

Menthol cigarettes: Research needs and challenges

Jack E. Henningfield, Mirjana V. Djordjevic

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The First Conference on Menthol Cigarettes: Setting the Research Agenda provided a forum for discussion of the origins, uses, and health consequences of adding menthol to cigarettes.¹ A major purpose of the conference was to review the state of the science on menthol cigarettes, identify knowledge gaps, and set an agenda for research that would lay the foundation for improving public health by reducing tobacco-caused disease. The conference planning process made evident the many ways that addition of menthol to cigarettes may have contributed to tobacco-attributable addiction, morbidity, disability, and mortality as well as to tobacco use and health disparities among specific population groups. Thus, individuals representing wide tobacco research diversity were invited to present papers on menthol cigarettes and participate in discussions in order to thoroughly evaluate the state of knowledge and the needs for future research. Papers published in this supplement to *Nicotine & Tobacco Research* are based on those presentations and provide an invaluable platform for drawing general conclusions about the potential role of menthol in initiation and progression of smoking as well as in the augmentation of tobacco-related disease burden. These conclusions have major implications for public health interventions. Equally important, the papers identified major gaps in knowledge that stand as barriers to tobacco disease control. Addressing

the research needs and challenges implied by these knowledge gaps could significantly contribute to improved public health.

This paper summarizes research needs and challenges discussed at the conference as well as several that emerged as the presenters prepared their papers for publication in this volume. Some general conclusions and observations from the conference are summarized in the following list.

- The factors which contribute to the addictiveness and toxicity of menthol cigarettes, their patterns of actual use, their social place, and their marketing and advertising, must be well understood in order to control tobacco disease.
- Menthol is a specific ingredient that is not necessary to the function or use of cigarettes. However, it is very plausible that smoking menthol cigarettes contributed to tobacco-caused disease by one or more mechanisms. These include but are not limited to the following: increased toxicity of cigarette smoke, increased addictiveness of cigarettes, altered patterns of smoke inhalation, and marketing and branding strategies that have served well to establish and sustain cigarette smoking in various populations.
- Compared to other U.S. subpopulations, African Americans have been disproportionately exposed to menthol cigarettes, been targeted by aggressive menthol cigarette marketing, and as a result smoke predominantly menthol cigarette brands. It is notable that the marketing to and the prevalence of menthol cigarette use among other ethnic minorities appear to have increased in recent years.
- Continuing progress in reducing the prevalence and health effects of smoking, particularly, in ethnic minority populations, will require a substantial increase in the knowledge about the use and effects of menthol in tobacco.
- There is a strong need for research by the public health scientific community to address the diversity of research challenges.
- A strong science base is critical to the rational

Jack E. Henningfield, Ph.D., Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, and Pinney Associates, Bethesda, MD; and Mirjana V. Djordjevic, Ph.D., Tobacco Control Research Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.

¹The conference was not intended to serve as a consensus conference, and some participants may not agree with the conclusions and research recommendations contained in this paper. Therefore, the authors accept full responsibility for trying to faithfully distill the extensive discussions into the conclusions and research recommendations presented here.

Correspondence: Jack E. Henningfield, Ph.D., Pinney Associates, Inc., 4800 Montgomery Lane, Suite 1000, Bethesda, MD 20814-3472 USA. Tel.: +1 (301) 718-8440; Fax: +1 (301) 718-0034; E-mail: jhenning@pinneyassociates.com

development of policy and potential regulation of tobacco product design, advertising, and marketing.

Cross-cutting research issues and challenges

At the menthol conference, and as evident in the articles in this supplement, several major cross-cutting research issues and challenges were evident. Some of these issues also have been discussed elsewhere with respect to menthol and other tobacco product ingredients and emissions (Henningfield et al., 2003; World Health Organization, 2001; World Health Organization Scientific Advisory Committee on Tobacco Product Regulation, 2003) but are more implicit in the research questions outlined in this paper. For example,

- Does menthol make cigarettes more addictive?
- Does menthol make cigarettes more toxic or carcinogenic?
- Does menthol play a role in initiation and progression of smoking as well as in deterring cessation?
- How does menthol affect cigarette smoking topography and other smoking behaviors?
- What are the underlying reasons for profound ethnic and cultural differences in menthol cigarette use and tobacco-related disease outcomes?
- What knowledge does the tobacco industry have that bears on these issues?

From the presentations and discussions at the conference, and the papers published in this supplement, several areas of research focus emerged, each posing distinct challenges. The articles in this supplement provide comprehensive background and great detail for consideration regarding these research areas.

