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Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, rm. 1061

**RE: Docket No. FDA-2013-N-0521**

November 22, 2013

Dear Commissioner Hamburg,

With this letter I would like to provide new scientific data in response to the pending inquiry of the Food and Drug Administration into the manufacture and sale of mentholated cigarettes.

As a Professor in the Department of Pharmacology at Yale School of Medicine I direct a research laboratory that investigates the effects of chemical irritants and natural products on the respiratory and nervous systems. Over the last 10 years my laboratory has made key discoveries related to the physiological and pharmacological effects of menthol, published in leading scientific journals such as Nature, the FASEB Journal and Pain [1-3]. Moreover, we identified a key respiratory irritant receptor, the TRPA1 ion channel, a discovery for which I was awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) by President Bush in 2007, among other honors [4-7].

Following the signing into law of the Smoking Prevention and Tobacco Control Act by President Obama in 2009 I submitted a research grant application to the National Institutes of Health proposing to investigate the effects of menthol in smoking using advanced molecular and physiological techniques. This application was funded by grant 5R01HL105635 since 1/1/2011 and we were recently awarded a FDA-supported supplement to this grant (5R01HL105635-03S1). Additional support is provided by the new Yale Tobacco Center of Regulatory Research (TCOR P50DA036151).

Supported by these programs the research in my laboratory has progressed rapidly, and I would like to take this opportunity to describe our most recently published research data to further inform FDA's evaluation of menthol as a cigarette additive. These data were published in 2011 and in 2013 [1,2], and only the 2011 paper was briefly mentioned in FDA's recent *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes (Reference Addendum)*. This FDA-issued document provides a very comprehensive description of menthol's pharmacology. The purpose of the present submission is to summarize new data from my laboratory that were published afterwards, or were insufficiently discussed.

**Summary of newly published data**

**1. Menthol is a potent and efficacious respiratory counterirritant, strongly reducing respiratory irritation by the major tobacco smoke irritants.**

In our paper published in 2011 we performed a thorough analysis of the effects of vaporized menthol on the respiratory irritation response to three major tobacco smoke irritants, acrolein, cyclohexanone and acetic acid in mice [2]. Mice respond to respiratory irritant exposures with respiratory depression, a characteristic drop in the respiratory rate. This response is mediated by airway-innervating sensory neurons expressing chemical irritant receptors such as TRPA1, activated by acrolein. We hypothesized that menthol would suppress the irritant response through activation of cold-sensing nerve endings in the upper airways. Indeed, we observed profound counterirritant effects of menthol towards all three smoke irritants tested, occurring at menthol concentrations similar to those measured in smoke of mentholated cigarettes [2]. ***These data document that menthol has potent and efficacious pharmacological effects masking the presence of inspired irritants.***

**2. Menthol has analgesic action towards multiple forms of acute and inflammatory pain.**

Menthol is widely used as an analgesic. However, very few studies have been published so far examining the pain modalities inhibited by menthol. Pain is mediated by somatosensory neurons very similar to the neurons innervating the airways sensing smoke irritants. We performed a detailed and systematic study in mice, documenting that L-menthol (the isomer also added to cigarettes) is a potent and efficacious analgesic of a wide range of acute and chronic inflammatory pain modalities. L-menthol inhibited capsaicin (TRPV1)-, acrolein (TRPA1)-, heat (TRPV1)- and acid-induced pain in mice [1]. L-menthol also diminished pain in an inflammatory model, the widely used CFA (complete Freund's adjuvant) model of inflammatory mechanical hyperalgesia [1]. ***These findings document that menthol has similar effects in both the respiratory system and in pain, inhibiting the irritating and painful effects of a wide range of chemical stimuli.***

