

Center for Regulatory Effectiveness (CRE) assessment of
the following research report:

**“Does menthol attenuate the effect of bupropion among
African American smokers?”**

By:

Kolawole S. Okuyemi, Jasjit S. Ahluwalia, Maiko Ebersole-Robinson, Delwyn
Catley, Matthew S. Mayo & Ken Resnicow (20003)

August 2010

Reference:

- a. Research Report: “Does menthol attenuate the effect of bupropion among African American smokers?” Society for the Study of Addiction to Alcohol and Other Drugs, No. 98, February 2003, pp. 1387-1393, by Dr. Kolawole S Okuyemi, et al.
- b. Clinical Study: “Sustained-Release Bupropion for Smoking Cessation in African Americans.” Journal of the American Medical Association, July 2002, Vol 288, No 4, pp. 468-474, by Jasjit S. Ahluwalia, Kari Jo Harris, Delwyn Catley, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its focus on the efficacy of medication on menthol smokers among African Americans. The researchers presented the following primary results:

- At the 6-week follow-up point, non-menthol cigarette smokers (younger than 50 years old category) were more likely to quit smoking than menthol cigarette smokers;
- At the 6-week follow-up point, when data was separated by treatment, non-menthol cigarette smokers (younger than 50 years old category) who received the bupropion pill, were more likely to quit smoking than menthol cigarette smokers;

The researchers concluded “African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with [the] bupropion-SR [medicated pill], thereby putting menthol smokers at greater risk from the health effects of smoking.”

The reader should be aware that data used for this report “...derived from a [previous] study (reference (b)) which was not designed to test whether menthol smokers have lower quit rates than non-menthol smokers.” [p. 1392] “The parent (previous) study was a double-blind, placebo-controlled, randomized trial of 600 African American smokers.” [p. 1388] So, both the patient and the administrator of medications did not have knowledge of the type of treatment they were receiving/administering (the placebo (a fake pill) vs. bupropion SR). All smokers had the following characteristics: at least 18 years of age, smoked at least 10 cigarettes a day and were

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interested in quitting within the next 30 days. The following timeline generally illustrates the 7-week clinical study plan:

Week 0	Weeks 1-2	Weeks 3-6	End of Trial	Month 6
<ul style="list-style-type: none"> • 150 mg bupropion (1/day), or • Placebo (1/day) • Individuals established target quit date 	<ul style="list-style-type: none"> • 150 mg bupropion (2/day), or • Placebo (2/day) • Assessments/counseling at clinic (wk 1) 	<ul style="list-style-type: none"> • 150 mg bupropion (2/day), or • Placebo (2/day) • Assessments/counseling at clinic (wks 3 & 6) 		<ul style="list-style-type: none"> • Assessment at clinic. • End of study

The CRE conducted a limited assessment which comprised a review of the report, the primary clinical study, and internet research of the bupropion drug.

Under the Data [Information] Quality Act, the FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by Okuyemi et al., and has identified the following shortcomings, which if valid after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

Summary of Findings and Issues

Class sizes within the sample should be the same in order to avoid biased results.

The authors of this secondary study acknowledged the inherent limitation in that the primary study sample was predominantly menthol smokers. Indeed, the 600 subjects comprised of 471 menthol smokers and only 129 non-menthol smokers. The primary objective of the secondary study was to test (prove) the hypothesis that menthol smokers are less likely to quit. While it is reasonable to expect that several menthol smokers will be unable to quit smoking, the roughly 4-to-1 ratio of menthol smokers to non-menthol smokers likely resulted in an inflated/lop-sided comparison. The authors concluded that "...having a larger sample of non-menthol smokers in the study is unlikely to change factors that were found to be significant in this study." [p. 1392]

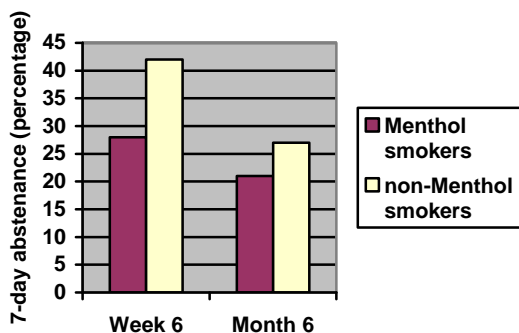
This conclusion should be supported by data analysis.

Future studies of this nature should select a sample size that has equal, or near equal, classes (e.g. menthol smokers, non-menthol smokers).

What should be the most meaningful milestone for assessing cessation results, 6 weeks or 6 months?

The researchers computed statistics for reported cessation (quit smoking) responses at week 6 (28% menthol smokers vs. 42% non-menthol smokers) as well as month 6 (21% menthol smokers vs. 27% non-menthol smokers). The following graph illustrates these reported statistics:

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Only the cessation results of week 6 were found to be statistically significant and in line with the researcher’s hypothesis: that menthol smokers are less likely to quit. [p. 1388] The researchers reported cessation rates at 6 months were lower for menthol smokers, but not statistically significant. Therefore, over the extended period (6 months) of the study, one cannot support the claim that menthol smokers are less likely to quit. Indeed, the researchers acknowledged there could be a number of reasons that could explain the near equal cessation rate at the 6 month mark, including delayed quitting among menthol smokers or higher relapse among non-menthol smokers.

Is age a factor in cessation rates?

The TPSAC is studying the effects of smoking on young adults. This study included two age categories: younger than 50 years, and 50 years or older. Researchers used a logistic regression model and included the variables: smoker type along with age to conclude that “among those younger than 50 years, non-menthol smokers were more likely to quit smoking [by a 2-to-1 ratio].”

This study result may have been different if the smoking class sizes were the same.

Are the data and statistical models transparent?

Unlike previous studies that the CRE has assessed, the data for this study was not publically available for independent verification of results. The CRE has submitted a request for data in separate correspondence. The CRE reviewed the primary clinical study (reference b) and discovered interesting facts such as the rather large attrition rate of participants: of the original 600 smokers who initially agreed to participate in the study, only 470 (78.3%) participated at week 6 and 411 (68.5%) at month 6. This attrition parameter underscores the human factors challenge in such studies.

The researchers used a logistic regression model to conclude the relationship between menthol smoking and abstinence rates. Logistic regression models are becoming increasingly useful for researchers to use since they allow a comparison between variables that include discrete data (i.e. abstinence rates would be considered as discrete data since it is a counted measure). The researchers reported that the regression modeling was only used for Week 6; results were inconclusive for month 6.

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Future studies should include transparency and completeness of such models (i.e. the error component alone can be used by modelers to compensate for unexplained behavior/factors).

