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How History Informs FDA Tobacco Regulation: Retrospective Application of a Public Health Assessment Framework to "Low Tar" Cigarettes

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

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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.[1] 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.[2] 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.[3] 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.[4] 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.[5] 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."[6]

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:*

1. OFF. OF THE SURGEON GEN., U.S. DEP'T OF HEALTH & HUM. SERVS., THE HEALTH CONSEQUENCES OF SMOKING—50 YEARS OF PROGRESS 679 (2014).

2. Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified in scattered sections of 5 U.S.C.).

3. A.C. Villanti et al., *Food and Drug Administration Regulation of Tobacco: Integrating Science, Law, Policy, and Advocacy*, 101 AM. J. PUB. HEALTH 1160, 1160 (2011).

4. Min-Ae Song et al., *Cigarette Filter Ventilation and its Relationship to Increasing Rates of Lung Adenocarcinoma*, J. NAT'L CANCER INST., Dec. 2017, at 1, 12-13.

5. NAT'L CANCER INST., U.S. DEP'T OF HEALTH & HUM. SERVS., SMOKING AND TOBACCO CONTROL MONOGRAPH NO. 13, RISKS ASSOCIATED WITH SMOKING CIGARETTES WITH LOW MACHINE-MEASURED YIELDS OF TAR AND NICOTINE 10 (2001).

6. ROBERT N. PROCTOR, GOLDEN HOLOCAUST: ORIGINS OF THE CIGARETTE CATASTROPHE AND THE CASE FOR ABOLITION 365 (2012).

1. *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.[7] They marketed these as "light" or "low-tar" cigarettes, implicitly and explicitly claiming that they were less harmful cigarettes.[8] 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.[9] 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.[10] 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").

10. Mitchell Zeller et al., *The Strategic Dialogue on Tobacco Harm Reduction: A Vision and Blueprint for Action in the US*, 18 TOBACCO CONTROL 324, 325 (2009); Amy Fairchild & James Colgrove, *Out of the Ashes: The Life, Death, and Rebirth of the "Safer" Cigarette in the United States*, 94 AM. J. PUB. HEALTH 192, 193–95 (2004); OFF. ON SMOKING AND HEALTH, U.S. DEP'T OF HEALTH AND HUM. SERV'S, THE HEALTH CONSEQUENCES OF SMOKING - THE CHANGING CIGARETTE 5–7 (1981).

purportedly lower-risk products did not decrease disease risk.[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.[12]

B. A Public Health Framework for Tobacco Regulation

Building on earlier work,[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"[14] and "Silver Book"[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

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").

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).

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 RSCH. (Supplement 1), Aug. 2019.

14. COMM. ON THE INSTITUTIONAL MEANS FOR ASSESSMENT OF RISKS TO PUB. HEALTH, NAT'L RSCH. COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS 3 (1983).

15. COMM. ON IMPROVING RISK ANALYSIS APPROACHES USED BY THE U.S. EPA, NAT'L RSCH. COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT 4 (2009).

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,

toxicological, behavioral, or physiologic effects of a tobacco product.[16] 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.[17] These ranged from laboratory studies (e.g., smoke chemistry and toxicology) to epidemiology.[18] 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.[19] In both databases, we combined cigarettes with the following terms: smoking machine, lights, ultralights, tar, filter ventilation, air dilution, Ames, mutagenicity, tumorigenicity, adenocarcinoma, polycyclic aromatic hydrocarbons, nitrosamines, chemical yields, inhalation, puff topography, compensation, and smoking behavior.[20] For this paper, we limited our search to papers published in 1990 or before. We also supplemented our review with studies included in NCI Monograph 13 that were published before or during 1990.[21]

Two independent reviewers conducted the primary data collection. One extracted the data (MA) and another verified the extraction (MB). Data collection included study design, sample size, inclusion criteria, products tested, study

16. Lisa Bero, *Implication of the Tobacco Industry Documents for Public Health and Policy*, 24 ANN. REV. PUBLIC HEALTH 267 (2003); Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified in scattered sections of 5 U.S.C.).

17. Min-Ae Song et al., *supra* note 4.

18. *Id*.

19. *Id*.

20. *Id*.

21. NAT'L CANCER INST., *supra* note 5.

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.

