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Risk Assessment for Tobacco Regulation

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Abstract

Risk assessment is a process that uses a transparent, reproducible and pre-established methodology to evaluate alternatives for managing health-related risks. Although an array of federal agencies regularly use risk assessment to inform regulatory decisions, its application to tobacco regulation is new. By comparing examples of FDA risk assessments for food and tobacco, this paper highlights some of the challenges inherent in applying risk assessment methodologies to tobacco regulation. In doing so, it calls upon researchers to work with the FDA to develop a tobacco-specific approach to risk assessment that reflects the Tobacco Control Act's regulatory framework and the distinctive features of tobacco products and tobacco use.

Abstract

Objective: Risk assessment is a process that uses a transparent, reproducible and pre-established methodology to evaluate alternatives for managing health-related risks. Although an array of federal agencies regularly use risk assessment to inform regulatory decisions, its application to tobacco regulation is new.

Methods: This paper provides an overview of the risk assessment framework developed by the National Research Council and typically applied by federal regulatory agencies. It then reviews examples of the U.S. Food and Drug Administration's (FDA's) application of this risk assessment framework to both food and tobacco, identifying some of the challenges involved in applying standard risk assessment methodologies to tobacco regulation.

Results: There are inherent challenges in applying standard risk assessment methodologies to tobacco regulation, including the need to (a) apply a unique population-level legal standard and (b) consider many factors that risk assessments have not traditionally emphasized, including marketing and promotion, packaging/branding, price, social influences, consumer perception, and addiction.

Conclusion: In order for the FDA to address these challenges, it must work with researchers to develop a tobacco-specific approach to risk assessment that reflects the Tobacco Control Act's regulatory framework and the distinctive features of tobacco products and tobacco use.

Keywords

risk assessment; population health; modeling; product standard; tobacco regulation

INTRODUCTION

“Risk assessment” is a process for “evaluating the relative merits of various options (or interventions) for managing risk” through a transparent, reproducible, and pre-established methodology.¹ In addition to the Environmental Protection Agency (EPA), which has promoted the standardization of risk assessment practices, federal agencies ranging from the Department of Defense to the Consumer Products Safety Commission regularly conduct risk assessments.¹ Though risk assessment is a well-established tool for informing regulatory decisions, its application to tobacco regulation is in its nascent phase.²

Congress granted the U.S. Food and Drug Administration (FDA) authority to regulate tobacco products in 2009.³ The FDA has actively employed risk assessment methods in non-tobacco contexts, and it is interested in exploring how risk assessment can be applied to inform its regulatory decisions on tobacco products.⁴ There are of course many approaches to modeling the impact of potential policy decisions, but the objective, transparent, and replicable process that risk assessment can provide may be particularly important in the context of tobacco regulation, where nearly all important regulatory decisions are likely to be challenged in court.⁵ As the Institute of Medicine (IOM) noted in 2001: “The more complex the science base and the more controversial the policy implications, the more a rational and explicit framework is needed.”²

In January 2017, when the FDA issued a proposed rule to regulate the levels of *N*-Nitrosonornicotine (NNN) in smokeless tobacco, it applied risk assessment methods to estimate the likely impact of its proposal on oral cancer incidence and mortality.⁶ (NNN is a highly carcinogenic tobacco-specific nitrosamine produced during the process of treating and curing tobacco.⁷ To date, the FDA has not released a final rule.) In doing so, the FDA applied methods that had been developed by the EPA to assess the risk of environmental pollutants⁸ and other cancer-related hazards.⁹ But borrowing risk assessment methods developed in other regulatory contexts raises important challenges. Perhaps most importantly, in the tobacco context, the FDA must apply a unique “public health standard” that considers the population as a whole, including possible effects on initiation, cessation, and relapse.³ Further, though the issues are not entirely unique to tobacco regulation, tobacco-related risk assessments must address complex challenges relating to behavioral responses to regulation (including the effects of addiction), product promotion and marketing, diverse patterns and purposes of use (including dual use), potential harm reduction, and unknown long-term effects of newer products such as e-cigarettes. These issues all present themselves differently in other regulatory contexts.

This paper seeks to provide a broad overview of the “standard” risk assessment process used by federal regulatory agencies and to examine the additional considerations and conceptual adjustments that need to be made in order to apply the standard risk assessment approach to the tobacco regulatory context.

