SIMULATION MODELING AND HOW IT INFORMS THE WORK OF FDA'S CENTER FOR TOBACCO PRODUCTS

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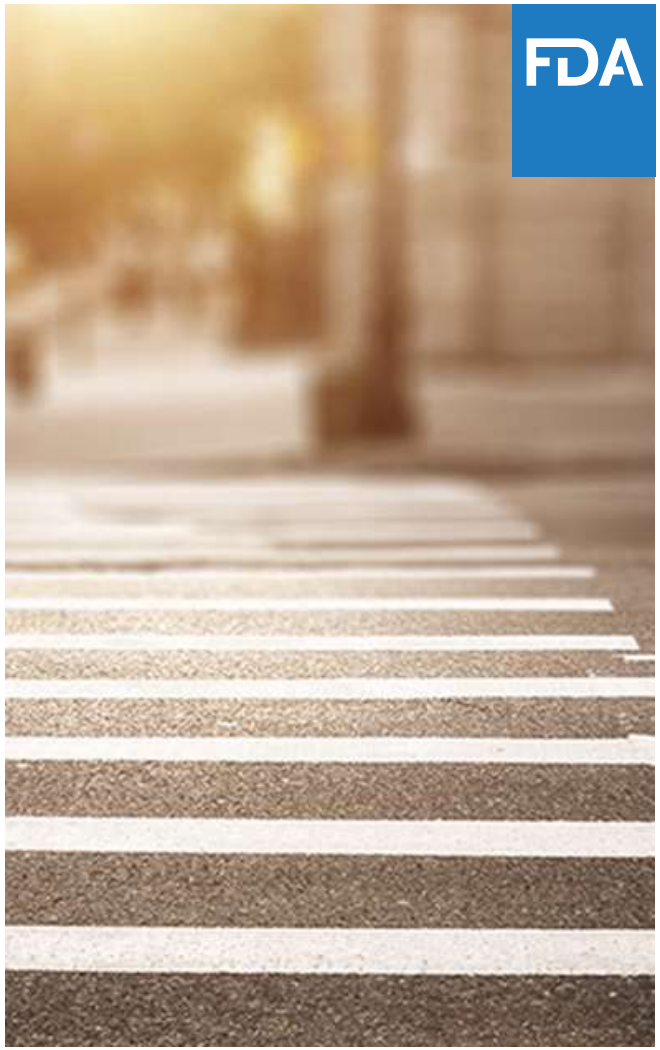
CENTER FOR TOBACCO PRODUCTS

AGENDA

- Background and Regulatory Authorities
- Modeling in Policy Decision Making
- Examples of FDA Using Modeling to Inform Decisions
- Advantages and Limitations
- Questions



BACKGROUND AND FDA'S TOBACCO AUTHORITIES

THE TOBACCO CONTROL ACT BECAME LAW ON JUNE 22, 2009

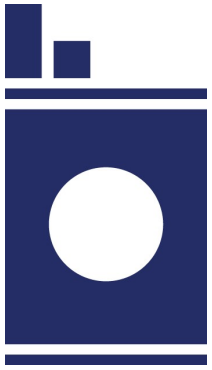
- To protect the public and create a healthier future for all Americans – particularly youth – Congress passed the Tobacco Control Act

- FDA's goal is to reduce the harm from all regulated tobacco products across the entire U.S. population:
  - Reducing the number of people who start using tobacco products
  - Encouraging more people to stop using these products
  - Reducing the adverse health impact for those who continue to use these products

THE TOBACCO CONTROL ACT BECAME LAW ON JUNE 22, 2009

When FDA began regulating all tobacco products intended for human consumption in an effort to protect the public health in 2009, the agency was granted the authority to:

- Regulate the manufacturing, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own, and smokeless
- "Deem" products meeting the statutory definition of tobacco product by issuing a regulation



FINAL DEEMING REGULATION

- On August 8, 2016, a final rule went into effect that "deems" all products meeting the statutory definition of tobacco product, including components or parts (but excluding accessories), to be subject to FDA's tobacco product authorities, including:
  - ✓ ENDS (e-cigarettes, e-cigars, vape pens, etc)
  - ✓ All cigars
  - ✓ Pipe tobacco
  - ✓ Nicotine gels
  - ✓ Waterpipe (hookah)
  - ✓ Dissolvables not already under the FDA's authority
  - ✓ Future tobacco products

EMPLOYING A PUBLIC HEALTH STANDARD

- Pursue a “public health” standard as tobacco cannot be regulated using FDA’s traditional “safe and effective” standard
- Take into account the effects on both users and non-users of tobacco products
- Assess the “net” population-level health impacts of tobacco products

THE TOBACCO CONTROL ACT'S AUTHORITIES

The Tobacco Control Act amended the Food, Drug, and Cosmetic Act to provide FDA authority for:

- Premarket review of new and modified risk tobacco products
- Post-market surveillance
- Product standards
- Testing and reporting of ingredients
- Reporting of harmful and potentially harmful constituents
- Adverse event reporting
- New warning labels
- Advertising and promotion restrictions
- User fees – entirely funded through industry-paid user fees based on market share (not applications)

HOW FDA IS USING ITS REGULATORY AUTHORITY

- Understand the regulated products
- Restrict product changes to protect public health
- Prohibit modified risk claims that state/imply reduced exposure or risk without an order
- Restrict marketing and distribution to protect public health
- Decrease the harms of tobacco products

HOW FDA IS USING ITS REGULATORY AUTHORITY

- Ensure industry compliance with FDA regulation through education, inspections, and enforcement
- Educate the public about FDA's regulatory actions
- Prevent youth initiation and encourage cessation via public education campaigns designed to create behavior change
- Expand the science base for regulatory action and evaluation
- Use authority to now regulate e-cigarettes, cigars, hookah, and other tobacco products, in addition to cigarettes and smokeless products

