The Mentholation of Cigarettes:
A Position Statement of The American Council on Science and Health

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Abstract

Menthol has been used as a cigarette flavoring agent for almost 90 years, until recently without any concerns over the biological effects of mentholation. Two recent reviews have examined in considerable detail the toxicological sequelae of mentholation, by assessing analytical smoke chemistry, smoking behavior, biomarkers of exposure, airway patency, absorption of nicotine, metabolism of other smoke components, initiation, dependency and cessation, risk of lung cancer, lung cancer in African Americans, and risk of other diseases. The conclusions of the two reviews (and of other recent papers) are identical, suggesting imponderable and therefore inconsequential differences between the effects of smoking mentholated or non-mentholated cigarettes. At the same time, the use of menthol in cigarettes has been criticized on political grounds, largely based on such non-scientific issues as “social justice”, “predatory marketing”, and “mental health issues”, to support contentions that the FDA ban mentholated cigarettes under its new regulatory powers. Yet, whatever the dialectical value of these non-scientific issues, the factually defensible message emerging from the scientific reports is very clear: “Any toxicological effects of cigarette mentholation on smokers are beyond detection and are probably immaterial.”
Introduction

Menthol is used in cigarettes to give attributes of mint and “coolness” to the smoke, and is viewed as pleasurable to the smokers who prefer mentholated cigarettes. In the United States nearly 25% of smokers choose mentholated cigarettes [1], the proportion being considerably greater for African American men [2]. There have been two recent reviews on the toxicology of menthol as a cigarette ingredient [3, 4], and the present paper simply copies the most important points from those reviews and, wherever possible, provides updates. Another review, with quite different conclusions, has also been prepared [5] and submitted to the FDA with a request for political action. The present paper highlights the clear distinctions between the testable work published in the scientific literature and the political contentions [5].

1.1. Political contentions.

The following ten contentions were given as the justification for an FDA ban of mentholated cigarettes, claiming they: (1) are a starter product for youth, (2) are promoted as a healthier cigarette, (3) represent a greater addiction potential, (4) make it harder to quit, (5) have a greater potential for relapse, (6) induce poorer mental health, (7) provide unique sensory stimulation, (8) inhibit detoxification of NNAL (this is the abbreviation for (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), (9) inhibit cotinine clearance, and (10) are contrary to social justice issues. Notably, the
request for a ban does not include the previous concerns over the higher rates of lung cancer in African American men, presumably because this issue has now been rigorously shown to be unrelated to the disproportionate consumption of mentholated cigarettes in this population (see below).
2. Results.

The first part (sections 2.1.1 to 2.1.5) will address each of the contentions listed above [5], made in support of a ban on mentholated cigarettes.

Additional data will then be presented (sections 2.2.1 to 2.2.4) on relevant areas such as the epidemiology for lung cancer and other diseases in smokers of mentholated cigarettes, the associated smoke chemistry, and *in vitro* and *in vivo* toxicology.
2.1.1. Does cigarette mentholation affect initiation, dependency, and cessation?

Mentholation may influence “determinants of exposure” which in turn may include an earlier age at initiation of the smoking habit (contention # 1 above, the “starter product for youth”), an increased dependence (contention #3, “greater addiction potential”), and a reduced rate of cessation (contention #4, “harder to quit”, and #5, “greater potential for relapse”).

A study based on over 13,000 smokers in 11 communities (10 in the USA, one in Canada) examined some of these variables [6]. Subjects were interviewed in 1988 and re-interviewed in 1993. Multivariate techniques were used to assess the association of baseline menthol use with various factors, including sex, age, race/ethnicity, education, amount smoked, time until first cigarette, age of starting to smoke and alcohol use. After adjustment, menthol use was weakly associated with lower cigarette consumption, longer time to first cigarette in the morning, and increased quit attempts. Between 1988 and 1993, 24% of the baseline smokers had successfully stopped smoking. For the entire sample, the adjusted relative risk of quitting for menthol vs. non-menthol smokers was 1.00 (95% confidence interval, hereafter “CI”, 0.90–1.11) and no significant association was seen in subgroups by race/ethnicity. No associations were observed between menthol use in 1988 and amount smoked among continuing smokers in 1993.
Some epidemiological studies have compared smokers of mentholated and non-mentholated cigarettes in respect of amount smoked or age of cessation. In a cross-sectional case control study of nearly 20,000 current and former smokers, it was reported that, among African Americans, the prevalence odds ratio (POR) for heavy smoking (>20 cigs/day) for mentholated compared to non-mentholated cigarettes was 0.7 (CI, 0.5–0.9) in current smokers, and 0.6 (CI 0.4– 0.9) in former smokers [7]. However, the reduced consumption of cigarettes per day associated with mentholation did not explain the lower daily consumption of cigarettes in African American smokers. Caucasians also had a reduced POR of 0.9 (CI 0.8–1.0), both for current and former smokers. Furthermore, the POR of continued smoking versus quitting associated with mentholated cigarettes was 1.1 (CI 1.0–1.2) for both African Americans and Caucasians. The authors concluded that mentholation was independently associated with reduced daily cigarette consumption, but not with the risk of quitting [7].

A cohort of 600 African American smokers were enrolled in a clinical trial that assessed the efficacy of sustained-release bupropion for smoking cessation [8]. Menthol (n = 471) and non-menthol (n = 129) smokers were compared on smoking-related characteristics and abstinence rates at 6 weeks and 6 months. Menthol smokers were younger (41.2 versus 52.9 years), more likely to be female (73.7% versus 56.6%) and more likely to smoke their first cigarette within 30 minutes of waking up (81.7% versus 69.8%) compared to non-menthol smokers. Cigarette taste (50% versus 40%, P = 0.054) was rated non-significantly higher by menthol
smokers. Seven-day point-prevalence abstinence from smoking at 6 weeks was 28% and 42% and at 6 months were 21% and 27% for menthol and non-menthol smokers, respectively. At 6 weeks follow-up, stepwise logistic regression revealed that among those younger than 50 years, non-menthol smokers were more likely to quit smoking (odds ratio = 2.0; CI = 1.03-3.95) as were those who received bupropion (odds ratio = 2.12; CI = 1.32-3.39). However, this reduced short-term smoking cessation success for younger smokers was not statistically significant at the terminal 6-month follow-up, nor in the placebo group who were not receiving bupropion treatment.

A further study of African Americans compared 407 menthol smokers with 73 non-menthol smokers [9]. The authors noted that smokers in both groups reported similar cigarette consumption and age of starting to smoke, and a similar number of life-time quit attempts, and did not differ in their readiness to quit smoking. The durations of most recent and longest-ever quit attempts were non-significantly shorter for menthol, compared to non-menthol smokers. The authors reported only surrogate measures of smoking cessation; they noted that “being a cross-sectional study, causal relationships between menthol and smoking cessation cannot be implied.” Scores on the Fagerström Test for Nicotine Dependence (FTND) [10] were identical for menthol and non-menthol smokers.

Seven-day smoking cessation was related to various factors in 535 African American smokers taking part in a randomized control trial of bupropion [11]. Over the 7 days, 167 smokers quit, with quit rates about twice as high with bupropion as with placebo.
Quit rates were significantly lower with mentholated than non-mentholated cigarettes (28.3% vs. 41.5%), but after adjustment for baseline predictors in a multivariate model, mentholation was no longer significantly associated with lower quit rates.

Menthol was part of a study to determine if the recalled response to the first cigarette is predictive of the development of symptoms of nicotine dependence, and whether it is influenced by the type of cigarette smoked [12]. The study was a retrospective/prospective longitudinal study of the natural history of nicotine dependence employing individual interviews conducted three times annually in two urban school systems over 3 years. A total of 237 subjects were asked to recall their first smoking experience. Reactions to the initial smoking experience were unrelated to gender or cigarette brand, strength, or mentholation.