Risk Assessment at the FDA: Food Safety and Tobacco Products

At its core, risk assessment is the process of making complex—and often conflicting—scientific data relating to potentially harmful exposures useful to regulatory decision-makers. Through a risk assessment, data can be harnessed to help quantify risks and project the potential effects of regulatory decisions. For instance, if the FDA were concerned about consumers contracting listeria from read-to-eat (RTE) foods, a possible risk assessment could examine the extent of such risks (to the population as a whole, as well as to sensitive populations such as infants) and the extent to which regulatory approaches (eg, required “use by” dates) would be expected to reduce the risk.^{11,12}

Although federal agencies differ somewhat in their practices, they generally base their risk assessments on the 4 step framework outlined by the National Research Council (NRC) in the 1983 “Red Book”: *hazard identification*, *dose-response assessment*, *exposure assessment*, and *risk characterization*.¹¹ The Red Book’s approach was modified by the NRC’s 2009 “Silver Book,” which added the additional steps of “planning and scoping” and “problem formulation” at the outset of a risk assessment.¹ Figure 1, from an EPA report, summarizes the central elements of the Silver Book’s approach to risk assessment.

In its regulation of food and drugs, the FDA has embraced the NRC’s risk assessment framework as the gold standard for analyzing population risk, and therefore it makes sense to use it as the starting point for developing a framework for tobacco-related risk assessment.^{12–16} To provide an example of the application of the risk assessment process used by the FDA and other federal agencies, this paper reviews the FDA’s recent risk assessment of inorganic arsenic in rice and rice products (“arsenic risk assessment”).¹⁶ Though obviously a very different context from tobacco, this a typical example of an FDA risk assessment conducted on a toxin that poses both cancer- and non-cancer health hazards due to cumulative long-term exposure and that – like tobacco – has risks that vary depending on consumers’ consumption patterns. Through analyzing each phase of the arsenic risk assessment, this section also discusses and critiques the FDA’s use of risk assessment tools in its NNN proposed rule, thereby identifying some of the major challenges of applying risk assessment methodologies to tobacco regulation. (This paper focuses on the NNN proposed rule because to date it is the only example of the FDA using risk assessment tools to inform tobacco regulatory decisions. To be clear, though, the FDA did not purport to be conducting a full risk assessment, and it may well conduct a risk assessment differently if doing so outside the context of a proposed rule.)

Two important caveats must be noted at the outset. First, nothing in the 2009 Tobacco Control Act (TCA) or other law *requires* the FDA to conduct risk assessments. Risk assessment is, we believe, a valuable tool that the FDA can use to both inform its own decisions and communicate the scientific basis for its actions to the courts—but it is not a required step. If an FDA regulation is challenged in court, it will generally be upheld so long as the action was “appropriate for the protection of the public health”³ and was not “arbitrary, capricious, [or] an abuse of discretion.”¹⁷ The standard of review is exceedingly deferential and requires the FDA only to “examine the relevant data and articulate a satisfactory explanation for its action.”¹⁸ (Where there are constitutional issues involved, such as First Amendment claims, the evidentiary standard may be higher.) The scientific

rigor expected of well-conducted risk assessments should not be confused for the applicable legal standard.

Second, risk assessments can be very time consuming; it took approximately 3 years to finalize the arsenic risk assessment discussed here, and in other regulatory contexts, risk assessments may take as long as ten years to complete.¹ Given the nearly half a million deaths caused each year by tobacco use, such delays in the tobacco context could cost many lives. The FDA will need to make difficult decisions about how comprehensive risk assessments need to be, given time and resource constraints. There may be a tension between doing (a) an “ideal” risk assessment that takes into account all possible considerations, and (b) a faster risk assessment that is more limited in scope but nonetheless scientifically valid. In many cases, the latter approach may better account for the fact that tobacco use harms are enormous and ongoing. As the FDA has previously done in the food context,¹¹ it should delineate criteria for determining when full-blown risk assessments are needed and when more abbreviated assessments are appropriate.

