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## Direct Disease-Inducing Effects of Menthol through the eyes of Tobacco Companies

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### Abstract

**Objective**—Menthol is an important additive in most tobacco products and is an identifying characteristic of many brands. We assessed tobacco companies' research on direct disease-inducing effects of menthol and menthol cigarettes.

**Methods**—A search was conducted among documents included in the Legacy Tobacco Documents Library. Relevant documents addressed subject areas such as pharmacology, short and long-term effects and biomarkers of smoking exposure.

**Results**—The documents contain little internal industry research on the disease-inducing effects of menthol. Most information in the tobacco industry documents is reviews of the published biomedical literature, from which the companies concluded that menthol did not have any direct disease-inducing effects. Evidence that contradicted this conclusion was downplayed. Except for one study, there was no evidence of the companies following up on industry-positive findings in the literature with their own studies. In one case, results were presented at a public scientific meeting concluding that “There were no effects from addition of menthol to test or reference cigarettes”, when a company's internal pathology analysis contradicted this statement.

**Conclusion**—The available industry documents suggest that tobacco companies conducted little research on the potential disease-inducing effects of menthol and did not pursue studies that suggested adverse effects.

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#### Conflict of interest

The authors declare that they have no conflict of interest.

#### Contributorship

Dr. Salgado prepared the original FDA white paper that forms the basis for this paper. Dr. Glantz worked with her to build on that work to prepare it this manuscript.

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## Keywords

menthol; tobacco; adverse effects; health effects; tobacco industry

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## INTRODUCTION

Though menthol has been used in foods and confections for many years, this does not necessarily mean that its addition to cigarettes (which are burned and then inhaled) is innocuous. Although a 2010 published paper from Lorillard Tobacco Company states that “menthol employed as a cigarette tobacco flavoring ingredient does not meaningfully affect the inherent toxicity of cigarette smoke or the human risks that attend smoking”,<sup>[1]</sup> this conclusion is not supported by all the scientific literature. In a 2010 commentary, Hammons noted that, although a limited number of epidemiological studies that examined the relationship between menthol cigarette smoking and disease risk found no association with increased deaths from cancer, coronary heart disease or other cardiovascular diseases, their limitations (including the difficulty in classifying subjects as exclusively menthol or non-menthol smokers for a long enough time or large enough sample size to detect an increment in risk above the large risk due to smoking in general) caution against treating these results as conclusive.<sup>[2]</sup> The presence of menthol and alcohol increases the flux of tobacco carcinogens across porcine esophagus<sup>[3]</sup> and menthol enhances the penetration of nicotine through porcine buccal mucosa<sup>[4]</sup> in *in vitro* systems. Menthol might also inhibit the detoxification of the potent carcinogen NNAL.<sup>[5]</sup> In addition, menthol’s interaction with biomarkers of smoking exposure such as cotinine and carbon monoxide remains unclear: published studies have shown contradicting results,<sup>[5–9]</sup> with one of these studies<sup>[7]</sup> published by the Altria Client Services Inc., part of Altria/Philip Morris.

Although menthol is a Food and Drug Administration (FDA) approved food additive, the FDA is now evaluating menthol as a cigarette additive. This paper summarizes studies that were either conducted or supported by tobacco companies concerning the direct disease-inducing effects of menthol.

## METHODS

A search was conducted among the tobacco industry documents in the University of California, San Francisco Legacy Tobacco Documents Library (LTDL), which contains more than 11 million documents created by major tobacco companies related to their advertising, manufacturing, marketing, sales, and scientific research activities,<sup>[10]</sup> as described in detail in this supplement by Anderson’s paper on research methodology.<sup>[11]</sup> Based on the questions posed by the FDA, initial keyword searches combined terms related to: menthol, adverse effects, carcinogen, pharmacokinetics, cotinine, carboxyhemoglobin. This initial set of keywords resulted in the development of further search terms and combinations of keywords (e.g., biomarker, permeation, conjugation). Relevant documents addressed the pharmacology of menthol, short and long-term effects of menthol, role of menthol on disease risk, and menthol’s effects on biomarkers of smoking exposure. A final collection of 209 documents was deemed relevant to this study. Nineteen documents which provided illustrative, detailed, or exemplary information supporting these themes are cited in this paper.

