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1401 H Street, NW | Suite 740
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202-898-6499 | 202-898-0966 Fax
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Dockets Management Staff (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted to: https://www.federalregister.gov/documents/2022/05/04/2022-08994/tobacco-product-standard-for-menthol-in-cigarettes#open-comment

RE: Docket No. FDA-2021-N-1349, Tobacco Product Standard for Menthol in Cigarettes

To Whom It May Concern:

On behalf of the American Association for Cancer Research's (AACR) more than 50,000 laboratory researchers, physician-scientists, other health professionals, and patient advocates who constitute our national and international membership, we thank the U.S. Food and Drug Administration (FDA) for the opportunity to express our support for FDA's proposed tobacco product standard that prohibits menthol cigarettes and to suggest some additional ways to strengthen the overall proposal.

Tobacco use is responsible for more than 480,000 premature deaths in the United States every year (1). Smoking tobacco products is known to cause 18 types of cancer, accounting for 19 percent of all cancers diagnosed in the United States and nearly 30 percent of cancer deaths each year (2). In addition, more than 85 percent of annual lung cancer cases and deaths are attributed to smoking. These effects are driven by the incredibly addictive nature of nicotine and the high levels of carcinogens resulting from burning tobacco (3–5). As detailed below and in the draft product standard, menthol increases the addictiveness of nicotine and associated harms of inhaling combustion-related carcinogens.

The Family Smoking Prevention and Tobacco Control Act (TCA) required FDA to determine if the continued market availability of menthol was "appropriate for the protection of public health." Scientific evidence has strongly supported the public health benefits of prohibiting menthol in cigarettes for more than a decade, as determined by the FDA Tobacco Products Scientific Advisory Committee in 2011 (6). Partially due to the relatively steady levels of menthol cigarette use while non-mentholated cigarette use declined (7), the market share of menthol cigarettes increased from 29 percent of all cigarettes sold in 2009 to 37 percent in 2020 (8). Additionally, predatory advertising practices from the tobacco industry have resulted in disproportionately high rates of menthol cigarette smoking among racial and ethnic minority groups. For example, 84.6 percent of African Americans who smoke use menthol cigarettes (9). Between 1980 and 2018, menthol cigarettes were responsible for an additional 10.1 million Americans initiating smoking, and an estimated additional 378,000 premature deaths (10). Furthermore, 157,000 of the additional premature deaths (41 percent) caused by menthol cigarettes were among African Americans, despite only comprising approximately 12 percent of the U.S. population (11). These health disparities caused by the tobacco industry's business practices are unacceptable.

A large body of evidence demonstrates menthol increases the harms of tobacco use by increasing the ease of initiation and decreasing success of cessation attempts (12–18). Increased abundance of nicotinic acetylcholine receptors in human brains and inhibition of nicotine metabolism by menthol cigarette use are key mechanisms that enhance the addictiveness of nicotine (19–21). For these reasons, AACR issued a policy statement in 2010 and also joined 17 other organizations in signing a Citizen's Petition in 2013 urging the FDA to take the much needed action it is now proposing (22,23). AACR appreciates the opportunity to once again support this important regulation.

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AACR Strongly Supports a Tobacco Product Standard that Prohibits Menthol-Flavored Cigarettes, and It Should be Strengthened to Prohibit Any Amount of Natural or Synthetic Cooling Agent

Overall, the proposed product standard is very strong and clearly details the scientific and legal justification for prohibiting menthol as a characterizing flavor. It is estimated this product standard would prevent 650,000 premature deaths from tobacco related illness in the United States by 2060 (24). AACR particularly appreciates and supports that the product standard includes tobacco product accessories, flavoring added to packaging, and product labeling. These provisions will help address loopholes used by the tobacco industry to circumvent the spirit of a similar menthol cigarette ban in the European Union (25). However, the definition of characterizing flavor could be improved with further clarification that sets clear limits on allowable levels of small molecule cooling agents. AACR is concerned about a potential loophole whereby tobacco manufacturers could argue the presence of a low level of menthol or odorless and tasteless synthetic cooling agents do not constitute a "characterizing flavor," but nonetheless reduce irritation from smoke and increase appeal of harmful products (26). The cooling and analgesic properties of menthol contribute significantly to tobacco product appeal and initiation, according to independent scientific studies as well as the tobacco industry's own findings (17,27–30).