Planning, scoping and problem formulation.—A risk assessment typically begins with planning, scoping, and problem formation. *Planning* focuses on identifying the purpose of the risk assessment, allocating needed resources, and developing a work plan. In the arsenic risk assessment, the FDA determined the purpose of its risk assessment was to “provide a scientific basis for the development of risk-management policy and consumer options for reducing exposure to arsenic from the consumption of rice grain and rice products.”¹⁶ The purpose of the risk assessment should relate to the criteria for regulatory action set by the authorizing statute.¹⁰ In the case of food, the FDA has the authority to set regulations limiting the amount of a naturally-occurring “poisonous or deleterious substance” to levels that will “not ordinarily render [the food] injurious to health.”¹⁹ Determining what arsenic levels in rice and rice products rendered the foods “injurious to health”—to at least some subset of consumers—was therefore central to the risk assessment’s purpose. (Soon after the risk assessment was completed, the FDA proposed a limit on arsenic levels in rice cereals for infants.)²⁰

Following the initial planning stage, *scoping* specifies the “proposed boundaries of the assessment” by identifying the specific sources of possible health harms (or benefits), populations (including susceptible populations), life stages, pathways of exposure, timeframes and geographic areas, and stakeholder concerns that the risk assessment will address.¹⁰ As the FDA recognized in its arsenic risk assessment, it must balance the inherent trade-offs between conducting a fully comprehensive risk assessment and providing timely evidence to support regulatory decision-making. Although emerging evidence suggested that arsenic was associated with cardiovascular disease, diabetes, and other non-cancer health effects, the FDA determined “it would not be in the best interest of public health to wait to include all endpoints in this risk assessment, because it would add considerable time to the completion of our assessment.”¹⁶ Instead, it focused on quantifying the “well-documented cancer effects” associated with arsenic exposure—specifically those relating to lung cancer and bladder cancer—and it also provided a qualitative assessment of non-cancer risks.¹⁶

Planning and scoping then inform the *Problem Formulation* stage, in which a conceptual model and analysis plan are developed. In its arsenic risk assessment, the FDA created an analysis plan that included the following considerations:

- **Hazard:** The focus is on inorganic arsenic.
- **Food products:** The focus is rice grain ... and products that contain rice grain as an ingredient (eg, cereals).
- **Populations of interest:** Total U.S. population, infants, children, and average- and higher- consumers of rice.
- **Health effects of concern:** Lung cancer, bladder cancer.
- **Analysis outputs (results):** Predicted lifetime risk of cancer cases per million and cancer cases associated with a single serving per day.¹⁶

In the tobacco context, the hazard posed by any particular product or constituent may already be well-established (although for newly-emerging products, it may not be). Regardless, engaging in the preliminary steps of planning, scoping, and problem formulation is critical. These steps require the FDA to think systematically and carefully about the objectives of its risk assessment and what types of data are needed to answer the relevant questions. In its proposed NNN rule, the FDA did not include a formal planning, scoping and problem formulation analysis. By omitting these phases of analysis, the FDA did not (or at least did not publicly) go through the process of identifying and considering which populations (including vulnerable populations) and what disease endpoints it needed to consider.

Ultimately, the FDA's NNN risk assessment considered only oral cancer health outcomes, despite noting that the NNN standard may also reduce the risks of esophageal, pancreatic, laryngeal, prostate, and lung cancer. This limitation may well have been acceptable in this case, given the more limited evidence quantifying the link between NNN and these other types of cancers, but it should have been discussed in a planning and scoping process—ideally one that applied clear, pre-set criteria. In future cases dealing with cigarette product standards, this issue will prove more challenging given that smoking is causally linked to at least a dozen different types of cancer, as well as many other diseases—ranging from strokes to erectile dysfunction—that affect “nearly all organs of the body.”²¹ Limiting the analysis to a subset of endpoints may grossly understate baseline smoking harms and could impede efforts to estimate the health benefits from the rule. On the other hand, trying to account for all smoking-related harms would make it extremely difficult for the FDA to conduct timely risk assessments and would likely result in wasted resources.

By failing to seriously engage with these initial phases, the FDA also missed an opportunity to more clearly link the scope of its risk assessment to the relevant population-level regulatory standard. Under the 2009 Family Smoking Prevention and Tobacco Control Act (TCA), the FDA can issue “product standards” that regulate the properties of tobacco products (such as NNN levels) only if it can show that such a standard would be “appropriate for the protection of the public health,” after “consider[ing] scientific evidence concerning ... the risks and benefits to the population as a whole, including users and

nonusers of the tobacco product.”³ Given this population-level standard, which focuses on the effect of regulations on the “population as a whole,” tobacco-related risks assessments cannot rely solely on individual-level risks, as might be appropriate in other regulatory contexts. Instead, the FDA must be cognizant that regulations that reduce the toxicity of tobacco products could theoretically *increase* population-level harms if they, for example, facilitate dual use, prevent or delay cessation among current users, and/or increase youth experimentation and initiation. In the NNN proposed rule, the FDA acknowledged that these behavioral responses would be relevant to its risk assessment, but it did not develop a plan for quantifying their impact.⁶