## RESULTS

### Pharmacokinetics of menthol

**Internal tobacco company' research**—In the early 1970s, the British American Tobacco (BAT) Company commissioned a confidential literature survey by the British Industrial Biological Research Association (BIBRA) that established the paucity of definitive data on the pharmacodynamics and pharmacokinetics of menthol following ingestion and inhalation in either experimental animals or humans.[12] During that time (1974), the World Health Organization was discussing what would be an acceptable maximum daily intake for orally ingested menthol.[12] In response, in 1975, BAT worked to develop analytical chemical methods to detect menthol in blood samples, including preliminary studies using data collected from two middle-aged BAT scientists who switched from their regular cigarettes to mentholated cigarettes and also ingested menthol orally.[12] The study found blood levels of menthol below 10 ppb (parts per billion) in all but one experiment that involved only one of the subjects smoking 32 cigarettes in an 8-hour period, where 40 ppb of menthol was measured.[12]

In 1976, the contract research organization Life Science Research delivered a “confidential” report to the BAT’s Group Research & Development Centre summarizing animal experiments to determine absorption and pharmacokinetics of orally administered menthol. [13] Four protocols of oral administration of menthol to rats were conducted, with subsequent collection of blood and urine samples. In one of these experiments, in which 224 rats were used, adipose and liver tissue samples were taken from a subsample of the rats. A fifth experiment was conducted using one male dog to examine for possible species-variation in absorption and elimination of menthol. Free and conjugated menthol (glucuronide, which the body produces by reacting menthol with glucuronic acid to facilitate excretion) were measured. Menthol was found to be poorly absorbed after oral administration in both species (less than 2% of the oral dose was recovered in the urine of rats over the first 48 hours), and to be excreted mostly as glucuronide (conjugated menthol) in urine. Liver samples taken 8 weeks after the beginning of a daily oral administration of menthol showed an increase in the activity of hepatic UDP-glucuronyl transferase that seemed to be dose-dependent, suggesting that menthol was metabolized by the liver and that this was the enzyme that conjugates menthol. Menthol was not found in any of the samples of adipose tissue analyzed.[13]

A second Life Science Research report delivered in 1976 described five protocols using rats, guinea pigs, mice and hamsters.[14] Of these five experiments, two rats were used in the one with the smaller sample size, while groups of 24 mice, hamsters and guinea pigs were used for the experiment with the biggest sample size. In all cases, radiolabeled menthol was administered by intraperitoneal injection. Maximum average blood levels of radioactivity were observed within two hours in all four species. Menthol was excreted mostly as glucuronide in urine, with some excretion through feces.[14]

A 1978 report from the BAT’s Group Research and Development Center[15] described two studies performed using humans subjects (3 in one study and 5 in the other). Participants were told to smoke mentholated cigarettes during the day. Urine samples were collected in both studies before and after the smoking period and blood sample were taken in one study. When comparing the pre and post-smoking blood samples, no increase in the levels of free menthol were found after smoking up to 21 cigarettes in an eight-hour period. Excretion rate was maximal at the end of the smoking period, with 80–90% of the menthol being eliminated during the smoking period or within 4 hours post-exposure.[15]

## Pyrolysis of menthol

**Study published in the open literature**—In 1968, *Nature* published a paper (Schmeltz and Schlotzhauer, from the US Department of Agriculture) reporting that the pyrolysis of menthol at 860°C produced benzo[a]pyrene, a mutagen and carcinogen.[16] In 1970, Robert Jenkins *et al.* from Philip Morris' Research Center published a paper[17,18] in *Beitraege zur Tabakforschung* (Contributions to Tobacco Research, which the German Cigarette Manufacturers Association founded in 1961[19]) presenting an analysis of menthol's smoke distribution and pyrolytic composition. They used radiolabeled <sup>14</sup>C-menthol in machine-smoked cigarettes and reported that the mainstream smoke contained 28.9% of the total activity, sidestream smoke contained 44.3% and the butt contained 26.9%. They reported that pyrolysis products of menthol in the mainstream smoke constituted only 0.4% of the total mainstream activity and that the major <sup>14</sup>C-menthol smoke product in the mainstream smoke was unchanged menthol (98.9%), concluding there was very little, if any, pyrolysis and combustion of menthol during puffing of a cigarette. They noted that Schmeltz and Schlotzhauer had found that menthol pyrolysis at 600°C did not result in the formation of benzo[a]pyrene. They also argued that because the boiling point of menthol (212°C) was well below 600°C, very little menthol pyrolysis would be expected.[17,18] However, as Schmeltz and Schlotzhauer had noted,[16] the burning temperature of cigarettes exceeds 800°C (information also found in a 1966 American Tobacco Company confidential report[20]).

