SPECIAL REPORT

Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States

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Tobacco is addictive, primarily because of the presence of nicotine.[1] Although nicotine itself is not the direct cause of most smoking-related diseases, addiction to nicotine in tobacco is the proximate cause of these diseases because it sustains smoking behavior.[2,3] Thus, the magnitude of public health harm that is caused by tobacco is inextricably linked to its addictive nature.

There is a continuum of risk for products that deliver nicotine, ranging from the most harmful combusted products (e.g., cigarettes) to medicinal nicotine products. As the most widely used tobacco products, cigarettes are the leading cause of preventable death and disease in the United States.[4] In 2014, the Surgeon General estimated that approximately 480,000 deaths annually are caused by cigarette smoking.[4]

The majority of cigarette smokers in the United States began smoking during their youth,[4-6] which is a cause for concern. The age at which people begin smoking can greatly influence how much they smoke per day and how long they smoke, which ultimately influences their risks of tobacco-related disease and death.[7-9] Addiction to nicotine in tobacco is critical in the transition of smokers from experimentation to sustained smoking and in the continuation of smoking for those who want to quit.[4,10]

In July 2017, in an acknowledgment of the link between smoking-related harms and the addictive qualities of nicotine, as well as the disproportionate effect of nicotine addiction on children and teenagers, the Food and Drug Administration (FDA) announced a regulatory plan to explore lowering the nicotine level in cigarettes.[11,12] To enact a regulation lowering the nicotine level in cigarettes, the FDA must consider scientific evidence regarding "the risks and benefits to the population as a whole, including users and nonusers of tobacco products," along with "the increased or decreased likelihood that existing users of tobacco products will stop using such products" and "the increased or decreased likelihood that those who do not use tobacco products will start using such products."[13]

Simulation models can be used to project the potential population-level effects of regulatory actions.[14] The purpose of this analysis is to quantify the potential public health effects of enacting a regulation in the United States that makes cigarettes minimally addictive by setting a maximum level of nicotine in cigarettes. Using a simulation model with inputs derived from empirical evidence and expert opinion, we estimated the effect of such a policy on the prevalence of tobacco use, tobacco-related mortality, and life-years gained.

DESCRIPTION OF THE SIMULATION MODEL

MODEL FRAMEWORK

We used a discrete dynamical systems population model, as described by Vugrin et al.[15] The model is initiated with a starting population, which is divided into subgroups that are defined according to age, sex, and tobacco-use status. The analysis projects population changes in 1-year increments while accounting for births, net migration (including both immigration and emigration), and deaths (a function of age, sex, and tobacco-use status). Members of each subpopulation have a specified probability of dying and of transitioning from one tobacco-use status to another.

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Using baseline inputs from the year 2000, we have found that projections of smoking prevalence based on a previous version of our model were aligned closely with National Health Interview Survey (NHIS) estimates through 2012 and that projections of the total U.S. population and annual mortality were similar to those of the Census Bureau.[15] In this analysis, we updated the baseline to 2015 to account for recent changes in smoking initiation and cessation.

Using a projection period from 2016 through 2100, we simulated a baseline scenario that predicted the future use of cigarettes and noncombusted tobacco products (including smokeless tobacco and e-cigarettes) and then compared the baseline scenario with the policy scenario described below. Although longer-term projections are subject to increased uncertainty, this time period was chosen to account for the potential effects of reduced initiation of smoking on tobacco-related mortality, since such effects would not be observed until many decades into the future. The model, which was implemented with the use of MATLAB software, version R2017a (MathWorks), projects the effect of the policy on the prevalence of the use of cigarettes and noncombusted tobacco products and the effect on tobacco-related mortality and life-years gained.