Request to Author for Background Data

Dear Dr. Okuyemi,

My name is Jim Tozzi, I am a member of the Center for Regulatory Effectiveness, a nationally recognized clearinghouse for methods to improve the federal regulatory process. The CRE has two paramount goals: (1) To ensure that the public has access to data and information used to develop federal regulations, and (2) To ensure that information which federal agencies disseminate to the public is of the highest quality.

We are studying the possible adverse health effects that may result from the use of tobacco additives, such as menthol. We came across two of your studies which both reference data from an earlier clinical trial titled, “Sustained-Release Burping for Smoking Cessation in African Americans.” *Journal of the American Medical Association*, July 2002, Vol 288, No 4, pp. 468-474, by Jasjit S. Ahluwalia, Kari Jo Harris, Delwyn Catley, et al.

We would like to know if I can have access to the data from the above listed report.

Your assistance would be greatly appreciated.

Respectfully,

Jim Tozzi
Center for Regulatory Effectiveness

Center for Regulatory Effectiveness (CRE) assessment of
the following research report:

**“Relationship between menthol cigarettes and
smoking cessation among African American light
smokers”**

by:

Kolawole S. Okuyemi, Babalola Faseru, Lisa Sanderson Cox,
Carrie A. Bronars & Jasjit S. Ahluwalia (2007)

August 2010

Center for Regulatory Effectiveness

References:

- a. Research Report: “Relationship between menthol cigarettes and smoking cessation among African American light smokers” Society for the Study of Addiction, No. 102, May 2007, pp. 1979-1986, by Dr. Kolawole S Okuyemi, et al.
- b. Clinical Study: “The effects of nicotine gum and counseling among African American light smokers: a 2 x 2 factorial design.” Society for the Study of Addiction, June 2006, Vol 101, pp. 883-891, by J.S. Ahluwalia, K. Okuyemi, N. Nollen, W.S. Choi, H. Kaur, K. Pulvers, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its focus on the efficacy of medication on menthol smokers among African Americans. The researchers presented the following primary results:

- Compared to non-menthol smokers, menthol smokers were younger and less confident to quit smoking;
- At the 26-week [follow-up point], the 7-day verified abstinence rate was significantly lower for menthol smokers.

The researchers concluded “[a]mong African American light smokers, use of menthol cigarettes is associated with lower smoking cessation rates.” [p. 1979]

The reader should be aware that “...this study was a secondary analysis that used data from a clinical trial (reference (b)) that was not designed for testing differences in smoking cessation by menthol status.” [p. 1984] The parent (previous) trial was a double-blind, placebo-controlled, randomized trial of 755 African American light smokers. So, both the patient and the administrator of medications did not have knowledge of the type of treatment they were receiving/administering (the placebo (fake gum) vs. nicotine gum). All smokers had the following characteristics: at least 18 years of age, smoked no more than 10 cigarettes a day and

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Smoker categories	Weeks 1-4	Weeks 5-6	Weeks 7-8	End of Trial	Weeks 8, 16, 26
<5 Cigarettes	6 Pieces of Gum	4 Pieces of Gum	2 Pieces of Gum		Follow up assessment and cotinine verification
5-7 Cigarettes	8 Pieces of Gum	6 Pieces of Gum	4 Pieces of Gum		
8-10 Cigarettes	10 Pieces of Gum	8 Pieces of Gum	6 Pieces of Gum		

were interested in quitting within the next 14 days. The following timeline generally illustrates the 8-week clinical trial plan:

Table 1.

The 755 smokers were placed into 4 Treatment Study Groups (see Table 2). The following information, which was gathered from the primary trial report, illustrates classical issues that are sometimes overlooked when researchers use data from a previous trial in which the study objectives are not complementary:

- Firstly, notice the disproportionate amount of menthol smokers-to-total smokers. Each treatment group comprised approximately 80% of menthol smokers. This will cause results to be biased/misleading.
- Secondly, a careful review of the primary trial report (reference (b)) revealed a significant attrition rate (i.e. failure of participants to show-up for their follow-up assessments and cotinine verifications). Neither report provided information as to how the menthol vs. non-menthol groups were affected by the attrition rates. The attrition rates could cause results to be biased/misleading (an example is provided in the Summary section of this assessment).

Table 2.

The 4 Treatment Study Groups:	Distribution of All Smokers at Start	Distribution of Menthol Cigarette Smokers (%) at Start	All Remaining Smokers at Week 8	All Remaining Smokers at Week 16	All Remaining Smokers at Week 26
Nicotine Gum and Motivational Interviewing	189	153 (81.4%)	145	145	157
Nicotine Gum and Health Education	189	156 (83%)	171	142	168
Placebo Gum and Motivational Interviewing	189	158 (83.6%)	134	137	150

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Placebo Gum and Health Education	188	148 (78.7%)	153	156	162
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The CRE conducted a limited assessment which comprised a review of the report, the primary clinical study, and internet research of the nicotine drug.

Under the Data [Information] Quality Act, the FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by Okuyemi et al., and has identified the following shortcomings, which if valid after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

Summary of Findings and Issues

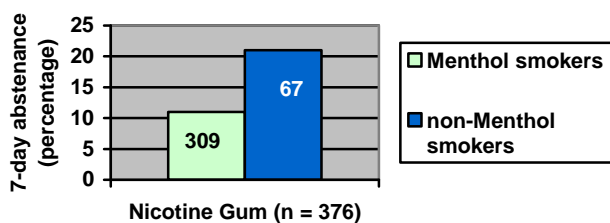
Class sizes within the sample should be the same in order to avoid biased results.

The authors of this secondary study acknowledged the inherent limitation in that the primary clinical study sample was predominantly menthol smokers. In fact, the 755 subjects comprised of 615 menthol smokers and only 140 non-menthol smokers. The primary objective of the secondary study was to test (prove) the hypothesis that menthol smokers are less likely to quit. While it is reasonable to expect that several menthol smokers will be unable to quit smoking, the roughly 4.5-to-1 ratio of menthol smokers to non-menthol smokers likely resulted in an inflated/top-sided comparison.

The following is just one example of how the secondary report statistics do not match the data provided in the primary clinical report (reference (b):

The authors of this secondary study reported that "...at week 26, non-menthol smokers who received nicotine gum (n = 67) had significantly higher abstinence (quit) rates than menthol smokers who received nicotine gum (n = 309)." [p. 1981] The figure directly below illustrates the results and was included in their report. [p.1982]

Figure 1. Seven-day abstinence rate at week 26



However, when the reader compares this graph against the data in Table 2, which came from the original report, it can be seen that, by week 26, there were a total of only 325 (as opposed to the

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stated 376 in Figure 1) smokers-using-nicotine gum who returned for assessments and verification ($157 + 168 = 325$). This means there were a total of 53 smokers (in the two nicotine gum-use study groups) who failed to return for the final check-up at week 26. Moreover, neither study provides the reader with information as to final size of the menthol vs. non-menthol classes. So, it is very likely that the final (week 26) size of the non-menthol group was smaller than 67 and consisted primarily of abstaining traits.

