Reference Addendum:

Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol versus Nonmenthol Cigarettes

Food and Drug Administration

Contents

Reference Addendum to the "Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol versus Nonmenthol Cigarettes"

The "Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol versus Nonmenthol Cigarettes" was submitted for Peer Review in August 2011. Since that time, several peer-reviewed articles have been published that relate to this topic. This reference addendum provides a summary of updated research relevant to the full scientific review.

On March 27, 2013, a systematic literature search was conducted in the PubMed database using the search term "menthol" and including articles published between July 1, 2011 and March 27, 2013. As with the full scientific review, only original peer-reviewed publications were used. Basic information on menthol has been included here only as background; as with the full scientific review, this addendum is not intended to be a comprehensive review of menthol itself but rather menthol as related to its use in menthol cigarettes. General methodology caveats (e.g., self-report) and descriptions (e.g., TRPM8 channels, large national surveys) were discussed in the full scientific review, and will not be duplicated here.

NOTE: The 2012 SGR, "Preventing Tobacco Use Among Youth and Young Adults", did not contain any information on the public health effects of menthol versus nonmenthol cigarettes that was not included in the original report.

Smoke chemistry and nonclinical toxicology

Seven additional articles regarding the association between menthol in cigarettes and smoke chemistry and nonclinical toxicity were reviewed.

Smoke chemistry

One study compared the Federal Trade Commission (FTC)-measured nicotine levels of menthol and nonmenthol cigarette brands smoked by smokers who participated in the 2001-2006 National Health and Nutrition Examination Survey (NHANES), a nationally representative household survey. Participants either provided a cigarette pack or information on their usual brand, and Universal Product Code information was used to verify menthol versus nonmenthol classification. The researchers found that the brands of menthol cigarettes smoked by African Americans had a higher average FTC nicotine level than the menthol cigarettes smoked by White smokers (Caraballo et al., 2011).

In another study, cigarettes with four different menthol levels were created and smoked through a linear-port smoking machine. The collected total particulate matter (TPM) was analyzed for menthol,

nicotine, tobacco-specific nitrosamines (TSNAs), polynuclear aromatic hydrocarbons, cotinine, and quinolone, and whole smoke was collected for measurement of volatile organic compounds. Although differences in the amount of menthol present in the TPM existed, there were no differences in any of the other target constituents. Thus, while menthol in TPM increased in a linear fashion, the other measured constituents remained unchanged (Gordon et al., 2011).

Using the Health Canada method of machine smoking, Bodnar and colleagues (2012) compared levels of 19 constituents in 61 brand styles of fire-standard compliant cigarettes. The researchers found few differences in the measured levels of constituents between menthol and nonmenthol cigarettes. In some cases, for some styles, there were greater levels of a constituent (e.g., 2-aminonaphathalene, catechol) in menthol cigarettes, while levels of other constituents (e.g., benzo[a]pyrene, catechol, crotonaldehyde) were greater for nonmenthol cigarettes. There was no consistent direction of difference and, in the case of catechol, the difference occurred in the opposite direction when "full flavor" and "lights" were compared (Bodnar, Morgan, Murphy, & Ogden, 2012).

Brinkman and colleagues (2012) examined participant-specific mainstream smoke for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), nicotine, ultrafine and fine particulate matter by simulated use (used topography measurements) using a programmable linear smoking machine. Overall, the researchers found no differences in fine particulate matter between menthol and nonmenthol test cigarettes. However, a significantly larger mass of ultrafine particulate was collected from the menthol cigarettes ($p<0.05$) (Brinkman et al., 2012).

Menthol as a singular compound – toxicology, pharmacology and therapeutic applications

Another study found that, when added to mucoadhesive patches, menthol increased permeability of the oral mucosa, as measured with a porcine buccal tissue preparation. This allowed greater absorption of fenretinide, a chemopreventive compound (Wu et al., 2012).

Antiproliferative effects of menthol as a singular compound

Valero and colleagues (2012) examined the effects of menthol on cell survival and cell proliferation of normal and cancerous human prostate cell lines. The prostate-derived cell lines were cultured, expression of TRMP8 receptors was confirmed, and proliferation was estimated using the methyl tetralam (MTT) assay (which assesses metabolic activity). Menthol increased metabolic activity but there was no consistent change in growth after stimulation of TRPM8 channels with menthol (Valero, Mello de, Stuhmer, Viana, & Pardo, 2012).

In vitro toxicity of menthol tobacco exposure

Fowler and colleagues (2012) treated six cell types (rodent cell lines V79, CHL and CHO, p-53 competent human peripheral blood lymphocytes, TK6 human lymphoblastoid cells, and the human liver cell line HepG2) with racemic menthol. Treatment with menthol was cytotoxic. However, the authors suggest that this is a "false positive" since there was no genotoxic effect as measured by micronucleus induction. The authors note that testing was limited by cytotoxicity, and even though required levels of cytotoxicity

were induced, micronucleus induction was not (Fowler et al., 2012). Thus, the dose-response curve may have been too narrow to detect micronucleus induction.

Conclusion

The addition of these articles did not change the finding of the full scientific review, namely that the weight of evidence supports the conclusion that, from a nonclinical toxicity standpoint, menthol in cigarettes is not associated with either increased or decreased smoke toxicity.

Physiology

Seventeen additional articles regarding the association between menthol in cigarettes and physiological response to tobacco smoke were reviewed.

Sensory effects

The effect of menthol on cough threshold was evaluated in 13 subjects (12 nonsmokers) during single-inhalation capsaicin challenges. Inhalation of menthol vapor prior to measuring cough thresholds resulted in reduced sensitivity to cough in some subjects. That is, for some, but not all, of the subjects, the amount of capsaicin needed to trigger a cough response was increased following menthol vapor exposure. The authors concluded that adding menthol to cigarettes may increase the tolerability of tobacco smoke by reducing the sensitivity of an airway defense mechanism (coughing) (Wise, Breslin, & Dalton, 2012).

A study of 14 patients with chronic cough and airway sensitivity to environmental irritants and 15 control subjects evaluated the effect of inhaling nebulized menthol on cough threshold provoked with capsaicin inhalation. Inhaled menthol reduced cough sensitivity to the inhaled capsaicin and influenced inspiratory flows in the patients, an effect that did not occur in the control group ($p<0\text{-}05$). Furthermore, in people with chronic cough (without asthma, chronic obstructive pulmonary disease or infection), pre-inhalation of menthol reduced the threshold to capsaicin-stimulated cough ($p<0.05$). The authors state that “the use of menthol in different cigarette brands could be questioned since it could conceal the natural irritation following smoking” (Millqvist, Ternesten-Hasseus, & Bende, 2013).

The somatosensory effects of topically-applied capsaicin and menthol were assessed in a cross-over study with 15 subjects. When menthol was topically applied to the gingiva, nine subjects reported mild levels of pain. Pain ratings were lower than those reported following application of capsaicin, and were also more short-lived. Menthol elicited hypersensitivity to both cold and warm stimuli (Lu, Baad-Hansen, List, Zhang, & Svensson, 2013).

A laboratory study involving 22 adults (age 21-46 years) investigated the effect of menthol on stimulated nasal irritation. In this study, participants simultaneously sniffed clean air into one nostril while sniffing a chemical vapor into the other. Acetic acid and allyl isothiocyanate produced nasal irritation, and menthol pretreatment had different effects. Menthol exposure prior to stimulation with acetic acid resulted in decreased sensitivity to irritation but prompted increased sensitivity to allyl isothiocyanate ($p<0.005$). Thus, menthol can modify irritating stimuli differently (Wise, Preti, Eades, & Wysocki, 2011).

In another study, researchers applied the irritant capsaicin to the nasal mucosa in order to assess threshold to cough and urge to cough. When menthol alone was applied, subjects reported a refreshing feeling and cooling sensation. Menthol administration decreased cough sensitivity produced by capsaicin ($p<0.05$), such that higher levels of capsaicin were needed to produce coughing, and fewer coughs were produced ($p<0.01$). Urge to cough also increased with higher capsaicin concentrations ($p<0.01$), indicating that subjects were less sensitive to capsaicin. Subjects reported that menthol reduced the intensity of capsaicin irritation of the nasal mucosa, thus increasing capsaicin tolerability (Buday et al., 2012).

A randomized cross-over study by Pereira and colleagues (2013) investigated the effect of inhaled menthol on upper airway resistance during quiet breathing. The upper airway resistance of ten participants was examined following exposure to menthol and was compared to regular room air. Nine out of 10 participants reported that that they could breathe more easily on the menthol test day; however, upper airway resistance was not significantly affected (Pereira, Sim, Driver, Parker, & Fitzpatrick, 2013). The discordance between sensation and physiological response has been noted in the full scientific review.

Twenty subjects participated in a lateralization test of menthol, eucalyptol, mustard oil, a mixture of menthol and eucalyptol, and a mixture of menthol and mustard oil. After exposure, participants identified which nostril was presented with the target odorant. They also rated the intensity and pleasantness of each odorant, and attached three descriptors. All odorants activated the trigeminal system and were easily accurately lateralized ($p<0.001$). Menthol was described as cool, fresh and tickling. Agonists of different trigeminal receptors had clearly dissociated lateralization scores. Thus, activation of the trigeminal nerve by TRPM8 agonists (menthol, eucaluptol) elicited a different response than the TRPM1 agonist mustard oil (Frasnelli, Albrecht, Bryant, & Lundstrom, 2011).

Ashley et al. (2012) conducted a study in Japan and Poland to investigate mouth level exposure (MLE) to nicotine using filter analysis. In this cross-over study, 800 subjects (regular nonmenthol smokers, occasional and regular menthol smokers) smoked each of five types of test cigarettes (nonmenthol and four levels of natural or synthetic menthol, matched for their usual tar level) and completed questionnaires assessing the sensory characteristics of the test cigarettes. Both Japanese and Polish smokers who occasionally smoked menthol cigarettes reported increased perceived irritation as compared to those who regularly smoked menthol cigarettes ($p<0.05$). In all Japanese smokers, the level of menthol loading affected the perceived strength of menthol taste and intensity of cooling ($p<0.05$); this effect was less notable among the Polish smokers. Both Japanese and Polish smokers reported differences in how synthetic and natural menthol cigarettes were perceived (Ashley, Dixon, Sisodiya, & Prasad, 2012). Taken together, these data suggest that use of synthetic or natural menthol may impact the sensory characteristics of the cigarette. Since the cigarette styles were matched for the country, product differences may have contributed to country-related differences.

Mechanisms of menthol action

Using isolated dorsal root ganglion neurons from rats, the effects of heat, anthralic acid (ACA) and 2-aminoethyl diphenylborinate (2-APB), both putative TRPM8 channel blockers, on stimulation of TRPM8

currents by noxious cold or menthol. Menthol consistently produced TRPM8 currents, confirming its activity at that receptor. Heat inhibited TRPM8 channel currents. Unlike the currents produced by noxious cold, currents produced by menthol were blocked by neither ACA nor 2-APB (Naziroglu & Ozgul, 2012). According to the authors, this study confirms that menthol activates TRPM8 channels; however, it is unclear whether one or both of the putative TRPM8 blockers are acting at the TRPM8 site, given conflicting reports of their blocking actions.

TRPM8 channel sensitivity to menthol was investigated using tetrameric TRPM8 constructs. Using electrophysiological and intracellular Ca2+ as measurements for current activity in HEK293 cells transfected with TRPM8 channels, researchers assessed the stoichiometry of menthol ligand attachment. Up to four menthol molecules can independently bind to a single TRPM8 channel, with each bound molecule producing a similar energetic stabilization of the open channel, resulting in a step- wise stabilization of the open state (Janssens & Voets, 2011). This provides more specific information about how menthol interacts with the TRPM8 channel.

An in vitro model of CYP2A6 and CYP2A13 activity (part of the metabolism pathway of nicotine and NNK) was used to assess relative inhibition produced by several compounds, including menthol. When activity was stimulated with coumarin, menthol was less potent as an inhibitor than the other tested compounds. There was no evidence that menthol inactivated CYP2A6 or CYP2A13. The authors concluded that menthol may not influence nicotine and NNK metabolism in smokers (Kramlinger, von Weymarn, & Murphy, 2012).

Cheang and colleagues (2013) investigated the effect of treatment with menthol on rat aortae and mesenteric and coronary arteries. Menthol induced relation (e.g., dilation) in the three types of arteries in a concentration-dependent manner. Using a smooth muscle cell line, the researchers determined that this effect was mediated by inhibition of calcium influx (Cheang et al., 2013). This demonstrates menthol activity at a receptor other than the TRPM8 receptor.

A study by Willis and colleagues (2011) used a mouse model to study the sensory irritation response elicited by acrolein, acetic acid and cyclohexane vapors (smoke irritants). The irritation produced by these chemicals was reversed by menthol, even at concentrations lower than in menthol cigarette smoke ($p<0.005$). The TRPM8 receptor mediated this effect; other TRPM8 agonists also abolished the irritant effect, and menthol's effects were reversed by a TRPM8 antagonist. Menthol also acted via the capsaicin receptor. The authors concluded that menthol may facilitate smoke inhalation (Willis, Liu, Ha, Jordt, & Morris, 2011).

Hans and colleagues (2012) investigated how nicotinic receptors are modulated by menthol. Menthol reversibly bound to both native and recombinant nicotinic receptors in a concentration-dependent manner ($p<0.005$). Single channel and whole-cell recordings from nicotinic receptors expressed in HEK tsA201 cells established that menthol acts as a negative allosteric modulator (Hans, Wilhelm, & Swandulla, 2012). This finding suggests that menthol directly interacts with nicotinic receptors.