MODEL INPUTS

The model accounts for initiation, cessation, and dual use of tobacco products, along with switching between two products: cigarettes (including the very-low-nicotine cigarettes introduced in the policy scenario) and noncombusted tobacco products. Inputs are summarized below and described in detail in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Initial Population, Births, and Migration Inputs

We used 2015 Census estimates to determine the population distribution according to age and sex[16] and age distribution among immigrants.[17] We used the 2015 NHIS to determine the prevalence of tobacco use among adults (accounting for all combinations of current, former, and never use for cigarettes and noncombusted tobacco products) according to age, sex, and time since cessation, with the last variable evaluated for cigarettes only.[18] We used the 2015 National Youth Tobacco Survey to determine the prevalence of current use and nonuse of cigarettes and noncombusted tobacco products among children and teenagers under the age of 18 years, according to age and sex[19] (see the Supplementary Appendix). We derived inputs for annual births and net migration[20] according to sex from Census projections for 2015 through 2060; we projected inputs for births and migration for the period from 2061 through 2100 using a state space model for exponential smoothing.[21,22] We used NHIS data from 2011 through 2015 to estimate the prevalence of smoking among immigrants according to sex.[18] In these analyses, we assumed no consumption of noncombusted tobacco products by immigrants.

Mortality Inputs

We applied the rates of death among persons who had never smoked that were derived from the NHIS Linked Mortality Files[15] to persons who had never used tobacco in the model. We adjusted the rates for low mortality in the civilian noninstitutionalized population in the NHIS, which were projected to account for expected improvements in life expectancy with the use of the Lee–Carter mortality forecasting method (see the Supplementary Appendix) and were converted into probabilities of death with the use of standard demographic methods.[23,24]

We used the NHIS Linked Mortality Files to estimate hazard ratios for death among cigarette smokers, as compared with persons who had never smoked, according to age and sex, using age as the time scale and adjusting for race or ethnic group, education, alcohol consumption, and body-mass index.[15] We also estimated hazard ratios among former smokers according to age at cessation. For some age groups, hazard ratios among persons who had recently quit smoking were greater than among current smokers, as has been observed previously,[25,26] since some persons quit smoking because of smoking-related illnesses. We used the observed hazard ratios in the baseline scenario, given that the increased risks among persons who had recently quit smoking were attributable to smoking. In the policy scenario, we capped hazard ratios for former smokers at the levels for current smokers of the same age group and sex, since an increased rate of smoking cessation in

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this scenario would be due to the policy rather than the cessation of smoking because of illness. To be conservative, we excluded the first 3 years after the implementation of the policy from our cumulative estimates of tobacco-related deaths averted and life-years gained.

We applied estimates of the risk of death for smokeless tobacco use from the Cancer Prevention Study II (CPS-II) to estimate mortality in our model among users of noncombusted tobacco products. In the CPS-II, current users of chewing tobacco or snuff at baseline had a higher risk of death than did persons who had never used such tobacco products (hazard ratio, 1.18), whereas no increased risk was observed among former tobacco users.[27] In an analysis involving persons who had switched from cigarette smoking to the use of smokeless tobacco, the risk of death was significantly higher than that among those who had quit smoking entirely (hazard ratio, 1.08).[28]

Given the limited data on long-term health risks of e-cigarettes, the model applies the risks of using traditional smokeless tobacco to e-cigarette users. Although we recognize that e-cigarettes may vary widely in their attributes and the potential to expose users to harmful and potentially harmful constituents, implicit in our assumption about risk is the fact that since the FDA is responsible for premarket approval of new tobacco products, including e-cigarettes, over time the market would come to be dominated by the least harmful of these products.

Among adults who are 35 years of age or older, the model applies a relative risk of 1.18 for current users of noncombusted tobacco products, as compared with those who had never used tobacco products, and a relative risk of 1.08 for former cigarette smokers who subsequently use noncombusted tobacco, as compared with former smokers who did not use such tobacco products. In sensitivity analyses, we applied relative risks up to 1.50 for current users of noncombusted tobacco products, as compared with persons who had never used tobacco products, and relative risks up to 1.30 for former cigarette smokers who currently used noncombusted tobacco products, as compared with former smokers who did not use such products. We assumed that dual users of cigarettes and noncombusted tobacco maintained the same risk as cigarette smokers who did not use noncombusted tobacco products.

