences.

The authors report that by the last year in high school, about one-third of Asian American youth smoked and that 60 percent of those youth reported that their usual brand was menthol.¹ The authors further indicate that nearly 40 percent of Asian American respondents who currently smoked tried their first cigarette in middle school.

When the quality of the research presented in the article is considered in light of the authors’ stated objectives to investigate the association between race and ethnicity and smoking uptake and other smoking behaviors, the reviewers rated the overall quality of the article as “Good”. The reviewers noted that the study’s measures were sound and that the analysis was based on a nationally representative sample of Asian American youth. However, when the appropriateness of the study is considered in light of its ability to draw inferences regarding menthol and initiation behaviors, the reviewers provided a “Fair” rating based on the study design and statistical methods, as follows:¹

1. the data used were not designed to examine the association between menthol flavoring and initiation behavior and does not purport to do so; and
2. as a purely descriptive investigation, this study was not designed to evaluate causal relationships and thus no causal inferences can be made based on the reported results.

In another study related to initiation, DiFranza and colleagues (2004) examined whether youths’ recalled response to first smoking experience was predictive of future nicotine dependence and whether reactions to first smoking experience were influenced by cigarette type smoked.² The research reported in this article was based on the Development and Assessment of Nicotine Dependence in Youth (DANDY) study, a longitudinal study of a cohort of 679 seventh grade students residing in two small cities in central Massachusetts. The final study sample was composed of the 237 DANDY study participants who had reported inhaling a cigarette.²

Participants were interviewed regarding their smoking experiences and smoking behaviors three times annually over a three year period (1998-2000). The study’s survey instrument included items assessing current and prior tobacco use, including dates of first puff and first inhalation, as well as an assessment of nicotine dependence using the 10-item Hooked on Nicotine Checklist (HONC). Starting with the sixth of eight interviews, participants also were asked to recall their first smoking experiences. Specifically, participants were asked to indicate a range of sensations or feelings associated with these experiences, such as whether it felt good or bad, and whether they experienced symptoms broadly characterized as irritation, nausea, dizziness, or relaxation.²

Results reported in the article indicate that reactions to first smoking experiences were unrelated to cigarette brand or mentholation and that relaxation, nausea, and dizziness in response to first smoking experience were predictive of future nicotine dependence. The strongest predictor of future dependence was relaxation in response to first smoking experience. It should be noted that only about half of 237 participants who had reported inhaling a cigarette were able to recall

the brand, strength, or mentholation status of their first cigarette, thus all analyses involving these variables were based on sub-samples of youth from the larger study (e.g., 120 of the 237 participants were able to recall whether their first cigarette was mentholated).²

Reviewers rated the overall quality of the research presented in this article as “Fair.” The reviewers noted that the study’s strengths included a longitudinal design as well as clear and sound measures; however the exceptionally small sample of students able to recall the mentholation status of their first cigarette limited the generalizability of the results. When the appropriateness of the study was considered in light of its ability to draw inferences regarding menthol and initiation or cessation behaviors, the reviewers also provided it a “Fair” rating. The primary reasons for this rating were threefold:

1. the research reported in the article was not explicitly designed to examine the association between menthol flavoring and initiation or cessation behavior;
2. the study’s independent variables rely on the memory of the respondents, leading to the potential of recall bias; and
3. only half of the 237 subjects could recall the mentholation status of their first cigarette, thus all analyses using this variable were based on a subset of an already small study sample.

2. “Fair to Poor” Menthol Rating

Using the 2000 and 2002 NYTS, Hersey and colleagues (2006) examined the prevalence of menthol and non-menthol smoking among current smokers, as well as the association between cigarette type and nicotine dependence.¹⁶ Response rates for the 2000 and 2002 surveys were 84% and 75%, respectively. Data were weighted for non-response and the probability of selection. The analyses reported in the article were based on the subset of youth who reported smoking a cigarette on at least one of the previous 30 days and who indicated that they had a usual brand of cigarettes. Youth were classified as menthol or non-menthol smokers based on their responses to two questions: (1) “During the past 30 days, what brand of cigarettes did you usually smoke?” and (2) “Is the brand of cigarettes that you usually smoked during the past 30 days mentholated?”. The six-item Nicotine Dependence Scale for Adolescents (NDSA) was used to measure dependence.¹⁶

A sizeable proportion (22%) of respondents were excluded from the analysis due to non-response or misclassification of cigarette preference (i.e., some respondents indicated that they were menthol smokers but identified an exclusively non-menthol brand as their usual type). Taking this misclassification into consideration, the researchers conducted a series of sensitivity analyses employing different definitions or classification schemes of menthol smoking (for example, predominant menthol smokers, inconsistent menthol smokers, etc.); reported results of these analyses considering alternative definitions were largely consistent with those observed based on the primary definition employed.¹⁶

Results indicate that menthol use increased significantly among regular smokers between 2000 and 2002. This finding was observed regardless of the definition of menthol smoking used. Results also indicated that the proportion of students who smoked menthols was higher among middle school students who had been smoking for less than one year compared to similar

students who had been smoking for more than one year. Regarding dependency, the authors report that youth who regularly smoked menthol cigarettes had higher scores of nicotine dependence and were less likely to report that they had serious intentions of quitting compared to youth who did not regularly smoke menthol cigarettes. With these results, the authors conclude that menthol cigarettes are a starter product that may be associated with uptake among youth and may be more difficult to quit than non-menthol cigarettes.¹⁶

Initially, the Hersey article was rated by both reviewers as “Good to Fair” overall, and in its ability to make reasonable menthol inferences based on the study methods.¹⁶ However, while writing this report, reviewers identified several inconsistencies, which prompted a re-evaluation. Based on this re-evaluation, reviewers agreed the overall quality of the research presented in this article was “Fair to Poor”, at best. Strengths of the study identified by reviewers included the study’s large and (initially) nationally representative samples, extensive sensitivity analyses to investigate the impact of alternative definitions of menthol smoking on study outcomes, and appropriate statistical testing for the analytic objectives. However, the updated rating for the article overall, and related to menthol inferences, was “Fair to Poor” for the following reasons:

1. overall, the study suffered from significant loss of sample from multiple sources, including loss due to non-response to the survey (overall response rates were 84% in 2000 and 75% in 2002) and loss due to indeterminate menthol status (22.2%);
2. the items listed in Table 2 from the NDSA reflect the items in the NYTS 2002 version, but are not consistent with the questions listed in the 2000 NYTS version, which was also evaluated as part of the study;
3. researchers question the use of the median rather than mean NDSA score in Table 5;
4. it is unclear what data were evaluated to determine menthol smoking status in Table 1 (for example, was the 2002 NYTS data used?); and
5. the study’s cross-sectional design does not allow for the attribution of causality.

3. “Poor” Menthol Rating

Finally, Kreslake et al. (2008)²⁵ report on a content analysis of 440 tobacco industry documents to investigate the relationships between sensory perception, attitudes, preferences, and patterns of cigarette use among menthol smokers. Documents reviewed for the study were obtained from the Tobacco Documents Online, the British American Tobacco Document Archive, and the Legacy Tobacco Documents Library. To identify the documents for review, the authors employed a snowball sampling design using an initial set of key terms including “menthol,” “sensory,” “attributes,” and “perception” to identify additional search terms to be used. The authors report inclusion of all documents, including reports, correspondence, and results of internal research by product development and marketing departments that met the study’s search criteria.²⁵

Through their content analysis, the authors identified two types of menthol smokers: 1) those who cannot tolerate the harshness and irritation associated with smoking non-menthol cigarettes, and 2) those seeking out the specific menthol flavor and associated physical sensation. The authors contend that the first group may include a large portion of occasional smokers and young people, while the latter category has historically been disproportionately African American and male.²⁵

Reviewers rated the overall quality of the research presented in this article as “Fair”. Of note, this study included a range of documents based on a wide-variety of investigations in its sample. A noted weakness of the article (rather than the research per se) was the somewhat ambiguous description of the sampling procedure for the content analysis. When the quality of the study design was considered in light of its ability to draw inferences regarding menthol and initiation or cessation behaviors, the reviewers provided a “Poor” rating. The primary reasons for this rating were twofold:

1. the study focused on menthol smokers only, thus no comparisons could be made between menthol and non-menthol smoking; and
2. the study was not designed to test the relationship between menthol flavoring or menthol smoking and initiation or cessation.

E. Dependence/Smoking Behavior

Of the 18 studies related to smoking dependence or other behaviors, only one study (Moolchan, 2006³) was evaluated as “Good” in its ability to address questions related to menthol. One study was rated as “Good to Fair”, one was rated as “Fair”, and the remaining 15 were evaluated as “Poor”. Many of these studies are discussed below in order to provide summary-level explanations for the evaluations of the reviewers.

1. “Good” and “Good to Fair” Menthol Rating

Moolchan (2006) compared the metabolism of cotinine among Caucasian and African American adolescents.³ Measures included 3 hydroxycotinine/cotinine ratios (3HC/COT) and cotinine/cigarettes per day (COT/CPD) ratios. Consistent with previous research, it was observed that despite African Americans’ smoking fewer CPD, Fagerström Test for Nicotine Dependence (FTND) scores were similar to those of whites. Additionally, the results suggest differences in metabolic disposition independent of menthol. The study was well-designed and utilized sound measures, leading to a “Good” rating. However, the small sample limits the generalizability of the results.

Data for the one study rated as “Good to Fair” were obtained from a poster presentation (Muhammad-Kah, R. 2010)⁴, as well as a review of a publication by Roethig et al. (2009)⁴³ and a presentation by Sakar et al. (2010)⁴⁴ in order to better understand the underlying methods. Based on the initial review of the poster, both reviewers suggested a “Fair to Poor” rating for this study because the statistical and other methods were not described in sufficient detail. It was not clear from the poster alone if menthol status was validated in any way, and the reviewers questioned the appropriateness of the model used. However, the reviewers then went back to the “source” publications (Roethig et al. ,2009⁴³, Sakar et al., 2010⁴⁴) that provide more clarity on the methods of the overall study. Following this, the rating for the study by Muhammad-Kah was revised to “Good to Fair”, both overall and in terms of it’s ability to make menthol inferences.

The analysis was based on a stratified, cross-sectional, multicenter study (39 sites in 31 states) of 3,585 adult cigarette smokers and 1,077 nonsmokers. As suggested by the presentation by Sakar, smoking behavior was a secondary study objective.⁴⁴ Specifically, “eligible subjects did not use

a different brand of cigarette outside their regular brand's tar delivery category for more than 10% of their daily cigarette consumption nor used any nicotine-containing products other than the manufactured cigarettes for the three months prior to the study".⁴³ Reviewers provided a rating of "Good to Fair" to Muhammad-Kah (2010) because the study design ensured that subjects used a consistent cigarette brand for the three months prior to the study.⁴

2. "Fair" Menthol Rating

The other study receiving a "Fair" rating was conducted by Okuyemi et al. (2003).⁵ This study was a secondary analysis of data from a RCT evaluating the efficacy of sustained-release bupropion in a cohort of 600 African American menthol (n = 471) and non-menthol (n = 129) smokers. Although the proportion of menthol smokers with a seven-day point prevalence abstinence at six weeks was significantly less compared to non-menthol smokers (p=0.006), no significant differences between the groups were observed by six months of follow-up.

Initially, the reviewers gave the Okuyemi (2003) study a "Good" overall quality rating related to menthol inferences.⁵ However, as the researchers were revising this draft study report, inconsistencies in the follow-up timeframes and reported results were noted. Using the information provided in the methods section, subjects began receiving placebo or bupropion one week prior to when they returned to the clinic to set a target quit date, which was considered "Week 0". Therefore, subjects received their medication at "Week -1". Following this, measures of cessation were taken at Weeks 1, 3, 6 and 26; however, because the target quit date is selected by subjects, the time between the start of treatment and the intended quit date is variable. Depending upon the target quit date selected, relapse may be measured for one patient, while cessation is being measured for another subject who chooses a different quit date. Reviewers also noted that Okuyemi et al. (2003) do not provide the distribution of quit dates, nor do they provide the proportion that actually quit by the selected quit date. Given these limitations, the reviewers agreed on a "Fair" rating (at best).

3. "Poor" Menthol Rating

Allen and Unger (2007) conducted a cross-sectional study using a convenience sample of 432 adult African American smokers (296 menthol smokers and 136 non-menthol smokers) and concluded that social and cultural norms contributed to the preference of menthol cigarettes among African Americans (e.g. a belief that most African Americans smoke menthol cigarettes).¹⁸ This study employed a survey that consisted of a variety of non-validated, often single-item measures. Although the authors mention using the "Fagerström scale", they did not provide any further information such as whether they used one question or the entire scale, they did not discuss how the scale was analyzed, and did not provide a summary of the results. In addition, use of menthol cigarettes was assessed by a single question, "Is your current brand of cigarette menthol or non-menthol?" Other questions related to menthol and non-menthol cigarettes always asked about menthol first. Because it is not clear if the questions used had previously been validated, the order (menthol or non-menthol) can bias responses. Finally, a convenience sample was recruited, limiting the potential for this population to be representative. Therefore, raters gave this study a "Poor" quality rating related to menthol inferences.

Wackowski and Delnevo (2007) analyzed data from the 2004 NYTS to measure nicotine

dependence among “current established smokers” in grades 9 to 12.²⁶ However, the 2004 NYTS survey did not include a dependence scale. Instead, the authors evaluate dependence using four items from this survey. It is not clear if these four items have been validated, and therefore the ability to make inferences about menthol cigarettes and dependence behaviors is questionable. The authors also note that there were inconsistent responses among individuals between the two questions evaluating menthol cigarette use. For those individuals, the authors excluded their surveys. However, they do not indicate what impact this had to the overall sample size. In addition, the authors state that “Race/ethnicity was significantly associated with menthol smoking” (page 1968, 1st paragraph). However, the reader is unable to confirm this using the data provided in the article (e.g., no p-value reported).

In another study, Bover et al. (2008) described the characteristics of a convenience sample of 2,312 smokers seeking cessation treatment who wake up at night to smoke.²⁷ Data were collected at 4 and 26 weeks after participants’ target quit date had been set. Although smoking menthol cigarettes was included in a model of cessation, the key variable assessed was whether night smoking was a predictor of relapse. Two of the key reasons this study received a “Poor” rating with regards to menthol inferences are presented below:

1. the study was not designed to assess relationships between menthol and behavior, and
2. by 26 weeks, the attrition rate was approximately 40 percent.

Collins and Moolchan (2006) studied a convenience sample of 572 adolescent smokers (531 menthol and 41 non-menthol) recruited by telephone for a cessation treatment study. The purpose of the article was to examine differences in consumption and dependence of menthol and non-menthol smokers.²² The sample was evenly split between African Americans and whites. A key finding was that despite similar FTND scores menthol smokers had a shorter time to first (TTF) cigarette than did non-menthol smokers. Differences in outcomes by race were not addressed. This study received a “Poor” rating because:

1. the primary measure is based upon a single question from the FTND, TTF cigarette.
2. demographic differences between the menthol/non-menthol groups not tested;
3. the small sample of non-menthol smokers (41 vs. 531) limits the ability to make comparisons.

A study based upon the results of three surveys of adolescents (Kaufman et al., 2004) focused on changes in brand preferences between 1989 and 1996.²⁴ This article was rated as “Poor” in relation to menthol inferences because:

1. the article does not describe their model selection process;
2. it is not clear that the authors controlled for design effects (sampling frame) in the model;
3. the study did not relate menthol to any smoking behavior; and, therefore,
4. the study did not adequately address key questions associated with menthol smoking.²⁴

Similarly a study based on a review of industry documents, laboratory tests and data from the NSDUH (Kreslake, 2008) concluded that tobacco companies manipulate the menthol content of

cigarettes for various purposes which may include promoting initiation.⁴⁵ This article was less a scientific study of the key questions than an editorial, and therefore was rated as “Poor”.

Screening data from 10 of 22 communities in the Community Intervention Trial for Smoking Cessation (COMMIT) trial (Hymowitz et al., 1995) suggested that blacks, Puerto Ricans, and females, the youngest smokers, those with higher income, and those who smoked fewer cigarettes were associated with a preference for menthol.⁴⁶ The primary objective of this study was to describe the relationship of ethnicity with several response variables, including menthol preference, while controlling for other smoking behavior variables (such as number of CPD and age started smoking). However, the authors do not describe the question(s) asked related to menthol smoking, limiting the ability to make any conclusions about menthol vs. non-menthol cigarette smoking. Thus, this study received a “Poor” quality rating.

Moolchan (2004) also reported data from a telephone survey of 1,273 youth. Data on menthol preference were obtained for 622 participants, of which 593 teens identified themselves as African American (n = 271) or white (n = 322).⁴⁷ The overall preference for menthol in this sample was 93.7%; the proportion of preferring menthol varied by race, with 98.5% of blacks preferring menthol compared to 89.8% of whites. Reviewers were concerned with the unusually high proportion of whites preferring menthol in this study and noted that geography or cultural factors specific to the study sample (i.e., selection bias) may have influenced these results. Additionally, it was not clear from the article why data on smoking preferences was obtained for only 622 of the 1,273 youths in the telephone interview. Given these concerns and limitations, the quality of this study was rated to be “Poor”.

The effects of menthol on nicotine dependence, tobacco exposure, and NNAL Glucuronidation were investigated by Muscat et al. (2009) in a cross-sectional study of 525 African American and white volunteers.²⁰ Some of the results of this study simply replicated what is already known, such as the findings that African Americans were more likely to smoke menthol products and whites smoke more CPD, whether mentholated or not. Menthol was not a significant predictor of daily cigarette consumption or heavy smoking. When race-specific levels of smoking biomarkers were considered, there were no differences by menthol or non-menthol smokers. Despite several limitations, Muscat et al. concluded that menthol was not associated with a higher exposure to smoke carcinogens.²⁰

The “Poor” menthol inference quality rating was given because the study did not control for the menthol content variation by brand and the results may not be generalizable to all smokers (e.g. light smokers). Finally, although one of the goals of the study was to evaluate nicotine dependence, the authors suggest that the FTND was administered to 278 of the 525 subjects. However, data shown in the tables (particularly Table 3, page 38) suggest that as many as 348 participants completed the FTND. These inconsistencies make the ability to draw firm conclusions questionable.

Using a convenience sample of 187 African American women who largely smoked mentholated cigarettes, Ahijevych et al. (1993) investigated a model of nicotine dependence that included coping, positive outcome expectancies, number of CPD and interest in quitting.⁴² Subjects completed a written questionnaire that assessed nicotine dependence and positive outcome

expectancies of cigarette smoking. Additionally, saliva samples were collected to confirm smoking status. Because this study was based on a convenience sample, there are limitations to the generalizability of the study results. Furthermore, the authors did not define “daily cigarette smoker” or “serious intention to quit” in the article. Additionally, the authors did not control for demographic characteristics in their regression models. Finally, and most importantly for present purposes, the study did not assess the relationship of menthol smoking on smoking behaviors and thus received a rating of “Poor”. Two additional studies by Ahijevych et al. also received a “Poor” rating regarding their ability to address questions related to the impact of menthol on smoking behaviors.^{17, 21}

F. Cessation

Table 4.3 summarizes the cessation definitions used (when identified). In addition, Appendix 11 summarizes the definitions of cessation and menthol cigarettes used by author.