## Long and short-term studies on the effects of menthol

**Document developed for external release**—In 1963, the Liggett & Myers Tobacco Company prepared a report for the Surgeon General's Advisory Committee on Smoking and Health reporting on long-term carcinogenicity assays in mice and rabbits.[21] Using 100 female mice, smoke condensates were applied to the back of the animals and the rate of incidence and time of appearance of skin papillomas and carcinomas were recorded (follow-up period: 24 months). The incidence of tumors in mice painted with the condensate from mentholated cigarettes was not significantly different from that observed with condensates from non-mentholated cigarettes.[21]

**Internal tobacco company research**—In 1984–85, RJ Reynolds Sensory Evaluation Division prepared a “secret” review of the literature to be used in an internal RJ Reynolds training program entitled “Menthol and the design of mentholated cigarettes.”[22] This material aimed to provide a summary of the information researchers needed to develop mentholated cigarettes mostly focused on details of how to design mentholated cigarettes to control menthol delivery and perception. The review did, however, include a summary of the literature on health effects, which concluded that no long-term studies (greater than 1 year) of the effects of menthol cigarettes were found in the literature and that, while case reports in man had appeared, the lack of controls in these cases made the results questionable, that “menthol is not carcinogenic, as shown in studies by [the National Cancer Institute]” and that “no detrimental effects of menthol were observed in short term biological studies”.[22]

In 1988, as part of its research to develop Premier cigarettes[23] (a new product that delivered nicotine by heating beads covered with nicotine rather than burning tobacco) RJ Reynolds developed 90 day inhalation study (denoted TRD-ATS-017) to “compare toxicological responses produced by menthol and non-menthol test [heated tobacco] and reference [burned tobacco] cigarettes ... [using] 12 groups each containing up to 35 Sprague-Dawley rats per sex. Three graded concentrations of smoke from both sets [menthol and non-menthol] of test and reference cigarettes will be used, and the comparisons of test and reference will be made on the basis of the amounts of wet total particulate matter

(WTPM) presented to the animals.”[24] Endpoints included histopathology, plasma levels of nicotine and cotinine, hematology, organ and body weights, and measurements of respiratory physiology. The results of this study were to be kept confidential inside RJ Reynolds; the protocol stated, “This study will not be listed as a regulated study and the results are not intended to be submitted to any regulatory agency”.[24]

In 1990, RJR submitted an abstract for the Society of Toxicology Annual Meeting, reporting the results of study TRD-ATS-017, that stated "There were no effects from addition of menthol to test or reference cigarettes".[25] Later that same year, however, the TRD-ATS-017 final histopathologic report, prepared for internal RJR use, concluded that “for the reference cigarette [i.e., conventional cigarettes], the histopathologic changes noted in the upper airways of the menthol cigarette groups were more severe than those noted in the non-menthol cigarette groups”.[26] Four years later, in May, 1994, RJR dismissed the results in an interoffice memorandum,[23] arguing that the comparisons between the reference cigarettes were not valid since the configuration of the two cigarettes was different. The same memo stated that “no comparisons across reference groups were required in the study protocol and are also not germane to the purpose of this study”.[23] But in August, 1994, the RJR scientific & regulatory affairs team[27] questioned the reasons for dismissing the results because:

This argument is made principally on the grounds that the two cigarettes are in fact different with regard to distinct blend and physical characteristics. However, given that the mentholated conventional product utilized as a control in this study contained more reconstituted tobacco sheet and more non-tobacco ingredients, one would have predicted that it would have displayed reduced activity relative to the Kentucky 1R4F [non-menthol] reference cigarette. In short, study TRDATS-017 may have understated the potential for menthol to produce adverse effects.[27]

A “PM confidential” “Risk Assessment for Menthol” prepared by Philip Morris Product Integrity in 1999[28] provided a comprehensive review of the regulatory environment around menthol and the state of the open literature. It remarked that most studies using human subjects were case reports and that conclusions were therefore anecdotal. It also concluded that, considering the ubiquitous use of menthol, it was almost certain that the presence of clinical symptoms in those cases (such as a case of psychological disturbance due to 3 years of nasal application of an “over the counter” medication that contained menthol) were due to instances of extreme exposure.[28] The review also contained results from a few unpublished PM internal studies, including results from eye and skin irritation studies. Results of the primary skin irritation test in rabbits using showed no dermal irritation. When instilling microcapsules into the rabbit’s eye, slight conjunctival redness was observed one hour after dosing, but later evaluations at 24, 48 and 72 hours post-treatment showed no irritation. The final conclusion was that menthol was non-irritating. Under the same protocol, a second study of microcapsules instillations produced a group average score of 2 (out of possible 110) at 24 and 48 hours after treatment and this response resolved by 72 hours post-treatment, led to the conclusion that menthol was minimally irritating to the rabbit eye.[28] The risk assessment did note that that there was some evidence that menthol had adverse health effects, but dismissed these studies on technical grounds. For example,

