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What's New in *Nicotine & Tobacco Research*?

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Additives: Where the gaps are

Cigarettes have about 600 ingredients, but menthol is the only one the tobacco industry advertises and about which consumers make conscious buying choices. A fourth of all cigarettes sold in the United States are mentholated, but as this *N&TR* supplement—and the presentations at the First Conference on Menthol Cigarettes, convened in 2002, that it reports on—make abundantly clear, there are far more questions than answers about menthol's effects. The tobacco industry began looking into menthol's toxic effects in the 1940s, but health researchers have come to the table only in recent years. Clark and colleagues (p. S5) review some of the urgent questions on the research agenda:

- Does the popularity of menthol cigarettes among African Americans contribute to the health disparity between Euro American smokers, who smoke more, and African Americans, who have a higher incidence of smoking-related disease?
- A 1999 study revealed that the "tar," nicotine, carbon monoxide, and several carcinogenic compounds in the smoke from selected menthol cigarettes were 30% to 50% higher than in nonmenthol brands. Was that due to the menthol or to other factors, such as the filter system, paper quality, or amount of tobacco per cigarette?
- In another study, the biological marker for the potent carcinogen, polycyclic aromatic hydrocarbons, was 2.7 times higher in the urine of menthol smokers than in the urine of those who smoked nonmenthol brands. Was menthol the culprit, or some other factor, such as racial differences in metabolism, smoking styles, or susceptibility to disease?

"Studies of the epidemiology and toxicology of menthol cigarettes and behavioral issues involved in their use are beginning to receive appropriate attention," they note, but "significant gaps in knowledge persist." Filling those gaps will not only instruct about menthol's role in the initiation, progression and addiction to tobacco and its health consequences, but "it is hoped that studying menthol as an additive will lead to development of models to study the health impact of other cigarette additives and cigarette designs, including emerging potential reduced-exposure tobacco products."

Enormous, important challenges

Adding menthol to cigarettes may contribute to tobacco-related disease and death in many ways. Does it make cigarettes more addictive or more carcinogenic? Does it add new, possibly toxic, substances to cigarette smoke? Does it speed the absorption of nicotine in the mouth and lungs? Does it entice more people to smoke and deter them from quitting? Does it cause smokers to inhale more deeply, to take bigger puffs, to hold them longer? Is menthol so much more appealing to African Americans than other groups because of taste preference, or is it because of skillful marketing?

Answering such questions will require the efforts of a rich diversity of researchers, write Henningfield and Djordjevic (p. S11) in summing up the challenges that emerged from the First Conference on Menthol Cigarettes. For example, "The burning cigarette functions as a micro chemical factory…. [I]t is important to address not only the pharmacology of menthol inhaled by way of cigarette smoke, but also to address how the pharmacology of the smoke is changed by the addition of menthol."

A strong science base will be essential for informing public health and regulatory policies, they write. This can be achieved only by harnessing the resources of a broad range of government and nongovernment research agencies, because "the challenges are enormous, important, and beyond the scope of any single government agency." The challenges will require not only biological and behavioral research expertise, but historical analysis, anthropological investigation, and social marketing research not typical of the National

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Institutes of Health portfolio. The payoff of such research will be large, they point out. "Building capacity and infrastructure that can address the challenges and issues raised by menthol could also serve to prepare an infrastructure to address the many challenges that are emerging as we enter a century in which tobacco product modification, novel products, and potentially novel product ingredients and marketing may become the norm."

Menthol: So cool, soothing…and risky

It's known that menthol smokers have higher nicotine dependence, and that African American smokers are both three times more likely than Whites to prefer mentholated cigarettes and have lower quit rates. Might menthol be playing a part in their addiction by, for example, affecting nicotine's metabolism? Menthol cools and soothes, but current evidence suggests it also has many other—potentially dangerous—effects. Ahijevych and Garrett reviewed what research has been done (p. S17) and say much more study is warranted to answer this and a host of related questions, among them:

- Is menthol addictive on its own? Calcium aids the release of neurotransmitters, but menthol appears able to hinder that; if it does so in nerve cells that contain neurotransmitters involved in drug reinforcement, menthol may be able to enhance directly the reinforcing effects of tobacco.
- Menthol dilates bronchial tubes and increases drug absorption; does that mean more nicotine is absorbed in the lungs? It also enhances saliva flow; does that mean more nicotine is absorbed orally?
- By making smoke seem less harsh, does menthol encourage inhaling more deeply and holding the smoke longer?
- A menthol-sensitive receptor has been identified; does menthol produce central nervous system effects via specific binding sites, especially in those areas that mediate tobacco addiction and reinforcement?
- Menthol may inhibit detoxification of one tobacco carcinogen and lead to higher concentrations of another, but much more needs to be learned about the mechanisms involved. One study, for example, has shown that burning menthol at the same temperature as tobacco can produce a carcinogen.
- Six separate studies, some of men only and others of women only, produced conflicting results when they compared smoking patterns and exhaled carbon monoxide levels. Identifying the differences requires puff-monitoring research that combines both men and women, both African Americans and Whites, and both menthol and nonmenthol cigarette smoking.

