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Menthol's Potential Effects on Nicotine Dependence: A White Paper

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ABSTRACT

Publicly available internal tobacco industry documents were analyzed to answer the following questions regarding menthol's role in nicotine dependence: 1) What are the addiction and exposure measures and what are their relationships to menthol cigarette use? 2) Do menthol smokers show different signs or levels of nicotine dependence compared to non-menthol smokers? 3) Does menthol affect cigarette consumption (cigarettes per day) and do menthol smokers smoke more or fewer cigarettes per day compared to non-menthol smokers? 4) What is menthols' effect on nicotine metabolism (i.e. glucuronide formation) and do menthol smokers experience different nicotine exposure and/or altered nicotine metabolism as compared to non-menthol smokers? (i.e. serum cotinine levels) 5) Does menthol have an effect on nicotine delivery? 6) Does menthol alter the addictiveness of smoking through sensory stimulation?

Tobacco industry documents reveal at least two important reasons for menthol's use in cigarettes. A final collection of 309 documents was analyzed for this report, of which 72 were deemed relevant to one or more of the research questions and cited in this paper. Our analyses of these documents indicate 1) menthol is used in cigarettes to override the harsh taste of tobacco; 2) menthol has physiological effects, and it synergistically interacts with nicotine; 3) menthol makes low tar, low nicotine tobacco products that would otherwise be tasteless and unsatisfactory acceptable to smokers. Tobacco manufacturers manipulated menthol levels to produce tobacco products that would be easier to consume, especially for new and inexperienced smokers.

INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act (Act) gives the US Food and Drug Administration (FDA) regulatory authority over tobacco products. On September 22, 2009, the FDA exercised this authority when it announced the ban of some cigarette flavorings. However, this ban did not include menthol, as it was excluded from the list of banned flavorings originally identified in the Act. Menthol's exclusion from the list of prohibited flavor additives in cigarettes has promoted discussion among many in the public health arena.¹ The Act included a requirement to create the Tobacco Products Scientific Advisory Committee (TPSAC) within the FDA's Center for Tobacco Products. TPSAC is charged with advising the FDA Commissioner on the regulation of tobacco products, including the use of menthol as a cigarette ingredient and the impact of mentholated cigarettes on public health, with special attention given to children, African Americans, Hispanics and other racial and ethnic minorities.

The wide use of menthol in cigarettes is due to its minty flavor, aroma, and cooling characteristics and physiological effects on the smoker.^{2,3} The isomer *l*-menthol is the largest component of peppermint oil extracted from the two significant types of peppermint plants, *Mentha piperita* and *Mentha arvensis*. There are significant taste differences among the various isomers. Only *l*-menthol imparts the well-known mint-like taste and desired cooling effect.³ The concentration of menthol in tobacco products varies according to the product and the flavor desired, but is present in 90% of all tobacco products, both "mentholated" and "non-mentholated."^{3,4} The market-share of filter-tipped mentholated products has ranged from 1.1% in 1956 to 27.3% in 1983 to 20% in 2006.^{3,5} Available data currently show that past month use of mentholated brands among cigarette smokers aged 12 or older varies by race and ethnicity:⁶

- 82.6% African American
- 53.2% Native Hawaiian

- 32.3% Hispanic
- 31.2% Asian
- 24.8% American Indian/Alaska Native
- 23.8% non-Hispanic white

Although menthol is an FDA-approved food additive, the FDA is now evaluating the use of menthol as a characterizing flavor in cigarettes (menthol cigarettes) and has requested a review of tobacco industry documents to answer questions regarding a number of menthol-related topics: smoking initiation, topography, cessation, health effects, and marketing and consumer perceptions. This paper will address the following questions asked by the TPSAC related to the role of menthol in nicotine dependence:

1. What are the addiction and exposure measures and what are their relationships to menthol cigarette use?
2. Do menthol smokers show greater signs or higher levels of nicotine dependence compared to non-menthol smokers?
3. Does menthol affect cigarette consumption (cigarettes per day)? Do menthol smokers smoke more or fewer cigarettes per day compared to non-menthol smokers?
4. What is menthol's effect on nicotine metabolism (i.e. glucuronide formation)? Do menthol smokers experience altered nicotine exposure and/or altered nicotine metabolism (i.e., serum cotinine levels) as compared to non-menthol smokers?
5. Does menthol have an effect on nicotine delivery?
6. Does menthol alter the addictiveness of smoking through sensory stimulation?

The goal of this research is to determine what the tobacco industry knows about the potential effects menthol may have on nicotine dependence.

METHODS

In this qualitative research study of the digitized repository of previously internal tobacco industry documents, a snowball sampling design⁷ was used to search the Legacy Tobacco Documents Library (LTDL) (<http://legacy.library.ucsf.edu>). We systematically searched the LTDL between February 22, 2010 and April 29, 2010, utilizing standard documents research techniques. These techniques combine traditional qualitative methods⁸ with iterative search strategies tailored for the LTDL data set.⁹

Based on the FDA staff-supplied research questions (see INTRODUCTION above), initial keyword searches combined terms related to: menthol, nicotine, dependence, addiction; and brand names such as Kool, Newport and Salem. This initial set of keywords resulted in the development of further search terms and combinations of keywords (e.g., “scientific issues,” “menthol pharmaco*,” “menthol/nicotine interaction,” and “nicotine delivery”). Of the approximately 11 million documents available in the LTDL, the iterative searches returned tens of thousands of results. (See table A in the appendix for the full list of search terms and number of results returned.) For example, a search of all tobacco industry document collections on the LTDL for the keyword “menthol” alone would yield over 800,000 documents. The results that are returned in the LTDL include multiple copies of many documents, so researchers must decide which irrelevant and duplicate documents to exclude. Relevance was based on whether, upon electronically searching or reading a document, it included content related to the topic or the specific questions presented by the FDA staff. Tobacco companies investigated issues in order to increase their share of market, rather than to understand public health issues; thus many of the tens of thousands of returned documents with these search terms did not appear to be directly relevant.

For each set of results, the researchers reviewed the first 100-200 documents. If documents did not appear to be relevant to the research questions, or if there was a repetitive pattern of documents, the researchers moved on to the next search term. Among the reports, correspondence, and studies conducted by product development and research departments of the major tobacco companies (American Tobacco, British American Tobacco (BAT), Brown & Williamson, Lorillard, Philip Morris, and RJ Reynolds), relevant documents were found in the following subject areas: 1) addiction and exposure measures and their relationships to menthol cigarette use; 2) nicotine dependence in menthol smokers versus non-menthol smokers; 3) menthol's effect on nicotine metabolism; 4) menthol and nicotine delivery; and 5) menthol's role in cigarette addiction through sensory stimulation. A final collection of 309 documents were deemed relevant to one or more of the research questions. Memos were written to summarize the relevant documents to further narrow down to the 72 relevant documents that are cited in this white paper. Appendix A details the results of the searches and the number of documents screened and further reviewed.

Limitations

Tobacco industry document research presents unique challenges,⁷ and results should be interpreted within the context of known limitations, such as the vast number of available documents, time restrictions, and the use of code words and acronyms. The sheer quantity of available documents forces researchers to make decisions about which search terms retrieve the most relevant material. Further, the LTDL is frequently updated as tobacco companies provide additional material and documents become available through litigation. The document searches were conducted over a ten-week period. Given the short period of time for conducting this

project (LTDL archival research often takes a year or more to complete), the research team had to strategically screen the documents through the process discussed above.

In analyzing the documents in a limited timeframe, context may have been lost and, therefore, this white paper cannot be a comprehensive report of all documents related to the role menthol may play in nicotine dependence. Understanding the time period when a document was written, who wrote a document, why a document was written, or why a study was performed requires time for reviewing and linking documents together. It is also difficult to compare statistics gathered using different methodologies used by numerous companies over several decades.