A telephone survey was used to examine differences in consumption and tobacco dependence, including smoking urgency among menthol and non-menthol adolescent smokers [13]. Data were collected from adolescent smokers applying to a cessation treatment study. Of 572 adolescent smokers (mean age=15.6 ± 1.6 years; 55.1% female; 46.9% African American, 48.2% European American), 531 smoked menthol cigarettes and 41 smoked non-menthol as their usual brand. Analysis revealed that menthol smokers had a significantly shorter time to first (TTF) cigarette of the day compared to non-menthol smokers (smoking within the first 5 min of the day, 45% vs. 29%, respectively; p<0.04). Independent t tests revealed no significant
difference in number of cigarettes per day (CPD) (mean=12.2 ± 8.5 vs. 11.4 ± 8.8; p<0.28) or FTND scores (3.4 ± 1.4 vs. 3.2 ± 1.3; p<0.23).

Data from the National Youth Tobacco Survey indicated that menthol cigarette use was significantly more common among newer, younger smokers [14]. Additionally, youth who smoked menthol cigarettes had significantly higher scores on a scale of nicotine dependence compared with non-menthol smokers, controlling for demographic background and the length, frequency, and level of smoking. The study suggested to the authors that menthol cigarettes may be a starter product that may be associated with smoking uptake by youth. The authors commented that “these analyses were conducted with cross-sectional data, and association does not necessarily imply causality. The evidence discussed in this article would be strengthened by longitudinal data.”

Measures of cumulative exposure to menthol and non-menthol cigarettes and smoking cessation behavior (1985-2000), coronary calcification (2000), and 10-year change in pulmonary function (1985-1995) were made in African American and European American smokers recruited in 1985 for the Coronary Artery Risk Development in Young Adults Study [15]. There were 1535 smokers in 1985 (972 menthol and 563 non-menthol); 89% of African Americans preferred menthol vs. 29% of European Americans (P<.001). After adjustment for ethnicity, demographics, and social factors, there were non-significant trends in menthol smokers toward lower cessation (odds ratio [OR], 0.71; CI, 0.49-1.02; P = .06) and recent quit attempt (OR, 0.77; CI, 0.56-1.06; P = .11) rates and a significant increase in the risk
of relapse (OR, 1.89; CI, 1.17-3.05; P = .009). Per pack-year of exposure, however, there were no differences for menthol in tobacco-related coronary calcification (adjusted OR, 1.27; CI, 1.01-1.60 for menthol cigarettes and 1.33; CI, 1.06-1.68 for non-menthol cigarettes per 10-pack-year increase; P = .75 for comparison) or 10-year pulmonary function decline (adjusted excess decline in forced expiratory volume in 1 second, 84 ml; CI, 32-137 for menthol cigarettes and 80 ml; CI, 30-129 for non-menthol cigarettes, per 10-pack-year increase; P = .88 for comparison). The author’s conclusion was that “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.”

The comparison of variables associated with menthol vs. non-menthol cigarette use was examined among 432 adult African American smokers in Los Angeles, California [16]. Menthol smoking was most prevalent among women, 18-30-year-olds, and employed respondents. Controlling for age and employment, the significant correlates of menthol use among women were parents’ menthol smoking, the belief that most African American smokers smoke menthols, and disagreement with the belief that smoking menthol cigarettes is a "Black thing." Among men, the only significant correlate of menthol smoking was the belief that most African American smokers smoke menthols. The authors also noted “Despite the proliferation of advertisements for menthol cigarettes in African American magazines, newspapers, neighborhoods, and entertainment venues, self-reported exposure to menthol advertising was not a significant correlate of menthol smoking.”
The Lung Health Study (LHS) enrolled 5,887 adult smokers in a clinical trial of smoking cessation and ipratropium in the prevention of chronic obstructive pulmonary disease. LHS participants have been subjected to surveillance for mortality from all causes for 14 years. The LHS data were examined for differences between self-reported smokers of menthol cigarettes versus plain cigarettes [17]. Using proportional hazards regression methods, the authors found no differences in hazard ratios for coronary heart disease, cardiovascular disease, lung cancer, or death from any cause. The authors commented: “Contrary to expectations about nicotine dependence, we found that users of menthol cigarettes had smoked fewer pack-years at baseline. We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking”, and this similarity between mentholated and non-mentholated cigarettes is clearly presented as Figure 1 in the original publication.

A clinical trial was designed to determine whether African American light smokers who smoked menthol cigarettes had lower cessation when treated with nicotine replacement therapy and counseling [18]. Data were derived from a clinical trial that assessed the efficacy of 2 mg nicotine gum (versus placebo) and counseling (motivational interviewing counseling versus Health Education) for smoking cessation among 755 African American light smokers (smoked ≤ 10 cigarettes per day). The primary outcome variable was verified (by salivary cotinine) 7-day
point-prevalence smoking cessation at 26 weeks follow-up. Compared to non-menthol smokers, menthol smokers were younger and less confident to quit smoking \( (P = 0.023) \). At 26 weeks post-randomization, 7-day verified abstinence rate was significantly lower for menthol smokers (11.2\% versus 18.8\% for non-menthol, \( P = 0.015 \)). The authors concluded that “among African American light smokers, use of menthol cigarettes is associated with lower smoking cessation rates.”

A secondary analysis was made of the data from the above clinical trial that assessed the efficacy of nicotine gum and counseling for smoking cessation among African American light smokers [19]. This work assessed nicotine dependence among participants enrolled in the clinical trial using three measures of nicotine dependence. The Cigarette Dependence Scale (CDS), the FTND, and the Nicotine Dependence Syndrome Scale (NDSS) were administered to 700 participants (67\% female; mean age=45 years). Approximately 82\% of the participants smoked mentholated cigarettes. Exhaled carbon monoxide (CO) and serum cotinine were assessed. The CDS showed the strongest association with biochemical markers \( (r=0.28 \text{ for cotinine and } 0.25 \text{ for CO}) \). Factor analysis of the NDSS revealed five factors: drive, priority, tolerance, continuity, and stereotypy. Compared to those who smoked 1-5 CPD, smokers who averaged 6-10 CPD scored higher on all three dependence \( (p<0.001) \) and two biochemical measures \( (p<0.001) \), and on three of the five NDSS subscales \( (\text{Drive, } p<0.001; \text{ Stereotypy, } p<0.01; \text{ and Tolerance, } p<0.01) \). Given the different domains tapped by each instrument, the use of multiple measures might yield the most comprehensive assessment of nicotine dependence. Results
suggest the validity of these scales for African American light smokers and point to
the need for sensitivity to differential levels of nicotine dependence among
subgroups of light smokers. There was no difference between the percentages of
users of mentholated cigarettes in the light-smoking group (84%) and the moderate-
smoking group (80%).

Measures of nicotine dependence among adolescent menthol and non-menthol
cigarette smokers were analyzed in a nationally representative sample. The authors
examined rates of menthol smoking and measures of nicotine dependence among
1345 current established smokers in grades 9-12 who participated in the 2004
National Youth Tobacco Survey [20]. Logistic regression was used to generate an
adjusted odds ratio (OR) for menthol smoking for four measures of nicotine
dependence, controlling for demographic characteristics and smoking patterns.
Approximately 46% of all current established cigarette smokers were menthol
smokers. Menthol smokers had 2.6 and 1.6 greater odds than non-menthol smokers
for reporting that they could go for less than 1 h before feeling like they need a
cigarette and that they experience cravings after not smoking for a while,
respectively. The authors concluded that “menthol cigarette smoking was associated
with two dependence measures and may be more addictive than regular cigarettes
in young smokers”, even though they had stated earlier that the NYTS “was not
designed to test hypotheses related to menthol use and dependence.”
There is concern that cigarette flavors such as menthol might mask smoke harshness, making inhalation easier. A pilot study [21] evaluated differences in puff topography and cigarette ratings among 20 college student smokers smoking Camel Light (10mg Tar, 0.9mg nicotine, 35% filter ventilation) and Camel Exotic Blend cigarettes (11mg Tar, 0.9mg nicotine, 23% filter ventilation). Carbon monoxide boost was measured by assessing alveolar carbon monoxide (CO) levels before and after smoking each cigarette. Participants also rated each cigarette on characteristics such as strength, irritation, and taste. The authors found that participants took smaller puffs on the Exotic Blend versus Camel Light (42ml vs. 48ml, p<0.001), but there was no reliable difference in total smoke volume (613.9ml vs. 630.7ml, p=0.79) or CO boost (6.2ppm vs. 6.2ppm, p=0.90). Exotic Blend cigarettes were rated as more different from the participant’s usual brand, but otherwise the taste ratings did not differ. Overall, these preliminary data suggest that adding flavors to cigarettes may not significantly impact how they are smoked by current smokers.