Table 4.3. Summary of Cessation and Recent Quit Attempt Definitions Used

Measures of Cessation, Recent Quit Attempts or Abstinence	Author(s)
Salivary cotinine–verified self-reported cessation at Week 26	Berg, 2010
Did not smoke at least 1 cigarette each day for the preceding year	Muscat, 2002
Smoked 100 cigarettes in a lifetime and now smoking “not at all”	Gunderson, 2009
“Have you smoked any cigarettes in the last 6 months?”	Hyland, 2002
Self-report abstinence in previous 6 months (8 year follow-up)	Li, 2010
Self-report abstinence (at annual visit)	Murray, 2007
Sustained cessation (no current smoking in the past 2 times examined). Measured at 2, 5, 7, 10, and 15 years follow-up	Pletcher, 2006
7-day point prevalence smoking abstinence	
At current time	Fu, 2008
4 weeks	Foulds, 2006; Gandhi, 2009
6 weeks	Okuyemi, 2003
7 weeks	Harris, 2004
3 months	Bover, 2008; Cropsey, 2009
6 months (26 weeks)	Cropsey, 2009; Foulds, 2006; Gandhi, 2009; Okuyemi, 2003; Okuyemi, 2007
12 months	Cropsey, 2009
Measures of Recent Quit Attempts	
“How many times during the past 12 months have you stopped smoking for 1 day or longer because you were trying to quit...?”	Fagan, 2007; Hymowitz, 1995
Number of prior quit attempts of at least 24 hours duration	Pollak, 2006
Number of lifetime quit attempts, time since/duration of most recent quit attempt, and duration of longest ever quit attempt	Okuyemi, 2004
“Have you tried/made any attempts to quit smoking in past 2, 3, 5 years?”	Pletcher, 2006

Note: Although the article by Rose and Behm (2004) was reviewed under the “Cessation” category, the article focuses on the pre-cessation period and therefore is not discussed in the table above.

Based on the methods described, seven cessation studies received a “Good” overall quality rating.^{9, 12-15, 29, 48} However, only one of these studies also received a “Good” menthol rating.¹⁵ For the remaining studies, the quality ratings related to their ability to make inferences related to menthol use ranged from “Good to Fair” to “Poor”.

1. “Good” Menthol Rating

Across all cessation articles reviewed that compared menthol and non-menthol cigarette smokers, only one article (Pletcher et al., 2006¹⁵) was rated as “Good” overall and in terms of its ability to make inferences regarding the relationship between menthol smoking and cessation behaviors based on the methods described.

In a nested case-control study, Pletcher et al. (2006) examined menthol vs. non-menthol cigarette smokers in the Coronary Artery Risk Development in Young Adults (CARDIA) study.¹⁵ The CARDIA study followed 1,535 healthy American smokers (563 non-menthol and 972 menthol smokers) for up to 15 years, with follow-up examinations at years 2, 5, 7, 10 and 15. Preference for menthol /non-menthol cigarettes was self-reported using the item “Is [your current brand of cigarettes] mentholated or non-mentholated?” In addition to following participants over a long period of time, other strengths of this study included the measures of smoking cessation as well as the statistical methods used to evaluate the relationship between cigarette type preference and cessation. Other strengths included:

1. “Sustained smoking cessation” was defined as no reported current smoking in the past two intervals at which participants were examined (as previously noted, follow-up examinations occurred at years 2, 5, 7, 10 and 15).
2. “Documented relapse” consisted of baseline smokers who reported no current smoking at a subsequent visit (exam) and then current smoking during their final examination.
3. Logistic regression was used to assess the independent contribution of menthol and non-menthol exposure on cessation outcomes, with one observation per participant.

2. “Good to Fair” Menthol Rating

Three cessation studies were rated as “Good to Fair” with regard to their ability to make inferences related to menthol smoking and cessation based on the methods described.^{7, 9, 13} Two of these three studies (Gunderson, et al. 2009¹³ and Rose and Behm, 2004⁹) received a “Good” overall quality rating.^{7, 13} The third study (Murray, et al. 2007) received a “Good to Fair” rating overall.⁷

Gunderson et al. (2009)¹³ conducted an exploratory analysis to examine the relationship between menthol smoking and cessation. Data from 7,815 white, black, and Hispanic current and former smokers completing the 2005 NHIS-Cancer Control Supplement (NHIS-CCS) were analyzed. The study examined the odds of quitting using menthol status and race/ethnicity as the key independent variables. Reviewers provided a “Good to Fair” rather than a “Good” rating of the study’s ability to make inferences about menthol because this was a non-interventional, cross-sectional study, in which independent and dependent variables were measured at a single point in time.

Rose and Behm (2004)⁹ reported on findings from a randomized interventional trial. The authors examined the effectiveness of various pharmacological and behavioral treatments designed to promote extinction of the rewarding response to nicotine. This article describes the outcomes during the two-week pre-cessation treatment period. A sub-sample of 233 participants were randomly selected from the larger participant population (n = 454) recruited for a smoking cessation study for inclusion in the pre-cessation study. During the pre-cessation period, participants were either assigned to their usual brand or menthol-switch (from whatever their usual brand was). Although the authors clearly explain how they determined mentholated and non-mentholated cigarette-brand switching “*the terms mentholated and nonmentholated are based on package labeling, inasmuch as nonmenthol cigarettes contain a small amount of menthol*” (page 524, 2nd column), it is unclear from the article whether package labels were collected to confirm each participant’s initial preference for menthol vs. non-menthol cigarettes prior to randomization. In addition, firm conclusions related to cessation and use of menthol vs. non-menthol cannot be made using data from this study, as post-treatment outcomes are not described in the article. For these reasons the study was “Good to Fair” related to menthol inferences, rather than “Good”.

Murray et al. (2007) reported on findings of a secondary analysis of data collected as part of the Lung Health Study (LHS) data.⁷ The LHS was an interventional RCT that enrolled 5,887 male and female adult smokers (35–60 years old), with early evidence of obstructive lung impairment for a smoking cessation and ipratropium study. Data were available for 14 years of follow-up. The eligibility for study inclusion was clear; authors reported some differences at baseline between groups. Study participants had impaired lung function, representing a specific subgroup of smokers. A strength of this study is the long-term follow-up at 5 and 14 years. Cessation outcomes were measured at Year 5; no interim analyses were conducted. Rather than providing the adjusted percentages, the authors report the unadjusted percentage of participants who were sustained quitters, intermittent quitters, or continuing smokers during the 5 years of LHS by menthol status; as such the study was “Good to Fair” related to menthol inferences, rather than “Good”.

3. “Fair” Menthol Rating

Across the smoking cessation articles, seven studies received a “Fair” rating from reviewers with regards to the respective study design’s abilities to make inferences related to menthol and smoking behaviors.^{5, 6, 8, 10-12, 14} Three of the four non-RCTs with this rating (Foulds et al., 2006; Gandhi et al., 2009; Muscat et al., 2002) were based on volunteer, convenience samples, limiting the generalizability of results.^{8, 11, 12} Of the seven studies, one (Muscat et al. 2002) employed a cross-sectional design, which limited sufficient analyses of differences between menthol and non-menthol smokers in relation to smoking cessation.⁸ The other six studies evaluated participants for six months^{5, 10-12, 14} to several years.⁶

Although the quality reviewers provided a “Good” overall rating to Okuyemi et al., (2007), the study design described in this article was rated “Fair” in its ability to allow for inferences regarding menthol and smoking behavior. This “Fair” rating was given primarily because the study was a secondary analysis of a larger clinical study and the article did not discuss how the study sample compared to the population of African American light smokers seeking to quit smoking.¹⁴

Similarly, the article by Gandhi et al. (2009) received a “Good” overall rating, but only a “Fair” rating in its ability to make menthol inferences for the following reasons:

1. it was a retrospective analysis,
2. loss to follow-up (attrition) by six months was high (i.e., more than 42%), and
3. the type of participants (motivated quitters seeking treatment for tobacco dependence) may limit the generalizability of results.¹²

Foulds et al. (2006) sought to identify factors associated with successful quitting at a free tobacco treatment clinic.¹¹ Logistic regression was used to identify factors associated with abstinence at 4-week and 6-month follow-up. The quality reviewers rated both the overall quality as well as the study’s ability to allow for inferences regarding menthol and smoking cessation as “Fair”, for the following reasons:

1. researchers used a convenience sample of volunteers seeking treatment at a clinic (as compared to those who quit without clinic treatment), thereby limiting generalizability to a specific sub-group of smokers;
2. determination of menthol smoking via "current brand" is somewhat unclear;
3. approximately one-third of the sample was lost to follow-up by 26 weeks; and
4. biochemical confirmation of smoking abstinence was only completed at baseline.

Muscat et al. (2002) conducted a cross-sectional analysis of case-control data from a study on smoking and lung cancer that included over 19,500 current and former cigarette smokers.⁸ The purpose of the study was to determine if use of menthol cigarettes was associated with smoking frequency and with quitting, and whether cigarette mentholation explains racial differences in these two smoking behaviors.

The quality reviewers provided a “Fair” overall rating and a “Fair” rating for the study’s ability to allow for inferences regarding menthol and smoking cessation, for the following reasons:

1. this cross-sectional study used a convenience sample of cancer patients (limited generalizability).
2. the participant population was disproportionately old and male (limited generalizability).
3. using the definition of “ex-smoker” provided in the article, (“Ever smokers who did not smoke at least one cigarette each day for the preceding year”) it is possible that participants who were still smoking could be classified as ex-smokers, as long as they didn’t smoke at least one CPD in the preceding year.

Okuyemi et al. (2003) was a secondary analysis of a double-blind, placebo-controlled RCT designed to test the effectiveness of bupropion as a smoking cessation aid.⁵ Participants received either bupropion (the intervention) or placebo for seven weeks. Of the 600 African American smokers enrolled, 471 smoked menthol and 129 smoked non-menthol. Use of menthol cigarettes was self-reported using the following item: “Do you usually smoke menthol cigarettes?”.

In this study, the “intervention” (i.e., primary predictor) was menthol/non-menthol cigarettes. Therefore, comparisons were made between menthol and non-menthol smokers, and the authors controlled for treatment in their analyses. Smoking cessation was self-reported using seven-day point prevalence at six weeks and six months. Abstinence was confirmed via expired carbon-monoxide (CO) assessment and saliva (when required). Reviewers noted several limitations of the study, as follows:

1. the extent to which the study population compares to the US population of African American adult smokers is unclear, making it difficult to generalize the results;
2. the authors incorrectly state the cessation rates after “six weeks of treatment” when subjects actually had seven weeks of treatment by study week 6;
3. depending upon the target quit date selected, one might argue that while relapse is being measured for one patient, for another patient with a different quit date, efficacy is being measured. Okuyemi et al. do not provide the distribution of quit dates, nor do they provide the proportion that actually quit by the selected quit date; and
4. since this is a secondary analysis using data from the parent study, it is unclear whether a power calculation was conducted to determine the sample size needed for comparisons between menthol and non-menthol smokers.

Given these limitations, the reviewers agreed on a “Fair” quality rating for menthol inferences.

The study reported by Hyland et al. (2002) was the only study in this rating group to enroll a random sample of over 13,000 smokers from a representative sample of households in 10 US communities.⁶ The authors used multivariate techniques to assess the association between baseline menthol use and sex, age, race/ethnicity, education, amount smoked, TTF cigarette, age of starting to smoke and alcohol use. There was a weak association between menthol use and lower cigarette consumption, longer TTF cigarette in the morning, and increased quit attempts. Nearly one-quarter (24%) of baseline smokers quit smoking between 1988 and 1993, and the adjusted relative risk of quitting for menthol vs. non-menthol smokers was 1.00 (95% CI: 0.90–1.11). However, key reasons this study was rated as “Fair” quality by the reviewers included the high rate of attrition (35%) over time and because menthol status only was collected at baseline (1988), but was used to predict outcomes in 1993.

Finally, Berg et al. (2010) conducted a secondary analysis of data from a placebo-controlled RCT of African American light smokers (light: ≤ 10 CPD).¹⁰ In this article, the authors evaluated the predictors of smoking reduction among African American light smokers enrolled in a 26-week cessation trial. A primary limitation of this study is that it was not designed to examine the relationship between menthol and cessation. A second limitation of this study is that it was based on a very limited convenience sample of African American light smokers, which according to the authors represent about 50 percent of African Americans smokers.¹⁰ Thus, the results of this study cannot be generalized to all African American smokers.

4. “Poor” Menthol Rating

The nine remaining cessation studies that included a comparison of menthol and non-menthol smokers were all evaluated as “Poor” in their ability to make inferences about menthol. While the *overall* study quality of both Cropsey et al. (2009)²⁹ and Pollak et al. (2002)⁴⁸ was

determined to be “Good” by the quality reviewers, reviewers believed that neither could sufficiently be used to make inferences related to menthol and smoking cessation behaviors.

Cropsey et al. (2009) compared the cessation rates of black and white female prisoners.²⁹ This was a secondary analysis; the parent study was a RCT evaluating a smoking cessation intervention among this prisoner population. Overall, the quality reviewers rated this as a “Good” study, based on the study design and statistical analyses conducted. However, quality reviewers note several reasons why this study received a “Poor” rating related to menthol inferences. First, although the authors counted dropouts as “smokers”, only about half of the participants completed the treatment program (the parent study), resulting in a high attrition rate. Next, this study was limited to a sample of prisoners in a medium-maximum security female prison, restricting the ability to make generalizations beyond this population. Finally, the impact of mentholated cigarettes on treatment outcomes was not the primary analysis in this article, and only those receiving treatment were included in the menthol analysis. Rather, the authors note that the impact of menthol cigarette smoking was conducted as a secondary analysis.

Like Cropsey et al. (2009), Pollak et al. (2002) was rated as a “Good” quality study overall, but “Poor” with regards to its ability to make menthol inferences.⁴⁸ Reviewers note that this was a well-designed study that included good measures suited to the study objectives. However, the study was not designed to assess the relationship between menthol and cessation and the design limited the ability to assess this relationship.

The following studies received a “Fair” rating overall, but a “Poor” rating related to menthol: Bover et al. (2008),²⁷ Fu et al. (2008),³¹ and Hymowitz et al. (1995).⁴⁶

Bover et al. (2008) conducted a cross-sectional study to investigate the relationship between night-time smoking (as an indicator of dependency) and cessation.²⁷ Study subjects were treatment seeking smokers recruited at a dependency clinic. Loss to follow-up was a significant limitation of this study. At Week 4, 75.5 percent of subjects completed the assessment, while just 61.9 percent completed the assessment at Week 26, representing a loss to follow-up of greater than 40 percent. In addition to the limitation of high sample attrition, the study was not designed to assess the relationship between menthol smoking and cessation behavior and is limited in its ability to do so.

Fu et al. (2008) conducted a secondary data analysis of a RCT of smokers trying to quit within the Veterans’ Affairs (VA) population.³¹ Smokers were asked about their use of menthol cigarettes in the two years prior to data collection, leading to significant potential recall bias. The potential for significant recall bias was a key factor influencing the “Poor” quality rating given to this study in its ability to inform inferences related to menthol and smoking behaviors. In addition, the wording of the item(s) assessing menthol cigarette smoking in the two years prior was unclear from the article. The exact wording of survey items is essential for determining whether or not an item is valid, and the assessment of menthol use is key to this study. For example, when asked about menthol use in the two years prior, some participants who smoked a few menthol cigarettes may have responded one way, while other participants who smoked a few menthol cigarettes may have responded in a completely different way. An additional limitation

of this study is that its primary outcome, seven-day point prevalent smoking abstinence, was self-reported and only measured at one point in time.

Hymowitz et al. (1995) conducted a secondary data analysis of white, black, Mexican, and Puerto Rican current smokers from the COMMIT trial.⁴⁶ The primary objective was to describe the relationship between ethnicity and several smoking characteristics among these ethnic groups. For this study, communities with higher percentages of ethnic groups were sampled, restricting the sampling frame. Therefore inferences about menthol may be biased or only applicable to these populations. Odds ratios are reported in the article to describe the relationship between the number of cigarettes smoked per day and age at which menthol smoking began. These results either were not significant or marginally significant.

The methodological quality of the remaining cessation studies was generally considered “Fair to Poor” overall and “Poor” related to menthol (Fagan, 2007)³⁰ or “Poor” both overall and related to ability to make inferences related to menthol (Harris et al., 2004; Li, 2008; and Okuyemi et al., 2004).^{28, 32, 33} Reviewers identified several methodological concerns with these studies, described below.

Fagan et al. (2007) conducted a cross-sectional study using the 2003 Tobacco Use Special Cessation Supplement (TUSCS) to the Current Population Survey (CPS).³⁰ The author’s estimated smoking prevalence and examined factors associated with smoking cessation for persons between 18 and 30 years old (“young” adult smokers). The authors do not adequately describe the measure representing “intention to quit” or number of quit attempts and do not indicate whether these measures have previously been validated. In addition, the authors cite several references to the FTND, but it is not clear from the article that the authors are actually using the FTND measure or if they are just citing FTND to support their own measure.

Harris et al. (2004) conducted a secondary analyses to identify factors that predict successful quitting using data from a double-blind, randomized controlled smoking cessation trial that included 600 African Americans.³² Participants were either assigned to the intervention, bupropion, or placebo groups. This study received a “Poor” rating with regard to its ability to make inferences related to menthol because cessation at Week 7 was used as the primary outcome. The authors indicated that this length of follow-up was selected because “more participants were quit at Week 7 compared to any other later time point” (page 500, 1st paragraph, left side).³² An additional limitation of this study is that it was based on a convenience sample of volunteers responding to advertisements for a smoking cessation program.

Li et al. (2008) conducted a secondary data analysis of the COMMIT trial to describe the use rate of menthol cigarettes between 1988 and 2001 in a cohort of smokers, to examine who is using menthol cigarettes, and to examine if menthol in cigarettes are associated with increased nicotine dependence.²⁸ The authors described the screening criteria for study eligibility in the secondary analysis in the article, but did not describe the eligibility criteria for the COMMIT trial. It was not clear whether a probability sample was used. In addition, it was not clear how the survey measures were selected; therefore, it is also unclear whether the selected questions are from validated measures. The authors did not control for repeated measures in the study population

over time, nor did authors specify how the intervention exposure was measured or controlled for. Most importantly, race, menthol, and/or their interaction were not explored.

