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HOW HISTORY INFORMS FDA TOBACCO REGULATION:
RETROSPECTIVE APPLICATION OF A PUBLIC HEALTH ASSESSMENT FRAMEWORK TO “LOW TAR” CIGARETTES

MICAH L. BERMAN, MAHMOOD A. ALALWAN, DAVID T. LEVY, JONATHAN M. SAMET, AND PETER G. SHIELDS*

ABSTRACT

The 2009 Tobacco Control Act requires the U.S. Food and Drug Administration (FDA) to make tobacco-related regulatory decisions using a population-level Public Health Standard. This article proposes a thought experiment to assist the FDA in determining how it implements this standard: if the FDA had possessed the authority to regulate tobacco in 1990, would it have been able to accurately determine that the sale of “low-tar” cigarettes did not meet the requirements of the Public Health Standard?

To answer this question, we analyzed scientific publications and internal tobacco industry documents gathered in a systematic search to inform previous work examining the health effects of filter-ventilated cigarettes. We only included relevant papers published during or before 1990. We examined and synthesized the extracted data using a framework designed specifically to inform tobacco regulatory decision-making.

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We found that studies assessing individual-level disease risk of low-tar cigarettes as of 1990 had conflicting findings, and population-level studies of usage patterns were limited. However, population-level lung cancer data and changes in histology by gender and age would have predicted that low-tar cigarettes were contributing to an increased risk of adenocarcinoma.

We conclude that if the FDA had possessed the authority to regulate tobacco in 1990 using a population health standard, it is unclear whether the data would have been sufficient to promulgate regulations governing “low tar” cigarettes.” This thought experiment highlights the need for FDA regulation to be informed by (a) detailed data on population-level use trends, and (b) careful attention to health-related data, including changes in trends by gender and other demographic characteristics.
I. INTRODUCTION

Tobacco use remains the leading preventable cause of mortality and disease in the United States. To protect the population’s health, the 2009 Family Smoking Prevention and Tobacco Control Act (TCA) gave the U.S. Food and Drug Administration (FDA) authority to regulate tobacco products and apply a new population-based “Public Health Standard” to gauge the impact of regulations and new tobacco products. This standard requires the FDA to make regulatory decisions that are “appropriate for the protection of the public health,” taking into account the population-level risks and benefits of potential regulations, including the likelihood of cessation among current users and initiation among non-users. Although the FDA has had the authority to regulate tobacco products since 2009, it has not yet explained how it makes decisions about when evidence is considered sufficient to take regulatory action under the Public Health Standard.

To assist the FDA in considering this question, this paper proposes a thought experiment. We now know that, for several reasons relating to the effects of cigarette filter ventilation, so-called “light” or “low-tar” cigarettes are not less harmful than “regular” cigarettes and, indeed, may be more harmful. The National Cancer Institute (NCI) Monograph 13, published in 2001, demonstrated that these products did not reduce smoking-related risks because of the “more intensive smoking of lower yield cigarettes,” but that they “may [have] promote[d] initiation and impede[d] cessation,” thereby harming public health overall. Historians have subsequently shown that the tobacco industry knew, but hid from the public and government officials, that even though “[h]ighly ventilated cigarettes deliver low levels of tar when smoked on a smoking [machine]…humans are able to smoke such cigarettes in ways that deliver far more tar and nicotine.”

The thought experiment proposed here is: Since we now know how this history played out, if the FDA had possessed the authority to regulate tobacco products at an earlier point in history, would it have been able to accurately determine:

that the sale of “light” cigarettes using filter ventilation was not “appropriate for the protection of public health,” and
2. that the sale of “light” cigarettes should have been restricted (by regulating product characteristics and the use of misleading descriptors)?

We think this retrospective approach is valuable for two reasons. First, it presents a concrete case study through which to assess the types of evidence needed to inform FDA’s determinations about whether the sale of a product is “appropriate for the protection of the public health.” Secondly, it allows for an assessment of whether or not the FDA can accurately predict the impact of its tobacco-related regulations. If our analysis shows that this “grand fraud” would have been difficult to detect in real time, how can the FDA take steps to avoid mistaken regulatory decisions—with potentially immense public health consequences—today?

A. “Light” and “Low-Tar” Cigarettes

Starting in the 1950s, the tobacco industry responded to the emerging evidence on the health risks of cigarettes by adding filters with ventilation holes to reduce tar and nicotine yields in laboratory smoking machine studies. They marketed these as “light” or “low-tar” cigarettes, implicitly and explicitly claiming that they were less harmful cigarettes. From the outset, the tobacco industry knew, based on internal company research, that these products would not reduce tobacco-related harms because smokers would compensate by smoking more, and that changes in how the tobacco burns might worsen lung cancer risks. In the 1960s, public health entities and authorities, including the Surgeon General—who remained unaware of the tobacco companies’ knowledge—encouraged smokers who were unable to quit to switch to lower-tar cigarettes, and these products quickly achieved widespread consumer acceptance. However, as the tobacco companies had (secretly) predicted, these