A recent study examined the effect of menthol cigarette smoking on cessation among a multi-ethnic sample of smokers making a pharmacotherapy-aided quit attempt [22]. The authors hypothesized that menthol cigarette smoking would be associated with lower smoking abstinence rates and conducted a secondary analysis of data from a multi-site randomized controlled trial of an intervention designed to facilitate repeat tobacco cessation treatment (N = 1,343). The intervention consisted of a patient phone call and a computerized provider prompt. The primary outcome for this analysis was 7-day point prevalence smoking abstinence. The average age of
the sample was 56 years old. Overall, 25% of the sample smoked menthol cigarettes: 19% of Whites, 62% of Blacks, and 25% of other ethnicity (p<.001). The authors observed no significant effects for menthol cigarette smoking or ethnicity on smoking abstinence rates. The conclusion, combined with findings from previous research, was that this study suggests that smoking menthol cigarettes does not decrease smoking cessation among older smokers during a quit attempt aided with pharmacotherapy.

Another recent study assessed the relationship between menthol smoking, race/ethnicity and smoking cessation among a diverse cohort of 1688 patients attending a specialist smoking cessation service [23]. 46% of the patients smoked mentholated cigarettes, but significantly more African American (81%) and Latino (66%) patients than Whites (32%) smoked menthols. African American and Latino menthol smokers smoked significantly fewer cigarettes per day (CPD) than non-menthol smokers (15.7 vs. 20.3, for African American, and 17.0 vs. 22.1, for Latinos), with no differences among White menthol and non-menthol smokers. At 4-week follow up, African American, Latino and White non-menthol smokers had similar quit rates (54%, 50% and 50% respectively). In contrast, among menthol smokers, AAs and Latinos had lower quit rates (30% and 23% respectively) compared with Whites (43%, < 0.001). AA and Latino menthol smokers had significantly lower odds of quitting [odds ratio (OR) = 0.34; CI = 0.17, 0.69 for African Americans, and OR = 0.32; CI = 0.16, 0.62 for Latinos] than their non-menthol counterparts. At 6-month follow up, a similar trend was observed for the
race/ethnicity subgroups, with African American menthol smokers having half the odds of being abstinent compared with African American non-menthol smokers (OR = 0.48; CI = 0.25, 0.9). The author’s conclusions were that 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. The authors were not able to explain why the reported effects of long-term smoking cessation are not manifested in white smokers; they also found that full-time employment status was highly and negatively associated with preference for menthol cigarettes, and other negative indicators of socioeconomic status showed similar strong statistical associations with preference for mentholated cigarettes.

The racial differences in smoking cessation in which Black smokers have demonstrated lower smoking cessation rates than White smokers mentioned above was examined in a female prison population [24]. The study used data from a smoking cessation intervention and compared White and Black female prisoners (N = 233) on a 10-week intervention of group psychotherapy and nicotine replacement (patch). Generalized estimating equations were used to model smoking cessation across the 12-month follow-up. Compared with an untreated control group, both Black and White smokers benefited from the cessation treatment. However, after controlling for potential confounders, White smokers had significantly higher overall smoking cessation rates across time compared with Black smokers (e.g., 30% vs.
24% abstinent at 6 weeks; 13% vs. 10% abstinent at 12 months). Smoking mentholated cigarettes was not associated with these differences in quit rates. African Americans are less likely than the general population to be heavy smokers; a recent study [25] compared the baseline demographic, smoking, and psychosocial characteristics of light (5-10 cigarettes per day; n=86) and moderate to heavy (>10 cigarettes per day; n=286) African American smokers enrolled in a smoking cessation clinical trial. Results indicated no differences between groups on demographic variables. However, light smokers (LS) were less dependent on smoking, reported more previous quit attempts, and had higher self-efficacy to quit than moderate to heavy smokers (MHS). On a measure of withdrawal, LS reported less pre-quit craving and less difficulty concentrating than MHS. In addition, LS reported lower perceived stress, fewer symptoms of depression, and greater positive affect than African American MHS. Although menthol was mentioned in the article, the only data presented was to show that there was no difference between the percentages of menthol smokers in the LS and MHS groups. The authors considered that “these findings highlight important similarities and differences between African American LS and MHS, and have implications for the treatment of African American smokers”; menthol is not one of those differences.

Another recent study examined the relationship between race/ethnicity, menthol smoking, and cessation in a nationally representative sample of adults [26]. Data from the 2005 U.S. National Health Interview Survey was analyzed. Analyses were restricted to 7,815 white, black, and Hispanic current and former cigarette smokers
who indicated they do not currently use other tobacco products and have made a quit attempt. Multiple logistic regressions were used to test the relationship of menthol smoking and cessation controlling for various factors. Significant interaction effects were found indicating that the association between menthol smoking and cessation differs between whites and blacks, and whites and Hispanics. When blacks and Hispanics are collapsed as non-white, the authors found that non-white menthol smokers were significantly less likely to have quit smoking (adjusted odds ratio=0.55, \( p<.01 \)) compared to their non-menthol smoking counterparts. In contrast, among whites, menthol smokers were more likely to be former smokers than non-menthol smokers (adjusted odds ratio=1.17, \( p<.05 \)). The author’s conclusion was that “Our findings provide some support for the hypothesis that menthol smoking can lead to poorer cessation outcomes, but only for non-white smokers.”

A very recent study on smoking cessation in African Americans [27] did not even evaluate the role of menthol, suggesting that the authors did not consider this to be a major influence in their study population.

Studies with experimental cigarettes containing menthol, but no nicotine, did not show any pharmacological effects [28, 29].

Section 2.1.1. Conclusion

Overall, the evidence summarized in this section does not suggest that mentholated cigarettes are associated with any independent reduction in age of starting to smoke
(“starter product for youth”), increase in cigarette consumption or dependency
(“greater addiction potential”); there may in African Americans be some evidence for
poorer results in cessation (“harder to quit” and “greater potential for relapse”). Data
from the FTC in 2006 indicate that the menthol percentage of the total cigarette
market has been remarkably stable over the last 35 years. If menthol cigarettes
were more addictive than non-menthol, or otherwise increased likelihood of usage,
then menthol’s share of market would have steadily increased over the last 35 years.
2.1.2. Does mentholation affect the metabolism and clearance of nicotine and other smoke constituents?

It has been hypothesized that menthol may increase lung cancer risk by inhibiting the enzyme responsible for the glucuronidation of NNAL, [30], the major byproduct of 4-(methylnitrosoamino)-1-(3pyridyl)-1-butanone (NNK) metabolism (contention #8, “inhibits detoxification of NNAL”). If occurring, the slower detoxification and elimination of NNAL via glucuronidation could result in longer biological persistence and the potential for increased carcinogenicity of NNAL. NNK requires activation by I-hydroxylation to form a reactive species that can methylate or pyridyloxobutylate DNA to form DNA adducts. These DNA adducts have been detected in rodent and human tissues and are associated with K-ras gene activation [31]. NNK is found in cigarette smoke and produces adenocarcinoma in the lungs of mice, rats, and hamsters when administered by the oral, topical, subcutaneous or intraperitoneal routes [31]. In man, NNK is first reduced to NNAL which is in turn glucuronidated to form NNAL-Gluc. Thus the NNAL-Gluc/NNK ratio may be used to measure the capacity to detoxify and eliminate NNK. Phenotypic differences exist for NNAL glucuronidation capacity, and individuals in the low NNAL-Gluc/NNK ratio group might be at greater risk for lung cancer [31].