Future studies of this nature should select a sample size that has equal, or near equal, classes (e.g. menthol smokers, non-menthol smokers).

Is age a factor in cessation rates?

The TPSAC is studying the effects of smoking on young adults. This study included two age categories: younger than 50 years, and 50 years or older. Researchers used a logistic regression model and included the variables: smoker type along with age to conclude that “[i]n the < 50 age group, non-menthol smokers had marginally significant higher cessation rates than menthol smokers [by a 2-to-1 ratio].”

This study result may have been different if the smoking class sizes were the same.

Are the data and statistical models transparent?

Unlike previous studies that the CRE has assessed, the data for this study was not publically available for independent verification of results. The CRE has submitted a request for data in separate correspondence. The CRE reviewed the primary clinical study (reference b) and discovered interesting facts such as the attrition rate of participants: of the original 755 smokers who initially agreed to participate in the study, 637 (84.4%) participated at week 26. The attrition rate for this primary study was not as high as a previous study assessed by CRE, but the menthol-vs-non-menthol smoker ratio was more lop-sided in this study. This attrition parameter underscores the human factors challenge in such studies.

The researchers used a logistic regression model to conclude the relationship between menthol smoking and abstinence rates. Logistic regression models are becoming increasingly useful for researchers to use since they allow a comparison between variables that include discrete data (i.e. abstinence rates would be considered as discrete data since it is a counted measure). Future studies should include transparency and completeness of such models (i.e. the error component alone can be used by modelers to compensate for unexplained behavior/factors).

Posted For Public Comment
May 7, 2010

“Are Menthol Cigarettes a Starter Product for Youth?”

By:

James C. Hersey, Shu Wen Ng, James M. Nonnemaker, Paul Mowery,
Kristin Y. Thomas, My-Charllins Vilsaint, Jane A. Allen, M. Lyndon
Haviland

Center for Regulatory Effectiveness

References:

- a. Study: “Are menthol cigarettes a starter product for youth?” *Nicotine & Tobacco Research* Volume 8, No. 3 (June 2006), pp. 403-413, by James C. Hersey, et al.
- b. 2002 National Youth Tobacco Survey Data and Codebook, Centers for Disease Control
- c. 2000 National Youth Tobacco Survey Data and Codebook, Centers for Disease Control

Background

The harmful effect of cigarette smoking on our nations’ youth is an important issue. On June 22, 1999, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with an exception for menthol cigarettes.

The Nation’s Centers for Disease Control sponsors the conduct of a predominantly biennial National Youth Tobacco Survey, to study the cigarette smoking trends in middle school and high school aged students. These publically available surveys include data regarding menthol cigarette use as well as cessation efforts.

The reference Study was identified for review and public discussion due to its focus on the effects of menthol smoking on children. The study used 2000 and 2002 data from the National Youth Tobacco Survey (NYTS) to assess the relationship between menthol use and nicotine dependence. Middle School and High School students comprised the NYTS data set. The researchers made two primary claims:

- menthol cigarette use was significantly more common among newer, younger smokers;
- menthol smokers had higher nicotine dependence than non-menthol smokers

The researchers suggested that menthol cigarettes are a starter product that may be associated with smoking uptake by youth.

The CRE conducted an assessment which comprised of a review of the: reference study, 2000 and 2002 National Youth Tobacco Survey data and Codebook, and internet research (including comparison of various state level studies such as the Iowa, Hawaii and Connecticut Youth Tobacco Surveys, years 2008, 2007 and 2003, respectively). Since the NYTS is a biennial national survey, the assessment approach considers the NYTS as the “population” and more focused (regional) surveys, such as the Connecticut and Iowa studies as “samples” from which to generally compare and contrast.

The Tobacco Products Scientific Advisory Committee provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this assessment is to consider the merits

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and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

Summary

Is there really an increase in menthol cigarette smoking among our youth?

As a part of its review as to whether or not menthol cigarette smokers have a higher nicotine dependence, the FDA is analyzing the study by *Hersey et al.* and its attendant review of the Connecticut Youth Tobacco Study (which used 2002 state data) which concluded that “[m]ore than 1 in 2 middle school current smokers smoke menthol cigarettes.” The 2007 Hawaii Youth Tobacco Survey reported an increase of menthol smoking among middle school students, from 61.5% in 2000 to 70.3% in 2007.

Under the Data [Information] Quality Act FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by *Hersey et al.* And has identified the following shortcomings, which if stand after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

1. *Is there a clear, unambiguous definition of menthol smoker category?*

The most important aspect of the reference report is the lack of a clear and consistent definition for the menthol smokers group. On page 405 of the study, the menthol group appears to be defined as smokers who smoke Kool and Newport brands. However, Table 1 includes other categories. While the “true” size of menthol smokers may not be attainable, an over-inflated size will inaccurately impact the researchers’ two primary claims.

2. *Are the survey responses consistent?*

The researchers’ first claim, illustrated by the bar chart at Figure 2, page 408, is suspect since the authors counted brand and/or menthol status. Specifically, a student could select a non-menthol brand, but then respond positively to smoking menthol cigarettes. A young student (particularly Middle School students) may not be sufficiently knowledgeable about menthol cigarettes. Using a more comprehensive brand selection list would contribute towards reducing subjectivity and response errors.

3. *Are the researcher’s models transparent?*

The researchers’ second claim lacks the supporting analysis. Specifically, the authors provide the formulas for the logistic regression models that were used to conclude the relation between menthol smokers and nicotine dependence. However, the data in Table 3 of the study does not show the composition of the model (i.e. the beta (β) co-efficient values associated with the variable (M, L, T, A, X) values and the error (ϵ) amount was not provided). These missing components of the model make it impossible for the reader to verify or validate the model (i.e. the error amount alone can be used by modelers to compensate for unexplained

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behavior/factors). The relationship between menthol smoking and nicotine dependence is a primary claim for the study. Therefore, models should be transparent, complete and well illustrated.

4. Should future survey questions be changed to improve communication with our youth?

It is difficult for the study to present a comprehensive correlation between menthol smoking and high nicotine dependence based on pre-dated national survey questions (and unchanged over the years). More recent youth tobacco surveys, at the state level (i.e. Hawaii and Iowa), indeed indicate a increase over the years, of menthol cigarette smoking by middle school and high school students. For example, a 2008 Iowa study indicated 44% and 138% increases among middle school students and high school students, respectively, over an eight year period (2000-2008). In response to changing metrics, state level surveys and subsequent studies are being tailored to analyze the effectiveness (or lack thereof) of preventative programs.