Okuyemi et al. (2004) conducted a cross-sectional survey to examine smoking patterns of menthol cigarette smokers and their cessation experiences.³³ The authors report that menthol smokers are more likely to smoke cigarettes with higher tar content; however, there is no mention of the statistical tests used for this analysis. It is also not clear how tar level was captured. The primary limitation of this study is that authors make generalizations about African American smokers using an inner city population from a single location.

V. RESULTS: VALIDITY OF AUTHORS’ DISCUSSION/CONCLUSIONS BASED ON REPORTED FINDINGS WITH RESPECT TO MENTHOL

In total, 15 of the 38 reviewed studies earned a “Fair” or better methodological quality rating both overall and with regards to making inferences on menthol and smoking behaviors (NOTE: one of these studies, [Okuyemi et al. 2003] is summarized in both the dependence and cessation sections). Table 6.1 summarizes the findings of the study outcomes by menthol rating across all studies reviewed.

Table 5.1. Summary of All Studies Reviewed: Study Outcomes by Menthol Quality Rating

Overall	No Difference*	Difference*
“Good”, “Good to Fair”, or “Fair” Studies (n = 15)		
Overall	Eight studies	Seven studies
Initiation	Two studies ^{1, 2}	None
Dependence/Other Behavior	Two studies ^{3, 4}	N/A
Both Dependence and Cessation	N/A	One study ⁵
Cessation	Four studies ⁶⁻⁹	Six studies ¹⁰⁻¹⁵
“Fair to Poor” or “Poor” Studies (n = 18)		
Overall	Ten studies	Eight studies
Initiation	None	One study ¹⁶
Dependence/Other Behavior	Four studies ¹⁷⁻²⁰	Six studies ²¹⁻²⁶
Both Dependence and Cessation	Two studies ^{27, 28}	N/A
Cessation	Four studies ²⁹⁻³²	One study ³³

NOTE: Five studies are not included in this table. One initiation study (Kreslake, 2008) was more of an editorial. Two dependence studies (Ahijevych, 1993; Moolchan, 2004) and one study in both dependence and cessation (Hymowitz, 1995) only reported the baseline characteristics (no outcomes) by menthol/non-menthol. Finally, once cessation study (Pollack, 2002) reported cessation advice given by menthol status, but not outcomes.

* Between menthol and non-menthol cigarette smokers.

Detailed tables presenting the authors’ conclusions, assessment of the validity of those conclusions, and any relevant comments are presented in Tables 5.1 – 5.3 for studies receiving a “Fair” rating or better. Researchers did not review the authors’ conclusions for studies receiving a “Fair to Poor” or “Poor” menthol quality rating, because, based on these ratings, no valid conclusions should be drawn from the data.

A. Smoking Initiation Behavior

As discussed in Section IV.D two of the four initiation studies reviewed (50%) received a “Fair” rating or better in analyses of methodological quality (Appleyard et al., 2001¹ and DiFranza et al., 2004²). Although these studies are classified as smoking initiation studies, our review suggests that neither study is appropriate to use to evaluate true initiation behaviors. An assessment of the conclusions discussed in these studies is provided below and in Table 5.2. Based on these reviews, neither study provides sufficient and appropriate data to make conclusions regarding the impact of menthol cigarette smoking on initiation behaviors.

Appleyard et al. (2001) conclude that “during the last year of high school, one third of Asian American youth are smokers”. Of these youth 60% report that their usual brand of cigarette is a menthol brand. Among female Hawaiian/Pacific Islander youth in middle school, more than 25 percent reported having smoked in the past month.¹ The author’s conclusions were based on responses to the following questions:

- “How old were you when you smoked a whole cigarette for the first time?”
- “Is the brand of cigarette that you usually smoked during the past 30 days mentholated?”
- “During the past 30 days, what brand of cigarette did you usually smoke?”

Analysis of responses to these questions can appropriately characterize current smoking habits among these youth; the data do not address “true” initiation behaviors and brand preference together.

Similar to Appleyard et al. (2001), the study by DiFranza et al. (2004) does not truly address menthol cigarette smoking and initiation (or dependence) behaviors. However, the data do suggest that menthol does not affect the novice smoker’s reaction to their first cigarette.

Table 5.2. Best Available Science on Menthol and Smoking Initiation

Author	Summary of conclusion	Do results support study’s conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Appleyard, 2001	NYTS 2000 data indicate that during the last year of high school, 1/3 of Asian American youth smoke. Of these youth, 60% reported that that their usual brand of cigarettes is mentholated. Among female Hawaiian/Pacific Islander youth in middle school, more than 25% report having smoked during the past month.	Not able to make conclusions on initiation based on study data	Reasonable descriptive study. However, it is not appropriate for the authors to conclude that because 60% report their USUAL brand is menthol, this also is the type used when they initiated smoking.

Author	Summary of conclusion	Do results support study's conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
DiFranza, 2004	Increased sensitivity to nicotine as manifested by relaxation, dizziness, or nausea in response to the first exposure to nicotine represents a risk factor for the development of nicotine dependence.	Cant really get at true 1 st initiation; however menthol does not affect novice smoker's reaction to first cigarette	Menthol is not one of the factors that influence your reaction to first cigarette. Overcoming of nausea suggested as "tolerance".

B. Smoking Dependence and Other Behaviors

Three of the 18 studies of menthol's effect on smoking dependence behavior earned a "Fair" rating or better in analyses of methodological quality (Moolchan, 2006³, Muhammad-Kah, R. 2010 and Okuyemi et al., 2003⁵). These three studies represent the best available peer-reviewed/published information with regards to menthol and smoking dependence behaviors (Table 5.3).

Table 5.3. Best Available Science on Menthol and Smoking Dependence

Author	Summary of conclusion	Do results support study’s conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Moolchan, E. 2006	Our results underscore the need for measures independent of consumption for determining degree of nicotine dependence and treatment selection across ethnicities, even among youths.	Conclusions appear to be supported by results	No differences in FTND; tells us African American smokers smoke less/day; differences may be explained by metabolism or reasons other than menthol cigarette use.
Muhammad-Kah, R. 2010	Results add to the existing evidence that menthol does not increase nicotine dependence.	Conclusions on nicotine dependence appear to be supported by results	FTND: no difference in Odds Ratio between adult menthol and non-menthol smokers.
Okuyemi, 2003 (also summarized in the cessation section)	African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, putting menthol smokers at greater risk from the health effects of smoking. Lower overall cessation rates among African American menthol smokers may partially explain ethnic differences in smoking-related disease risks.	Conclusion doesn’t fit with the totality of data, and statements made in the conclusions are incorrect.	2 nd analysis; at 6 months, there are no significant differences between menthol and non-menthol. Authors incorrectly state that there were lower smoking cessation rates for menthol smokers after “6 weeks” of treatment, but subjects are actually evaluated after 7 weeks of treatment. The authors state that their hypothesis is to test whether menthol smokers are less likely to quit, so the follow-up evaluations should occur based on each individual’s target quit date. Therefore, evaluations using “6 weeks of treatment” (which is actually 7 weeks) are not appropriate to use. NOTES: p-value on “employed status” in table different than p-value in text; sample size of placebo and bupropion menthol/non-menthol groups not provided.

Moolchan et al. (2006) conclude that the “results...suggest that the observed differences are due to factors other than menthol smoking”.³ Based on our review of the study findings, we believe that these conclusions are appropriate. This study benefits from a good overall study design and use of appropriate and rigorous methods for assessing menthol’s impact on smoking dependence; in addition, the study data support the authors’ conclusions. No differences were found in Fagerström scores between menthol and non-menthol groups. The results tell us African

American smokers smoke fewer CPD; differences in dependence scores may be explained by metabolism or reasons other than menthol cigarette use.

Muhammad-Kah (2010) conclude that the “results add to the existing evidence that menthol does not increase nicotine dependence”.⁴ Using FTND scores as the measure of dependence, no differences were seen in the odds ratios between adult menthol and non-menthol smokers. Therefore, we found that the study data support the authors’ conclusions.

Okuyemi et al. (2003) earned a “Fair” overall rating and a “Fair” rating for the study design and statistical methods in their ability to produce data addressing the impact of menthol on dependence.⁵ The authors conclude that “African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, thereby putting menthol smokers at greater risk from the health effects of smoking”. At the second follow-up assessment (6 months), no significant differences were found. It raises substantial concerns that the authors chose to draw conclusions based on six week findings when six month data are available. More concerning, however, is that the authors measured smoking cessation six weeks after the date they met with the study staff to **set** a target quit date, **instead of** evaluating outcomes six weeks **following** their target quit date. Additionally, researchers noted several errors/inconsistencies within the publication, including a statement that menthol smokers had lower smoking cessation rates after six weeks of treatment when, in fact, this was measured seven weeks following treatment initiation. Reviewers also noted discrepant p-values within text and tables and absent sample sizes for placebo and bupropion menthol/non-menthol groups.

C. Smoking Cessation Behavior

Eleven of the 20 studies of menthol’s effect on smoking cessation behavior earned a “Fair” rating or better in analyses of methodological quality.⁵⁻¹⁵ These eleven studies represent the “best available science” with regards to menthol and smoking cessation behaviors based on studies published in peer-reviewed journals. Table 5.4 summarizes our review of each study’s conclusions and whether they were appropriate or not based on the data provided in the article.

Table 5.4. Best Available Science on Menthol and Smoking Cessation

Author	Summary of conclusion	Do results support study’s conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Berg, C. 2010	Conclusions do not mention menthol. Discussion states more non-reducers used menthol cigarette than did reducers	Can’t draw definitive conclusions. Discussion section doesn’t fit with totality of data	Discussion states more non-reducers used menthol cigarettes than did reducers – but this was not significant.
Foulds, 2006	Forty-one percent of the patients smoked menthol cigarettes. They were less likely to achieve abstinence in univariate analyses, and this item remained in the model predicting 4-week outcome.	Reasonable to assume that menthol at 26 weeks is not a predictor of abstinence	Discussion states that “menthol cigarettes remained in model” at 4 weeks, but it is not included in model at 26 weeks. Although it remained in the model, it is not a significant predictor at 4 weeks (p=0.053).

Author	Summary of conclusion	Do results support study's conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Gandhi, 2009	Despite smoking fewer CPD, African American and Latino menthol smokers experience reduced success in quitting as compared with non-menthol smokers within the same ethnic/racial groups.	Can't draw definitive conclusions; conclusion doesn't fit with the totality of data	Don't adjust for confounding/ socioeconomic factors (which significant in Table 1). Stretch to say that saying menthol alters cigarette smoking in a way that increases addictiveness. Results show 2/3 population white and no difference with respect to abstinence. NOTE: white menthol/ non-menthol cigarette smokers smoke same # CPD.
Gundersen, 2009	Our findings provide some support for the hypothesis that menthol smoking can lead to poorer cessation outcomes, but only for non-white smokers.	Can't draw definitive conclusions	Different direction for African Americans and Hispanics vs. whites, which may be explained by reasons other than menthol cigarette use (e.g., metabolism, socioeconomic). NOTE: cross-sectional study, no intervention.
Hyland, 2002	No clear associations between menthol use and three self-reported indicators of nicotine dependence (even after controlling for race/ethnicity and other demographics) in this large, prospective study with data on a variety of measures associated with cessation.	Findings consistent with data	Found no differences, which seems to be contrary to their initial belief that is due to a biological mechanism; these data suggest menthol cigarette smokers do not exhibit greater signs of dependence
Murray, 2007	In this 14 year follow-up, no evidence that baseline menthol cigarettes are associated with greater nicotine dependence	Reasonable conclusions	No difference in smoking cessation success, no indication that menthol contributes to well-known harm from smoking.
Muscat, 2002	2 nd analysis; cross-sectional study of case-control data of newly diagnosed lung cancer patients; conclusion is that menthol does not increase the addictive properties of nicotine dependence	Reasonable conclusions (conclusion is stated in abstract) that risk of quitting was not associated with cigarette flavor	Limited generalizability; newly diagnosed lung cancer patients. NOTE: last paragraph in discussion has to do with advertising to young black consumers; article not related to collection or evaluation of this information. In addition, the percent of menthol cigarette smokers among blacks is lower than typically reported.

Author	Summary of conclusion	Do results support study’s conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Okuyemi, 2007	Among African American light smokers, menthol cigarette use associated with lower cessation rates	Drawing conclusions via reviewing study population and the way they looked at “cells” is tenuous (at best).	Authors mention the study not designed to look at menthol; conclusion based on Figure 1, which suggests that menthol is associated with lower abstinence, but didn’t control for things in that figure. Also, small sample size of non-menthol smokers; when individual treatment cells (Figure 2) combined, only then is there significance, but in Figure 3 (actual randomization based on study design) shows no significance.
Okuyemi, 2003 (also summarized in the dependence section)	African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, putting menthol smokers at greater risk from the health effects of smoking. Lower overall cessation rates among African American menthol smokers may partially explain ethnic differences in smoking-related disease risks.	Conclusion doesn’t fit with the totality of data.	Secondary analysis At 6 months, there are no significant differences between menthol and non-menthol, but authors based their conclusion on 6 week findings. Conclusions also state that menthol smokers had a lower smoking cessation rate after 6 weeks of treatment, but their 6-week follow-up is actually after 7 weeks of treatment. Authors make conclusions about results following 6 weeks of treatment, but participants had a variable quit date. That is not the appropriate endpoint to use. NOTES: p-value on employed status in table different than p-value in text; sample size of placebo and bupropion menthol/non-menthol groups not provided.

Author	Summary of conclusion	Do results support study's conclusions about menthol?	Comments related to ability of study to support menthol conclusions.
Pletcher, 2006	Menthol and non-menthol cigarettes seem to be equally harmful per cigarette smoked in terms of atherosclerosis and pulmonary function decline, but menthol cigarettes may be harder to quit smoking.	Conclusions don't fit the totality of the data	Four of 5 indicators of dependence showed no difference; no difference in coronary calcification and pulmonary function, but report difference in risk of relapse – from the ONE indicator. In addition, documented relapse could be reported if person smoked one time during period, but “sustained cessation” relies on person “not smoking” at two different follow-up intervals. How is smoking defined in study? If person smoked ≥ 1 cigarette, could be defined as a “documented relapser”
Rose, 2004	These findings demonstrate the importance of sensory cues in determining subjective reward and show that the reward value of these cues can be altered by removal of nicotine from tobacco or by pharmacological manipulations that interfere with the reinforcing effects of nicotine.	Article more a decoupling nicotine from addiction. Not good article for making conclusions about menthol initiation and/or cessation.	Huge imbalance in cells; non-menthol smokers didn't really like menthols; but doesn't really tell about cessation. People who like menthol, like menthol; people who don't like menthol, don't like it.

Our researchers determined that the author's conclusions were inappropriate and/or that definitive conclusions regarding menthol could not be made based on the study findings in seven of these 11 studies (64%).^{5, 9, 10, 12-15}

In their discussion section, Berg et al. (2010) state “more non-reducers used menthol cigarette than did reducers”, however the results show that this was not a statistically significant difference.¹⁰ Lack of statistical significance suggests that a similar difference could have just as easily resulted by chance. Thus, this statement does not fit the totality of the data, and no definitive conclusions about menthol's impact on cessation can be drawn from the study data.

Similarly, the conclusions stated by Gandhi et al. (2009)¹² and Pletcher et al. (2006)¹⁵ do not fit the totality of the data.

Results shown in Table 1 of Gahdhi et al. (2009) demonstrate that there were significant differences in baseline demographics.¹² However, the authors do not control for differences in subsequent analyses. Given the data, the reviewers felt it was a stretch to claim that “menthol alters the way cigarette is smoked in a way that increases addictiveness”. The data does not

suggest this. For example, there were no differences with respect to abstinence between white menthol and non-menthol smokers, who represented nearly two-thirds (1,086/1,688; 64%) of the population. Therefore, no definitive conclusions about menthol's impact on cessation can be drawn from the study data.

The conclusion stated by Okuyemi et al. (2003) do not fit the totality of the data at 6 months follow-up, at which point there were no significant differences between menthol and non-menthol groups.⁵ Similarly, Okuyemi et al. (2007) draws conclusions based on Figure 1, which suggests that menthol is associated with lower abstinence, but the analyses did not include controlling for between-group differences at baseline. Figure 3, which shows results according to the actual randomization defined in the Methods, no significant difference is apparent.⁵ Additional discrepant findings are discussed in Section V.B (above).

The conclusion stated by Pletcher et al. (2006) also does not fit the totality of the data. With the exception of “Documented relapse,” the other four of five indicators of dependence showed no difference between groups after adjusting for baseline characteristics. In addition, the study found no differences in coronary calcification and pulmonary function; there were significant differences in risk of relapse. Risk of relapse was an outcome of much interest and debate within the review team given that “documented relapse” could be reported if a participant smoked one time during the follow-up intervals, but “sustained cessation” relies on a participant “not smoking” at two different follow-up intervals, leading to potential inconsistencies or holes in the definition. If a participant smoked ≥ 1 cigarette, he/she could be defined as a “documented relapser”.¹⁵

Findings reported by Gundersen et al. (2009) do not allow for definitive conclusions about menthol's impact on cessation. The results of cessation outcome measures differed by race/ethnicity, with opposite directions for African Americans and Hispanics compared to whites. These data suggest the differences may be explained by reasons other than menthol cigarette use, including metabolic and/or socioeconomic differences.¹³

The analysis conducted by Rose et al. (2004) truly represents a decoupling of nicotine from addiction. While the results are interesting, they essentially confirm that menthol smokers like menthol, while non-menthol smokers do not like menthol. Based on the data presented, the reviewers do not believe it is appropriate to use this information to make conclusions about menthol cessation.⁹

Only four studies (Foulds et al. 2006; Hyland, A. 2002; Murray, R. 2007; Muscat, J. 2002) provided sufficient data and made appropriate conclusions on menthol's impact on smoking cessation using these data.^{6-8, 11}

Based on the data presented by Foulds et al. (2006), one can conclude that menthol is not a predictor of abstinence at 26 weeks. The discussion states that “menthol cigarettes remained in the model” at 4 weeks, but it is not included in the model at 26 weeks. Although it remained in the model at 4 weeks, it was not a significant predictor even then ($p = 0.053$).¹¹

The conclusions of Hyland et al. (2002) are consistent with the data. Although it appears to be contrary to their initial hypothesis that differences in cessation outcomes between menthol and non-menthol smokers is due to a biological mechanism, Hyland et al. found no differences between menthol and non-menthol smokers.⁶ The authors then suggest that menthol cigarette smokers do not exhibit greater signs of dependence or greater difficulty quitting.