**3. Menthol's pharmacological actions in the respiratory and pain systems are mediated by the TRPM8 receptor.**

The two studies published by us in 2011 and 2013 made use of TRPM8-deficient mice and a selective TRPM8-inhibitors (AMG2850, from Amgen Pharmaceuticals, or AMTB, GSK Pharmaceuticals) to probe the role of this menthol-activated ion channels in the counterirritant and analgesic action of menthol . The analgesic action of L-menthol was completely eliminated in TRPM8-deficient mice, and in mice treated with the TRPM8 antagonist [1]. A TRPM8 antagonist also inhibited the effects of menthol on respiratory irritation by acrolein, the major cigarette smoke irritant [2]. ***Together, these observations support the exclusive role of TRPM8 in mediating menthol-induced counterirritation in the airways and of menthol analgesia.***

**4. Synthetic and natural menthol analogs have similar pharmacological actions mediated by the TRPM8 receptor.**

In our 2013 publication we also investigate the pharmacological actions of a synthetic menthol analog, named WS-12 ((1R*,2S*)-N-(4-Methoxyphenyl)-5-methyl-2-(1-methylethyl)cyclohexanecarboxamide), CAS 68489-09-8) [1]. WS-12 was developed by the consumer products company, Wilkinson Sword, in a search to generate new cooling agents with properties superior to menthol [8]. Menthol may cause irritation due to its poor selectivity and its high volatility (especially in the eyes), and its minty smell and chemical instability may not desirable for some products [2].

Similar to L-menthol, treatment of mice with WS-12 caused profound analgesia of a wide range of pain modalities, including capsaicin (TRPV1)-, acrolein (TRPA1)- and heat-induced pain (Figure 5 of [1]). In all cases, the analgesic effects of WS-12 were eliminated in TRPM8-deficient mice.

We also examined the pharmacological effects of eucalyptol, the cooling natural product in the oil of the eucalyptus tree. Eucalyptol caused TRPM8-dependent analgesia of acid-induced pain, very similar to L-menthol (Figure 3 of [1]).

***Together, our data suggest that synthetic and natural menthol analogs have the same analgesic and counterirritant pharmacological effects as menthol.***

**Recommendations**

Our data clearly demonstrate that menthol has potent and efficacious effects in the respiratory system of mammals, effects that are mediated largely by the TRPM8 ion channels in sensory nerve endings leading to suppression of the sensation of irritation. Based on these findings we are concerned that menthol may inhibit irritation also in smokers. Especially in initiating smokers the addition of menthol is likely to diminish aversion to smoke inhalation, resulting in absorbance of higher amounts of nicotine and acceleration of becoming addicted to nicotine. ***Thus, our data strongly support the concern of the Tobacco Products Scientific Advisory Committee to the FDA "that the availability of menthol cigarettes has led to an increase in the number of smokers and that this increase does have adverse public health impact in the United States.".***

Based on our data we recommend that the addition of L-menthol to cigarettes should not be permitted. Menthol, even at vapor concentrations 30-fold below of those typically found in smoke of mentholated cigarettes, had significant counterirritant effects towards acrolein, the major tobacco smoke irritants.

Moreover, we also observed that a synthetic sensory cooling agent, WS-12, and a natural product known to activate TRPM8, eucalyptol, had effects very similar to menthol. We therefore suggest that, ***in addition to menthol, no permission should be given to add any other synthetic or natural TRPM8 agonists to tobacco***. The consumer product and flavor industry has identified a wide range of novel synthetic cooling agents, with the intention to add these to processed foods, topical treatments and many other products. This discovery process has strongly improved since TRPM8 was cloned as the major cold receptor, allowing high throughput discovery of novel ligands. In addition to published compounds such as WS-12 and WS-23 (added to chewing gum products, for example) a wide range of proprietary cooling agents are developed, several receiving GRAS (generally recognized as safe) approval. Therefore, FDA is advised against controlling the use of individual cooling agents in tobacco, since these can be chemically modified and repurposed. Rather, it is advised that FDA considers control of all synthetic and natural TRPM8 agonists.

Please don't hesitate to contact me if you have further questions.

Yours sincerely,

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Appendix: References and new publications from Jordt laboratory

## References


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