Discussion/Detailed Technical Issues

Menthol Group Size (page 405). The study includes a very detailed Table 1 (page 405), providing a roll-up of the numbers that were considered for the menthol smokers group. However, the roll-up includes sub-groups described as “Possible menthol brand” and “Brand not described,” which comprise 16.2% and 2.3%, respectively, of the total 36.9% of menthol smokers group. A review of the 2002 NYTS Code Book reveals that there was no category described as “Possible menthol brand.” The addition of this subjective sub-group can lead to artificially increasing the group size. The Menthol Group should be defined, such as the reported Kool- and Newport-brands. Alternatively the researchers should have only computed the percentage of reported “menthol smokers” ($1661/4288 = 38.7\%$).

Analysis Comparing Menthol and Non-menthol Smokers (page 406). The authors state that they “...used the Nicotine Dependence Scale for Adolescents (Nonnmaker et al., 2004). [A] scale that consisted of six items that asked respondents how soon they smoked after they woke up and whether they experienced cravings for cigarettes (Table 2).” However, the authors do not show the results from the model. The reader should also be aware that these six questions are standard questions contained in the NYTS (i.e. the researchers did not “add” or conduct an additional survey). So, this analysis can be independently verified since the raw data responses are publically available.

Results (pages 406-407). Statements made regarding the increased use of menthol cigarettes and the bar charts at Figure 1, appear to be incorrect. The authors state that “...between 2000 and 2002, the percentage of smokers who regularly used menthol cigarettes increased significantly...from 40% to 47.4% - an increase of 18.5%.” Taken at face value, this only represents a 7.4% increase. Figure 1 was further studied: the 2002 and 2000 NYTS Code Books and data were reviewed to verify the “Total” percentages of menthol smokers. For the year 2002, 1,661 students responded positive to smoking menthol cigarettes while 1,866 students responded negative to smoking menthol cigarettes. The year 2002 “Total” percentage in Figure 1 was therefore confirmed, $1,661/3527 = 47.2\%$. However, for the year 2000, 2,701 students responded positive to smoking menthol cigarettes while 3,674 students responded negative to

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smoking menthol cigarettes. Therefore, the year 2000 “Total” percentage in Figure 1 was found to be $2,701/6,375 = 42.3\%$. This resulted in an increase of menthol cigarette use of only 4.9% (from 42.3% to 47.2%) between the years 2000 and 2002 (as opposed to the stated 18.5% and illustrated 7.4% in the study).

Logistic Regression Models (pp. 408-409). The study does not adequately lay-out the complete models (values for coefficients and variables are missing). Typical statistical analysis includes a first-step of developing simple correlation plots (an x-variable (the explanatory variable) and a y-variable (the response variable)). An initial study of correlation contributes towards identifying the explanatory variable(s) that could be incorporated into a more complex regression model.

Center for Regulatory Effectiveness (CRE) assessment of
the following research report:

**“Predictors of smoking cessation among African-Americans
enrolled in a randomized controlled trial of bupropion”**

by

Kari Jo Harris, Kolawole S. Okuyemi, Delwyn Catley, Matthew S. Mayo, Bin Ge,
and Jasjit S. Ahluwalia (2004)

August 2010

Reference:

- a. Predictors of smoking cessation among African-Americans enrolled in a randomized controlled trial of bupropion. *Preventive Medicine*, 2004 Apr;38(4):498-502, by Dr. Kari Jo Harris, et al.
- b. Does menthol attenuate the effect of bupropion among African American smokers? *Addiction*, 2003 Oct;98(10):1387-93, by Dr. Kolawole S. Okuyemi, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its evaluation on the efficacy of medication on menthol smokers among African Americans. The researchers presented the following primary results:

- Among African-Americans participating in a randomized trial of bupropion SR 300 mg for smoking cessation, independent baseline predictors of cessation were: assignment to bupropion condition, not smoking within 30 min of waking, and lower cotinine levels.
- Univariate predictors of cessation also included not using mentholated cigarettes, smoking fewer cigarettes per day, and being older in age.

The reader should be aware that this report "...constitutes a secondary analysis for which the original study was not primarily designed". There may be important predictor variables that were not included in our baseline measures..." "Caution should be used in generalizing our results to other groups of smokers."

Summary of Findings and Issues

Smoking menthol cigarettes is not a predictor for smoking cessation.

The authors concluded “univariate predictors of cessation also included not using mentholated cigarettes, smoking fewer cigarettes per day, and being older in age”. However, the analyses results in this paper show that smoking menthol cigarettes might not have any significant effect on either smoking cessation or bupropion treatment among African-Americans. Two types of analyses were conducted in this paper: multiple logistic regression and univariate analyses. Menthol cigarettes is not a significant factor in the Logistic Regression results. The interactions between smoking menthol cigarettes and bupropion treatment or addiction are also not significant (suggesting that menthol cigarettes does not affect the observed treatment or addiction effects on smoking cessation. While the univariate analysis showed that menthol cigarettes effect is significant, this result should not be taken as evidence since effects of other major factors such as treatment and level of addiction were not balanced.

The observed smoking menthol cigarettes effects could be caused by other related real predictors.

The authors further explored the effect of smoking menthol cigarettes on quit in another previous report (reference b). They concluded that fewer African-Americans under 50 years old who smoked menthol cigarettes quit in multivariate models. However, they didn't include the interaction effects between smoking menthol cigarettes, age, and/or treatment in the models here. Collinearity, which means correlations between factors, is also not examined.

Since the original data is not available, it is not possible for us to explore further why the smoking menthol cigarettes effect is significant in univariate analysis but not in logistic regression. In their previous report (reference b), they reported that menthols smokers is more likely to be younger, female and more likely to smoke their first cigarette within 30 minutes of waking up (all $p < 0.01$). It is then not surprising to see that menthol cigarettes showed significance on quit when these strong predictors were not balanced in the univariate analysis. We didn't see any collinearity tests conducted for the logistic regression model development in this paper. Collinearity is a common phenomenon in multivariate studies and should always be checked. Without such considerations, the automatic regression modeling processes that the authors used could select a wrong factor that happens to correlate to real predictors. The failure of detection of gender and age effects on smoking cessation, which has been proved in other publications, further enhanced our suspicion of potential collinearity.

Class sizes within the sample should be the same in order to avoid biased results.