Using PET scans, Brody and colleagues (2012) compared the relative densities of $\alpha 2\beta 4$ nicotinic acetylcholine receptors (AChRs) of menthol (n=22) and nonmenthol (n=41) smokers. Menthol smokers

exhibited greater densities in the brainstem, cerebellum and corpus callosum ($p<0.05$), but not the thalamus or prefrontal cortex. According to the author, this may be a result of greater exposure, and may help explain why menthol smokers have a more difficult time quitting compared to nonmenthol smokers (Brody et al., 2012).

Effect of menthol on smoking topography

In a cross-over study by Brinkman and colleagues (2012), nine participants smoked either menthol or nonmenthol cigarettes for one week. During a single laboratory session, smoking topography measurements were taken. When smoking the menthol test cigarettes, participants had greater volume of inhaled smoke, took longer puffs and took more time while smoking ($p<0.05$). This suggests that, when smoking menthol cigarettes, there was greater exposure to smoke. There were no inter-puff interval differences or differences in inspiration time (Brinkman et al., 2012).

In a laboratory study, Strasser and colleagues (2013) randomized 32 adult smokers to an experimental group (menthol Camel Crush for 15 days followed by nonmenthol Camel Crush for 15 days) or a control group (usual brand for 30 days). Every five days, laboratory assessments of smoking topography (total puff volume of each of two cigarettes) were taken. Compared to baseline, the experimental group evidenced a slight increase in total puff volume when smoking menthol Camel Crush cigarettes, compared to a larger increase under the nonmenthol Camel Crush condition ($p=0.02$) (Strasser et al., 2013). That is, although both conditions produced increased puff volumes, there was a smaller increase under the menthol Camel Crush condition. It is unclear whether these differences are the result of the brand or the presence/absence of menthol versus nonmenthol. It is unknown if there was an influence of time since usual brand on smoking behavior since there was no randomization to avoid order effects; menthol Camel Crush always preceded nonmenthol Camel Crush, and increased exposure to Camel Crush generally and/or greater time away from usual brand may impact behavior.

Conclusion

The addition of these articles did not change the conclusion presented in the full scientific review: the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with altered physiological responses to tobacco smoke.

Biomarkers

Eleven additional articles evaluating the association between menthol in cigarettes and biomarkers of exposure were reviewed.

Biomarkers of exposure to carbon monoxide (CO)

In the Strasser et al. study described above, laboratory assessments of biomarkers of exposure (including breath carbon monoxide [CO] before and after smoking each of two cigarettes) were taken every five days. CO measurements decreased from baseline in Camel Crush smokers ($p=0.033$), with no differences between the Camel Crush conditions (Strasser et al., 2013). It is unknown if there was an influence of time since usual brand on smoking behavior since there was no randomization to avoid

order effects; menthol Camel Crush always preceded nonmenthol Camel Crush, and increased exposure to Camel Crush generally and/or greater time away from usual brand may impact behavior.

Using data and biospecimens from the Total Exposure Study, a large cross-sectional study of smokers at least 21 years, levels of carboxyhemoglobin of 1044 menthol and 2297 nonmenthol smokers were compared. There was no difference (Sarkar, Wang, & Liang, 2012). It is unclear what, if any, adjustments were made for this analysis.

Biomarkers of exposure to nicotine

A nonclinical study by Abobo and colleagues (2012) examined the effect of menthol on the pharmacokinetics of nicotine. Rats were exposed to mainstream smoke under either a single-cigarette smoke inhalation procedure (1 puff/minute for 10 minutes) or a multiple-cigarette smoke inhalation procedure (equivalent to 17 cigarettes via 10 puffs every 12 hours). Following both the single- and multiple-cigarette smoke inhalation procedures, menthol cigarette smoke resulted in lower maximum plasma levels of nicotine and cotinine ($p<0.05$). Following the multiple-cigarette smoke inhalation procedure, menthol appeared to influence nicotine metabolism as indicated by a shorter relative half-life. The authors suggest that the reduced maximum levels of nicotine associated with menthol smoke may be impacted by differences in aversiveness (i.e., the rats inhale less menthol smoke as compared to nonmenthol smoke), and/or an altered nicotine half-life (Abobo, Ma, & Liang, 2012).

In a cross-over study, Brinkman and colleagues (2012) found no differences in urine levels of cotinine in subjects who smoked either menthol or nonmenthol test cigarettes for a week each ; When MLE to nicotine was estimated by quantifying solanesol levels in cigarette butts, menthol cigarettes had higher levels than nonmenthol cigarettes ($p<0.05$) (Brinkman et al., 2012).

In the study by Ashley et al. (2012) described above, Japanese smokers in the higher tar group (4 mg tar yield) exhibited no effects of menthol loading or type of menthol on nicotine MLE. In the lower tar group (1 mg tar yield), the occasional menthol smokers had higher nicotine MLE when smoking the high loading natural menthol cigarette as compared to the nonmenthol cigarette. Among Polish smokers, smokers in the lower tar group with the low synthetic menthol cigarettes had higher MLE to nicotine as compared to the high synthetic nicotine product (Ashley et al., 2012). Taken together, these data suggest that use of synthetic or natural menthol may impact MLE to nicotine. As noted earlier, since the cigarette styles were matched for the country, product differences may have contributed to country-related differences.

MLE was also assessed by Nelson and colleagues (2011). In this study, 1330 subjects who smoked their usual brand-style of cigarettes collected their butts for two days. A subset of this group repeated the test cycle as a check of replicability. Saliva samples were collected after two days when the subjects returned their butts. Six of the 26 brands included in this study were menthol brands. There were no differences in MLE per cigarette for menthol brands as compared to nonmenthol brands (Nelson, Chen, Dixon, & Steichen, 2011). There were three times as many test-cycles with nonmenthol cigarettes as menthol cigarettes; such a skewed sample may have implications regarding confidence in the statistical analyses. There was no information on the possible inclusion of menthol as an additive to the

nonmenthol brands; even low levels of menthol may impact smoking behavior and, therefore, MLE of nicotine.

In the study described above, Strasser and colleagues (2013) conducted laboratory assessments of biomarkers of exposure (including nicotine and cotinine on days five, 20 and 35) every five days. The researchers found no effect of menthol/nonmenthol on nicotine or cotinine levels (Strasser et al., 2013). It is unknown if there was an influence of time since usual brand on smoking behavior since there was no randomization to avoid order effects; menthol Camel Crush always preceded nonmenthol Camel Crush, and increased exposure to Camel Crush generally and/or greater time away from usual brand may impact behavior.

In a study of adult smokers, Benowitz and colleagues (2011) compared the plasma nicotine levels of 60 menthol smokers to those of 67 nonmenthol smokers. Plasma nicotine levels and urine nicotine equivalents were significantly higher in regular compared to menthol cigarette smokers ($p<0.05$) (Benowitz, Dains, Dempsey, Wilson, & Jacob, 2011). Over 70% of African American smokers smoked menthol cigarettes, compared to 25% of White smokers; thus, race/ethnicity may be a factor mediating these results.

Using 1999-2004 NHANES data, Jones and colleagues (2012) investigated possible associations between current menthol versus nonmenthol cigarette smokers and peripheral artery disease. As part of this study, serum cotinine levels were compared. Menthol cigarette smokers (n=310) were observed to have higher serum cotinine compared to nonmenthol cigarette smokers (n=734). As noted by the authors, a cautious interpretation is warranted since this was a descriptive finding and the data were not adjusted for smoking patterns, sociodemographic characteristics, smoking history (e.g., pack years), or other factors (Jones, Apelberg, Samet, & Navas-Acien, 2012).

A large cross-sectional study of 221 menthol and 274 nonmenthol smokers examined the association between menthol and nicotine update as measured by plasma cotinine levels. Although several covariates were associated with cotinine levels (e.g., time to first cigarette, race, age, BMI, cigarettes per day [cpd]), smoking menthol cigarettes was not ($p=0.66$) (Muscat, Liu, Stellman, & Richie, Jr., 2012).

Using data and biospecimens from the previously described Total Exposure Study, total urinary cotinine, glucuronide metabolite ratios for nicotine (nicotine-N-glucuronide/free nicotine) and cotinine (cotinine-N-glucuronide/free cotinine, *trans* 3'-hydroxy cotinine-O-glucuronide/*free* trans 3'-hydroxy cotinine) were calculated for 1044 menthol and 2297 nonmenthol smokers. There was no difference in total levels of serum cotinine. Although there was no overall difference reported, menthol was a significant factor ($p=0.0145$) for the cotinine metabolite ratios; they were higher among menthol smokers as compared to nonmenthol smokers. There was also a menthol x age effect on *trans* 3'-hydroxy cotinine-O-glucuronide ratios, however this effect was not described (Sarkar et al., 2012). Although other factors were found to be significant (e.g., race, age, cpd), it is unclear what, if any, adjustments were made for these analyses.

Menthol and nonmenthol smokers

An analysis of data from 1918 menthol and nonmenthol smokers who participated in the 2001-2006 NHANES compared serum cotinine levels of non-Hispanic adult smokers (age ≥20 years) who reported smoking a menthol brand of cigarettes (n=677) with those who reported smoking a nonmenthol brand (n=1241). After adjusting for cpd, there were no differences between the serum cotinine levels of menthol smokers as compared to nonmenthol smokers (Caraballo et al., 2011). Sample sizes were sufficiently large that the uneven subpopulations are not a concern (Caraballo et al., 2011).

Rostron (2012) used data from the 2007-2010 NHANES to analyze data on total urinary cotinine concentrations of 1452 everyday smokers and compare levels found between everyday menthol and nonmenthol smokers. There were no differences in cotinine levels of menthol and nonmenthol smokers, despite menthol smokers generally smoking fewer cpd. The author noted that nicotine exposure as measured by cotinine generally increased with cpd across race/ethnicity groups for U.S. smokers, but he did not compare menthol subpopulations (e.g., African American menthol smokers compared to White menthol smokers) and nonmenthol subpopulations (African American nonmenthol smokers compared to White nonmenthol smokers). Less than 30% of those surveyed smoked menthol cigarettes, suggesting that sample size may be a limitation (Rostron,B, 2012b).

Biomarkers of exposure to TSNAs

Jones et al. (2013) used data from 1999-2010 NHANES to compare urine 4-(methylnitrosamino) -1-(3-pyridyl)-1-butanol (NNAL) levels in menthol smokers versus nonmenthol smokers. After adjusting for demographic factors, serum cotinine levels were similar for menthol and nonmenthol smokers (Jones, Apelberg, Tellez-Plaza, Samet, & Navas-Acien, 2013).

In a study of adult smokers, Benowitz and colleagues (2011) compared the urine NNAL levels of 60 menthol smokers to those of 67 nonmenthol smokers and found no differences in urine NNAL levels (Benowitz et al., 2011).

A cross-over study involving participants who smoked menthol and nonmenthol test cigarettes for a week each found no significant differences in urinary levels of NNAL or the carcinogen metabolite 1-hydroxypyrene. When MLE to NNK was estimated by quantifying solanesol levels in cigarette butts, menthol cigarettes were associated with higher estimated MLE NNK levels than nonmenthol cigarettes (Brinkman et al., 2012).

An analysis of 2007-2010 NHANES data on 1447 everyday smokers compared the total urinary NNAL concentrations (adjusted for urinary creatinine levels) of menthol and nonmenthol smokers. Overall, menthol use was associated with lower NNAL concentrations ($p<0.05$), an effect that was primarily driven by White smokers. However, menthol smokers overall, and White menthol smokers specifically, also smoked fewer cpd and cpd was not included as a control variable. The author notes that NNAL generally increased with cpd across race/ethnicity groups for U.S. smokers. Less than 30% of those surveyed smoked menthol cigarettes, suggesting that sample size may be a limitation. Since the same analysis found that lower cpd did not result in differences in cotinine levels, the pharmacokinetic profiles of these constituents may differ (Rostron,B, 2012b).

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Using data and biospecimens from the previously described Total Exposure Study, total serum NNAL, and glucuronide metabolite ratios for NNAL (NNAL-O- and N-glucuronide/free NNAL) were calculated for 1044 menthol and 2297 nonmenthol smokers. There was no difference in total levels of NNAL or the glucuronide metabolite ratio (Sarkar et al., 2012).

Conclusion

The addition of these articles did not change the finding of the full scientific review that the weight of evidence supports the conclusion that menthol in cigarettes is likely not associated with increased or decreased levels of biomarkers of exposure.

Patterns of Use

Five additional articles related to the association between menthol in cigarettes and smoking patterns were reviewed.

Tobacco use supplement to the current population survey (CPS-TUS)

In a cross-sectional study, Delnevo and colleagues (2011) analyzed data from 2003 and 2006/7 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) and compared the smoking cessation prevalence of menthol and nonmenthol smokers. Five different sample restrictions (using other tobacco products, ever making a quit attempt, etc.) were used, so the sample size ranged from 71,193 to 24,465 participants. Overall, menthol smokers were more likely to be female and aged 18-24 years (Delnevo, Gundersen, Hrywna, Echeverria, & Steinberg, 2011).

National Survey on Drug Use and Health (NSDUH)

Hickman and colleagues (2012) analyzed data from 24,157 people who participated in the 2008 and 2009 National Survey on Drug Use and Health (NSDUH). Data were categorized for menthol or nonmenthol use, and for level of psychological distress (none/mild, moderate, severe). The overall prevalence of menthol cigarette use was 33.3%. Menthol use was more prevalent among young adults, African Americans, Native Hawaiians/Pacific Islanders, those with severe psychological distress, lower education level, lower income level, and those who were unmarried and uninsured. The authors suggest that menthol's anesthetic and bronchodialation effects may influence metabolism of psychotropic medications. This study agrees with previously discussed prevalence data (Hickman, III, Delucchi, & Prochaska, 2012).