Even if there had been more time for searching, it is unlikely that a complete picture of the tobacco industry's research about menthol and nicotine dependence could be compiled. There is evidence that the industry tried to hide its findings, although it is unclear from whom. For example, in a 1974 BAT memo about a visit to BIBRA, a toxicology consulting firm, it was noted that "Reference to menthol should be omitted from such documents [invoices], which should refer generally to toxicity studies."¹⁰ Brown and Williamson used the code terms, such as "Kintolly," "Tolkin," "Harpat," "Polar Bear," and "Cenmap" when referring to menthol.¹¹ However, the search of these code terms did not return results relevant to the role menthol may play in nicotine dependence. Acronyms were also commonly used, which are often unclear if the context is unknown.

Research in the LTDL typically involves repeating the iterative search process (including searching all code words and acronyms we learn through the process) until we reach saturation of both keywords and documents. Unfortunately, we could not reach saturation for this white paper; however, the documentary evidence presented in this paper supports our primary findings.

RESULTS

Table 1 presents the research questions and summarizes the basic findings.

Table 1: RESEARCH QUESTIONS AND BASIC FINDINGS

Question	Summary of finding based on review
1) What are the addiction and exposure measures and what are their relationships to menthol cigarette use?	The Fagerström Test of Nicotine Dependence (FTND) is used to measure addiction. Cotinine, carbon monoxide (CO), carboxyhaemoglobin (COHb), and thiocyanate have been identified in the tobacco documents as the biochemical markers used to measure cigarette smoke exposure. According to industry-funded research and research conducted internally by tobacco companies, menthol has no effect on nicotine absorption, nicotine metabolism or nicotine dependence. We located no documents presenting any evidence of industry research specifically linking menthol to addiction or to the biomarkers of tobacco exposure measures.
2) Do menthol smokers show altered levels of nicotine dependence compared to non-menthol smokers?	Despite the industry’s claim that menthol is only a flavorant, the addition of menthol to cigarettes masks the harshness of tobacco and provides an “extra something,” ¹² which make cigarettes more desirable to some smokers.
3) Does menthol affect cigarette consumption (cigarettes per day)? Do menthol smokers smoke more or fewer cigarettes per day compared to non-menthol smokers?	Tobacco documents suggest nicotine and pH levels, and not menthol, determine cigarette consumption. Philip Morris, in particular, found cigarette consumption to be related to the level of tar in cigarettes. However, among non-menthol smokers was the fear that switching to menthol cigarettes would increase their consumption.
4) What is menthol’s effect on nicotine metabolism (i.e. glucuronide formation)? Do menthol smokers experience altered nicotine exposure and/or altered nicotine metabolism (i.e., serum cotinine levels) than non-menthol smokers?	It is unclear what the tobacco industry knew about the relationship between menthol and nicotine metabolism or if menthol smokers experienced altered exposure and/or altered nicotine metabolism than non-menthol smokers. However, tobacco company researchers reviewed the scientific literature and concluded that menthol did not induce hepatic cytochrome P450, at least in rats.
5) Does menthol have an effect on nicotine delivery?	Tobacco industry documents reveal menthol has an effect on the amount of nicotine delivered in smoke.

	Tobacco manufacturers came to discover they could manipulate the level of tar and nicotine in their cigarettes, and with the help of menthol, design acceptable cigarettes that could meet consumer demand for reduced tar and nicotine.
6) Does menthol alter the addictiveness of smoking through sensory stimulation?	Menthol produces some nicotine-like effects on the central nervous system and stimulates the trigeminal cold fibers, the gustatory (taste) and olfactory (smell) nerves, and nociceptors. Menthol is minty (olfactory fibers), bitter (gustatory fibers) and cooling (trigeminal fibers). In addition to making cigarettes smoother and less harsh, menthol's cooling effect alleviates nicotine's irritating effect. This trigeminal stimulation is essential to eliciting a "liking" response for a tobacco product.

i. What are the addiction and exposure measures and what are their relationships to menthol cigarette use?

The Fagerström Test of Nicotine Dependence (FTND) is used to measure addiction. Cotinine, carbon monoxide (CO), carboxyhaemoglobin (COHb), and thiocyanate have been identified in the tobacco documents as the biochemical markers used to measure cigarette smoke exposure. According to industry-funded research and research conducted internally by tobacco companies, menthol has no effect on nicotine absorption, nicotine metabolism or nicotine dependence. We located no documents presenting any evidence of industry research specifically linking menthol to addiction or to the biomarkers of tobacco exposure measures.

Although menthol's relationship to the biomarker cotinine remains unclear, as a review of the published literature shows mixed findings,¹³⁻¹⁶ two recently published articles written by tobacco industry scientists concluded menthol has no effect on cotinine levels, whether subjects regularly smoked menthol or non-menthol cigarettes.^{17, 18} An undated Brown and Williamson study on nicotine and cotinine intentionally excluded menthol smokers from the sample,¹⁹ as did

a report on a plasma cotinine study done for RJ Reynolds.²⁰ Although Brown and Williamson had considered in 1985 to do comparative blood cotinine testing on menthol and non-menthol smokers,²¹ subsequent searching in the LTDL did not reveal evidence that this research was done. An industry study conducted in 1989 by RJ Reynolds collected data on nicotine, menthol and cotinine levels in rats. However, the document provides only raw data and does not contain any analytical discussion about the data.²²

Despite smoking fewer cigarettes per day, black smokers reportedly have higher serum cotinine levels than do white smokers, suggesting the metabolism of nicotine or the excretion of cotinine may differ by race. As the majority of black smokers prefer mentholated cigarettes, investigators have suggested menthol may play a role in the differences in nicotine metabolism that has been observed between black and white smokers. Wagenknecht et al.²³, a study mentioned in industry documents,²⁴⁻²⁶ found racial differences in daily nicotine exposure and serum thiocyanate levels. Whereas the serum cotinine levels were higher in the black subjects, the serum thiocyanate levels were higher in the White subjects. These differences persisted after controlling for number of cigarettes, nicotine content, frequency of inhalation, weekly sidestream smoke exposure, age, gender, and education.

A 1995 document reveals comments prepared by Philip Morris Europe to address claims made in a class action suit filed in a US District Court, naming the major tobacco companies as defendants. The plaintiffs, led by the Reverend Jesse Brown of the Philadelphia-based “National Association of African Americans for Positive Imaging” (NAAAPI), claim that the tobacco companies had known for “many decades... that menthol and nicotine contained in their tobacco products [were] harmful drugs” and that black people, in particular, continue to smoke to “satisfy their nicotine and menthol cravings.”²⁶ Philip Morris Europe was prepared to respond to these

allegations, citing the Wagenknecht studies on serum cotinine levels that found ethnic differences and a menthol effect.^{23, 27}

It was suggested that an ethnic difference in the metabolism of nicotine might account for the higher levels of serum cotinine in African Americans...data did not indicate a significant effect of menthol on serum cotinine levels in either African Americans or Caucasians smoking mentholated cigarettes.²⁶

...

Studies investigating whether the presence of menthol in cigarettes increases either serum cotinine or nicotine levels have, in most cases, failed to take into account both the ethnicity of the study subjects and the nicotine yields of the cigarettes smoked. Thus [,] the presented data are confounded by at least two different effects which can influence serum cotinine and nicotine levels in the absence of an assumed and claimed effect of menthol.²⁶

A Philip Morris document marked “priority”²⁵ reveals the company developed discussion points to respond to published studies that investigated differences in cigarette use and nicotine metabolism between black and white smokers.²⁸⁻³⁰ Noting that serum cotinine levels were higher in black smokers than white smokers,^{23, 31} Philip Morris concluded that race, not menthol, was the variable that could explain the observed differences. A Philip Morris report on the risk assessment of menthol referenced the Gardner et al. study on the relationship between cigarette smoking and serum thiocyanate (SCN) levels,³² noting that of the seven variables examined, it was cigarette consumption, and not menthol, that most significantly contributed to the variations in SCN. Menthol was among the other variables that “contributed relatively little.”³³ A review of the published literature of industry-funded research on the effects of smoking on biomarkers of exposure and potential harm located two industry studies that included menthol as a variable³⁴ and revealed a number of other industry-funded studies that menthol was not included as a variable in the analyses.³⁶⁻⁴⁶

ii. Do menthol smokers show altered signs or levels of nicotine dependence compared to non-menthol smokers?