The authors of this secondary study acknowledged the inherent limitation in that the primary study sample was predominantly menthol smokers. Indeed, the 600 subjects comprised of 471 menthol smokers and only 129 non-menthol smokers. The primary objective of the secondary study was to find predictors of smoking cessation. The unbalanced sample size might lead to biased results especially when there are as many factors to evaluate as this study.

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Long term smoking cessation is more important for the public interests.

The selected smoking cessation at 7-weeks as the outcome of interest might be statistically reasonable but not practically make sense. Obviously long term cessation is much more important than short term one. The reason that only 7 week time period is selected is that there were more quit at this time and gives the analysis more power to draw conclusion. However, such a conclusion might not be the most important one for the public interests. At least the long term cessation results should also be included here. Even the negative results would be valuable.

Center for Regulatory Effectiveness (CRE) assessment of
the following research report:

**“Tobacco Industry Control of Menthol in
Cigarettes and Targeting of Adolescents and
Young Adults”**

by:

Jennifer M. Kreslake, Geoffrey F. Wayne, Hillel R. Alpert, Howard K. Koh,
and Gregory N. Connolly

August 2010

References:

- a. Research Report: “Tobacco Industry Control of Menthol in Cigarettes and Targeting of Adolescents and Young Adults.” American Journal of Public Health, Vol. 98, No. 9, September 2008, pp. 1685-1692, by Jennifer M. Kreslake, et al.
- b. Substance Abuse & Mental Health Data Archive, website: www.oas.samhsa.gov
- c. Research Report: “What do Marlboro Lights smokers know about low-tar cigarettes?” Nicotine and Tobacco Research, Volume 00, No. 0, October 2004, pp. 1-10, by K. Michael Cummings, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its stated conclusion that additives to cigarettes, such as menthol, should be federally regulated. Leading up to this conclusion, the researchers presented the following primary results:

- The tobacco industry has attracted new smokers by promoting cigarettes –
 - with lower menthol content to adolescents and young adults, and
 - with higher menthol content to long-term smokers
- Menthol cigarette sales remained stable from 2000 to 2005 in the U.S., despite a 22% decline in overall packs sold.

The researchers further concluded “[t]obacco companies manipulate the sensory characteristics of cigarettes, including menthol content, thereby facilitating smoking initiation and nicotine dependence.” [p. 1685]

The report at reference (a) used three separate methods of analysis to formulate their aforementioned results and conclusions. Specifically:

- Marketing advertisement analysis (approximately 580 menthol-related tobacco industry documents were text-tagged to determine: market share trends, as well as advertising expenses - menthol vs. non-menthol brands, and industry strategies for introducing varying levels of menthol products).

- Laboratory tests (a smoking machine was used to “...analyze tar, nicotine...and menthol in smoke, as well as menthol and nicotine in the menthol cigarette rod” [p. 1686])
- “[M]enthol brand use by age and race/ethnicity from the National Survey on Drug Use and Health (using data from 2005 and 2006).” [p. 1686]

The CRE conducted a limited assessment which comprised a review of the report, internet research on “ventilated cigarettes,” and publically available data from the reference (b) website.

Under the Data [Information] Quality Act, the FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by Kreslake, et al., and has identified the following merits and shortfalls. The shortfalls (issues), if valid after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

Summary of Findings and Issues

Publically available data supports the transparency requirements of the Data [Information] Quality Act.

For parts of their report, the authors used data from a publically available database at reference (b). The data and associated reporting provided by the Substance Abuse & Mental Health Data Services Administration (SAMHDA) – Office of Applied Studies was assessed as meeting the DQA transparency requirements .. In particular, the website provides the public the flexibility to conduct statistical analysis on the annual data sets, from the website.

Consequently, CRE was able to check the statistical findings reported in the survey-part of the subject report.

Is there an age and race correlation with cigarette choice (menthol)?

The researchers stated “[n]ational survey data showed that significantly more adolescents and young adults than older persons smoked menthol cigarettes.” [p. 1688] Using year 2006 survey data, they reported:

Current smokers (menthol or regular cigarettes in past 30 days)	
Age category	Percentage who smoked menthols
12 to 17 years old	43.8%
18 to 24 years old	35.6%
Older than 35 years old	30.6%

The above statistics were verified at <http://www.icpsr.umich.edu/SAMHDA>. The data set variable “CIG30MEN” (which is described as “menthol or regular cigarettes smoked most in the past 30 days.”) was used as the variable of interest and the data set variable “CATAGE” (defined as age categories) was used as the filter. These statistics indicate that a higher percentage of

menthol cigarettes are being smoked by younger smokers than older-aged smokers (e.g. 43.8% vs. 30.6%)

The researchers focused on year 2006 data. The following graph (“Figure 1”) shows menthol statistics, filtered by age groups, across the years 2004-2008. This graphic indicates a correlation between menthol cigarette preference and young-aged smokers.

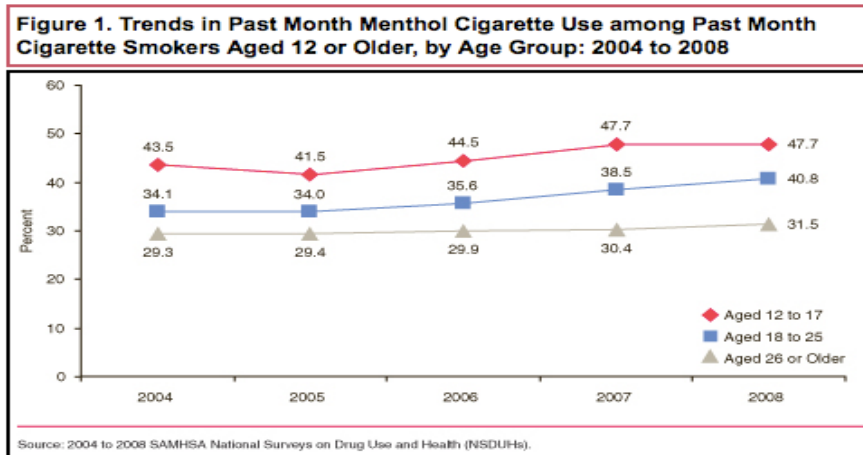


Figure 1 Table. Trends in Past Month Menthol Cigarette Use among Past Month Cigarette Smokers Aged 12 or Older, by Age Group: 2004 to 2008

Age Group	2004	2005	2006	2007	2008
Aged 12 to 17	43.5%	41.5%	44.5%	47.7%	47.7%
Aged 18 to 25	34.1%	34.0%	35.6%	38.5%	40.8%
Aged 26 or Older	29.3%	29.4%	29.9%	30.4%	31.5%

Source: 2004 to 2008 SAMHSA National Surveys on Drug Use and Health (NSDUHs).