National Health and Nutrition Examination Survey (NHANES)

Data from 1943 smokers who participated in the 2001-2006 National Health and Nutrition Examination Survey (NHANES) were analyzed. Serum cotinine levels of non-Hispanic adult smokers (≥20 years) who reported smoking a menthol brand of cigarettes (n=677) were compared with those who reported smoking a nonmenthol brand (n=1218). Less than 20% of White smokers smoked menthol cigarettes, compared to more than 70% of African American smokers (Caraballo et al., 2011).

Another analysis using 1999-2010 NHANES data estimated that 74.3% of smokers smoked nonmenthol cigarettes compared with 25.7% who smoked menthol cigarettes. This finding is similar to that of Caraballo et al. (2011), but may be more representative of current use patterns since this analysis is based upon more recent datasets (Jones et al., 2013).

National Youth Cessation Survey

The National Youth Smoking Cessation Survey (NYSCS) data were collected in 2003 from 2582 16-24 year olds who had ever smoked 20 lifetime cigarettes and had smoked within the past 30 days. From baseline to the two-year follow-up, more baseline menthol smokers switched to nonmenthol cigarettes than vice versa (Villanti et al., 2012).

Conclusion

The addition of these articles did not change finding in the full scientific review, namely that the weight of evidence supports the conclusion that menthol in cigarettes is associated with particular patterns of smoking.

Marketing and Consumer Perception of Risk

Five additional articles related to menthol cigarette marketing and consumer perception of risk were reviewed.

Marketing

Marketing strategies

Researchers performed a cross-sectional analysis of tobacco retail advertising in a California community with a greater proportion of African Americans than in California as a whole, and a "menthol share of voice" (the proportion of all cigarette advertisements in a store that featured menthol brands) was calculated. On average, the menthol share of voice was higher in this community (36.9%) than the state average (25.7%) (Dauphinee, Doxey, Schleicher, Fortmann, & Henriksen, 2013).

Henriksen and colleagues (2012) examined 407 stores within walking distance of 91 California high schools and counted advertisements for menthol and nonmenthol cigarettes, and for promotions and prices for Newport (leading menthol brand) and Marlboro (leading nonmenthol brand). The proportion of advertisements for menthol cigarettes increased with the proportion of African-American students. For each 10 percentage-point increase in the proportion of African American students, there was an increase of 5.9 percent in menthol share of voice, and stores were 1.5 times more likely to advertise a Newport promotion. The menthol share of voice increased by 11.6 percentage points with each 10 percentage-point increase in the proportion of neighborhood residents aged 10–17 years. Although this is not a national study, it supports the notion that at least some menthol brands target some African American neighborhoods, as well as those with younger demographics (Henriksen, Schleicher, Dauphinee, & Fortmann, 2012).

Tobacco advertising prevalence and placement at the point of sale by neighborhood and store characteristics in the ethnically and economically diverse St. Paul, MN area was assessed using data from

a cross-sectional assessment of the advertising environment in 654 licensed tobacco vendors (conducted in 2007) and demographic data taken from the Year 2000 US census. Sixty percent of the establishments had an average of six menthol cigarette advertisements. About 10% of those had health words such as "low tar", "light", "natural or "additive free" in their advertisements, and 47.5% had advertisements of price deals. For total number of menthol ads, the proportion African American, Asian, below 150% of the poverty line, on public assistance, and under the age of 18 years were associated with more advertisements, the proportion White was associated with fewer advertisements ($p<0.05$). Gas/convenience stores had more menthol advertisements than all other types of stores except for tobacco shops and liquor stores (Widome, Brock, Noble, & Forster, 2012).

Consumer perceptions

A study of brand recognition among 2589 6th through 9th graders (ages 11-15) in California found that the top three recognized brands were Camel (52%), Marlboro (36%) and Newport (32%). However, there was disproportionate recognition of Newport by African American students, with over double the brand recognition levels for those students. This held true after adjustment for smoking by parents and peers. This analysis was based on a cross-sectional sample from the longitudinal Survey of Teen Opinions about Retail Environments (STORE) (Dauphinee et al., 2013).

In another study, adult smokers (n=923) who participated in the New Zealand International Tobacco Control (ITC) project survey were classified as either menthol or nonmenthol users and queried on their beliefs about the harmfulness of menthol cigarettes. Current menthol users and smokers from the Pacific region of New Zealand believed that menthols were less harmful than nonmenthol cigarettes. Although these results reflect New Zealand's cultural and advertising histories, these results are applicable to the U.S. in that both countries have a documented history of advertising that links healthfulness and menthol cigarettes (Wilson, Weerasekera, Peace, & Edwards, 2011).

Conclusion

The addition of these articles did not change the finding of the full scientific review that 1) the weight of evidence supports the conclusion that the marketing of menthol cigarettes is likely associated with brand preference and use among adolescents and the African American community and 2) the weight of evidence is not sufficient to support a conclusion that consumer perceptions are associated with the use of menthol cigarettes

Initiation and Progression to Regular Use

Four additional articles regarding the association between menthol and smoking initiation and progression to regular use were reviewed.

First smoking experience

The study by Dauphinee et al. (2013) described above evaluated the relationship between brand recognition and smoking initiation. A greater proportion of students who recognized Newport (a menthol brand) brand at baseline initiated smoking; they were 49% more likely to initiate. Brand recognition of Camel (menthol) or Marlboro (nonmenthol) did not predict initiation. Recognition of

Newport explained some of the variance attributed to the finding that African American students were more likely to initiate smoking (22%) compared to other students (15%), as recognition of Newport predicted smoking initiation regardless of race. Although the original survey (STORE) was longitudinal, it has only been administered three times, and some students only participated in two of the three waves. There was disproportionate loss-to-follow-up among boys, Hispanic students, younger students, and students in lower grade levels. It is also unknown how smoking behavior was evaluated (e.g., experience versus regular smoking). Despite these limitations, this study provides support that there may be additional factors in the relationship of exposure to advertising on smoking initiation. Although Newport was third in brand recognition, it was the only brand recognition that was associated with future smoking behavior (Dauphinee et al., 2013).

A cross-sectional study of 928 treatment-seeking women in the Boston area was performed by Rosenbloom and colleagues (2012). Menthol (n=123) and nonmenthol (n=121) smoking women recalled the age at which they started smoking. There was no difference; both groups started smoking at around 16 years of age. Since the participants were asked generally about the age they started smoking, it is unclear whether they were reporting the age when they had their first cigarette or when they became regular smokers (Rosenbloom, Rees, Reid, Wong, & Kinnunen, 2012).

Faseru and colleagues (2013) compared the baseline characteristics of 540 African American light (≤10 cpd) smokers participating in a clinical smoking cessation study. There was no difference between menthol and nonmenthol smokers in the age of first cigarette smoked. Given the specific population included as participants (African American light smokers), generalizability is limited. In addition, drastically uneven numbers of menthol (452) and nonmenthol (88) smokers might have skewed the results (Faseru et al., 2013).

Progression to regular smoking

The Faseru study cited above also found no difference in the age at which menthol and nonmenthol smokers started smoking regularly (Faseru et al., 2013).

Using data from the longitudinal American Legacy Longitudinal Tobacco Use Reduction Study (ALLTURS), a three-wave longitudinal school-based survey of middle- and high school students, Nonnemaker and colleagues (2012) calculated the odds of escalating from non-established to established smoking. Menthol was associated with a higher likelihood of progressing to established smoking (odds ratio [OR] = 1.8, confidence interval [CI]: 1.02-3.16). Of the 638 participants, it is unclear how many were menthol versus nonmenthol smokers (Nonnemaker et al., 2013).

Conclusion

The addition of these articles does not alter the finding of the full scientific review, namely that the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with increased initiation and progression to regular smoking of cigarettes.

Dependence

Nine additional articles related to the association between menthol cigarette use and tobacco dependence were reviewed.

Time to first cigarette (ttfc)

The study by Rosenbloom and colleagues (2012) described above found a significant effect of menthol on ttfc. Menthol smokers were more likely to smoke within the first five minutes of waking (49%) as compared to nonmenthol smokers (36%) ($p<0.01$). The authors concluded that menthol smokers showed evidence of greater tobacco dependence compared to nonmenthol smokers (Rosenbloom et al., 2012).

A survey of Minnesota Quitline users who registered for services and had a phone or mail survey follow-up 7 months post-registration was analyzed for self-reported cessation success of menthol (n=1172) versus nonmenthol (n=5085) participants. Baseline demographic data found a difference in ttfc, with a greater percentage of menthol smokers reporting smoking within the first 5 minutes of waking, and lower percentage reporting smoking their first cigarette more than 5 minutes after waking ($p<0.05$) (D'Silva, Boyle, Lien, Rode, & Okuyemi, 2012).

A large cross-sectional study of 221 menthol and 274 nonmenthol smokers examined the association between menthol and ttfc. There was a relationship between menthol and shorter ttfc ($p<0.02$), which was driven by African American smokers. This suggests that while menthol smokers may be more dependent, this effect is driven by African American menthol smokers. That is, the differences between a single subpopulation's menthol and nonmenthol smokers was strong enough to drive overall population differences, however it is unclear what is driving this difference between African American menthol and nonmenthol smokers (Muscat et al., 2012).

Cigarettes per day (cpd)

During a cross-over study by Brinkman and colleagues (2012), nine subjects were given either menthol or nonmenthol cigarettes to smoke for a week each. On average, participants smoked fewer menthol cpd. However, of the nine participants, only one reported a study method brand as their usual brand. Therefore, it is difficult to generalize this finding to national menthol versus nonmenthol smoking populations (Brinkman et al., 2012).

The cross-sectional study by Rosenbloom and colleagues (2012) evaluated menthol preference on cpd. Although race effects were found, there was no effect of menthol preference on cpd (menthol = 16.8 cpd; nonmenthol =18.8 cpd) (Rosenbloom et al., 2012).

The demographics of menthol and nonmenthol smokers participating in a PET scan study allowed comparison of self-reported cpd by group. There were no differences between the menthol (n=22) and nonmenthol (n=41) groups, with menthol smokers smoking 19.9 ±5.8 cpd and nonmenthol smokers smoking 18.4 ±3.7 cpd (Brody et al., 2012).

Scales of nicotine dependence

The study by Brody et al. (2012) cited above allowed comparison of Fagerstrom Test of Nicotine Dependence (FTND) score by group. The researchers found no differences between the menthol (n=22) and nonmenthol (n=41) groups (Brody et al., 2012).

Faseru and colleagues (2013), in the study described earlier, found no difference in the FTND scores between menthol and nonmenthol smokers (Faseru et al., 2013).

Using data from ALLTURS study described earlier, Nonnemaker and colleagues (2012) calculated a scale of nicotine dependence based on five questions that focus on ttfc on weekdays, ttfc on weekends, and craving. Participants who initiated with menthol cigarettes had higher nicotine dependence scores (β-1.25, CI: 0.1-2.4) (Nonnemaker et al., 2013).

The association between menthol use status and Heaviness of Smoking Index (HSI) was examined as part of the baseline characteristics of 183 (83 menthol, 100 nonmenthol) smokers from a longitudinal study examining risk perceptions over time among community smokers attempting to quit. The HSI of menthol smokers was no different from that of nonmenthol smokers (p=0.579) (Reitzel et al., 2013).

Industry documents research

Yerger (2011) reviewed publicly available tobacco industry documents on the topic of menthol and nicotine dependence. The documents mainly focused on menthol's sensory and physiological effects and how these effects may interact with nicotine. According to these documents, the cooling and anesthetic effects of menthol may alleviate nicotine's irritating effects. Menthol may also act synergistically with nicotine, may stimulate the trigeminal nerve, and may make low tar, low nicotine tobacco products more acceptable. According to the documents, menthol level (but not nicotine level) affects level of "impact" felt by the user (Yerger, 2011).

Conclusion

The addition of these articles does not change the conclusion of the full scientific review, namely that the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with increased dependence.

Cessation

Seven additional studies addressing the link between menthol and smoking cessation were reviewed.

Cohort studies

The association between menthol use status and biochemically-verified short term abstinence was examined by Reitzel and colleagues (2013) in the study described above. Smoking status was assessed via self-report and exhaled CO at weeks 1, 2 and 3 post-quit. There was no effect of menthol status on continuous short-term abstinence (p=0.44); however, this was moderated by race. After adjusting for demographic factors, menthol use was significantly associated with short-term continuous abstinence among White smokers (p=0.05), but not African American smokers. White menthol smokers were five

times less likely to maintain abstinent as compared to White nonmenthol smokers (OR = 0.21m CI 0.05-0.98) (Reitzel et al., 2013).

Cross-sectional studies

Data collected as part of a randomized clinical trial were analyzed for race/ethnicity effects on post-partum maintenance of smoking abstinence. Participants smoked prior to pregnancy (n=123 menthol; n=121 nonmenthol) and stopped either during their pregnancy or within two months of becoming pregnant. The outcome measure was continuous abstinence since delivery date, and was assessed at eight and 26 weeks postpartum. Although responses were self-reported, there was cotinine verification of smoking abstinence. White menthol users, but not menthol smokers of other race/ethnic subgroups, were less likely to maintain continuous abstinence rates. Analyses were adjusted for a variety of factors, including cpd and ttfc. As discussed in the full scientific review, since level of dependence may be an intermediate factor impacting cessation success, thus, these analyses may have been overadjusted (Reitzel et al., 2011).

The smoking cessation prevalence of menthol and nonmenthol smokers was compared by Delnevo and colleagues (2011). This cross-sectional study analyzed data from 2003 and 2006/7 TUS-CPS. Adjusted odds of cessation were calculated using multiple logistic regressions. Overall, menthol smokers were less likely to be former smokers than were nonmenthol smokers (AOR 0.91, 95% CI 0.87, 0.96), an effect that was relatively small but consistent (Delnevo et al., 2011).