Going forward, the FDA should use these initial phases of the risk assessment process to articulate how simple or complex its tobacco-related risk assessments need to be—and why. The ideal way for the FDA to do so would be to develop a decision-making framework that could be used as a basis from which to begin all future tobacco-related risk assessments. This is what the FDA has done for food-related risk assessments¹¹ and what the EPA has done for a variety of different types of risk assessments.^{10,22,23} This can ensure thoughtful discussion not only of relevant populations, health endpoints, and data needs, but also of important overarching issues such as distributional justice.¹⁰

In the tobacco context, the FDA’s framework could highlight overarching issues such as youth initiation and experimentation, health disparities, dual use, and tobacco industry data quality (which is an obvious concern, given the historical record)²⁴ that should be considered in the problem formulation phase. Notably, the FDA’s authority to regulate tobacco products includes not only product standards like the proposed NNN rule, but also other regulatory powers including new product reviews, modified risk product reviews (the review of health- or exposure-related claims), advertising and sales restrictions, warning labels, and more. Different health endpoints, measures, behaviors, populations/life stages, and other considerations may be more or less relevant in these different regulatory contexts, and somewhat different decision-making frameworks may be needed.

The existence of such decision-making frameworks would require a significant up-front investment of time and resources. Ultimately, however, they would allow the FDA to conduct timely, comprehensive and defensible risk assessments within a shorter period of time. As discussed below, such frameworks could also be extended to include the other components of the risk assessment process.

Hazard identification.—The hazard identification step consists of a literature review that examines what is known about the possible health effects of the toxin(s) or toxicant(s) at issue as well as the biological mode(s) of action (MOA) through which it causes harm. Though risk assessments have generally focused on specific biological or chemical agents, the same approach could also be adapted to examine the hazards posed by industry marketing or product characteristics.

This step is similar to a weight-of-scientific-evidence (WOSE) review and ideally includes similar processes to assess the strength, quality, and relevance of each individual study using objective, pre-determined criteria.²⁵ Studies reviewed may range from *in vitro* laboratory

studies to population-level epidemiological studies. Additionally, in recent years, “risk assessors have begun to consider additional types of data during hazard identification, for example, those from computational toxicology ... and genomic response assays.”¹⁰

Agencies also rely on reviews and studies measuring analogous risks (eg, risk posed by the same toxin in other products). For example, the FDA’s hazard identification for arsenic relied primarily on epidemiological studies, building on reviews by the International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), both of which found arsenic to be a human carcinogen. Most of these studies involved “case control and prospective studies on the impact of arsenic in drinking water,” rather than in rice or other foods.¹⁶ These studies consistently found that long-term exposure to elevated levels of arsenic in drinking water was associated with elevated risks for lung cancer, bladder cancer, and skin cancer.

In the NNN proposed rule, the FDA’s hazard assessment relied on animal studies and human epidemiological studies. For example, epidemiological studies have found that smokeless tobacco use increased the risk of oral cancer by 2.6-fold in the United States but did not so in Sweden and Norway, where NNN levels in smokeless tobacco products are lower.²⁶ These studies confirm the finding of classic toxicology experiments demonstrating the carcinogenicity of NNN in rats and mice.⁶

In this case, the hazards of NNN exposure were quite evident, making the hazard assessment fairly straightforward at the individual level. Yet here again, the FDA missed the opportunity to develop a framework to inform future tobacco-related risk assessments that focuses on population-level health effects. For example, most animal studies—and even most human studies—do not account for dual use of multiple tobacco products (to the contrary, they tend to exclude dual users). Given the pervasiveness of dual use, poly-use, and other drug use (eg, alcohol and marijuana), especially among adolescents and young adults, any tobacco-related hazard assessment must be able to incorporate hazards associated with such use patterns. For example, there may be multiplicative health risks associated with dual use that would bear on whether a modified risk tobacco product (MRTP) claim should be authorized. (In the MRTP context, unlike in the product standard context, it is the company, not the FDA that bears the burden of proving that approval is appropriate. However, the FDA could still use risk assessment tools to evaluate the companies’ claims.)