It is notable that nearly all cigarettes contain amounts of menthol greater than levels naturally occurring in tobacco plants, whether marketed as mentholated cigarettes or not (31–34). In tobacco plants, Paschke, *et al.* detected very low naturally occurring levels of the cooling agents menthol (0.30 ppm), linalool (0.31 ppm), and carvone (0.28 ppm) (34). Concentrations of menthol vapors as low as 8 ppm have been shown to significantly attenuate the irritating effects of smoke and smoke constituents in mice via activation of the TRPM8 receptor (21,35), the primary protein responsible for a cold sensation in mammals. At least one type of cigarette branded as a non-menthol cigarette had detectable menthol concentrations greater than 100 ppm prior to burning (32). Furthermore, following a ban on menthol as a characterizing flavor in the European Union, alternative natural and synthetic cooling agents have been detected in combustible cigarettes (33), representing a significant loophole based on a definition of characterizing flavor instead of a clear threshold of cooling agent concentrations. Of particular concern are the synthetic Wilkinson Sword (WS) cooling agents that are odorless and flavorless, but still capable of providing a cooling sensation via activation of the TRPM8 receptor (33,34,36,37). Setting definitive thresholds for the amount of TRPM8 agonists, within the proposed characterizing flavor definition would enable more effective and objective implementation of the product standard by creating clear metrics for enforcement actions. For these reasons, AACR recommends FDA specify maximum allowed concentrations of natural and synthetic cooling agents within the product standard that do not exceed natural levels of cooling agents found in tobacco plants (i.e., no flavoring or cooling agents may be added to cigarettes in any way). In summary, the tobacco industry should not be allowed to increase the addictiveness of their products by masking the taste or harshness of cigarette smoke with any amount of added small molecules. FDA should revisit specific thresholds on cooling agents and cellular receptors if new biological insights suggest alternate receptors can elicit these effects.

Examples of menthol cigarette bans demonstrate they are effective at reducing smoking. A recent analysis of a menthol cigarette ban in Canada found that 21.2 percent of adults who mainly smoked menthol cigarettes had quit smoking compared to 13.2 percent of adults who did not smoke menthol cigarettes between 2016 and 2018 (38). Extrapolating this effect size to U.S. adults who mainly smoke menthol cigarettes on a daily basis would estimate nearly 800,000 more adults quitting smoking due to a ban on menthol cigarettes. In June 2020, Massachusetts implemented a comprehensive ban on flavored cigarettes and cigars. In the year following the ban, per capita menthol cigarette sales declined 92 percent and overall cigarette sales declined 33 percent (39). In comparison states during the same time frame, per

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capita menthol sales declined 3 percent and overall cigarette sales declined 4 percent. These real-world results demonstrate that prohibition of menthol flavors benefits and promotes public health.

Responses to Solicited Questions:

AACR Supports Further Efforts to Emphasize the Product Standard Does Not Criminalize Personal Use or Possession of Tobacco Products

The draft product standard and the TCA clearly delineate that the FDA's current authority regarding enforcement of tobacco regulations pertains exclusively to the manufacture, distribution, importation, and sale of tobacco products. AACR recognizes there are concerns regarding local law enforcement efforts for tobacco products and related violence disproportionately affecting historically marginalized racial and ethnic minority groups. However, these concerns are not applicable to FDA's current jurisdiction regarding the development of federal tobacco product standards to promote public health. Historical predatory marketing practices of the tobacco industry targeted vulnerable populations as a business strategy to maintain market share as overall smoking rates declined (27,40). It is important to emphasize that the proposed product standard will rectify the tobacco industry's damage done to the health of African Americans and other historically marginalized groups. AACR encourages FDA to continue emphasizing its specific role to enforce federal tobacco regulations as well as engage with the U.S. Department of Justice, state and local agencies, and community stakeholders to address disparate enforcement of local and state tobacco laws and regulations.

AACR Strongly Disagrees with Exempting Certain Cigarette Products from the Menthol Rule

Exempting any cigarette product from this product standard would allow a dangerous loophole for the tobacco industry to exploit. While very low nicotine cigarettes (VLNCs) reduce smoking and increase abstinence compared to standard cigarettes, menthol significantly reduces these effects. A secondary analysis of a clinical trial examining the effect of switching to VLNCs found that compared to standard nicotine content cigarettes, those who chose to smoke non-mentholated VLNCs had an odds ratio of 9.11 for abstinence at week 20, while participants who chose to smoke mentholated VLNCs had an odds ratio of 1.88 (41). This finding suggests that allowing an exemption for mentholated VLNCs would reduce the cessation promoting effects of VLNCs substantially. This finding supports the inclusion of VLNCs in the proposed product standard.