Menthol pharmacology and toxicology

Research challenges. Because of the widespread use of menthol in foods and drugs, a substantial but by no means comprehensive base body of research exists on the pharmacology (including toxicology) of menthol in cigarette smoke as discussed by Ahijevych and Garrett (2004). The fact that the age-adjusted smoking-related lung cancer death rates in the United States were about 50% higher among Black male cigarette smokers (most of whom smoked menthol-treated cigarettes) in 1990 compared with White smokers (Centers for Disease Control and Prevention [CDC], 2003) suggests that menthol addition to cigarettes may increase the carcinogenic potential of the smoke.

The major gap in this research domain concerns the effects of menthol when it is added to cigarettes and ingested in the form of cigarette smoke inhalation. Thus, it is important to address not only the pharmacology of menthol inhaled by way of cigarette smoke but also how the pharmacology of the smoke is changed by the addition of menthol. The first issue is complex enough because it involves assessing the

effects of menthol when inhaled deeply into the lung approximately 200–300 times per day over several decades (Djordjevic et al., 2002).² The second issue is far more complex because the burning cigarette functions as a microchemical factory in which about 3000 substances present in tobacco yield more than 4,000 substances in the smoke of the cigarette (International Agency for Research on Cancer, in press). Introducing a single agent, such as menthol, may theoretically result in the additional formation of a number of substances in the inhaled smoke that would not have emerged had menthol not been present. Addressing such questions requires sophisticated methods for tobacco product assessment. Presently, National Institutes of Health (NIH)-supported laboratories have a limited capacity for such research, although the CDC has developed its own laboratory in recent years and carries out studies on tobacco and smoke constituents (Stanfill et al., 2003; Wu, Ashley, & Watson, 2002).

Research questions.

- What are the pharmacological, physiological, and toxicological effects of repetitively inhaled menthol as a nontobacco additive?
- What new substances are emitted in cigarette smoke owing to the addition of menthol to the cigarette, and what are the effects of these substances?
- How do cigarette design characteristics (e.g., ventilation and filters) alter the resultant substances in the inhaled smoke of menthol-treated cigarettes?
- Does the smoke of menthol-treated cigarettes cause or exacerbate cardiovascular disease, lung cancer, emphysema, or other diseases?
- Does the addition of menthol to cigarettes alter the inhaled dosages of other substances by reducing the irritant properties of the smoke and thereby enabling deeper inhalation?
- What are the influences of menthol and menthol metabolism on the metabolic activation or detoxification of carcinogens residing in tobacco smoke?
- Do adequately validated biomarkers exist that might reveal menthol-specific alteration of cigarette toxicity?

Behavioral effects of menthol

Research challenges. An extension of the pharmacology of menthol is the effects that contribute to the high addiction liability of cigarette smoke. Cigarettes have been documented to be among the most addictive of all substances (U.S. Department of Health and Human Services, 1988; Royal College of Physicians of London, 2000). However, it is plausible that menthol increases cigarette abuse liability either by direct pharmacological effect or by enabling deeper

²Blacks smoke on average 16 menthol cigarettes per day and draw 13 puffs per cigarette whereas Whites smoke 20 menthol cigarettes per day and draw 14 puffs per cigarette.

and more efficient absorption of nicotine and other reinforcing substances in the smoke. Because cigarette smoking is controlled by the actions of nicotine in the brain, as well as by sensory effects of the smoke (e.g., Rose, 1996; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999), it is plausible that menthol could contribute to the reinforcement of cigarettes smoking by virtue of its own reinforcing effects and by serving as a sensory stimulus that effectively acquires conditioned reinforcing properties. Menthol also might facilitate the absorption of nicotine by its potential actions to mitigate the noxious effects of the smoke. Finally, menthol might provide a sensory cue that people associate with therapeutically beneficial cough and cold, and throat medications that use menthol. These are all potential behavioral mechanisms by which menthol might contribute to the addictive potential of cigarettes. These possibilities were discussed at the conference as well as in this issue (Ahijevych & Garrett, 2004) and elsewhere (Henningfield et al., 2003).

Research questions.