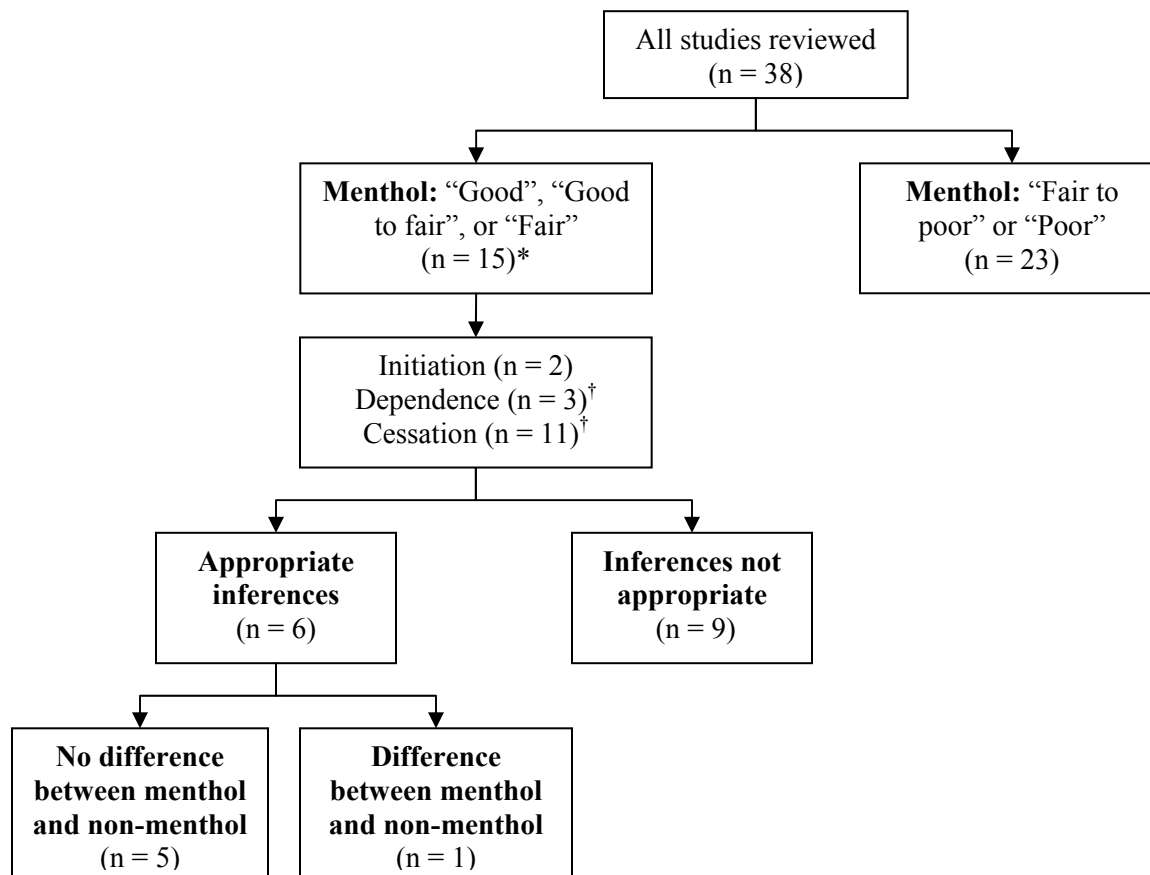
Murray et al. (2007) also makes reasonable conclusions given the available data.⁷ After 14 years of follow-up, no differences between menthol and non-menthol smokers were detected in success with smoking cessation. The data also suggest that there is no additional harm resulting from use of menthol flavoring in cigarettes.

Muscat et al. (2002) concludes “the risk of quitting was not associated with cigarette menthol flavor”.⁸ While the conclusions are appropriate given the data, it is important to note that the study population (patients with newly diagnosed lung cancer) limits the generalizability of these results, making it difficult to apply the information to a broader smoking population.

D. Summary: Study Outcomes

Overall, we found that only six out of 38 studies^{3, 4, 6-8, 11} were rated as “Fair” or better based on a methodological review and made appropriate conclusions based on the data. Five of these six studies found no difference in outcomes between those smoking menthol and non-menthol cigarettes (Figure 5.1).

Figure 5.1 Outcomes by “Fair” or Better Menthol Quality and Valid Author Inferences



† One study discusses both dependence and cessation, and is counted in both totals

* Five studies did not evaluate how menthol smoking impacted outcomes

VI. RESULTS: REVIEW OF NATIONAL SURVEYS/SECONDARY DATA SOURCES

As described in the previous section, smoking-related items in the national surveys listed below were reviewed to evaluate whether they contained at least one item/question related to the concepts that can adequately assess whether menthol in cigarettes affects smoking behaviors.

- NSDUH
- NYTS
- NHANES
- NHIS

Table 6.1 provides information on which surveys included at least one item related to the concepts we were interested in reviewing. There were 12 concepts absent from all four national surveys that the team felt important to consider in a survey looking at smoking behaviors.

The seven initiation concepts not included in any of the surveys were as follows:

- type first tried,

- more than 1 type tried when began "experimenting",
- type tried (menthol/non-menthol) at initiation,
- time smoking 1st type prior to trying another type,
- how first cigarette was obtained,
- number cigarettes smoked within 30 days of initiation, and
- types smoked within 30 days of first cigarette tried (% menthol/non-menthol).

Similarly, the five smoking flavor and brand preference concepts not included in any of the four surveys included:

- cigarette type used when started smoking regularly,
- more than 1 type ever smoked,
- more than 1 type currently used,
- age when started smoking current cigarette type, and
- cigarette types smoked (% menthol vs. % non-menthol).

Table 6.1. Concepts Identified in the NSDUH, NYTS, NHANES, and/or NHIS

Category	Concept	Evaluated in at least one survey
Initiation	Initiation age	Yes*
	Type first tried	No
	Regular smoking vs. experimentation	Yes
	More than 1 type tried when began "experimenting"	No
	Type tried (menthol/non-menthol) at initiation	No
	Time smoking 1st type prior to trying another type	No
	How was first cigarette obtained?	No
	Number cigarettes smoked within 30 days of initiation	No
	Types smoked w/in 30 days (% menthol/non-menthol)	No
Smoking Status	Ever smoked	Yes*
	Current smoker	Yes*
	Former smoker	Yes*
Smoking Flavor/ Brand Preferences	Cigarette type used when started smoking regularly	No
	More than 1 type ever smoked	No
	More than 1 type currently used	No
	Current cigarette type preferred	Yes*
	Age when started smoking current cigarette type	No
	Cigarette types smoked (% menthol vs. % non-menthol)	No
Smoking Dependency	Age when started smoking regularly	Yes
	Number of cigarettes smoked daily	Yes*
	Time of first cigarette smoked each day	Yes
Cessation	Quitting/cessation attempts	Yes
	Number of quit attempts	Yes
	Age during each quit attempt	Yes
	Cigarette type smoked prior to quitting identifiable?	Yes
	Quit method(s) used (e.g., nicotine replacement, pharmaceuticals, counseling, etc.)	Yes

* Concept evaluated in all four national surveys

The question number(s) for each item identified for the concepts reviewed are provided in Table 6.2. Our evaluations of the survey content as it relates to menthol cigarette smoking and initiation and cessation behavior are provided below. We identified six concepts that were included in all four national surveys. There was one concept related to smoking initiation evaluated in all four surveys (initiation age). All three concepts related to smoking status (ever, current, and former) were evaluated in all four surveys. Similarly, for brand preference, all four surveys collected data on current cigarette type preferred. Finally, the concept within smoking dependency collected across all surveys was the number of cigarettes smoked daily.

Table 6.2 Concepts Included in the NSDUH, NYTS, NHANES, and/or NHIS

Category	Concept	NSDUH Item(s)	NYTS Item(s)	NHANES Item(s)	NHIS Item(s)
Initiation	Initiation age	4a-4d	9	SMQ630	AHB.020
	Regular smoking vs. experimentation	CG16	12	SMQ030	
Smoking Status	Ever smoked	1, 16a	8, 10	SMQ020, SMQ620	AHB.010
	Current smoker	5, 6, 7	13, 14	SMQ040, SMQ641	AHB.030
	Former smoker*	5, 6, 7, 15	12 + 13	SMQ020 + SMQ040	AHB.010 + 0.30, NAE.020 1-4
Smoking Flavor, Brand Preference	Current cigarette type preferred	11, 11a, 12, 13	15, 16, 17	SMD100 BR, FL, MN, SMQ660, SMQ664"X", SMQ666"X", SMDUPCA	NAE.06
Smoking Dependency	Age when started smoking regularly	16		SMD030	AHB.020
	Number of cigarettes smoked daily	8	14	SMQ641 + 650, SMQ710 + 720, SMD070	AHB.050, AHB.070, NAE.15, NAE.17 (quitters only)
	Time of first cigarette smoked each day			SMQ077	
Cessation	Quitting/cessation attempts		29	SMQ670, SMQ050Q, SMQ050U	AHB.080, NAE.100, NAE.075
	Number of quit attempts		28		
	Age during each quit attempt			SMQ055	
	Type smoked prior to quitting identifiable				NAE.010
	Quit method(s) used (pharmaceuticals, nicotine replacement, counseling, etc.)		32	SMQ680, SMQ690A, SMQ690F, SMQ830	NAE.020_1 – 4 (success), NAE.080_01-4, NAE.085_01-07 (quit attempt)

* Must use at least 2 of these items to determine former smoker.

A. Smoking Initiation Behavior

Survey items addressing initial smoking experiences, whether the age at which the first cigarette was tried or when regular smoking began, are integral to the investigation of smoking initiation behaviors. Each of the four surveys contained items assessing age at initiation. Two of the surveys contained items assessing age when the first cigarette was tried (NYTS and NSDUH); the NYTS item assesses the age at which respondents smoked a whole cigarette for the first time, while the NSDUH item assesses the age at which respondents smoked part or all of a cigarette for the first time (Table 6.3).

Additionally, three of the surveys contained items that could be used to determine the age at which regular smoking began (NSDUH, NHANES, and NHIS). Both NHANES and NHIS contained items assessing the age at which respondents began smoking “Fairly regularly,” while the related item in the NSDUH asked respondents to indicate the age at which they began smoking every day. Also since the NSDUH consists of a large sample in which there is continuous data collection, incidence data could be obtained from this dataset. The NYTS survey does not contain an item assessing the age at which regular or daily smoking began.

Table 6.3. Items Assessing Age at Initiation Concept

Concept	NSDUH	NYTS	NHANES	NHIS
Age Initiated	How old were you the first time you smoked part or all of a cigarette?	How old were you when you smoked a whole cigarette for the 1 st time?	How old were you when you first started to smoke cigarettes fairly regularly?	How old were you when you 1 st started to smoke fairly regularly?
	How old were you when you first started smoking cigarettes every day?		How old were you when you first started to smoke cigarettes fairly regularly?	

1. Cigarette Type and Smoking Initiation

None of the four national surveys reviewed contained an item asking respondents to indicate the type of cigarette smoked during initial smoking experiences. Without such an item, the relationship between cigarette type or menthol flavoring and smoking initiation cannot be ascertained. See Table 6.1 for a summary of the other smoking initiation concepts that were not identified in any of the four national surveys.

B. Smoking Status

In order to investigate relationships between menthol smoking and smoking initiation or cessation, surveys must contain items that allow the investigator to determine the smoking status of respondents. For example, “experimenters”, “ever smokers”, and former smokers must be distinguishable from current smokers in order to investigate relationships between cigarette type and cessation behaviors. Each of the four surveys examined included items describing smoking status, as shown in Table 6.4.

Each of the surveys contained items assessing past smoking experience, or whether or not respondents had ever tried smoking. The NYTS, NSDUH, and NHANES contained items assessing whether respondents had ever tried smoking cigarettes. The NYTS further asked respondents to indicate the approximate number of cigarettes smoked in their lives and if they had ever smoked daily, while NSDUH, NHANES, and NHIS asked respondents to indicate if they had smoked at least 100 cigarettes in their lives. These items could be used to characterize respondents as “ever smokers.” However, these items alone cannot be used to identify current or former smokers.

Each of the surveys also contained items assessing current smoking status. The NYTS asked respondents to indicate on how many of the previous 30 days they smoked and, further, how many cigarettes were smoked per day on the days that they smoked. The NSDUH asked respondents if they had smoked at all during the past 30 days, how many of the past 30 days they smoked, as well as how long it had been since they last smoked. NHANES asked respondents if they currently smoked cigarettes and how many of the past 30 days they had smoked. Finally, the NHIS asked respondents to indicate if they currently smoked daily, some days, or not at all. Responses to items assessing past and current smoking experience could be used to distinguish current smokers from ever smokers and former smokers. For example, NYTS respondents answering “yes” to the item asking if they had ever smoked daily and further indicated that they had not smoked in the last 30 days could be characterized as former smokers. Likewise, NHIS respondents who indicated that they had smoked at least 100 cigarettes in their lives and who also indicated they currently did not smoke could be identified as former smokers.

While former smokers could be identified in each of the surveys using a combination of the items assessing past and current smoking behavior, only the NSDUH contains items that allow one to investigate time since last smoking experience (i.e., “How long has it been since you last smoked part or all of a cigarette?”).

Table 6.4. Items Assessing Smoking Status Concepts

Smoking Status Concept	NSDUH	NYTS	NHANES	NHIS
Ever smoked	Have you ever smoked part or all of a cigarette?	Have you ever tried cigarette smoking, even one or two puffs?	Have you ever tried cigarette smoking, even 1 or 2 puffs?	Have you smoked at least 100 cigarettes in your entire life?
	Have you smoked at least 100 cigarettes in your entire life?	About how many cigarettes have you smoked in your entire life?	Have you smoked at least 100 cigarettes in your entire life?	
		Have you ever smoked cigarettes daily, that is, at least one cigarette every day for 30 days?		
Current smoker	Now think about the past 30 days –... During the past 30 days, have you smoked part or all of a cigarette?	During the past 30 days, on how many days did you smoke cigarettes?	[Do you] now smoke cigarettes?	Do you NOW smoke cigarettes every day, some days or not at all?
	During the past 30 days, on how many days did you smoke part or all of a cigarette?	During the past 30 days, on the days you smoked, how many cigarettes did you smoke/day?	On how many of the past 30 days did you smoke a cigarette?	
	How long has it been since you last smoked part or all of a cigarette?			
Former smoker	During the past 30 days, that is, since [DATEFILL], on how many days did you smoke part or all of a cigarette?	Have you ever smoked cigarettes daily, that is, at least one cigarette every day for 30 days?	[Have you] smoked at least 100 cigarettes in [your] entire life?	Have you smoked at least 100 cigarettes in your entire life?
	Has there ever been a period in your life when you smoked cigarettes every day for at least 30 days?	During the past 30 days, on how many days did you smoke cigarettes?	[Do you] now smoke cigarettes?	Do you NOW smoke cigarettes every day, some days or not at all?
	Now think about the past 30 days – that is, from [DATEFILL] up to and including today. During the past 30 days, have you smoked part or all of a cigarette?			Thinking back to when you stopped smoking completely, did you use ANY of the following products: A nicotine gum? A nicotine patch? Any of these other nicotine products--- nasal spray, inhaler, lozenge or tablet? A prescription pill...?
	How long has it been since you last smoked part or all of a cigarette?			

C. Smoking Flavor/Brand Preference

The review of the four national surveys also included evaluations of cigarette flavor/brand preferences concepts. Data around cigarette flavor/brand preferences would be essential for establishing a link between cigarette type and any variety of smoking behaviors.

All four of the surveys reviewed included items assessing current cigarette type preferred (Table 6.5). The number of items in each survey around this concept varied between the surveys from one item to seven items. NHIS asked only whether the individual’s current brand is menthol or non-menthol. NYTS, NHANES, and NSDUH ask respondents to select the brand “usually smoked” or “most often” smoked during the past 30 days. NSDUH uses two follow-up questions to confirm the brand. In addition to the brand usually smoked, NYTS and NSDUH also ask whether the cigarette type “usually” smoked in the past 30 days is mentholated. NHANES includes items regarding brand, filter type, mentholation, cigarette type (regular, light, or ultralight), and for the Universal Product Code-UPC.

Table 6.5. Items Assessing Current Cigarette Type Concept

Concept	NSDUH	NYTS	NHANES	NHIS
Current Cigarette Type Preferred	During the past 30 days, what brand of cigarettes did you smoke most often?	During the past 30 days, what brand of cigarettes did you usually smoke?	During the past 30 days, on the days that you smoked, which brand of cigarettes did you usually smoke?	Is your usual cigarette brand menthol or non-menthol?
	During the past 30 days, what type of [Brand] cigarettes did you smoke most often?	What type of cigarette did you usually smoke in the past 30 days?	Was [Brand] regular, lights, or ultralights?	
	Were the [Brand] cigarettes you smoked during the past 30 days menthol?	Are the cigarettes you usually smoke menthol cigarettes?	Was [Brand] menthol or non-menthol?	
			Cigarette 12-digit Universal Product Code	

Of note, none of the four included any items assessing the following five smoking flavor and brand preference concepts: cigarette type used when started smoking regularly, more than 1 type ever smoked, more than 1 type currently smoked, age when started smoking current cigarette type, cigarette types smoked (% menthol vs. % non-menthol).

D. Smoking Dependency

Items that may be used to evaluate nicotine or smoking dependency concepts were also evaluated in our review of the four national surveys. Three of the surveys contained items assessing the age at which respondents began smoking regularly, which could be used in combination with

respondents’ date of birth or current age to determine the number of years respondents have smoked (Table 6.6). The NSDUH evaluated when respondents began smoking every day, while both NHANES and NHIS asked respondents to indicate when they began smoking “Fairly regularly.”

Each of the surveys also contained items assessing the number of cigarettes smoked per day; the NYTS, NHANES, and NHIS limited this evaluation to the number smoked per day (on days smoked) during the past 30 days, while the NSDUH asked respondents to indicate, on average, how many smoked per day during the past 30 days. The NHIS additionally asked respondents to indicate on average, how many cigarettes they now smoked per day. Only one survey (NHANES) included an item indicating the time of day the first cigarette is smoked.

Table 6.6. Items Assessing Dependency Concepts

Dependency Concept	NSDUH	NYTS	NHANES	NHIS
Age when started smoking regularly	How old were you when you first started smoking cigarettes every day?		How old [were you] when you first started to smoke cigarettes fairly regularly?	How old were you when you FIRST started to smoke fairly regularly?
Time of first cigarette smoked each day			How soon after you wake up do you smoke?	
Number of cigarettes smoked daily	On the days you smoked cigarettes during the past 30 days, how many cigarettes did you smoke per day, on average?	During the past 30 days, on the days you smoked, how many cigarettes did you smoke per day?	On how many of the past 30 days did you smoke a cigarette?	On the average, how many cigarettes do you now smoke a day?
			During the past 5 days [including today], on how many days did you smoke cigarettes?*	On the average, when you smoked during the past 30 days, about how many cigarettes did you smoke a day?
			During the past 5 days, on the days you smoked, how many cigarettes did you smoke each day?*	What is the average number of cigarettes that you smoked daily during the longest period that you smoked?