We located no evidence that tobacco manufacturers conducted epidemiological studies that could answer this question from an industry perspective. However, tobacco documents reveal that despite the industry's claim that menthol is only a flavorant, the addition of menthol to cigarettes masks the harshness of tobacco and provides an "extra something," which make cigarettes more desirable to some smokers.

A 1976 confidential RJ Reynolds interoffice memo written by chemist Dr. Mary Evelyn Stowe to Dr. Donald H. Piehl, manager of the company's chemical research division, provides evidence that the tobacco manufacturer had known that even at "low or subliminal levels of menthol," smokers "felt that nasal sting, tongue bite, and harshness were somewhat reduced."⁴⁷ This demonstrates that menthol has non-flavor-related effects on unfavorable aspects of smoking cigarettes.

Reduction of harshness

In 1982, the Creative Research Group (CRG) conducted discussion groups on consumer perceptions of menthol cigarettes. CRG produced its report "Project Crawford" to the Imperial Tobacco Company.⁴⁸ Discussion group participants were either menthol smokers or "potential or occasional users", ranging from 18 to 50 years of age. They found menthol cigarettes to "undeniably impart a cooling influence" and that this effect made menthol cigarettes more preferable to them than non-menthol cigarettes.

It is the cooling effect which constitutes the major attraction, this and the concomitant reduction in both harshness and tobacco taste.⁴⁸

Participants shared that the flavor of menthol was not a "significant reward."⁴⁸ Regarding menthol's ability to mask tobacco taste, the report disclosed,

There is no question that menthol has a significant masking effect on both the taste of the tobacco and the harshness of the smoking experience. Some menthol smokers seek as much masking effect as possible, attempting to eradicate the tobacco taste altogether.⁴⁸

The report also included quotes from some of the participants, some of which reveal the role menthol plays in covering up tobacco taste.

As for as I am concerned, I want the menthol to completely cover up the taste of the tobacco. I don't like the taste of tobacco [emphasis in original].

...

If the menthol was gone, I wouldn't be able to stand the cigarette [emphasis in original]!

However, some participants were less enthusiastic about menthol, wishing for a somewhat lower level of masking effect.

"I don't like to have the tobacco taste covered up completely [emphasis in original]."

What the researchers found interesting was that mentholation "can still function in its masking role and yet can have lost a large portion of its own [flavor]."⁴⁸ The researchers concluded that menthol smokers build up a tolerance to the menthol taste, but that menthol's effects were still present. The researchers could not explain this phenomenon but admitted to its existence. "It is difficult to attach a value judgement [sic] to this phenomenon, but it certainly does seem to exist."⁴⁸ Participants disclosed how their perception of the menthol taste waned throughout time.

"When I first started to smoke them, I could taste the mint. As you get used to them, there is no way you are going to taste the mint [emphasis in original]."

...

"[I]f you wake up first thing in the morning and take a cigarette, a menthol cigarette, you taste it. After that, forget it [menthol taste][emphasis in original]."⁴⁸

In a 1982 RJ Reynolds interoffice memo written in anticipation of questions from consumers concerning menthol, biochemist Charles Nystrom told Tim Cahill of the company's

public relations department that there was no evidence that menthol had any “effect on the smoker other than the effect of menthol on the taste and flavor of the cigarette.”⁴⁹ Mr. Cahill subsequently responded to consumer letters inquiring about the effects of menthol in cigarettes, assuring consumers that menthol was used as a flavor additive that had no other effect or addictive properties.⁵⁰ Cahill, in a letter to another consumer, recommended the use of menthol cigarettes.

We make no health claims for any of our cigarettes. However, if you have not already done so, you might try a low “tar” [emphasis in original] menthol cigarette, such as Salem Lights.⁵¹

While citing the 1964 Surgeon General Report on smoking and health that “nicotine in cigarettes ‘probably does not represent a significant health problem’ [emphasis in original],”^{52, 53} Cahill recommended the use of low “tar” menthol cigarettes.⁵³

Menthol’s ‘extra something’

Despite RJ Reynolds’ denial, tobacco manufacturers had known menthol to be more than just a flavoring for their tobacco products. For example, in 1979, the Roper Organization conducted for Philip Morris a study to investigate smokers’ habits and attitudes with a special emphasis on low tar and menthol cigarettes. Survey results from the 1979 Roper report revealed that “[B]lack, young people and women who... are light smokers [and] all tend to like menthols, reinforces the concept that menthol provides an ‘extra something’.”¹² The Roper report also found that smokers preferred menthol cigarettes not just for taste, but also for this “extra something” effect. The report concluded that menthol had drug-like properties, which attracted smokers.

The key effects that seem to appeal to menthol smokers are menthol’s perceived

- cooling effects
- clean, antiseptic effects
- slightly numbing, anesthetic effects
- heady, lifting effects

The report suggested to Philip Morris that if it wants to design a tobacco product that will be competitive in and appealing to the menthol market, then “two separate qualities should be considered: the effects the menthol will create and the “extra something” it will provide. This is because “menthol seems to compensate or make up both for few cigarettes or light cigarettes” smoked by these smokers.¹²

iii. Does menthol affect cigarette consumption (cigarettes per day)? Do menthol smokers smoke more or fewer cigarettes per day compared to non-menthol smokers?

Tobacco documents suggest nicotine and pH levels, and not menthol, determine cigarette consumption. Philip Morris, in particular, found cigarette consumption to be related to the level of tar in cigarettes. However, among non-menthol smokers was the fear that switching to menthol cigarettes would increase their consumption.

A 1974 RJ Reynolds document suggests nicotine and pH levels, and not menthol, determines cigarette consumption.⁵⁴ Whether or not menthol affects cigarette consumption appears to depend on the brand, the amount of nicotine and pH levels in the cigarette. In 1974, Philip Morris found young smokers to be lighter smokers than average, and menthol smokers to be even lighter smokers.⁵⁵ A few years later, Philip Morris market research found cigarette consumption to be related to the level of tar in cigarettes.

The number of cigarettes smoked per day per smoker continues to climb, in part at least because low tar cigarettes seem to cause people to increase the number of cigarettes they smoke.¹²

For a number of years prior to its disclosure in a 1980 document, Philip Morris had observed a steady increase in the average daily cigarette consumption among smokers. This

observation was seen in every cigarette category, among both sexes, and among black and white smokers. However, the “correlations for menthol brands, while high, did not reach significances [sic] because of the small number of menthol brand [smokers] for which we have reliable data on average daily consumption.”⁵⁶ Philip Morris found that as the weighted average tar and nicotine deliveries were declining, average daily consumption of cigarettes was increasing.

...declining [nicotine] delivery levels over time account for at least a part of the observed increase in average daily cigarette consumption...cross-sectional data suggest strongly that the decline in nicotine deliveries is the most important [variable for predicting average daily cigarette consumption].⁵⁶

Though recognizing that the lower nicotine delivery design of its cigarettes was, at least in part, responsible for the increase in average daily consumption,⁵⁷ there were “other variables that tend to cloud the issue”:

Menthol smokers smoke fewer cigarettes per day than non-menthol smokers, [B]lacks smoke fewer cigarettes per day than whites, females smoke fewer than males, and smokers of 100’s smoke more than smokers of 80-85’s.⁵⁸

Smokers of non-menthol cigarettes, however, reported that one of the deterrents to their switching to menthol cigarettes, even among those who do like the taste of the menthol, is the fear that their smoking volume would automatically increase.⁴⁸

Since the whole smoking experience is “softened”, as it were, there is the assumption that one’s capacity will increase. The number of cigarettes per day will escalate. Some smokers, in fact, believe that they have experienced this very phenomenon [emphasis in original].

...

I seem to smoke more (menthols), and therefore you are getting more nicotine and tar into your body.

...

Well, I find them easier, so it's easier to pick one up and light one, whereas if there was an ordinary cigarette I would probably turn it down.

...

There is the opposite point of view as well, though it is considerably less predominant. That is to say, there are people who dislike the flavor of menthol and who deliberately force themselves to smoke a menthol brand in the hope that this will serve as an aid to reducing their consumption. A somewhat dubious posture, to say the least.

...