7. Donald R. Shopland, Historical Perspective: The Low Tar Lie, 10 TOBACCO CONTROL (Supplement 1) i1, i1–i2 (2001).
8. Id.
9. See supra notes 6. See also U.S. v. Philip Morris USA, Inc., 449 F. Supp. 2d 1, 14–18 (D.D.C. 2006) (finding that industry defendants marketed such products as less harmful when they knew they were not less harmful); Catalin Marian et al., Reconciling Human Smoking Behavior and Machine Smoking Patterns: Implications for Understanding Smoking Behavior and the Impact on Laboratory Studies, 18 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 3305, 3306 (2009) (explaining that “[w]e now know that smoking machine yields were misunderstood in relation to human exposure and tobacco companies intentionally misrepresented the impact of lowering tar yields on smokers’ health”).
purportedly lower-risk products did not decrease disease risk.\textsuperscript{11} Partly due to a lack of product regulation at the time, these effects were not detected until more than thirty years later, and only after the tobacco industry was forced to reveal its research results during litigation.\textsuperscript{12}

B. A Public Health Framework for Tobacco Regulation

Building on earlier work,\textsuperscript{13} we propose a framework designed to inform tobacco regulatory decision-making (Figure 1). This framework builds on concepts used by the federal government in environmental risk assessments and is designed to structure decision-making around the TCA’s unique Public Health Standard. The goal is to produce a systematic and transparent process for making complex—and sometimes conflicting—scientific data useful to regulatory decision-makers. We do not propose a quantitative model of how these various inputs should be combined and weighed to predict the effects of regulatory decisions. However, we propose that quantitative modeling based on the inputs described here should be a necessary step in the FDA’s assessment of the public health impact of potential regulatory decisions.

The framework uses the four broad steps—hazard identification, dose-response assessment, exposure assessment, and risk characterization—described in the National Research Council’s “Red Book”\textsuperscript{14} and “Silver Book”\textsuperscript{15} risk assessment frameworks as its starting point, and tailors these concepts to reflect the tobacco-related context. It then incorporates modifications and additions to reflect the TCA’s population-based public health standard. In particular, we have clarified that in the tobacco context, the assessment must distinguish between (and consider both) individual disease risk and population-level exposure. Individual-level disease risk is the product of both the effects assessment, which examines factors related to the product’s toxicity and abuse liability, and the individual exposure assessment, which considers how differences in the way

\begin{itemize}
\item \textsuperscript{11} See supra note 5. See also CTRS. FOR DISEASE CONTROL AND PREVENTION, ACHIEVEMENTS IN PUBLIC HEALTH, 1900-1999: TOBACCO USE – UNITED STATES, 2–3 (1999) (describing how although “low tar” cigarettes were purportedly designed to reduce risk, “many smokers compensated by smoking more intensely and by blocking the filter's ventilation holes,” precipitating an “increase in adenocarcinoma [that] parallel[ed] the changes in cigarette design and smoking behavior”).
\item \textsuperscript{12} See supra note 1. See also Catalin Marian et al., supra note 9, at 2 (noting that it took until 2008 for the FTC to rescind its guidance for reporting tar yields determined by smoking machines, in belated recognition that machine reported yields did not accurate reflect human exposure); LT Kozlowski & RJ O’Connor, Cigarette Filter Ventilation Is a Defective Design Because of Misleading Taste, Bigger Puffs, and Blocked Vents, 11 TOBACCO CONTROL (SUPPLEMENT 1) i40, i40–i42 (2002) (discussing evidence from tobacco industry documents).
\item \textsuperscript{13} Micah L. Berman et al., Risk Assessment for Tobacco Regulation, 5 TOBACCO REGUL. SCI., Jan. 2020; Micah L, Berman & Allison M. Glasser, Nicotine Reduction in Cigarettes: Literature Review and Gap Analysis, 21 NICOTINE & TOBACCO R Sch. (Supplement 1), Aug. 2019.
\item \textsuperscript{14} COMM. ON THE INSTITUTIONAL MEANS FOR ASSESSMENT OF RISKS TO PUB. HEALTH, NAT’L R SCHL. COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS 3 (1983).
\item \textsuperscript{15} COMM. ON IMPROVING RISK ANALYSIS APPROACHES USED BY THE U.S. EPA, NAT’L R SCHL. COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT 4 (2009).
\end{itemize}
individual users consume a tobacco product may impact their exposure to harmful constituents (e.g., intensity and frequency of use). The population exposure assessment then considers how the presence or absence of a product (or product characteristic) influences population-level use trends such as initiation, cessation, and product switching—factors that FDA must consider as part of the TCA’s Public Health Standard. The FDA must also consider differences in subpopulation trends; some products may be marketed to (and used differently by) specific demographic groups, as, for example, tobacco companies have designed and marketed products specifically to appeal to women, African Americans, and adolescent boys.