23. 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 ventilation and cigarette combustion from Richard P. Baker to the Group Research and Development Centre, Brit.-Amer. Tobacco Co. 17–22 (1997) (on file with the University of California San Francisco Library); Report on cigarette ventilation from K.D. Kilburn to the Group Research and Development Centre, Brit.-Amer. Tobacco Co. (1978) (on file with the University of California San Francisco Library); Report titled "Heat Treatment of Tobacco" from unknown author to R.J. Reynolds Tobacco Co. 2–3 (1991) (on file with the University of California San Francisco Library); Memorandum on ventilated cigarettes from R.J. Leahy to Hugh Cullman, Philip Morris, Inc. 4–5 (Oct. 25,1955) (on file with the University of California San Francisco Library); Memorandum on ventilation and cigarette burn rates from Lydia J. Holt & Larry W. Renfro, Eastman Chem. Co., to Philip Morris, Inc. (January 1994) (on file with the University of California San Francisco Library); Richard R. Baker, *Mechanisms of Smoke Formation and Delivery*, 6 RECENT ADVANCES IN TOBACCO SCI. 184, 205–07 (1980); Report on tobacco combustion studies by Richard R. Baker 15, 49 (1982) (on file with the University of California San Francisco Library); Memorandum on the effect of ventilation on smoke deliveries from R.P. Ferris to A.L. Heard 1–2 (1982) (on file with the University of California San Francisco Library); *Filter Ventilation Systems*, MALAUCÈNE TECH. BULLETIN 1–2; CIGARETTE SMOKE 119 (1978).

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

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.[25] 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.[26] 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.[27]

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.[28] Fischer et al. reported results as yields per cigarettes, and data were not presented in a way that compared tobacco-blend similar cigarettes.[29] 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),[30] internal industry documents were documenting how and why smoke mutagenicity increased as ventilation levels rose.[31]

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

Library); Memorandum on ventilation and cigarette combustion from Richard P. Baker to the Group Research and Development Centre, Brit.-Amer. Tobacco Co. 17–22 (1997) (on file with the University of California San Francisco Library); S. Fischer, B. Spiegelhadler, R. Preussmann, *Tobacco-specific nitrosamines in mainstream smoke of West Gennan cigarettes-tar alone is not a sufficient index for the carcinogenic potential of cigarette smoke*, CARCINOGENESIS, 169, 169–73 (1989); Memorandum on in vitro biological activity of cigarette smoke condenstates from experimental cigarettes–a summary from T. Yu. To Dr. E. B. Sanders, Philip Morris (Oct. 3, 1984) (on file with the University of California San Francisco Library).

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.

30. Jeffrey E. Harris, *Incomplete Compensation Does Not Imply Reduced Harm: Yields of 40 Smoke Toxicants Per Milligram Nicotine in Regular Filter Versus Low-Tar Cigarettes in the 1999 Massachusetts Benchmark Study*, 6 NICOTINE & TOBACCO RSCH. 797, 802–06 (2004); J. E. Swauger et al., *An Analysis of the Mainstream Smoke Chemistry of Samples of the US Cigarette Market Acquired Between 1995 and 2000*, 35 REGUL. TOXICOLOGY & PHARMACOLOGY 142, 149–52 (2002); Thomas Adam et al., *Influence of Filter Ventilation on the Chemical Composition of Cigarette Mainstream Smoke*, 657 ANALYTICA CHIMICA ACTA 36, 37–40 (2010); J.A. Bodnar et al., *Mainstream Smoke Chemistry Analysis of Samples from the 2009 US Cigarette Market*, 64 REGUL. TOXICOLOGY & PHARMACOLOGY 35, 37–41 (2012).

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 and PAHs 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 brand[36] 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.

33. D. Hoffmann et al., *Dose-Response Study of the Carcinogenicity of Tobacco-Specific N-Nitrosamines in F344 Rats*, 108 J. CANCER RSCH. AND CLINICAL ONCOLOGY 81, 84 (1984).

34. Ruggero Montesano et al., *Brief Communication: Synergistic Effects of Benzo[a]pyrene and Diethylnitrosamine on Respiratory Carcinogenesis in Hamsters*, 53 J. NAT'L CANCER INST. 1395, 1395–97 (1974); R.P. Deutsch-Wenzel et al., *Experimental Studies on the Carcinogenicity of Five Nitrogen Containing Polycyclic Aromatic Compounds Directly Injected Into Rat Lungs*, 20 CANCER LETTERS 97, 99–100 (1983); Curtis C. Harris et al., *Ultrastructural L Effects of N-Methyl-N-Nitrosourea on the Tracheobronchial Epithelium of the Syrian Golden Hamster*, 12 INT'L J. CANCER 259, 263–67 (1973); Umberto Saffiotti et al., *Respiratory Tract Carcinogenesis Induced in Hamsters by Different Dose Levels of Benzo-[a]pyrene and Ferric Oxide*, 49 J. NAT'L CANCER INST. 1199, 1200–03 (1972).