*I really don't like the taste of menthol, but I smoke them because it helps me cut back in the number of cigarettes I smoke a day.*⁴⁸

Based on its own analysis of data from the 1988 Community Intervention Trial for Smoking Cessation (COMMIT), the Lorillard research department reported there were no differences between non-menthol smokers and menthol smokers in terms of daily cigarette consumption rate, time to first daily cigarette, or subsequent success in smoking cessation. Lorillard researchers concluded from this relatively large study “that menthol does not appear to have any meaningful effect on the evaluated behavioral indices of nicotine dependence.”²⁴

A 1989 Philip Morris document contains data from the company's internal study of 747 menthol and non-menthol smokers and the time of their first cigarette in the morning. A slightly higher percentage of non-menthol smokers had their first cigarette within fifteen minutes of waking compared to menthol smokers, suggesting a higher nicotine dependence among non-menthol smokers.⁵⁹

iv. What is menthol's effect on nicotine metabolism (i.e. glucuronide formation)? Do menthol smokers experience increased nicotine exposure and/or decreased nicotine metabolism than non-menthol smokers? (i.e. serum cotinine levels)

It is unclear what the tobacco industry knew about the relationship between menthol and nicotine metabolism or if menthol smokers experienced increased exposure and/or decrease nicotine metabolism than non-menthol smokers. However, tobacco company researchers

reviewed the scientific literature and concluded that menthol did not induce hepatic cytochrome P450, at least in rats.

Tobacco manufacturers understood menthol to be metabolized primarily in the liver, via its conjugation with glucuronic acid, and subsequently excreted in the urine as glucuronide. The amount excreted varies, depending on the dose of menthol and in which type of animal.³

According to a study on glucuronidation in humans⁶⁰ cited in a Covington & Burling document that summarized a number of studies on menthol, human subjects given 500g of *l*-menthol rapidly but incompletely metabolized the compound into menthol glucuronide. In humans, 77.5% of 10-20 mg of menthol administered orally to human volunteers was recovered in the urine in 11 hours. No additional menthol was recovered in the remaining 25 hours of the study. “The metabolic fate of the menthol that is not conjugated is unknown.”³

According to 1990 documents showing correspondence between Philip Morris scientist Dr. Richard Carchman and researchers Ulrich Hackenberg and Hans-Jürgen Haussmann of Philip Morris’ European-based biological research institute INBIFO,⁶¹ Carchman requested Hackenberg and Haussmann to read an article⁶² on a study of the metabolism of *l*-menthol in rats. The referenced article reported that there was “[m]aximal induction of cytochrome P-450 and its reductase...upon 3 days of repeated treatment with *l*-menthol.”⁶² Although the study was done on rats, it had relevance for humans as, in most smokers, nicotine is eventually metabolized to cotinine via a pathway that is catalyzed by hepatic cytochrome P4502A6 (CYP2A6).^{63, 64}

On April 12, 1990, Carchman received a telefax from Hackenberg, who along with Haussmann had reviewed the article. Hackenberg informed Carchman that the “article – especially the section on Materials and Methods – give no indication which could lead to any doubts about the quality of the work performed.”⁶⁵ Hackenberg surmised that the high dose level

of menthol administered to rats in the study “possibly attributed” to the reduction of the P450 and NADPH cytochrome c reductase levels noted. However, Hackenberg sent a follow-up telefax on April 20, 1990 indicating he and Haussmann did “some further investigations into the menthol problem” and that Haussmann would be sending Carchman a summary. In his summary to Carchman, Hackenberg referenced another article on the “inducibility of cytochrome P-450 by menthol”.⁶⁶ Dr. Haussmann, who after a closer review of the literature, had decided that menthol did not induce the P450 in rats. Dr. Haussmann recommended that Dr. Carchman take a look at RJ Reynolds’ inhalation studies for “further insight into the biological activity of menthol.”⁶⁷

...we have gathered more information on the inducibility of cytochrome P-450 by menthol...The observed isozyme-specificity of the induction by menthol may be helpful in the discussion of the toxicological relevance of a possible induction of the metabolic activation of suspected carcinogens in tobacco smoke by tobacco additives.

...

The results of repeated treatment of *l*-menthol at the dose of 800 mg/kg of body weight/day for 7 days...elicited a statistically significant effect on the levels of cytochrome P-450 and NADPH cytochrome *c* reductase... In fact, after 3 days of repeated treatment, the cytochrome P-450 content and NADPH-cytochrome *c* reductase were enhanced by about 80%.

...

... in the present investigation it has been observed that both cytochrome P-450 and NADPH cytochrome P450 reductase were induced to significant levels upon oral administration of *l*-menthol to rats. In fact[,] very few reports have appeared in the literature regarding the ability of chemicals to induce the microsomal NADPH-cytochrome P-450 reductase. Maximal induction of cytochrome P-450 and its reductase was observed upon 3 days of repeated treatment with *l*-menthol.⁶² [as cited in ⁶⁷]

A search in LTDL for additional correspondence between Carchman, Hackenberg and/or Haussmann on this topic did not produce any follow-up letters or telefaxes. However, there is evidence that Carchman had reviewed a brochure for a company that provided “immortal human cell lines which stably express human cytochrome P450s.”⁶⁸ A 2001 report on the use of menthol as an ingredient in cigarettes presents evidence that Philip Morris continued to cite published

studies concluding menthol had no effect on nicotine metabolism. There was no indication that Philip Morris had conducted its own in-house studies.⁶⁹

v. Does menthol have an effect on nicotine delivery?

Tobacco industry documents reveal menthol has an effect on the amount of nicotine delivered in smoke. Tobacco manufacturers came to discover they could manipulate the level of tar and nicotine in their cigarettes, and with the help of menthol, design acceptable cigarettes that could meet consumer demand for reduced tar and nicotine.

Due to consumer demands for reduced tar cigarettes, tobacco manufacturers sought to design low tar products. However, reductions in tar level altered the nicotine/tar ratios, resulting in more nicotine per unit of tar.⁷⁰ In 1972, Philip Morris considered how a reduction in tar level would affect a cigarette's nicotine/tar ratio and if such a change in the ratio would affect that cigarette's acceptability and marketability.

The nicotine/tar ratio of all cigarettes...is $.07 \pm .01$. We have no acceptability data for nicotine/tar ratios outside this range. Since the trend in tar delivery is downward, and since nicotine is presumed to be that which is sought by the smoker, does a cigarette with a high nicotine/tar ratio have market potential?⁷¹

In its 1975 marketing study conducted on behalf of Lorillard, Marketing Corp of America acknowledged the market demand for low tar/nicotine brands, recognizing that though the market would be very tough to enter, there was a "strong likelihood of continued growth."⁷² In order to achieve substantial reductions in nicotine and tar yields, tobacco manufacturers also developed and used a number of manufacturing and design techniques. These included "highly efficient filters, perforations of the filter tipping paper, adjusted porosities and burn characteristics of the cigarette rod wrapping paper, and the use of expanded tobacco."⁷³ An undated Brown & Williamson document shows that the transfer efficiency rate of menthol

decreases with increasing filtration and ventilation (see table 2). “Thus, lower nicotine delivery products require higher menthol levels to maintain perception.”⁷⁴

Table 2: Menthol Transfer Efficiency⁷⁴

Tar Range	% Transfer Efficiency	% Menthol Applied
Full Flavor	15 – 16	0.35 – 0.45
Milds	12 – 13	0.45 – 0.55
Lights	8 – 10	0.60 – 0.80
Ultras	1 – 5	0.80 – 1.25

However, reducing the tar level produced cigarettes with undesirable features. Low tar cigarettes were tasteless, failed to satisfy the smoker, and harder to smoke, as described in the 1979 Roper Report provided to Philip Morris.

The appeal of low tars is simple and single—better for you, less harmful, easier on the lungs, throat, etc. The weakness or objection to low tars is also simple—tasteless, lacking in satisfaction, and the related factor of hard to draw on... But since lack of taste is the #1 drawback to low tars, the question occurs as to whether it is possible to “spray” or “inject” extra taste into low tars à la bac-o-bits or other synthetic flavors...[emphasis in original]¹²

The Roper Report also disclosed some of the habits and attitudes of black and white smokers, with a special emphasis on low tar and menthol cigarettes.