The framework also distinguishes other driving factors that should be considered in conjunction with the main assessments described in the previous paragraph. These factors are related to regulations, industry actions, and behaviors. The regulatory context, the industry’s activities, and the social context all shape how a tobacco product is accessed and used, both at the individual and societal level.

All these pieces of the framework feed into the public health modeling phase, in which a quantitative model of the potential population harms and benefits of different regulatory options can be produced. Importantly, the models used should be transparent, consistent, and objective, with the methodology developed (and ideally published) in advance to boost public confidence in the assessment’s reliability. Such models would provide projections designed to inform policy-making, but without the intention of leading to a particular policy. In other words, such modeling may provide strong indication that a particular policy action would be beneficial for public health, but the FDA may still decide not to move forward with the policy because of overall agency priorities, litigation risk, technical limitations, or other factors. However, if FDA’s own assessment suggests that a policy measure would not benefit public health overall, then presumably it would lack the evidence required by the Public Health Standard to move forward.

II. AIM

We use the historical case of “low-tar” cigarettes to illustrate the application of our framework, focusing on the outcome of increased risk of lung cancer. (A more complete analysis would consider other health endpoints as well.) We constructed a hypothetical scenario in which the FDA regulated cigarettes in 1990 and was considering whether it would be “appropriate for the protection of the public health” to stop “light” cigarettes sales at that time. Although tobacco industry documents were shielded from disclosure for decades, documents that predate 1990 are included in this review because under the TCA, FDA can require tobacco companies to disclose all their internal research on the health,
while the reliability of tobacco industry research may be viewed with skepticism, we
found no indication that the industry manipulated its internal studies; rather, the
industry’s wrongful actions consisted of not disclosing the relevant studies to the
public and instead suggesting that “low-tar” cigarettes were less harmful.

If our application of this framework indicates that FDA would have been able to
clearly identify the harms (or lack of benefit) of “light” cigarettes roughly a
decade before the scientific community otherwise did, it suggests that the FDA
now has the ability to make proactive science-based regulatory decisions to
protect the public’s health, and that this framework might be a useful tool in
doing so. By contrast, if more than three decades after these products were
introduced the FDA still would have been unable to detect the harms caused by
the marketing of “light” cigarettes, it would suggest problems with the proposed
framework and perhaps with the foundation for the entire enterprise of FDA
product regulation.

III. METHODS

The studies and other documents used in this analysis were identified in
our prior study reviewing the impact of cigarette filter ventilation on lung cancer
risk. These ranged from laboratory studies (e.g., smoke chemistry and
toxicology) to epidemiology. For that study, we searched the MEDLINE
electronic database via PubMed to identify scientific publications, and we used
the online Tobacco Documents Bibliography archived by the library of the
University of California, San Francisco’s Center for Knowledge Management to
identify internal tobacco industry documents. In both databases, we combined
cigarettes with the following terms: smoking machine, lights, ultralights, tar,
filter ventilation, air dilution, Ames, mutagenicity, tumorigenicity,
adeno...
procedures, measures, results, limitations, funding, article type (industry/peer-reviewed), study topic (health effects/use patterns/toxicity/smoking cessation/dependence potential/measurement/perceptions/other), and study type (smoking machine/animal/human).

IV. Results

We reviewed 91 studies, as indicated in Table 1, and identified data relevant to each component and topic identified in our public health framework.22

A. Effects Assessment

Under the heading of an effects assessment, our framework adapts two components from traditional risk assessments: (1) toxicity and (2) dose-response assessment. We then added a dependence potential as a third component, given that this is a salient feature for tobacco regulation.

1. Toxicity

There were sixty-seven publications that assessed the toxicity of differing levels of cigarette filter ventilation. Some studies, including tobacco industry documents, showed that filter ventilation leads to several changes in physical and chemical properties of cigarette smoke. Increased filter ventilation leads to reduced burning rates of the tobacco rod, reduced airflow through the burning coal tip, and reduced coal temperatures.23 Taken as a whole, these changes prolong coal smoldering and reduce airflow passing through the burning coal tip. This consequently leads to higher incomplete combustion, higher toxicant production, and inferred harmful biological effects to smokers.24 An example of

22. See infra Table I.


24. Memorandum on air dilution and TA98 Ames activity from R.L. Blakly to M. D. Shannon, R.J. Reynolds Tobacco Co. 4 (Nov. 7, 1990) (on file with the University of California San Francisco Library); Memorandum on air dilution and TA98 Ames activity from R.L. Blakly to M. D. Shannon, R.J. Reynolds Tobacco Co. 4 (Nov. 7, 1990) (on file with the University of California San Francisco Library).
a study assessing physical and chemical changes is Fischer et al. (1989), which indicates the complexity of laboratory studies and how they could be misleading to the FDA. The researchers analyzed fifty-five types of German commercial cigarettes for tobacco-specific nitrosamines (TSNAs) in mainstream smoke under standard smoking-machine settings on a per cigarette basis. They concluded that tobacco composition was more important than filter ventilation in determining TSNA levels, and that tar delivery (determined by filter ventilation) was not sufficiently predictive of biological activity.