35. Neal L. Benowitz et al., *Influence of Smoking Fewer Cigarettes on Exposure to Tar, Nicotine, and Carbon-Monoxide*, 315 NEW ENG. J. MED. 1310 (1986) [hereinafter, Benowitz et al., *Influence of Smoking Fewer Cigarettes*]; R. B. Bridges et al., *Smoking History, Cigarette Yield and Smoking-Behavior as Determinants of Smoke Exposure*, 146 EUROPEAN J. RESPIRATORY DISEASE 129 (1986); Neal L. Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide Exposure While Smoking Ultralow- but Not Low- Yield Cigarettes*, 256 JAMA 241 (1986) [hereinafter, Benowitz et al., *Reduce Tar, Nicotine, and Carbon Monoxide Exposure*]; J. C. Robinson et al., *A Comparative Study of the Amount of Smoke Absorbed from Low Yield ('Less Hazardous') Cigarettes Part 2: Invasive Measures*, 78 BRIT. J. ADDICTION 79 (1983) [hereinafter, Robinson et al., *Part 2*]; James P. Zacny & Maxine L. Stitzer, *Cigarette Brand-Switching: Effects on Smoke Exposure and Smoking Behavior*, 246 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 619 (1988); J.C. Robinson, et al., *A Comparative-Study of the Amount of Smoke Absorbed from Low Yield (Less Hazardous) Cigarettes. Part 1: Non-Invasive Measures*, 77 BRIT. J. ADDICTION 383 (1982) [hereinafter, Robinson, et al., *Part 1*].

36. Benowitz et al., *Influence of Smoking Fewer Cigarettes*, supra note 35, at 1310; Bridges et al., *supra* note 35, at 129–37.

37. Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide*, *supra* note 35, at 241–246; Robinson et al., *Part 2*, *supra* note 35, at 79–87; James P. Zacny & Maxine L. Stitzer, *supra* note 35, at 619–27; Benowitz et al., *Influence of Smoking Fewer Cigarettes*, *supra* note 35, at 1310–13.

38. James P. Zacny & Maxine L. Stitzer, *supra* note 35, at 620; Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide Exposure*, *supra* note 35, at 241–246.

conducted in residential (in-patient) settings,[39] where smokers can be directly observed. Other studies were conducted in the smokers' natural settings (with follow-up lab visits)[40] 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.[41] When smokers switched from their self-selected brands to higher tar yields, there were no significant changes in biomarkers.[42]

Cross-sectional studies examined the exposure of smoking-related toxicants using plasma cotinine, nicotine, and carboxyhemoglobin (COHb) measurements.[43] 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.[44] If found that despite considerable variation in machine-tested cigarette yields, differences in exposure biomarkers were minimal.[45] Also, other factors, such as

39. Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide Exposure*, *supra* note 35, at 241–246; Robinson et al., *Part 1*, *supra* note 35 at 383–97; Robinson et al., *Part 2*, *supra* note 35 at 79–87; James P. Zacny & Maxine L. Stitzer, *supra* note 35 at 619 – 27; Benowitz et al., *Influence of Smoking Fewer Cigarettes*, *supra* note 35, at 1310–13.

40. Robinson et al., *Part 1*, *supra* note 35, at 383–97; Robinson et al., *Part 2*, *supra* note 35, at 79–87; James. P. Zacny & Maxine L. Stitzer, *supra* note 35, at 619–28; Bridges et al., *supra* note 35 at 129–37.

41. Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide Exposure*, *supra* note 35, at 241–46; Robinson et al., *Part 2*, *supra* note 35, at 79–87.

42. Benowitz et al., *Reduced Tar, Nicotine, and Carbon Monoxide Exposure*, *supra* note 35, at 241–46.

43. Gio B. Gori & Cornelius J. Lynch, *Analytical Cigarette Yields as Predictors of Smoke Bioavailability*, 5 REGUL. TOXICOLOGY & PHARMACOLOGY 314, 314–26 (1985); M.A. Russell et al., *Long-Term Switching to Low-Tar Low-Nicotine Cigarettes*, 77 BRIT. J. ADDICTION 145, 145–58 (1982); M.A. Russell et al., *Relation of Nicotine Yield of Cigarettes to Blood Nicotine Concentrations in Smokers*, 280 BRIT. MED. J. 972, 972–76 (1980) [hereinafter Russell, *Long-Term Switching*]; Raymond B. Bridges et al., *Population Characteristics and Cigarette Yield as Determinants of Smoke Exposure*, 37 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 17, 17–28 (1990); M.A. Russell et al., *Reduction of Tar, Nicotine and Carbon Monoxide Intake in Low Tar Smokers*, 40 J. EPIDEMIOLOGY & CMTY. HEALTH 80, 81, 83 (1986) [hereinafter Russell, *Reduction*]; Richard V. Ebert et al., *Amount of Nicotine and Carbon Monoxide Inhaled by Smokers of Low-Tar, Low-Nicotine Cigarettes*, 250 JAMA 2840, 2842 (1983); W.S. Rickert & J.C. Robinson, *Estimating The Hazards of Less Hazardous Cigarettes*, 7 J. TOXICOLOGY & ENV'NT HEALTH 391, 391-403 (1981).