Epidemiology presents conflicting data with respect to biological effects from mentholated cigarette smoke in humans. African American men have been reported to have a 60% higher lung cancer incidence than the U.S. white male population. Although the number of cigarettes smoked per day is significantly lower among African Americans, they smoke cigarettes with higher tar content. Fifty-five percent of African Americans smoke mentholated brands of cigarettes. Some

studies have reported increases in lung cancer incidence in long-term mentholated cigarette smoking individuals from different races, while other studies report menthol smoking is not a strong risk factor for lung cancer. Although many hypotheses have been advanced with respect to the possible mechanisms associated with the reported lung cancer "increases", these hypotheses remain unproven. Confounding factors such as socioeconomic status, access to health care, quality and usage of care, smoking behavior, physiological changes from menthol affecting smoking mechanics, and racial differences in levels and activity of P450 enzymes have generally not been evaluated in this context.[28]

The bottom line conclusion of the report was that "There are no anticipated risks associated with the use of menthol in cigarettes at the current application levels." [28]

In 2001, Philip Morris prepared an extensive review of regulatory issues related to menthol, together with an extensive summary of the available scientific literature, including some internal studies on smoke chemistry. (The intended audience for this report is not clear.) This review reported the evidence of adverse effects on pulmonary function in workers exposed to menthol, epidemiological evidence linking smoking menthol cigarettes with lung cancer in men and esophageal cancer in women, and that adding menthol increased the amount of total particulate matter in the smoke, but downplayed these results, concluding that "menthol has a low order of acute toxicity and has been demonstrated to be non-carcinogenic and non-teratogenic." [29]

**Study published in the open literature**—In 1999, RJ Reynolds published the results from a study [30,31] that assessed psychophysiological (EEG and heart rate) and subjective (such as mental alertness and anxiety/nervousness) effects of smoking menthol versus non-menthol cigarettes smokers using denicotinized cigarettes (to study the effects of menthol independently of the effects of nicotine). Twenty-two volunteers (12 regular menthol smokers, 10 regular non-menthol smokers) were recruited. Both type of smokers smoked two commercial denicotinized cigarettes (which still contain low levels of nicotine): menthol and non-menthol. Menthol smokers showed a greater increase in heart rate following smoking either cigarette (around 5 bpm) than did non-menthol smokers (around 2 bpm), which could indicate that menthol smokers were more sensitive to the low levels of nicotine in the denicotinized cigarettes, implying they could be more sensitive to the effects of nicotine itself. Menthol smokers had a slower EEG alpha rhythm (9.35 Hz) than non-menthol smokers (10.08 Hz) with the eyes closed, leading to the conclusion that regular menthol smokers seemed to be less aroused by menthol than regular non-menthol smokers. [30,31] The conclusion in the abstract of the draft manuscript located in the industry documents was "We also report evidence that menthol smokers may be chronically less aroused and more sensitive to the effects of nicotine than non-menthol smokers." [32] In the published paper, an additional conclusion was added to the abstract: "We found little evidence that menthol in cigarettes has central pharmacological effects." [30,31]

### **Menthol, nicotine, cotinine and carbon monoxide**

**Study published in the open literature**—In 1997, Lorillard published an article in *Food and Chemical Toxicology* [33,34] reporting the results of a study of two rats inhaling smoke non-menthol (reference) or menthol cigarettes (21 rats per sex for reference and 15 per sex for menthol) for an hour a day, five days a week, for 13 weeks. Within each group, three different concentrations of target smoke were used (200, 600 and 1200 mg/m<sup>3</sup> TPM), defining 3 subgroups. A third group of rats (15 per sex) exposed to filtered air was used as control. The objective was "to determine any significant alteration of smoke-related biological effects resulting from menthol addition". [33,34] At the 200 mg/m<sup>3</sup> smoke concentration, cotinine levels were lower among the menthol group (118.6±21.6 [SD] ng/ml



vs.  $144.1 \pm 20.1$  [SD] ng/ml;  $p \leq 0.05$ ). Authors interpreted this finding as “apparently incidental”.[33,34] The final conclusion was that “The results of this 13-wk inhalation study of mentholated tobacco smoke indicate that the addition of menthol to cigarettes does not significantly alter the pattern, incidence, severity or reversibility of any of the effects attributable to smoke exposure in rats.”[33,34]