- Are menthol's pharmacological and physiological effects mediated by menthol-specific receptor(s) or some other nervous system-mediated action?
- What is the role of menthol in tobacco addiction and reinforcement? In the absence of nicotine, is menthol reinforcing?
- Is the role of menthol in enhancing cigarette attractiveness more analogous to the apparently synergistic role of acetaldehyde with nicotine (Belluzi, Wang, & Leslie, 2003; Food and Drug Administration [FDA], 1996) or more like flavorings and agents added to increase the sensory palatability of cigarette smoke?
- Does menthol alter the sensory characteristics of cigarettes so as to alter the palatability of cigarettes and thereby make them more acceptable for some populations?
- Do menthol smokers smoke cigarettes differently than nonmenthol smokers, and, if so, are these differences caused by menthol or are they related to differences in people who smoke menthol cigarettes?
- Do differences exist in cigarette smoking topography in relation to the interaction of race and ethnicity, sex, and menthol cigarette preference?

Social and marketing issues with menthol cigarettes

Research challenges. The conference showed that menthol has indisputably been a powerful marketing tool and that important social implications are associated with being a menthol cigarette smoker (Gardiner, 2004; Sutton & Robinson, 2004). It is plausible that the addition of menthol to cigarettes provided a powerful marketing tool to enlist

compelling social forces that have contributed to initiation and maintenance of smoking in persons who might not otherwise have taken up smoking or persisted in smoking (Sutton & Robinson). Understanding these relationships and their genesis could be critical for the development of more effective prevention and cessation strategies to reach these populations as well as regulatory strategies to more effectively prevent such manipulation of population behavior if that is what occurred through the use of menthol treatment of cigarettes and its associated marketing. Exploring these relationships may require a combination of historical analysis, anthropological investigation, and social marketing research techniques that are not typically the focus of NIH research. However, the implications of the latter research for public health, for understanding behavior, and for developing the science foundation for improved public health are as important as the more biological research challenges and questions discussed earlier. The major question that needs to be answered is what drives the use of menthol cigarettes: (a) the preference of certain communities, such as Blacks, for the feel and impact of menthol or (b) the targeted marketing of mentholated brands to specific populations by the tobacco companies.

Research questions. The following questions also need to be a research focus:

- Did the effectiveness of menthol marketing to Blacks depend on preexisting social or biological factors, and, if so, what were they?
- Are other population segments being steered toward menthol cigarettes using marketing approaches based on gender, race and ethnicity, age, mental health, sexual orientation, cultural background, state, or other demographics in ways that are similar to what occurred with Blacks?
- Does any relationship exist between marketing and the uptake of mentholated products by population subgroups as well as the tobacco disease burden?
- Does an association exist between use of menthol cigarettes and illicit drugs?
- Why has the use of menthol cigarettes reached a plateau at about 25% of the U.S. market?
- What characteristics of menthol (e.g., its history, its medicinal uses, its potential physical effects in smoking, its flavor and odor) made it such an effective marketing tool? What other potential cigarette additives might be expected to be similarly effective?
- What is the importance of consumer perceptions of menthol as a potential "harm reduction" additive, and what are the lessons of such knowledge for regulating potential future tobacco products in which harm or exposure reduction claims are contemplated?
- Are the factors accounting for population-specific differences in menthol use within the United States

similar to those accounting for the cross-national differences in menthol use reported elsewhere (Giovino et al., 2004)?

- What are the reasons for the large international variation in menthol cigarettes use (DMG World Media, 2001; Giovino et al., 2004)?

Some answers to the many questions posed in this supplement may be obtained by exploring more thoroughly the extensive research on menthol cigarettes featured in the tobacco industry documents, as shown by Wayne (2004).

Menthol cigarette research will be important to public health and policy

Developing a stronger scientific foundation is critical for meeting the diverse challenges that must be addressed to substantially reduce the adverse health effects of tobacco. At this point, it is difficult to estimate the impact of menthol addition to cigarettes in terms such as population prevalence of smoking, lung cancer risk, addictiveness, and other health effects (Giovino et al., 2004). However, it appears implausible that there have not been adverse health consequences due to the addiction. Resolving these issues may be important in improved efforts to prevent tobacco use initiation and the development of addiction, particularly in ethnic minority populations and among adolescents as discussed in the Brief Report in this issue (Moolchan, 2004). Similarly, given the possibility that menthol increases the addictiveness of cigarettes, deters quitting, or promotes relapse, resolving these issues will be important for achievement of higher rates of tobacco cessation, particularly among ethnic minority populations.

