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Editorial

EDITORIAL

Should the FDA Ban Cigarette Filter Ventilation?

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Does ventilation of cigarette filters by tiny holes increase risk for adenocarcinoma of the lung? In this issue, Song and colleagues conclude that the answer is "yes," based on their weight-of-evidence review of an array of relevant literature, both peer reviewed and from tobacco industry documents (1). Their affirmative conclusion has regulatory implications under the 2009 Family Smoking Prevention and Tobacco Control Act (TCA) (2) and leads them to propose that "thus, the FDA should consider regulating its use, up to and including a ban. . ."

They draw on multiple lines of evidence to reach this conclusion: the impact of cigarette ventilation on tobacco smoke characteristics, compensation by smokers for the dilution of smoke by ventilation, altered puffing and lung dosimetry, and increased smoking initiation and decreased cessation because of the perception that the lower yields measured by machine and the associated marketing lead smokers to view ventilated cigarettes as conveying a lowered risk for disease. Song et al. also cite the intriguing changes in the epidemiology of adenocarcinoma over the many years since the association of smoking with lung cancer was first identified (3). The shifts are dramatic: Adenocarcinoma has become the predominant histological type, and the risk for adenocarcinoma associated with smoking has risen dramatically in men and women (3). The 2014 Surgeon General's report has already concluded that the changes in the epidemiology of adenocarcinoma have been caused by changes in the design of cigarettes (3). This new review by Song et al. identifies filter ventilation as at least one responsible element of the many manipulations of manufactured cigarettes that have taken place since the 1950s (3,4).

Does the evidence gathered, evaluated, and synthesized support the indictment of filter ventilation as increasing risk for adenocarcinoma? Song and colleagues carry out a review that they term "an evidence-based causation analysis"—in actuality an effort to capture a large and somewhat poorly circumscribed body of literature, both published and unpublished, and to apply causal inference guidelines modeled after those used in the Surgeon General's reports (3,5). The authors are transparent in their application of this methodology, although they use an unconventional weighting of the various elements of the guidelines that lacks validation. They mention consideration of mode of action and adverse outcomes pathways, an approach that remains under development (6). Nonetheless, given the coherence of the multiple lines of evidence considered, the conclusion with regard to the contribution of filter ventilation to the rise of adenocarcinoma in smokers is well justified.

What are the regulatory implications of the conclusions of Song et al. under the Tobacco Control Act? Under Section 907(a)(4), the US Food and Drug Administration (FDA) is authorized to establish the product standards it deems appropriate for the protection of public health (2). Standards may cover the construction, components, and constituents of the products, such as filters. To assess what is "appropriate for the protection of the public health," the FDA must consider scientific evidence of the risks and benefits of the standard to the population as a whole, including users and nonusers; the increased or decreased likelihood that existing users will stop using the products; and the increased or decreased likelihood that those who do not use tobacco products will start using the new products. Thus, the FDA considers the population-level net effect of any proposed product standard. This "public health standard" differs from the "safe and effective" standard that the FDA uses to govern pharmaceutical drugs. To meet that requirement, clinical trial findings are requisite. By contrast, such trials cannot often be carried out to address the public health standard, and hence there is a reliance on all relevant data and modeling to estimate public health impact.

To date, we have one example of how the FDA justified a proposed product standard—that of N-nitrosonornicotine (NNN) in smokeless tobacco. The FDA found that NNN is a major contributor to the elevated oral cancer risk among smokeless tobacco users and that limiting the level of NNN would reduce the oral cancer morbidity and mortality attributable to smokeless tobacco (Docket No. FDA -2016-N-2527, proposed January 23, 2017) (7). In its considerations, the FDA also

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took into account the feasibility for manufacturers to produce smokeless products with much lower levels of NNN. Unlike the case of cigarette filter ventilation, the product standard for NNN sets limits on a single agent in one category of tobacco products.

We also have the example of menthol as a characterizing flavor, the only such flavoring allowed under the TCA. The Tobacco Products Scientific Advisory Committee (TPSAC), formed under the TCA, was required to submit a report on menthol within the first year after it was constituted. The TPSAC report found that menthol cigarettes harmed public health and that removing menthol from cigarettes as a characterizing flavor would have overall benefit for the population (8). These conclusions were based on literature review, evidence synthesis, and modeling of population impact in order to address the public health requirements of the Act. To date, the FDA has taken no action on menthol.

Thus, the TCA incorporates a standard for public health net benefit, but to date a record of precedents has not been established for the evidentiary threshold to be reached for FDA action. If the evidentiary standard required by the TCA is for certainty beyond equipoise (ie, the preponderance of evidence indicates harm from ventilation), then the findings of the review by Song et al. (1) are sufficient to support a ban on filter ventilation. Given a lack of evidence for countervailing harms, ending filter ventilation could be a "no regrets" action that would benefit public health.

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