* Note: An alternative for of the question asked using the “past 30 days” instead of the “past 5 days”

E. Smoking Cessation Behavior

As shown in Table 6.7, three surveys (NYTS, NHANES and NHIS) include items asking respondents to indicate if they had quit smoking for at least 1 day in the past 12 months because they were trying to quit (NYTS phrases the item to ask how many times they had quit smoking for at least 1 day in the past 12 months because they were trying to quit). The NHIS contains an additional item asking respondents to indicate if they had ever tried to quit. Additionally, both NHANES and the NYTS contain items that attempt to evaluate time since quitting. In NHANES, respondents were asked to indicate how long it has been since they quit smoking, while the NYTS item asks respondents to indicate how long they had remained abstinent the last time they tried to quit.

Only one of the four surveys (NYTS) includes an item assessing the number of quit attempts. The survey item focuses on the number of recent quit attempts (in the past 12 months). Similarly, one of the four surveys (NHANES) includes an item assessing the individual’s age during the quit attempts. Although these items would not be necessary to determine whether an individual had quit or not, both of these questions, and the number of quit attempts specifically, would help researchers better interpret some of the other cessation data.

Three of the four surveys contained one or more items asking respondents to identify methods used during cessation attempts (NYTS, NHANES, and NHIS). The methods described in the survey items include school or community programs, help or quit hotlines, nicotine replacement therapies and nicotine containing items, and prescription medications. The NSDUH contains no items evaluating cessation attempts.

Table 6.7. Items Assessing Cessation Experience Concepts*

Cessation Concepts	NYTS	NHANES	NHIS
Quitting/cessation attempts	How many times during the past 12 months have you stopped smoking for one day or longer because you were trying to quit smoking?	During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?	During the past 12 months, have you stopped smoking for more than one day because you were trying to quit smoking?
	When you last tried to quit, how long did you stay off cigarettes?	How long has it been since you quit smoking cigarettes?	Would you like to completely quit smoking cigarettes?
		Unit of measure (day/week/month/year)?	Have you ever stopped smoking for one day or longer because you were trying to quit smoking?
Age during each		How old were you when you last smoked cigarettes fairly	

Cessation Concepts	NYTS	NHANES	NHIS
quit attempt		regularly?	
Type smoked prior to quitting identifiable			Think back to the 12 months BEFORE you quit smoking. During that time, was your usual cigarette brand menthol or non-menthol?
Quit methods used	In the past 12 months, did you do any of the following to help you stop smoking? (Choose one or more answers)	During the past 5 days, did you use any product containing nicotine including cigarettes, nicotine patches, nicotine gum, or any other product containing nicotine? Which of these products did you use?	Thinking back to when you stopped smoking completely, did you use any of the following products: A nicotine gum? A nicotine patch? Any of these other nicotine products---nasal spray, inhaler, lozenge or tablet? Prescription pill, such as Zyban, Bupropion, or Wellbutrin?
		During the past 5 days (including today), on how many days did [you] use any product containing nicotine to help [you] stop smoking? Include nicotine patches, gum, or any other product containing nicotine?	Thinking back to when you tried to quit smoking in the past 12 months, did you use any of the following products: Nicotine gum or patch? Any of these other nicotine products--nasal spray, inhaler, lozenge or tablet? Prescription pill...?

* NOTE: The NSDUH survey did not ask any questions related to cessation.

1. Cigarette Type and Smoking Cessation

Only one (NHIS) of the four national surveys reviewed contained an item asking respondents to indicate the type of cigarette smoked or smoking type preferences prior to or during quit attempts. Without such an item, the relationship between cigarette type or menthol flavoring and smoking cessation cannot be ascertained.

F. Summary: Menthol and Initiation

In order to form inferences regarding the relationship between menthol flavoring or cigarette type preference and smoking initiation behavior, items assessing cigarette type first tried or cigarette type used when regular smoking began and initiation behaviors must be included. While each of the surveys had some measure of age at initiation or age at which respondents began smoking regularly, none of the surveys contained items assessing the following:

- the type of cigarette respondents either first tried or were smoking when they began smoking regularly, or
- the type first purchased (which may better reflect preference).

G. Summary: Menthol and Dependence

In order to form inferences regarding the relationship between menthol flavoring or cigarette type preference and smoking/nicotine dependence, items assessing smoking status, smoking flavor/brand preference, and dependency must be included. While each of these surveys measured smoking status and some aspects of smoking flavor/brand preference and dependence, only NYTS and NHANES include sufficient items to capture the brand, type, and mentholation of individual’s current preferences. Additionally, the NHANES included an item that captures TTF cigarette of the day.

H. Summary: Menthol and Cessation

In order to form inferences regarding the relationship between menthol flavoring or cigarette type preferences and smoking cessation behaviors, items assessing cigarette type smoked, prior to cessation and while attempting to quit must be included. While each of the surveys had some measure of cessation attempts, including number of quit attempts in past year and quitting methods used, only the NHIS Cancer Supplement survey contained at least one item assessing the type of cigarette respondents smoked prior to quitting, as shown below in table 6.8.

Table 6.8. Items Assessing Cessation Experience Concepts*

Item	Question	Response Options
NAE.010	Earlier you said you used to smoke cigarettes. Think back to the 12 months BEFORE you quit smoking. During that time, was your usual cigarette brand menthol or non-menthol?	<ul style="list-style-type: none"> • Menthol • Non-menthol • No usual type • Refused

VII. DISCUSSION

Whether there are differences in initiation, cessation, and dependence between individuals who smoke menthol vs. non-menthol cigarettes has been the topic of much debate. For example, although it is clear that the overall prevalence of use, even among adolescent smokers is greater for non-mentholated cigarettes, emphasis has been put on the fact that a large proportion of adolescents smoke menthol brands. The inference seems to be that if menthol cigarettes were not available then the incidence of smoking among adolescents would decrease.

The goal of this methodological quality review was to (1) evaluate all publications comparing and/or drawing conclusions regarding menthol and non-menthol smokers in the US since 1993 and (2) to make judgments about whether the studies were of sufficient rigor to support the conclusions. These quality ratings are important to consider when interpreting the results and conclusions presented in these studies. Two reviewers independently evaluated the methodological quality of each study reported in the articles using criteria developed by the Agency for Healthcare Research and Quality’s (AHRQ) for their report on tobacco prevention, cessation and control. For each study, reviewers provided both an overall quality rating, as well as a quality rating specific to the study’s ability to yield inferences or conclusions about the relationship between menthol flavoring and smoking behaviors. Reviewers rated the quality of each study from “Good” to “Poor” (“Good”, “Good to Fair”, “Fair”, “Fair to Poor”, and “Poor”).

A number of outcomes have been used to evaluate initiation and/or smoking dependency. Many of these studies used survey-based data to explore smoking initiation, smoking status, current cigarette use and changes in patterns over time as well as cigarette type preferred. However, they do not attempt to assess and/or understand why someone chooses to initiate smoking, whether they choose menthol or non-menthol, and/or the reasons they decide to quit.

Variation and inconsistencies in both the methods used and the results were observed across the studies reviewed. Such variation may be attributable, in part, to inconsistencies in some of the key definitions included in the different studies. Based on our evaluations, the extent to which data reported in the articles reviewed may be used to develop inferences regarding the relationship between menthol and smoking behaviors is quite limited. Common methodological themes identified resulting in a “Fair” or “Poor” quality rating regarding menthol inferences are highlighted below.

- The initiation studies were not properly designed to evaluate menthol and non-menthol smoking.
- Across all studies, several different definitions of smoking status and/or abstinence were used, limiting the ability to combine the results to draw conclusions.
- The length of follow-up was too short (six months or less) to evaluate the maintenance of cessation.⁴¹
- Many of the studies used data from a parent study not specifically designed or powered to evaluate and/or compare behaviors of menthol vs. non-menthol smokers.
- Many studies used a convenience sample for data collection rather than a probability sample, limiting the generalizability of the results.
- Definitions of menthol preference from the four national surveys reviewed varied to the degree that prevalence estimates obtained from the surveys varied widely. For example, in one study, the estimated prevalence of smoking was much higher using data from the NSDUH compared to the NHIS survey because different definitions were used to define a smoker; the NSDUH survey does not discriminate between smoking “some days” and smoking “every day”.⁴⁹
- Finally, the measures used in the studies were often either not described or inadequately described.

VIII. CONCLUSION

The overarching purpose of this review given the mandate to TPSAC and their responsibility to make a policy recommendation to the FDA was whether the available data were of sufficient rigor to support recommendations for or against menthol.

Methodological faults within the available studies further hamper the ability to reach a consistent conclusion on the central question: “Does menthol cigarette flavoring differentially affect smoking behavior compared to non-menthol cigarettes, and if so, how and to what extent?” Many of the studies were not designed to address this question. Additionally, there are conflicting results from the numerous studies that attempted to answer whether menthol affects smoking behavior.

Combining all behaviors of interest (initiation, dependence, and cessation), studies rated “Fair” or better (n = 15 [one is included in both the dependence and cessation section]) were evenly split in their findings (8 no difference vs. 7 difference), and among those studies rated as “Fair to Poor” or “Poor” more found no difference (10 no difference vs. 8 difference). The body of literature is clearly mixed.

Overall, we found that only six out of 38 studies^{3, 4, 6-8, 11} were both rated as “Fair” or better based on a methodological review and made appropriate conclusions based on the data (Appendix 12).

Taken together, the quality of research reviewed precludes definitive conclusions regarding the relationship between menthol and smoking behavior. Results from the studies on the impact of menthol flavoring on initiation, cessation, and other behaviors are inconclusive. Additionally, the overall quality of the studies is inadequate with regard to supporting policy recommendations.

In order to gather data to legitimately support policy recommendations, large-scale well-controlled studies on diverse smoking populations with adequate follow-up periods to investigate these outcomes should be designed and implemented.

IX. SUMMARY OF NEXT STEPS AND OTHER RECOMMENDATIONS

Based on our review of the 38 articles reporting on studies that investigate the role of menthol in smoking behaviors, we have identified several short-term “Next Steps” as well as one longer term recommendation for Lorillard’s consideration to facilitate a more accurate and comprehensive understanding of the relationship between menthol cigarette preference, use, and smoking behavior.

- 1. Prepare a PowerPoint slide deck, manuscript, white paper, and/or conference abstract for publication to disseminate the key findings of this methodological quality review.**
 - TPSAC is currently reviewing the information gathered to date regarding menthol smoking in order to help inform public policy. The data used to make such policies should be objective and accurate. Therefore, we believe that it is important for TPSAC to review our independent evaluation of these studies.
 - To limit potential criticism and accusations of bias in any such documents, we recommend working with a qualified third party (i.e., Covance) to prepare a manuscript and/or PowerPoint presentation summarizing the findings in this report. Because it takes several months to publish a manuscript, we recommend providing to TPSAC the draft that will be submitted for peer review ahead of publication, indicating the targeted journal on the draft.
- 2. Conduct a quality check of the articles reviewed for this report.**
 - Evaluate the accuracy of statements in the 38 reviewed studies that summarize or cite other studies’ findings regarding the association of menthol use and smoking behavior.
- 3. Review the smoking-related content of additional surveys used to evaluate the relationship of menthol and smoking behavior.** The goal of this endeavor would be to

assess the validity of studies that are based on these survey data. Therefore, in addition to the surveys already evaluated in this report (i.e., NSDUH, NYTS, NHANES, and NHIS), Lorillard may be interested in determining what can and cannot be addressed based on the survey questions from one or more of the following surveys cited in the articles used in this evaluation and/or during a TPSAC meeting:

- Assessing Hardcore Smoking Survey (AHCSS),
- Behavioral Risk Factor Surveillance System (BRFSS),
- Centers for Disease Control and Prevention (CDC) Teenage Attitudes and Practices Surveys (TAPS),
- National Youth Smoking Cessation Survey (NYSCS),
- Social Climate Survey of Tobacco Control (SCS-TC),
- Tobacco Use Special Cessation Supplement to the Current Population Survey (TUSCS-CPS) and Tobacco Use Supplement to the Current Population Survey (TUS-CPS), and
- The Robert Wood Johnson Foundation 1996 National Survey of Tobacco Price Sensitivity, Behavior, and Attitudes among Teenagers and Young Adults.

3.1 Retrospective Study

- If it is determined that one or more of these additional survey data sources contain high-quality measures of menthol/non-menthol use and smoking behaviors, a quantitative study utilizing these data could be conducted to assess the relationship between menthol preference and smoking behaviors.

4. **Design and conduct one or more qualitative studies that could be used to inform public health policy and/or future research**, using interviews and/or focus groups to identify similarities and differences between menthol and non-menthol smokers in the following:

- Perceived benefits and harms associated with cigarette smoking;
- Factors that influence the decision to start smoking among recent initiators;
- Characteristics of smokers who want to quit versus those who do not; and/or
- Adolescent smoking habits, buying power, and preferences.

5. **Review and evaluate the most recently published literature (i.e., articles published since September 2010) that addresses the role of menthol flavoring in smoking behavior**, including the menthol supplement in *Addiction* (December, 2010).

6. **Provide an unrestricted grant for the design and conduct of a quantitative study to examine the role of menthol flavoring in smoking behaviors.**

The findings of this methodological quality assessment of published research and national survey content addressing cigarette smoking experiences and behaviors suggest the need for additional studies that employ more rigorous methodological standards and are designed to address the specific questions of interest rather than secondary analyses of existing work that was designed to address other research questions. Therefore, in TPSAC's March 2011 report, it should be indicated that due to the limitations of currently available research and the lack of quality studies specifically designed to investigate the role of menthol in smoking

behavior, additional research is warranted prior to making evidence-based recommendations regarding the sale of menthol cigarettes. Therefore, we recommend implementation of one or more studies that are designed to investigate relationships between menthol preference/menthol smoking and smoking behavior (e.g., initiation, dependence and/or cessation).

Specifically, we recommend that Lorillard (or Lorillard and other tobacco manufacturers) provide an unrestricted grant for the design and implementation of a study investigating the role of menthol flavoring in smoking behavior. Covance can work with Lorillard to develop the grant announcement, including the key questions to be addressed by the research, as well as additional content for the request for application (RFA). Additionally, we recommend an independent review committee which, at a minimum, would include selected Covance staff, academic researchers, and others. To avoid the appearance of bias, we suggest that Lorillard not be involved in the selection of the grantee. Following a review of the proposals, a grant would be awarded to an independent third party to design and conduct a prospective study to investigate the key questions related to menthol use and smoking behaviors highlighted in the grant announcement. Below we outline and discuss a series of methodological and technical considerations that may be used to guide such research. These methodological considerations can also be used to develop the content of the grant announcement or RFA as well as the selection criteria to be used to identify the grantee.

The considerations provided below are generally applicable to the design and conduct of both observational and RCTs that may be conducted to examine relationships between menthol preference/menthol smoking and smoking initiation, dependence and cessation. The key elements and/or study design criteria recommended for future research are summarized in Table 8.1, and detailed below.

Table 8.1. Study Design Considerations for Future Research Investigating the Relationship between Menthol Smoking and Smoking Behaviors

Recommendation	
1.	Specify hypotheses to guide the study design that state the expected relationships between cigarette type (i.e., menthol vs. non-menthol as the independent or predictor variable) and behavioral outcomes.
2.	Select an appropriate study design for the outcome(s) of interest (i.e., initiation, cessation, dependence).
3.	Implement a study design where the primary comparison is between menthol and non-menthol smokers.
4.	Precisely define the concepts to be measured and include measures that reflect these concepts. Consider the appropriate use of biomarkers.
5.	Include valid and reliable indicators of cigarette type preference (i.e., menthol status) and employ techniques to confirm self-reported menthol preference.
6.	Select an appropriate sample for the population of interest and where appropriate, conduct power calculations to determine the minimum sample size required to detect differences between menthol and non-menthol smokers.
7.	Employ rigorous statistical techniques to control for any potential design effects, sampling, and potential confounding factors that have demonstrated association with menthol status in previous studies.

Considerations for Inclusion in an RFA:

6.1. Specify hypotheses to guide the study design that state the expected relationships between cigarette type (i.e., menthol vs. non-menthol as the independent or predictor variable) and behavioral outcomes.

The first step in a scientific investigation of a potential causal relationship between a given attribute (or variable) and an outcome is to formulate the key question(s) to be answered by the research and to specify hypotheses that state the expected relationships between the attribute and outcome(s). To adequately assess the impact of menthol cigarette smoking on smoking behaviors, including initiation, cessation, and dependence, a study must be designed with these objectives in mind. The hypotheses should be specified a priori in order to guide the study design, and should state the expected relationships between cigarette type (i.e., menthol vs. non-menthol as the independent or predictor variable) and behavioral outcomes.

6.2. Select an appropriate study design for the outcome(s) of interest (i.e., initiation, cessation, dependence).

Once the study hypotheses are developed, an appropriate study design can be identified that is suited to testing the hypotheses. The study design should reflect the causal order that is implied by the hypothesized relationship. Key components of study designs for investigations of initiation, cessation, and dependency outcomes are listed below:

Initiation (cannot conduct a RCT for initiation)

- We recommend conducting a prospective, extended longitudinal study with a cohort of youth non-smokers at baseline

- Study duration should be long enough to capture and distinguish “experimentation” from initiation of “regular smoking”
- Include an indicator of the type of cigarette smoked at initiation as well as the type smoked if/when participant began to smoke regularly

Cessation

- Study design should be longitudinal and statistical methods should account for repeated measures when applicable
- Include an adequate length of follow-up to determine prolonged abstinence. We recommend a minimum follow-up of six months following onset of abstinence in order to evaluate prolonged abstinence
 - The Society for Research on Nicotine and Tobacco (SRNT) recommends prolonged abstinence (abstinence for at least 6 months after the start of treatment or initiation of cessation) as the primary outcome in smoking cessation studies
- Include precise definitions of smoking cessation and the onset of cessation among smokers who quit
- Where relevant, include methods to measure exposure to the intervention
- Include biochemical confirmation of self-reported abstinence
- If the study is a RCT, ensure adequate randomization and concealment of allocation

Behavior/Dependencies

- Depending on the hypothesis, a longitudinal or cross-sectional study design may be appropriate
- Use validated instruments that measure dependency, such as the FTND

6.3. *Implement a study design for which the primary comparison is between menthol and non-menthol smokers.*

In order to make empirically-based comparisons of the smoking initiation, cessation, and/or dependency behaviors of menthol and non-menthol smokers, a study must be designed to allow for such comparisons. In such studies, menthol smoking status or cigarette type preference should be included as the primary independent variable. Any sample size calculations conducted for such studies should be based on the number of menthol and separately, non-menthol smokers required to detect differences between these groups.