However, when evaluating this and other studies, it is important to note whether results are reported as yields or toxicity per cigarette or per mg tar. The former assumes that smokers will smoke like machines, which they do not. The latter infers exposure per puff, and recognizes that there are more puffs per cigarettes with higher ventilation when used by smokers. Fischer et al. reported results as yields per cigarettes, and data were not presented in a way that compared tobacco-blend similar cigarettes. Though researchers had not yet come to understand the importance of reporting results per mg of tar (or per mg of nicotine, because nicotine is the major determinant of smoking behavior), internal industry documents were documenting how and why smoke mutagenicity increased as ventilation levels rose.

As of 1990, there was sufficient data from experimental animal studies to show that some cigarette smoke constituents were lung carcinogens. Five animal studies examined lung carcinogenicity related to TSNAs and polycyclic aromatic

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25. Fischer et al., supra note 24, at 171–72.
26. Id. at 169.
27. Id. at 171–72.
28. Marian et al., supra note 9, at 5–6.
29. Fischer et al., supra note 24.
31. Memorandum from R.L. Blakly to M.D. Shannon, supra note 28. “Mutagenicity” refers to the ability of a chemical or biological substance (or complex mixture, as in the case of tobacco smoke) to “produce genetic damage that leads to gene mutations.” Michael D. Johnson, et al., Evaluation of In Vitro Assays for Assessing the Toxicity of Cigarette Smoke and Smokeless Tobacco, 18 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 3263, 3288 (2009).
hydrocarbons (PAHs), which are among the toxicants that increase with higher ventilation levels.32 One study, where researchers subcutaneously injected 372 rats with three types of TSNAs, indicated that NNK, even at low doses, induced high percentages of lung tumors, including peripheral lung adenomas.33 Several other studies showed that PAHs, administered intra-tracheally, were more likely to induce central squamous cell lung tumors.34 These studies, along with in vitro studies for different susceptible cell types in the lung, known prior to 1990, indicated that distal airways may be more susceptible to the effects of TSNAs than proximal airways, which may indicate a relationship between filter ventilation—which increases the levels of these toxicants—and lung adenocarcinoma.

We identified thirteen observational cross-sectional studies or switching studies assessing the effects of filter ventilation as of 1990.35 The switching studies varied widely in their designs. Some only tested the smokers’ usual cigarette brand36 while others considered brand-switching and tested up to five brands.37 The duration was also variable, ranging from two days to three weeks on each brand.38 The study setting also varied. Some of these studies were

32. See infra notes 38 through 39.
conducted in residential (in-patient) settings, where smokers can be directly observed. Other studies were conducted in the smokers’ natural settings (with follow-up lab visits) without any interference to their smoking behaviors. Sample sizes ranged from 10 to 270 participants; comparison groups were smokers who used their usual brand or nonsmokers. However, some studies did not have a control group and only conducted within-subject comparisons. Biomarkers of smoking showed some significant reductions when smokers switched to the ultralow tar yields, albeit not in line with the expected reduction relative to the reductions in tar yields, and switching to cigarettes with less dilution (e.g., the “low tar” cigarettes) had no change in biomarkers. When smokers switched from their self-selected brands to higher tar yields, there were no significant changes in biomarkers.

Cross-sectional studies examined the exposure of smoking-related toxicants using plasma cotinine, nicotine, and carboxyhemoglobin (COHb) measurements. Study participants smoked self-selected brands available in the market, which may differ in characteristics other than tar yields or ventilation. Nonetheless, these studies showed no statistically significant difference in exposure biomarkers between people smoking high-yield cigarettes and low-yield cigarettes, except when comparing the most extreme differences in tar yields. The largest cross-sectional study included in our review recruited 865 smokers who used a representative sample of brands with a large market share. If found that despite considerable variation in machine-tested cigarette yields, differences in exposure biomarkers were minimal. Also, other factors, such as

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42. Benowitz et al., Reduced Tar, Nicotine, and Carbon Monoxide Exposure, supra note 35, at 241–46.
45. Id.
mean cigarette consumption, were not affected by differences in cigarette yields. Several smaller studies showed similar findings.\(^\text{46}\)

As of 1990, there were eight cohort studies and nineteen case-control studies focused on lung cancer outcomes.\(^\text{47}\) These studies mostly compared smokers of filter-ventilated cigarette versus either: (a) smokers of regular cigarettes, or (b) machine-measured tar and nicotine yield levels.\(^\text{48}\) While some cohort studies showed significant reductions in lung cancer risk with filter-ventilated cigarettes,\(^\text{49}\) other cohort studies showed a non-significant decrease in

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48. E. C. Hammond et al., supra note 47; Colin Borland et al., Carbon Monoxide Yield of Cigarettes and its Relation to Cardiorespiratory Disease, 287 BRIT. MED. J. 1583, 1584-85 (1983); P.N. Lee & L. Garfinkel, Mortality and Type of Cigarette Smoked, 35 J. EPIDEMIOLOGY CMTY. HEALTH 16,
risk. Studies that analyzed data from the American Cancer Society’s CPS-I, a 12-year follow-up of more than 1 million men and women, were featured in the 1981 Surgeon General’s Report and were very influential for public health officials. The CPS analyses showed significant reductions in lung cancer mortality among low-tar yield cigarette smokers. As later understood, with the 2001 NCI Monograph 13, the analysis was flawed because smoking status at the time of diagnosis and time since quitting were not considered. When recognizing that smokers of lower yield cigarettes in the earlier years were more health conscious and therefore more likely to quit, the same ACS data indicated that smoking lower tar cigarettes did not reduce lung cancer risk.