In conclusion, AACR supports the proposed product standard to prohibit menthol flavored cigarettes. However, the proposed definition of characterizing flavor could be further strengthened by specifying a threshold amount of natural or synthetic cooling agents allowed in cigarettes, based on naturally occurring levels in tobacco plants. This clarification would increase the ease of regulatory enforcement and ensure the tobacco industry does not violate the spirit of the new rule with alternative cooling agents that may not meet the criteria of having a characterizing flavor. It would also benefit public health if FDA were to establish a similar threshold for tobacco product sweeteners. Additionally, the TCA tasks FDA with developing product standards appropriate for public health based on scientific evidence, and therefore concerns regarding local law enforcement agencies outside of FDA's jurisdiction should not impact the federal rule making process. Lastly, AACR believes there should be no exemptions from the product standard. These comments are based on careful discussion and evaluation by the AACR's Tobacco Products and Cancer Subcommittee (roster attached) and are approved by AACR's CEO, Chair of the Tobacco Products and Cancer Subcommittee, and Chair of the Science Policy and Government Affairs

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Committee. If AACR can provide any additional information or assistance to FDA, please do not hesitate to contact Dana Acton, Director of Science Policy and Legislative Affairs, at dana.acton@aacr.org.

Thank you again for the opportunity to comment on this important issue.

Sincerely,

Margaret Foti, PhD, MD (h.c.)
Chief Executive Officer
American Association for Cancer Research

Roy S. Herbst, MD, PhD
Chair, Science Policy and Government Affairs Committee
Chair, Tobacco Products and Cancer Subcommittee
American Association for Cancer Research

References

1. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK179276/

2. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68:31–54.

3. Benowitz NL. Nicotine addiction. N Engl J Med. 2010;362:2295–303.

4. Palmer AM, Toll BA, Carpenter MJ, Donny EC, Hatsukami DK, Rojewski AM, et al. Reappraising choice in addiction: novel conceptualizations and treatments for tobacco use disorder. Nicotine Tob Res. 2021;

5. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst. 1999;91:1194–210.

6. FDA Tobacco Products Scientific Advisory Committee. Preliminary scientific evaluation of the possible public health effects of menthol versus nonmenthol cigarettes. 2011; Available from: https://www.fda.gov/media/86497/download

7. Mattingly DT, Hirschtick JL, Meza R, Fleischer NL. Trends in prevalence and sociodemographic and geographic patterns of current menthol cigarette use among U.S. adults, 2005–2015. Prev Med Rep. 2020;20:101227.

8. U.S. Federal Trade Commission. Cigarette Report for 2020. 2021. Available from: https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2020-smokeless-tobacco-report-2020/p114508fy20cigarettereport.pdf

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9. Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. Tob Control. BMJ Publishing Group Ltd; 2016;25:ii14–20.

10. Le TT, Mendez D. An estimation of the harm of menthol cigarettes in the United States from 1980 to 2018. Tob Control. BMJ Publishing Group Ltd; 2021;

11. Mendez D, Le TTT. Consequences of a match made in hell: the harm caused by menthol smoking to the African American population over 1980–2018. Tob Control. 2021;

12. Villanti AC, Johnson AL, Halenar MJ, Sharma E, Cummings KM, Stanton CA, et al. Menthol and mint cigarettes and cigars: initiation and progression in youth, young adults and adults in waves 1–4 of the PATH study, 2013–2017. Nicotine Tob Res. 2020;23:1318–26.

13. Villanti AC, Collins LK, Niaura RS, Gagosian SY, Abrams DB. Menthol cigarettes and the public health standard: a systematic review. BMC Public Health. 2017;17:983.

14. Hersey JC, Nonnemaker JM, Homsi G. Menthol cigarettes contribute to the appeal and addiction potential of smoking for youth. Nicotine Tob Res. 2010;12:S136–46.

15. Okuyemi KS, Faseru B, Sanderson Cox L, Bronars CA, Ahluwalia JS. Relationship between menthol cigarettes and smoking cessation among African American light smokers. Addiction. 2007;102:1979–86.