6.4. *Include valid and reliable indicators of cigarette type or preference (i.e., menthol status) and employ techniques to confirm self-reported menthol preference.*

A clear determination of cigarette type preference (i.e., menthol or non-menthol) is integral to any study that examines differences between menthol and non-menthol smokers.

Consistent across the national surveys reviewed in this quality assessment was the absence of items assessing the type of cigarette respondents either first tried or the type they smoked when they began smoking regularly. In order to form inferences regarding the relationship between menthol flavoring or cigarette type preference and smoking initiation, items assessing cigarette type first tried or cigarette type used when regular smoking began must be included. Likewise,

studies examining the relationship between menthol preference and smoking cessation should include indicators of cigarette type smoked most frequently throughout respondents' smoking histories, rather than the type smoked just prior to any quit attempts.

Where cigarette type preferences are obtained via self-reports, we recommend the use of multiple indicators to discern menthol and non-menthol preferences. In observational studies, for example, survey items assessing cigarette type (i.e., menthol and non-menthol), brand preferences, and strength of brand(s) used could be used together to serve as a superior indicator of cigarette type preference than either item used alone. Single-item, self-reported dichotomous indicators of cigarette type preference (i.e., “yes” or “no” indicators) are imperfect measures that can result in misclassification of actual type smoked or preferred. Consistent responses across multiple indicators increase our confidence that the information elicited from respondents is accurate. Inconsistent responses, however, indicate a problem of accuracy of self-reports. In such cases, additional methods may be developed to address the misclassification that results from inconsistent self-reports, or respondents with inconsistent responses may be omitted from the study population altogether.

Another method that could be used (in addition to or as an alternative to self-report) to determine or confirm cigarette type preferences would be to collect and classify cigarette butts smoked in the last day (for example); laboratory determination of menthol content from cigarette butts brought in by study participants may also be used.

In order to accurately link cigarette smoking “initiation” behaviors, questions relating to use of menthol vs. non-mentholated cigarettes must be carefully worded to evaluate the type used at initiation, experimental vs. regular smoking, whether more than one type was tried during an “experimental” period (and if so, what types), type first purchased, etc. In addition, techniques such as frequently evaluating participants to see if they have had any change related to smoking would limit the potential for recall bias associated with a time lapse between TTF cigarette tried and the study evaluation period. Depending on the sample size, age group(s) included, and other regulatory issues, asking participants to collect and store each cigarette butt tried over a period of time may be an appropriate way to confirm self-reported data.

In studies of dependency or cessation outcomes, the determination of cigarette type preference should take into account the length of time participants smoked their preferred or current type. Such studies should be able to distinguish long-time or consistent smokers of one type of cigarette (menthol vs. non-menthol) from those who may have recently switched cigarette types (for example, in an attempt to reduce their smoking or to quit). Such measures would maximize the potential of observing differences in behaviors based on menthol flavoring where actual differences exist. Where such long-term assessments of cigarette type preference are not possible, we would recommend including indicators of cigarette preference for at least one year prior to the start of the study and/or quit attempts. We also recommend capturing information on the predominant type preferred throughout the course of smoking, as well as indicators of all types of cigarettes smoked over the past year (or some other period of time).

6.5. *Precisely define the concepts to be measured and include measures that reflect these concepts.*

Concepts to be investigated, for example “menthol smoker”, “smoking cessation” or “nicotine dependence” should be precisely defined so that appropriate measures of the study concepts can be identified. Precise definitions of concepts facilitate the selection of valid and reliable measures that reduce measurement error, which should be a goal of any scientific study. A key function of hypothesis generation (Recommendation #1) is the specification of the concepts to be addressed in a given study. As such, hypotheses can be used to guide the development or selection of appropriate measures to promote consistency between the concepts included in the hypotheses and the measures or indicators used to represent these concepts.

Depending on the outcomes of interest, validated instruments may be available to measure the study concepts, such as the FTND which measures nicotine dependence.

One explanation for disparate findings in the cessation literature is that while such studies claim to examine “cessation” as an outcome, they often define cessation differently. Studies that define cessation as abstinence for a two-week period are likely to yield different results than those that define cessation as abstinence for a six-month period. This example serves to illustrate the importance of precisely defined concepts and the selection of measures that represent those concepts. In the case of studies of smoking cessation, a minimum period of abstinence should be defined and made explicit in the measure selected and conclusions based on the results obtained with a given measure should be similarly limited.

6.6. Select an appropriate sample for the population of interest and where appropriate, conduct power calculations to determine the minimum sample size required to detect differences between menthol and non-menthol smokers.

The underlying research question of a given study should guide the selection of the study sample. For example, if a given study is conducted to examine the association between cigarette type and smoking initiation among current regular smokers, current regular smokers should be distinguished from individuals who have only experimented with smoking at some time in the past. If the purpose of a study is to examine other smoking-related behaviors such as dependence, efforts should be made to distinguish between smoking frequency (daily vs. non-daily) and/or number of cigarettes smoked per day among individuals who currently smoke regularly and have smoked for some minimum specified period of time.

Many of the observational studies reviewed in this methodological evaluation were based on convenience and/or volunteer samples. The quality of evidence from such studies would be improved, however, if they were based on either the entire eligible population or a national probability sample. Where inclusion of the entire eligible population or the selection of a national probability sample is not feasible in a given study, power analyses should be conducted to determine the minimum sample size required to test the study’s hypotheses or to detect differences in outcomes between menthol and non-menthol smokers. The methods used for the power calculation should be clearly described in the protocol and reported in the study report and/or relevant publications. In the case of longitudinal designs, it is important to consider a realistic attrition rate (i.e., the proportion of original study participants who are lost to follow-up) when determining the minimum sample size required to detect differences between groups.

6.7. *Employ appropriate statistical techniques to control for any potential design effects, complex sampling methodologies, and potential confounding factors that may impact the relationships between menthol use and other smoking behaviors.*

The study hypotheses and statistical tests to be employed should be defined a priori in the study protocol or analysis plan. The analysis plan should clearly define the comparison or control groups that will be included in the study and specify the methods to be used to describe the baseline characteristics of menthol and non-menthol smokers, as well as which statistical tests will be conducted to compare the distributions of baseline socio-demographic and clinical characteristics (for example, race, gender, age, years smoked) of the key study groups.

Various studies have suggested there are significant differences in socio-demographic characteristics between menthol and non-menthol smokers. For example, menthol smokers are disproportionately African American and tend to be younger and of lower socioeconomic status than non-menthol smokers. Race, age, indicators of socioeconomic status, and other characteristics may act as intervening variables in the relationship between menthol preference and smoking behavior. These and other potential confounding variables (for example, total number of brands smoked, length of time smoking each brand), including potentially relevant interactions between variables (for example race and menthol preference), should be included in studies of menthol preference and smoking behavior. Any multivariate analyses conducted in a given study should adjust for baseline differences in these characteristics between groups, where appropriate. The study protocol and/or analysis plan should provide a detailed description of the methods to be used to identify potential differences in these characteristics between key study groups and the statistical techniques to be used to adjust for significant differences in these characteristics between menthol and non-menthol smokers.

Where appropriate, sensitivity analyses can be conducted to determine the sensitivity of study results to biases such as those that may result from different measures used to classify study participants (that is, measurement or classification error) and selection bias. Various methods of sensitivity analysis exist that can be applied to different types of measures and which take into account sampling variability.

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Appendix 1: Database Descriptions

EMBASE[®] has long been recognized as an important, comprehensive index of the world's literature on human medicine and related disciplines. Approximately 450,000 records are added annually, over 80 percent of which contain abstracts. Each record is classified and indexed by medical research specialists who assign terms and codes in accordance with EMTREE, a highly developed classification schedule and controlled vocabulary, consisting of over 45,000 terms and nearly 190,000 synonyms.

EMBASE[®] provides access to periodical articles from more than 3,700 primary journals from approximately 70 countries. An additional 350 journals are screened for drug articles.

EMBASE[®] consists of two files; File 73 contains records from January 1974 to the present, and File 72 contains records from 1993 to the present.

The EMBASE[®] database is used to produce 41 print abstract bulletins and one print drug literature bibliography. All journal articles are added to the database within 15 days after receipt of the journal, and all records appear online with complete indexing.

MEDLINE[®] (**Medical Literature, Analysis, and Retrieval System Online**), produced by the US National Library of Medicine (NLM), is the US NLM's premier bibliographic database that contains over 11 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the clinical sciences since 1966 including nursing, dentistry, veterinary medicine, pharmacy, allied health, and pre-clinical sciences. MEDLINE[®] also covers life sciences that are vital to biomedical practitioners, researchers, and educators, including some aspects of biology, environmental science, marine biology, plant and animal science as well as biophysics and chemistry. Increased coverage of life sciences began in 2000.

MEDLINE[®] is indexed using NLM's controlled vocabulary, MeSH[®] (Medical Subject Headings). An online thesaurus is available to aid in locating MeSH[®] descriptors.

Abstracts, which are taken directly from the published articles, are included for over 59 percent of the records added from 1975 forward. Records added before 1975 do not contain abstracts; records added from 1985 to the present have abstracts for about 69 percent of the records. Approximately 400,000 records are added per year, of which more than 76 percent are in English.

Records that previously would have been added to AIDSLINE[®], HealthSTAR, and Toxline[®] are now part of the MEDLINE[®] database. The MEDLINE[®] database also now contains In Process records (formerly known as PreMEDLINE).

BIOSIS Previews[®] contains citations from *Biological Abstracts*[®] (BA) and *Biological Abstracts/Reports, Reviews, and Meetings*[®] (BA/RRM) (formerly *BioResearch Index*[®]), the major publications of BIOSIS[®]. Together, these publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences.

BA includes approximately 350,000 accounts of original research yearly from nearly 6,000 primary journal and monograph titles. BA/RRM includes an additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, selected institutional and government reports, and research communications. US patents are included from 1986 through 1989.

Abstracts are available for records from the BA portion of the database starting in mid-1976 and for book synopses in BA/RRM starting in 1985. Most BA/RRM records do not contain abstracts.

The **PsycINFO® Psychological Abstracts** database provides access to the international literature in psychology and related behavioral and social sciences, including psychiatry, sociology, anthropology, education, pharmacology, and linguistics. Records for virtually all journal articles are accompanied by abstracts. All records from 1967 to the present are indexed using controlled vocabulary from the *Thesaurus of Psychological Index Terms*.

PsycINFO® contains citations and abstracts for journal articles, books, book chapters, reports, and dissertations from *Dissertation Abstracts International*. Journal material represents substantive articles selected on the basis of relevance to psychology from more than 1,700 journals published throughout the world in more than 25 languages.

Appendix 2: Content of Literature Tracking Database Spreadsheets

Article Information	All Articles Retrieved		Articles Evaluated*
	Literature Search	NCI Bibliography	
Author(s)	X	X	X
Title	X	X	X
Publication	X	X	X
Article Abstract	X	X	X
Retrieve?	X	X	
Article Review Required?	X	X	
Evaluate?	X	X	
Initiation	X	X	X
Cessation	X	X	X
Other Behavior	X	X	X
Reason (for not abstracting)	X	X	

* Also includes articles identified by Lorillard. NCI = National Cancer Institute

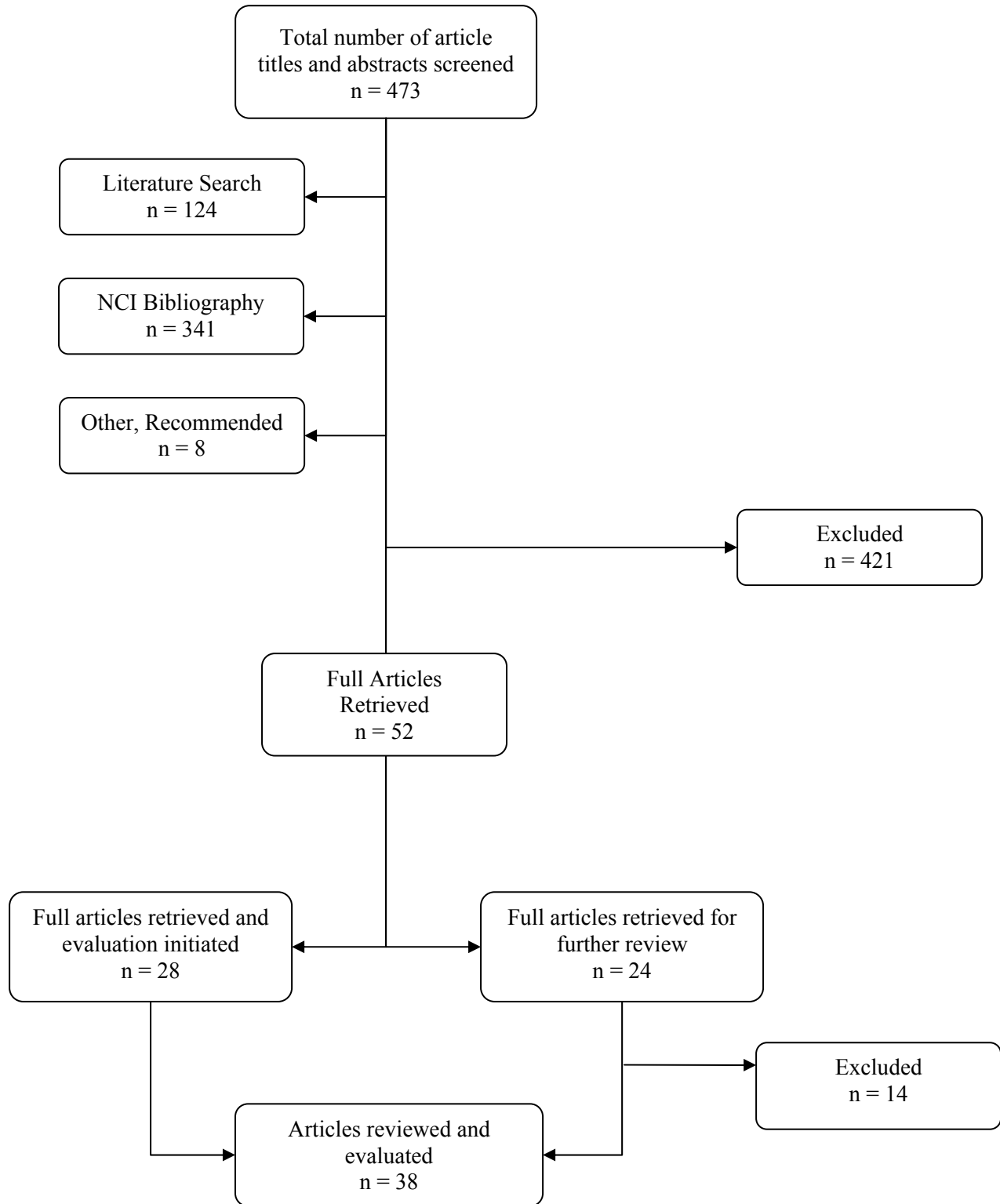
Appendix 3: Quality Review Form for Randomized Controlled Trial Studies

Question
1. Is this a drug study?
2. Was randomization adequate?
3. Was allocation of concealment adequate?
4. Are the groups similar at baseline?
5. Was the eligibility criteria specified?
6. Was blinding adequate?
7. Was the outcome assessor (Researcher) blind to the study participants?
8. Are participants blind to the study treatment?
9. Reporting of crossovers, adherence, and contamination.
10. Was attrition less than 25%? Please report percentage.
11. Was the differential attrition less than 15%?
12. Was a power analysis performed for the study?
13. Did the study use Intention to Treat analysis (impute missing responses)?
14. Did post randomization of exclusions occur in the study?
15. Was the standard of care described for the control group?
16. Is the study population representative of the population of interest?
17. Non-bias selection?
18. Low overall attrition at follow-up (less than 25%)?
19. Ascertainment techniques (instruments) were non-biased and adequately described?
20. Statistical analysis of potential confounders?
21. Was there adequate duration of follow-up (at least 6 months)?
22. What is the quality rating for this study? Please provide a rationale in the comment box.

Appendix 4: Quality Review Form for Non-Randomized Controlled Trial Studies

Question
1. Was the study population well described? (Study should describe both intervention and comparison populations and all relevant characteristics such as age, gender, SES).
2. Was the intervention well described? (What was done? how was it delivered? Who was targeted? Where it was done?)
3. Did the authors specify the sampling frame or universe of selection for the study population?
4. Did the authors specify the screening criteria for study eligibility?
5. Was the population that served as the unit of analysis the entire eligible population or a probability sample?
6. Are there other selection bias issues not identified above? This might include a very low participation rate (or a high refusal rate), a volunteer sample (as opposed to a convenience sample selected by the investigators), an inappropriate control or comparison group, or extremely restricted sampling inappropriate for measuring the effectiveness of intervention being studied.
7. Did the authors attempt to measure exposure to the intervention? (observation, interviews, self administered questionnaire, record review, lab test).
8. Was the exposure variable valid? (i.e., measured exposure in different ways, consistency checks for self-reports).
9. Was the exposure variable reliable? (measures of internal consistency were used, Cronbach's alpha, inter rater reliability).
10. Were the outcome and other (or predictor) variables valid?
11. Were the outcome and other (or predictor) variables reliable?
12. Conducted statistical testing when appropriate.
13. Reported which statistical tests were used.
14. Controlled for design effects in the statistical model.
15. Controlled for repeated measures in populations that were followed over time.
16. Controlled for differential exposure to the intervention.
17. Used a model designed to handle multilevel data when they included group-level and individual covariates in the model.
18. Were there other problems with the data analysis?
19. Was the attrition greater than 25% (if a survey, please write in the response rate)?
20. Did author assess whether unit of analyses were comparable prior to exposure to intervention?
21. Did author correct for controllable variables or institute procedures to appropriately limit bias (e.g., randomization, restriction, matching, stratification, statistical adjustment)?
22. Based on your overall impression of the study please rate the quality of article. Important issues: who are the participants, how are they selected, are good instruments used to measure the results, and are the results analyzed using appropriate methods. Can the results be replicated and are the outcomes generalizable? If not, this study may have a fatal flaw.

