Potential Health Effects of Menthol: A White Paper

Written by Maria Victoria Salgado, MD

Document searching by Maria Victoria Salgado, MD and Rachel Taketa, MLS

University of California, San Francisco

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Correspondence concerning this manuscript should be addressed to Maria Victoria Salgado. E-mail: salgadov@medsfgh.ucsf.edu

ABSTRACT

The objective of this paper is to assess tobacco industry views and research on potential health effects of menthol and menthol cigarettes. A search was conducted among the documents included in the Legacy Tobacco Documents Library. An initial set of words was used, followed by snowball design search. Relevant documents addressed the following subject areas: (1) pharmacology of menthol; (2) menthol's effect on nicotine metabolism; (3) short and long-term effects of menthol and menthol cigarette use, including carcinogenesis; (4) role of menthol on disease risk; and (5) menthol's effects on biomarkers of smoking exposure. It is important to underscore that, regarding the health effects of menthol, most of the information tobacco companies used and based their decisions on came from the biomedical literature and not from studies carried out by the companies themselves, who seem to have conducted very little in-house research on the subject. Although menthol pharmacology is well documented, the effect of menthol on levels of biomarkers of smoke exposure is less well examined; however, results collected in the present white paper suggest that menthol does not seem to modify them. In addition, menthol itself appears to be non-carcinogenic, though no documents related to in-house studies analyzing its role in absorption of other carcinogens were found. Reported short-term effects were rare. The tobacco industry documents did not discuss long term long term studies on menthol's health effects, making it difficult to assess any link to disease risk. We conclude that the tobacco industry works under the assumption that menthol is an innocuous and widely use additive without adverse effects.

INTRODUCTION

The Family Smoking Prevention and Tobacco Control 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.

Menthol is one of the most used additives worldwide. As proof of it, a RJ Reynolds document stated that "...mint (both peppermint and spearmint) represents the third largest taste trend worldwide. It is surpassed only by vanilla and citrus. As opposed to many other taste trends, mint appeals to all consumer groups, irrespective of age, sex, and ethnic background" [2].

The wide use of menthol in cigarettes is due to its minty flavor, aroma, cooling characteristics and physiological effects on the smoker [3,4]. 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"[5], and the market-share of filter-tipped mentholated products has ranged from 1.1% in 1956 to 27.3% in 1983 to 20% in 2006 [4,6].

Although menthol is an FDA-approved food additive, the FDA is now evaluating menthol as a characterizing cigarette flavor and has requested a review of tobacco industry documents to answer questions regarding a number of menthol cigarette-related topics (menthol's potential health effects, smoking initiation, marketing and consumer perception, possible effects on topography, potential effect on nicotine dependence and smoking cessation behavior). Questions provided by the FDA in order to assess the

knowledge and research conducted by tobacco companies on the subject of health effects of menthol, and menthol cigarettes as compared to non-menthol cigarettes, were as follow:

i. What is the overall pharmacology of menthol? What are the major pathways of metabolism of menthol? (i.e. conjugation to form glucuronides, oxidative pathways) Does menthol affect the rate of nicotine metabolism, altering smoking behavior?

ii. Does menthol affect the rate of carcinogen metabolism?

iii. What is menthols' impact on biological mechanisms? Does it alter body burdens of cotinine and carbon monoxide? Does menthol alter detoxification of carcinogens delivered in cigarette smoke? Does it alter permeability of cell membranes?

iv. What is menthol's possible role in disease risk (i.e. cardiovascular disease (CVD), cancer, respiratory illness, mental health, etc.)?

v. Are the biomarkers of smoke exposure and toxicity different for menthol smokers as compared to non-menthol smokers?

METHODS

In this qualitative research study of the digitized repository of previously internal tobacco industry documents, a snowball sampling design[7] was used to search the Legacy Tobacco Documents Library (LTDL) (http://legacy.library.ucsf.edu). We systematically searched the LTDL between June 1st and August 4th 2010, utilizing standard documents research techniques. These techniques combine traditional qualitative methods[8] with iterative search strategies tailored for the LTDL data set.

Based on the FDA staff-supplied research questions (see INTRODUCTION above), initial keyword searches combined terms related to: menthol, health effects, adverse effects, carcinogen, pharmacokinetics, pharmacodynamics, cotinine, carboxyhemoglobin, carbon monoxide. This initial set of keywords resulted in the

development of further search terms and combinations of keywords (e.g., biomarker, membrane permeation, menthol conjugation, irritancy). Of the approximately 11 million documents available in the LTDL, the iterative searches returned tens of thousands of results (see table 2, Appendix A). 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, RJ Reynolds), relevant documents were found in the following subject areas: (1) pharmacology of menthol; (2) menthol's effect on nicotine metabolism; (3) short and long-term effects of menthol, including carcinogenesis; (4) role of menthol on disease risk; and (5) menthol's effects on biomarkers of smoking exposure. A final collection of 189 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 thirty-one relevant documents that are cited in this white paper. Table 2 (see Appendix A) details the results of the searches and the number of documents screened and further reviewed.