44. Gori & Lynch, *supra* note 43, at 314–26.

45. *Id*.

mean cigarette consumption, were not affected by differences in cigarette yields. Several smaller studies showed similar findings.[46]

As of 1990, there were eight cohort studies and nineteen case-control studies focused on lung cancer outcomes.[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.[48] While some cohort studies showed significant reductions in lung cancer risk with filter-ventilated cigarettes,[49] other cohort studies showed a non-significant decrease in

46. Russell, *Long-Term Switching supra* note 43, at 145–48; M. A. Russell et al., *Relation of Nicotine Yield of Cigarettes to Blood Nicotine Concentrations in Smokers*, 280 BRIT. MED. J. 972, 972–76 (1980); Bridges et al., *supra* note 43, at 17–28; Russell et al., *Reduction, supra* note 43, at 80–86; Ebert et al., *supra* note 43, at 2840–42; W.S. Rickert & J.C. Robinson, *supra* note 43, at 391-403.

47. E. C. Hammond, *"Tar" and Nicotine Content of Cigarette Smoke in Relation to Death Rates*, 12 ENV'T RSCH. 263, 263–74 (1976); P. A. Buffler et al., *Environmental Associations with Lung Cancer in Texas Coastal Counties*, 27 LUNG CANCER: CURRENT STATUS AND PROSPECTS FOR THE FUTURE, 34 (1986); Diana B. Petitti & Gary D. Friedman, *Cardiovascular and Other Diseases in Smokers of Low Yield Cigarettes*, 38 J. CHRONIC DISEASE 581, 588 (1985); E. Benhamou et al., *Changes in Patterns of Cigarette Smoking and Lung Cancer Risk: Results of a Case-Control Study*, 60 BRIT. J. CANCER 601, 601–04 (1989); Charles R. Gillis et al., *Cigarette Smoking and Male Lung Cancer in an Area of Very High Incidence. I. Report of a Case-Control Study in the West of Scotland*, 42 J. EPIDEMIOLOGY CMTY. HEALTH 38, 40–1 (1988); Annamma Augustine et al., *Compensation as a Risk Factor for Lung Cancer in Smokers who Switch from Nonfilter to Filter Cigarettes*, 79 AM. J. PUB. HEALTH 188, 189–90 (1989); D.R. Pathak et al., *Determinants of Lung Cancer Risk in Cigarette Smokers in New Mexico*, 76 J. NATL CANCER INST. 597, 597-604 (1986); I.D. Bross, *Effect of Filter Cigarettes on Lung Cancer Risk*, HARMFUL CIGAR (1968); G.F. Todd et al., *Four Cardiorespiratory Symptoms as Predictors of Mortality*, J. EPIDEMIOLOGY & CMTY. HEALTH 267, 267-74 (1978); E.L. Wynder & S.D. Stellman, *Impact of Long-term Filter Cigarette Usage on Lung and Larynx Cancer Risk: A case-control study*, J. NATL CANCER INST. 471, 471-77 (1979); S. Benhamou et al., *Lung Cancer and Use of Cigarettes: A french case-control study*, 74 J. NATL CANCER INST. 1169, 1169-75 (1985); E Benhamou et al., *Lung Cancer and Women: Results of a french case-control study*, 55 BRIT. J. CANCER 91, 91-95 (1987); C. Vutuc & M. Kunze, *Lung Cancer Risk in Women in Relation to Tar Yields of Cigarettes*, 11 PREVENTATIVE MED. 713, 713-16 (1982); J. H. Lubin et al., *Modifying Risk of Developing Lung Cancer by Changing Habits of Cigarette Smoking*, 288 BRIT. MED. J. CLINICAL RSCH. ED. 1953, 1953-56 (1984); P.N. Lee & L. Garfinkel, *Mortality and Type of Cigarette Smoked*, 35 J. EPIDEMIOLOGY & CMTY. HEALTH 16, 16-22 (1981); J.H. Lubin et al., *Patterns of Lung Cancer Risk According to Type of Cigarette Smoked*, 35 INT'L J. CANCER 569, 569-75 (1984); I. D. Bross & R. Gibson, *Risks of Lung Cancer in Smokers who Switch to Filter Cigarettes*, 58 AM. J. PUB. HEALTH 1396, 1396-1403 (1968); M.R. Alderson et al., *Risks of Lung Cancer, Chronic Bronchitis, Ischaemic Heart Disease, and Stroke in Relation to Type of Cigarette Smoked*, 39 J. EPIDEMIOLOGY & CMTY. HEALTH 286, 286-93 (1985); V.M. Hawthorne & J.S. Fry, *Smoking and Health: The association between smoking behaviour, total mortality, and cardiorespiratory disease in west central Scotland*, 32 J. EPIDEMIOLOGY & CMTY. HEALTH 260, 260-66 (1978); H.B. Wilcox et al., *Smoking and Lung cancer: Risk as a function of cigarette tar content*, 17 PREVENTATIVE MED. 263, 263-72 (1988); E.C. Hammond et al., *Some Recent Findings Concerning Cigarette Smoking*, 4 COLD SPRING HARBOR CONF. ON CELL PROLIFERATION (1977); D.W. Kaufman et al., *Tar Content of Cigarettes in Relation to Lung Cancer*, 129 AM. J. EPIDEMIOLOGY 703, 703-11 (1989); C. Vutuc & M. Kunze, *Tar Yields of Cigarettes and Male Lung Cancer Risk* 71 J. NATL CANCER INST. 435, 435-37 (1983); J. Rimington, *The Effect of Filters on the Incidence of Lung Cancer in Cigarette Smokers*, 24 ENV'T RSCH. 162, 162-66 (1981); E.L. Wynder & G.C. Kabat, *The Effect of Low-Yield Cigarette Smoking on Lung Cancer Risk*, 62 CANCER 1223, 1223-30 (1988); E.L.Wynder et al., *The Epidemiology of Lung Cancer: Recent trends*, 213 JAMA 2221, 2221-28 (1970).