Appendix 5. Abstract Review and Study Selection Flow Chart




Appendix 6. Classification of All Studies Reviewed

Author, Year	Initiation	Cessation	Dependence
Ahijevych, K. 1999			X
Ahijevych, K. 1993			X
Ahijevych, K. 2002			X
Allen, B. 2007			X
Appleyard, J. 2001	X		
Berg, C. 2010		X	
Bover, M. 2008		X	X
Collins, C. 2006			X
Cropsey, K. 2009		X	
DiFranza, J. 2004	X		
Fagan, P. 2007		X	
Foulds, J. 2006		X	
Fu, F. 2008		X	
Gandhi, K. 2009		X	
Gundersen, D. 2009		X	
Harris, K. 2004		X	
Hersey, J. 2006	X		
Hooper, M. 2011			X
Hyland, A. 2002		X	
Hymowitz, N. 1995		X	X
Kaufman, 2004			X
Kreslake, J. 2008 ²⁵	X		
Kreslake, J. 2008 ⁴⁵			X
Li, Q. 2005		X	X
Moolchan, E, 2004			X
Moolchan, E. 2006			X
Muhammad-Kah, R. 2010			X
Muilenburg, J. 2008			X
Murray, R. 2007		X	
Muscat, J. 2009			X
Muscat, J. 2002		X	
Okuyemi, K. 2007		X	
Okuyemi, K. 2003		X	X
Okuyemi, K. 2004		X	
Pletcher, M. 2006		X	
Pollak, K. 2002		X	
Rose, J. 2004		X	
Wackowski, O. 2007			X

Appendix 7: Table of Contents for Article Summary Tables and Imbedded Tables File

INITIATION	Page	CESSATION	Page	OTHER BEHAVIOR	Page
Appleyard J. (2001)	5	Berg C. (2010)	18	Ahijevych K. (1993)	67
DiFranza J. (2004)	6	Bover M. (2008)	20	Ahijevych K. (1999)	67
Hersey J. (2006)	8	Cropsey K. (2009)	22	Ahijevych K. (2002)	70
Kreslake J. (2008)	13	Fagan P. (2007)	24	Allen B. (2007)	71
		Foulds J. (2006)	29	Collins C. (2006)	72
		Fu F. (2008)	31	Hooper M. (2011)	73
		Gandhi K. (2009)	33	Kaufman (2004)	78
		Gundersen D. (2009)	36	Kr66eslake J. (2008)	80
		Harris K. (2004)	38	Moolchan E. (2004)	81
		Hyland A. (2002)	40	Moolchan E. (2006)	82
		Hymowitz M. (1995)	42	Muhammad-Kah R (2010)	83
		Li Q. (2005)	44	Muilenburg J. (2008)	84
		Murray R. (2007)	46	Muscat J. (2009)	86
		Muscat J. (2002)	48	Wackowski O. (2007)	88
		Okuyemi K. (2004)	52		
		Okuyemi K. (2003)	53		
		Okuyemi K. (2007)	55		
		Pletcher M. (2006)	59		
		Pollak K. (2002)	62		
		Rose J. (2004)	64		


 Article Summaries

Appendix 7a: Additional Smoking Definitions Used in Reviewed Studies

First Author	Smoking Status	Definition
Ahijevych, K. 2002	Non-smoker	Those with at least 7 days of smoking abstinence
Berg, C. 2010	Light smoker	≤10 CPD
Bover, M. 2008	Night smoker, Non-night smoker	Definitions not provided
DiFranza, J. 2004	Tobacco user	Those who ever used any form of tobacco
Fagan, P. 2007	Current smoker	Smoked every day (daily smoker) or some days (non-daily smoker)
	Former smoker	Smoked ≥ 100 cigarettes in life, now smoking “not at all”
	Never smoker	Smoked <100 cigarettes in life
Gundersen, D. 2009	Former smoker	Smoked ≥ 100 cigarettes in life, now smoking “not at all”
	Current smoker	Smoked ≥ 100 cigarettes in life, now smoking “everyday” or “some days”
Hersey, J. 2006	Current smoker	Smoked cigarettes on ≥ 1 of past 30 days*
	Menthol smoker	Youth who reported that they smoked menthol cigarettes
	Non-menthol smoker	Youth who smoked possible non-menthol brands and youth who reported that they smoked non-menthol cigarettes
Hymowitz, N. 1995	Heavy smoker	Smoked >25 CPD
Kreslake, J. 2008	Beginning, Occasional smoker	Definitions not provided
Kreslake, J. 2008	Long-term smoker	Definition not provided; defined in other articles
Li, Q. 2005	Ex-smoker	Had not smoked the 6 months before the survey
Murray, R. 2007	Sustained quitter	Those biochemically confirmed at 5 annual visits and did not recall at any annual visit any months where smoked >1 CPD
	Intermittent smoker	Bio-chemically confirmed as quitters at some annual visits and as smoking at some annual visits
	Continuing smoker	Those smoking at all annual visits
Muscat, J. 2002	Ever smoker	Smoked ≥ 1 one CPD in one year
	Ex-smoker (Former)	“Ever smokers” who did not smoke at least one cigarette each day in the preceding year
Okuyemi, K. 2007	Light smoker	Smoked <10 CPD
Okuyemi, K. 2003	Abstinence	Confirmed by expired CO (and saliva in case of discrepancy)
Wackowski, O. 2007	Current established smoker	9 th – 12 th graders who smoked ≥ 100 cigarettes in their lifetime and also smoked in the past 30 days

CO = carbon monoxide; CPD = Cigarettes per day

* NYTS definition

Appendix 7b. Evaluation of Menthol vs. Non-Menthol Cigarette Smokers in Reviewed Studies

First Author	Menthol Variable [†]	Comments
Ahijevych, K. 1999	I,C	<ul style="list-style-type: none"> Smoke constituent exposure by ethnicity and menthol preference (women only) Decisional balance and habit strength by stage of change, ethnicity and menthol preference
Ahijevych, K. 1993	N/A	<ul style="list-style-type: none"> African American women 90% of sample smoked menthol, but menthol not used as a variable otherwise
Ahijevych, K. 2002	I	<ul style="list-style-type: none"> Study examined race/ethnicity, menthol status, body composition, and alcohol use history on cotinine half-life during 6 days of abstinence Factors explaining 52% of variance (and associated with longer half-life) were: African American, menthol smoker, fewer years of alcohol use, and greater lean body mass
Allen, B. 2007	D	<ul style="list-style-type: none"> Results indicate menthol smoking among African American is at least partly due to complex set of social, cultural norms
Appleyard, J. 2001	D	<ul style="list-style-type: none"> Report differences in age/grade of menthol cigarette use by race in youth
Berg, C. 2010	C	<ul style="list-style-type: none"> Secondary analysis of African American smokers in randomized clinical trial (RCT)
Bover, M. 2008	I	<ul style="list-style-type: none"> Age: 24-64, African American, or Hispanic Menthol smoking tested as predictor of night-smoking and smoking abstinence
Collins, C. 2006	I	<ul style="list-style-type: none"> Examined differences in youth consumption, tobacco dependence by menthol smoking using Fagerström Test for Nicotine Dependence (FTND), cigarettes per day (CPD), and time to first (TTF) cigarette
Cropsey, K. 2009	I,C	<ul style="list-style-type: none"> Examined cessation success by race
DiFranza, J. 2004	I	<ul style="list-style-type: none"> Examined predictors (including mentholation of first cigarette) of recalled response to first smoking experience and whether it predicts future dependency No significant difference in novice smoker's reaction to cigarettes or strength of addiction of different menthol status
Fagan, P. 2007	I	<ul style="list-style-type: none"> Nicotine dependence measures significantly associated with "quitting" and "intention to quit" among daily smokers; Socio-demographics (young [18-30] adult smokers) associated with "quitting" and "intention to quit" among non-daily smokers
Foulds, J. 2006	I	<ul style="list-style-type: none"> Convenience sample; menthol preference is one of many predictors of abstinence examined
Fu, F. 2008	I	<ul style="list-style-type: none"> Observed no significant effects for menthol smoking or ethnicity on smoking abstinence rates
Gandhi, K. 2009	I	<ul style="list-style-type: none"> Convenience sample of 1,688 consecutive patients of different ethnicities
Gundersen, D. 2009	I	<ul style="list-style-type: none"> Menthol and race were focal independent variables
Harris, K. 2004	I	<ul style="list-style-type: none"> Logistic regression identified three significant independent predictors
Hersey, J. 2006	I	<ul style="list-style-type: none"> Smoking uptake in youth; Menthol self-reported

First Author	Menthol Variable [†]	Comments
Hooper, M. 2011 ²³	D	<ul style="list-style-type: none"> State analyses un-weighted because they did not intend to generalize the findings to a population level
Hyland, A. 2002	I	<ul style="list-style-type: none"> No consistent associations observed for menthol use/dependence in overall and race-specific analyses
Hymowitz, N. 1995	D	<ul style="list-style-type: none"> Compared smoking characteristics of non-Hispanic white, non-Hispanic black, Mexican-origin, and Puerto Rican-origin smokers
Kaufman, 2004	D	<ul style="list-style-type: none"> Brand preferences and switching patterns in adolescents
Kreslake, J. 2008 ²⁵	N/A	<ul style="list-style-type: none"> One quality reviewer noted several inconsistencies between report and references
Kreslake, J. 2008 ⁴⁵	D	<ul style="list-style-type: none"> Menthol content and target groups across several brands
Li, Q. 2005	C	<ul style="list-style-type: none"> Self-reported menthol status Data drawn from Behavioral Risk Factor Surveillance System (BRFSS) survey
Moolchan, E, 2004	D	<ul style="list-style-type: none"> Convenience sample: youth 13-17 years old
Moolchan, E. 2006	C	<ul style="list-style-type: none"> Described ethnic/racial differences, with a focus on nicotine metabolism
Muhammad-Kah, R. 2010	I	<ul style="list-style-type: none"> Poster on menthol (OR) and nicotine dependence/time to first cigarette
Muilenburg, J. 2008	I	<ul style="list-style-type: none"> Menthol smoking status one of several predictor variables analyzed included in the analysis
Murray, R. 2007	I	<ul style="list-style-type: none"> Associations of menthol and (1) health risks, (2) nicotine dependence
Muscat, J. 2009	I	<ul style="list-style-type: none"> Effects of menthol on smoke exposure, nicotine dependence, and NNAL glucuronidation
Muscat, J. 2002	I	<ul style="list-style-type: none"> Cross-sectional analysis; risk of quitting was not associated with cigarette menthol flavor Authors note most subjects who smoked menthol during their lifetime also smoked non-menthol cigarettes Subjects classified as menthol smoker if the LAST brand smoked (current and former smokers) was menthol
Okuyemi, K. 2007	I	<ul style="list-style-type: none"> Specific to African American light smokers
Okuyemi, K. 2003	I	<ul style="list-style-type: none"> Secondary analysis of data from RCT of sustained-release bupropion for smoking cessation
Okuyemi, K. 2004	I	<ul style="list-style-type: none"> Convenience sample, menthol smoking status self-reported
Pletcher, M. 2006	I	<ul style="list-style-type: none"> 74% retention of surviving cohort at 15 years follow-up
Pollak, K. 2002	C	<ul style="list-style-type: none"> Focused on advice received from physicians to quit smoking
Rose, J. 2004	C	<ul style="list-style-type: none"> Findings demonstrate the importance of sensory cues in determining subjective reward
Wackowski, O. 2007	I	<ul style="list-style-type: none"> Examined relationship between dependence measures and (1) Smoke menthol exclusive brand, (2) Usually smoke menthol cigarettes (3) Regular menthol use

[†] C = Control Variable; D = Dependent Variable; I = Independent Variable

BRFSS: Behavioral Risk Factor Surveillance System; **CPD:** Cigarettes per Day; **FTND:** Fagerström Test for Nicotine Dependence; **OR:** Odds Ratio; **RCT:** Randomized controlled trial; **TTF:** Time to first (cigarette).

Appendix 8a. Quality Rating by Author: Initiation Studies

Author, Year	Quality Rating Overall	Rating: Menthol Inferences
Appleyard, J. 2001	Good	Fair
DiFranza, J. 2004	Fair	Fair
Hersey, J. 2006	Fair/poor	Fair/poor
Kreslake, J. 2008	Fair	Poor

Appendix 8b. Quality Rating by Author: Dependence/Other Behavior Studies

Author, Year	Quality Rating Overall	Rating: Menthol Inferences
Ahijevych, K. 1999	Poor	Poor
Ahijevych, K. 1993	Fair	Poor
Ahijevych, K. 2002	Fair	Poor
Allen, B. 2007	Fair/poor	Poor
Bover, M. 2008 [†]	Fair	Poor
Collins, C. 2006	Poor	Poor
Hooper, M. 2011	Poor	Poor
Hymowitz, N. 1995 [†]	Fair	Poor
Kaufman, 2004	Fair/poor	Poor
Kreslake, J. 2008	Fair	Poor
Li, Q. 2005 [†]	Poor	Poor
Moolchan, E 2004	Fair	Poor
Moolchan, E. 2006	Good	Good
Muhammad-Kah, R. 2010	Fair/good	Fair/good
Muilenburg, J. 2008	Poor	Poor
Muscat, J. 2009	Fair	Poor
Okuyemi, K. 2003 [†]	Fair	Fair
Wackowski, O. 2007	Fair/poor	Poor

[†] Article also considered under “Cessation” section

Appendix 8c. Quality Rating by Author: Cessation Studies

Author, Year	Quality Rating Overall	Rating: Menthol Inferences
Berg, C. 2010	Fair	Fair
Bover, M. 2008 [‡]	Fair	Poor
Cropsey, K. 2009	Good	Poor
Fagan, P. 2007	Fair/poor	Poor
Foulds, J. 2006	Fair	Fair
Fu, F. 2008	Fair	Poor
Gandhi, K. 2009	Good	Fair
Gundersen, D. 2009	Good	Fair/good
Harris, K. 2004	Poor	Poor
Hyland, A. 2002	Fair	Fair
Hymowitz, N. 1995 [‡]	Fair	Poor
Li, Q. 2005 [‡]	Poor	Poor
Murray, R. 2007	Fair/good	Fair/good
Muscat, J. 2002	Fair	Fair
Okuyemi, K. 2007	Good	Fair
Okuyemi, K. 2003 [‡]	Fair	Fair
Okuyemi, K. 2004	Poor	Poor
Pletcher, M. 2006	Good	Good
Pollak, K. 2002	Good	Poor
Rose, J. 2004	Good	Fair/good

[‡]Article also considered under “Dependence/Other Behaviors” section

Appendix 9a. Summary of Quality Rating for All Studies Reviewed

Study Type	Overall	Related to Menthol
All Studies Reviewed (n = 38)	Good: 9 Good to Fair: 2 Fair: 15 Fair to Poor: 5 Poor: 7	Good: 2 Good to Fair: 4 Fair: 9 Fair to Poor: 1 Poor: 22
RCTs (n = 3)	Good: 2 Good to Fair: 0 Fair: 0 Fair to Poor: 0 Poor: 1	Good: 0 Good to Fair: 1 Fair: 1 Fair to Poor: 0 Poor: 1
Non-RCTs (n = 31)	Good: 6 Good to Fair: 1 Fair: 13 Fair to Poor: 5 Poor: 6	Good: 2 Good to Fair: 2 Fair: 6 Fair to Poor: 1 Poor: 20
Both (n = 4)	Good: 1 Good to Fair: 1 Fair: 2 Fair to Poor: 0 Poor: 0	Good: 0 Good to Fair: 1 Fair: 2 Fair to Poor: 0 Poor: 1

Appendix 9b. Summary of Quality Rating: Initiation Studies

Study Type	Overall	Related to Menthol
Initiation Studies (n = 4)	Good: 1 Good to Fair: 0 Fair: 2 Fair to Poor: 1 Poor: 0	Good: 0 Good to Fair: 0 Fair: 2 Fair to Poor: 1 Poor: 1
RCTs (n = 0)	Good: 0 Good to Fair: 0 Fair: 0 Fair to Poor: 0 Poor: 0	Good: 0 Good to Fair: 0 Fair: 0 Fair to Poor: 0 Poor: 0
Non-RCTs (n = 4)	Good: 1 Good to Fair: 0 Fair: 2 Fair to Poor: 1 Poor: 0	Good: 0 Good to Fair: 0 Fair: 2 Fair to Poor: 1 Poor: 1

Appendix 9c. Summary of Quality Rating: Dependence/Other Behavior Studies*

Study Type	Overall	Related to Menthol
“Other” Studies (n = 18)	Good: 1 Good to Fair: 1 Fair: 8 Fair to Poor: 3 Poor: 5	Good: 1 Good to Fair: 1 Fair: 1 Fair to Poor: 0 Poor: 15
RCTs (n = 0)	N/A	N/A
Non-RCTs (n = 17)	Good: 1 Good to Fair: 1 Fair: 7 Fair to Poor: 3 Poor: 5	Good: 1 Good to Fair: 1 Fair: 0 Fair to Poor: 0 Poor: 15
Both (n = 1)	Good: 0 Good to Fair: 0 Fair: 1 Fair to Poor: 0 Poor: 0	Good: 0 Good to Fair: 0 Fair: 1 Fair to Poor: 0 Poor: 0

* Four studies also evaluated under the “Cessation” section

Appendix 9d. Summary of Quality Rating: Cessation Studies*

Study Type	Overall	Related to Menthol
Cessation Studies (n = 20)	Good: 7 Good to Fair: 1 Fair: 8 Fair to Poor: 1 Poor: 3	Good: 1 Good to Fair: 3 Fair: 7 Fair to Poor: 0 Poor: 9
RCTs (n = 3)	Good: 2 Good to Fair: 0 Fair: 0 Fair to Poor: 0 Poor: 1	Good: 0 Good to Fair: 1 Fair: 1 Fair to Poor: 0 Poor: 1
Non-RCTs (n = 13)	Good: 4 Good to Fair: 0 Fair: 6 Fair to Poor: 1 Poor: 2	Good: 1 Good to Fair: 1 Fair: 4 Fair to Poor: 0 Poor: 7
Both (n = 4)	Good: 1 Good to Fair: 1 Fair: 2 Fair to Poor: 0 Poor: 0	Good: 0 Good to Fair: 1 Fair: 2 Fair to Poor: 0 Poor: 1