While the percentage of low tar smokers who smoke menthols is lower than the percentage of all filter smokers who do, and while the percentage of ultra low tar smokers who smoke menthols appears still lower, nevertheless, low and ultra low tar menthol smokers are better satisfied by their cigarettes than their non-menthol counterparts. This suggests that menthol makes up in some way for the light or “pale” qualities of a low tar cigarette.¹²

In 1985, RJ Reynolds conducted product development studies of full flavor (FF) and full flavor low tar (FFLT) among full flavor menthol smokers. These qualitative studies indicated that higher overall acceptance among full flavor menthol smokers was associated with high

nicotine flavor, regardless of menthol delivery. However, the interaction between menthol and nicotine was significant in regressions for strength, mildness, tobacco versus menthol taste, lasting aftertaste and sweet aftertaste. “[K]ey attributes such as strength, were dependent on the levels of both menthol and tar/nicotine [ratio].”⁷⁵ Menthol was the more important of the two variables that significantly affected consumer acceptance and perceptions of a number of attributes. In terms of strength perceptions, the regression was significant at the 98% confidence level and explained 93% of the variance in strength ratings, which ranged from 3.51 to 3.95 in the design products. Strength increased as a function of both menthol and nicotine level, decreased as a function of interaction between the two variables. A number of combinations of menthol and nicotine levels resulted in “optimum strength ratings.” The mean ideal strength achieved between menthol and its interaction with nicotine was 3.69.

At moderately high tobacco nicotine levels (~2.00%), almost any pack menthol...approximates the mean ideal strength. However, at lower tobacco nictines (~1.45% - ~1.83%), pack menthols must increase (from 0.34% - 0.62%), in conjunction with tobacco nictines, to maintain mean ideal strength.⁷⁵

In 1989, Philip Morris scientists discovered that “menthol and nicotine interact in a very interesting fashion.”⁷⁶ Therefore, the tobacco manufacturer continued its research on menthol cigarettes, combining menthol with varying levels of nicotine and tar, further supporting that the interaction between tar, nicotine, and menthol depended on the nicotine/tar ratio.^{77, 78} Philip Morris found in a study of factorial combinations of four levels of menthol (0.00, 0.41, 0.85, and 1.95 mg per cigarette) and three levels of nicotine (0.08, 0.41, and 0.91 mg per cigarette) that the addition of menthol either increased or decreased impact, depending on whether, and to what degree, nicotine was present.⁷⁹

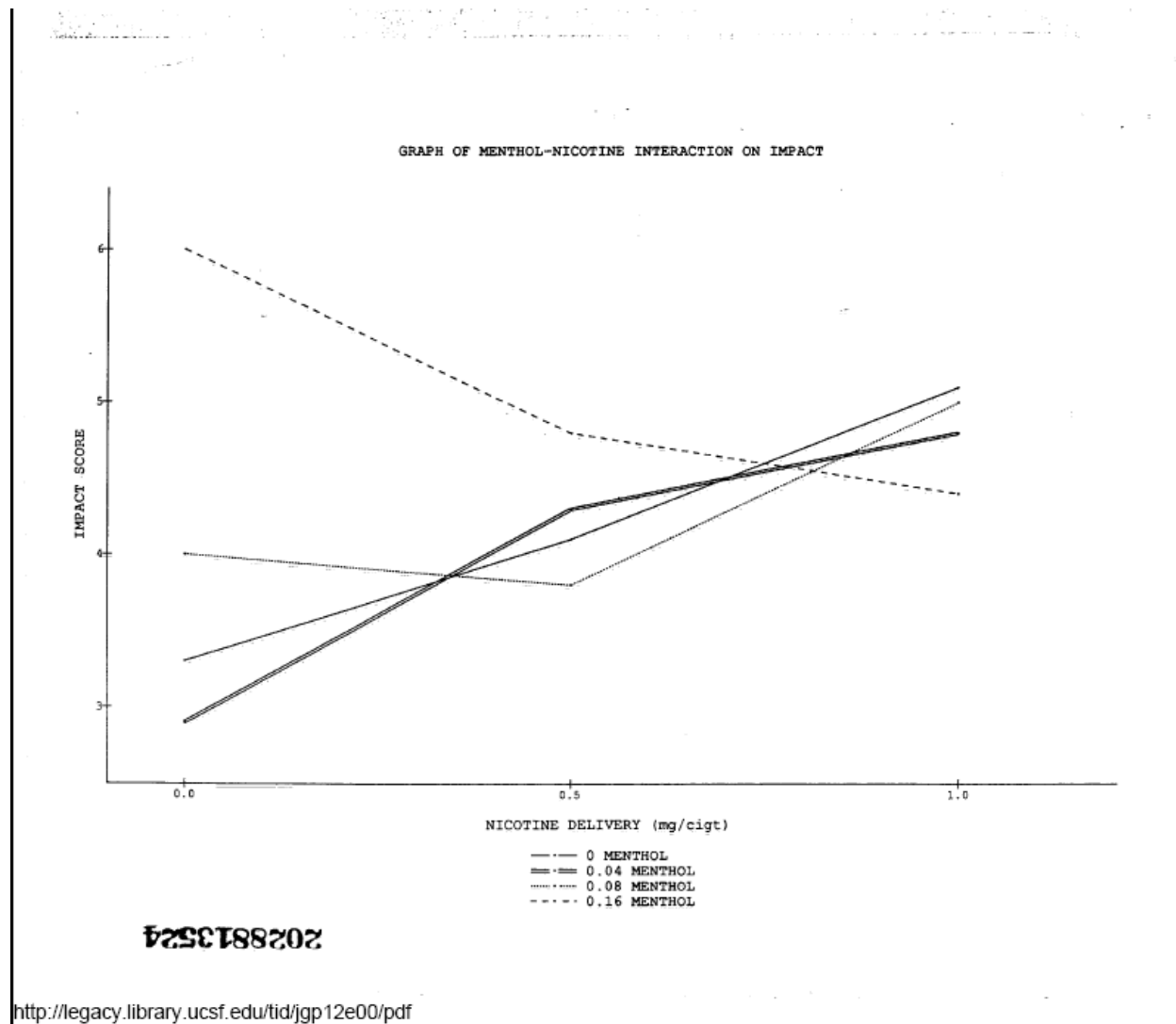
[P]erceived impact seems to vary as a function of the delivery levels of menthol and/or nicotine in smoke...it seems that menthol level almost exclusively determines degree of impact. In low nicotine delivery cigarettes, it appears that nicotine and menthol combine in an additive manner to determine degree of impact.⁷⁶

Though impact is perceived by the smoker as a “kick” or “grab” in the back of the mouth and throat when inhaling a cigarette,^{80, 81} it has been demonstrated that this physical “tracheal stimulation” is crucial in providing much of the immediate satisfaction gained from smoking.⁸² Philip Morris scientists conducted smoking panel tests to predict the amount of menthol needed in low nicotine delivery cigarettes to attain a desired impact. These tests allowed Philip Morris to determine how specific combinations of menthol and nicotine affect perceived impact.^{81, 83-85} Philip Morris scientists then applied data they collected from these panel tests to predict the amount of menthol needed to attain a desired impact at any given nicotine level.⁸⁶

...as we had seen before, adding menthol to the extracted model had the effect of increasing impact. More interestingly, and something we had not seen before however, menthol had the effect of [lowering] impact in those cigarettes containing nicotine.⁸⁷

Figure 1 is a graph taken from a 1990 Philip Morris document and shows how the menthol-nicotine interaction affects impact. Varying the amount of menthol and nicotine delivery affected the impact scores of the prototypes. For example, the prototype with the highest level of menthol but the lowest level of nicotine delivery had the highest score for impact.⁸⁸