Regulatory implications exist relevant to potential regulation of tobacco by the FDA in the United States (Henningfield & Zeller, 2003; Kennedy, 2003) as well as by global regulatory efforts such as the World Health Organization's Framework Convention on Tobacco Control. For example, these efforts contemplate setting of standards or even bans on the use of additives and ingredients in cigarettes that adversely affect public health by increasing their toxicity and addictiveness. However, a science base will be critical to enable rational development of such regulation and is called for in efforts to develop such regulations. Whether or not menthol treatment of cigarettes warrants specific regulation must be determined with the strongest scientific base possible.

Implications beyond tobacco and health

The research challenges and questions summarized in this paper are not exhaustive, but we have attempted to summarize those representing the diversity of the conference. Some of the questions delve into areas

that will push the envelope of theory in certain areas, but their resolution may have important implications for understanding phenomena that do not necessarily involve tobacco. For example, do peripherally acting and centrally acting substances interact to produce a combination with stronger addictive effects than those of the drug (*viz.* nicotine) assumed to be primarily responsible for the high addiction potential of cigarettes, and if so, how? Advances in this area may have implications for the development and appropriate regulation of new medications for which a potential for abuse exists (Schuster & Henningfield, 2003).

Another such area with potential impact beyond tobacco and health is determination of the underlying mechanisms that account for the overwhelmingly strong preference for menthol cigarettes among Blacks, as compared with Whites. Specifically, is this purely a socially mediated phenomena fostered by the marketing practices of the tobacco industry, or does a genetically based component make Blacks particularly vulnerable to marketing efforts based on menthol? Resolving this question may have implications for other areas of health and marketing involving the increasingly diverse U.S. population.

The approach offered by Castro (2003) to study the interaction among physiological, behavioral, social, and cultural factors addresses one of the recurrent themes in the conference. Specifically, although it is a useful research strategy to isolate potential determinants of the menthol preference among Black and Hispanic populations, the patterns of menthol use at the population level are most plausibly the result of interactions of these factors. This approach, in turn, has implications for understanding other population-associated behaviors and may contribute to public health well beyond factors involving cigarette smoking.

How to move needed research forward

Although the conference was not able to exhaustively cover all aspects of menthol in cigarettes, and this brief paper has not attempted to capture all of the important research challenges and questions emerging from the conference, it remains evident that the challenges are enormous, important, and beyond the scope of any single government agency, such as NIH, the CDC, or the FDA, or nongovernmental research organization (e.g., The Institute for Cancer Prevention [formerly the American Health Foundation], the American Legacy Foundation, the Battelle Memorial Research Institute).

Yet each of these institutions and others have potential unique resources and expertise that could be brought to bear. For example, basic biological, epidemiological, and sociological research questions would appear well within the purview of NIH research

mandates and the expertise of its researchers. Within NIH, various institutes fund research and have a cadre of extramural and intramurally funded researchers with experience relevant to many of the challenges raised by this conference. For example, the National Cancer Institute has the expertise to unravel the potential role of menthol in cancer; the National Heart, Lung, and Blood Institute has the expertise to explore the potential role of menthol in lung and cardiovascular disease; the National Institute on Drug Abuse has the expertise to explore the potential role of menthol in the addicting effects of tobacco; and other NIH institutes could similarly be engaged to explore the range of potential effects of menthol in cigarette smoking. Arguably, such a coordinated assault would lead to more effective approaches to exploration of other existing or contemplated tobacco product constituents with respect to their health effects.

In addition to NIH, many other institutions have a potentially equally important role to play in contributing to public health in this area. The FDA has extensive experience in investigating the role of specific additives, determining the relevance of research to actual human use, evaluating the public health effects of marketing and communications based on those additives, and translating such research into regulatory policy. It is unclear whether the FDA requires authority to regulate tobacco products in order to justify the initiation of such research. The CDC has extensive experience in exploring the transmission of disease, including that spread by commercial products, that could be brought to bear to more systematically explore the role of menthol in the prevalence and patterns of menthol cigarette use and its role in disease production. The CDC also has an emerging laboratory capability that could explore many aspects of menthol chemistry, biomarkers of exposure, pharmacology, and toxicology.

Nongovernmental research organizations such as the Battelle Memorial Research Institute, whose scientists were active participants in the conference development and funding, also have a potential invaluable role to play in furthering the process of scientific discovery that is crucial to reducing the prevalence of tobacco use and tobacco-caused disease. For example, a variety of private laboratories, including Battelle, are experienced in the pharmacological (including toxicological) evaluation of food and drug additives, of aerosolized drugs, and of complex aerosols and vapors ranging from those emitted by cigarettes to those emitted by motor vehicles and power plants.

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