Inputs Regarding Tobacco-Use Behavior

Annual rates of smoking initiation and cessation were derived by Cancer Intervention and Surveillance Modeling Network (CISNET) researchers on the basis of analyses of NHIS data from 1965 through 2015.[29] We generated sex- and age-specific initiation rates for exclusive cigarette use, exclusive use of noncombusted tobacco products, and dual use by scaling the 2015 rates according to the prevalence estimates for current use of cigarettes, smokeless tobacco, and e-cigarettes from the 2015 National Youth Tobacco Survey[19] (see the Supplementary Appendix). We used smoking-cessation rates from 2015 for cessation of both cigarettes and noncombusted tobacco products. In the baseline scenario, age-specific initiation and cessation rates were assumed to remain constant in all years, with no new product initiation (and therefore no new switching between products or new dual use) after the age of 30 years. This assumption was relaxed in the policy scenario, which allowed for uptake of noncombusted tobacco among smokers at any age, either as dual users or product switchers. During model development, we conducted sensitivity analyses that allowed product switching in the baseline scenario, a variable that did not materially affect the results. We also conducted sensitivity analyses in which we assumed that baseline rates of smoking initiation in the future would be 20% higher and 20% lower than those estimated for 2015.

Policy Scenario Inputs

We obtained data inputs for the policy scenario from a formal expert elicitation, which is a systematic process of formalizing and quantifying judgments about uncertain quantities. This process is typically conducted with subject-matter experts who provide subjective probability distributions for questions of interest. A contractor selected experts on the basis of mutually agreed upon, prespecified criteria that identified authors with extensive publication records on relevant topics. Candidates were required to certify that they had no actual, apparent, or potential conflict of interest in any tobacco-related business or any nicotine- or tobacco-related pharmaceutical products.

Eight experts were asked to provide estimates of the anticipated effects of a hypothetical policy that would require the reduction of nicotine in

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cigarettes to minimally addictive levels. This reduction would be achieved through setting a maximum limit on the amount of nicotine in cigarette tobacco filler and, therefore, the amount that could be extracted by the user. Experts were asked to assume that combusted tobacco products that are highly likely to serve as substitutes for traditional cigarettes (e.g., roll-your-own tobacco, pipe tobacco, and nonpremium cigars) would be included in the policy, whereas other tobacco products (e.g., premium cigars, water pipe or hookah, e-cigarettes, and smokeless tobacco) would be excluded. Experts estimated the effect of the policy on rates of cigarette-smoking cessation, switching from cigarette smoking to products excluded from the policy, dual use, cigarette-smoking initiation, and initiation of products excluded from the policy. For this model, we made the simplifying assumption that switching to and initiation of tobacco products that were excluded from the policy would be restricted to noncombusted tobacco products. This assumption was largely consistent with the views of the experts.

Experts were asked to provide their best estimate of the true value of each variable, minimum and maximum plausible values, and the 5th, 25th, 75th, and 95th percentile values. They were also asked to estimate the effects of the policy for the year immediately after implementation and in subsequent years. Experts could provide separate estimates for men and women. To account for uncertainty in responses to the policy, we used the distributions of the experts' estimates in a Monte Carlo simulation. There were 20 distribution responses associated with each expert; these captured each expert's response for each of the five questions (related to cessation, product switching, dual use, cigarette initiation, and initiation of other products), including differences according to sex and year (first year after implementation vs. subsequent years).

The distributions of the responses from the eight experts varied widely (Table 1). For example, the experts' median estimate of the percentage of smokers who would quit smoking in the first year after the introduction of the policy ranged from 4.5 to 55.0%, and estimates for subsequent years ranged from 4.5 to 80.0% (Tables F4 and F5 in the Supplementary Appendix). Estimates of the percent change in annual rates of cigarette-smoking initiation that resulted from the policy in its first year were similarly variable, ranging from –21 to –70% for the median estimate; for subsequent years, median estimates ranged from –21 to –75% (Tables F14 and F15 in the Supplementary Appendix). For each expert's distributions, a Latin Hypercube sampling with 1000 sample values was performed, resulting in a total of 8000 simulations. In the simulation, the policy scenario is introduced in 2020. We ran the model using each of the 8000 sample parameters, and results were aggregated into one set of output distributions. We report median estimates from the output distributions, with ranges that represent 5th and 95th percentile estimates. (Additional details regarding the expert elicitation and statistical methods are provided in the Supplementary Appendix.)