RESULTS

Table 1: RESEARCH QUESTIONS AND SUMMARY OF ANSWERS

Question	Summary of answers based on review
1) What is the overall pharmacology of menthol? What are the major pathways of metabolism of menthol? (i.e. conjugation to form glucuronides, oxidative pathways) Does menthol affect the rate of nicotine metabolism, altering smoking behavior?	• Secondary alcohol, naturally occurring monocyclic terpene • Four pairs of enantiomorphic forms for each diasteroisomers (d- and l-), and four dl- forms (racemates) • Only l- and dl- menthol impart the desired cooling effect • L-menthol: natural / dl-menthol: synthetic • Absorption: multiple routes (orally, skin, peritoneal injection, inhalation) • Metabolism: metabolized via conjunction with glucuronic acid in the liver • Excretion: in the urine • Nicotine metabolism: doesn't seem to be affected, but this topic was addressed in another white paper (see Valerie B. Yerger, ND, *"Menthol's Potential Effects on Nicotine Dependence: A White Paper"*)
2) Does menthol affect the rate of carcinogen metabolism?	Industry's view is that menthol has no carcinogenic effect itself and it does not increase the carcinogenic risks of other substances, although we were not able to find documents specifically comparing the rate of absorption of carcinogens between menthol and non-menthol smokers.
3) What is menthols' impact on biological mechanisms? Does it alter body burdens of cotinine and carbon monoxide? Does menthol alter detoxification of carcinogens delivered in cigarette smoke? Does it alter permeability of cell membranes?	• Data about menthol's effect on biomarkers of smoking exposure found among the documents tends to suggest that menthol does not affect the levels of those biomarkers, although the information may not be conclusive. • We were not able to find documents that linked menthol to detoxification of carcinogens using research conducted by the tobacco industry • Possible deterioration of biological membranes
4) What is menthol's possible role in disease risk (i.e. cardiovascular disease (CVD), cancer, respiratory illness, mental health, etc.)?	Except for cancer, we were not able to find documents linking menthol to disease risk Short term effects seem to be rare
5) Are the biomarkers of smoke exposure and toxicity different for menthol smokers as compared to non-menthol smokers?	Question previously addressed (see question 3). Also, please refer to: Valerie B. Yerger, ND, *"Menthol's Potential Effects on Nicotine Dependence: A White Paper"*.

i. What is the overall pharmacology of menthol? What are the major pathways of metabolism of menthol? (i.e. conjugation to form glucuronides, oxidative pathways) Does menthol affect the rate of nicotine metabolism, altering smoking behavior?

Several tobacco industry documents addressed the pharmacology of menthol, summarized below.

Structure and Stereochemistry.

Menthol, a secondary alcohol having the formula $C_{10}H_{20}O$, is a naturally occurring monocyclic terpene with numerous isomers [9-11]. It contains 3 asymmetric carbons, and therefore 4 geometrical isomers (diastereoisomers) exist. They are called menthol, isomenthol, neomenthol, and neoisomenthol. These geometrical isomers also exist in the d- and l- forms, making a total of four pairs of enantiomorphic forms for each diasteroisomers, and four dl- forms (racemates) [10]. The characteristic flavor of l-menthol is dependent on its conformation.

Synthesis

Of the menthol isomers, only 1-menthol and dl-menthol are of large-scale commercial importance [10], with only l-menthol imparting the well-known desired cooling effect [9].

l-menthol occurs in nature, mainly in its free state, in peppermint oils obtained from various species of *Mentha piperita* and *Mentha arvensis* and has been known since early history [9]. Natural l-menthols from different areas of the world (i.e., from different species and varieties) have slightly different crystal structures and specific rotations as well as slightly different flavor notes (no doubt due to very small impurities) [9].

Methods for obtaining dl-menthol, a synthetic form of menthol, were developed due to a decrease in production with a concomitant increase in the price of menthol in the 70´s. During that decade, Brazil, menthol's main producer at that time, started to suffer the consequences of destructive cultivation methods (destructive monoculture), and the rising production in other countries could not compensate for the decline in areas available for cultivation. As a result of multiple efforts to produce synthetic menthol, several methods are currently available [9].

