



Deniz Bagdas, DVM, PhD  
Eric J. Nunes, PhD  
Nii A. Addy, PhD  
Stephanie O'Malley, PhD  
Andrew Strasser, PhD

October 13, 2019

**To:** Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**Subject:** Tobacco Products; Required Warnings for Cigarette Packages and Advertisements; Proposed Rule (Docket No. FDA-2019-N-3065)

Dear Acting Commissioner Sharpless,

We appreciate the opportunity to offer recommendation on the Tobacco Products; Required Warnings for Cigarette Packages and Advertisements Proposed Rule.

We came together as a unique group of preclinical, clinical, and regulatory scientists to comment on Docket FDA-2019-N-3065. We would like to take this opportunity to describe why menthol cigarette packages need additional information on menthol's ability to increase nicotine dependence. Drs. Bagdas, Nunes, and Addy have expertise in behavioral neuroscience and in the biology of nicotine addiction and dependence, and drug abuse. Their preclinical research revealed that oral menthol increases nicotine taking behavior in rodents. Dr. Addy is a co-PI of preclinical studies at the Yale Tobacco Center of Regulatory Science (TCORS) and his projects are focused on investigating the effects of flavors, particularly menthol, on nicotine dependence. Dr. O'Malley is co-director of the Yale TCORS with a broad knowledge of mentholated tobacco product use in adolescent and adults. Dr. Strasser's work focuses on the impact of advertising, marketing and labeling on risk perceptions and tobacco product use. Taken together, this group of scientists have specific knowledge and expertise that is valuable for this public comment. In

response to this request for comment about proposed rules regarding required warnings for cigarette packages and advertisements, **we recommend FDA inform smokers about the harmful effects of menthol on packages of menthol cigarettes.**

**Background:**

**Menthol is not an inert flavor; it impacts nicotine use.**

Nicotine addiction continues to be a major health concerns in the US and worldwide. Nicotine is the main active ingredient in tobacco smoke that leads to and maintains tobacco addiction (Benowitz, 2009). Flavorings, such as menthol, have been shown to enhance the appeal of nicotine taking behavior in humans (Kong et al., 2015; Krishnan-Sarin et al., 2017; Villanti et al., 2017) and rodents (Bagdas et al., 2019; Wickham et al., 2018). Preclinical studies reveal that menthol increases oral nicotine intake (Bagdas et al., 2019; Fan et al., 2016; Wickham et al., 2018), enhances nicotine intravenous (i.v.) self-administration (Palmatier et al., 2019), reduces oral nicotine aversion (Fan et al., 2016) and enhances nicotine reward that is evidenced by increases in dopamine neuron firing (Henderson et al., 2017, 2016). Consistently, human data suggest that menthol enhances nicotine dependence (Delnevo et al., 2011; Garten and Falkner, 2004; Giovino et al., 2015). In addition to the sensory effects of menthol, the literature supports that menthol also alters brain physiology. For example, menthol cigarette smokers show higher upregulation of nicotinic receptors than non-menthol smokers (Brody et al. 2013). Furthermore, menthol cigarette use is popular among young smokers (Delnevo et al., 2016; Nonnemaker et al., 2012; Rath et al., 2015). As a result of smoking menthol cigarettes, young people may increase smoking frequency and nicotine intake, which has detrimental effects on the developing brain and may make it more difficult to quit smoking (Yuan et al., 2015).

In November 2018, the Food and Drug Administration proposed to ban menthol cigarettes (Wailoo, 2019). We strongly recommend this ban. However, in the meantime, **we suggest that cigarette packaging inform smokers about the harmful effects of menthol. This would be an intermediate step prior to a ban on menthol cigarettes. And, should the menthol ban be delayed through litigation, the package warnings may serve a more prolonged and substantial purpose.** Because of the demonstrated potentiating effects of menthol on nicotine use and addiction, we recommend that warnings for menthol cigarettes include information about the risks of menthol.

Moreover, while a ban of menthol cigarettes could have a positive effect on public health, menthol is also found in other tobacco products such as electronic nicotine delivery systems (i.e. e-cigarettes), little cigars and cigarillos, cigars, smokeless tobacco, and dissolvable tobacco products (Odani et al., 2019; Villanti et al., 2017). Therefore, we believe that new package warnings about menthol will increase awareness of harmful effects of menthol in cigarettes and other tobacco products.

The effects of menthol on nicotine intake and dependence result from its pharmacological effects. We summarized these effects below.