Cigarette mentholation could increase systemic exposure to tobacco smoke toxins and affect metabolism of nicotine or tobacco smoke carcinogens [32] (contention #9, “inhibits cotinine clearance”). Based on a crossover study involving seven Caucasian
and seven African-American smokers who smoked mentholated and non-mentholated cigarettes, systemic intake of nicotine and carbon monoxide (CO) was unaffected by mentholation. By using intravenous infusions of nicotine and cotinine, mentholation significantly inhibited nicotine metabolism, both by slower oxidative metabolism to cotinine and by slower glucuronide conjugation [32]. Nicotine clearance was 1289 ml/min in mentholated cigarette smokers and 1431 ml/min in non-menthol smokers. While these differences are relatively small, the data may help to explain why African-Americans tend to smoke fewer cigarettes per day. The authors reported that their data did not support the hypothesis that smoking mentholated cigarettes results in greater absorption of tobacco smoke toxins and they found no evidence that menthol accelerated nicotine metabolism, “thus excluding the possibility that more rapid metabolism of nicotine might explain a greater intake of cigarette smoke and, therefore, a greater carcinogen risk.”

A study was made of nicotine metabolism and intake in African American and Caucasian smokers [33]. In this study, the 40 African American smokers, 31 of whom used mentholated cigarettes, and 39 Caucasian smokers, only 2 of whom did, had similar average consumption of 14–15 cigarettes/day, and similar total and non-renal clearance of nicotine. However, in the African American smokers, total and non-renal clearance of cotinine was significantly lower, and the cotinine half-life was significantly longer (1064 vs. 950 min) than in Caucasians. The investigators also reported that nicotine intake in the African-American smokers was 30% greater than in Caucasians; they concluded that the higher levels of cotinine per cigarette smoked
by African Americans compared to Caucasians is due to their slower clearance of cotinine and higher intake of nicotine per cigarette [34, 35]. The reason for the increase in nicotine uptake was not determined, but may be related to some aspect of smoking behavior such as puffing intensity, number of puffs per cigarette, under-reporting of number of cigarettes smoked or shorter butt length. While the data suggest that mentholation may decrease cotinine clearance in some smokers, this effect is of unknown biological significance.

In a community-based cross-sectional study on 525 Black and White volunteers, comparisons were made of concentrations of urinary and plasma cotinine, plasma thiocyanate, urinary NNAL, and its detoxified form (NNAL-Gluc), between menthol and non-menthol smokers [30]. In regression models that adjusted for daily cigarette intake, no significant differences were observed in the concentration of these biomarkers by menthol status in both races. There was no significant association between high FTND scores and the use of menthol cigarettes (odds ratio, 1.1; CI, 0.6-2.0), but an increased risk was observed with smoking a cigarette soon (<30 minutes) after waking (odds ratio, 2.1; CI, 1.0-3.8). The ratio of NNAL-Gluc to NNAL, a possible indicator of lung cancer risk, was significantly lower in menthol versus non-menthol smokers. The NNAL-Gluc/NNAL ratio was 34% lower in Whites (P < 0.01) and 22% lower in Blacks. In subsequent human liver microsome studies, menthol inhibited the rate of NNAL-O-glucuronidation and NNAL-N-glucuronidation. Collectively, the authors considered that “these results show that menthol does not
affect biological exposure to tobacco smoke constituents but indicates that menthol might inhibit the detoxification of the potent lung carcinogen NNAL.”

The possibility of menthol affecting lung carcinogenesis by some biochemical and/or genetic pathway is not supported by multiple epidemiology studies, reviewed below. One hundred twelve male and female smokers participated in a study to determine whether the ad libitum smoking of menthol cigarettes resulted in differences in biomarkers of smoke exposure in blood and urine, relative to those smoking non-menthol cigarettes having similar machine-measured yields of ~ 9 to 10 mg "tar" [36]. The study subjects were provided cigarettes of their preferred menthol or non-menthol types prior to two 24-hour study intervals spaced one week apart. Carboxyhemoglobin levels were measured in blood samples drawn at mid-afternoon following the two 24-hour urine collection periods. Six urinary nicotine metabolites (nicotine, cotinine, trans-3'-hydroxycotinin and respective glucuronides) were determined as measures of nicotine intake, and urinary NNAL and its glucuronide were determined to assess exposure to NNK. Blood carboxyhemoglobin values did not differ significantly between the cigarette types. Neither total urinary NNAL nor urinary nicotine equivalents exhibited statistically significant differences between the menthol and non-menthol cigarette smokers. Moderately heavy smokers of menthol and non-menthol cigarettes of similar machine-generated smoke yield exhibit essentially identical levels of biomarkers of smoke constituent exposure such as NNAL.
Section 2.1.1. Conclusion

Although there are only a few studies, cigarette mentholation does not appear to have any major effects on either the absorption of nicotine and smoke, or the metabolism and elimination of tobacco smoke constituents. When effects were noted, they appear to be related to genetically determined metabolic characteristics of African American men [37].
2.1.3. Does cigarette mentholation affect smoking behavior?

This section addresses contention #7, “unique sensory stimulation.”

Various studies have investigated possible effects of cigarette mentholation on smoking behavior (also known as smoking “topography.”) The overlying theory is of an anesthetic effect of menthol, hence the subtitle of the submission to FDA [5]. The concept is often examined by simple measures of smoking topography, by measurements of biomarkers of smoke exposure, or both.

A relatively old study described a protocol in which, in six separate sessions, 15 regular smokers were presented with a medium and a low yield cigarette of each of three taste categories—mentholated, dark tobacco, and blond tobacco [38]. The sessions took place each week with the subject required to smoke no cigarettes other than the test cigarette during the 5 days preceding the session. Each session included a “natural” and a “forced” smoking procedure of the cigarette type being tested, forced smoking consisting of smoking 30 puffs whereby a new half-length cigarette was presented after every third puff. After the six sessions, in which the order of testing the cigarettes varied systematically between subjects, habitual brand cigarettes were smoked as a reference during the seventh session. Analysis of variance was used to evaluate the effect of the two main factors taste (mentholated, dark, and blond) and smoke yield (high, low) on subjective ratings, physiological variables, puffing parameters, and respiratory inhalation parameters. Although
general acceptability of the cigarettes, smoking satisfaction and pleasantness of
taste were clearly lower for all test cigarettes as opposed to the habitual brand
reference cigarettes, these measures remained unaffected by taste or smoke yield of
the test cigarettes. Harshness of smoke was higher in the dark tobacco category and
generally decreased with the lower smoke yield cigarettes. Independent effects of
taste and smoke yield were obtained for total puff volume, inhalation time and CO
absorption, suggesting a compensatory intensification of smoking behavior for low
yield cigarettes and an independent increase of smoking intensity from mentholated
to dark tobacco to blond tobacco. The results suggest therefore that factors which
affect cigarette smoke taste have effects on smoking behavior which are separate
from those obtained by comparing smoke yields.

In another experimental study [39], 12 subjects (nine African Americans, three
Caucasians) smoked mentholated cigarettes and 16 (eight African Americans, eight
Caucasians) smoked non-mentholated cigarettes. Each subject participated in two
separate sessions at a 1 week interval, one involving experimenter-supplied
mentholated cigarettes (1.2 mg nicotine, 17 mg tar, and 17 mg CO) and one non-
mentholated cigarette (1.2 mg nicotine, 17 mg tar, and 15 mg CO). In each session
baseline levels of exhaled breath CO, blood pressure, and heart rate were
determined. Subjects then underwent a modified rapid smoking procedure using a
controlled-dose smoke delivery system where they were asked to inhale 40 ml of
cigarette smoke every 15 s for as long as they could continue. Immediately
afterwards, exhaled breath CO, blood pressure, and heart rate were determined
again. The number of puffs taken before stopping, the main endpoint of the study, was related to race, cigarette preference (only tested in African Americans), and type of experimental cigarette. The authors “hypothesized that menthol and regular cigarette smokers would take more puffs from menthol cigarettes than from regular cigarettes before stopping in the controlled-dose rapid smoking procedure.” However, no difference was observed for the number of puffs taken from regular as opposed to menthol cigarettes (cigarette type condition) and no differences were found for Cigarette Preference (regular smokers vs. menthol smokers).