48. *Id*.

49. 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.[50] 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.[51] The CPS analyses showed significant reductions in lung cancer mortality among low-tar yield cigarette smokers.[52] 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.[53] 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.[54]

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.[55] 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.[56] 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.[57] 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.[58] 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,

20–1 (1981); J. Rimington, *The Effect of Filters on the Incidence of Lung Cancer in Cigarette Smokers*, 24 ENV'T RSCH. 162, 162–166 (1981).

50. Diana Petitti & Gary Friedman, *Cardiovascular and Other Diseases in Smokers of Low Yield Cigarettes*, 38 J. CHRONIC DISEASES 581, 585–87 (2004); Tim Higenbotttam et al., *Cigarettes, Lung Cancer, and Coronary Heart Disease: The Effects of Inhalation and Tar Yield*, 36 J. EPIDEMIOLOGY & CMTY. HEALTH 113, 114–16 (1982); G. Todd et al., *Four Cardiorespiratory Symptoms as Predictors of Mortality*, 32 J. EPIDEMIOLOGY & CMTY. HEALTH 267, 268–271 (1978); V. Hawthorne & J. Fry, *Smoking and Health: The Association Between Smoking Behavior, Total Mortality, and Cardiorespiratory Disease in West Central Scotland*, 32 J. EPIDEMIOLOGY & CMTY. HEALTH 260, 262, 264, 266 (1978).

51. OFF. ON SMOKING & HEALTH, U.S. DEP'T OF HEALTH & HUM. SERVS., *supra* note 12, at 81; E. C. Hammond et al., *supra* note 47, at 263; P. Lee & L. Garfinkel, *supra* note 54, at 16; E.

52. *Id*.

53. NAT'L CANCER INST., *supra* note 5, at 76.

54. *Id*.

55. Some of these studies showed statistically significant reductions, while some showed non-significant reductions.

56. Jay Lubin et al., *supra* note 47, at 1955; William Blot et al., *supra* note 54, at 573.

57. Annamma Augustine et al., *supra* note 47, at 188–89.

58. *Id*.

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).[59] 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.[60] 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.[61] 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).[62] 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.[63] 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.[64]

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).

62. Todd F. Heatherton et al., *The Fagerström Test for Nicotine Dependence: A Revision of the Fagerström Tolerance Questionnaire*, 86 BRITISH J. ADDICTION 1119, 1119–1121 (1991).

63. Neal Benowitz et al., *supra* note 35, at 243; J. C. Robinson et al., *supra* note 35, at 394; J. Zacny & M. Stitzer, *supra* note 35, at 622-26.