An analysis of data from a survey of Minnesota Quitline users, described above, found no significant difference in quit status reported during the follow-up; menthol was not a significant predictor of 30-day abstinence (D'Silva et al., 2012).

Data from the 2003 and 2006/7 TUS-CPS were used to examine quit rates among menthol and nonmenthol smokers. Although menthol smokers were more likely to have made a quit attempt, they were either 4% (2003) or 12% (2006/7) less likely to have quit successfully in the past year. The final sample sizes are unclear, since the study authors did not indicate the number of subjects who met the inclusion requirements (Levy et al., 2011).

A randomized double-blind, placebo-controlled smoking cessation study investigated the efficacy of bupropion in promoting cessation in adult African American light (≤10 cpd) treatment-seeking smokers (n=540). Cotinine-verified seven-day point prevalence abstinence at week 7 (end of drug treatment) and week 26 were compared. Compared to continuing smokers, those who were abstinent were more likely to smoke nonmenthol cigarettes at week 7 (p=0.001) and week 26 (p=0.005). However, being a menthol or nonmenthol smoker did not alter the efficacy of bupropion, which was higher than placebo at week 7 (24% versus 13%), but not at week 26 (13% versus 10%). Thus, although smoking menthol cigarettes was negatively associated with successful abstinence, it did not affect response to pharmacotherapy (Faseru et al., 2013).

Industry documents research

In a study of publicly available tobacco industry documents, Anderson (2011) reviewed documents on the topic of menthol and smoking cessation behavior. The documents mainly focused on the cooling and anesthetic effects of menthol. According to the documents, these effects may mask the short-term negative physiological effects of smoking such as throat pain, burning, cough. Documents also suggest that these sensory effects may also allow some smokers who were dissatisfied with the smoking experience to continue to smoke, and discourage them from quitting (Anderson, 2011).

Conclusion

The addition of these articles did not change the conclusion of the full scientific review, namely that the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with reduced success in smoking cessation, especially among African American menthol smokers.

Disease Risk

Four additional articles related to menthol and disease risk were reviewed.

Lung cancer

Using data from the 1987 National Health Interview Survey Cancer Control Supplement (with links to the National Death Index), Rostron (2012) estimated lung cancer mortality hazards for menthol and nonmenthol smokers. Menthol cigarette use had a lower hazard ratio (HR) for lung cancer mortality (HR = 0.59, CI 0.37-0.95) among 50+ year olds as compared use of nonmenthol cigarettes, but there was no similar association with other causes of mortality. The author concluded that it is unknown how differences in smoking behavior and/or cigarette design may have impacted these findings. (Rostron,B, 2012a). These findings were commented on by Villanti et al. (Villanti, Giovino, Burns, & Abrams, 2013) with a rebuttal by Rostron (Rostron, 2013).

Multiple cancers

Kabat and colleagues (2012) used data on age-adjusted incidence rates of lung, esophageal, oropharyngeal, and laryngeal cancers from the Surveillance, Epidemiology, and End Results (SEER) program. Although not directly comparing menthol and nonmenthol smokers, Kabat and colleagues inferred that menthol did not alter multiple types of cancer risk since the market share of menthol cigarettes has remained stable over the past two decades, whereas cancer incidences have changed over the past 35 years, and these changes differ greatly depending on race and sex. The authors conclude that if menthol cigarettes had a “discernible effect” on the risk of smoking-related cancers, the incidence of these cancers in African Americans, especially African American females, would be higher, since this group smokes menthol cigarettes at a higher prevalence than White smokers (Kabat, Shivappa, & Hebert, 2012).

Multiple non-cancer diseases

Using data from the 1999-2004 NHANES, Jones and colleagues (2012) investigated possible associations between current menthol versus nonmenthol cigarette smokers and peripheral artery disease. An ankle-brachial blood pressure index (ABI) calculation was made for 734 nonmenthol smoking adults and

310 menthol smoking adults who were at least 40 years old. This calculation is a highly specific marker for subclinical peripheral artery disease. After adjusting for risk factors, demographics, pack-years of smoking and serum cotinine, there was no significant difference in the association between smoking and peripheral artery disease for current smokers of menthol and nonmenthol cigarettes. Although there were half as many menthol smokers as nonmenthol smokers, it is unlikely that small sample size contributed to the negative results since even a directional trend did not exist (p=0.59) (Jones et al., 2012).

Data from the 2001-2008 NHANES was used to examine possible relationships between menthol smoking and the odds of stroke, hypertension, myocardial infarction, congestive heart failure, and COPD. The data were adjusted for demographic factors, and smoking quantity and duration. There were increased odds of stroke in menthol smokers (OR= 2.25, CI: 1.33-3.78), particularly women and non-African Americans, as compared to the nonmenthol smoking counterparts. This increase was slightly reduced, but still significant, when data were adjusted for being diagnosed by a health professional, self-reported hypertension, diabetes mellitus and dyslipidemia (OR=2.19, CI: 1.05-4.58). There were no significant differences in the odds of any of the other diseases and smoking either menthol or nonmenthol cigarettes. The author suggests that the menthol cigarette-stroke association may be underestimated since former smokers were not included in the analysis (Vozoris, 2012).

Conclusion

The addition of these articles did not change the conclusion of the full scientific review: the weight of evidence supports the conclusion that menthol in cigarettes is not associated with an increase in disease risk to the user.

Overall Conclusion

None of the additionally reviewed peer-reviewed articles altered the findings of the full science report.

Reference Addendum

Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
Abobo CV, Ma J, Liang D.	Effect of menthol on nicotine pharmacokinetics in rats after cigarette smoke inhalation.	2012	NIH Grants and the state tobacco settlement funds (Texas)	Nonclinical	Rats	N=8/group	Consistent with the findings after single-cigarette exposure, multiple-mentholated cigarette exposures caused significant reductions in the mean maximum nicotine plasma concentration… Similar to that observed after single cigarette smoke inhalation, menthol appreciably reduced the mean maximum plasma concentration of cotinine The mean elimination half-lives after multiple - nonmentholated and – mentholated cigarette smoke exposures were significantly different (49.4 vs. 37.3 min; Table 2). We found that single inhalation of mentholated cigarette significantly decreased the maximum plasma level and the area under the curve of nicotine but not the terminal half-life of nicotine.
Anderson SJ.	Menthol cigarettes and smoking cessation behaviour: a review of tobacco industry documents.	2011	Contract from DHHS HHSN261201000035I	Documents	N/A	509 documents qualitatively analyzed, 46 documents included	Menthol's cooling and anaesthetic effects mask the short-term negative physiological effects of smoking such as throat pain, burning and cough. This provides superficial physical relief as well as psychological assurance against concerns about the health dangers of smoking that would otherwise motivate smokers to quit.
Ashley M, Dixon M, Sisodiya A, Prasad K.	Lack of effect of menthol level and type on smokers' estimated mouth level exposures to tar and nicotine and perceived sensory characteristics of	2012	British American Tobacco (BAT)	Human subjects	Smokers (age 21-65) who smoked at least 10 cpd	N=800 menthol and nonmenthol smokers (this was a "target"; number of actual completers	There were no effects of menthol loading or type on mean nicotine MLE in the 4 mg tar yield smoker groups, but within the 1 mg tar yield smoker groups the occasional menthol smokers obtained higher mean nicotine MLE when smoking the high loading natural menthol product (J1N 11.6) compared with smoking the non-menthol cigarette (J1 0).

* Note: these statements are taken directly from articles and may not include all relevant results/conclusions.

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Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
	cigarette smoke.					wasn't given)	The only significant effect of menthol loading on mean nicotine MLE was in the regular 1 mg tar yield group where the low synthetic menthol loading product (P1S 3.9) produced higher mean nicotine MLE than the high synthetic menthol product (P1S 6.1 and the high natural menthol product (P1N 6.3). . . . for the two occasional menthol smoker groups, the addition of menthol to the products was associated with a marked and significant increase in perceived irritation. The effects of menthol loading on the intensities of the strength of menthol taste and the cooling effect were less clear-cut than those observed in the Japanese smoker groups. However, in most groups there were trends towards higher intensities of menthol taste and cooling effect with increasing menthol loading, but unlike the results from the Japanese study these differences were not significant in all cases.
Benowitz NL, Dains KM, Dempsey D, Wilson M, Jacob P.	Racial differences in the relationship between number of cigarettes smoked and nicotine and carcinogen exposure.	2011	NIH Grants	Human laboratory study	Healthy adult (age 18-65) smokers who smoked an average of ≥10 cpd for the past year or longer	N=127	Plasma nicotine levels were significantly higher in regular compared to menthol cigarette smokers.
Bodnar JA, Morgan WT, Murphy PA, Ogden MW.	Mainstream smoke chemistry analysis of samples from the 2009 US cigarette	2012	R.J. Reynolds Tobacco Co.	Nonclinical	N/A	N/A	Menthol cigarette mean constituent yields were observed to be within the range of the non-menthol cigarettes of similar "tar" categories.

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Abobo CV, Ma J, Liang D.	Effect of menthol on nicotine pharmacokinetics in rats after cigarette smoke inhalation.	2012	NIH Grants and the state tobacco settlement funds (Texas)	Nonclinical	Rats	N=8/group	Consistent with the findings after single-cigarette exposure, multiple-mentholated cigarette exposures caused significant reductions in the mean maximum nicotine plasma concentration… Similar to that observed after single cigarette smoke inhalation, menthol appreciably reduced the mean maximum plasma concentration of cotinine The mean elimination half-lives after multiple - nonmentholated and – mentholated cigarette smoke exposures were significantly different (49.4 vs. 37.3 min; Table 2). We found that single inhalation of mentholated cigarette significantly decreased the maximum plasma level and the area under the curve of nicotine but not the terminal half-life of nicotine.
Anderson SJ.	Menthol cigarettes and smoking cessation behaviour: a review of tobacco industry documents.	2011	Contract from DHHS HHSN261201000035I	Documents	N/A	509 documents qualitatively analyzed, 46 documents included	Menthol's cooling and anaesthetic effects mask the short-term negative physiological effects of smoking such as throat pain, burning and cough. This provides superficial physical relief as well as psychological assurance against concerns about the health dangers of smoking that would otherwise motivate smokers to quit.
Ashley M, Dixon M, Sisodiya A, Prasad K.	Lack of effect of menthol level and type on smokers' estimated mouth level exposures to tar and nicotine and perceived sensory characteristics of	2012	British American Tobacco (BAT)	Human subjects	Smokers (age 21-65) who smoked at least 10 cpd	N=800 menthol and nonmenthol smokers (this was a "target"; number of actual completers	There were no effects of menthol loading or type on mean nicotine MLE in the 4 mg tar yield smoker groups, but within the 1 mg tar yield smoker groups the occasional menthol smokers obtained higher mean nicotine MLE when smoking the high loading natural menthol product (J1N 11.6) compared with smoking the non-menthol cigarette (J1 0).

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Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
	market.						
Brinkman MC, Chuang JC, Gordon SM, Kim H, Kroeger RR, Polzin GM, Richter PA.	Exposure to and deposition of fine and ultrafine particles in smokers of menthol and nonmenthol cigarettes.	2012	Contract from the Centers for Disease Control and Prevention (CDC)	Nonclinical and Laboratory	Smokers (age 18-30) who smoked at least 1 pack/day for at least 6 months	N=9	… there were no significant differences measured in daily MLE *[mouth level exposure]* and participant specific mainstream smoke when participants smoked the two test cigarettes. There were no significant differences in the level of urinary cotinine between the menthol and the nonmenthol cigarettes. Urinary 1-HOP levels were not significantly different between the two test cigarettes. The menthol test cigarette showed a significantly higher number (11%) and mass (33%) of ultrafine particles than the nonmenthol test cigarette. Participants smoked significantly fewer menthol cigarettes/day… as compared to nonmenthol test cigarettes. …participants took longer puffs (0.24 s) and required a longer period of time (25 s) for each menthol cigarette, which resulted in a larger volume of smoke inhaled per menthol cigarette (73 ml/cigarette) as compared to nonmenthol.
Brody AL, Mukhin AG, La Charite J, Ta K, Farahi J, Sugar CA, Mamoun MS, Vellios E, Archie M, Kozman M,	Up-regulation of nicotinic acetylcholine receptors in menthol cigarette smokers.	2012	Tobacco-Related Disease Research Program, NIH grant, Veterans Affairs Type I Merit Review Award, endowment from the Richard Metzner Chair in Clinical Neuropharmacology	Clinical study	Healthy adult smokers (10-40 cpd)	N=22 menthol smokers, N=41 nonmenthol smokers	Menthol and non-menthol cigarette smokers did not differ on any demographic or rating scale measure, other than race/ethnicity… Follow-up tests revealed between-group differences for the brainstem, cerebellum and corpus callosum…