16. Leas EC, Benmarhnia T, Strong DR, Pierce JP. Effects of menthol use and transitions in use on short-term and long-term cessation from cigarettes among US smokers. Tob Control. 2021;

17. Kingsbury JH, Mehrotra K, D'Silva J, Nichols E, Tripp R, Johnson D. Perceptions of menthol cigarettes and reasons for unsuccessful quits in an African American community sample. J Immigr Minor Health. 2021;23:137–44.

18. Leas EC, Benmarhnia T, Strong DR, Pierce JP. Use of menthol cigarettes, smoking frequency, and nicotine dependence among US youth. JAMA Netw Open. 2022;5:e2217144.

19. Brody AL, Mukhin AG, La Charite J, Ta K, Farahi J, Sugar CA, et al. Up-regulation of nicotinic acetylcholine receptors in menthol cigarette smokers. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2013;16:957–66.

20. Benowitz NL, Herrera B, Jacob P. Mentholated cigarette smoking inhibits nicotine metabolism. J Pharmacol Exp Ther. American Society for Pharmacology and Experimental Therapeutics; 2004;310:1208–15.

21. Ha MA, Smith GJ, Cichocki JA, Fan L, Liu Y-S, Caceres AI, et al. Menthol attenuates respiratory irritation and elevates blood cotinine in cigarette smoke exposed mice. PLOS ONE. Public Library of Science; 2015;10:e0117128.

22. Tobacco Control Legal Consortium. Citizen petition: asking the U.S. Food and Drug Administration to prohibit menthol as a characterizing flavor in cigarettes. St. Paul, MN; 2013. Available from: https://www.publichealthlawcenter.org/sites/default/files/resources/tclc-fdacitizenpetition-menthol-2013.pdf

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23. Viswanath K, Herbst RS, Land SR, Leischow SJ, Shields PG, Writing Committee for the AACR Task Force on Tobacco and Cancer. Tobacco and Cancer: An American Association for Cancer Research policy statement. Cancer Res. 2010;70:3419–30.

24. Levy DT, Meza R, Yuan Z, Li Y, Cadham C, Sanchez-Romero LM, et al. Public health impact of a US ban on menthol in cigarettes and cigars: a simulation study. Tob Control. 2021;tobaccocontrol-2021-056604.

25. Brink A-L, Glahn AS, Kjaer NT. Tobacco companies' exploitation of loopholes in the EU ban on menthol cigarettes: a case study from Denmark. Tob Control. 2022;

26. Krishnan-Sarin S, Green BG, Kong G, Cavallo DA, Jatlow P, Gueorguieva R, et al. Studying the interactive effects of menthol and nicotine among youth: an examination using ecigarettes. Drug Alcohol Depend. 2017;180:193–9.

27. Klausner K. Menthol cigarettes and smoking initiation: a tobacco industry perspective. Tob Control. 2011;20:ii12–9.

28. Yerger VB, McCandless PM. Menthol sensory qualities and smoking topography: a review of tobacco industry documents. Tob Control. 2011;20:ii37–43.

29. Dessirier J, Omahony M, Carstens E. Oral irritant properties of menthol: sensitizing and desensitizing effects of repeated application and cross-desensitization to nicotine. Physiol Behav. 2001;73:25–36.

30. Wackowski OA, Evans KR, Harrell MB, Loukas A, Lewis MJ, Delnevo CD, et al. In their own words: young adults' menthol cigarette initiation, perceptions, experiences and regulation perspectives. Nicotine Tob Res. 2018;20:1076–84.

31. Ai J, Taylor KM, Lisko JG, Tran H, Watson CH, Holman MR. Menthol content in US marketed cigarettes. Nicotine Tob Res. 2016;18:1575–80.

32. Ai J, Taylor KM, Lisko JG, Tran H, Watson CH, Holman MR. Menthol levels in cigarettes from eight manufacturers. Tob Control. 2018;27:335–6.

33. Reger L, Moß J, Hahn H, Hahn J. Analysis of menthol, menthol-like, and other tobacco flavoring compounds in cigarettes and in electrically heated tobacco products. Contrib Tob Nicotine Res. 2018;28:93–102.

34. Paschke M, Tkachenko A, Ackermann K, Hutzler C, Henkler F, Luch A. Activation of the cold-receptor TRPM8 by low levels of menthol in tobacco products. Toxicol Lett. 2017;271:50–7.

35. Willis DN, Liu B, Ha MA, Jordt S-E, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB J. 2011;25:4434–44.

36. Leventhal AM, Tackett AP, Whitted L, Jordt SE, Jabba SV. Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: a review. Tob Control. 2022;Published Online First.