* Four studies also evaluated under the “Dependence” section

Appendix 10. Inconsistencies or Comments on Studies Reviewed

Author, Year	Inaccuracies or Comments
Ahijevych, K. 1999	<p>Authors measure nicotine dependence by measuring time to first cigarette in minutes (as a continuous variable). However, cited reference (Heatherton <i>et al.</i>, 1989) recommends collecting this information categorically.</p>
Ahijevych, K. 2002	<p>Authors measure nicotine dependence by measuring time to first cigarette in minutes (as a continuous variable). However, cited reference (Heatherton <i>et al.</i>, 1989) recommends collecting this information categorically.</p>
Fu, F. 2008	<p>Total % by race (Table 1) is not consistent with the % race in results (top of 2nd column on page 459)</p>
Gundersen, D. 2009	<p>Authors note in the Strengths and Limitations section that the cross-sectional design only allows for examination of associations and generation of hypotheses, but can not identify predictors or causal factors. Nonetheless, on the same page within the Discussion, authors state, “menthol smoking has a different effect on cessation among whites and non-whites”.</p>
Harris, K. 2004	<p>Discussion section, page 501 2nd column, 3rd full paragraph, authors state “participants in our study were not only African-American, but were also predominantly female and middle aged.” Unable to confirm from information provided that they were predominantly middle aged. Although Table 2 shows the mean age, without more information on the inclusion/exclusion criteria or additional information on age of participants, this is hard to confirm. Also, last full paragraph in 1st column on page 501, 1st and 3rd sentence don’t seem to make sense together (see below)</p> <p style="padding-left: 40px;">In contrast to some prior studies, we found that men were only slightly more likely to quit compared to women (33.73% vs. 30.8%). Even though 70% of the participants in this study were women, there were sufficient number of men enrolled to detect a meaningful difference in quit rates if one existed. One possible explanation for this finding is that bupropion, compared to nicotine replacement products, may be particularly useful in helping women remain abstinent [29]. However, quit rates at 7 weeks in other trials using bupropion are inconclusive. A dose-response study</p>
Hersey, J. 2006	<p>Authors indicate in table 1 that there were 1,552 menthol smokers. However, calculating backwards using the numbers and percents provided in Figure 1, data from more than 1,552 menthol smokers were analyzed. Where is this 1,552 coming from? The 2002 NYTS?</p> <p>In addition, Figure 1 notes there were 3,202 youth, while Figure 2 suggests there were 3,095 youth evaluated in the 2002 NYTS:</p> <p>Figure 1: 3,202 youth (817 middle school and 2,385 high school students) in the 2002 NYTS who had smoked on one or more of the prior 30 days and who indicated the brand and/or the menthol status of the cigarettes they usually smoked.”</p> <p>Figure 2: “Data were based on 760 middle school students and 2,335 high school</p>

Author, Year	Inaccuracies or Comments																		
	students in the 2002 NYTS who had 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.”																		
Hooper, M. 2011	Kassel, 2003 (ref 31) for the Nicotine Dependence Syndrome Scale. Discrepant p-values reported in Table 2 and in the text (page 9) with regards to nicotine dependence among menthol and non-menthol smokers (p = 0.005 vs. p = 0.0005).																		
Hyland, A. 2002	In their discussion, the authors based menthol status on self-reported measure because the universal product code (UPC) was not available for many people. However, the methods make no mention of collecting the UPC, and it is not clear whether participants were required to bring a UPC code with them. The authors relied on self-reported menthol status because UPC was missing for a large number of people. Although there was 98% agreement between self-report and the UPC code for those providing a UPC code, this could be a small sample overall.																		
Kaufman, 2004	Authors do not cite a reference for the Robert Wood Johnson Foundation survey																		
Kreslake, 2008 (menthol smoker)	Inaccurate information provided in Figure 4 according to their referenced sources.																		
Moolchan, 2004	The discussion states that the findings are consistent with data showing that adolescents smoke the most heavily advertised brands. However, the results do not provide any information on brand(s) smoked.																		
Muscat, J. 2009	Inconsistencies with FTND. Materials and Methods section (page 36, 1 st column) states that the FTND administered to 278 subjects. However, the numbers reported in Table 3 don't add up to 278 subjects. Numbers in table 3 also the same for High vs. Low FTND and TTF. <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Measure</th> <th>Nonmenthol</th> <th>Menthol</th> <th>Covance Comment</th> </tr> </thead> <tbody> <tr> <td>Low or medium FTND</td> <td>96 (46)</td> <td>96 (45)</td> <td rowspan="2">Same numbers/ different standard errors</td> </tr> <tr> <td>High FTND</td> <td>78 (53)</td> <td>78 (55)</td> </tr> <tr> <td>TTF > 30</td> <td>26 (34%)</td> <td>26 (21%)</td> <td rowspan="2">Same numbers/ different percents</td> </tr> <tr> <td>TTF = 30</td> <td>98 (66%)</td> <td>98 (79%)</td> </tr> </tbody> </table>	Measure	Nonmenthol	Menthol	Covance Comment	Low or medium FTND	96 (46)	96 (45)	Same numbers/ different standard errors	High FTND	78 (53)	78 (55)	TTF > 30	26 (34%)	26 (21%)	Same numbers/ different percents	TTF = 30	98 (66%)	98 (79%)
Measure	Nonmenthol	Menthol	Covance Comment																
Low or medium FTND	96 (46)	96 (45)	Same numbers/ different standard errors																
High FTND	78 (53)	78 (55)																	
TTF > 30	26 (34%)	26 (21%)	Same numbers/ different percents																
TTF = 30	98 (66%)	98 (79%)																	
Okuyemi, K. 2003	p-value in results for employment (p=0.0002) different than p-value for employment in Table 1 (p=0.004)																		
Okuyemi, K. 2004	The authors cite Ahluwalia (2002) in their discussion section (reference 20, 1 st full sentence in 1 st column on page 1211). "However, in one study, menthol smokers rated cigarette taste and satisfaction more favorably than nonmenthol smokers." Cannot confirm this using the Ahluwalia article.																		
Okuyemi, K. 2007	In the Statistical Analysis section of the methods, the authors state “As use of menthol cigarettes is known to differ substantially between smokers younger than 50 years (90%) and those ≥ 50 years (66%) and in order to replicate findings from a previous study of bupropion in African Americans...” and cite a previous publication by the same author (Okuyemi K., 2003). The percentages reported here are not correct according to Okuyemi K., 2003. Okuyemi K., 2003 reports that use of menthol among smokers younger than 50 years is 88.7%, and menthol among smokers ≥ 50 years is 49.7%. Additionally, the Results section focuses primarily on outcomes not identified as the primary outcome in the Methods. The randomization explained in detail in the Methods seemed to be “thrown out” when analyzing the data, as many of the results																		

Author, Year	Inaccuracies or Comments
	<p>did not reflect the randomized study groups.</p> <p>Finally, on page 1984, 2nd column, 1st paragraph, the authors sentence makes no sense: <i>“In summary, the current study has shown for the first time that, similar to what has been reported for moderate and heavy smokers, African American light smokers who smoke menthol cigarettes have lower cessation rates at 26 weeks after enrollment than menthol smokers.”</i></p>
Pollak, K. 2002	<p>Authors don't mention what measures (if any) were used in their study, and therefore not clear whether validated measures used to evaluate (for example) TTF. Also, authors cite Prochaska (1983) as the basis for their questions on readiness to stop smoking. However, based on the current stages of change model, they did not use the correct wording for their questions.</p>

Appendix 11. Definition of Cessation Outcome and Menthol Cigarette Use by Author

First Author	Definition(s) Cessation Outcome	Definition of Menthol Cigarette Use
Bover, M. 2008	Self-reported 7-day point prevalent smoking abstinence at 26 weeks	Not described
Cropsey K. 2009	Biochemically verified, self-reported 7-day point prevalent smoking abstinence at 3, 6, 12 months follow-up; confirmed by CO \leq 2 ppm	Not described
Fagan, P. 2007	Self-reported quit attempts in previous 12 months via the following: “How many times during the past 12 months have you stopped smoking for 1 day or longer because you were trying to quit smoking?” (1 or more quit attempts; 0 quit attempts)	Not described
Fu, F. 2008	Self-reported 7-day point prevalent smoking abstinence	Asked if they smoked menthol cigarettes 2 years ago.
Gandhi, K. 2009	Biochemically verified, self-reported 7-day point prevalent smoking abstinence at 4 weeks/ 6 months; confirmed by CO \leq 10 ppm	Not described
Gundersen, D. 2009	Self-reported former smoker (smoked 100 cigarettes in a lifetime and now smoking “not at all.”)	Self-report whether usual cigarette brand in past 12 months/ 12 months prior to quitting was mentholated.
Harris, K. 2004	Biochemically verified, self-reported 7 day point-prevalence abstinence at end of week 7; confirmed by CO level \leq 10 ppm or CO $>$ 10 ppm but salivary cotinine \leq 20 ng/ml	Not described
Hyland, A. 2002	Self-reported smoking status, defined by “Do you smoke now?” and “Have you smoked any cigarettes in the last 6 months?”	Not described
Hymowitz, N. 1995	Self-reported attempts to quit smoking in past 12 months	Not described
Murray, R. 2007	Biochemically verified, self-reported abstinence at annual visits	“Do you now smoke cigarettes?”, “What type of cigarettes are they? Are they plain or menthol?”
Muscat, J. 2002	Self-reported former smokers defined as ever smokers who did not smoke at least 1 cigarette each day for the preceding year	Self-report information on menthol content (menthol vs. unflavored)
Okuyemi, K. 2007	Biochemically verified 7 day point-prevalence abstinence at 26 weeks -up; confirmed by CO \leq 10 ppm or salivary cotinine \leq 20 ng/ml	Participants self-reported use of menthol or non-menthol cigarettes
Okuyemi, K. 2003	Biochemically verified, self-reported 7 day point-prevalence abstinence at 6 weeks and 6 months; confirmed by CO level \leq 10 ppm or salivary cotinine \leq 20 ng/ml	Not described
Okuyemi, K. 2004	Success in past cessation assessed by asking: number of lifetime quit attempts, time since most recent quit attempt, duration of most recent attempt, and duration of longest ever quit attempts	Preferred cigarette brand (menthol or non-menthol, strength, length, etc.) and how long they have smoked at current rate
Pletcher, M. 2006	Current smoking status, recent quit attempts (“Have you [tried, made	“Is [your current (brand of cigarettes)] mentholated or

First Author	Definition(s) Cessation Outcome	Definition of Menthol Cigarette Use
	any attempts] to quit smoking in the past [2, 3, 5] years?”, cessation if recent quit attempt, sustained cessation (no current smoking in the past 2 times examined); all measured at 2, 5, 7, 10, and 15 years follow-up.	non-mentholated?”
Pollak, K. 2002	Self-reported number of prior quit attempts \geq 24 hours duration	Whether they smoked menthol cigarettes (yes/no).....
Rose, J. 2004	Self-reported number of CPD; CO to verify overnight abstinence	The terms mentholated and non-mentholated are based on package labeling
Berg, 2010	Biochemically verified, self-reported cessation at 26 weeks; confirmed by salivary cotinine of \leq 20 ng/ml.	Not described
Foulds, J. 2006	Self-reported 7 day point-prevalence abstinence (“Have you used any tobacco in the past 7 days?”) at 4 weeks and 6 months; confirmed by CO level \leq 10 ppm during in-person follow-up	Not described
Li, Q. 2005	Self-reported abstinence in previous 6 months at 8 year follow-up	Subjects reported whether current cigarette brand was menthol or not in 1988, 1993 and 2001

Appendix 12. Summary of Findings: Conclusion

Findings by Author: “Good”, “Good to Fair”, or “Fair” Studies

Author	No difference*	Difference*	Comments
Initiation			
Appleyard, J. 2001	X		NYTS 2000 data indicate that during the last year of high school, 1/3 rd of Asian American youth smoke. Of these youth, 60% reported that that their usual brand of cigarettes is mentholated.
DiFranza, J. 2004	X		Menthol does not affect novice smoker’s reaction to first cigarette.
Dependence/Other			
Moolchan, E. 2006	X		African American smokers smoke fewer cigarettes per day; differences may be explained by metabolism or reasons other than menthol cigarette use.
Muhammad-Kah, R. 2010	X		Results add to the existing evidence that menthol does not increase nicotine dependence.
Okuyemi, K. 2003		X	African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, putting menthol smokers at greater risk from the health effects of smoking. Important to note that the authors’ conclusion doesn’t fit with the totality of data; at 6 months there were no differences.
Cessation			
Berg, C. 2010		X	Discussion states more non-reducers used menthol cigarette than did reducers. Important to note that the authors’ conclusion doesn’t fit with the totality of data; discussion states more non-reducers used menthol cigarettes than did reducers, but this finding was not significant.
Foulds, J. 2006		X	Menthol smokers were less likely to achieve abstinence in univariate analyses, and this item remained in the model predicting 4-week outcome. Important to note that the authors’ conclusion doesn’t fit with the totality of data; menthol smoking status did not remain in the model at 26 weeks, and though it remained in the model at four weeks, it was not a significant predictor (p=0.053).

Author	No difference*	Difference*	Comments
Gandhi, K. 2009		X	Despite smoking fewer CPD, African American and Latino menthol smokers experience reduces success in quitting as compared with non-menthol smokers within the same ethnic/racial groups. Important to note that the authors' conclusion doesn't fit with the totality of data; didn't adjust for significant differences in confounding/ socioeconomic factors.
Gundersen, D. 2009		X	Our findings provide some support for the hypothesis that menthol smoking can lead to poorer cessation outcomes, but only for non-white smokers. Important to note different direction for African Americans and Hispanics vs. whites, which may be explained by reasons other than menthol cigarette use (for example, metabolism, socioeconomic). Also a cross-sectional study; no intervention.
Hyland, A. 2002	X		No clear associations between menthol use and three self-reported indicators of nicotine dependence (even after controlling for race/ethnicity and other demographics) in this large, prospective study with data on a variety of measures associated with cessation.
Murray, R. 2007	X		No difference in smoking cessation success; no indication that menthol contributes to well-known harm from smoking.
Muscat, J. 2002	X		Menthol does not increase the addictive properties of nicotine dependence, and risk of quitting not associated with cigarette flavor. Important to note limited generalizability: newly diagnosed lung cancer patients.
Okuyemi, K. 2007		X	Menthol cigarette use associated with lower cessation rates among African American light smokers. Important to note that the authors' conclusion doesn't fit with the totality of data; didn't adjust for significant differences in confounding/ socioeconomic factors. Figure 3 (actual randomization based on study design) shows no significance.

Author	No difference*	Difference*	Comments
Okuyemi, K. 2003		X	African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR. Important to note that the authors' conclusion doesn't fit with the totality of data; at 6 months, there are no sig. differences between menthol and non-menthol, but authors based their conclusion on 6 week findings.
Pletcher, M. 2006		X	Menthol and non-menthol cigarettes seem to be equally harmful per cigarette smoked in terms of atherosclerosis and pulmonary function decline, but menthol cigarettes may be harder to quit smoking. Important to note that the authors' conclusion doesn't fit with the totality of data; 4 of 5 indicators of dependence showed no difference; no difference in coronary calcification and pulmonary function, but report difference in risk of relapse – from the ONE indicator.
Rose, J. 2004	X		Analysis focused more on decoupling nicotine from addiction. Not able to make conclusions about menthol initiation and/or cessation.

* Between menthol and non-menthol

Findings by Author: “Fair to Poor” or “Poor” Studies

Author	No difference*	Difference*	Comments
Initiation			
Hersey, J. 2006		X	Results indicate that the proportion of students who smoked menthols was higher among middle school students who had been smoking for less than one year compared to similar students who had been smoking for >1 year. Important to note that current brand and flavor preferences (past 30 days) cannot be assumed to be the initiation product.
Kreslake, J. 2008	N/A	N/A	Article tended toward editorializing, and no primary analyses were conducted using menthol status.
Dependence/Other			
Ahijevych, K. 1999		X	Menthol smokers had significantly shorter time to first cigarette of the day compared to non-menthol smokers. Important to note that authors selected just one item from FTND, which has not been validated as a single-item measure of dependence.
Ahijevych, K. 1993	N/A	N/A	Summarized menthol and non-menthol smoking status at baseline, but the authors did not use this as a variable in the data analysis.
Ahijevych, K. 2002	X		No significant difference in time to first cigarette between menthol and non-menthol smokers. Nicotine dependence was not predicted by menthol smoking status. Important to note that authors selected just one item from FTND, which has not been validated as a single-item measure of dependence.
Allen, B. 2007	X		Results indicate that menthol smoking among adult African Americans is at least partly a consequence of a complex set of social and cultural norms.
Bover, M. 2008	X		Several socioeconomic and tobacco use characteristics are shared among people that wake at night to smoke, and this behavior was strongly related to other measures of nicotine dependence. Menthol smoking status was not significant at 26 weeks.
Collins, 2006		X	While preliminary, findings suggest greater smoking urgency among menthol compared to non-menthol adolescent cessation-treatment seekers. Important to note smoking urgency is not equivalent to smoking dependency.

Author	No difference*	Difference*	Comments
Hooper, M. 2011		X	Significant difference in nicotine dependence between menthol and non-menthol groups ($p = 0.005$), such that non-menthol smokers reported greater dependence compared to menthol smokers. Important to note while a difference was found, it is in the opposite direction .
Hymowitz, 1995	N/A	N/A	Authors did not conduct analyses of dependence between menthol and non-menthol smokers.
Kaufman, 2004		X	Newport's market share has increased among adolescents from 1989 to 1996. Important to note that the study did not include any validated measure of dependence; study only reports on brand choice.
Kreslake, J. 2008		X	Newport's market share has increased among adolescents from 2000 to 2005. Important to note that the study did not include any validated measure of dependence; study only reports on market share.
Li, Q. 2005	X		No consistent pattern was found between use of menthol cigarettes and nicotine dependence.
Moolchan, E, 2004	N/A	N/A	Only ethnicity and gender were tested for associations with preference for menthol.
Muilenburg, J. 2008	X		Differences were found between menthol and non-menthol smokers; however, none of these differences were measured or validated to assess dependence.
Muscat, J. 2009	X		Menthol is not associated with a higher exposure to tobacco smoke carcinogens, but findings on nicotine dependence are inconclusive.
Wackowski, O. 2007		X	Menthol cigarette smoking was associated with two dependence measures and may be more addictive than regular cigarettes in young smokers. Important to note that the two other measures of dependence used in the analysis were not significantly different. The correct interpretation would be that the results are mixed or unclear.
Cessation			
Bover, M. 2008	X		Several socioeconomic and tobacco use characteristics are shared among people that wake at night to smoke, and this behavior was a strong predictor of 26-week abstinence. Menthol smoking status was not significant at 26 weeks.
Cropsey, K. 2009	X		Smoking menthol cigarettes was not associated with differences in quit rates.
Fagan, P. 2007	X		Menthol and non-menthol smokers did not significantly differ in their odds of making one or more quit attempts in the past 12 months.

Author	No difference*	Difference*	Comments
Fu, F. 2008	X		Observed no significant effects for menthol cigarette smoking or ethnicity on smoking abstinence rates. Findings suggest that smoking menthol cigarettes does not decrease smoking cessation among older smokers during a quit attempt aided with pharmacotherapy.
Harris, K. 2004	X		Menthol smoking status was not a significant predictor of 7-day cessation.
Hymowitz, N. 1995	N/A	N/A	Analyses did not attempt to link menthol smoking status with cessation outcomes.
Li, Q. 2005	X		No consistent pattern was found between use of menthol cigarettes and cessation.
Okuyemi, K. 2004		X	African American menthol smokers are less successful with smoking cessation. Important to note that conclusions do not fit the totality of the data; menthol smokers reported more recent quit attempts ($p = .047$), but the duration of the more recent quit attempts and the duration of the longest-ever quit attempt were not different between menthol and non-menthol smokers ($p = .187$ and $p = .111$, respectively).
Pollak, K. 2002	N/A	N/A	Authors assessed factors associated with health providers giving smoking cessation advice; did not assess actual cessation.

* Between menthol and non-menthol smokers