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Reference Addendum

Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
Phuong J, Arlorio F, Mandelkern MA.							
Buday T, Brozmanova M, Biringerova Z, Gavliakova S, Poliacek I, Calkovsky V, Shetthalli MV, Plevkova J.	Modulation of cough response by sensory inputs from the nose - role of trigeminal TRPA1 versus TRPM8 channels.	2012	VEGA no 1/0031/11 and Centre of Experimental and Clinical Respirology II (CEKR) co-financed from EU sources	Human laboratory study	Healthy non-smoking adults (average age 23)	N=18	Both menthol isomers after nasal administration significantly modulated urge to cough, cough threshold, and total cough response probably via the reduction of airway irritation induced during capsaicin challenge.
Caraballo RS, Holiday DB, Stellman SD, Mowery PD, Giovino GA, Muscat JE, Eriksen MP, Bernert JT, Richter PA, Kozlowski LT.	Comparison of serum cotinine concentration within and across smokers of menthol and nonmenthol cigarette brands among non-Hispanic black and non-Hispanic white U.S. adult smokers, 2001-2006.	2011	No funding source(s). Authors affiliated with the Centers for Disease Control and Prevention, RTI International, Georgia State University, Columbia University, State University of New York at Buffalo, Penn State College of Medicine	Cohort survey (NHANES 2001-2006)	Smokers (age ≥20) who had smoked on the day of or the day prior to the NHANES visit	N=1943	Smoking a menthol cigarette brand versus smoking a nonmenthol cigarette brand was not associated (P< 0.05) with mean serum cotinine concentration in either black or white smokers. …only a minority (19.4%) of the sample of white smokers smoked menthol cigarettes, whereas the majority (73.9%) of black smokers smoked a menthol brand. Menthol cigarettes smoked by black smokers (1.24 mg) were on an average higher in FTC nicotine levels to the menthol cigarettes (0.94 mg) smoked by white smokers (P < 0.01).
Cheang WS, Lam MY, Wong WT, Tian XY, Lau CW, Zhu Z, Yao X, Huang Y.	Menthol relaxes rat aortae, mesenteric and coronary arteries by inhibiting calcium influx	2013	National Basic Research Program of China, a research grant from Research Grants Council of Hong Kong, and CUHK Focused Investment Scheme B.	Nonclinical	Rat tissue, cell culture	N/A	The present study demonstrates that menthol relaxes rat arteries through loweringCa2þ influx probably vianifedipine-sensitiveCa2þ channels in vascular smooth muscle. This effect appears independent of the reported TRPM8 activation.
Dauphinee AL,	Racial differences	2013	NIH grant	Longitudinal	6th-9th grade students	N=2589	On average, the proportion of cigarette ads that

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Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
Doxey JR, Schleicher NC, Fortmann SP, Henriksen L.	in cigarette brand recognition and impact on youth smoking.			study with some cross-sectional analyses	(age 11-15) in Vallejo, California		featured a menthol brand (menthol share of voice) was 36.9% (SD = 18.3), which was higher than the average for the state (25.7% (SD = 26.1)… …provide the brand name: 52% for Camel, 36% for Marlboro, and 32% for Newport. The odds of smoking initiation increased by 49% for students who recognized the Newport brand at baseline.
Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB.	Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes.			Cross-sectional TUS-CPS	Black, White and Hispanic current smokers and those who have quit in the past 5 years	N=71,193 to 24,465 (depending on sample restrictions)	…there was a small but consistent relationship between menthol cigarettes and cessation, whereby smokers of menthol cigarettes were significantly less likely to have quit smoking than smokers of non-menthol cigarettes.
D'Silva J, Boyle RG, Lien R, Rode P, Okuyemi KS.	Cessation outcomes among treatment-seeking menthol and nonmenthol smokers.	2012	No funding source(s). Authors were affiliated with ClearWay Minnesota; University of Minnesota; Professional Data Analysts; Minnesota Department of Health	Cross-sectional survey with single follow-up	Cigarette smokers who called the Minnesota Quitline and registered for services	N=1172 menthol smokers, N=5085 nonmenthol smokers	…the odds of quitting for menthol smokers was not significantly different from nonmenthol smokers (OR 1.29, 95% CI 0.77, 2.15) after controlling for the other covariates.
Faseru B, Choi WS, Krebill R, Mayo MS, Nollen NL, Okuyemi KS, Ahluwalia JS, Cox LS.	Factors associated with smoking menthol cigarettes among treatment-seeking African American light smokers.	2011	NIH Grant	Clinical trial	Treatment-seeking African-American light (≤10 cpd) smokers	N=452 menthol, N=88 nonmenthol	Table 1 Baseline characteristics of AA menthol and non-menthol smokers in KIS III.
Faseru B, Nollen NL, Mayo MS, Krebill R, Choi	Predictors of cessation in African American light smokers	2013	NIH Grants; NRSA grant, American Cancer Society Institutional Research Grant	Clinical trial	Treatment-seeking African-American light (≤10 cpd) smokers	N=540	Our current study has demonstrated a robust effect of menthol on smoking cessation. African American light smokers of menthol cigarettes were less likely to quit smoking compared to

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Author Name(s)	Article Title	Year Pub.	Funded By	Type of Study	Subject Description (Including Special Population(s))	Sample Size (N)	Authors' Results/Conclusion(s) Related to Menthol* (excerpted directly from article)
WS, Benowitz NL, Tyndale RF, Okuyemi KS, Ahluwalia JS, Sanderson Cox L.	enrolled in a bupropion clinical trial.						non-menthol cigarette smokers.
Fowler P, Smith K, Young J, Jeffrey L, Kirkland D, Pfuhler S, Carmichael P.	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type.	2012	European Cosmetic Industry Association, UK National Centre for the 3Rs (NC3Rs)	Nonclinical	6 in vitro cell lines	N/A	It was cytotoxic, inducing at least 50% reduction in RI at the top concentrations scored, but there were no increases in MN frequency. In other cases (e.g., d,l-menthol), testing was limited by cytotoxicity, and even though required levels of cytotoxicity were induced, MN were not.
Frasnelli J, Albrecht J, Bryant B, Lundström JN.Frasnelli J, Albrecht J, Bryant B, Lundström JN.	Perception of specific trigeminal chemosensory agonists.	2011	Postdoctoral fellowship from the Canadian Institutes of Health Research	Human laboratory study	Healthy adults with no reductions in sense of smell	N=20	All stimuli clearly activated the trigeminal system as demonstrated by the ease subjects had in lateralizing them. The scores for menthol and eucalyptol showed the highest correlation (r20 0.79; P< 0.001), Eucalyptol and menthol were described as predominantly cool (2.4 p and 2.3 p, respectively), fresh (both 1.4 p) and tickling (0.5 p and 0.7 p, respectively).
Gordon SM, Brinkman MC, Meng RQ, Anderson GM, Chuang JC, Kroeger RR, Reyes IL, Clark PI.	Effect of cigarette menthol content on mainstream smoke emissions.	2011	Battelle internal research and development funds	Nonclinical	N/A	N/A	Menthol in the TPM samples obtained from the cigarettes at each of the menthol levels investigated showed a linear increase with applied menthol concentration, but the amounts of nicotine, target TSNAs, PAHs, cotinine, and quinolone in the cigarettes remained essentially unchanged. Similarly, yields of the targeted VOCs in mainstream smoke from the MEN cigarettes that were measured in real-time on a puff-by-puff basis in whole smoke were largely unaffected by the levels of menthol present in

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							the cigarettes.
Hans M, Wilhelm M, Swandulla D.	Menthol suppresses nicotinic acetylcholine receptor functioning in sensory neurons via allosteric modulation.	2012	Altria Client Services, Inc.	Nonclinical	Nicotinic acetylcholine receptors (native and recombinant)	N/A	…we show that nAChRs expressed in sensory neurons are reversibly inhibited by menthol with an IC50 of 111 IM. Single channel recordings from human a4b2 nAChR in HEK tsA201 cells revealed that menthol causes an increase in single channel amplitude, a shorting of channel open time and a prolongation of its close time. We conclude that the mechanism underlying the menthol-mediated inhibition of nAChR is due to an allosteric modulation of the nAChR by menthol.
Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP.	Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods.	2012	California's Tobacco-Related Disease Research Program grant	Cross-sectional study	Stores within walking distance of California high schools	N=407	For each 10 percentage point increase in the proportion of Black students, the proportion of menthol advertising increased by 5.9 percentage points… The menthol share of voice increased by 11.6 percentage points with each 10 percentage-point increase in the proportion of neighborhood residents ages 10–17 years. For each 10 percentage-point increase in the proportion of Black students, the odds of a store advertising a Newport promotion were 1.5 times greater
Hickman NJ 3rd, Delucchi KL, Prochaska JJ.	Menthol use among smokers with psychological distress: findings from the 2008 and 2009 National Survey on Drug Use and Health.	2012	NIH grants	Nationally representative cohort study (NSDUH)	Current smokers (age ≥18) who answered the item on menthol use	N=24157	The prevalence of menthol smoking among this national sample of current smokers was 33.3%. The prevalence of menthol use was higher among individuals with severe psychological distress, women, young adults, African Americans, Native Hawaiians/Pacific Islanders, persons with fewer years of education and lower income, the unmarried and uninsured.

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Janssens A, Voets T.	Ligand stoichiometry of the cold- and menthol-activated channel TRPM8.	2011	Grants from the Belgian Federal Government, the Research Foundation-Flanders, and the Research Council of the KU Leuven	Nonclinical	TRPM8 ion channels expressed in HEK293 cells	N/A	This indicates that TRPM8 can simultaneously bind up to four menthol molecules, resulting in a stepwise stabilization of the open state.
Jones MR, Apelberg BJ, Samet JM, Navas-Acien A.	Smoking, menthol cigarettes, and peripheral artery disease in U.S. adults.	2012	NIH Grants	Nationally representative survey from 1999-2004 (NHANES)	Adults (age ≥ 40)	N=5973	Serum cotinine and blood cadmium concentrations were also higher in smokers of menthol cigarettes compared to smokers of nonmenthol cigarettes… We observed no significant difference in the association between smoking and peripheral artery disease for current smokers of nonmenthol and menthol cigarettes (p value for heterogeneity = 0.59).
Jones MR, Apelberg BJ, Tellez-Plaza M, Samet JM, Navas-Acien A.	Menthol cigarettes, race/ethnicity, and biomarkers of tobacco use in U.S. adults: the 1999-2010 National Health and Nutrition Examination Survey (NHANES).	2012	NIH grants	Cohort nationally representative survey from 1999-2010 (NHANES)	Adult current smokers (including White, African American and Mexican American smokers)	N=4603	In a representative sample of U.S. adult smokers, current menthol cigarette use was associated with increased concentration of blood cadmium, an established carcinogen and highly toxic metal, but not with other biomarkers. A total of 3,210 (74.3%) participants smoked nonmenthol cigarettes compared with 1,393 (25.7%) participants who smoked menthol cigarettes… After further adjustment for race/ethnicity, the corresponding ratios were markedly decreased and no longer statistically significant for serum cotinine (1.03; 95% CI, 0.9)
Kabat GC, Shivappa N, HÃ©bert JR.	Mentholated cigarettes and smoking-related cancers revisited: an ecologic	2012	NIH Grants	Multiple years of SEER data	Case and controls: lung. esophageal, oropharyngeal, laryngeal cancer	Not given/Not appropriate	Given the large differences in exposure to mentholated cigarettes by race and sex, if menthol had a discernible effect on the risk of smoking-related cancers, one might expect to see one or both of the following patterns: (1)

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	examination.						higher incidence rates among Blacks of both sexes compared to their White counterparts; (2) differences in the temporal trends between Blacks and Whites of both sexes.
Kramlinger VM, von Weymarn LB, Murphy SE.	Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, Î²-nicotyrine and menthol.	2012	NIH Grants	Nonclinical	In vitro	N/A	Inhibition of CYP2A6 by menthol was 100 times less potent (Ki of 100mM). There was no indication that menthol inactivated CYP2A6 or CYP2A13.
Levy DT, Blackman K, Tauras J, Chaloupka FJ, Villanti AC, Niaura RS, Vallone DM, Abrams DB.	Quit attempts and quit rates among menthol and nonmenthol smokers in the United States.	2011	Legacy	Nationally representative cross-sectional TUC-CPS from 2003 and 2006/7	Adult smokers who had smoked at least 100 cigarettes and are either current or former smokers	Unknown	Table 1 presents the proportions of smokers and former smokers who quit within the past 5 years by cigarette type. In both 2003 and 2007, about 70% smoked nonmenthol, 26% smoked menthol, and 4% had no preference. Although they had a higher likelihood of a quit attempt, menthol smokers compared with nonmenthol smokers were 4% less likely to have quit successfully in the past year in 2003 and 12%less likely in 2007.
Lu S, Baad-Hansen L, List T, Zhang Z, Svensson P.	Somatosensory profiling of intra-oral capsaicin and menthol in healthy subjects	2013	NIH research grant	Human laboratory study	Healthy adults (mean age 31.5±7.5)	N=15	More than half (9/15) of the subjects reported mild levels of pain during menthol application. Our study showed that topical application of menthol on the gingiva elicited cold and warmth hyperesthesia…
Millqvist E, Ternesten-Hasséus E, Bende M.	Inhalation of menthol reduces capsaicin cough sensitivity and influences inspiratory flows in	2013	Grants from the Regional Health Care Authority of West Sweden, the Swedish Asthma and Allergy Association and the Swedish Heart and	Human laboratory study	Patients: non-smokers with histories of cough and other airway symptoms induced by environmental irritants (average age 51).	N=14 (patients) N=15 (controls)	We conclude that in patients with chronic cough that is not caused by asthma, COPD or infections, pre-inhalation of menthol reduces cough sensitivity to inhaled capsaicin and influences inspiratory flows.