Existing hazard identification practices also generally fail to consider the issue of harm reduction—a factor that the TCA requires the FDA to weigh. For example, the NNN proposed rule persuasively demonstrates that NNN exposure is harmful and that reduced NNN exposure would correspondingly be beneficial. But it does not seek to quantify what health benefits (or slowed disease progression) might accrue to someone who switched entirely to low-NNN smokeless tobacco from smoking cigarettes, or how likely such transitions would be. Though transition between cigarettes and smokeless tobacco may be rare, future rules (such as those related to electronic cigarettes or reduced-nicotine cigarettes) will have to consider the role of product transitions and harm reduction.

Dose-response assessment.—This phase considers the relationships between the health risk(s) identified in the hazard identification and the amount of exposure (dose). In other words, it seeks to understand what levels of exposure are associated with meaningful health consequences and, accordingly, what effects would follow from increases or decreases in exposure.

In the arsenic risk assessment, the FDA developed dose-response curves for lung and bladder cancer risk over a range of exposure levels, building on prior epidemiological studies and consensus reports. The FDA then characterized levels of uncertainty, in order to generate higher and lower bound estimates.¹⁶

In the NNN proposed rule, the FDA's dose-response assessment assumed a linear dose-response relationship, and it used a cancer slope factor (CSF) for NNN that the California Environmental Protection Agency had previously developed.⁶ Because this CSF was based on a single-dose animal toxicity study (using oral exposure through drinking water), the FDA stated that was unable to quantify the uncertainty associated with using the CSF. As in earlier phases, the FDA was trying to use to best available evidence despite its limitations, but use of such an imprecise tool significantly hampered its ability to make any meaningful quantitative projections. Although acquiring new evidence may have been helpful in this phase, the National Toxicology Program's standard protocol for cancer bioassays involves 2 years of studies – time that would have significantly delayed the proposed rule.²⁷

Aside from the issues that arose with the NNN rule, there are numerous issues that may complicate this step of the risk assessment in the context of tobacco regulation. First, for newly emerging products such as electronic cigarettes (also referred to as e-cigarettes), there may not be adequate data to develop dose-response curves for diseases with long latency periods. Second, different dose-response curves exist for each tobacco-related disease. As noted above, the FDA limited its assessment in the NNN case to only oral cancer, but future tobacco-related risk assessments may have to identify or develop dose-response curves for multiple diseases. Finally, the FDA may need to develop mechanisms to account for variations of dose-response relationships due to age, sex, dual use, genetics, and possibly other factors as well. For example, lung cancer risk may be significantly associated with the rate at which one metabolizes nicotine (which appears to be genetically determined). Thus, a single dose-response curve could mask significant population variability and lead to regulatory decisions that fail to protect sensitive populations.²⁸

The FDA could help to advance this phase of the risk assessment by assembling a database of dose-response curves for harmful constituents found in tobacco products and funding research to address the apparent gaps. An obvious starting point would be the list of twenty Harmful and Potentially Harmful Constituents (HPHCs) that tobacco companies must already report to the FDA (a list that includes NNN).²⁹ Assembling such a database would enable dose-response assessments to be completed faster and more reliably.

Exposure assessment.—Exposure assessments seek to quantify how much people are exposed to the hazard at issue. The output of this phase typically includes estimates of average exposure levels (including ranges or distributions) for the population as a whole, as

well as for the “susceptible populations and life stages” identified in the problem formulation phase.¹⁰ Such estimates may be derived from more or less complex exposure modeling; a recent report from National Academy of Sciences catalogued an array of striking advances in the field of exposure assessment, including the emergence of computational exposure modeling and –Omics technologies.³⁰

For its exposure assessment of arsenic in rice, the FDA synthesized data from a variety of different sources. It used FDA surveys and published studies to estimate the amount of arsenic in various types of rice and rice products; market share and survey data (including the National Health and Nutrition Examinations Survey (NHANES)) to estimate the frequency and amount of rice consumption; and *in vitro* and *in vivo* animal and human studies to model the bioavailability of arsenic consumed in rice. All of this data was aggregated to estimate average levels (and distributions) of exposure to arsenic from rice for various population groups, including infants and young children. Notably, when conducting this exposure assessment, the FDA found that although only 3.4% of all NHANES respondents reported consuming rice at least once a day, “32.6% of individuals in the ‘other’ ethnic group, which includes Asians and multi-racial individuals, reported consuming rice or other cooked grains at least once a day.” Accordingly, it acknowledged the importance of separately modeling the health risks faced by those with higher levels of consumption in the risk characterization phase.¹⁶

In the NNN proposed rule, the FDA similarly mined the literature to develop estimates of NNN content in products currently in use, average intake, and bioavailability. Rather than create a model to estimate exposure levels, as the arsenic risk assessment did, the FDA incorporated its equation for exposure into its overall model of cancer risk (discussed in the following sub-section). The FDA did not develop separate exposure calculations for different population groups, and because it focused on lifetime exposure, it not did consider different life stages either. Such separate calculations, though they may add more time and expense to the process, can also help ensure that regulations are set at levels that adequately protect (or at least benefit) sensitive and vulnerable populations.