### Menthol and cell permeability

**Study published in the open literature**—A study published in 1983 partially funded by the Swedish Tobacco Company[35,36] analyzed the toxicity of menthol using 4 different *in vitro* systems: trachea from chicken embryos, Ascites sarcoma BP8 cells, isolated hamster brown adipocytes and rat liver mitochondria. In the mitochondrial model, menthol was found to cause increase in the state 4 respiratory rate and osmotic swelling, indicating a leakage of the mitochondrial membrane. The authors suggested that one effect of menthol could be a deterioration of biological membranes.[35,36]

## DISCUSSION

This paper assessed tobacco industry research on potential direct disease-inducing effects of menthol and mentholated cigarettes. In the studies presented here, menthol is described as an additive that does not accumulate in people smoking up to 21 cigarettes, that is metabolized in the liver and that is mostly excreted in urine as glucuronide.[13–15] Menthol’s effect on levels of biomarkers of smoke exposure is less well examined; however, one in-house study concluded menthol does not modify them.[33,34] Menthol was also suggested to degrade biological membranes[35,36] and to produce more severe histopathologic changes in the upper airways when compared to non-menthol cigarettes.[26] Menthol itself is presented as a non-carcinogenic substance. There is a lack of information on other long-term effects.

Results from the 1978 BAT’s Group Research and Development Center study on menthol’s pharmacokinetics on humans[15] were not reproduced in an article published in 1999.[37] While the BAT’s study found that 80–90% of the menthol was eliminated during the smoking period or within 4 hours post-exposure,[15] Gelal *et al* reported that the recovery of administered menthol as the glucuronide averaged only 45.6 and 56.6% in 24-hour urine samples.[37] In the BAT’s study menthol was absorbed through smoking mentholated cigarettes,[15] while in Gelal’s study, menthol was orally administered.[37]

Regarding RJR’s large TRD-ATS-017 study, the company decided to present results at a public scientific meeting indicating that “There were no effects from addition of menthol to test or reference cigarettes”,[25] when the company’s internal pathology analysis contradicted this statement.[26] There was an attempt to discard this conclusion internally as well,[23] a position contested inside the company.[27] In any event, the histopathological results suggesting an adverse effect of menthol do not appear to have been published. We did not find evidence that RJR did additional research designed to resolve the internal controversy about whether or not menthol had adverse histopathological effects.

Most of the information on menthol’s direct disease-inducing effects found among the tobacco industry documents comes from summaries that the companies prepared of the open biomedical literature, not from studies carried out by the companies themselves. The presence of several scientific literature reviews developed for internal purposes (such as training) seem to indicate that the industry in most cases considered this information to be sufficient to conclude that menthol did not have any direct disease-inducing effects. Evidence that contradicted this conclusion was downplayed. The companies did not seem interested in following up on the positive findings in the literature with their own studies,

except for one study designed to counter the conclusion that menthol was pyrolyzed into the carcinogen benzo[a]pyrene.[16–18]

Overall, menthol's main health effects seem to be indirect. For example, a 2010 paper that examined differences between self-reported health characteristics for menthol and non-menthol smokers using data from the 2005 National Health Interview Survey[38] found that a larger proportion of current menthol smokers reported having asthma and that former menthol smokers reported a higher proportion of emergency room visits due to asthma. The authors suggested that "perhaps the 'cooling' and 'soothing' effects of menthol allow smokers to engage longer in smoking behaviors that over an extended period of time may produce asthma-related symptoms that account emergency room visits".[38] This study also found that the mean number of cigarettes smoked per day was borderline significantly lower for menthol smokers when compared to non-menthol smokers controlling for sex, age and race in a multivariate analysis (odds ratio: 0.99; 95% confidence interval: 0.98, 1.00).[38] In contrast, another analysis of the same dataset that stratified on race/ethnicity (African American, Hispanic and White) and gender, controlling for age, income and education, did not find a significant difference in the number of cigarettes smoked per day between menthol and non-menthol smokers within each ethnic group.[39]

Evidence from internal tobacco documents research shows that menthol interacts directly with nicotine,[40] affecting nicotine delivery,[41] and that addition of menthol to cigarettes has been used to reduce smoker's concerns about the health effects of cigarettes[42] and to attract and retain new, younger smokers.[43,44] Menthol also reduces the negative sensory characteristics associated with smoking[45] and may encourage experimenters who find non-mentholated cigarettes too harsh to progress to regular smoking rather than quitting, and may inhibit the desire to quit among established menthol smokers who have become accustomed to the taste and sensation of menthol cigarettes.[46] Nevertheless, in the documents located, the tobacco industry has avoided integrating this information when discussing the disease-inducing effects of menthol.

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