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	chronic cough.		Lung Foundation		Controls: healthy non-smokers (average age 52).		
Muscat JE, Liu HP, Stellman SD, Richie JP Jr.	Menthol smoking in relation to time to first cigarette and cotinine: results from a community-based study.	2012	NIH Grants; contracts from DHHS; Pennsylvania Department of Health	Human laboratory study	Daily smokers (≥5 cpd for one or more years)	N=495	. Overall there was a trend between menthol smoking and a shorter TTFC ($P < 0.02$). When analyzed by race, the trend was significant in black subjects ($P < 0.04$). The time to first cigarette ($P < 0.01$) but not menthol ($P = 0.66$) was significantly associated with cotinine levels.
Naziroğlu M, Ozgül C.	Effects of antagonists and heat on TRPM8 channel currents in dorsal root ganglion neuron activated by nociceptive cold stress and menthol.	2012	No funding source(s). Authors affiliated with University of Suleyman Demirel, Turkey	Nonclinical	Rat dorsal root ganglia	N/A	In the current study, TRPM8 channels were activated by menthol.
Nelson PR, Chen P, Dixon M, Steichen T.	A survey of mouth level exposure to cigarette smoke in the United States.	2011	No funding source(s). Authors affiliated with R.J. Reynolds Tobacco Company	Human study	Healthy smokers (≥7 cpd) who smoked one of the selected brand styles as their usual brand style	N= 1330	The regression lines for the menthol cigarettes fell slightly below those for the non-menthol cigarettes suggesting a trend towards slightly lower MLEs per cigarette for the menthol brand-styles. However, differences in the slopes and intercepts of the regression lines were not statistically significant.
Nonnemaker J, Hersey J, Homsi G, Busey A, Allen J, Vallone D.	Initiation with menthol cigarettes and youth smoking uptake.	2012	DHHS contract	Cross-sectional survey	Middle and high school students from 83 schools in seven communities and five states	N=638 (progression analysis) or N=399 (dependence analysis)	The models reveal a positive and statistically significant association between menthol at initiation [odds ratio (OR) = 1.8, confidence interval (CI): 1.02–3.16) and escalation to established smoking. As shown, initiation with menthol is associated

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							positively and significantly with nicotine dependence (b = 1.25, CI: 0.1–2.4).
Pereira EJ, Sim L, Driver H, Parker C, Fitzpatrick M.	The effect of inhaled menthol on upper airway resistance in humans: A randomized controlled crossover study.	2013	Research grants from the Ontario Thoracic Society, William M. Spear Foundation, Queen's University and Clinical Teachers Association at Queen's University	Human laboratory study	Healthy adults (age 21±0.5 years)	N=10	…90% of participants reported that they could breathe easier on the menthol test day. The present study demonstrated that cold receptor stimulation of the upper airway with inhaled menthol does not alter UAR *[upper airway respiration]* in conscious resting human subjects.
Reitzel LR, Li Y, Stewart DW, Cao Y, Wetter DW, Waters AJ, Vidrine JI.	Race moderates the effect of menthol cigarette use on short-term smoking abstinence.	2013	NIH Grant; CDC grant, The University of Texas MD Anderson Cancer Center	Cohort study	Current smokers (age 18-65), smoking ≥5 cpd for at least a year, willingness to quit	N=183	The main effects of menthol use status on continuous short-term smoking abstinence were not significant… Menthol use was significantly associated with short-term continuous smoking abstinence among White participants… White menthol users were about 5 times less likely to maintain continuous smoking abstinence than White nonmenthol users (odds ratio = 0.21, 95% CI = 0.05–0.98).
Reitzel LR, Nguyen N, Cao Y, Vidrine JI, Daza P, Mullen PD, Velasquez MM, Li Y, Cinciripini PM, Cofta-Woerpel L, Wetter DW.	Race/ethnicity moderates the effect of prepartum menthol cigarette use on postpartum smoking abstinence.	2011	NIH Grants	Clinical trial	Women who smoked prior to pregnancy and quit either during pregnancy or within 2 months of becoming pregnant	N= 123 menthol smokers, 121 nonmenthol smokers	White menthol users were less likely to maintain continuous abstinence than White non-menthol users.
Rosenbloom J, Rees VW, Reid K, Wong J, Kinnunen T.	A cross-sectional study on tobacco use and dependence	2012	NIH Grant, the Harvard School Office for Enrichment Programs and the Harvard School of	Cross-sectional study	Women smokers	N=198 African American, N=730 White	A greater proportion of menthol smokers smoked their first cigarette within five minutes of waking ($p < 0.01$)…

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	among women: Does menthol matter?		Dental Medicine				The ANOVAs conducted showed no significant menthol preference main effects on cigarettes per day, age of smoking initiation…
Rostron B.	NNAL exposure by race and menthol cigarette use among US smokers.	2012 (epub)	No funding source(s). Author affiliated with FDA	Nationally representative survey (NHANES)	NHANES smoker participants from 2007-2010 (age ≥20)	N=1614	Menthol cigarette use was associated with lower NNAL concentrations among smokers overall. This difference was principally due to lower NNAL concentrations for menthol smokers compared with nonmenthol smokers among White smokers. Nicotine and carcinogen exposure as measured by NNAL and cotinine generally increases with CPD across race/ethnicity groups for U.S. smokers.
Rostron B.	Lung cancer mortality risk for U.S. menthol cigarette smokers.	2012	No funding source(s). Author affiliated with FDA	Nationally representative survey (NHIS-CCS)	Adult participants (age ≥ 18) who were smokers identified with either menthol or nonmenthol preference (pack verified)	N=4832	The HR for lung cancer mortality for menthol smokers at ages 50 and over was 0.59 (95% CI = 0.37 – 0.95).
Sarkar M, Wang J, Liang Q	Metabolism of nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-lbutanone (NNK) in menthol and non-menthol cigarette smokers	2013	No funding source(s). Authors affiliated with Altria Client Services	Multi-center, cross-sectional study (TES)	Adult participants (age ≥21) who reported smoking ≥1cpd for at least the past 12 months	N=1044 menthol; 2297 nonmenthol	Race, machine-smoked tar, age and menthol by age interaction term were statistically significant factors for the 3OHCOT glucuronide ratios. The biomarkers of exposure (NE, total NNAL, carboxyhemoglobin and serum cotinine) were not statistically significantly different (p>0.05).
Strasser AA, Ashare RL, Kaufman M, Tang KZ, Mesaros AC, Blair IA.	The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses.	2013	NIH Grants	Human laboratory study	Adult smokers (age 21-65); smoke ≥10 cpd, smoke menthol cigarettes at least 80% of the time	N=32	…the experimental group exhibited a marginal increase in total puff volume from period 1 (own brand) to period 2 (menthol; P = 0.06) and from period 2 (menthol) to period 3 (non-menthol; P = 0.06) and a significant increase between periods 1 and 3 (P = 0.02). There was a significant decrease in CO boost

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							from period 1 (baseline) to period 2 (menthol; mean difference=1.6 ppm, SE=0.47, P=0.033), but there was no difference between period 2 and 3 (non-menthol; P = 0.32) for the experimental group… Cotinine values had a similar pattern as the nicotine values; there were no significant main effects or interaction effect.
Topp R, Winchester L, Mink AM, Kaufman JS, Jacks DE.	Comparison of the effects of ice and 3.5% menthol gel on blood flow and muscle strength of the lower arm.	2011	No funding(s) sources. Authors affiliated with the University of Louisville	Human laboratory study	Healthy adults (mean age 24.4)	N=17	…at 5 minutes after application of the menthol gel blood flow significantly declined in the radial artery by 42%.
Topp R, Winchester LJ, Schilero J, Jacks D.	Effect of topical menthol on ipsilateral and contralateral superficial blood flow following a bout of maximum voluntary muscle contraction.	2011	University of Louisville Foundation, Hygienic Research Fund	Human laboratory study	Healthy adults (average age 24.19±2.97)	N=16	…the application of either 3.5% menthol gel or 10% menthol wipe to the thigh decreases blood flow… The application of 3.5% menthol gel or a 10% menthol wipe reduced arterial popliteal diameter on the side receiving these treatments...
Valero ML, Mello de Queiroz F, Stühmer W, Viana F, Pardo LA.	TRPM8 ion channels differentially modulate proliferation and cell cycle distribution of normal and cancer prostate cells.	2012	Financed by the Max-Planck Society and grants SAF2010-14990 and PROMETEO2010-046, and a predoctoral fellowship from the Spanish government.	Nonclinical	Three human prostate cell lines (normal and cancerous)	N/A	We observed no consistent acceleration of growth after stimulation of the channel with menthol…
Villanti AC, Giovino GA, Barker DC,	Menthol brand switching among adolescents and	2012	Schroeder Institute for Tobacco Research and Policy Studies at Legacy	Longitudinal random-digit telephone	Smokers (age 16-24) who had ever smoked 20 lifetime cigarettes	N=1045	After 2 years, proportionately more baseline menthol smokers had switched to nonmenthol cigarettes (15.0%; 95% CI = 10.8%,19.2%)

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Mowery PD, Sevilimedu V, Abrams DB.	young adults in the National Youth Smoking Cessation Survey.			survey	and had smoked within the past 30 days		than baseline nonmenthol smokers had switched to menthol brands (6.9%; 95% CI = 4.9%,8.9%).
Vozoris NT.	Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study.	2012	No funding source(s). Author affiliated with Kingston General Hospital; Queen's University	National representative survey (2001-2008 NHANES)	Current smokers (age ≥20) with ascertained menthol smoker status	N=5028	After also controlling for health professional–diagnosed, self-reported hypertension, diabetes mellitus, and dyslipidemia, the odds of stroke remained significantly increased among all (OR, 2.19; 95% CI, 1.05-4.58), women (OR, 3.54; 95% CI, 1.60- 7.84), and non–African American (OR, 3.02; 95% CI, 1.24- 7.34) mentholated cigarette smokers vs respective nonmentholated cigarette smokers.
Widome R, Brock B, Noble P, Forster JL.	The relationship of neighborhood demographic characteristics to point-of-sale tobacco advertising and marketing.	2013	Grant from the Robert Wood Johnson Foundation; Minnesota Department o fHealth	Cross-sectional study with US Census	Licensed tobacco vendors in St. Paul, MN	N=654 stores	…higher minority proportion (and lower income) areas were more likely to have greater amounts of ads for menthol tobacco products. Stores in block groups that had greater proportions of African-Americans/ Blacks, Asians, people living in poverty, and/or under the age of 18 years tended to have more menthol advertising.
Willis DN, Liu B, Ha MA, Jordt SE, Morris JB.	Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants.	2011	NIH Grants and the American Asthma Foundation	Nonclinical	mice	N/A	…counterirritant effects of menthol in this mouse model are apparent at concentrations below or equal to those present in mentholated cigarette smoke.
Wilson N, Weerasekera D, Peace J, Edwards R.	Smokers have varying misperceptions about the harmfulness of menthol cigarettes:	2011	Health Research Council of New Zealand	Cross-sectional analysis of ITC (International Tobacco Control Policy Evaluation Survey) data	Adult smokers from the 2008/2009 wave who participated in this telephone survey	N=923	…some groups of smokers (particularly menthol users and Pacific smokers) believed that smoking menthol cigarettes was less harmful than regular cigarettes.

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	national survey data.						
Wise PM, Breslin PA, Dalton P.	Sweet taste and menthol increase cough reflex thresholds.	2012	NIH Grants and Kraft Foods	Human laboratory study	Healthy adults (age 23-36); 12 nonsmokers, 1 light smoker	N=13	Inhalation of headspace above menthol solution decreased cough sensitivity, e.g., increased the concentration of capsaicin required to trigger cough, relative to inhalation of headspace above a solvent blank.
Wise PM, Preti G, Eades J, Wysocki CJ.	The effect of menthol vapor on nasal sensitivity to chemical irritation.	2011	Institutional funds from the Monell Chemical Senses Center	Human laboratory study	Healthy adults (age 21-46	N=22	Pretreatment with menthol vapor decreased sensitivity to nasal irritation from acetic acid (participants required higher concentrations to lateralize) but increased sensitivity to allyl isothiocyanate (lower concentrations were required).
Wu X, Desai KG, Mallery SR, Holpuch AS, Phelps MP, Schwendeman SP.	Mucoadhesive fenretinide patches for site-specific chemoprevention of oral cancer: enhancement of oral mucosal permeation of fenretinide by coincorporation of propylene glycol and menthol.	2012	Fanconi Anemia Research Fund and NIH grants	Nonclinical (porcine buccal preparation)	N/A	N/A	vitro and in vivo release of fenretinide from patch was not significantly increased by coincorporation of permeation enhancers, indicating that mass transfer across the tissue, and not the patch, largely determined the permeation rate control in vivo.
Yerger VB.	Menthol's potential effects on nicotine dependence: a tobacco industry perspective.	2011	DHHS Contract	Documents research	N/A	N=309 documents	The tobacco industry knows that menthol overrides the harsh taste of tobacco and alleviates nicotine's irritating effects, synergistically interacts with nicotine, stimulates the trigeminal nerve to elicit a 'liking' response for a tobacco product, and makes low tar, low nicotine tobacco products more acceptable to smokers than non-mentholated low delivery products.