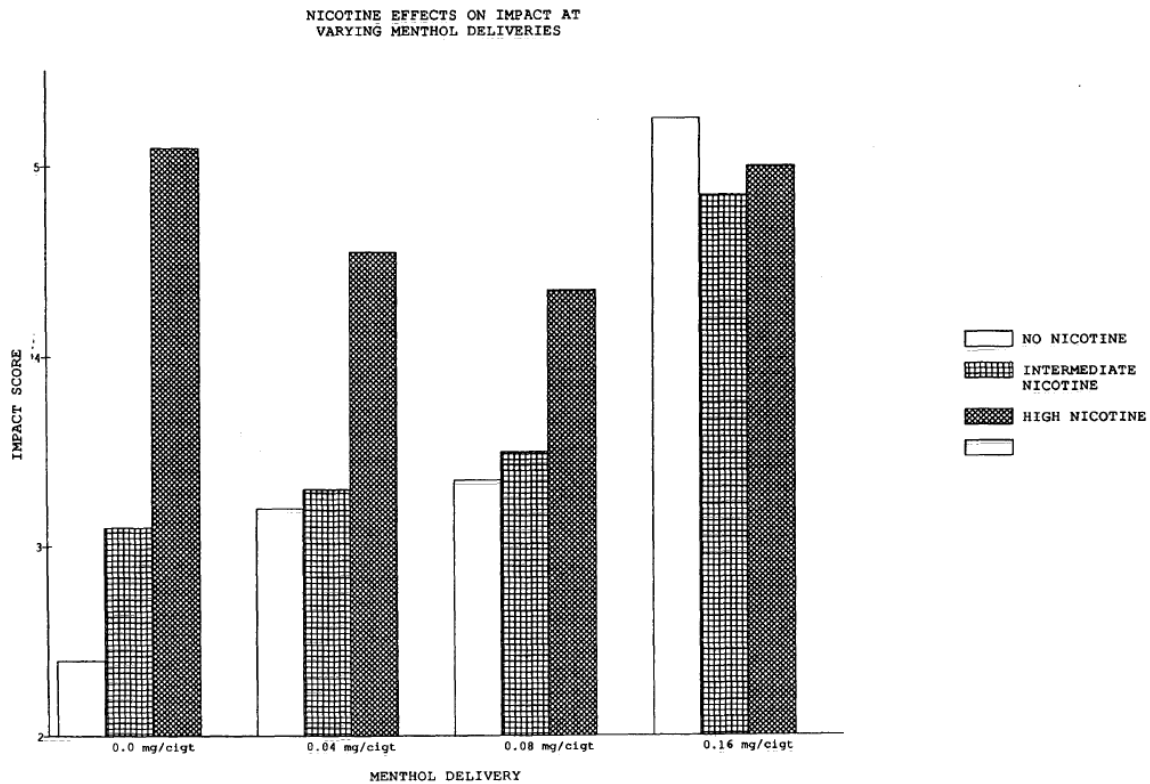
Figure 1: Menthol-Nicotine Interaction of Impact⁸⁸



A 1991 Philip Morris internal study on tar, nicotine and menthol found that the nicotine per puff appeared to have the greatest effect on impact, followed by menthol per puff. Tar per puff had very little effect on impact, except when tar per puff was high. As tar per puff increased, impact decreased even if both nicotine per puff and menthol per puff were high. However, these interactions become more complicated at higher levels. For example, high nicotine per puff and high menthol per puff had very little effect on impact. There was also evidence that increasing menthol per puff caused impact to decrease if both tar per puff and nicotine per puff were high.⁸⁹

The following chart provides a visual representation of nicotine effects on impact at varying menthol deliveries.⁸⁵

Figure 2: Nicotine Effects on Impact at Varying Menthol Deliveries⁸⁵



What became apparent to Philip Morris scientists is that impact increased when nicotine per puff was low and menthol per puff was high. Therefore, the levels of all three variables – tar, nicotine and menthol – are taken into account to predict and manipulate the impact of low nicotine delivery cigarettes.⁹⁰ Menthol’s ability to increase or decrease impact depended on the degree to which nicotine was present.⁹¹

The results from this study have provided us with information on tar per puff, nicotine per puff, and menthol per puff in terms of predicting impact...in order to increase the impact of a Merit half-nic menthol to that of a regular Merit menthol, the menthol per puff of Merit half-nic would need to be increased up to about .07.⁹²

[M]enthol increased “impact” for the low nicotine delivery cigarettes...as a function of the menthol content. The effect of menthol was most pronounced for the cigarette with

the lowest nicotine delivery...It was concluded that menthol has a pronounced effect on nicotine-derived “impact.” Therefore, menthol levels must be considered when targeting cigarettes for degree of perceived “impact.”⁹³

Continuing to address consumer concerns about the harmfulness and addictiveness of nicotine, the tobacco industry sought to design denicotinized cigarettes.⁹⁴ For example, during the late 1980s Philip Morris scientists conducted their own in-house testing of the cigarette prototype ART, an “alkaloid reduced tobacco” product.^{95, 96} ART cigarettes had 0.12 mg nicotine/cigarette, compared to 0.20 mg or more of nicotine per cigarette in conventional cigarettes. ART cigarettes also differed from conventional cigarettes in sensory characteristics and flavor. Another notable difference between ART and conventional cigarettes was that ART cigarettes lacked impact, which was due to the absence of or decreased nicotine delivery. The mentholated version of ART cigarettes was found to be subjectively superior to non-mentholated versions, as “ART cigarettes obtain virtually all of their impact from the menthol.”⁹⁷ When Philip Morris expanded its studies to include a mentholated version of its ART cigarettes, the results showed menthol also produced some nicotine-like electrophysiological and subjective effects. Philip Morris researchers were surprised to find that the menthol ART-extracted cigarette produced favorable subjective findings. Based on findings from its preliminary study, Philip Morris decided to investigate further the effects of nicotine and menthol interactions in a more systematic fashion.⁹⁶ Philip Morris attorneys maintained a list of research proposals and projects, some of which included topics on menthol and nicotine interaction. One such proposal sought to identify a menthol analogue that did not produce a cooling sensation, which would make it “an excellent candidate for providing impact in low delivery cigarettes [for non-menthol smokers].”⁹³

RJ Reynolds also conducted studies to determine optimal nicotine-menthol blends for its Salem brands to keep them competitive in the growing menthol market. RJ Reynolds found menthol eased the flow of smoke through the filter.

“Smoke through the filter perceptions were affected by levels of both menthol and tobacco nicotine. Increased pack menthol levels had the overall effect of increasing ease of getting smoke through the filter...Increased nicotine generally increased perceptions of hard to get smoke through the filter [emphasis in original].”⁷⁵

vi. Does menthol enhance the addictiveness of smoking through sensory stimulation?

Menthol produces some nicotine-like effects on the central nervous system and stimulates the trigeminal cold fibers, the gustatory (taste) and olfactory (smell) nerves, and nociceptors. Menthol is minty (olfactory fibers), bitter (gustatory fibers) and cooling (trigeminal fibers). In addition to making cigarettes smoother and less harsh, menthol’s cooling effect alleviates nicotine’s irritating effect. This trigeminal stimulation is essential to eliciting a “liking” response for a tobacco product.

Menthol has properties that stimulate sensory receptors, which could contribute to addiction by strengthening the conditioned aspects of smoking.⁹⁸ Menthol stimulates the neural fibers that are also stimulated by nicotine. Stimulation of these fibers, termed fast-acting nociceptors, produces inhalation impact.⁸¹ In 1975, Philip Morris researchers were intrigued with a finding specific to menthol’s role in strength and impact, a perception shared by participants in a study conducted with black and white menthol smokers.⁹⁹ The researchers were not convinced that the panelists in their study were responding simply to menthol delivery. Rather, the researchers considered the panelists to be responding to some combination of nicotine and menthol and that menthol’s role in strength and impact “over-rode the influence of nicotine.”⁹⁹

This suggested that the magnitude of sensory experiences resulting from small variations in menthol delivery may be greater than those resulting from small variations in nicotine delivery.

A survey conducted by the Roper Organization for Philip Morris in 1979 revealed that except for their specific liking for menthol, there were no other unique or distinctive taste preferences that distinguished menthol smokers from non-menthol smokers. What the study found was that the appeal of menthol cigarettes was more in terms of their effects than their tastes.¹² However, a focus group study conducted in 1982 by Philip Morris found two types of menthol smokers.¹⁰⁰ One type preferred tobacco taste balanced with a menthol taste or coolness. These menthol smokers found menthol cigarettes to be less strong, less dry, more refreshing, and having a non-tobacco aftertaste when compared to non-menthol cigarettes. The other type disliked tobacco taste. Those menthol smokers appeared to like a minty, sweet type flavor that did not have an overpowering effect.