The methods the FDA used to estimate exposure for the NNN rule dramatically simplified the complexities of tobacco exposure. The FDA did not factor in the wide reported variance in smokeless tobacco NNN levels, consumption, and bioavailability. For example, it assumed that smokeless tobacco users would extract 60% of the NNN in their products, based on a small study by Hecht, but it did not factor in the wide variability among participants in Hecht’s study, which indicated that extraction could be much higher for some individuals.³¹ This again reinforces the need for careful consideration of behavioral factors in the tobacco context; research suggests that exposure to toxins in smokeless tobacco may depend on how long smokeless tobacco remains in one’s mouth—not just on the quantity consumed.³²

We emphasize that what is needed is not necessarily more research, but standardized risk assessment practices (eg, the use of default values when data is unavailable) that provide risk assessors with guidance tailored to the TCA’s public health standard and enable the development of population-level exposure models. These models do not necessarily need to

be highly complex, but should be able to provide estimates for “‘average’ and ‘high-end’ exposures, as well as susceptible populations or life stages.”¹⁰

Risk characterization.—The final stage of the formal risk assessment, risk characterization, integrates findings from the previous 3 stages (hazard identification, dose-response assessment, and exposure assessment) to reach “overall conclusion[s] about the risk that [are] complete, informative, and useful for decision makers.”³³ This phase usually employs some form of modeling to estimate health outcomes for various populations, and includes discussions of uncertainty, variability, and limitations.

The FDA predicted cancer risk due to arsenic in rice by “integrating the dose-response model and the exposure assessment, using a Monte-Carlo simulation model.” The model components are presented in Figure 2. Risk estimates were presented in 2 forms: (1) per capita, based on average lifetime exposure, and (2) per serving, based on consuming one or more servings of rice per day over a lifetime. Separate risk estimates were also provided for rice consumption during infancy and childhood. Overall, the FDA estimated that inorganic arsenic in rice was responsible for 157 bladder and lung cancer cases in the U.S. annually, with the 90% confidence interval ranging from 0 cases to 319.¹⁶

The FDA then proceeded to discuss the health impact of possible regulatory options, including limiting the amount of arsenic in each serving of rice. It found, for example, that a regulatory limit of 75 parts per billion (ppb) of arsenic per serving would reduce the cancer risk by 17% to 79%. However, it noted that such a limit could also drastically reduce the availability of rice, which could have countervailing negative effects on nutrition. The FDA also explored voluntary measures that consumers could take to reduce arsenic levels, such as washing rice or cooking rice in with more water.¹⁶

In the NNN rule, the FDA combined its data from the previous phases of the risk assessment into an equation designed to provide an Estimated Lifetime Cancer Risk (ELCR) from smokeless tobacco use (Figure 3). As can be seen, this ELCR estimate does not, despite the name, actually estimate cancer risk; rather “the ELCR is used to estimate the percent reduction in cancer risk associated with implementing an NNN limit for smokeless tobacco products.”⁶ Based on this formula, the FDA estimated that a product standard limiting NNN levels to 1 microgram per gram of tobacco—as the FDA proposed—would reduce the ELCR by 66.3%. It then computed that this standard would result in 2,200 fewer oral cancer deaths over the course of 20 years, resulting in 15,200 cumulative years of life gained.

While the ELCR equation allowed the FDA to provide a rough estimate of the impact of various potential NNN standards, it did not model potential variability or uncertainty, or consider how the rule would affect different segments of the population. Though not a critical problem in this case, where the overall public health benefit of reduced NNN levels was clear, such modeling is important to fully inform decision-makers. Without such modeling, for instance, a rule may appear to have a very limited population level benefit if it makes little difference to much of the population, when it might actually have an enormous impact for a specific subgroup (which may be the case, for example, for tobacco products targeted at specific demographics). Likewise, failing to account for sensitive populations (eg,

youth whose brains and lungs are still developing) may lead to regulatory approaches that are not adequately protective of those populations.