A study involving 65 African American and 96 Caucasian non-Hispanic adult established smokers reported data on their smoking habits [40]. Details of the cigarettes they usually smoked (mentholated or not, length, tar yield) were taken from a pack provided. Butts were collected from all cigarettes smoked in a week. At a second visit, blood was taken for serum cotinine analysis and CO in breath was measured after smoking one of their usual cigarettes. Serum cotinine and CO levels were related to cigarette mentholation after adjustment for race, cigarettes per day and the amount of each cigarette smoked. After adjusting for race, cigarettes per day, and mean amount of each cigarette smoked, menthol was associated with higher cotinine levels (p = 0.03) and carbon monoxide concentrations (p = 0.02).

In a study involving 37 women reporting smoking up to 20 cigarettes/day 18 subjects (8 African Americans, 10 Caucasians) were regular smokers of American blended mentholated cigarettes and 19 (10 African Americans, nine Caucasians) of non-men-
tholated cigarettes [41]. Expired air CO, blood nicotine and cotinine were measured before smoking and expired air CO and blood nicotine after smoking. Puffing topography measures were determined by a flow-meter cigarette holder with respiratory variables of inhalation and exhalation volume and duration measured by inductive plethysmography. Analyses investigating possible effects of cigarette, race and their interaction were carried out. There were significant main and interaction effects of race and menthol/non-menthol use on CO boost. Black women had a mean CO boost of 10.1 ppm vs. 7.2 ppm for white women, while women using non-menthol cigarettes had a higher CO boost (mean = 10.6 ppm) compared to those regularly using menthol cigarettes mean = 6.5 ppm). White menthol smokers had the lowest CO boost of all subgroups. There was a trend for black women to have higher nicotine boost than white women (21.4 ng/ml vs. 15.9 ng/ml). Black women had non-significantly higher puff volumes compared to white women (mean = 48.4 vs. 43.5 ml), while non-menthol smokers had non-significantly higher puff volumes than menthol smokers (mean = 48.5 vs. 42.7 ml). Lower CO boost with mentholated cigarettes suggests factors beyond mentholation may affect elevated smoke constituent exposure among black women.

The same group described results of another study in women, similar in design to the previous one, but larger [42]. Forty-nine subjects (27 African Americans, 22 Caucasians) were smokers of mentholated cigarettes and 46 (21 African Americans, 25 Caucasians) of non-mentholated cigarettes. Measures of smoking topography, plasma cotinine and nicotine, and expired carbon monoxide were obtained in
addition to self-report of the pros and cons of smoking, time to first cigarette, and smoking history. Black women smoked significantly fewer cigarettes per day, but had higher cotinine levels compared to White women. Menthol smokers (n = 49) had significantly larger puff volumes, higher cotinine levels, and shorter time to first cigarette compared to non-menthol smokers (n = 46). Pre-contemplators (n = 44) were significantly lower on beliefs about the negative aspects of smoking compared to contemplators and those in preparation stage. Black women, all stages combined, had higher negative beliefs about smoking than did White women.

An experimental study involved 12 male African American smokers of at least 15 cigarettes per day, six primarily menthol and six primarily non-menthol cigarette smokers [43]. Each subject participated in three separate trials at 1 week intervals, in which they inhaled a controlled dose of 1200 ml of smoke from a commercial cigarette (1.1 mg nicotine, 16 mg tar, and 14 mg CO) injected with 0, 4 or 8 mg menthol. Pre- and post-experiment measures of exhaled CO, blood pressure, and pulse were collected at each session. The order of smoking the three cigarettes was balanced. Statistical analyses related puff volume, number of puffs, change in blood pressure, heart rate, and exhaled CO pre- to post-smoking to the dose of menthol in the cigarettes and to whether the subjects were mentholated or non-mentholated cigarette smokers. There were no differences in smoking topography across the 3 conditions.
A similar experiment involved 20 smokers of at least 15 cigarettes per day. Ten subjects (five African Americans, five Caucasians) were smokers of mentholated cigarettes and 10 (five African Americans, five Caucasians) were smokers of non-mentholated cigarettes [44]. As in the previous study, each subject participated in two separate trials a week apart involving experimenter-supplied mentholated or non-mentholated cigarettes. Both cigarettes had the same yields of nicotine (1.2 mg), CO (15 mg) and tar (16 mg). In each session subjects first smoked one of their own cigarettes and then, 30 min later, smoked the experimental cigarette using an apparatus designed to measure smoking topography and the amount of tar inhaled and retained in the lung. For each of a number of topographic, smoke constituent and subjective rating variables, the joint relationship of the variable to race, cigarette preference and type of experimental cigarette was studied by analysis of variance. Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide, despite the fact that mentholated cigarettes decreased average and total cumulative puff volumes and increased mean puff flow rates of inhaled smoke. These chemical and topographic differences were independent of race. No significant differences in depth of inhalation of the smoke or in the amount of insoluble smoke particulates delivered to or retained in the respiratory tract were noted between the two types of cigarettes. The authors concluded that “mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide.”
Another similar experiment involved 11 smokers (eight African Americans, three Caucasians) of American blended mentholated cigarettes and 19 (nine African Americans, 10 Caucasians) of non-mentholated cigarettes [45]. As above, each subject participated in two separate trials a week apart, again involving the same experimenter-supplied mentholated and non-mentholated cigarettes, with the measurements made similar to before. Again, a rapid smoking procedure was used with puffs taken every 15 s for as long as the subject could continue, but here the puff volume was chosen by the subject and not fixed. Statistical analyses related puffing parameters, expired air CO, blood pressure, heart rate to race, cigarette preference, and the experimental cigarette. When smoking the non-mentholated brand of cigarettes, participants smoked 22% more puffs and had 13% higher mean volumes per puff than they did when smoking the mentholated brand of cigarettes. The aggregate 39% excess exposure to cigarette smoke in the regular-cigarette condition was not accompanied by commensurate excesses in expired carbon monoxide or in physiological measures normally correlated with nicotine exposure.

In yet another similar study, 18 subjects (17 African Americans, one Caucasian) smoked mentholated cigarettes and 18 (three African Americans, 15 Caucasians) non-mentholated cigarettes [46]. Each subject participated in a single session during which three cigarettes were smoked 45 min apart in random order. The nicotine yields of the cigarettes smoked were 0.2, 1.2, and 2.5 mg, the 1.2 mg cigarette being a commercial cigarette and the others research cigarettes. Subjects that ordinarily smoked mentholated cigarettes received mentholated cigarettes in the study while
non-mentholated smokers received non-mentholated cigarettes. Analyses separated out potential effects of nicotine yield and of mentholation on heart rate, blood pressure, exhaled breath CO, number of puffs, and time to smoke the cigarettes. Participants smoked commercial cigarettes faster and with fewer puffs than either of the research cigarette indicating production differences can affect topography. There was a significant group by cigarette interaction on satisfaction, and relief from cigarette craving. High-yield non-menthol cigarettes reduced craving and were rated as more satisfying than high-yield menthol cigarettes. No differences between menthol and non-menthol cigarettes on other subjective measures (strength, psychological reward negative effects) were observed. Nicotine delivery, but not mentholation, influenced cardiovascular and most subjective measures. The relationship of tobacco exposure variables to race, gender, and mentholation was estimated in a sample of 307 smokers participating in a smoking cessation trial [47]. Analysis of covariance was used to relate race, gender, and mentholation to salivary cotinine and to salivary cotinine per cigarette per day while adjusting for tobacco exposure (nicotine content of the cigarette, breath CO, and cigarettes per day), nicotine dependence (based on the Fagerström Tolerance Questionnaire) and biological variables (age, body mass index, heart rate, and blood pressure). The pattern of correlations between tobacco exposure measures and cotinine showed a consistently positive correlation between cotinine and CO in all smokers and a correlation between cotinine and CPD in those who smoked non-menthol cigarettes. Cotinine and CPD correlations varied by gender and race among menthol cigarette smokers. There was a significant gender x race x menthol interaction on salivary
cotinine level as well as cotinine/CPD ratio. These findings suggest that the relationship between number of cigarettes consumed and salivary cotinine is more complex than previously believed. The authors suggested: “It is not sufficient to look at race alone; researchers and clinicians need to look at race and gender concurrently, as well as type of cigarette consumed.”

Breathing and smoke inhalation patterns were monitored using inductive plethysmography in 74 smokers, including 18 smokers of mentholated cigarettes, as part of a study on biomarkers [48]. There were no differences “in inhalational tidal ratio found between smokers of mentholated and un-mentholated products.”