People want to know they are smoking a cigarette, not just sucking air...Many of the smokers describe the non-menthol low delivery cigarette as lacking taste, papery, or like burning leaves...Most of the smokers believed menthol cigarettes are smoother and less harsh than non-menthol.¹⁰⁰

During a Philip Morris meeting held on March 1-2, 1979, the use of menthol was the topic of discussion.

The reasons for having this discussion were based on several recent problems which have arisen and a contention about the olfactory [sic] response to “pure” *l*-menthol...[menthol is] an interesting problem...that relates to terpenes as...elicitors of favorable smoker response and to the basic question of the biochemical and physiological response to tobacco additives.¹⁰¹

One of the Philip Morris researchers attending the meeting recommended one area of study be the “chemical aspects of menthol and its biochemical and physiological

consequences.”¹⁰¹ Menthol has been demonstrated to elicit taste and smell responses by stimulating the trigeminal cold fibers, the gustatory (taste) and olfactory (smell) nerves, and nociceptors. This provides the total menthol response. That is, it is minty (olfactory fibers), bitter (gustatory fibers) and cooling (trigeminal fibers). There is also a change in sensitivity in the olfactory and gustatory fibers after sustained menthol exposure.¹⁰² The impact provided by menthol is probably mediated by the nociceptive fibers of at least two nerves: glossopharyngeal and trigeminal.⁷⁹ The trigeminal nerve is the fifth cranial nerve and is widely distributed throughout the head. Trigeminal chemoreception was of interest to the tobacco industry, as nicotine stimulated this nerve. The trigeminal is essential to eliciting a “liking” response for a tobacco product. Philip Morris conducted research to find other compounds that could evoke comparable physiological effects as nicotine. Nicotine has been found to be the most effective elicitor of trigeminal stimulus.¹⁰³

Philip Morris scientists took great interest in menthol’s effect on the senses, including taste, olfaction, and feeling (e.g., trigeminal).

The continued financial success of our business will rely to an ever increasing degree upon our understanding of the chemical senses and the application of this information in the design of new products. The consumers’ demands or government’s requirements for new, nontraditional products ...Successful development of novel products demands additional, innovative approaches.⁷⁷

Philip Morris established its ‘Trigeminal Panel’ in August 1989 “in order to screen for compounds which might possess nicotine-like sensory characteristics.”¹⁰⁴ The panel identified compounds for their abilities to elicit trigeminal responses and to exhibit nicotine-like sensory characteristics.¹⁰⁵ Those compounds that appeared to be nicotine-like were tested and assessed for their electrophysiological and subjective effects on the central nervous system (CNS).^{93, 97, 106,}

¹⁰⁷ Menthol was found to be such a compound that produced some nicotine-like CNS and subjective effects.¹⁰⁵

Purpose of the Trig Panel[:] Identification of compounds with nicotine-like sensory characteristics by focusing on trigeminal properties...trigeminal [is] one of [the] most important aspects to mainstream...No good replacement for nicotine...Menthol partial replacement.⁸⁴

Menthol affects hot and cold receptors, giving a variety of thermal responses. Based on the thickness of the stratum corneum, body parts have different levels of sensitivity and respond differently to menthol. The sensitivity of the stratum corneum is influenced by the ease with which menthol can penetrate this barrier. The body part's sensitivity is also likely to be influenced by the number of cold-sensitive nerve endings per unit area and the efficiency with which the central nervous system processes nerve signals vary with the location on the skin.⁸¹ Menthol's cooling effect appears not to be a result of volatilization of menthol, but rather a result of the chemical action that occurs at or near those nerve endings which are associated with the sensation of cold.¹⁰⁸ These nerve endings are located in the nasal, oral and skin membranes. When menthol is added to cigarettes and smoked, this cooling sensation is also experienced in the lungs. The cooling sensation is dose sensitive. Increasing the amount of menthol beyond a certain limit would not generally result in a greater degree of cooling, but would cause an increase in other sensations such as tingling, stinging and burning. Apart from the cooling effect and a degree of flavor potentiation and odor modification, there are no common sensory properties of cooling compounds. For instance, there is no association between minty smell and cooling.¹⁰²

In addition to making cigarettes smoother and less harsh, menthol's cooling effect alleviates nicotine's irritating effect. The tobacco industry was well aware that younger,

inexperienced smokers had low tolerance for irritation and tobacco taste.^{70, 109} RJ Reynolds conducted studies in 1983 on nicotine and menthol to better understand the “independent and joint effects of nicotine and menthol on smoker perception.”¹¹⁰

Nicotine [is]...a major irritant in cigarette smoke while menthol is known to produce a cooling effect and is often used to alleviate sensations of irritation.¹¹⁰

By 1990, Philip Morris understood menthol was a complex compound and that liking menthol cigarettes was complex. Philip Morris scientists produced a 199-page report on their chemical senses research, which encompassed “the development of a fundamental understanding of those physical/chemical and biological system interactions that result in a favorable subjective response to the product.”⁷⁷ This report included the work of a number of Philip Morris scientists, documenting their research findings on the physical, chemical and biological interactions between nicotine, tar and menthol as they relate to consumer subjective responses and expectations of Philip Morris tobacco products.

The chemical senses report also provides an insight as to how Philip Morris would participate in the development of “novel products, those products that would be “liked” and could withstand the test of “feeling.”

Responses to products could be analyzed to tell us how much menthol we want to have in a cigarette. That’s a routine test today whereas several years ago we didn’t have that kind of information. It’s an analytical tool that we now use that allows us to design products that are competitive with what’s in the market place... Every sensory test we perform using cigarettes (mainstream or sidestream) involves measuring “feeling” factors. This is due to the fact that all of our experience to date suggests that liking is driven by “strength” in non-menthol and a combination of “strength” and “cooling” in menthol mainstream.⁷⁷

However, Philip Morris scientists were limited in their ability to measure these feeling factors and realized that product development would require a more focused program on chemical senses research. Menthol was an integral part of this plan. The 1993 operational plans for a Sensory Technology Program reveal that Philip Morris scientists intended to utilize their knowledge of the “synergistic interaction” between menthol and nicotine to develop a product that was low tar yet had superior sensory characteristics.¹¹¹ Philip Morris’ strategic plan for 1993-1997 included the development of models to identify the molecular processes that lead to human sensory perceptions, including the mechanisms by which nicotine and menthol bind to receptor sites to elicit sensory effects. Philip Morris was specifically interested in understanding these mechanisms in order to improve the “sensory efficacy” of both nicotine and menthol.¹¹²

While conducting these studies, menthol’s electrophysiological effects on the CNS became apparent. Philip Morris, in particular, conducted Pattern-Reversal Evoked Potential (PREP) studies to record and measure the electrophysiological effects of nicotine delivery on the CNS.^{113, 114} Menthol affects the response of many receptors to stimulation. Physiological effects of menthol are dose sensitive. Small concentrations of menthol are more effective than large quantities, which will depress receptor stimulation. After prolonged, chronic exposure, response to receptor stimulation is also depressed.

An undated document indicates that British American Tobacco also recognized menthol had a physiological effect that interacted with nicotine.

Another aspect to consider is the balance between the menthol and the nicotine in the smoke. This should not be a problem in lower delivery products as the combined effects, remembering menthol produces a physiological effect ‘menthol impact’, would not be unacceptably high. Problems can arise if there is a high level of either or both. The theory is that the two components stimulate the same receptors and compete with one another.¹¹⁵

DISCUSSION

According to the tobacco manufacturers, there is no evidence that menthol has any “effect on the smoker other than the effect of menthol on the taste and flavor of the cigarette.”⁴⁹ The evidence presented in this paper shows menthol is not just an ingredient added in a recipe to make cigarettes taste a certain way. Tobacco manufacturers explored a number of ways to manipulate the levels of menthol and take advantage of the physiological effects of menthol on the trigeminal cold fibers, the gustatory and olfactory nerves, and nociceptors to alter the smoking experience. Indeed, the tobacco industry has known at least since the early 1980s that the flavor of menthol is not a “significant reward” to menthol smokers.⁴⁸ Rather, the ability of menthol to provide an “extra something” to smokers has been of interest to the tobacco manufacturers who have attempted to understand menthol beyond its role as an ingredient that adds flavor to cigarettes.