COMPARISON OF BASELINE AND POLICY SCENARIOS

Figure 1 shows the projected prevalence of tobacco use among adults in the United States under the baseline and policy scenarios. According to the models, smoking prevalence declines from a median of 12.8% in the baseline scenario to a median of 10.8% (5th to 95th percentile range, 5.4 to 12.7) in the policy scenario within a year after the implementation of the policy, owing to large estimated increases in smoking cessation. We estimate that approximately 5.0 million additional smokers (5th to 95th percentile range, 110,000 to 19.7 million) would quit smoking within a year after implementation of the hypothetical policy, a number that would increase to a total of 13.0 million additional former smokers (5th to 95th percentile range, 430,000 to 30.5 million) within 5 years. In subsequent years, the difference in smoking prevalence continues to grow because of sustained increases in cessation and decreases in initiation in the policy scenario. By 2060, smoking prevalence drops from 7.9% in the baseline scenario to 1.4% (5th to 95th percentile range, 0.2 to 5.9) in the policy scenario, which is similar to the prevalence in 2100. Although the prevalence of dual-product use is projected to be greater in the policy scenario (3.8%; 5th to 95th percentile range, 2.2 to 6.2) than in the baseline scenario (2.3%) within the initial year after the implementation of the poli-

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Table 1. Effects of a Nicotine-Reduction Policy on Tobacco-Related Behavior, According to Projections Provided by Eight Experts.*

Behavioral Projection and Timing after Implementation	Minimum	Percentile					Maximum
		5th	25th	50th	75th	95th	
				percentage of persons			
Current smokers who quit smoking as a result of the policy							
Women and girls							
Yr 1	4.0	7.5	11.0	19.0	30.0	40.0	50.0
≥Yr 2	3.9	5.5	8.4	13.5	23.8	37.5	45.0
Men and boys							
Yr 1	4.0	7.5	12.0	21.0	30.0	40.0	50.0
≥Yr 2	3.9	5.5	9.4	15.0	26.3	37.5	45.0
Current smokers who quit and switch to noncombusted tobacco products							
Women and girls							
Yr 1	15.0	20.0	25.0	35.0	52.5	72.5	80.0
≥Yr 2	15.0	20.0	27.5	37.5	52.5	72.5	80.0
Men and boys							
Yr 1 and yr 2	15.0	20.0	30.0	40.0	55.0	72.5	80.0
Continuing smokers among both sexes who become dual-product users							
Yr 1	20.0	30.0	42.5	60.0	75.0	82.5	92.5
≥Yr 2	8.8	12.5	20.0	30.0	57.5	70.0	75.0
Reduction in annual rate of smoking initiation among both sexes							
Yr 1	10.0	15.0	25.0	50.0	65.0	80.0	90.0
≥Yr 2	10.0	15.0	25.0	50.0	70.0	80.0	90.0
Would-be smokers among both sexes who instead initiate use of noncombusted tobacco products							
Yr 1 and yr 2	10.0	15.0	22.5	37.5	62.5	77.5	85.0

* In each category, the values indicate the median of eight responses. Experts were able to make separate estimates of the effects of the policy on men and women. If the values are the same for men and women or for the two time periods, the values have been merged into combined categories. For comparison purposes, the population-weighted average annual rate of smoking cessation was 3.7% among women and 3.3% among men in the baseline scenario (all years). At the beginning of the policy scenario (year 2020), the prevalence of dual use of cigarettes and noncombusted tobacco products was 2.3% among both men and women. At baseline, the initiation rates for cigarette smoking varied according to age, peaking at the age of 16 years among girls (at 2.5% per year) and at the age of 17 years among boys (at 3.4% per year). The initiation rates for noncombusted tobacco products also varied according to age, peaking at the age of 16 years among girls (at 1.8% per year) and at the age of 17 years among boys (at 5.5% per year).