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	market.						
Brinkman MC, Chuang JC, Gordon SM, Kim H, Kroeger RR, Polzin GM, Richter PA.	Exposure to and deposition of fine and ultrafine particles in smokers of menthol and nonmenthol cigarettes.	2012	Contract from the Centers for Disease Control and Prevention (CDC)	Nonclinical and Laboratory	Smokers (age 18-30) who smoked at least 1 pack/day for at least 6 months	N=9	… there were no significant differences measured in daily MLE *[mouth level exposure]* and participant specific mainstream smoke when participants smoked the two test cigarettes. There were no significant differences in the level of urinary cotinine between the menthol and the nonmenthol cigarettes. Urinary 1-HOP levels were not significantly different between the two test cigarettes. The menthol test cigarette showed a significantly higher number (11%) and mass (33%) of ultrafine particles than the nonmenthol test cigarette. Participants smoked significantly fewer menthol cigarettes/day… as compared to nonmenthol test cigarettes. …participants took longer puffs (0.24 s) and required a longer period of time (25 s) for each menthol cigarette, which resulted in a larger volume of smoke inhaled per menthol cigarette (73 ml/cigarette) as compared to nonmenthol.
Brody AL, Mukhin AG, La Charite J, Ta K, Farahi J, Sugar CA, Mamoun MS, Vellios E, Archie M, Kozman M,	Up-regulation of nicotinic acetylcholine receptors in menthol cigarette smokers.	2012	Tobacco-Related Disease Research Program, NIH grant, Veterans Affairs Type I Merit Review Award, endowment from the Richard Metzner Chair in Clinical Neuropharmacology	Clinical study	Healthy adult smokers (10-40 cpd)	N=22 menthol smokers, N=41 nonmenthol smokers	Menthol and non-menthol cigarette smokers did not differ on any demographic or rating scale measure, other than race/ethnicity… Follow-up tests revealed between-group differences for the brainstem, cerebellum and corpus callosum…

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Phuong J, Arlorio F, Mandelkern MA.							
Buday T, Brozmanova M, Biringerova Z, Gavliakova S, Poliacek I, Calkovsky V, Shetthalli MV, Plevkova J.	Modulation of cough response by sensory inputs from the nose - role of trigeminal TRPA1 versus TRPM8 channels.	2012	VEGA no 1/0031/11 and Centre of Experimental and Clinical Respirology II (CEKR) co-financed from EU sources	Human laboratory study	Healthy non-smoking adults (average age 23)	N=18	Both menthol isomers after nasal administration significantly modulated urge to cough, cough threshold, and total cough response probably via the reduction of airway irritation induced during capsaicin challenge.
Caraballo RS, Holiday DB, Stellman SD, Mowery PD, Giovino GA, Muscat JE, Eriksen MP, Bernert JT, Richter PA, Kozlowski LT.	Comparison of serum cotinine concentration within and across smokers of menthol and nonmenthol cigarette brands among non-Hispanic black and non-Hispanic white U.S. adult smokers, 2001-2006.	2011	No funding source(s). Authors affiliated with the Centers for Disease Control and Prevention, RTI International, Georgia State University, Columbia University, State University of New York at Buffalo, Penn State College of Medicine	Cohort survey (NHANES 2001-2006)	Smokers (age ≥20) who had smoked on the day of or the day prior to the NHANES visit	N=1943	Smoking a menthol cigarette brand versus smoking a nonmenthol cigarette brand was not associated (P< 0.05) with mean serum cotinine concentration in either black or white smokers. …only a minority (19.4%) of the sample of white smokers smoked menthol cigarettes, whereas the majority (73.9%) of black smokers smoked a menthol brand. Menthol cigarettes smoked by black smokers (1.24 mg) were on an average higher in FTC nicotine levels to the menthol cigarettes (0.94 mg) smoked by white smokers (P < 0.01).
Cheang WS, Lam MY, Wong WT, Tian XY, Lau CW, Zhu Z, Yao X, Huang Y.	Menthol relaxes rat aortae, mesenteric and coronary arteries by inhibiting calcium influx	2013	National Basic Research Program of China, a research grant from Research Grants Council of Hong Kong, and CUHK Focused Investment Scheme B.	Nonclinical	Rat tissue, cell culture	N/A	The present study demonstrates that menthol relaxes rat arteries through loweringCa2þ influx probably vianifedipine-sensitiveCa2þ channels in vascular smooth muscle. This effect appears independent of the reported TRPM8 activation.
Dauphinee AL,	Racial differences	2013	NIH grant	Longitudinal	6th-9th grade students	N=2589	On average, the proportion of cigarette ads that

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Doxey JR, Schleicher NC, Fortmann SP, Henriksen L.	in cigarette brand recognition and impact on youth smoking.			study with some cross-sectional analyses	(age 11-15) in Vallejo, California		featured a menthol brand (menthol share of voice) was 36.9% (SD = 18.3), which was higher than the average for the state (25.7% (SD = 26.1)… …provide the brand name: 52% for Camel, 36% for Marlboro, and 32% for Newport. The odds of smoking initiation increased by 49% for students who recognized the Newport brand at baseline.
Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB.	Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes.			Cross-sectional TUS-CPS	Black, White and Hispanic current smokers and those who have quit in the past 5 years	N=71,193 to 24,465 (depending on sample restrictions)	…there was a small but consistent relationship between menthol cigarettes and cessation, whereby smokers of menthol cigarettes were significantly less likely to have quit smoking than smokers of non-menthol cigarettes.
D'Silva J, Boyle RG, Lien R, Rode P, Okuyemi KS.	Cessation outcomes among treatment-seeking menthol and nonmenthol smokers.	2012	No funding source(s). Authors were affiliated with ClearWay Minnesota; University of Minnesota; Professional Data Analysts; Minnesota Department of Health	Cross-sectional survey with single follow-up	Cigarette smokers who called the Minnesota Quitline and registered for services	N=1172 menthol smokers, N=5085 nonmenthol smokers	…the odds of quitting for menthol smokers was not significantly different from nonmenthol smokers (OR 1.29, 95% CI 0.77, 2.15) after controlling for the other covariates.
Faseru B, Choi WS, Krebill R, Mayo MS, Nollen NL, Okuyemi KS, Ahluwalia JS, Cox LS.	Factors associated with smoking menthol cigarettes among treatment-seeking African American light smokers.	2011	NIH Grant	Clinical trial	Treatment-seeking African-American light (≤10 cpd) smokers	N=452 menthol, N=88 nonmenthol	Table 1 Baseline characteristics of AA menthol and non-menthol smokers in KIS III.
Faseru B, Nollen NL, Mayo MS, Krebill R, Choi	Predictors of cessation in African American light smokers	2013	NIH Grants; NRSA grant, American Cancer Society Institutional Research Grant	Clinical trial	Treatment-seeking African-American light (≤10 cpd) smokers	N=540	Our current study has demonstrated a robust effect of menthol on smoking cessation. African American light smokers of menthol cigarettes were less likely to quit smoking compared to

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WS, Benowitz NL, Tyndale RF, Okuyemi KS, Ahluwalia JS, Sanderson Cox L.	enrolled in a bupropion clinical trial.						non-menthol cigarette smokers.
Fowler P, Smith K, Young J, Jeffrey L, Kirkland D, Pfuhler S, Carmichael P.	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type.	2012	European Cosmetic Industry Association, UK National Centre for the 3Rs (NC3Rs)	Nonclinical	6 in vitro cell lines	N/A	It was cytotoxic, inducing at least 50% reduction in RI at the top concentrations scored, but there were no increases in MN frequency. In other cases (e.g., d,l-menthol), testing was limited by cytotoxicity, and even though required levels of cytotoxicity were induced, MN were not.
Frasnelli J, Albrecht J, Bryant B, Lundström JN.Frasnelli J, Albrecht J, Bryant B, Lundström JN.	Perception of specific trigeminal chemosensory agonists.	2011	Postdoctoral fellowship from the Canadian Institutes of Health Research	Human laboratory study	Healthy adults with no reductions in sense of smell	N=20	All stimuli clearly activated the trigeminal system as demonstrated by the ease subjects had in lateralizing them. The scores for menthol and eucalyptol showed the highest correlation (r20 0.79; P< 0.001), Eucalyptol and menthol were described as predominantly cool (2.4 p and 2.3 p, respectively), fresh (both 1.4 p) and tickling (0.5 p and 0.7 p, respectively).
Gordon SM, Brinkman MC, Meng RQ, Anderson GM, Chuang JC, Kroeger RR, Reyes IL, Clark PI.	Effect of cigarette menthol content on mainstream smoke emissions.	2011	Battelle internal research and development funds	Nonclinical	N/A	N/A	Menthol in the TPM samples obtained from the cigarettes at each of the menthol levels investigated showed a linear increase with applied menthol concentration, but the amounts of nicotine, target TSNAs, PAHs, cotinine, and quinolone in the cigarettes remained essentially unchanged. Similarly, yields of the targeted VOCs in mainstream smoke from the MEN cigarettes that were measured in real-time on a puff-by-puff basis in whole smoke were largely unaffected by the levels of menthol present in

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							the cigarettes.
Hans M, Wilhelm M, Swandulla D.	Menthol suppresses nicotinic acetylcholine receptor functioning in sensory neurons via allosteric modulation.	2012	Altria Client Services, Inc.	Nonclinical	Nicotinic acetylcholine receptors (native and recombinant)	N/A	…we show that nAChRs expressed in sensory neurons are reversibly inhibited by menthol with an IC50 of 111 IM. Single channel recordings from human a4b2 nAChR in HEK tsA201 cells revealed that menthol causes an increase in single channel amplitude, a shorting of channel open time and a prolongation of its close time. We conclude that the mechanism underlying the menthol-mediated inhibition of nAChR is due to an allosteric modulation of the nAChR by menthol.
Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP.	Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods.	2012	California's Tobacco-Related Disease Research Program grant	Cross-sectional study	Stores within walking distance of California high schools	N=407	For each 10 percentage point increase in the proportion of Black students, the proportion of menthol advertising increased by 5.9 percentage points… The menthol share of voice increased by 11.6 percentage points with each 10 percentage-point increase in the proportion of neighborhood residents ages 10–17 years. For each 10 percentage-point increase in the proportion of Black students, the odds of a store advertising a Newport promotion were 1.5 times greater
Hickman NJ 3rd, Delucchi KL, Prochaska JJ.	Menthol use among smokers with psychological distress: findings from the 2008 and 2009 National Survey on Drug Use and Health.	2012	NIH grants	Nationally representative cohort study (NSDUH)	Current smokers (age ≥18) who answered the item on menthol use	N=24157	The prevalence of menthol smoking among this national sample of current smokers was 33.3%. The prevalence of menthol use was higher among individuals with severe psychological distress, women, young adults, African Americans, Native Hawaiians/Pacific Islanders, persons with fewer years of education and lower income, the unmarried and uninsured.

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Janssens A, Voets T.	Ligand stoichiometry of the cold- and menthol-activated channel TRPM8.	2011	Grants from the Belgian Federal Government, the Research Foundation-Flanders, and the Research Council of the KU Leuven	Nonclinical	TRPM8 ion channels expressed in HEK293 cells	N/A	This indicates that TRPM8 can simultaneously bind up to four menthol molecules, resulting in a stepwise stabilization of the open state.
Jones MR, Apelberg BJ, Samet JM, Navas-Acien A.	Smoking, menthol cigarettes, and peripheral artery disease in U.S. adults.	2012	NIH Grants	Nationally representative survey from 1999-2004 (NHANES)	Adults (age ≥ 40)	N=5973	Serum cotinine and blood cadmium concentrations were also higher in smokers of menthol cigarettes compared to smokers of nonmenthol cigarettes… We observed no significant difference in the association between smoking and peripheral artery disease for current smokers of nonmenthol and menthol cigarettes (p value for heterogeneity = 0.59).
Jones MR, Apelberg BJ, Tellez-Plaza M, Samet JM, Navas-Acien A.	Menthol cigarettes, race/ethnicity, and biomarkers of tobacco use in U.S. adults: the 1999-2010 National Health and Nutrition Examination Survey (NHANES).	2012	NIH grants	Cohort nationally representative survey from 1999-2010 (NHANES)	Adult current smokers (including White, African American and Mexican American smokers)	N=4603	In a representative sample of U.S. adult smokers, current menthol cigarette use was associated with increased concentration of blood cadmium, an established carcinogen and highly toxic metal, but not with other biomarkers. A total of 3,210 (74.3%) participants smoked nonmenthol cigarettes compared with 1,393 (25.7%) participants who smoked menthol cigarettes… After further adjustment for race/ethnicity, the corresponding ratios were markedly decreased and no longer statistically significant for serum cotinine (1.03; 95% CI, 0.9)
Kabat GC, Shivappa N, HÃ©bert JR.	Mentholated cigarettes and smoking-related cancers revisited: an ecologic	2012	NIH Grants	Multiple years of SEER data	Case and controls: lung. esophageal, oropharyngeal, laryngeal cancer	Not given/Not appropriate	Given the large differences in exposure to mentholated cigarettes by race and sex, if menthol had a discernible effect on the risk of smoking-related cancers, one might expect to see one or both of the following patterns: (1)

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	examination.						higher incidence rates among Blacks of both sexes compared to their White counterparts; (2) differences in the temporal trends between Blacks and Whites of both sexes.
Kramlinger VM, von Weymarn LB, Murphy SE.	Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, Î²-nicotyrine and menthol.	2012	NIH Grants	Nonclinical	In vitro	N/A	Inhibition of CYP2A6 by menthol was 100 times less potent (Ki of 100mM). There was no indication that menthol inactivated CYP2A6 or CYP2A13.
Levy DT, Blackman K, Tauras J, Chaloupka FJ, Villanti AC, Niaura RS, Vallone DM, Abrams DB.	Quit attempts and quit rates among menthol and nonmenthol smokers in the United States.	2011	Legacy	Nationally representative cross-sectional TUC-CPS from 2003 and 2006/7	Adult smokers who had smoked at least 100 cigarettes and are either current or former smokers	Unknown	Table 1 presents the proportions of smokers and former smokers who quit within the past 5 years by cigarette type. In both 2003 and 2007, about 70% smoked nonmenthol, 26% smoked menthol, and 4% had no preference. Although they had a higher likelihood of a quit attempt, menthol smokers compared with nonmenthol smokers were 4% less likely to have quit successfully in the past year in 2003 and 12%less likely in 2007.
Lu S, Baad-Hansen L, List T, Zhang Z, Svensson P.	Somatosensory profiling of intra-oral capsaicin and menthol in healthy subjects	2013	NIH research grant	Human laboratory study	Healthy adults (mean age 31.5±7.5)	N=15	More than half (9/15) of the subjects reported mild levels of pain during menthol application. Our study showed that topical application of menthol on the gingiva elicited cold and warmth hyperesthesia…
Millqvist E, Ternesten-Hasséus E, Bende M.	Inhalation of menthol reduces capsaicin cough sensitivity and influences inspiratory flows in	2013	Grants from the Regional Health Care Authority of West Sweden, the Swedish Asthma and Allergy Association and the Swedish Heart and	Human laboratory study	Patients: non-smokers with histories of cough and other airway symptoms induced by environmental irritants (average age 51).	N=14 (patients) N=15 (controls)	We conclude that in patients with chronic cough that is not caused by asthma, COPD or infections, pre-inhalation of menthol reduces cough sensitivity to inhaled capsaicin and influences inspiratory flows.