Importantly, because the FDA's equation did not incorporate how individuals might respond to the new rule, it also did not reflect the public health standard that the FDA must apply. If consumers found that their current brand of smokeless tobacco was withdrawn from the market, they could respond to shifting to a higher-risk tobacco product—or, to the contrary, they could decide to quit smokeless tobacco use altogether. The FDA's calculation contemplates neither possibility. Thus, although these possibilities were mentioned briefly in the text of the proposed rule, the FDA has not developed a framework through which future risk assessments can take these considerations into account. Industry tactics, such as advertising, promotion, and new product development (though limited by the TCA), could also influence how consumers respond to new regulations. Importantly, models have been developed that seek to account for these factors, and the FDA could build on these models to develop a more comprehensive—and population-based—approach to characterizing risk.^{20,34}

DISCUSSION

Advancing Tobacco Risk Assessment

The contrast between the FDA's risk assessments for arsenic in rice and NNN in smokeless tobacco suggests some general lessons that the FDA's Center for Tobacco Products should consider as it develops a framework for tobacco-related risk assessments. Some of these are relatively straightforward (though their application may not be) and reflect to the need to for the FDA to apply existing best practices for risk assessment. For example, both the EPA and the FDA (in non-tobacco contexts) have set forth key principles for risk assessment that include *transparency* and *consistency*.^{10,11,35} The FDA's arsenic risk assessment included a detailed appendix providing the details of its models and all related calculations (including sensitivity analyses), thus making its risk assessment much more transparent.¹⁶ Additionally, it followed previously published FDA guidance for conducting risk assessments (including the use of default values),¹¹ which contributes to the consistency and objectivity of FDA risk assessments. In contrast, the FDA has not yet developed guidance for conducting tobacco-related risk assessments, and the decision-making underlying its NNN assessment was not fully transparent. Moving forward, an important priority should be to develop guidance for tobacco-related risk assessment that embodies these key principles.

Similarly, as explained in the NRC's Silver Book, it is critical for much more focus to go into the initial phases of the risk assessment: planning, scoping, and problem formulation.¹ This is work that, at least publicly, the FDA has not yet done for tobacco-related risk assessments. Given the scope of the public health harms caused by tobacco use, the trade-off between the comprehensiveness of a risk assessment and the need to make it manageable and timely may be particularly acute. While in some cases it may be preferable to wait for more and better data before conducting a risk assessment, regulatory decisions will need to be made one way or the other in the meantime. As the arsenic risk assessment suggests, this tension could be relieved somewhat by conducting quantitative risk assessments where the evidence is strong enough to support doing so, while conducting qualitative reviews of

emerging evidence (eg, disease endpoints where the evidence is less developed). Additionally, the arsenic example provides an illustration of how the best available data (eg, data relating to arsenic exposure from drinking water) can still be used to inform risk assessments when data about the precise question at issue (arsenic exposure from rice products) is limited. Whatever its ultimate decisions, the FDA needs to fully engage with this part of the process and be transparent about the decisions it makes.

Other lessons are more geared towards the unique legal and factual context of tobacco, and likely defy easy solutions. First, as previously mentioned, the FDA's tobacco-related risk assessments should reflect the TCA's population-focused legal standard. They must include a logical framework for considering not just the impact of a product on individual users, but population-level effects. This perspective is particularly important when examining potentially reduced-risk products; even if a product is less harmful for any given individual (in comparison to conventional cigarettes, for example), population-harms could increase if the product promotes youth initiation, discourages cessation, or leads to widespread dual use. This suggests the need to consider many factors that risk assessments have not traditionally emphasized but that tobacco-related risk assessments must, including: marketing and promotion, packaging/branding, price, social influences, consumer perception (including health-related beliefs), behavioral patterns, levels of addiction, motivation to quit, and more. (The Tobacco Products Scientific Advisory Committee's (TPSAC's) 2011 report on the public health effects of menthol cigarettes provides a helpful starting list of factors that should be considered.³⁶)

Second, once the FDA develops a conceptual framework that accounts for population-level effects, it will need to determine whether it can use the same framework (or modified versions of the same framework) for assessments conducted under different regulatory powers. Regulating NNN levels in smokeless tobacco is obviously very different from mandating warning labels or restricting e-cigarette flavors that appeal to youth. Use of one uniform conceptual framework would promote consistency and transparency, but different endpoints, measures, behaviors, and populations/life stages may be more or less relevant in different regulatory contexts.