In general, case-control studies showed a lower risk of lung cancer for users of low-yield cigarettes, with some using hospital-based controls and others using population-based controls. Two reports from one of the most extensive case-control studies conducted in parts of Europe showed more than a 40% reduction in lung cancer risk among lifetime filtered cigarette smokers. While most of the reviewed studies adjusted for the number of cigarettes per day, only one case-control study directly addressed compensation by examining the difference in the number of cigarettes per day after switching to filtered cigarettes. The later study assessed lung cancer risk for those who increased their daily consumption and found that odds ratios increased steadily as daily consumption increased. In summary, while some data prior to 1990 indicated that reduced cigarette yields reduced toxicity, there were methodological problems with this data, and internal tobacco company data indicated adverse biological effects.

2. **Dose-Response**

The extent to which toxicity is dependent on the amount of exposure (the dose-response assessment) may be important in other tobacco-related contexts,
such as when considering a product standard that would limit the amount of a particular constituent to a specified level. For this reason, we have included a dose-response assessment in our framework (Figure 1). However, we did not identify any studies or documents as of 1990 that specifically examined the dose-related toxicity of filter ventilated cigarettes or sought to develop dose-response curves. For the assessment of filter ventilated cigarettes, most studies focused on comparisons to unventilated cigarettes (or cigarettes with different levels of ventilation), rather than assessing dose-related effects.

3. Dependence Potential

Despite the nicotine reductions in machine-measured yields in filter ventilation cigarettes, smokers were able to obtain the same levels of nicotine by changing their smoking behaviors, in a process known as compensation. The studies addressing compensation are reviewed below as part of the Individual Exposure Assessment. Our review did not identify any studies directly assessing differences in the dependence potential of filter-ventilated cigarettes, such as with the Fagerström Test for Nicotine Dependence (which was not published until 1991). However, the data demonstrating compensation reflects a more intensive smoking pattern for lower-yield cigarettes, which is indicative of high dependence potential.

B. Individual Exposure Assessment

As of 1990, data showed that when smokers switched to lower yield cigarettes, the level of exposure to toxicants changed because they smoked more cigarettes per day or smoked more intensely. Seven switching studies reported a significant increase in the number of cigarettes smoked per day when participants switched from their usual brand to lower yield cigarettes. Similarly, both RCTs and cross-sectional studies indicated that cigarette consumption either increased or remained unaffected despite the wide differences in machine-measured tar yields.

We identified fourteen studies that examined compensation leading to changes in smoking intensity measured through puff topography – puff volume, duration, puff interval and puffs per cigarette. Most studies, but not all, reported

59. See infra Figure 1.
60. Id.
61. K. Battig et al., Smoke Yield of Cigarettes and Puffing Behavior in Men and Women, 76 PSYCHOPHARMACOLOGY 139, 143 (1982).
that smokers of lower yield cigarettes took more frequent, longer, or more intense puffs, resulting in larger puff volumes.65 Other mechanisms to maintain the smokers’ nicotine intake may include increasing cigarette consumption or consuming more tobacco per cigarette.66

Smoking topography studies conducted by the tobacco industry, purporting to replicate human smoking patterns on smoking machines, found that standardized smoking machine profiles failed to predict exposure to filter-ventilated cigarette smokers.67 For instance, Goodman found that 0% and 25% ventilation delivered similar amounts of tar.68 She also concluded that tar delivery to smokers increases proportionally with the increase in puff volume resulting from added dilution.69

Blocking ventilation holes is one compensation method used by smokers to maintain their nicotine intake. This can be detected by visual examination of cigarette filters.70 Kozlowski and colleagues estimated the prevalence of ventilation hole blocking by examining a sample of filters in public ashtrays.71 They inspected about 1,000 cigarette butts to obtain a sample of 135 machine measured low-tar yield butts (1-4 mg tar).72 The majority of filters (58% ±10 SEM) showed some signs of hole-blocking and 19% (±8) showed signs of extreme hole-blocking.73


69. Id.


C. Population Exposure Assessment

The previous phases of the assessment indicated that individual users did not benefit from switching from “regular” to “low-tar” cigarettes, because compensation negated the assumption that there might be reduced exposure based on smoking machine yields. However, at the population level, even if individual risk could be lowered, the population-level effects would depend on the prevalence and patterns of use. For example, if “low tar” cigarettes fostered smoking uptake and decreased smoking cessation, they could increase population-level harms even if there was some theoretical harm reduction potential. These effects could be driven by abuse liability and perceptions that “low tar” cigarettes are safer.