64. Gio Gori & Cornelius Lynch, *supra* note 50, at 323; M. A. Russel et al., *supra* note 43, at 148, 150.

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]

65. Memorandum titled "Puffing Behavior on High and Low Delivery Cigarettes" by F. Ryan & B. Hancock to Philip Morris U.S.A. Rsch. Ctr. (Sept. 1973) (on file with the University of California San Francisco Library); Memorandum titled "Technical Report on 'Tar' and Nicotine" (Nov. 25, 1966) (on file with the University of California San Francisco Library); S. Graham et al., *Variations in Amounts of Tobacco Tar Retrieved from Selected Models of Smoking Behavior Simulated by Smoking Machine*, 23 CANCER RSCH. 1025, 1026–30 (1963); Rico Nil et al., *Effects of Different Cigarette Smoke Yields on Puffing and Inhalation: Is the Measurement of Inhalation Volumes Relevant for Smoking Absorption?*, 24 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 587, 593 (1986); G. Woodman et al., *Response and Acclimatisation of Symptomless Workers on Changing to a Low Tar, Low Nicotine Cigarette*, 42 THORAX 336, 339–40 (1987); Memorandum titled "Changes in Smoker Profiles with Changes in Nicotine and Tar Deliveries, Both On and Off Smoking Profile Recorders" by Barbro L. Goodman to Philip Morris U.S.A. Rsch. Ctr. 1 (Mar. 16, 1977) (on file with the University of California San Francisco Library).

66. M. A. Russell et al., *supra* note 50, at 155–57; BARBRO GOODMAN, *supra* note 71, at 7-10; Karl-Olov Fagerström, *Effects of a Nicotine-Enriched Cigarette on Nicotine Titration, Daily Cigarette Consumption, and Levels of Carbon Monoxide, Cotinine, and Nicotine*, 77 PSYCHOPHARMACOLOGY 164, 166–67 (1982).

67. Report titled "The Influence of Dilution on Smoker Parameters" by Barbro Goodman to Philip Morris U.S.A. Rsch. Ctr. (July 22, 1975) (on file with the University of California San Francisco Library); Correspondence titled "Marlboro - Marlboro Lights study Delivery Data" from Barbro Goodman, Philip Morris U.S.A., to Leo F. Meyer, Philip Morris U.S.A. (1975) (on file with the University of California San Francisco Library).

68. Barbro Goodman, *supra* note 67, at 7-8.

69. *Id.*

70. Thomas Lombardo et al., *When Low Tar Cigarettes Yield High Tar: Cigarette Filter Ventilation Hole Blocking and Its Detection*, 8 ADDICTIVE BEHAVS. 67, 67–69 (1983).

71. Lynn T. Kozlowski et al., *Prevalence of the Misuse of Ultra-Low-Tar Cigarettes by Blocking Filter Vents*, 78 AM. J. PUB. HEALTH 694, 694 (1988).

72. *Id.*

73. *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.[74] 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).[75] He found that smokers who switched halfway through the study to lower-tar yield cigarettes were more likely to be former smokers by the last follow-up, compared to middle- to higher-tar yield smokers.[76] However, this association may reflect other characteristics of smokers who switched to lower-tar 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.[77] 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,[78] they perceived lower-tar cigarettes to be less harmful.[79] A large industry survey found that about 17% of

74. E. Cuyler Hammond, *The Long-term Benefits of Reducing Tar and Nicotine in Cigarettes*, 3 BANBURY REPS. 13 (1980).

75. *Id.*

76. *Id.*

77. *See infra* note 85.

78. Sandford R. *Internal memorandum to E.E. Kohnhorst. Research Development and Engineering*. Minnesota Trial Exhibit 13250 1985.; 1985. Accessed December 28, 2020. https://www.industrydocuments.ucsf.edu/docs/#id=pzgd0136.

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/Krall Marketing Resources to Philip Morris, U.S.A. (June 1979) (on file with the University of California San Francisco Library); GOLDSTEIN KRALL MARKETING RESOURCES, PHILIP MORRIS REC.,

participants thought cigarettes with ventilated paper were better for them, compared to only 9% who thought they were worse.[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.[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.

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 (**Figure 2**).[82] For women, who were more likely to have initiated smoking with

SMOKERS' REACTIONS TO AN ULTRA-LIGHT BRAND EXTENSION FOR MARLBORO A QUALITATIVE STUDY (THREE FOCUSED GROUP INTERVIEWS) (1979).

80. ELMO ROPER, *supra* note 79.

81. GOLDSTEIN KRALL MARKETING RESOURCES, supra note 79.

82. *Cancer Stat Facts: Lung and Bronchus Cancer*, NAT'L. CANCER INST., https://seer.cancer.gov/statfacts/html/lungb.html (last visited November 28, 2022).

low-yield cigarettes,[83] 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.[84] 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.[85] 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.[86]

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

83. Carrie Carpenter et al., *Designing Cigarettes for Women: New Findings from the Tobacco Industry Documents*, 100 ADDICTION 837, 839–40, 842 (2005); R. Pollay & T. Dewhirst, *The Dark Side of Marketing Seemingly "Light" Cigarettes: Successful Images and Failed Fact*, 11 TOBACCO CONTROL 18, 18, 20, 28–29 (2002).