Absorption, metabolism and excretion

Menthol can be absorbed orally, through skin, through peritoneal injection and through inhalation [9,12,13].

Pyrolysis of menthol in the burning cone of a cigarette is not expected due to its high vapor pressure and low boiling point [14]. A 1985 document from RJ Reynolds summarized the results of a study conducted in 1966 in which menthol was labeled using ^{14}C-menthol and then smoked:

> "About 42 % of the radiolabel was found in the mainstream solids with 96% of this being in unchanged menthol; 33 % of the activity was recovered in the sidestream solids with 92% being in unchanged menthol. Approximately 20% of the label was located in the butts and filters and about 4% in the mainstream and sidestream gases." [15]

Tobacco companies understood that, once absorbed, menthol was primarily metabolized via conjugation with glucuronic acid in the liver, and excreted in the urine as the glucuronide [16]. Regarding other pathways of metabolism, a document from the Brown & Williamson collection (1986) noted:

> "…the metabolic fate of the menthol that is not conjugated is unknown",

but it was stated, based on results from the biomedical literature, that:

> "…it is possible that ring fission occurs with considerable degradation of the menthol molecule" [4].

A 1978 document from British American Tobacco [17] described two studies performed using humans subjects. Participants were told to smoke mentholated cigarettes during their work day. Later, a urine sample was collected in all cases and a blood sample only in one of the studies. No increase in l-menthol blood levels was found among people smoking up to 21 cigarettes in an eight-hour period. Neither was there any indication of an increase or an accumulation in the blood of l-menthol conjugate due to smoking at this rate. No free l-menthol was found in urine samples of smokers, which indicates that any retained l-menthol was rapidly conjugated [17].

The pattern of excretion described involved an increase in urine concentration of conjugated l-menthol during the smoking period, with 80-90% of the conjugated excreted during the smoking period plus four hours. Excretion rate was maximal at the end of the smoking period and rapidly reduced when smoking stopped [17].

Studies conducted by British American Tobacco in different animals also suggested that a small fraction of conjugated menthol was excreted through feces [13,18], although we were not able to find a study that described the same phenomenon in humans among the tobacco documents.

Actions. Cooling effect

A 1994 document from the Lorillard collection that summarized different investigations regarding menthol commented about a 1993 TCRC presentation:

> "Menthol affects the response of many receptors to stimulation. The response to menthol is enhanced in small concentrations and depressed in large concentrations or after exposure. The electrophysiological response to menthol was first demonstrated for thermal receptors, then for chemoreceptors of the carotid body..." [19]

Both the previously mentioned document and one from RJ Reynolds (1984) [9] stated that cooling effect is not obtained by volatilization but seems to result from chemical action at or near those nerve endings which are associated with the sensation of cold. [9,19]

Nicotine metabolism and menthol

Another white paper has already addressed this issue (please, refer to: Valerie B. Yerger, ND, *"Menthol's Potential Effects on Nicotine Dependence: A White Paper"*, question iv: what is menthol's effect on nicotine metabolism?) [20]. Nevertheless, it is worth noting here a RJ Reynolds document from 1994. It described a study in which they measured the urinary nicotine metabolic output among seventeen volunteers (9 male and 8 female) smoking the brand "Premier", and stated in its summary that "Smokers of menthol Premier absorbed much less nicotine than smokers of non-menthol Premier" [21]. The same document later reported:

> "…it is difficult to separate the influence of gender and menthol for measured nicotine output" [21].

Finally, the authors commented on these findings in the following way:

> "The greatly reduced nicotine absorption by menthol cigarette smokers is not as easily reconciled. Menthol cigarette smokers are not distinguished by gender or weight but absorb only 54% of the nicotine that nonmenthol cigarette smokers absorb. In addition, they smoked 65% of the cigarettes smoked by nonmenthol cigarette smokers. The impact of smoke laced with menthol may be a factor here and this observation should be examined further" [21]

Other documents seem to be more categorical in their conclusions. For example, a study conducted by Lorillard (and found among the RJ Reynolds collection, 1995), where rats were exposed to mentholated or regular cigarette smoke for an hour a day, five days a week, over the course of 13 weeks, concluded:

> "Addition of menthol to the tobacco did not significantly alter the serum nicotine or cotinine levels in smoke-exposed rats" [14].

ii. Does menthol affect the rate of carcinogen metabolism?

The risk of cancer due to menthol use is widely analyzed in abstracts, published journal articles and industry responses to those articles among the tobacco documents, but studies conducted by the tobacco industry specifically testing menthol and carcinogenicity have not been as prevalent. Some documents analyzed the potential for carcinogenesis of menthol itself, but we were not able to find any that referred specifically to a carcinogenetic effect of menthol through changes in the absorption of other cigarette components.