cy, by 2029 the pattern reverses. Within a year after the implementation of the policy, the use of any tobacco product is 15.6% (5th to 95th percentile range, 11.8 to 16.8) in the policy scenario, as compared with 16.7% in the baseline scenario. The prevalence of any tobacco use is projected to be slightly lower (11.6%; 5th to 95th percentile range, 9.7 to 14.3) in 2060 under the policy scenario than under the baseline scenario (14.0%) and remains constant beyond this time frame.

Table 2 shows the projected number of persons who would not become established smokers over time because of the policy. Since a

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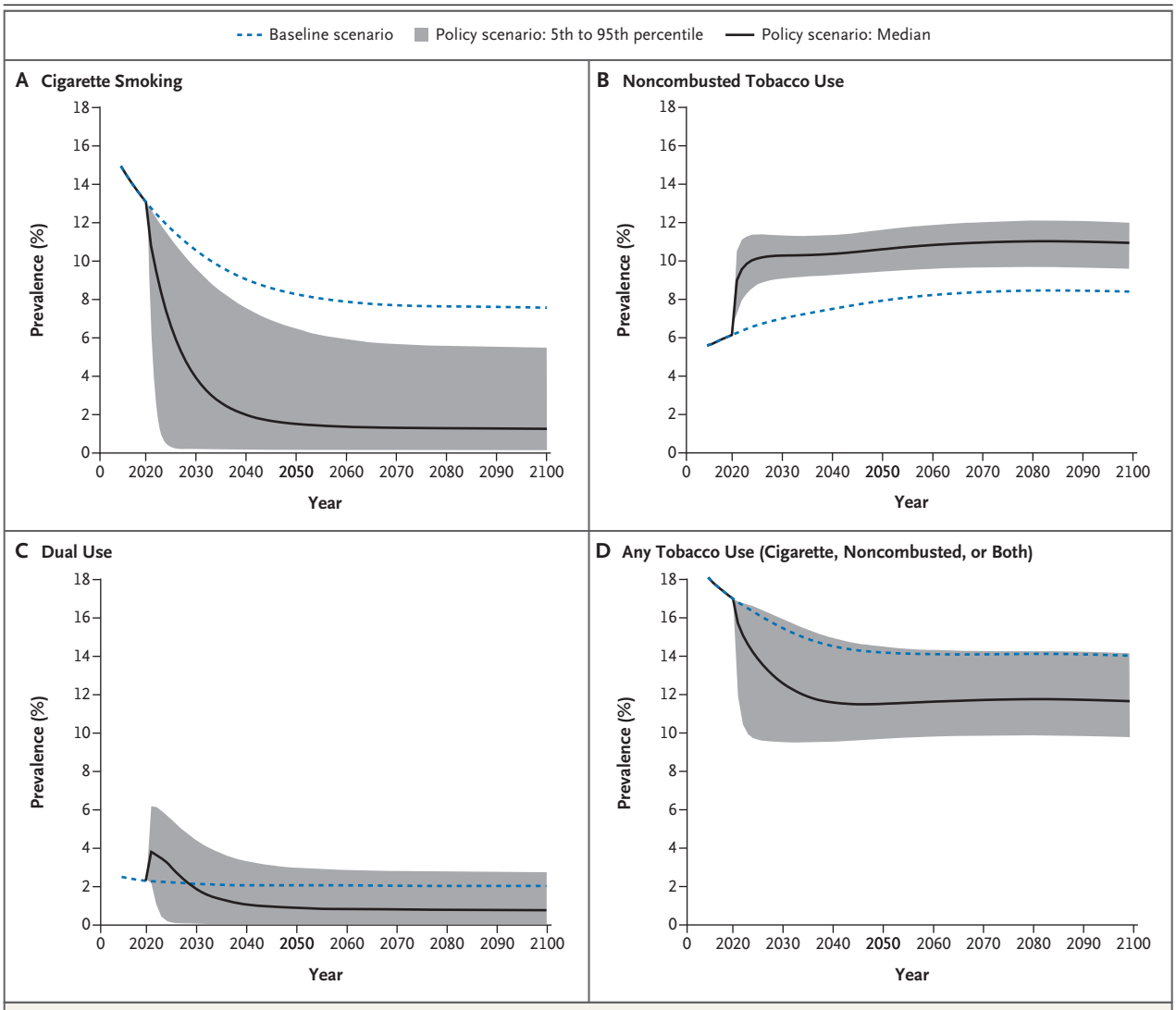