While experimenting with varying ratios of tar, nicotine and menthol in test cigarettes, industry researchers discovered menthol synergistically interacts with nicotine. Nicotine levels can be reduced in cigarettes when the appropriate level of menthol is added, resulting in low delivery cigarettes that could also be appealing to consumers. Menthol’s role in the design of low delivery cigarettes, which could have lower amounts of tar and nicotine, became apparent, as tobacco manufacturers found that menthol interacted with nicotine in an “interesting way.”

Tobacco manufacturers used their findings to manipulate the impact experienced by smokers and maximize overall acceptance of tobacco products. Described as “throat grab” or “throat scratch”, impact is the tracheal stimulation shown to provide much of the immediate satisfaction gained from smoking.⁸² Tobacco manufacturers were able to predict the amount of menthol needed to attain a desired impact at any given nicotine level. By increasing the amount

of menthol up to a certain threshold level, tobacco manufacturers can design cigarettes with lower nicotine content without sacrificing impact. The use of menthol, especially in low tar delivery cigarettes, provides the strength and impact that the higher nicotine level cigarettes deliver. These findings suggest that, should nicotine levels in cigarettes be reduced, menthol levels might be adjusted by tobacco companies to compensate for the reduced impact/strength effects, potentially undermining the impact of nicotine reductions.

Menthol also plays a significant role in modulating nicotine's sensory effects. Menthol's enhancement of nicotine's physiological effects was a tool used by tobacco manufacturers to control the dosing of nicotine. By adding menthol to lower nicotine yield cigarettes, tobacco manufacturers could manipulate the smokers' perceived sensory impact.^{99, 110} As a cooling or anesthetic agent, menthol masks the harshness of tobacco and alleviates the irritation associated with nicotine, thereby making mentholated products attractive to young and inexperienced smokers.^{70, 109} Menthol, even in subliminal levels, alters the smoking experience by reducing the harshness and irritation that normally accompanies non-mentholated cigarettes.^{47, 48, 110}

Tobacco manufacturers studied menthol in order to increase their share of the cigarette market. Tobacco company scientists reviewed studies on menthol and smoking that have been published in peer-reviewed journals. Despite mixed findings in the scientific literature on how menthol affects the biomarkers of exposure to smoking, tobacco company scientists have concluded that menthol has no effect on nicotine absorption, nicotine metabolism or nicotine dependence. A review of the scientific literature revealed the tobacco industry published four articles on menthol and smoking, tobacco or topography; two are literature reviews^{17, 18} and the other two report findings from internal industry studies.^{34, 35} However, numerous articles on the effects of smoking on the biomarkers of exposure have been published and in none of these

studies was menthol as a variable considered in the analyses.³⁶⁻⁴⁶ Although menthol has clearly been of interest to the tobacco industry, its role in how smoking may affect the biomarkers of exposure has not been explored in these research opportunities.

We found no documentary evidence of any industry research on the role of menthol in nicotine dependence, nicotine metabolism, nicotine exposure, or cigarette consumption. However, the lack of documentary evidence does not clearly indicate a lack of evidence, especially given the fact that the LTDL currently exceeds 11 million documents. Therefore, searching publicly available tobacco documents archives has limitations and may not provide a comprehensive review of on-going industry research, especially those studies currently underway or recently conducted since the 1998 Master Settlement Agreement. What can be summarized from the documents that we retrieved through the LTDL is that menthol interacts directly with nicotine, affecting nicotine delivery, and that menthol has a direct influence on a smoker's sensory perception and behavior of smoking.

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APPENDIX

Appendix A: Smoking Topography Search Terms (listed alphabetically) and Results from Legacy Tobacco Documents Library

Search Terms	# of Results	# of Docs Screened	# of Docs Retrieved
“A study of smokers’ habits and attitudes with special emphasis on low tar and menthol cigarettes”	26	26	1
“addicted to menthol”	8	8	5
“Alarie menthol not “non-menthol” not dt:PRINTOUT; REPORT”	1,001	1,001	19
Appleton AND menthol [w/o dates]	2,979	400	0
“Appleton, S” menthol [docs dated 1986-1987]	133	50	2
“Applied R & D” AND menthol	13,716	100	0
“Ban menthol”	30	30	0
“Benzopyrene menthol” ~ 25 NOT “non-menthol” not dt:testimony not di:deposition	18	18	0
Butadiene AND menthol not “non-menthol”	2,363	50	0
Cotinine + nonmenthol vs. menthol NOT Publication/Published Doc/Abstract/Scientific [document type]	222	222	4
‘deBethizy menthol [docs dated 1986-87]	133	133	2
Ennis [.d] AND menthol	2,042	100	1
“First cigarette in morning” + menthol	15	15	1
“First cigarette in the morning” + menthol	245	245	1
“Free nicotine” menthol not “non-menthol”	2,818	100	0
Fruit OR “fruit-flavored” menthol not “non-menthol”	9,106	100	0
Gullotta [.f] AND menthol	2,104	250	4
“Habituated menthol” ~ 25 not non-menthol “non-menthol”	4	4	0
“Habituation menthol” ~ 25 not nonmenthol not “non-menthol”	22	22	3
India AND menthol AND inhalation not “non-menthol”	1,939	100	0
“Inhalation study” menthol not “non-menthol”	2,165	100	2
“Internal test results of tar/nicotine/menthol interaction study”	20	20	1
Jeltema AND menthol NOT “non-menthol”	2,352	100	4
Jeltema menthol nicotine	350	350	11
Lockhart (dd:1990* or dd:0000*) menthol	168	168	17
“Low tar” menthol and “non-menthol”	87,274	100	0
“Menthol addiction” ~ 25 not dt: “Printout; report” not “Non-menthol”	542	542	34
Menthol AND inhalation not “non-menthol”	14,957	250	34
“Menthol derivative”	73	73	0
“Menthol morbidity” ~ 25	35	35	4
Menthol NOT non-menthol AND nicotine AND interaction	9,941	150	23
Menthol pharmaco*	13,874	250	7
Moates AND menthol	1,309	100	0
Neuropharm* AND menthol NOT “non-menthol”	622	200	3

“Nicotine and addiction” + menthol + cotinine + letter [doc type] [date: 1988-1990]	149	149	4
“Nicotine/menthol RSM test”	1	1	1
“Nicotine receptor” AND menthol	850	100	1
N01221	76	76	5
Per:”Oey, J” menthol	131	131	3
Per:Walk menthol not (cn:pm and wsa)	216	216	20
Roethig menthol	176	176	10
“Scientific issues” AND menthol (in PM Collection)	447	447	15
Solana, Camines PM menthol	280	280	0
Suber, R AND menthol	424	424	3
Thiocyanate + nonmenthol vs. menthol NOT Publication/Published doc/abstract/scientific [document type]	95	95	0
“Throat grab” menthol NOT “non-menthol” not dt; deposition	165	165	1
Ti:ph not ti:”ph.d” menthol not “non-menthol”	423	423	11
“Tobacco blending technology” AND menthol	417	100	0
Trigeminal AND menthol replace:	1,225	300	5
Tricker Haussman “white paper” menthol	3	3	1
Tricker menthol	938	400	9
Trigeminal menthol replace* “menthol/nicotine”	54	54	0
“Wellington group”	99	99	3
WSA AND menthol (in PM Collection)	976	976	29
2023062681	3	3	1
2031421329	2	2	1
2062951249	2	2	1
TOTALS:	179,764	10,040	309

Notes: (1) An asterisk (*) indicates a “wildcard” search, such that the stem of the word indicated will yield results containing that stem. For instance, “menthol*” will yield “menthol,” “mentholated,” “mentholation,” etc. (2) A string of words in quotation marks (“”) indicates a “phrase” search, such that the string included in order within the quotation marks will be searched. For instance, “puff duration” as a single phrase will be searched. (3) A tilde (~) indicates a “proximity” search such that words appearing within a specified proximity to each other in a document will be searched. For instance, “nicotine menthol ~25” will yield documents in which the words “nicotine” and “menthol” appear within 25 words of each other.