In 1963, the Liggett & Myers tobacco company prepared a report for the Surgeon General's advisory committee on smoking and health. They performed long-term carcinogenicity assays in mice and rabbits. Regarding an experiment using 100 female mice, and among other conclusions, they noted:

> "… the condensate prepared from a mentholated king-size filter cigarette. The incidence of tumors was not significantly different from that observed with condensates from non-mentholated cigarettes." [22]

Philip Morris conducted an experiment testing the potential of various cigarette components (benzo(a)pyrene, acetaldehyde, formaldehyde, menthol, ethanol, among others) in developing lymphoma, using a special strain of mice (L5178Y/TK'- mouse lymphoma point mutation assay). Using the specific activity parameter for comparison purposes, menthol was found to have one of the lowest activities of the 15 materials evaluated:

> "When the menthol activity was evaluated on a µg or molar basis, menthol had consistently lower activity which was orders of magnitude lower than other test materials." [23]

A 2001 report prepared by Philip Morris analyzing both in house and external studies concluded:

> "Menthol has a low order of acute toxicity and has been demonstrated to be non-carcinogenic and non-teratogenic." [24].

Another document from the Philip Morris collection stated that there was no evidence of carcinogenicity of menthol in rats or mice [25].

Along the same line of reasoning, an RJ Reynolds memorandum from 1985 cited a study from the National Cancer Institute in which menthol was not determined to be carcinogenic [15].

iii. What is menthols' impact on biological mechanisms? Does it alter body burdens of cotinine and carbon monoxide? Does menthol alter detoxification of carcinogens delivered in cigarette smoke? Does it alter permeability of cell membranes?

Tobacco companies were concerned about possible adverse effects of menthol and its impact on biological mechanisms, although most of the information they had and used came from literature reviews, not from in-house studies.

A 1988 document from RJ Reynolds described a protocol for an inhalation study that would compare toxicological responses produced by exposure to smoke from menthol and non-menthol test and reference cigarettes in rats [26]. Variables like weight and plasma levels of cotinine, nicotine and carboxyhemoglobin were recorded in both menthol and non-menthol groups. Raw data can be found in several documents [27-29], but results obtained when comparing the exposure to smoke from the reference menthol and non-menthol cigarettes were discarded:

> "…comparisons made between the non-menthol K1R4F reference cigarette and the PD-2756B menthol-containing reference cigarette. No valid comparisons between the K1R4F and the PD-2756B are possible because the two reference cigarette configurations are substantially different (...)
>
> The PD-2756B menthol-containing reference cigarette was designed to match the menthol Premier cigarette (8-033 B) in terms of delivery of WTPM and was much different from the KIR4F reference cigarette in terms of physical components." [30]

In 1997, Lorillard published a study using a similar protocol, and the respective document can be found among the RJ Reynolds collection at the LTDL. In this study, two different groups of rats inhaled through the nose smoke coming from either non-menthol (reference) or menthol cigarettes (21 per sex for reference and 15 per sex for menthol) for an hour a day, five days a week, over the course of 13 weeks. Within each groups, three different concentrations of target smoke were used, 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." [31]

In the results section, the following table was presented summarizing findings on serum levels of nicotine, cotinine, and carboxyhemoglobin:

Table 2. Summary of biomarkers used to monitor exposure to reference or mentholated tobacco smoke

Parameter	Group	Target smoke concentration (mg/m³) 0	200	600	1200
Exposure					
Serum nicotine (ng/ml)	Air control	0	—	—	—
	Reference	—	77.9 ± 25.1	170.3 ± 57.2	310.0 ± 134.9
	Menthol	—	69.3 ± 22.4	174.0 ± 57.7	250.9 ± 60.4
Serum cotinine (ng/ml)	Air control	1.3 ± 0.7	—	—	—
	Reference	—	144.1 ± 20.1	189.1 ± 33.7	290.0 ± 75.6
	Menthol	—	118.6 ± 21.6*	196.6 ± 44.1	266.8 ± 60.5
Carboxyhaemoglobin (%)	Air control	2.0 ± 0.5	—	—	—
	Reference	–	9.9 ± 1.8	22.1 ± 3.6	34.8 ± 6.3
	Menthol	–	8.5 ± 11.9*	18.8 ± 2.6*	30.1 ± 6.5*
Recovery					
Serum nicotine (ng/ml)	Air control	†	—	—	—
	Reference	—	†	†	†
	Menthol	—	†	†	†
Serum cotinine (ng/ml)	Air control	2.3 ± 0.5	—	—	—
	Reference	—	2.1 ± 0.3	2.7 ± 0.6	5.8 ± 6.1
	Menthol	—	1.4 ± 0.2	1.8 ± 0.3	2.1 ± 0.5*
Carboxyhaemoglobin (%)	Air control	0.2 ± 0.1	—	—	—
	Reference	—	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
	Menthol	—	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1