The researchers also stated that “[r]ace was also a factor in use and brand choice. African American adolescents and young adult smokers used menthol as frequently as did older African American smokers, but they were more likely to choose a lower-menthol variety.” [p. 1688]

However, the researchers did not provide the statistics and CRE was not able to identify the variables at the SAMHDA website to verify their statement. Therefore, the reader must be cautioned about the validity regarding the correlation between race and mentholated cigarettes.

The report stated that “[c]igarettes were analyzed for tar...,” but the report provided no data on tar delivery.

Researchers used a smoking machine to “...analyze tar, nicotine...and menthol in smoke, as well as menthol and nicotine in the menthol cigarette rod.”

However, only nicotine and menthol analysis was presented. A completeness issue.

Is the use of a smoking machine a realistic mechanism for determining smoke and nicotine delivery from menthol ventilated cigarettes?

“Machine smoking was conducted under Federal Trade Commission, and more intensive Health Canada smoking conditions.” [p. 1686] Here is a synopsis of their findings:

Figure 2. Summary of reported statistics from laboratory results.

Cigarettes ranked from least menthol content (top) to most menthol content (bottom)	Menthol in smoke (under FTC smoking conditions)	Nicotine per puff (under FTC smoke conditions)	Nicotine per cigarette (under FTC smoke conditions)	Nicotine per puff (under intense Health Canada smoking conditions)	Nicotine per cigarette (under intense Health Canada smoking conditions)	Menthol in the smoke (under intense Health Canada smoking conditions)	
						Total menthol	Menthol per puff
Newport	0.45 mg/cigarette	0.16 mg/puff	1.20 mg/cigarette	0.26 mg/puff		0.88 mg/cig	0.10 mg/puff
Marlboro Milds	0.27 mg/cigarette	0.11 mg/puff	0.82 mg/cigarette	0.22 mg/puff	1.91 mg/cig	0.80 mg/cig	0.09 mg/puff
Salem Black Label	0.52 mg/cigarette					0.96 mg/cig	0.09 mg/puff
Camel Menthol	0.59 mg/cigarette						0.12 mg/puff
Kool Milds	0.34 mg/cigarette			0.26 mg/puff			0.14 mg/puff

The researchers stated that, “[o]verall, the smoke menthol ratings were comparable to the menthol content analysis, with Newport and Marlboro Milds consistently lowest in menthol ratings.” [p. 1687] The highlighted brands (Newport, Marlboro Milds, Camel Menthol and Kool Milds) were designated as brands that target younger smokers.

CRE compiled the above table to confirm that several statistics were not provided. The lack of comparable data precludes the reader from making any meaningful comparisons or inferences.

Does the use of a smoking machine provides the opportunity for precise measurement?

There are interesting pros and cons associated with experiments that use human smoking subjects versus the smoking machines, as revealed in this excerpt from a study at reference (c):

“In the smoking machine the puff volume is constant so that with dilution the quantity of ‘equivalent undiluted smoke’ delivered to the Cambridge filter is reduced. Not so with the

human smoker who appears to adjust to the diluted smoke by taking a larger puff so that he still gets about the same amount of equivalent smoke.... The smoker is thus apparently defeating the purpose of dilution to give him less smoke per puff. He is certainly not performing like the standard smoking machine; and to this extent the smoking machine data appear to be erroneous and misleading. It probably always has been so for diluted smoke cigarettes, whether dilution is obtained by porous paper or holes in the filter (Wakeham, 1967).”

Hence, the smoking machine does not appear to capture the real smoking nuances. A data utility issue.

**Center for Regulatory Effectiveness (CRE) assessment
of the following research report:**

“Mentholated Cigarette Use among Multiphasic Examinees, 1979-86”

By:

STEPHEN SIDNEY, MD, IRENE TEKAWA, MS, AND GARY D. FRIEDMAN, MD (1989)

August 2010

Reference:

Research Report: “**Mentholated Cigarette Use among Multiphasic Examinees, 1979-86**” *Am J Public Health*. 1989 Oct;79(10):1415-6, by Drs. Sidney S, Tekawa I, and Friedman GD.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference was identified for review and public discussion due to its focus on the mentholated cigarette use in relation to age and race. The study used 1979 to 1986 data from the Kaiser Permanente Medical Care Program. The researchers presented the following primary results:

- Black and Asian current smokers were more likely to be mentholated cigarette users than White current smokers, especially in the younger age groups;
- Among Black and Asian current smokers, the younger the smokers, the more likely they used mentholated cigarettes; however, this relationship was not presented in White current smokers.
- In young Black current smokers (aged 40 or younger), nonmentholated users were 4.2 times more likely to switch than mentholated users while quitting was equally likely in both groups, after adjusting for age and sex.

The researchers therefore suggested that “the steep decline in the proportion of mentholated cigarette users with age in Blacks can be explained predominantly as a cohort effect, since the findings regarding switching from cigarettes of one mentholation status to another in this study suggest that **the prevalence of mentholated cigarette use increases over time in younger Black smokers.**” and that “If mentholation does cause cancer, it may contribute substantially to the excess incidence of certain smoking related cancers in Blacks relative to Whites. A potential consequence of the very large differences in the prevalence of mentholated cigarette use in younger Blacks relative to Whites would be a widening of the difference between Blacks and Whites of these incidence rates in the future, when younger Blacks reach the higher risk age range for cancer.”

The CRE conducted a limited assessment which comprised a review of the report.

Summary of Findings and Issues

1. *How is the studied population representative?*

The study population was limited to Oakland and San Francisco areas' Kaiser Permanente Medical Care Program members. These area populations should be predominantly Hispanics. Questions if Hispanic-Black are the same as African-Americans?

2. *Are key concepts such as current smokers, mentholated cigarette users, and nonmentholated cigarette users clearly defined?*

There were no definitions for the key concepts: current smokers, mentholated cigarette users, and nonmentholated cigarette users.

3. *Was the finding regarding the switching and quitting patterns biased due to sub-sampling?*

There were total 6297 Black current smokers aged 40 or under (based on Table 1 in the paper), only 1688 (27%) were included in the analyses of the switching and quitting patterns. Potential non-response bias could impact the researchers' findings on the switching and quitting patterns.

4. *Was longitudinal data used for a cross-sectional study to answer a question regarding change over time "Is there an increase in menthol cigarette smoking among Black youth"?*

At the beginning of the second paragraph in the Methods section, it stated that "If subjects had more than one check-up, only the first was included in this analysis.", implying that longitudinal data were available to be analyzed in order to answer the question "Is there an increase in menthol cigarette smoking among Black youth". However, the researchers didn't utilize the data; instead they cut data as a cross-sectional study, making it unable to answer the question.