While uptake of “low tar” cigarettes generally increased over time, there were no studies that examined initiation patterns with filter ventilation or the likelihood of population-level product switching. As of 1990, there were also no studies that assessed the impact of filter ventilation on specific vulnerable populations, such as people with mental illness. Similarly, studies did not assess adolescent uptake of “low tar” cigarettes compared to other yields.

Only a single study assessed changes in smoking cessation. Hammond (1980) examined the association between the use of low-yield cigarettes and smoking cessation using data from the first Cancer Prevention Study (CPS-I). He found that smokers who switched halfway through the study to lower-yield cigarettes were more likely to be former smokers by the last follow-up, compared to middle- to higher-yield smokers. However, this association may reflect other characteristics of smokers who switched to lower-yield cigarettes, such as higher educational attainment and socioeconomic status, intentions to quit, and behaviors associated with health-promoting behaviors.

There were five studies that assessed consumer perception. Tobacco industry studies indicated that the industry was aware that the filter ventilation design produced a subjectively less harsh and irritating smoke. Although smokers were unaware of the ventilation holes, they perceived lower-tar cigarettes to be less harmful. A large industry survey found that about 17% of

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75. Id.
76. Id.
77. See infra note 85.
79. Memorandum titled “A study of cigarette smokers’ habits and attitudes” by Elmo Roper to Philip Morris U.S.A. Rsch Ctr. 2 (Apr. 1960); Memorandum titled “Smokers’ Reactions to an Ultra Light Brand Extension for Marlboro: A Qualitative Study (Three Focused Group Interviews)” by Goldstein/Kral Marketing Resources to Philip Morris, U.S.A. (June 1979) (on file with the University of California San Francisco Library); GOLDSTEIN KRAL MARKETING RESOURCES, PHILIP MORRIS REC,
participants thought cigarettes with ventilated paper were better for them, compared to only 9% who thought they were worse.\textsuperscript{80} Another qualitative study found that most smokers perceived ultralight cigarettes to have a lighter taste compared to light cigarettes, and to be safer cigarettes with less tar and nicotine.\textsuperscript{81} These studies indicate that in addition to the direct health effects of filter ventilation, the products’ taste and the false perception of reduced risk are important considerations.

\textbf{D. Public Health Modeling}

The public health impacts that need to be modeled will vary depending on the type of regulatory decision. For example, in this hypothetical, the FDA could have modeled the impact of continuing (versus prohibiting) the continued sale of filter-ventilated cigarettes. In other contexts, it might model the impact of regulating product characteristics or of permitting “modified risk” health-related claims.

For our hypothetical, modeling was infeasible due to lack of population level datasets that have all the needed requirements for modeling population level exposure. An ideal dataset to model the population impact of filter-ventilated cigarettes would have included real-world data for the above-identified gaps in the critical Population Exposure Assessment phase, including initiation patterns with filter ventilation, the likelihood of population-level product switching, and differences in use/cessation rates by demographic characteristics. (Due to the Population Assessment of Tobacco and Health (PATH) and other such surveillance, such data should be more easily accessible to FDA today.) Despite the lack of appropriate datasets that would have informed FDA about population-level dynamics, individual-level and other potential surveillance data could have alerted FDA to the need to scrutinize filter-ventilated cigarettes.

Evidence reviewed in this study, especially from animals, smoking topography, and cross-sectional studies, showed an association between filter-ventilated cigarettes, which—due to compensation—increased the level of toxicants such as TSNAs and PAHs and induced changes in breathing and puffing patterns, with lung adenocarcinomas. Additionally, data from National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program showed that lung adenocarcinoma incidence rates were increasing before 1990, and the incidence of squamous cell carcinoma was declining (\textbf{Figure 2}).\textsuperscript{82} For women, who were more likely to have initiated smoking with

\textsc{Smokers’ Reactions to an Ultra-Light Brand Extension for Marlboro: A Qualitative Study (Three Focused Group Interviews)} (1979).

\textsuperscript{80} \textsc{Elmo Roper, supra} note 79.

\textsuperscript{81} \textsc{Goldstein Kral Marketing Resources, supra} note 79.

low-yield cigarettes, the rate of adenocarcinoma was more than twice as high as the rate of squamous cell carcinoma as of 1990. This change in lung cancer rate trends by histologic type, along with the overall evidence in this review, should have warranted further scrutiny of filter-ventilated cigarettes.

V. DISCUSSION

The paper presents a novel public health framework, built with reference to concepts used in risk assessment, but designed specifically to inform tobacco regulatory decision-making. The framework is intended to provide a guide to systematically examining the factors that need to be considered to inform regulatory judgments under the FDA’s public health standard.