Values are the means ± SD of six rats sampled on alternating weeks for carboxyhaemoglobin, or nicotine and cotinine (n = 38–41 for carboxyhaemoglobin and 23–24 for nicotine and cotinine).
†Below the limit of detection (0.78 μg/ml).
Asterisks indicate significant difference from reference cigarette (*$P \leq 0.05$; ANOVA and Tukey's HSD tests).

Later in the document, it was stated that:

> "A trend towards lower carboxyhaemoglobin in rats exposed to mentholated cigarette smoke compared with reference cigarette smoke was consistent with the reduced smoke carbon monoxide concentration observed for the menthol smoke exposures" [31]

It was also seen that, at the higher target smoke concentration, cotinine levels were lower among the menthol group, although the finding was considered to be "apparently incidental".

Regarding other biological effects such as weight, it was reported that both exposed groups had body weights significantly lower than the control group, but that did not differ between the two. Other parameters were not different among the exposed groups.

The final conclusion stated 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." [31]

A 1999 Lorillard document compared nicotine and carbon monoxide yields for all domestic menthol and non-menthol cigarette brands. Three hundred and fifty-four non-menthol brands and one hundred and sixty-seven menthol brands were compared, and information regarding nicotine and carbon monoxide was obtained from The Tobacco Institute Testing Laboratory (TITL) data from 1996. Utilizing the Kolmogorov-Smirnov two-sample test (used to determine whether two populations have the same distribution), they concluded that:

> "…the two carbon monoxide cumulative distributions for domestic menthol and non-menthol brands were not significantly different"

The same document stated before that this result would suggest that the addition of menthol didn't affect delivery of carbon monoxide [32].

We were not able to find documents that linked menthol to detoxification of carcinogens using research conducted by the tobacco industry. Regarding the effect of menthol on cell permeability, a study published in 1983 and partially funded by the Swedish Tobacco Company analyzed the toxicity of menthol on 4 different in vitro systems. In that article, authors suggested that:

> "…one effect of menthol is a deterioration of biological membranes" [33]

A 1995 document found among the Philip Morris collection summarized the medical literature regarding the following themes [34]:

> "African-American men are more vulnerable than white men to several tobacco-related cancers."
>
> and
>
> "Menthol in cigarettes may facilitate carcinogenesis."

In the former, special consideration was given to the possibility of permeability enhancement by menthol and different studies were searched regarding this topic. Among all of them, the following phrases were chosen for citation:

- "The irritant effect of menthol together with the lipophilic nature of menthol may aid topical drug penetration." [35]
- "Menthol (1 to 5 % w/v) on hairless mouse skin can aid the penetration of:
    - Indomethacin and cortisone" [36]
    - Morphine hydrochloride" [37]
    - Methyl salicylate" [38]
- "Further enhancement in combination with ethanol" [39,40]

The research team that created the report made no comments about these conclusions in the document [34].

iv. What is menthol's possible role in disease risk (i.e. cardiovascular disease (CVD), cancer, respiratory illness, mental health, etc.)?

Searching among the tobacco document archives, we were not able to find documents linking menthol to disease risk (except for cancer, an issue that was addressed previously). A literature review performed by RJ Reynolds and reported in a 1984 document [9] stated that no long-term studies (greater than 1 year) of the effects of menthol cigarettes were found in the literature, and that while case studies in man had appeared, the results were questionable because of lack of adequate controls. A 1999 Philip Morris document that reviewed the literature remarked that most studies using human subjects were case reports and conclusions were therefore anecdotal. It also concluded that, considering the ubiquitous use of menthol, it was almost certain that the presence of clinical symptoms were due to instances of extreme exposure [11].

Even though we were not able to find documents about disease risk, the ones about short-term clinical effects of the use of menthol are worthy of notation. The RJ Reynolds literature review cited previously [9], when talking about short-term outcomes, made reference to a study compiling the effects of menthol in the following way:

> "The effects of menthols administered by varying routes on functions of heart, kidney, liver, smooth muscle, and central nervous system of cats and rabbits were reported by Macht [41]"

and, although it does not mention the results of such study, it concluded that:

> "No detrimental effects of menthol were observed in short term biological studies"

and:

> "Menthol can stimulate the central nervous system but is not used for this purpose"

About this last conclusion, another section of the document stated that menthol is considered a brain stem stimulant and can cause clonic convulsions in very large doses.