Detailed Technical Issues

- 1) Table 1 not only should present absolute numbers but also the distribution percentage in order to make quick comparison.
- 2) The overall % of mentholated users was missed.
- 3) Assessment by sex was conducted but not mentioned in primary findings.

4) The presenting of decimal digit was not consistent. For example, on page 1415 in Methods section, it reported current smoker's percentage as 27.3 percent; but information on availability of mentholated smoking status was reported as 92 percent, which should be 92.4 percent.

5) In results section, the researchers briefly mentioned to use proportion hazard models to conclude a) the relationship between switch pattern and mentholated smoking status; b) the relationship between quitting smoke and mentholated smoking status, adjusted by age and sex. However, the outcomes (time to switch and time to quit) were not explicitly defined in the study and the complete models (values for coefficients and p-values or 95% CI) are missing.

Center for Regulatory Effectiveness (CRE) assessment of
the following research report:

**“Lower quit rates among African American and
Latino menthol cigarette smokers at a tobacco
treatment clinic”**

by:

K. K. Ghandi, J. Foulds, M. B. Steinberg, S. –E. Lu, J. M. Williams

August 2010

References:

- a. Research Report: “Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic” *The International Journal of Clinical Practice*, March 2009, pp. 360-367, by K. K. Ghandi, et al.
- b. Research Report: “Relationship between menthol cigarettes and smoking cessation among African American light smokers” *Society for the Study of Addiction*, No. 102, May 2007, pp. 1979-1986, by Dr. Kolawole S Okuyemi, et al.
- c. Clinical Study: “Factors associated with quitting smoking at a tobacco dependence treatment clinic.” *American Journal of Health Behavior*, 2006, pp. 400-412, by J. Foulds, K. K. Ghandi, M. B. Steinberg, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its focus on smoking cessation rates among African American and Latino menthol smokers. The researchers presented the following primary results:

- Compared to White menthol smokers, African American and Latino menthol smokers had lower quit rates at a four-week follow-up point;
- African American and Latino menthol smokers had significantly lower odds (approx 1-to-3) of quitting than their non-menthol counterparts;
- Compared to African American non-menthol smokers, African American menthol smokers had half the odds of being abstinent at a six-month follow-up point.

The researchers concluded “[d]espite smoking fewer cigarettes per day, African American and Latino menthol smokers experienced reduced success in quitting as compared with non-menthol smokers within the same ethnic/racial groups.” [p. 360]

The authors cite reference (b) findings as a motivator for further exploring the supposed association between light-smoking (less than 10 cigarettes per day) minority group menthol smokers and significantly lower quit rates. CRE would like to point out that reference (b) has

been assessed as having significant shortfalls (i.e. disproportionate comparisons between menthol and non-menthol treatment and control groups; and the lack of accounting for no-show patients by week 26). See Okuyemi, 2007.

The CRE conducted a limited assessment which comprised a review of the report and the referenced primary clinical study (cohort data). Under the Data [Information] Quality Act, the FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by Ghandi et al., and has identified the following shortcomings, which if valid after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

Summary of Findings and Issues

The cohort study described in reference (c) lacked control and replication, key elements to a valid experiment. A data utility concern.

This report, performed by Ghandi, was described as a ...“retrospective cohort analysis of 1688 consecutive patients who set a quit date and attempted to quit smoking between January 1, 2001 and June 30, 2005. They all attended a specialist tobacco dependence treatment outpatient clinic in New Jersey.” This cohort study group scheme had very similar study characteristics as the clinical trials that were used by the secondary Okuyemi (2007) report. However, unlike in the clinical set-up re-used by the Okuyemi report, the cohort patients were largely observed (as it should be with a cohort study). The cohort group of patients were given the opportunity to receive medications, but no formal statistical treatment and control groups (i.e. such as an administered placebo) were established. Furthermore, review of reference (c) does not include statistics on accepted treatments within menthol versus non-menthol smokers.

Regarding replication (the ability of an independent researcher to re-create the experimental setting), the Ghandi report cites 1688 consecutive patients studied between the period January 2001 and June 2005. However, a review of reference (c) indicates only an “...analysis of the first 1021 patients, ...from [the study’s] inception in January 2001.”

Are the statistical models valid?

The researchers reported that “African American and Latino menthol smokers had significantly lower odds of quitting (Odds Ratio of 0.34; 95% Confidence Interval of 0.17 to 0.69 for African Americans, and Odds Ratio of 0.32; 95% Confidence Interval of 0.16 to 0.62 for Latinos). All confidence intervals are built with the assumption of data being Normally distributed or that a researcher has a sufficient data size in its mean (average) tends to be Normal. In the Statistical vernacular, the Central Limit Theorem is used to establish confidence interval conditions. In particular, if the pedigree of a data set is unknown, then the Theorem states that the sample size must be greater than or equal to 30 in order for the mean to approximate a Normal-like distribution.

CRE reviewed reference (c), the source of the clinical data, and found the following statistics for Latino smokers (African American statistics are also shown for comparison sake):

Taken from Reference (c), Table 1, p.404			Abstinence at 4 weeks		Abstinence at 26 weeks	
	valid number N	%	n	%	n	%
Overall	1021	100%	463	45.3%	320	31.3%
Race/Ethnicity						
African American	219	21.4%	78	35.6%	48	21.9%
Hispanic/Latino	80	7.8%	21	26.3%	16	20%

Notice that the 4-week and 26-week sample sizes (n) for the Latino group are smaller than the required size of 30, in order to form confidence intervals. The main point is that when the sample size is small (less than 30), then confidence intervals cannot be relied upon, regardless of whether one is expressing intervals in terms of odds ratios or sample means.

What should be the most meaningful milestone for assessing cessation results, 4 weeks or 6 months?

The researchers computed statistics for reported abstinence responses, across three ethnic groups, at 4 weeks as well as 6 months. Their results were similar to that of the Okuyemi 2007 report (e.g. lower abstinence rates among menthol smokers versus non-menthol smokers). However, as was the case in the Okuyemi report, there appears to be a higher relapse rate among non-menthol smokers over the longer period of time. This should be investigated further.