Sera from 255 current smokers were analyzed for cotinine and linear regression was used to model the effect of race on cotinine level, after several adjustments were made for variables such as cigarette consumption [49]. Black smokers smoked fewer cigarettes than white smokers, yet had “crude mean cotinine levels nearly as high or higher than white smokers”. The authors concluded that “differences in cotinine levels among smokers suggest racial variation in exposure to and/or metabolism of tobacco smoke constituents, but our findings do not support a role for menthol preference in this disparity.”

A very large “total exposure study” compared biomarkers of exposure (BOE) to the cigarette smoke components nicotine and CO in menthol (MS) and non-menthol cigarette smokers (NMS) [50]. This was a cross-sectional, observational, ambulatory,
multi-centre study in 3,341 adult cigarette smokers. Nicotine equivalents (NE) in 24h urine, NE/cigarette, COHb and serum cotinine were measured. Statistical analyses included analysis of variance and Wilcoxon test. Analyses of variance revealed no statistically significant effects of mentholated cigarettes on NE/24h, COHb, serum cotinine and NE/cigarette. On average MS smoked 15.0 and NMS 16.8 cigarettes/day. The unadjusted mean differences were as follows: MS had lower NE/24h (5.4%) and COHb (3.2%), higher serum cotinine (3.0%) and NE/cigarette (5.7%) than NMS. African-Americans MS smoked 40% fewer cigarettes, showed lower NE/24h (24%) and COHb (10%) and higher NE/cig (29%) and serum cotinine (8%) levels than their White counterparts. The authors concluded that “smoking mentholated cigarettes does not increase daily exposure to smoke constituents as measured by NE and COHb. These findings are consistent with the majority of epidemiological studies indicating no difference in smoking related risks between MS and NMS.”

Section 2.1.3. Conclusion

Taken as a whole, the data presented here are inconsistent with the idea that mentholation may affect how a cigarette is smoked so as to increase uptake of toxic smoke constituents through a “unique stimulatory sensation.”
2.1.4. Could menthol cigarettes affect the mental health of smokers, and are there “social justice” issues?

The mental health issue raised elsewhere [5] as contention #6 does not appear to have any scientific content at all (no published papers were found on the subject).

Claims have been made that the tobacco industry has “targeted” African American communities in an attempt to influence purchase of mentholated cigarettes in those communities; this is contention #10, “social justice issues.” Simple economic theory would indicate however that it would not be worthwhile for the different components of the highly-competitive tobacco industry to concentrate their advertising for mentholated products into communities where menthol is not popular. The advertising by individual companies is probably “tailored’ to African American communities, who prefer mentholated products, just as the individual companies advertise long, slim cigarettes to certain classes of women who prefer long, slim cigarettes. The claim is also made of “predatory marketing”, but this phrase is undefined. Cigarette manufacturers presumably advertise menthol products in selected communities not so much to initiate the use of menthol cigarettes in non-smokers; instead, the goal is (presumably) an attempt to get existing smokers of competitive brands to switch brands (a much easier goal to achieve than smoking initiation). As noted above, “Despite the proliferation of advertisements for menthol cigarettes in African American magazines, newspapers, neighborhoods, and entertainment venues, self-reported exposure to menthol advertising was not a
significant correlate of menthol smoking.” These authors also noted [16] that “menthol smoking among African Americans is at least partly a consequence of a complex set of social and cultural norms.”

2.1.5. Could menthol cigarettes be claimed to be “healthier”?

This is contention #2: any such health claims without rigorous substantiation would instantly attract the attention of numerous regulatory authorities, such as the Federal Trade Commission. Since these authorities have continued for decades to allow the sale of mentholated cigarettes, it is safe to assume that mentholated cigarettes do not differ in any substantial way from non-mentholated cigarettes in terms of generalized health claims. This in fact is the overall conclusion of the present paper.
2.2. Literature reviews on other effects of mentholation.

Four additional concerns are present in the scientific literature on cigarette mentholation. As mentioned above, none of these were included in the political contentions submitted to the FDA.
2.2.1. Does mentholation of cigarettes affect other smoke constituents, and is the subsequent toxicology any different?

These related subjects have been covered in considerable detail in the two previous reviews [3, 4], and there are no additional data currently available.

The smoke chemistry data suggest that the addition of menthol to cigarettes has minimal impact upon the smoke chemistry. While the publications reviewed do not fully answer the question “does mentholation of cigarettes affect other smoke constituents?” the small increases in these few smoke constituents would not be expected to have much impact upon the cigarettes’ toxicity. However, it must be considered that cigarette smoke is a complex mixture, and it is not currently possible to predict how the toxicity of smoke might change when there is a change in the ratio of smoke constituents. Menthol itself is transferred from tobacco to smoke almost completely unchanged [51], largely as a result of its boiling point of only 212 °C.

The in vitro and in vivo toxicological properties of mentholated and non-mentholated cigarettes appear to be virtually identical.
2.2.2. Does menthol affect airway patency?

Menthol produces an irritant response in the respiratory tract that may actually inhibit respiration, in direct contrast with claims that menthol may "anesthetize" the respiratory tract, allowing for increased intake of smoke [41]. The reported responses to menthol are highly variable, depending upon the animal model or tissue, the level of menthol exposure, and the modality under investigation. There are limited studies on the effects of menthol in cigarette smoke, and studies of pure menthol may not be particularly relevant. The section above on biomarkers clearly shows that menthol does not "help the poison go down" [5], since if this were the case there would be substantial increases in the various biomarkers of smoke exposure (see above), which is clearly not the case.
2.2.3. Does mentholation increase the risk of lung cancer in smokers?

Seven relatively large epidemiological US studies, comparing lung cancer risk in smokers of mentholated and non-mentholated cigarettes, have been conducted.

The first study reported results based on the American Health Foundation multi-center case-control study [52]. The analyses described were based on current cigarette smokers (defined as subjects who had smoked within the year preceding diagnosis) interviewed between 1985 and 1990 in hospitals in four US cities. These included 588 males and 456 females with histologically confirmed lung cancer, and 914 male and 410 female control patients with conditions thought not to be associated with smoking. Statistical analyses estimated the risk of lung cancer associated with smoking mentholated cigarettes for 1–14 years or 15+ years relative to never having smoked mentholated cigarettes, with adjustment for age, race, education, cigarettes per day, inhalation, duration of smoking, body mass index and, where appropriate, gender. The prevalence of menthol usage did not differ between cases and controls of either sex. No significant association was observed between either short-term (1-14 years) or long-term (15+ years) menthol use and lung cancer in logistic regression analyses adjusting for covariates. For specific histological types of lung cancer there was no indication of an association with menthol usage.

A prospective study in California was based on 5771 men and 5990 women aged 30–89 years, who underwent a Kaiser Permanente multi-phasic health check-up
between 1979 and 1985, reported at that time that they were current cigarette smokers who had smoked for at least 20 years, and who provided details of the mentholation status of the brand of the cigarette they usually smoked [53]. During follow-up until the end of 1991, a total of 168 confirmed incident lung cancers were identified in males and 150 in females. Duration of mentholated cigarette use (up to the time of the check-up) was related to lung cancer risk, with adjustment for age, race, education, cigarettes per day and years of smoking. The relative risk of lung cancer associated with mentholation compared with non-mentholated cigarettes was 1.45 in men (CI, 1.03 to 2.02) and it was 0.75 in women (CI, 0.51 to 1.11), adjusted for age, race, education, number of cigarettes smoked per day, and duration of smoking. Further adjustment for tar content and self-reported smoking intensity characteristics did not substantially alter the estimate of relative risk. A graded increase in risk of lung cancer with increasing duration of mentholated cigarette use was present in men. The author's conclusion was that “this study suggests that there is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers.”