Regarding medical uses of menthol, this document reported that it has antipruritic properties and has been used for the relief of nasal congestion, headaches, and neuralgia.

An interesting document from RJ Reynolds (1998) stated that "there is little reason to believe that menthol as a flavorant in cigarettes has any psychoactivity, but we are not aware of any studies expressly addressing this issue". [42]

That document described a study that compared heart rate and electroencephalographic (EEG) activity among menthol and non-menthol smokers using denicotinized cigarettes (in order to study the effects of menthol independently of the effects of nicotine).

After stating that it was unknown the role played by racial balance in the results, the following can be read in the discussion section:

> "Menthol smokers did show a greater increase in HR following smoking either cigarette (around 5 bpm) than did non-menthol smokers (around 2 bpm). This did not appear to be due to greater smoke intake, since a parallel finding with respect to pre- to post-smoking increase in tidal-breath CO was not seen."
>
> "Menthol smokers globally had a slower eyes-closed dominant alpha frequency (DAF) than non-menthol smokers by over half a Hertz. This indicates that as a group menthol smokers may be less aroused than non-menthol smokers." [42]

A Philip Morris document from 1998 reported the results from studies regarding the irritant potential of menthol. Two studies evaluating primary skin irritation informed no dermal irritation. Two experiments were also conducted in which homogenized microcapsules were instilled into rabbit's eyes, and tested for irritation 1, 24, 48 and 72 hours later. In one of the studies, the menthol preparation was considered to be non-irritating to the eye. The other one concluded the material was minimally irritating [23].

A 1984 document from the RJ Reynolds collection summarized toxicological data on menthol in the following way:

> "In dermal testing in humans, menthol was non-irritating. However in certain rare instances, menthol has been reported to cause adverse reactions in some individuals. Most of these effects are manifestations of allergic hypersensitivity; they are transitory and rapidly disappear when exposure to menthol is ended"

No source for this information was quoted [43].

v. Are the biomarkers of smoke exposure and toxicity different for menthol smokers as compared to non-menthol smokers?

This question was previously addressed in the present white paper (see question iii.: "What is menthols' impact on biological mechanisms? Does it increase body burdens of cotinine and carbon monoxide?").

It's also important to note that another white paper widely described the industry knowledge and thoughts about biomarkers of smoking exposure (please, refer to: Valerie B. Yerger, ND, *"Menthol's Potential Effects on Nicotine Dependence: A White Paper"*, question i.: What are the addiction and exposure measures and what is their relationship to menthol cigarette use?). [20].

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 (over 60 million pages) 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 nine-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 potential health effects of menthol. 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 health effects 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." [44] Brown and Williamson used the code terms, such as "Kintolly," "Tolkin," "Harpat," "Polar Bear," and "Cenmap" when referring to menthol[45], although those terms were not found among the cited documents. 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.

DISCUSSION

Menthol's role in the smoking experience makes it a relevant substance for the tobacco industry. The health effects of menthol alone and its interaction with other cigarette components are widely analyzed among the tobacco library documents. But it is important to remark that most of the information tobacco companies used and based their decisions on came from the biomedical literature and not from studies carried out by the companies themselves, who seem to have conducted very little in-house research on the subject.

The health effects of menthol were (and are) of particular importance for the industry. Any evidence of adverse effects of menthol itself could lead to restrictions in its use, though it has been safely used in foods and confections for hundreds of years. However, this does not necessarily mean that its addition to cigarettes as a characterizing flavor is innocuous.

Menthol pharmacology is well known and there does not seem to be discrepancies about its pharmacological properties. Both natural and synthetic methods have been developed for obtaining menthol.

Data about menthol's effect on biomarkers of smoking exposure found among the documents tends to suggest that menthol does not affect the levels of those biomarkers, although the information may not be conclusive.

It is not evident from searching the tobacco library documents that menthol has adverse long-term effects, although the industry recognized that well done research had not been conducted in this area. This lack of information makes it difficult to analyze menthol's role in disease risk. In addition, short term effects seem to be rare.

Regarding its role in carcinogenesis, it seems that the industry's view is that menthol has no carcinogenic effect itself and it does not increase the carcinogenic risks of other substances, although we were not able to find documents specifically comparing the rate of absorption of carcinogens between menthol and non-menthol smokers. Also, biomedical literature may challenge this supposition. For example, a paper published in 2006 observed "markedly different extents of permeation and reservoir formation for the tobacco carcinogens applied to porcine esophageal mucosa in the presence of ethanol and menthol" [46].