84. *See infra* Table 1.

85. L. Kreyberg, *Histological Lung Cancer Types. A Morphological and Biological Correlation*, 157 ACTA PATHOLOGICA MICROBIOLOGICA SCANDINAVICA SUPPL. 1 (1962).

86. Annamma Augustine et al., *supra* note 47, at 190–91 (1989).

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.[87] 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,[88] 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.[89] 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[90] 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.

88. *See Simulation Modeling in Tobacco Regulatory Science: Where are we and Where Should we go Next? Proceedings of the CAsToR 2021 Symposium*, CASTOR (2021) (discussing multiple models to approach tobacco regulation in various settings).

89. Carrie Carpenter et al., *Designing Cigarettes for Women: New Findings from the Tobacco Industry Documents*, 100 ADDICTION 873 (2005); Richard Pollay & T. Dewhirst, *The Dark Side of Marketing Seemingly "Light" Cigarettes: Successful Images and Failed Fact*, 11 TOBACCO CONTROL 18, 25 (Mar. 2002).

90. S. Franceschi & E. Bidoli, *The Epidemiology of Lung Cancer*, 10 ANNALS ONCOLOGY 3, 3 (1999).

low-tar cigarettes was driven by industry promotion and mistaken risk perceptions, which were explicitly and implicitly shaped by industry advertising.[91] 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.[92] 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, but has appropriately found these approaches to be lacking. Recently, for example, the FDA authorized a premarket tobacco application (PMTA) for R.J. Reynolds' VUSE e-cigarette. During the FDA's review, it concluded that "the model inputs do not rely on actual product use from surveys or real-world prevalence data)… 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."[93] Surprisingly, though, FDA then failed to do its own modeling of the potential public health impact of authorizing this product

91. Lynn Kozlowski & R. O'Connor, *Cigarette Filter Ventilation is a Defective Design Because of Misleading Taste, Bigger Puffs, and Blocked Vents*, 11 TOBACCO CONTROL 40, 42 (2002); Rhonda Kropp & Bonnie Halpern-Felsher, *Adolescents' Beliefs About the Risks Involved in Smoking 'Light' Cigarettes*, 114 PEDIATRICS 445, 447 (2004); Michael Cummings et al., *Are Smokers Adequately Informed About the Health Risks of Smoking and Medicinal Nicotine*, 6 NICOTINE & TOBACCO RSCH. 333, 339 (2004); Lynn Kozlowski & Janine Pillitteri, *Beliefs About "Light" and "Ultra Light" Cigarettes and Efforts to Change those Beliefs: An Overview of Early Efforts and Published Research*, 10 TOBACCO CONTROL 12, 12 (2001); Christine Sweeney & Lynn Kozlowski, *Blocking Filter Vents Increases Carbon Monoxide Levels from Ultralight but Not Light Cigarettes*, 59 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 767, 771 (1998); R. O'Connor et al., *Cigarette Characteristic and Emission Variations Across High-, Middle-, and Low-Income Countries*, 124 PUB. HEALTH 667, 668 (2010); Maansi Bansal-Travers et al., *Educating Smokers about Their Cigarettes and Nicotine Medications*, 25 HEALTH EDUC. RSCH. 678, 678–79 (2010); Christine Sweeny et al., *Effect of Filter Vent Blocking on Carbon Monoxide Exposure from Selected Lower Tar Cigarette Brands*, 63 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 167, 172 (1999); Lynn Kozlowski et al., *Filter Ventilation and Nicotine Content of Tobacco in Cigarettes from Canada, the United Kingdom, and the United States*, 7 TOBACCO CONTROL 369, 369 (1998); R. O'Connor et al., *How Do Different Cigarette Design Features Influence the Standard Tar Yields of Popular Cigarette Brands Sold in Different Countries?*, 17 TOBACCO CONTROL Supp. I, i1, i5 (2008); Hua-Hie Yong et al., *Impact of the Removal of Misleading Terms on Cigarette Pack on Smokers' Beliefs about "Light/Mild" Cigarettes: Cross-Country Comparisons*, 106 ADDICTION 2204, 2204 (2011); Lynn Kozlowski et al., *Measuring Smokers' Perceptions of the Health Risks from Smoking Light Cigarettes*, 90 AM. J. PUB. HEALTH 1318, 1318–19 (2000).