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	chronic cough.		Lung Foundation		Controls: healthy non-smokers (average age 52).		
Muscat JE, Liu HP, Stellman SD, Richie JP Jr.	Menthol smoking in relation to time to first cigarette and cotinine: results from a community-based study.	2012	NIH Grants; contracts from DHHS; Pennsylvania Department of Health	Human laboratory study	Daily smokers (≥5 cpd for one or more years)	N=495	. Overall there was a trend between menthol smoking and a shorter TTFC ($P < 0.02$). When analyzed by race, the trend was significant in black subjects ($P < 0.04$). The time to first cigarette ($P < 0.01$) but not menthol ($P = 0.66$) was significantly associated with cotinine levels.
Naziroğlu M, Ozgül C.	Effects of antagonists and heat on TRPM8 channel currents in dorsal root ganglion neuron activated by nociceptive cold stress and menthol.	2012	No funding source(s). Authors affiliated with University of Suleyman Demirel, Turkey	Nonclinical	Rat dorsal root ganglia	N/A	In the current study, TRPM8 channels were activated by menthol.
Nelson PR, Chen P, Dixon M, Steichen T.	A survey of mouth level exposure to cigarette smoke in the United States.	2011	No funding source(s). Authors affiliated with R.J. Reynolds Tobacco Company	Human study	Healthy smokers (≥7 cpd) who smoked one of the selected brand styles as their usual brand style	N= 1330	The regression lines for the menthol cigarettes fell slightly below those for the non-menthol cigarettes suggesting a trend towards slightly lower MLEs per cigarette for the menthol brand-styles. However, differences in the slopes and intercepts of the regression lines were not statistically significant.
Nonnemaker J, Hersey J, Homsi G, Busey A, Allen J, Vallone D.	Initiation with menthol cigarettes and youth smoking uptake.	2012	DHHS contract	Cross-sectional survey	Middle and high school students from 83 schools in seven communities and five states	N=638 (progression analysis) or N=399 (dependence analysis)	The models reveal a positive and statistically significant association between menthol at initiation [odds ratio (OR) = 1.8, confidence interval (CI): 1.02–3.16) and escalation to established smoking. As shown, initiation with menthol is associated

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							positively and significantly with nicotine dependence (b = 1.25, CI: 0.1–2.4).
Pereira EJ, Sim L, Driver H, Parker C, Fitzpatrick M.	The effect of inhaled menthol on upper airway resistance in humans: A randomized controlled crossover study.	2013	Research grants from the Ontario Thoracic Society, William M. Spear Foundation, Queen's University and Clinical Teachers Association at Queen's University	Human laboratory study	Healthy adults (age 21±0.5 years)	N=10	…90% of participants reported that they could breathe easier on the menthol test day. The present study demonstrated that cold receptor stimulation of the upper airway with inhaled menthol does not alter UAR *[upper airway respiration]* in conscious resting human subjects.
Reitzel LR, Li Y, Stewart DW, Cao Y, Wetter DW, Waters AJ, Vidrine JI.	Race moderates the effect of menthol cigarette use on short-term smoking abstinence.	2013	NIH Grant; CDC grant, The University of Texas MD Anderson Cancer Center	Cohort study	Current smokers (age 18-65), smoking ≥5 cpd for at least a year, willingness to quit	N=183	The main effects of menthol use status on continuous short-term smoking abstinence were not significant… Menthol use was significantly associated with short-term continuous smoking abstinence among White participants… White menthol users were about 5 times less likely to maintain continuous smoking abstinence than White nonmenthol users (odds ratio = 0.21, 95% CI = 0.05–0.98).
Reitzel LR, Nguyen N, Cao Y, Vidrine JI, Daza P, Mullen PD, Velasquez MM, Li Y, Cinciripini PM, Cofta-Woerpel L, Wetter DW.	Race/ethnicity moderates the effect of prepartum menthol cigarette use on postpartum smoking abstinence.	2011	NIH Grants	Clinical trial	Women who smoked prior to pregnancy and quit either during pregnancy or within 2 months of becoming pregnant	N= 123 menthol smokers, 121 nonmenthol smokers	White menthol users were less likely to maintain continuous abstinence than White non-menthol users.
Rosenbloom J, Rees VW, Reid K, Wong J, Kinnunen T.	A cross-sectional study on tobacco use and dependence	2012	NIH Grant, the Harvard School Office for Enrichment Programs and the Harvard School of	Cross-sectional study	Women smokers	N=198 African American, N=730 White	A greater proportion of menthol smokers smoked their first cigarette within five minutes of waking ($p < 0.01$)…

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	among women: Does menthol matter?		Dental Medicine				The ANOVAs conducted showed no significant menthol preference main effects on cigarettes per day, age of smoking initiation…
Rostron B.	NNAL exposure by race and menthol cigarette use among US smokers.	2012 (epub)	No funding source(s). Author affiliated with FDA	Nationally representative survey (NHANES)	NHANES smoker participants from 2007-2010 (age ≥20)	N=1614	Menthol cigarette use was associated with lower NNAL concentrations among smokers overall. This difference was principally due to lower NNAL concentrations for menthol smokers compared with nonmenthol smokers among White smokers. Nicotine and carcinogen exposure as measured by NNAL and cotinine generally increases with CPD across race/ethnicity groups for U.S. smokers.
Rostron B.	Lung cancer mortality risk for U.S. menthol cigarette smokers.	2012	No funding source(s). Author affiliated with FDA	Nationally representative survey (NHIS-CCS)	Adult participants (age ≥ 18) who were smokers identified with either menthol or nonmenthol preference (pack verified)	N=4832	The HR for lung cancer mortality for menthol smokers at ages 50 and over was 0.59 (95% CI = 0.37 – 0.95).
Sarkar M, Wang J, Liang Q	Metabolism of nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-lbutanone (NNK) in menthol and non-menthol cigarette smokers	2013	No funding source(s). Authors affiliated with Altria Client Services	Multi-center, cross-sectional study (TES)	Adult participants (age ≥21) who reported smoking ≥1cpd for at least the past 12 months	N=1044 menthol; 2297 nonmenthol	Race, machine-smoked tar, age and menthol by age interaction term were statistically significant factors for the 3OHCOT glucuronide ratios. The biomarkers of exposure (NE, total NNAL, carboxyhemoglobin and serum cotinine) were not statistically significantly different (p>0.05).
Strasser AA, Ashare RL, Kaufman M, Tang KZ, Mesaros AC, Blair IA.	The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses.	2013	NIH Grants	Human laboratory study	Adult smokers (age 21-65); smoke ≥10 cpd, smoke menthol cigarettes at least 80% of the time	N=32	…the experimental group exhibited a marginal increase in total puff volume from period 1 (own brand) to period 2 (menthol; P = 0.06) and from period 2 (menthol) to period 3 (non-menthol; P = 0.06) and a significant increase between periods 1 and 3 (P = 0.02). There was a significant decrease in CO boost

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							from period 1 (baseline) to period 2 (menthol; mean difference=1.6 ppm, SE=0.47, P=0.033), but there was no difference between period 2 and 3 (non-menthol; P = 0.32) for the experimental group… Cotinine values had a similar pattern as the nicotine values; there were no significant main effects or interaction effect.
Topp R, Winchester L, Mink AM, Kaufman JS, Jacks DE.	Comparison of the effects of ice and 3.5% menthol gel on blood flow and muscle strength of the lower arm.	2011	No funding(s) sources. Authors affiliated with the University of Louisville	Human laboratory study	Healthy adults (mean age 24.4)	N=17	…at 5 minutes after application of the menthol gel blood flow significantly declined in the radial artery by 42%.
Topp R, Winchester LJ, Schilero J, Jacks D.	Effect of topical menthol on ipsilateral and contralateral superficial blood flow following a bout of maximum voluntary muscle contraction.	2011	University of Louisville Foundation, Hygienic Research Fund	Human laboratory study	Healthy adults (average age 24.19±2.97)	N=16	…the application of either 3.5% menthol gel or 10% menthol wipe to the thigh decreases blood flow… The application of 3.5% menthol gel or a 10% menthol wipe reduced arterial popliteal diameter on the side receiving these treatments...
Valero ML, Mello de Queiroz F, Stühmer W, Viana F, Pardo LA.	TRPM8 ion channels differentially modulate proliferation and cell cycle distribution of normal and cancer prostate cells.	2012	Financed by the Max-Planck Society and grants SAF2010-14990 and PROMETEO2010-046, and a predoctoral fellowship from the Spanish government.	Nonclinical	Three human prostate cell lines (normal and cancerous)	N/A	We observed no consistent acceleration of growth after stimulation of the channel with menthol…
Villanti AC, Giovino GA, Barker DC,	Menthol brand switching among adolescents and	2012	Schroeder Institute for Tobacco Research and Policy Studies at Legacy	Longitudinal random-digit telephone	Smokers (age 16-24) who had ever smoked 20 lifetime cigarettes	N=1045	After 2 years, proportionately more baseline menthol smokers had switched to nonmenthol cigarettes (15.0%; 95% CI = 10.8%,19.2%)

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Mowery PD, Sevilimedu V, Abrams DB.	young adults in the National Youth Smoking Cessation Survey.			survey	and had smoked within the past 30 days		than baseline nonmenthol smokers had switched to menthol brands (6.9%; 95% CI = 4.9%,8.9%).
Vozoris NT.	Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study.	2012	No funding source(s). Author affiliated with Kingston General Hospital; Queen's University	National representative survey (2001-2008 NHANES)	Current smokers (age ≥20) with ascertained menthol smoker status	N=5028	After also controlling for health professional–diagnosed, self-reported hypertension, diabetes mellitus, and dyslipidemia, the odds of stroke remained significantly increased among all (OR, 2.19; 95% CI, 1.05-4.58), women (OR, 3.54; 95% CI, 1.60- 7.84), and non–African American (OR, 3.02; 95% CI, 1.24- 7.34) mentholated cigarette smokers vs respective nonmentholated cigarette smokers.
Widome R, Brock B, Noble P, Forster JL.	The relationship of neighborhood demographic characteristics to point-of-sale tobacco advertising and marketing.	2013	Grant from the Robert Wood Johnson Foundation; Minnesota Department o fHealth	Cross-sectional study with US Census	Licensed tobacco vendors in St. Paul, MN	N=654 stores	…higher minority proportion (and lower income) areas were more likely to have greater amounts of ads for menthol tobacco products. Stores in block groups that had greater proportions of African-Americans/ Blacks, Asians, people living in poverty, and/or under the age of 18 years tended to have more menthol advertising.
Willis DN, Liu B, Ha MA, Jordt SE, Morris JB.	Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants.	2011	NIH Grants and the American Asthma Foundation	Nonclinical	mice	N/A	…counterirritant effects of menthol in this mouse model are apparent at concentrations below or equal to those present in mentholated cigarette smoke.
Wilson N, Weerasekera D, Peace J, Edwards R.	Smokers have varying misperceptions about the harmfulness of menthol cigarettes:	2011	Health Research Council of New Zealand	Cross-sectional analysis of ITC (International Tobacco Control Policy Evaluation Survey) data	Adult smokers from the 2008/2009 wave who participated in this telephone survey	N=923	…some groups of smokers (particularly menthol users and Pacific smokers) believed that smoking menthol cigarettes was less harmful than regular cigarettes.

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	national survey data.						
Wise PM, Breslin PA, Dalton P.	Sweet taste and menthol increase cough reflex thresholds.	2012	NIH Grants and Kraft Foods	Human laboratory study	Healthy adults (age 23-36); 12 nonsmokers, 1 light smoker	N=13	Inhalation of headspace above menthol solution decreased cough sensitivity, e.g., increased the concentration of capsaicin required to trigger cough, relative to inhalation of headspace above a solvent blank.
Wise PM, Preti G, Eades J, Wysocki CJ.	The effect of menthol vapor on nasal sensitivity to chemical irritation.	2011	Institutional funds from the Monell Chemical Senses Center	Human laboratory study	Healthy adults (age 21-46	N=22	Pretreatment with menthol vapor decreased sensitivity to nasal irritation from acetic acid (participants required higher concentrations to lateralize) but increased sensitivity to allyl isothiocyanate (lower concentrations were required).
Wu X, Desai KG, Mallery SR, Holpuch AS, Phelps MP, Schwendeman SP.	Mucoadhesive fenretinide patches for site-specific chemoprevention of oral cancer: enhancement of oral mucosal permeation of fenretinide by coincorporation of propylene glycol and menthol.	2012	Fanconi Anemia Research Fund and NIH grants	Nonclinical (porcine buccal preparation)	N/A	N/A	vitro and in vivo release of fenretinide from patch was not significantly increased by coincorporation of permeation enhancers, indicating that mass transfer across the tissue, and not the patch, largely determined the permeation rate control in vivo.
Yerger VB.	Menthol's potential effects on nicotine dependence: a tobacco industry perspective.	2011	DHHS Contract	Documents research	N/A	N=309 documents	The tobacco industry knows that menthol overrides the harsh taste of tobacco and alleviates nicotine's irritating effects, synergistically interacts with nicotine, stimulates the trigeminal nerve to elicit a 'liking' response for a tobacco product, and makes low tar, low nicotine tobacco products more acceptable to smokers than non-mentholated low delivery products.

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