Mapping menthol's popularity with minorities

The popularity of mentholated cigarettes among African Americans and Hispanics is likely the product of interactions among a variety of factors, from menthol's taste and physiological effects to targeted marketing by the tobacco industry that takes advantage of their cultural beliefs and self images. In his review of the literature, Castro (p. S29) identifies many of those factors and suggests two models for researchers to use in tracking them, one interactive, the other sequential, and identifies research questions that need to be addressed:

- Cultural mediator effects need investigating. For example, lower-income and less-acculturated African Americans and Hispanics believe that menthol has medicinal properties. (Some even swallow Vicks Vapo-Rub to treat colds.) Does this predispose them to believe menthol cigarettes are "healthier"?
- Little is known about why menthol's sensory effects motivate so many African Americans and Hispanics to smoke mentholated cigarettes.
- Social norms appear to lead some African Americans to take up menthol cigarettes as "cool" and as part of group identity, but might ethnic pride also protect against the use of menthol cigarettes? What about other cultural norms, such as devout Catholicism or strong spirituality—might they protect against tobacco use?
- Culturally-specific risk factors likely differ both within and among ethnic and racial groups. They need to be examined, and studies of cultural moderators are needed to identify the subgroups of African Americans or Hispanics at highest or lowest risk.
- Do Native Americans smoke menthol cigarettes more or less than African Americans? If less, could it be because tobacco industry advertising does not target them? If more, what role is played by the low cost of cigarettes on reservations, or cultural beliefs about the spiritual importance of tobacco?

"Studying these questions," Castro writes, "…can provide culturally rich opportunities to understand the physiological, psychological, social and cultural aspects of menthol cigarette use."

Don't ask, don't know: The marketers' mantra?

What did the tobacco industry know about lacing cigarettes with menthol and when did it know it? In their review of 286 internal industry documents, Ferris Wayne and Connolly (p. S43) found that cigarette makers knew a great deal about the effects of menthol, although what they chose to research may be as noteworthy as what they did. Some samples of what the industry knew:

- "Tar" and menthol act in concert; "tar" delivery can be used to enhance the menthol effect, while menthol can be added to replace decreasing "tar."
- Menthol, not nicotine, determines smoke impact for menthol smokers.
- Menthol, even at indiscernible levels, may smooth the taste of burning tobacco. This 1971 lesson justified inclusion of traces of menthol in most cigarettes.
- Menthol's primary effect is a cooling sensation, but in actuality, menthol is an irritant that stimulates mouth and throat receptors, just as nicotine does.
- Despite being an irritant, menthol is also a local anesthetic, dulling the negative effects of ingesting burning tobacco; increased menthol may reduce the harshness produced by higher levels of nicotine.

What the industry documents sidestep are menthol's likely health effects. As early as 1964, Philip Morris was urged by at least one scientist to explore the effects of menthol on respiration; apparently, the suggestion was rejected. And, although it acknowledged the need for long-term toxicity studies and more comprehensive analysis of toxic effects, the tobacco industry does not appear to have invested significantly in these areas.

Write Ferris Wayne and Connolly, "Any tobacco additive that demonstrates potentially significant pharmacological or toxicological effects should be carefully evaluated before it is approved for use in tobacco products. This is especially critical when these effects are directly advertised and marketed." They urge comprehensive investigation of the unique effects of menthol on the central nervous system, of menthol's interactions with nicotine delivery, and of the toxicity and biological effects of prolonged exposure to menthol inhalation. They also urge that future research, cessation treatment, and tobacco product regulations differentiate between menthol cigarettes and nonmenthol brands.

The African Americanization of menthol

In 1925, Lloyd F. (Spud) Hughes rolled himself a cigarette and inadvertently included some menthol crystals he was taking for a cold. That was the first menthol cigarette. In 1926 Hughes was awarded a patent for spraying cigarette tobacco with menthol and "Spuds" were born. The rest, as they say, is history. Menthol's market share rocketed from 5% in 1957 to 16% in 1963, and 29% in the late 1970s. It has held at about 26% since then, but that's only the broad-brush picture.

Some 70% of African American smokers now prefer mentholated cigarettes, compared with 30% of White smokers. How did that come about? Gardiner's review of industry and other documents (p. S55) builds the case that social factors during the 1960s and 1970s were manipulated by the tobacco industry to foster the demand:

- Early advertising planted seeds that menthol was healthful. "Why not play it safe and smoke Kools?" "Throat raw? Got a cold? Switch from Hots to Kools." African Americans became attached to the idea that menthol brands were less strong and "safer."
- Young urban African Americans, many of them engaged in the civil rights movement, considered smoking menthol brands as "slick" and sophisticated, modern, *avant garde* and distinctly African American.
- Kools led the pack, because they were "cool." They were identified with jazz, rebellion, youth, modern thinking, and Black Power, and were the cigarette of the 1960s. They also were thought to maintain the "high" of marijuana, or good to mix with marijuana, according to a tobacco industry report. (Kool has since been replaced by Newports as the top seller.)
- Cigarette ads, especially for menthol brands, blanketed African America media. African American athletes and musicians were recruited as spokespersons. *Ebony* magazine more than tripled its cigarette advertising from 1963 to 1965.
- Tobacco companies bestowed financial contributions on African American organizations, including civil rights groups, further cementing consumer loyalty.

