

*Editorial***Tobacco Research Methodology: First Things First****Kenneth E. Warner**

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Over the past half century, tobacco control arguably has been America's greatest public health success story. Anti-smoking campaign-induced decisions to quit smoking or not to start in the first place have translated into the avoidance of more than 5 million premature smoking-related deaths. On average, each of the affected individuals has gained 15 to 20 years of life expectancy as a consequence (1). This is a truly remarkable public health achievement.

The glass-half-empty side of the story is that tobacco consumption, primarily in the form of cigarette smoking, remains by far the nation's leading behavior-related cause of death, illness, and disability. Four hundred and thirty thousand Americans lose their lives annually to smoking, active or passive, constituting a sixth of all deaths; another 9 million are ill or disabled as a result of smoking (2), and many observers worry that the steady decline in the prevalence of smoking over the past four decades might be slowing significantly, with a fifth of all adults remaining smokers (3). Evidence points to a more addicted population of continuing smokers. Compared with previous generations of smokers, they are less educated and more likely to work in blue collar occupations than in the past. Importantly, a substantial proportion of smokers suffer from a mental illness or substance abuse comorbidity (4). And yet, as in the past, a sizable majority reports that they would like to quit smoking cigarettes if they could.¹

Although researchers in and outside of pharmaceutical companies seek more effective methods of helping smokers to quit, the tobacco industry, including both mainstream companies and a new cottage industry of innovators, has adopted a different approach: they are developing novel tobacco and nicotine-based products that, they hope, health-concerned smokers might adopt instead of smoking conventional cigarettes. The products range from cigarettes modified to reduce yields of specific toxins to low-nitrosamine forms of smokeless tobacco, from dissolvable tobacco lozenges to new electronic cigarettes (5, 6). Unlike the pharmaceuticals, these products have been brought to the market at the whim of their producers, subject to absolutely no regulation regarding their safety or efficacy as substitutes for conventional cigarettes.

Until now, that is. In 2009, Congress passed and President Obama signed legislation giving the U.S. Food and Drug Administration (FDA) the responsibility for regulating aspects of the sale and marketing of cigarettes, smoke-

less tobacco, and related products.² The agency's regulatory authority with regard to this product category differs dramatically from its responsibilities in its more traditional domains of pharmaceuticals, medical technologies, cosmetics, and food products, in which agency attention focuses narrowly on product efficacy and/or safety. Tobacco products are inherently unsafe, so the herculean task confronting the FDA will be to address issues of relative harm and population consequences of the introduction of novel products. Still, the critical fact is that companies wishing to bring novel tobacco and nicotine-related products to market will no longer be able to do so without regulatory approval. The FDA now also has the ability to impose performance standards for all tobacco products, including conventional ones. These performance standards would also be implemented in the context of relative harm.

Just as the tobacco control story itself represents only half a victory, the multi-year battle to secure FDA regulation must be considered only a partial win for public health. We the people now have at least partial authority to regulate the marketing of what has historically been the world's most toxic category of legal products. However, we don't have complete authority, nor do we yet possess the wherewithal to do the job assigned to the FDA. At the core of effective regulation in all of FDA's domains lies a base of scientific knowledge, both the methods to assess the safety, efficacy, and toxicities of products and the results of years of research to develop a foundation of data upon which subsequent studies, and regulatory decisions, can rely. For the task of assessing the relative toxicity of myriad novel tobacco and nicotine-related products, the essential need to achieve sound regulation, the cupboard is nearly bare.

Although the paucity of existent research represents a problem, it also constitutes a challenge and an opportunity. More precisely, it constitutes a challenge that is an opportunity, an opportunity to bring objective evaluation to a class of products that heretofore has wreaked havoc with the public's health, and thereby to reduce the morbidity and mortality associated with the core product, the cigarette. Although the interest in tackling this challenge in the United States is driven by the new FDA legislation, the opportunity it affords extends to all the world, for the toll of tobacco knows no geographic boundaries.

Consider a subset of the new issues facing the FDA:

- The FDA now has the ability to mandate performance standards regarding product-generated exposures. To

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¹ <http://www.gallup.com/video/109033/most-smokers-us-want-quit.aspx>

² http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h1256enr.txt.pdf

do so, the agency will need to understand how best to measure actual exposures and then how to interpret their health implications, at both the level of the individual consumer and the population as a whole (witness the multi-decade travesty of machine-measurement of tar and nicotine, the industry's associated "light" cigarette marketing triumph, and the subsequent public health tragedy; refs. 7, 8).