Individual disease risk data are important, but do not tell the whole story. In general, studies of individual disease risk of “low-tar” cigarettes—as of 1990—yielded conflicting findings. Experimental and cross-sectional studies suggested a possible increase in toxicant exposure compared to conventional cigarettes, while some cohort and case-control studies suggested that they posed a lower risk. In general, the studies consistently showed changes in smoking behaviors due to a compensatory response. This resulted in similar levels of exposures from different levels of ventilation, reflecting the high dependence potential of low-yield cigarettes. Studies that assessed lung cancer risk showed conflicting results with significant and non-significant reductions. However, they indicated an association of filter-ventilated cigarettes with lung adenocarcinoma, which was not previously thought to be a smoking-related disease.

Later analyses (though none of the studies included in our pre-1991 sample) suggested that some of these studies were systematically biased toward finding lower risks from low yield cigarettes, because controlling by CPD failed to account for lower-yield cigarette smokers compensating by smoking more cigarettes per day.

In applying the Public Health Standard, focusing on the population exposure assessment is key, which is why this framework introduces a population exposure assessment step. For products already on the market, the regulatory authority can look at real world patterns of use to inform this part of the analysis. This requires extensive—and rapid—surveillance sufficient to examine use by gender, ethnicity, and other population characteristics of interest. In our case, this level of data was largely lacking. Hammond found (in 1980) that

84. See infra Table 1.
those who used low-tar cigarettes were more likely to quit, but this potentially reflected that those who switched to these cigarettes might have been more likely to quit in any event. This suggests that the FDA should be careful about overreading real-world cessation effectiveness for a new product; methods are needed to compare what the quit rate would likely have been for that same population of smokers in the absence of the new product.

The Public Health Modeling phase brings evidence together. Typically, this would involve prospective modeling, using data from the previous three phases to inform modeling parameters. Much progress has been made in developing modeling approaches for tobacco regulation, but the FDA needs to provide more transparency about its approach. It would have been very difficult to do accurate population-level modeling for low-tar cigarettes in 1990 in the absence of more population-level use data. But for products that have been on the market for a long time, the FDA can examine relevant health-related outcomes to help inform this step. This requires careful attention to differences in the use patterns and health outcomes of different subpopulations of interest. In some cases, the FDA may have to rely, with caution, on shorter-term health data, which is not fully predictive of long-term health effects. In this hypothetical case, if FDA had been paying careful attention to lung cancer surveillance, it may have picked on divergent trends of adenocarcinoma and squamous cell carcinoma rates. This divergence was especially pronounced among women, who were more likely to smoke low-tar cigarettes, reflecting a history of the industry marketing these products specifically to women. If the FDA had possessed regulatory authority at the time, these trends may have raised concerns about the impact of low-tar cigarettes. Nonetheless, the fact that no one picked up on these changes in lung cancer histology until the late 1990s suggests how difficult it may be to identify such trends in real time. Doing so requires careful analysis of population-level surveillance data, separate and apart from the FDA’s review of data submitted from tobacco companies. The FDA must conduct its own analyses (or do so in collaboration with independent researchers) and incorporate such findings into its regulatory reviews.

Little information was available within our collected materials to assess the factors addressed at the top level of our framework (regulation & industry actions and behavior). Studies suggest that in addition to the product design, the harm of

87. Hammond, supra note 74.
low-tar cigarettes was driven by industry promotion and mistaken risk perceptions, which were explicitly and implicitly shaped by industry advertising. This specific problem has been partly addressed by modified risk tobacco product (MRTP) requirement, which requires both implicit and explicit health claims to receive prior FDA authorization. But it is important to note that mistaken risk perceptions can far outlast the health claims themselves, as has been the case with “light” cigarettes. The faulty risk perceptions that predated FDA regulation have transferred over to color-coded packs. Any risk perception intervention must be carefully designed to consider human behavior, behavioral responses to regulations, and existing misperceptions.

The framework outlined here incorporates new considerations that the FDA has not previously included in its published regulatory documents. Importantly, the FDA has not publicly proposed its own approach for modeling the potential public health impact of potential regulations. Instead, the FDA has required public health modeling in applications submitted by the industry, and do not account for periods of dual use,” and therefore “[was] not particularly informative in the evaluation of whether the new products are appropriate for the protection of public health.” Surprisingly, though, FDA then failed to do its own modeling of the potential public health impact of authorizing this product


93. U.S. FOOD & DRUG ADMIN. TECHNICAL PROJECT LEAD (TPL) REVIEW OF PMTAs PM0000S,L, PM0000553, PM0000560, 26 (2021),
before concluding that permitting its sale would be “appropriate for the protection of the public health.”  

As we have previously described, the FDA did exactly the same thing in its memo authorizing the sale of Philip Morris’s IQOS heat-not-burn product; it rejected the applicant’s modeling as flawed, but failed to conduct any form of public health modeling on its own. It is difficult to understand “how [the FDA] can make an ‘appropriate’ finding without making any estimates about the actual size of the possible harm reductions and harm increases.”