Whereas the first two studies only examined current cigarette smokers, the third study also included former smokers in the analyses [54]. The analyses included 202 males and 135 females with histologically confirmed lung cancers and 349 male and 129 female population controls who had ever smoked, were resident in Los Angeles County, aged 40–84, non-Hispanic Caucasians or African-Americans, and had no previous cancer (other than non-melanoma skin cancer). Menthol smoking was
classified based on response to the question “On average over your lifetime, out of every 100 cigarettes you smoked, how many were menthol?” Analyses were adjusted by age, race, total pack-years and years since quitting. The adjusted odds ratios did not differ appreciably between smokers of mentholated cigarettes versus exclusive non-mentholated cigarette smokers in the overall study group of smokers. The odds ratio (OR) for 32 pack-years or more of mentholated vs. non-mentholated cigarettes was 0.90 (CI = 0.38-2.12) in African Americans and 1.06 (CI = 0.47-2.36) in Caucasians, and did not differ for either ethnic group (p = 0.98). The author’s conclusions were “that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes. Our data do not support the hypothesis that the increased risk of lung cancer among African Americans is due to the increased prevalence of menthol smoking.”

The fourth study also included current and former smokers [55]. The analyses were based on a case-control study conducted in 1981 to 2000 in men and women in hospitals in the eastern United States. They involved 435 male and 208 female with confirmed lung cancer and 2123 male and 1987 female controls with conditions judged unrelated to cigarette smoking. Subjects were aged 40–74 with no history of cancer who had smoked cigarettes for at least 20 years and whose race was either Caucasian or African-American. Analyses related duration of use of mentholated cigarettes to risk of lung cancer, with adjustment for gender, age, race, year of interview, cigarettes per day, years of smoking, years since quit and proportion of years smoking filter cigarettes. The lung cancer risk for long-term smokers of
menthol cigarettes was similar to that for smokers of non-menthol cigarettes (odds ratio = 0.97, CI: 0.70, 1.34). Odds ratios were also close to 1.0 in separate analyses of male, female, Black, and White subjects. The authors said that “the results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking non-menthol cigarettes.”

The fifth study overlapped and extended the earlier report based upon the American Health Foundation multi-center case-control study, being based on hospitals in several US cities and including interviews conducted over a longer period (1984–1998) than previously [56]. The current smokers considered in the menthol analyses now included an estimated 963 males and 803 females with histologically confirmed lung cancer and 1098 males and 572 female control patients with conditions thought not to be associated with smoking. Statistical analyses estimated the risk of lung cancer according to preference for smoking menthol cigarettes, with adjustment for age, education, body mass index and pack-years of smoking. Long-term benefits of cessation were similar for white and black ex-smokers. Smokers of menthol flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands.

The sixth study examined 5,887 male and female smokers in the Lung Health Study, evaluating smokers aged 35-60 years with early evidence of obstructive lung impairment [17]. The main aim of the study was to evaluate the decline in the forced expiratory volume in one second (FEV₁) value over time, but the following data were also presented for the LHS participants evaluated over 14 years:
<table>
<thead>
<tr>
<th>Death from</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause</td>
<td>0.997</td>
<td>0.83-1.20</td>
</tr>
<tr>
<td>CHD</td>
<td>1.31</td>
<td>0.77-1.52</td>
</tr>
<tr>
<td>CVD</td>
<td>1.03</td>
<td>0.70-1.52</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0.96</td>
<td>0.70-1.32</td>
</tr>
</tbody>
</table>

The authors of this study concluded “Using proportional hazards regression methods, we found no differences in hazard ratios for coronary heart disease, cardiovascular disease, lung cancer, or death from any cause. Contrary to expectations about nicotine dependence, we found that users of menthol cigarettes had smoked fewer pack-years at baseline. We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking.” The authors appear to have a manuscript in preparation on “whether menthol cigarettes are indeed protective against cancer.”

The seventh study had 294 male and 197 female lung cancer patients, but few data on the actual effects of mentholation were presented [57]. The overall OR for mentholation was 0.69 with a CI of 0.46-1.03, leading the authors to conclude “In our analysis, we observed no significant risks of lung cancer among former or current
smokers who reported smoking mentholated cigarettes (OR range 0.69-0.99) and our data suggested a possible protective effect of mentholated cigarettes for current smokers.”

Section 2.2.3. Conclusion

An invited commentary on one paper [55] concluded that “it is becoming clear that if there is an elevation in risk of lung cancer from smoking mentholated cigarettes beyond that from smoking regular, filter-tipped brands, it is either subtle or refractory to the methods we have used thus far.” Accordingly, it appears to be very unlikely from the cumulative evidence that cigarette mentholation increases the risk of lung cancer, and may even protect from it.
2.2.4. Does mentholation increase the risk of other diseases?

One study which reported results for lung cancer [52] also reported results for current menthol and non-menthol smokers for some other smoking-related diseases.

Analyses on esophageal cancer [58] were based on 303 cases and 453 age-matched controls. After adjustment for education, religion, alcohol consumption and race, mentholated cigarette smoking was not associated with an increased risk in either males (OR 0.50, CI 0.23–1.07 for <10 years and 1.03, CI 0.39–6.89 for 10+ years) or females (OR 1.50, CI 0.54–4.17 for <10 years and 2.30, CI 0.93–5.72 for 10+ years).

Analyses on oropharyngeal cancer [59] involved 276 cases and 1256 controls. After adjustment for age, education, race, cigarette consumption, filter use, alcohol consumption and hospital, odds ratios were not elevated in relation to duration of use of mentholated cigarettes (e.g., 0.9, CI 0.5–1.6 in males and 0.7, CI 0.5–1.7 in females for 15+ years). There was also no significant evidence of a relationship with mentholation for specific sites within the oral cavity and pharynx. The authors concluded that “use of mentholated cigarettes is unlikely to be an important factor in oropharyngeal cancer development”.

The Kaiser Permanente study used to report results relating use of mentholated cigarettes to risk of lung cancer has also been used to report results relating to
various other forms of cancer [60]. The restrictions to those subjects considered and the numbers of subjects considered in the analysis were virtually as for the lung cancer analysis, but follow-up was longer, up to 1994. For all smoking-related cancers combined, based on 163 cases in men and 118 in women, mentholated cigarette smokers had non-significantly lower age-adjusted risks than non-mentholated cigarette smokers, with relative risks of 0.76 (CI 0.52–1.11) in men and 0.79 (CI 0.53–1.18) in women. No real indication of an effect was seen in either sex for any of the specific smoking-related cancer types studied—upper aero digestive, pancreas, renal adenocarcinoma, other urinary tract, uterine cervix—or for cancer of the prostate. While the study is limited by the small number of cases of specific types, the data provide little support for an effect of mentholation on cancer risk. These findings prompted the authors to comment in regard to their previous report [53] that “the association of mentholation with lung cancer in this study population may be merely a chance finding, particularly as it was absent in women and has not been replicated elsewhere.”

In terms of COPD, as noted above [15] there were no differences found between smokers of menthol (n=972) and non-menthol (n=563) cigarettes for 10-year pulmonary function decline (adjusted excess decline in FEV$_1$).

The authors of one of the lung cancer studies reviewed above [17] concluded “Using proportional hazards regression methods, we found no differences in hazard ratios for coronary heart disease, cardiovascular disease, lung cancer, or death from any
cause. Contrary to expectations about nicotine dependence, we found that users of menthol cigarettes had smoked fewer pack-years at baseline. We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking.”

Section 2.2.4. Conclusion

Overall, available epidemiological data on cancers other than lung cancer do not suggest any important pathogenic role of cigarette mentholation. As such, it seems unlikely that mentholation might explain the higher risk of various cancers not linked to smoking, seen in African Americans. Incidences of other diseases do not seem to differ between smokers of mentholated and non-mentholated cigarettes, and mortality rates are similar.
2.3. Summary

Menthol has a long history of use in food and pharmaceuticals and has been used in tobacco since the 1920s. Many clinical and non-clinical studies have addressed the toxicological properties of menthol, but the literature on the potential clinical effects of mentholation of cigarettes is much more limited. Because of the higher lung cancer risk in African American men in the USA and the much higher preference for mentholated cigarettes in African American smokers, and because of the concern (now known to be incorrect) that menthol’s cooling effect may “anesthetize” the respiratory tract making deeper inhalation possible, numerous hypotheses have been put forward regarding possible adverse effects of mentholation.