Figure 1. Projected Prevalence of Use of Tobacco Products among Adults under Baseline and Policy Scenarios.

Shown is a comparison between the projected prevalence of the use of tobacco products under the baseline scenario (dashed line) and the median projected prevalence after the implementation of a reduced-nicotine policy (solid line) from 2020 through 2100. Tobacco use is divided into cigarette smoking (Panel A), use of noncombusted tobacco (including smokeless tobacco and e-cigarettes) (Panel B), dual use of cigarettes and noncombusted tobacco (Panel C), and use of any tobacco product (Panel D). Shaded areas indicate the range of the projected prevalence from the 5th percentile to the 95th percentile for the policy scenario.

sustained decrease in rates of smoking initiation is expected, the cumulative number of persons who are dissuaded from starting to smoke continues to increase over time. We estimate that by 2060 16.0 million persons (5th to 95th percentile range, 3.9 to 31.0) who would have otherwise initiated smoking will not start because of the policy. This number increases to 33.1 million (5th to 95th percentile range, 8.0 to 64.1) by 2100.

Table 3 presents the estimated cumulative number of tobacco-related deaths avoided and life-years gained because of the policy. By 2060, we estimated the prevention of 2.8 million tobacco-related deaths (5th to 95th percentile range, 0.7 to 4.3), a number that would rise to 8.5 million by 2100 (5th to 95th percentile range, 2.2 to 11.2) as the effect of reductions in smoking initiation would be realized. The reduction in premature deaths would result in 33.1 million

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life-years (5th to 95th percentile range, 7.8 to 53.9) gained by 2060 and 134.4 million life-years (5th to 95th percentile range, 31.6 to 183.0) gained by 2100.

Sensitivity analyses revealed that variations in relative risk with respect to the use of noncombusted tobacco products did not have a substantial effect on the long-term model outcomes. When we assumed that there would be higher rates of smoking initiation in the future under the baseline scenario, the benefit of the policy increased because there were more smokers that the policy could affect, whereas lower rates of smoking initiation in the future were associated with a slightly lower effect (data not shown).

Table 2. Projected Cumulative Number of Smokers in the Baseline Scenario Who Would Not Initiate Smoking in the Policy Scenario.*

Year	Cumulative Reduction in Number of New Smokers		
	5th Percentile	Median	95th Percentile
	millions of persons		
2025	0.6	2.4	4.5
2030	1.1	4.3	8.2
2040	2.0	8.1	15.6
2050	2.9	12.0	23.2
2060	3.9	16.0	31.0
2070	4.9	20.2	39.0
2080	5.9	24.4	47.2
2090	7.0	28.7	55.6
2100	8.0	33.1	64.1

* The projected outcomes are based on the implementation of a nicotine-reduction policy in 2020. Estimates have been rounded to the nearest 100,000.

CONCLUSIONS

Our model indicates that enacting a regulation to lower the nicotine content of cigarettes to minimally addictive levels in the United States would lead to a substantial reduction in tobacco-related mortality, despite uncertainty about the precise magnitude of the effects on smoking behaviors. Since such a policy has never been enacted, reactions to the policy are difficult to predict. We used a formal expert-elicitation process to obtain informed estimates of likely behavioral responses. Although we followed a rigorous protocol designed to minimize bias in selecting the experts and eliciting their opinions, expert judgments are ultimately subjective. Despite wide variation in the magnitude of the estimated effects of the policy on smoking cessation and initiation and switching to noncombusted products, the direction of the experts' estimates was consistent, which was reflected in the positive public health outcomes projected across the range of simulations.