- Manufacturers have shown the ability to modify tobacco products so that they deliver reduced yields of selected toxins, but only as measured by standardized smoking machines, not when smoked by humans. Naturally, the manufacturers want to make advertising claims to effectively market their novel products. In the past, other than risking the ire of the Federal Trade Commission, which has exercised its authority to judge advertisements false and misleading only rarely, there were no significant barriers to making these claims. Now, the FDA has oversight of the scientific basis for these claims to ensure that consumers are not misled and that harm is not done. How will the agency assess the scientific basis of the claims? How will it determine that consumers are not misled and the public's health not damaged?
- Although novel products may deliver the reduced yield of toxins they claim, they might also introduce new or increased exposures. Illustrative was the discovery by independent scientists that Eclipse, a cigarette look-alike device marketed by R.J. Reynolds as dramatically reducing tars, exposed consumers to inhalation of microscopic fiberglass particles that broke off from the fiberglass shield on the distal end of the device during the process of packaging and shipping the product (9). The product also increases exposure to carbon monoxide (10, 11). As another example, palladium was added to a modified cigarette to reduce the yield of certain toxins, including polyaromatic hydrocarbons. Although the addition of palladium achieves this objective, it also causes an accumulation of palladium in the lungs, with unknown health consequences (12). How will the FDA acquire the requisite scientific data to ensure that consumers are not exposed to novel toxic exposures; or—a far more difficult challenge—that if they are so exposed, the reduction in more "traditional" exposures will be judged to warrant the (unknown) risk associated with the new exposure?

The FDA will not face these challenges alone. Canada and the European Union have a decade of experience with product reporting requirements. The Conference of the Parties to the Framework Convention on Tobacco Control³ will also begin to wrestle with these issues as protocols and implementation guidelines are developed under Articles 9 and 10 of that treaty, which deal with tobacco product regulations. The WHO's Study Group on Tobacco Product Regulation has produced two monographs (13, 14) and outlined proposals for maximal limits on toxicants (15) in an attempt to address major regulatory questions. However, much work remains to be done, particularly given the emergence of novel products around the world.

To describe the resolution of scientific problems such as these merely as "challenges" risks grossly understating

the difficulty and importance of resolving the problems. The scientific community must find the most effective ways to evaluate product-produced exposures and assess their effect on risks to health. They—we—must develop an effective surveillance system to monitor novel product usage and potential adverse health effects, and we have to develop means of ensuring that the tobacco companies do not subvert the process in practice or intent, a phenomenon for which they have shown substantial aptitude over the past many decades.

Assessment of tobacco products includes each of the following:

- Premarket and laboratory evaluation of exposure to toxicants in products
- Laboratory studies to assess the products' addiction potential
- Human clinical trials to determine how people actually use the product in practice, how much they are exposed to toxicants measured through biomarkers, and the expected effect of exposure reductions on health risk
- Assessment of consumer perception of novel products or product changes to ensure that consumers are not misled
- Surveillance to determine the population impact of the product.

This CEBP focus section on tobacco research has nine core articles, all of which provide extensive critical reviews of their subject matter, focusing on research methodology. The articles range in their foci from studying tobacco products in the laboratory to evaluating their implications in the population. They provide a detailed review of the literature and of tobacco company citations. These articles should be useful for readers with questions on what we know about studying tobacco and the best methods for approaching what we do not know. The articles identify specific research gaps and make recommendations about how to address them. They do not, however, attempt to report what we know about tobacco use and harm *per se*. Rather, they report what we know about how to study them (and what we don't know) and how to move the field forward. They also serve as a model for studying other toxic exposures and human disease risk. Because they are not intended to summarize what we have learned about tobacco research to date, the reader will not discover lessons learned or a bottom line conclusion that could affect public health.

Given our limited methodologies to address many of today's research questions about tobacco harm and harm reduction, two clichés come to mind: (a) "first things first" and (b) "garbage in, garbage out." These articles are novel because they assess the methodologies that we have relied on so heavily in the past. In some cases, they have evolved from "folklore," in others, they reflect limited science, and in still others, they derive from sound science. The articles in this section identify which are which.

The articles do not cover everything that would-be tobacco regulators need to know. In part because they are covered in other excellent articles, biomarkers are not discussed in this section (16). Also missing is consideration of smoke chemistry studies, an area in which research methods are well-defined and reported, at least by using conventional smoking machine studies (17). A review of

³ <http://www.who.int/fctc/cop/en/>

both methods and applications to tobacco product modifications and innovations is needed. The section also lacks a comprehensive review of the role of nicotine in product use and how nicotine delivery, in new products and old, affects product use and compensation. Finally, no article in this section addresses the final piece of the puzzle: how to integrate data across the various study types, while appropriately weighing the relative importance of each, to be followed by a risk assessment process considering risks to smokers. To begin, we need a conceptual framework for a comprehensive evaluation.

These omissions notwithstanding, the articles included herein should serve as an important resource to the research community, to research funders, such as the NIH, and to the ultimate arbiters of what manufacturers can—and cannot—do with their new or modified products, the FDA and similar regulatory agencies around the world.

As we venture into this new era of tobacco product innovation and regulation, it is imperative that we not lose sight of a scientific truth learned decades ago: the only certain way to reduce the harms associated with tobacco products is to avoid using them altogether. The new and essential search for means of evaluating novel products must not deflect the attention of the scientific community from the quest to prevent the initiation of tobacco use or the search to find effective means of quitting. However, the two objectives need not compete with each other for scarce tobacco control resources. This is not a zero sum game. With the advent of new regulatory authority, one hopes and indeed expects that the entire field of tobacco control research will be a vibrant—and more importantly, successful—growth industry.

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