Third, after the FDA designs a conceptual framework, it will also need to develop more complex statistical modeling tools for use in the risk characterization phase. Existing models used in the tobacco control field, like the model used in the recent National Academy of Sciences report on the health effects of e-cigarettes,³⁷ provide a strong starting point. This model estimated possible health impacts *if* population tobacco use patterns change in specified ways and *if* e-cigarette use is assumed to be far less harmful than cigarette use. Though the model was not informed by a full risk assessment process, the range of parameters used for changes in initiation, cessation, and the harms of e-cigarettes were informed by the literature review provided elsewhere in the report. This model, however, used life-years gained or lost as its only health endpoint and made a variety of other simplifying assumptions that should be reviewed (eg, that dual users have the same health risks as current cigarette users). Furthermore, it did not characterize the uncertainty and variability underlying its conclusions, as a risk characterization would need to do in order to be better inform regulatory decision-making. Although considerable work has been done in

recent years on tobacco control modeling, these models generally share similar limitations and have not been designed for use in risk assessment.^{20,28,38–40}

Finally, there is one additional issue that is uniquely salient in the context of tobacco: the FDA will need to consider how it addresses conflicts of interest when conducting risk assessments. For example, when conducting literature assessments to identify or quantify hazards, will it exclude industry produced or industry funded studies? Or weigh them differently? These issues come up in other regulatory contexts as well, but the tobacco industry's long history of deliberately manipulating science makes reliance on industry studies particularly concerning. Notably, the tobacco industry has been active in designing risk assessment frameworks and population risk models;^{41–44} given these concerns, it is imperative that the FDA develop its own risk assessment framework, rather than rely on those developed by the industry.

IMPLICATIONS FOR TOBACCO REGULATION

In this paper, we have suggested the need to develop a general conceptual framework to apply to risk assessments of tobacco product regulations, and we have outlined some—but certainly not all—of the additional considerations specific to tobacco risk assessment that will need to be accounted for at each stage of the analysis. The risk assessment included in the FDA's proposed NNN rule, its first proposed product standard, suggests that such an in-depth foundational framework for tobacco risk assessment has not yet been developed.

The FDA likely chose not to engage a more comprehensive risk assessment because by just focusing on the strong connection between NNN and oral cancer, it could find sufficient legal justification for issuing its product standard. There is strong and consistent evidence demonstrating NNN's association with oral cancer, and evidence from other countries shows that it is feasible to reduce NNN levels in smokeless tobacco.⁷ Nonetheless, the FDA's failure to develop a more comprehensive approach to risk assessment was a missed opportunity. Further, the FDA's decision to limit its analysis suggests that even with a proposed rule that focuses narrowly on one tobacco constituent, adding in multiple health and behavioral outcomes will be difficult. It foreshadows the degree of difficulty that the FDA faces as it moves into regulating cigarettes (which produce much more complex chemical mixtures) and newly emerging products (where the evidence base is much more limited).

We hope that the FDA will follow the example of other federal agencies and allow for an open dialogue with the research community in which experts can weigh in on the necessary elements of a risk assessment framework that can be applied to a range of different tobacco regulatory contexts. In working to develop this framework, there will be a tradeoff between fine-tuning the framework and taking action, as the need to reduce tobacco-related disease and death remains urgent. Likewise, a balance will need to be struck between the comprehensiveness of the risk assessment framework and need for the FDA to be able to conduct such assessments efficiently. Though there are many challenges ahead, it is imperative for the FDA to move expeditiously towards developing a conceptual model for risk assessments of tobacco products.

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Conflict of Interest Statement

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Figure 1.
Framework for Human Health Risk Assessment to Inform Decision Making¹⁰

Figure 2.
Arsenic in Rice Products: Risk Characterization Model Components

$$ELCR = C \times IR \times \frac{AB \times EF \times ED}{BW \times AT} \times CSF$$

C = Concentration of NNN in product as used (mg/g wet weight)

IR = Intake rate (mg of wet (as used)) product used per day (12 g/day; 2.5 g/day for dissolvables)

AB = Absorption rate, how much of product NNN is transferred to the user (60%)

EF = Exposure frequency (365 days/year)

ED = Exposure duration (60 years)

BW = Body weight in kg (70 kg)

AT = Averaging time (365 days/year; 78 years)

CSF = Cancer slope factor (1.4 mg/kg/day)

Figure 3.

Estimated Lifetime Cancer Risk (ELCR) Calculation⁶