Two final comments underscore the difficulty of the challenge facing the FDA. First, our thought experiment did not include an analysis of the political factors and social context. With some evidence pointing in both directions, there would have been extensive pressure from the industry not to take regulatory steps against a product that it claimed was reducing harm. Likewise, today, political and structural obstacles make effective FDA’s tobacco regulation difficult, even when the FDA possesses overwhelming evidence upon which to base its actions. In our view, this fact reinforces the need for FDA to have clear and transparent decision-making processes that can be defended in both courts of law and the court of public opinion.

Secondly, the hypothetical case of “light” cigarette regulation presented here is in many ways a best-case scenario for regulation. By 1990, the FDA would have had the benefit of approximately 30 years of these products being in wide circulation and use. Reaching the appropriate regulatory decision still would have been extremely difficult, which suggests the extraordinarily high degree of difficulty the FDA faces as it attempts to make regulatory decisions regarding products that have been on the market for a much shorter timeframe. Thus, any regulatory action by the FDA must include a plan for careful monitoring and re-evaluation of its decisions over time.

VI. CONCLUSION

Had FDA possessed regulatory authority over tobacco products in 1990, it might have been able to pick up on the increased low-tar cigarettes were causing. But doing so would have required both (1) better data collection on population-level use trends and (2) careful attention to population-level health data. It is notable that scientists did not come to a consensus that low-tar cigarettes were no

94. Id.
less harmful than “regular” cigarettes until the early 2000s, and only recently have papers suggested that filter ventilated cigarettes increased harm. The delay shows how difficult these assessments can be in the absence of long-term health outcome data, and it highlights the massive challenge faced by the FDA as it necessarily makes consequential regulatory decisions based on much shorter-term data.

Our framework can help inform the FDA about types of evidence needed to inform assessments (and predictive modeling) under the Public Health Standard. In particular, our review underscores the need for the FDA to incorporate population-level use and health data into its analyses, rather than relying solely on information submitted by tobacco companies. The FDA also needs to ensure that it has a plan for detailed monitoring and re-evaluation after regulatory decisions are made.

FDA tobacco regulation has immense potential to improve public health. Use of a transparent and standardized public health decision-making framework can help ensure that the FDA considers all relevant factors in a manner that will be best able to withstand both political pressures and legal challenges.

99. See NAT’L CANCER INST., supra note 6, at 47; IARC WORKING GRP. ON EVALUATION OF CARCINOGENIC RISKS TO HUMANS., INT’L AGENCY FOR R.SCH. ON CANCER, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS, NO. 83: TOBACCO SMOKE AND INVOLUNTARY SMOKING 94 (2004).

100. Min-Ae Song et al., supra note 4, at 5.

### Tables

Table 1. Outcomes Measured in Included Studies*

<table>
<thead>
<tr>
<th>Risk assessment Component</th>
<th>Topic</th>
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<th>Outcomes</th>
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<td>Effects Assessment</td>
<td>Toxicity</td>
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<td>Physical and chemical changes$^{102}$</td>
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<td>Urine mutagenicity$^{103}$</td>
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<td></td>
<td>Plasma or urine cotinine or nicotine$^{104}$</td>
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<td></td>
<td>Exhaled CO or COHb$^{105}$</td>
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<td></td>
<td>Plasma or saliva thiocyanate$^{106}$</td>
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<td></td>
<td>Carcinogens$^{107}$ Lung cancer risk$^{108}$</td>
</tr>
<tr>
<td>Dependence potential</td>
<td>$N = 16$</td>
<td></td>
<td>Dependence potential$^{109}$</td>
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103. See supra note 35.
104. See supra note 35.
105. See supra note 35.
106. See supra note 35.
107. Supra note 33.
108. Supra note 49.
109. Supra note 65.
<table>
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<tr>
<th>Individual Exposure Assessment</th>
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<td>Intensity of Use (Smoking Topography)</td>
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<td>Puff duration\textsuperscript{114}</td>
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<td>Lung exposure time\textsuperscript{116}</td>
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<td>Butt-length\textsuperscript{118}</td>
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<td>Population Exposure Assessment</td>
<td>Cessation</td>
<td>N = 1</td>
<td>Cessation\textsuperscript{119}</td>
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\textsuperscript{110} See supra note 35.
\textsuperscript{111} See supra note 35.
\textsuperscript{112} Id.
\textsuperscript{113} See supra note 65.
\textsuperscript{114} Id.
\textsuperscript{115} See supra note 35.
\textsuperscript{116} Id.
\textsuperscript{117} Id.
\textsuperscript{118} See supra note 34.
\textsuperscript{119} E. C. Hammond et al., supra note 74.
Behavior | Consumer Perceptions | $N = 5$ | Consumer perceptions

* 91 total studies reviewed; some are relevant to multiple topics. References do not include all studies reviewed; for full dataset, please contact the authors.

**Figures**

*Figure 1. Public health framework for informing tobacco regulatory decision making*
Figure 2. Age-adjusted incidence rates of squamous cell carcinoma and adenocarcinoma of the lung by sex, 1975-1990 (Source: Surveillance, Epidemiology, and End Results (SEER) Program, public use data.)