Even though the information found in the documents may not be the most current, it is unlikely that new research fundamentally changes tobacco companies' views. Based on the documents reviewed, we conclude that the industry works under the assumption that menthol is an innocuous and widely use additive without adverse effects.

APPENDIX A

Table 2: Search term and results

Search Terms	# of Results	# of Docs Screened	# of Docs Retrieved
metabolism menthol*	8627	100	9
glucaronides menthol*	5	5	0
oxidative pathways menthol*	40	40	0
(menthol cotinine) NOT dt:publi*	5925	50	2
(menthol NOT "non-menthol") AND cotinine NOT (dt:publi* OR dt:bib*)	3933	50	7
toxicity study of menthol	386	100	3
(menthol NOT "non-menthol") AND pharmacology NOT (dt:publi* OR dt:bib*)	4239	50	8
((menthol NOT "non-menthol") AND metabolism) NOT dt:publi*	5712	150	10
((menthol NOT "non-menthol") AND carcinogen) NOT dt:publi*	4504	100	3
(menthol NOT "non-menthol") (permeable OR permeability) cell	3717	150	5
((menthol NOT "non-menthol") AND ("side effects" OR "adverse effects")) NOT dt:publi*	4835	100	5
menthol (cancer OR tumor)	39136	100	0
(menthol AND (cancer OR tumor)) NOT dt:publi*	33230	100	6
behavior metabolis* menthol NOT dt:publi*	3772	100	4
(menthol NOT "non-menthol") (pyroliz* OR pyrolysis) toxic* NOT dt:publi* NOT dt:bib*	4845	100	5
menthol AND (cvd OR "cardiovascular disease") NOT dt:publi* NOT dt:bib*	3962	100	9
menthol carbon monoxide ~10 NOT dt:publi* NOT dt:bib*	1667	100	7
menthol pathway ~10 NOT dt:publi* NOT dt:bib*	49	49	3
menthol pharmacokinetics ~10 NOT dt:publi* NOT dt:bib*	45	45	6
menthol pharmacodynamics ~10 NOT dt:publi* NOT dt:bib*	7	7	0
menthol mucus secretion NOT dt:pub*	628	150	7
glucuranidase OR "liver damage"	589	100	0
au:alarie "sensory irritation"	47	47	1
menthol "sebaceous gland suppression"	200	100	1
menthol (oral OR mouth) mucosa permeability	918	100	1
menthol nicotine metabolism ~10 NOT dt:publi* NOT dt:bib*	15	15	2
pharmacokinetics menthol	1992	100	3
nicotine metabolism menthol ~10 NOT dt:publi* NOT dt:bib*	27	27	1

TRD-ATS-017	338	60	7
BIBRA menthol study	443	50	17
TRD-ATS-017 AND protocol	72	10	3
menthol cotinine ~5 NOT dt:publi* NOT dt:bib*	73	73	3
premier AND carboxyhemoglobin AND menthol NOT (dt:publi* OR dt:bib*)	274	50	2
menthol AND ("carcinogen absorption" OR "carcinogen metabolism" OR "absorbed carcinogen") NOT dt:publi* NOT dt:bib*	96	96	1
menthol conjugation ~10 NOT dt:publi* NOT dt:bib*	34	34	4
glucuronide AND menthol NOT dt:publi* NOT dt:bib*	632	100	4
menthol carcinogen detoxification NOT dt:publi* NOT dt:bib*	422	100	3
menthol AND (respiratory disease OR copd OR chronic obstructive pulmonary disease" OR asthma)" ~10 NOT dt:publi* NOT dt:bib*	0	0	0
parexel (menthol OR kintolly)	46	46	1
pm total exposure study tes	18434	100	3
521023219	1	1	1
508296951	2	2	1
“total exposure study” ~3 AND menthol	222	70	1
menthol "mouse irritancy"	6	6	0
menthol biomarker ~10 NOT dt:publi* NOT dt:bib*	5	25	1
menthol %COHb ~10 NOT dt:publi* NOT dt:bib*	48	48	7
JLI and menthol	2948	65	0
PAMPA AND Lorillard AND BaP AND NNK	2	2	0
PAMPA AND BaP AND NNK	9	9	0
membrane AND permeation AND menthol AND PAMPA	3	3	0
“membrane permeation” ~5 AND menthol	26	26	0
IN VITRO EFFECTS OF MENTHOL ON CYTOCHROME P450 ENZYMES	532	50	2
double-strand dna menthol cytotoxicity vitro	34	34	0
Kabat and Hebert and Lorillard	120	120	1
menthol AND permeation AND acrolein AND PAMPA AND spectroscopy	1	1	0
CYP AND menthol AND nicotine AND inhibition AND nitrosamine	123	123	0
CYP AND inhibition AND menthol AND nicotine	169	100	0
DNA AND cytotoxicity AND menthol AND PAH	470	65	1
Bernson AND Pettersson AND membrane AND menthol	104	50	2
Bertil Pettersson AND menthol	12	12	0
Margareta Curvall AND menthol	100	50	0
account 0087 ~5	11	11	0
ciliastasis menthol~15	16	16	0