37. Jabba SV, Erythropel HC, Torres DG, Delgado LA, Woodrow JG, Anastas PT, et al. Synthetic cooling agents in US-marketed e-cigarette refill liquids and popular disposable e-cigarettes: chemical analysis and risk assessment. Nicotine Tob Res. 2022;ntac046.

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38. Fong GT, Chung-Hall J, Meng G, Craig LV, Thompson ME, Quah ACK, et al. Impact of Canada's menthol cigarette ban on quitting among menthol smokers: pooled analysis of pre–post evaluation from the ITC Project and the Ontario Menthol Ban Study and projections of impact in the USA. Tob Control. BMJ Publishing Group Ltd; 2022;

39. Asare S, Majmundar A, Westmaas JL, Bandi P, Xue Z, Jemal A, et al. Association of cigarette sales with comprehensive menthol flavor ban in Massachusetts. JAMA Intern Med. 2022;182:231–4.

40. Campaign for Tobacco Free Kids, African American Tobacco Control Leadership Council, Association of Black Cardiologists, Inc., Black Women's Health Imperative, The Center for Black Health & Equity, National Association for the Advancement of Colored People, et al. Stopping menthol, saving lives: ending big tobacco's predatory marketing to Black communities. 2021. Available from: https://www.tobaccofreekids.org/assets/content/what_we_do/industry_watch/menthol-report/2021_02_tfk-menthol-report.pdf

41. Denlinger-Apte RL, Kotlyar M, Koopmeiners JS, Tidey JW, Luo X, Benowitz NL, et al. Effects of very low nicotine content cigarettes on smoking behavior and biomarkers of exposure in menthol and non-menthol smokers. Nicotine Tob Res. 2019;21:S63–72.

AACR Tobacco Products and Cancer Subcommittee Roster

1401 H Street, NW | Suite 740
Washington, DC 20005
202-898-6499 | 202-898-0966 Fax
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***Stephanie R. Land, PhD, *ex officio* (NCI liaison)**
Program Director and Statistician
Tobacco Control Research Branch
Behavioral Research Program
Division of Cancer Control and Population Sciences
National Cancer Institute
Bethesda, MD
***As *ex officio* NCI liaison, Stephanie Land is not an author or signatory to this comment.**

Scott J. Leischow, PhD
Professor and Director of Clinical and Translational Science
College of Health Solutions
Arizona State University
Phoenix, Arizona

Timothy R. Rebbeck, PhD
Vincent L. Gregory, Jr. Professor of Cancer Prevention, Harvard TH Chan School of Public Health and Division of Population Sciences, Dana Farber Cancer Institute
Boston, MA

Nancy A. Rigotti, MD
Professor of Medicine
Professor of Population Medicine
Harvard Medical School
Director, Tobacco Research and Treatment Center
Massachusetts General Hospital
Boston, MA

Peter G. Shields, MD
Deputy Director, Comprehensive Cancer Center
Professor, College of Medicine
Julius F. Stone Chair in Cancer Research
James Cancer Hospital
The Ohio State University Wexner Medical Center
Columbus, OH

Avrum E. Spira, MD, MSc
Professor of Medicine, Pathology and Bioinformatics
Global Head, Johnson & Johnson Lung Cancer Initiative
Boston University School of Medicine
Boston, MA

Benjamin A. Toll, PhD
Professor of Public Health Sciences and Psychiatry
Vice Chair for Research, Public Health Sciences
Chief of Tobacco Cessation and Health Behaviors
Co-Director, Lung Cancer Screening Program
Hollings Cancer Center
Director, MUSC Health Tobacco Treatment Program
Medical University of South Carolina
Charleston, SC

Kasisomayajula (Vish) Viswanath, PhD
Lee Kum Kee Professor of Health Communication
Harvard T. H. Chan School of Public Health
Dana-Farber Cancer Institute
Director, Center for Translational Health Communication Science, DFCI/HSPH
Director, Harvard Chan India Research Center
Co-Director, Lee Kum Sheung Center for Health and Happiness
Boston, MA

Wendell Gray Yarbrough, MD, MMHC, FACS
Chair, Thomas J. Dark Distinguished Professor
University of North Carolina at Chapel Hill
Otolaryngology, UNC Comprehensive Cancer Support Program
Chapel Hill, NC