**Center for Regulatory Effectiveness (CRE) assessment
of the following research report:**

**“Menthol Cigarettes, Smoking Cessation,
Atherosclerosis and Pulmonary Function”**

By:

Mark J. Pletcher, MD, MPH; Benjamin J. Hulley; Thomas Houston, MD; Catarina I. Kiefe, MD, PhD; Neal Benowitz, MD; Stephen Sidney, MD, MPH (2006)

August 2010

Reference:

Research Report: “Menthol Cigarettes, Smoking Cessation, Atherosclerosis, and Pulmonary Function” *Arch Intern Med.* 2006;166:1915-1922, by Dr. Mark J. Pletcher, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference was identified for review and public discussion due to its focus on young adults' mentholated cigarette use in relation to race (African Americans versus European Americans), smoking cessation behavior, and tobacco-related morbidity (coronary calcification and change in pulmonary function). The study used 1985 to 2000 data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The CARDIA Study is a longitudinal study of risk factors for coronary artery disease in 5115 African American and European American women and men aged 18 to 30 years and healthy at the time of enrollment in 1985. Participants underwent a baseline examination and then follow-up examinations at years 2, 5, 7, 10, and 15, with 74% retention of the surviving cohort at year 15. For this investigation, the researchers identified CARDIA smokers and measured associations between menthol/nonmenthol exposure and smoking cessation behaviors during follow-up, the prevalence of coronary calcification in 2000, and changes in pulmonary function test results between 1985 and 1995. The following timeline generally illustrates the time points when variables were measured.

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
Menthol smoking status	X	X	X	X	X	X
Smoking cessation behaviors						
Not currently smoking	X	X	X	X	X	X
Recent quit attempt	X	X	X	X	X	X
Cessation if recent quit attempt	X	X	X	X	X	X
Sustained smoking cessation			X	X	X	X
Documented relapse						X
Tobacco-related coronary calcification						X
Pulmonary function	X				X	

The researchers presented the following primary results:

- African American smokers were statistically significantly more likely to be menthol cigarette users than European American smokers (89% versus 29%, $p < 0.001$);
- Menthol smokers had statistically nonsignificant lower cessation and recent quit attempt rates and a statistically significantly higher risk of relapse than nonmenthol smokers (odds ratios [95% confidence interval] for cessation, recent quit attempt, and risk of relapse, in order, were 0.71[0.49, 1.02], 0.77[0.56, 1.06], 1.89[1.17, 3.05]), after adjusting for ethnicity, demographics, and social factors.
- There were no statistically significant differences from menthol in tobacco related coronary function or 10-year pulmonary function decline, after for ethnicity, demographics, and social factors.

The researchers therefore concluded that “Menthol and nonmenthol 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.”

The CRE conducted a limited assessment which comprised a review of the report.

Summary of Findings and Issues

1. Is the measurement of menthol exposure accurate and adequate?

The independent variable, menthol exposure, was defined as cumulative exposure to menthol pack-years and nonmenthol pack-years using information on current smoking, number of cigarettes smoked per day, menthol preference, and past years of smoking at baseline, assuming that participants smoked only menthol or nonmenthol cigarettes at any one time. This assumption needs to be justified. Intervals between two measurement points were two to five years; switch from menthol to nonmenthol cigarettes or vice versa is likely to happen. It was reported that younger smokers were highly likely to switch to menthol cigarettes (Sidney et al 1989). Therefore, this assumption potentially underestimated menthol pack-years.

In addition, menthol exposure was measured as a binary variable at every time point, as well as two independent numeric variables (menthol pack-years and nonmenthol pack-years). The study only explicitly described how the two numeric variables were defined and how they were analyzed in the logistic regression models with coronary calcification and change in pulmonary function as outcomes. There were no such descriptions regarding how menthol exposure was defined in logistic regression models with smoking cessation behavior variables as outcomes. From the title of Table 2, the reader learnt that only menthol preference at baseline was assessed in terms of its relationship with smoking cessation behavior variables. An advanced appropriate way is to treat it as time-dependent binary variable.

2. Problems with measurements of smoking cessation behaviors.

There were five measurements of smoking cessation behaviors. The definitions of those measurements were overlapped and confused. For example, the measurement cessation if recent quit attempt is a sub-group of recent quit attempt; it would be more efficient to define the two separate

binary variables as one categorical variable with 3-levels: no recent quit attempt/recent quit attempt but no cessation/recent quit attempt and cessation. The definitions of sustained smoking cessation and documented relapse in this study are confusing. By the definitions of this study, those two opposite behaviors (the former is considered as a positive smoking cessation behavior while the latter a negative behavior) can be obtained for one case. Suppose a subject had longitudinal smoking behaviors recorded as the following:

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status at the time (1=yes,0=no)	1	0	0	0	0	1

Based on the definition of sustained smoking cessation (no current smoking the past 2 times they were examined), the case was in sustained smoking cessation at time 1992, 1995, and 2000. Based on the definition of documented relapse (baseline smokers who reported no current smoking at a subsequent examination and then current smoking the final time they were examined), the case was also in documented relapse at time 2000. In addition, the definition of documented relapse didn't capture all the patterns for relapse over the time course of this study. For example, if a case with behavioral pattern as the following:

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status at the time (1=yes,0=no)	1	0	0	1	1	0

should it be accounted as a documented relapse? However, by the definition of relapse in this study, it's a non relapse case.

3. Was the logistic regression with 1 observation per participant adequate for sustained smoking cessation?

Based on the definition of sustained smoking cessation (no current smoking the past 2 times they were examined), a case should have as many as 4 measurements for this variable at times 1990, 1992, 1995, and 2000. But the researcher used logistic regression with 1 observation per participant for this outcome. Should repeated-measure analyses be conducted instead?

4. Missing data and sensitivity analysis

In this study, over a quarter of data (26%) were missed on key information such as coronary calcification. The researcher used a weight approach to adjust for the missing data and a sensitivity analysis showed that unweighted and weighted analyses had approximately equal results. Other alternatives are to conduct sensitivity analysis with Multiple Imputation (MI), Maximum Likelihood (ML), and Weighted Estimating Equation (WEE), especially when dealing with large proportion of missing data.

Detailed Technical Issues

- 1) On page 1917, in first sentence in section Study sample and menthol preference, (30%) can be added after the number 1544.
- 2) On page 1917, in the sentence “Before adjustment, menthol smokers were less likely to be noncurrent smokers at follow-up examinations...” in section Smoking cessation behavior, double negatives were used. It would be easier to understand if changing the sentence to ‘...menthol smokers were more likely to be current smokers at follow-up examinations...’.
- 3) Redundant information regarding statistical significance (both 95% CI and p-value) was presented all over the research paper. For example, on page 1915, in the Results section of the abstract, it presented “odds ratio [OR], 0.71;95% confidence interval [CI], 0.49-1.02; $P=.06$ ”.

Reference:

Sidney et al 1989. “**Mentholated Cigarette Use among Multiphasic Examinees, 1979-86**” *Am J Public Health*. 1989 Oct;79(10):1415-6, by Drs. Sidney S, Tekawa I, and Friedman GD.