92. 21 U.S.C. § 387k (2022) (Section 911 of the Tobacco Control Act).

93. U.S. FOOD & DRUG ADMIN. TECHNICAL PROJECT LEAD (TPL) REVIEW OF PMTAS PM0000SSL, PM0000553, PM0000560, 26 (2021),

before concluding that permitting its sale would be "appropriate for the protection of the public health."[94] 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.[95] 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."[96]

Two final comments underscore the difficultly 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.[97] 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.[98]

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 wer no

94. *Id*.

95. Micah Berman & Allison Glasser, *The Public Health Standard in Action—Analysis of the U.S. Food and Drug Administration's IQOS Review*, 6 JAMA ONCOLOGY 1864 (2020).

96. Eric Lindblom, *FDA's First PMTA Order Allowing the Legal Marketing of an E-cigarette is Seriously Flawed*, O'NEILL INST. (Oct. 13, 2021) https://oneill.law.georgetown.edu/fdas-first-pmta-order-allowing-the-legal-marketing-of-an-e-cigarette-is-seriously-flawed/.

97. Micah Berman et al., *The Faltering Promise of FDA Tobacco Regulation*, 12 ST. LOUIS U. J. HEALTH L. & POL'Y 145, 149–50 (June 10, 2019).

98. Micah Berman et al., *Providing a Science Base for the Evaluation of Tobacco Products*, 1 TOBACCO REGUL. SCI. 76, 87 (2015).

less harmful than "regular" cigarettes until the early 2000s,[99] and only recently have papers suggested that filter ventilated cigarettes *increased* harm.[100] 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.[101] 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 HUMS., INT'L AGENCY FOR RSCH. 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.

101. Benjamin Apelberg et al., *Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States*, 378 NEW ENG. J. MED. 1725, 1725, 1731–32 (2018).

Tables

Table 1. Outcomes Measured in Included Studies*

Risk assessment Component	Topic	Number of studies included	Outcomes
Effects Assessment	Toxicity	*N* = 67	Physical and chemical changes[102] Urine mutagenicity[103] Plasma or urine cotinine or nicotine[104] Exhaled CO or COHb[105] Plasma or saliva thiocyanate[106] Carcinogens[107] Lung cancer risk[108]
	Dependence potential	*N* = 16	Dependence potential[109]

102. *See supra* notes 23-24.
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.

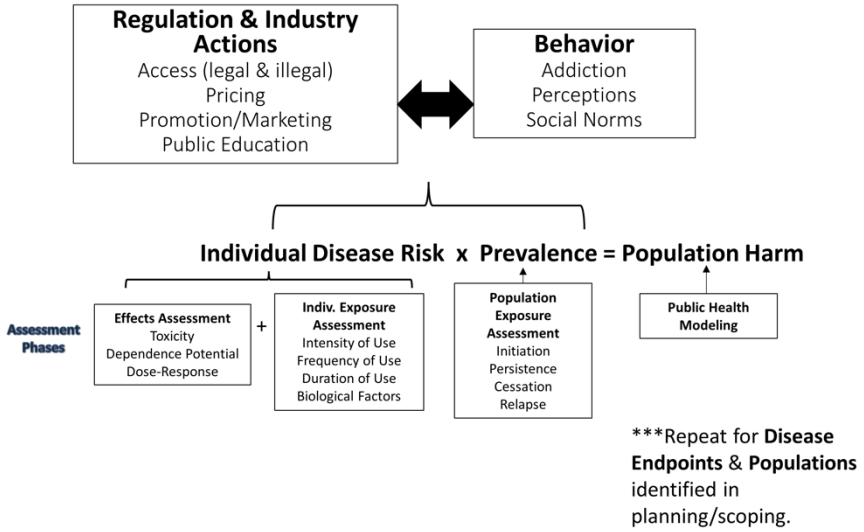
Individual Exposure Assessment	Frequency of Use	*N* = 7	Cigarettes per day[110]
	Intensity of Use (Smoking Topography)	*N* = 14	Number of puffs per cigarette[111] Interpuff interval[112] Puff volume (per puff or total per cigarette)[113] Puff duration[114] Inhalation volume[115] Lung exposure time[116] Hole-blocking[117] Butt-length[118]
Population Exposure Assessment	Cessation	*N=1*	Cessation[119]

110. *See supra* note 35.
111. *See supra* note 35.
112. *Id.*
113. *See supra* note 65.
114. *Id.*
115. *See supra* note 35.
116. *Id.*
117. *Id.*
118. *See supra* note 34.
119. E. C. Hammond et al., *supra* note 74.

Behavior	Consumer Perceptions	*N* = 5	Consumer perceptions[120]
* 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



120. *See supra* note 78.

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.)