(BIBRA AND "Life Science Research") OR (BIBRA AND LSR)	280	50	5
tolkin OR harpat OR cenmap	312	100	0
("menthol carcinogen"~10) NOT dt:publi* NOT dt:bib*	33	33	4
Pace AND menthol AND nicotine AND toxicologist AND 2010 and "in vitro"	67	67	0
("menthol biological mechanism"~10) NOT dt:publi* NOT dt:bib*	3	3	0
(TES OR "Total exposure study") AND menthol AND (nicotine equivalents OR NE) AND cotinine AND (carboxyhemoglobin OR COHb) AND serum	521	50	0
“Total exposure study” AND menthol AND "nicotine equivalents" AND cotinine AND (carboxyhemoglobin OR COHb) AND serum	0	0	0
(TES OR "Total exposure study") AND menthol AND willebrand AND monocyte AND prostaglandin	7	7	0
Menthol Consensus Team AND (PM OR Philip Morris)	0	0	0
Menthol Consensus Team	5	5	0
("menthol toxicity"~10) NOT dt:publi* NOT dt:bib*	661	50	7
TOTAL	**160769**	**4208**	**189**

APPENDIX B

Tobacco companies recently presented their submissions to the TPSAC about menthol. Using the information provided, we conducted searches in order to find the in-house studies they reported or the documents they mentioned. In all cases, if the search resulted in more than 100 documents, we reviewed the first 50 or 100.

R.J. Reynolds Tobacco Company:

A list of bates numbers was provided as having relevant information. Of that list, we were unable to find the following documents in either the Legacy Tobacco Library or the RJ Reynolds document website (http://rjrtdocs.com/rjrtdocs//index.wmt?tab=home):

556492215-2242;
545003994-4029;
521215985-5990;
521216071-6075;
521216160-6164;
525101670-1703;
524695089-5091;
525100688-0691;
545023031-3080;
521073388-3420

Lorillard Tobacco Company:

When referring to "Studies addressing the dosing relationship and the metabolic interactions between nicotine and menthol…", the authors mentioned the following studies (among others):

- "Recently, Lorillard researched the potential effect of menthol on membrane permeation. Lorillard examined the influence of menthol on the permeation of acrolein, benzo(a)pyrene (BaP) and NNK using a parallel artificial membrane assay (PAMPA) system."

  We conducted the following searches, but were not able to find this study:

  - PAMPA AND Lorillard AND BaP AND NNK
  - PAMPA AND BaP AND NNK
  - membrane AND permeation AND menthol AND PAMPA

- "membrane permeation" ~5 AND menthol
- menthol AND permeation AND acrolein AND PAMPA AND spectroscopy

➢ "Lorillard scientists conducted *in vitro* enzyme inhibition experiments using recombinant human CYP2A6, CYP2A13, CYP1A2 and CYP2E1 to investigate the potential of menthol to inhibit nicotine metabolism…"

We conducted the following searches, but were not able to find this study:

- IN VITRO EFFECTS OF MENTHOL ON CYTOCHROME P450 ENZYMES
- double-strand dna menthol cytotoxicity vitro
- CYP AND menthol AND nicotine AND inhibition AND nitrosamine
- CYP AND inhibition AND menthol AND nicotine
- DNA AND cytotoxicity AND menthol AND PAH

Altria Client Services, on behalf of PM USA:

A chapter was devoted to the Total Exposure Study or TES. We found several documents related to this study but we were not able to find documents related to the mentioned health effects of menthol.

Search terms used:

- pm total exposure study tes
- "total exposure study" ~3 AND menthol
- (TES OR "Total exposure study") AND menthol AND (nicotine equivalents OR NE) AND cotinine AND (carboxyhemoglobin OR COHb) AND serum
- "Total exposure study" AND menthol AND "nicotine equivalents" AND cotinine AND (carboxyhemoglobin OR COHb) AND serum
- (TES OR "Total exposure study") AND menthol AND willebrand AND monocyte AND prostaglandin

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