These results are generally consistent with findings suggesting that the use of cigarettes with very low nicotine levels could result in increased rates of smoking cessation, attempts

Table 3. Projected Cumulative Number of Tobacco-Related Deaths Averted and Life-Years Gained after the Implementation of a Nicotine-Reduction Policy in 2020.*

Year	Tobacco-Related Deaths Averted			Life-Years Gained		
	5th Percentile	Median	95th Percentile	5th Percentile	Median	95th Percentile
	millions					
2025	0	0.1	0.1	0.2	0.4	0.7
2030	0.1	0.3	0.5	0.8	1.6	2.7
2040	0.3	0.9	1.4	2.5	6.8	11.5
2050	0.5	1.7	2.8	4.8	17.0	28.9
2060	0.7	2.8	4.3	7.8	33.1	53.9
2070	0.9	4.2	6.2	11.6	54.4	84.7
2080	1.3	5.6	7.9	16.5	79.6	118.0
2090	1.7	7.1	9.6	23.3	106.7	150.8
2100	2.2	8.5	11.2	31.6	134.4	183.0

* Estimates have been rounded to the nearest 100,000.

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to quit, and intentions to quit (as shown in empirical studies[30-36]) and in decreases in the number of cigarettes smoked per day, puff volume, and biomarkers of exposure (as shown in several studies[31,33,37-41]). The real-world effects of a reduced-nicotine policy would probably be greater than the effects that have been reported in empirical studies, because these studies have been conducted in a context in which cigarettes with higher nicotine levels have been readily available to the participants.

Countervailing effects could diminish the projected benefits of a reduced-nicotine policy. For example, current smokers could use other combusted tobacco products to maintain their nicotine dependence. For this reason, our analysis assumed that the nicotine policy would include combusted tobacco products that are reasonably substitutable for cigarettes (e.g., roll-your-own tobacco, pipe tobacco, and nonpremium cigars). In the model, we also assumed that switching to and initiation of the use of tobacco products excluded from the policy would be restricted to noncombusted tobacco products. Although this assumption was largely consistent with expert judgments, some experts estimated that certain nonusers might initiate the use of water pipes instead of cigarettes because of the policy. In addition, current smokers could theoretically compensate for lower nicotine levels in cigarettes by increasing cigarette consumption.[42] A central assumption of this model, however, is that the policy would mandate an absolute reduction in nicotine to levels so low that there would not be enough nicotine available in cigarette tobacco for smokers to sustain addiction. This assumption is supported by the findings of long-term follow-up studies, which have shown that compensatory smoking is generally not observed among persons who smoke cigarettes with very low levels of nicotine.[31,38-40,43-45] Since smokers find it difficult to achieve desired nicotine levels from very-low-nicotine cigarettes, they may seek to replace cigarettes with other products delivering nicotine. Finally, current cigarette smokers could maintain their nicotine dependence by obtaining illicit cigarettes with current nicotine levels. The National Research Council and the Institute of Medicine report that although a strong conclusion cannot be drawn, limited evidence suggests that regulations modifying cigarettes are unlikely to produce substantial demand for illicit unmodified products.[46] A previous simulation model that projected the effects of a reduced-nicotine policy and accounted for compensatory smoking and the illicit market showed that the policy would probably produce a considerable public health benefit, results that are consistent with our findings.[47]

Despite inherent uncertainty, the data from our model contribute to a growing base of evidence about the role of nicotine reduction that can inform the development of policy with respect to tobacco products,[48] including an assessment of the risks and benefits to the population as a whole. Our findings show that reducing the nicotine level in cigarettes has the potential to substantially reduce the enormous burden of smoking-related death and disease. We estimate that a nicotine product standard for cigarettes in the United States could save millions of lives and tens of millions of life-years over the next several decades.

The views expressed in this article are those of the authors and do not represent the position or policy of the Food and Drug Administration (FDA), the Department of Energy, or the United States government.

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