**Menthol and its impact on nicotine:** Menthol, a flavor in cigarettes and alternative tobacco products, is found naturally in peppermint and corn mint plant oils. Menthol is preferred by ~25% of US smokers with 80% of African-American smokers consuming menthol cigarettes primarily (Giovino et al., 2004; TPSAC, 2011). It appeals to young inexperienced smokers and menthol in cigarettes may facilitate the initiation of smoking (Caraballo and Asman, 2011). There is growing evidence that smokers find it harder to quit menthol cigarettes versus non-menthol ones (Foulds et al., 2010; Rojewski et al., 2014; Uhl et al., 2011). Menthol cigarettes will be banned in 2020 in European countries, but not in the US. The typical menthol cigarette contains 1–20 mg of menthol (Ai et al., 2015) and ~1 (0.03-2.3) mg of nicotine (Rodgman and Perfetti, 2013). The effects of menthol on nicotine's behavioral effects have been clarified enough to suggest cigarette packaging should inform smokers about the harmful effects of menthol.

1. **Menthol increases nicotine addiction:** One effect of menthol is on the metabolism of nicotine (Alsharari et al., 2015; Benowitz et al., 2004; Hoffman, 2011; Kramlinger et al., 2012; MacDougall et al., 2003). Menthol reduces nicotine metabolism (Alsharari et al., 2015; Benowitz et al., 2004; Fagan et al., 2016) which could lead to higher plasma nicotine levels to further promote nicotine addiction.
2. **Menthol enhances nicotine intake:** Menthol is a potent ligand for transient receptor potential (TRP) cation channels, including TRPM8 (cold-sensitive) (Lau et al., 2014; Macpherson et al., 2006; Sherkheli et al., 2010). Menthol's sensory effects may lead to an increase in nicotine intake through a "cooling" effect and/or masking the bitter taste of nicotine. Indeed, it has been reported in mice that oral menthol can reduce the aversive effects of oral nicotine through actions at TRPM8 receptors (Fan et al., 2016). In addition, menthol affects the TRPA1 receptors to alter irritation (Talavera et al., 2009). Menthol increases nicotine intake in rodents (Bagdas et al., 2019; Wickham et al., 2018), as well

as enhances the appeal of nicotine taking behavior in humans (Kong et al., 2015; Krishnan-Sarin et al., 2017; Villanti et al., 2017).

3. **Menthol acts on nicotinic receptors:** Menthol is a non-competitive antagonist for multiple nicotinic acetylcholine receptors (nAChRs), such as the  $\alpha 4\beta 2$ ,  $\alpha 7$  and  $\alpha 3\beta 4$  nAChR subtypes (Ashoor et al., 2013; Hans et al., 2012; Ton et al., 2015). Indeed, it has been shown that application of menthol (30  $\mu$ M) inhibits expressed  $\alpha 7$  nAChR with a potency (IC<sub>50</sub>) of 30  $\mu$ M (Ashoor et al., 2013), compared to (EC<sub>50</sub> = 196  $\mu$ M) in activating TRPM8 channels, the cold receptor (Sherkheli et al., 2010). These reports suggest that, the  $\alpha 7$  nAChRs may play an important role in some of the effects of menthol. Moreover, chronic systemic exposure to relatively high doses of menthol causes an upregulation of  $\beta 2$  and  $\alpha 4$  nAChR subunit levels in several brain regions in mice (Alsharari et al., 2015). Menthol alone upregulates  $\alpha 4^*$  and  $\alpha 6^*$  nAChR subunits in midbrain DA neurons (Henderson et al., 2016). Human study also showed that menthol cigarette smokers tend to upregulate  $\beta 2^*$  nAChRs more than non-menthol cigarette smokers (Brody et al., 2013).
4. **Menthol enhances the reinforcing actions of nicotine.** Systemic menthol injections increased intra-venous self-administration (IVSA) of nicotine in male Sprague-Dawley rats in a dose-dependent manner (Biswas et al., 2016). Additionally, oral menthol cues facilitate IVSA via its cooling effect in adolescent female rats (Wang et al., 2014). These reports strongly support the hypothesis that menthol facilitates nicotine reinforcement and increases nicotine consumption via central and sensory mechanisms, respectively.

**Thus, menthol is not simply a flavoring agent but has pharmacological characteristics that can modulate the effects of nicotine.** Because of the demonstrated effects of menthol on nicotine use and addiction, we strongly recommend additional warnings for menthol cigarettes to include information about its risks. **Examples of warnings include: “menthol increases dependence on nicotine”, “menthol makes it harder to quit smoking”, “menthol impacts brain function”, etc. Please see additional examples below.**

Examples of suggested menthol cigarette warnings.



In conclusion, the FDA should consider requiring the inclusion of menthol's harmful effects on nicotine use on menthol cigarette packaging. Thank you for the opportunity to provide these recommendations and for taking action to advance the public's awareness of the effects of menthol on smoking.

Sincerely,

**Deniz Bagdas, DVM, PhD, Eric J. Nunes, PhD, Nii A. Addy, PhD, Stephanie O'Malley, PhD**  
Yale Tobacco Center of Regulatory Science, Department of Psychiatry, Yale School of  
Medicine, New Haven, CT, USA.

**Andrew A. Strasser, PhD**

Center for Interdisciplinary Research on Nicotine Addiction, Department of Psychiatry, Perelman  
School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

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