The published evidence relating to the various questions raised in the literature has been reviewed. The evidence includes whether mentholation increases exposure to other smoke constituents, affects absorption, distribution, metabolism and excretion of nicotine, affects smoking behavior, impacts upon airway patency, affects initiation, dependency or cessation, and crucially whether it increases the risk of lung cancer and other diseases, especially in African American smokers.

While mentholation might have an impact upon initiation, dependency and cessation as potential “determinants of exposure”, the hypothesis that initiation is easier in smokers of mentholated cigarettes due to the “smoother” smoke has not been evaluated. At any rate, it is well known that initiation is complex and multifaceted and
cannot be ascribed simply to the presence of a single cigarette ingredient. Studies reported in the literature show that mentholated cigarette smokers do not differ from non-menthol cigarette smokers in cigarette dependency. While some smaller smoking cessation studies suggest slightly lower rates of success in quitting in menthol cigarette smokers, the larger studies, and those taking more potential confounding factors into account, do not.

The underlying chemistry, and the available data—though somewhat limited—do not suggest that mentholation affects the absorption of nicotine or that it affects other smoke constituents so as to materially affect risk to the smoker. While pure menthol may decrease inflammation/irritation and bronchoconstriction in the respiratory tract, it is often associated with a perception of increased air flow and relief from breathing difficulty, both effects that have been shown to be artifacts.

There is more evidence available on possible effects of mentholation and clearance of nicotine and other constituents and on the smoker’s behavior. One study [32] suggests that mentholation significantly inhibits metabolism and delays clearance of nicotine, apparently inconsistent with the possibility that it might lead to a higher carcinogenic risk. As pointed out by the authors, the delayed metabolism and clearance of nicotine in smokers of mentholated cigarettes could reasonably be expected to reduce cigarette consumption in smokers of mentholated cigarettes [32], consistent with the observation that heavy consumption is substantially lower in African American than in Caucasian smokers.
Although the scientific literature reviewed here generally suggests that mentholation is associated with no effect or a decrease in number of puffs and puff volume, and that African Americans have lower cigarette consumption than Caucasians, the evidence is consistent that African Americans have higher cotinine levels. If African American smokers have higher smoke exposure (as indicated in the literature) and menthol is not the cause (as the data show), then some other aspect must account for the increase in exposure. This could be explained by differential variants in African Americans in the main nicotine-metabolizing enzyme in humans, cytochrome p450 2A6 (CYP2A6) [35, 37].

While the available data are limited in a number of areas, it is particularly important to note that there are seven quite large, well conducted, epidemiological studies (Table 1) that have related cigarette mentholation to lung cancer and in some cases other types of cancer, and that these studies are consistent with mentholation not increasing the risk for smokers, some studies showing a possible protective effect. The similar lung cancer risks in African American and Caucasian women, given their very different preferences for cigarettes, also argues against any material effect of mentholation on lung cancer risk. The limited data on oropharyngeal, esophageal and other cancers, for which African Americans also have higher risks, equally suggest no effect of mentholation. It should be noted, however, that the literature data are notable for the limited information on potential effects of mentholation on other major smoking-related diseases such as ischemic heart disease, chronic
obstructive pulmonary disease and stroke, or even on overall mortality.

Higher rates of lung cancer in African Americans may be related to susceptibility to lung carcinogens, perhaps due to differences in detoxification mechanisms. A genetic role in ethnic-specific risk for lung cancer has not been ruled out, because some studies have shown that African American populations have increased frequencies of rare alleles that may be associated with greater risks for developing lung cancer [35]. However, studies of these alleles in these populations have been inconclusive due to their low frequency. Socioeconomic factors may also play a role in the expression of disease. According to the US Surgeon General [61], socioeconomic and other characteristics are powerful determinants of health and disease and differ widely among various racial and ethnic groups in the US. Factors such as disposition to disease, access to and usage and quality of health care, lifestyle, alcohol consumption, diet, genetics, metabolic factors, and smoking behavior may also affect disease prevalence.

Other physiological parameters seem to be little, if at all, affected by exposure to menthol in cigarette smoke. Thus, change in blood pressure, heart rate or CO from smoking, all showed no clear relationship to cigarette mentholation in the studies reviewed. Taken together, the data reported in the scientific literature provide little support for the idea that cigarette mentholation may alter the way a cigarette is smoked, so as to increase smoke uptake and exposure. On the contrary, mentholation may reduce smoke exposure [32].
3. Overall Conclusion

This scientific review of the literature does not support the contentions submitted to the FDA recommending a ban on menthol as a cigarette ingredient [5]. The authors of that review appear then to have taken a politically motivated interpretation of the literature, and to have supported this one-sided view with non-scientific references to topics such as “social justice” and to “poorer mental health”. At a February 2010 conference of the Society for Research on Nicotine and Tobacco, Dr. Lawrence Deyton, the leader of the FDA’s Center for Tobacco Products, avowed that his mission was “Regulatory Science”, not the oxymoronic “Political Science.” The data presented here is factually relevant to Regulatory Science.

An FDA ban of menthol in cigarettes would affect 25% of the near 50 million U.S. smokers. The affected smokers are largely minorities who have a strong preference for mentholation, and the arbitrary removal of this choice by the FDA would almost certainly result in the rapid establishment of a black market, possibly accompanied by “do-it-yourself” attempts to modify non-menthol cigarettes through potentially more risky attempts at “home mentholation”. Neither of these scenarios represents the actions of a society dedicated to the factual, unbiased, and scientific assessment of the biological effects of consumer products.
Table 1. A collation of results of epidemiological studies on menthol cigarettes and lung cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kabat &amp; Hebert, 1991</td>
<td>588 M, 456 F.</td>
<td>“No significant association was observed between either short-term (1-14 years) or long-term (15+ years) menthol use and lung cancer in logistic regression analyses adjusting for covariates. For specific histological types of lung cancer there was no indication of an association with menthol usage.”</td>
</tr>
<tr>
<td>Sidney et al., 1995</td>
<td>51 M, 34 F.</td>
<td>“A graded increase in risk of lung cancer with increasing duration of mentholated cigarette use was present in men. This study suggests that there is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers.”</td>
</tr>
<tr>
<td>Kabat, 1990</td>
<td></td>
<td>“Our data provide little support for an association of smoking mentholated cigarettes (relative to smoking non-mentholated cigarettes) with lung cancer after adjustment for covariates, including number of cigarettes smoked per day.”</td>
</tr>
<tr>
<td>Friedman et al., 1998</td>
<td></td>
<td>“The association of mentholation with lung cancer in this study population may be merely a chance finding, particularly as it was absent in women and has not been replicated elsewhere.”</td>
</tr>
<tr>
<td>Carpenter et al., 1999</td>
<td>202 M, 135 F.</td>
<td>“Our results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes. Our data do not support the hypothesis that the increased risk of lung cancer among African Americans is due to the increased prevalence of menthol smoking.”</td>
</tr>
<tr>
<td>Brooks et al., 2003</td>
<td>435 M, 208 F.</td>
<td>“The lung cancer risk for long-term smokers of menthol cigarettes was similar to that for smokers of non-menthol cigarettes (odds ratio = 0.97, 95% confidence interval: 0.70, 1.34). Odds ratios were also close to 1.0 in separate analyses of male, female, Black, and White subjects. The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking non-menthol cigarettes.”</td>
</tr>
<tr>
<td>Stellman et al., 2003</td>
<td>1,964 M, 1,484 F.</td>
<td>“While Black smokers in our study were more likely to choose menthol than non-menthol brands, our data provide no evidence that menthol cigarettes per se produce greater lung cancer risk than do non-menthol brands.”</td>
</tr>
</tbody>
</table>
| Murray et al., 2007  
240 M+F. | “Using proportional hazards regression methods, we found no differences in hazard ratios for coronary heart disease, cardiovascular disease, lung cancer, or death from any cause. Contrary to expectations about nicotine dependence, we found that users of menthol cigarettes had smoked fewer pack-years at baseline. We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking.” |
|---|---|
| Etzel et al., 2008  
294 M, 197 F. | “In our analysis, we observed no significant risks of lung cancer among former or current smokers who reported smoking mentholated cigarettes (OR range 0.69-0.99) and our data suggested a possible protective effect of mentholated cigarettes for current smokers.” |
References