Writes Gardiner: "[U]tilization and promotion of segregated marketing and practices meant different smokes for different folks." The marketing strategies continue today.

'Sweetening the poison' and charting the risks

Menthol cigarettes are at least as dangerous as nonmenthol brands, but are they more so? The evidence is scant and contradictory, report Giovino and colleagues (p. S67). One study found an increased risk of lung cancer among men who smoked menthol brands, but not among women; two studies found no such difference. Some research has found increased risks of other cancers and has determined that menthol appears to increase the metabolism of some carcinogens, but no studies have investigated menthol's association with cardiovascular or other noncancer diseases.

By improving the taste and soothing the harshness of cigarettes, menthol might be encouraging more people to smoke and suppressing motivation to quit. Some studies indicate that menthol smokers have more trouble quitting, although others show no such difference. Some studies show that menthol smokers take larger puffs, others that they take smaller puffs. Clearly, research is needed to address these and other concerns, including health outcomes:

- Factors that influence menthol preference;
- How their marketing influences perceptions of health risks;
- How the menthol content differs from brand to brand, and how those differences relate to health outcomes;
- The relationship of menthol smoking to other drugs, such as marijuana.

Even the international distribution of menthol smoking needs to be examined—why, for example, fully 60% of smokers in the Philippines choose menthol cigarettes; and why menthol cigarettes are so much more popular among African Americans than in Africa itself?

"We note," the authors write, "that adding menthol to cigarettes appears to 'sweeten the poison.' We question whether it makes sense to permit tobacco manufacturers to continue to add menthol flavoring to an admittedly toxic product in order to make it more palatable. Public health researchers and practitioners would have a far greater understanding of the many components of the risks posed by mentholated cigarettes if a comprehensive surveillance system… were established."

"Widening the lens": Women, FUBYAs, et al.

Cigarette market researchers have long drawn clear distinctions between smokers of mentholated and nonmenthol cigarettes, but public health research has done little beyond noting big tobacco's successful targeting of African Americans. As Sutton and Robinson point out in their commentary (p. S83), "[U]nderstanding the relationship of African Americans and menthol cigarettes only gives us part of the picture." Other important groups of menthol smokers include women, middle-school adolescents (they tend to "graduate" to nonmenthol brands in high school), and Asians and Asian Americans. To "widen the lens," the authors reviewed the history of menthol marketing strategies. They found four dominant themes:

- The earliest was to promote menthol as healthier, akin to throat lozenges. Willie the Penguin, Kool's cartoon mascot, often appeared dressed as a physician.
- When the health risks of smoking were made public in the 1950s, direct health messages were replaced with terms like *cool*, *clean*, *fresh*, and *crisp*. Salem captured that market. Smoking menthols came to be portrayed as romantic, making women who smoked them more desirable. Efforts to target White men fell mostly on deaf ears.
- Direct outreach to African American men paid handsome dividends beginning in the mid-1960s. Advertising of menthols dominated African-American magazines and featured African American models and "Black experience" slang like *groovy*, *baby,* and *soul*. Kool surged ahead again.

The latest appeal is to youthfulness and fun, launching Newport into market leadership as the cigarette for people who get "high on life," the ideal starter brand for what the market segment that the industry calls FUBYAs—first usual brand young adults—likely to lead to long-term brand loyalty. Newport's central advertising theme: "Kids just want to have fun."

Research is needed to document advertising targeted to women, youth, and other specific populations in addition to African Americans, including immigrants from South and Central America, Africa, Asia and the Pacific Islands, the Middle East, and Europe. Key questions await answers: Are these groups being targeted with approaches similar to those used so successfully on African Americans? And can understanding the marketing of menthol cigarettes teach the public health community lessons that might improve efforts to combat smoking?

Youth: Will menthol smoking make quitting harder?

Preliminary findings suggest that adolescents who smoke mentholated brands get more enjoyment and make fewer quit attempts than do young nonmenthol smokers. Given the relationship between daily smoking during youth and later difficulty quitting, it's possible that smoking menthols makes it even harder for them to quit and increases the adverse health effects, but data are limited on menthol smoking by youth and whether it persists into adulthood. To begin filling that gap, Moolchan (p. S93) recruited 13- to 17-year-old smokers in the Baltimore area for an outpatient cessation program, then analyzed brand-preference data from the 593 who identified themselves as either African American or Caucasian. He found significant associations between both smokers' gender and ethnicity and their menthol preference, with African American girls showing the greatest preference and Caucasian boys the lowest.

In general, rates of menthol smoking in both ethnic groups were much higher than those reported from national samples, perhaps because of cross-cultural influences, but his findings, he reports, "send a signal for vigilance because of mounting evidence that menthol smoking may be perceived as less harmful, exacerbate the addictive and other deleterious consequences of tobacco and potentially reduce the effectiveness of quitting strategies for addicted smokers." Further investigation is needed into factors that contribute to menthol smoking and its effects on young people's tobacco use and ability to quit.