HOW FDA ISSUES TOBACCO REGULATIONS

Rule/Regulation Proposed	Public Comments Considered	Final Rule Issued
We publish a Notice of Proposed Rulemaking (NPRM) in the *Federal Register* that explains the rule, relies on scientific research, and may ask specific questions An Advance Notice of Proposed Rulemaking (ANPRM) may be issued prior to a NPRM	Researchers and the public submit comments to the proposals within a 60–90-day review period FDA is required to solicit, review, and respond to all public comments before a proposed regulation becomes final	After considering all comments, we may issue a final rule Final rule is published with agency's conclusions on comments and thorough explanation of reasons for decisions

CTP AND POPULATION HEALTH

- The FD&C Act requires FDA to apply a population health standard when making certain regulatory decisions, including determinations regarding:
  - Premarket Tobacco Product Application (PMTA) Review
  - Modified Risk Tobacco Product (MRTP) Review
  - Tobacco Product Standards

PREMARKET TOBACCO PRODUCT APPLICATIONS

Appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account…

1. the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

2. the increased or decreased likelihood that those who do not use tobacco products will start using such products

Source: Section 910(c)(4) of the FD&C Act

MODIFIED RISK TOBACCO PRODUCT APPLICATIONS

The FD&C Act requires FDA to determine if a proposed modified risk tobacco product (MRTP), as it is actually used by consumers, will:

(1) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and

(2) benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products

TOBACCO PRODUCT STANDARDS

FDA can issue product standards for tobacco products if they're appropriate. To do so, we must consider scientific evidence concerning…

1. the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard;
2. the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
3. the increased or decreased likelihood that those who do not use tobacco products will start using such products

Source: Sections 907(a)(3)(A) and 907(a)(3)(B) of the FD&C Act

COMPUTATIONAL MODELING AND POPULATION HEALTH

- Decisions about tobacco product regulation often include the integration of multiple lines of evidence, such as product appeal, addictiveness, toxicity, and their impacts on tobacco product use behavior and disease risk.

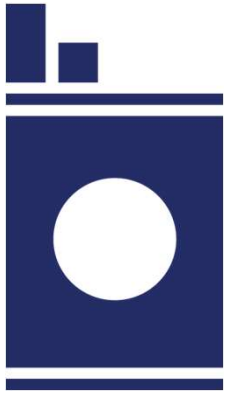
- Computational modeling can be a useful tool to integrate such evidence to assess the potential impacts of new or modified risk tobacco products or new regulatory actions on short and long-term measures of tobacco product use, morbidity, and mortality.

COMPUTATIONAL MODELING TO INFORM POTENTIAL PRODUCT STANDARDS

ANPRM – TOBACCO PRODUCT STANDARD

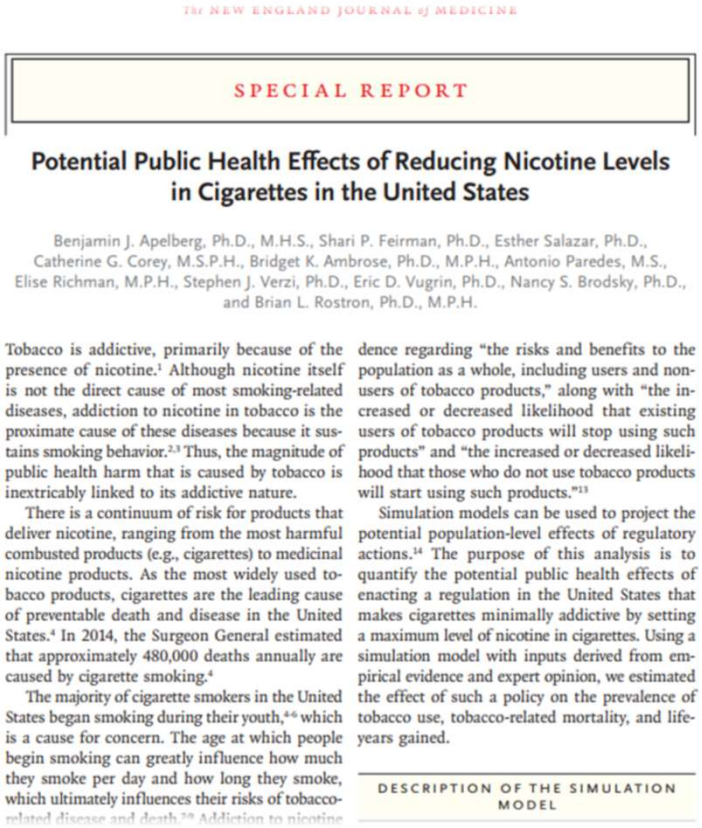
- In March 2018, FDA issued an advance notice of proposed rulemaking, *Tobacco Product Standard for Nicotine Level of Combusted Cigarettes*

- Sought public comment for consideration in developing a product standard to lower nicotine to a minimally addictive or non-addictive level in cigarettes



POTENTIAL IMPACT OF A REDUCED NICOTINE POLICY

An FDA-funded study published in the March 2018 issue of the *New England Journal of Medicine* that quantified a range of potential impacts of reducing nicotine levels in cigarettes.



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

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

Benjamin J. Apelberg, Ph.D., M.H.S., Shari P. Feirman, Ph.D., Esther Salazar, Ph.D., Catherine G. Corey, M.S.P.H., Bridget K. Ambrose, Ph.D., M.P.H., Antonio Paredes, M.S., Elise Richman, M.P.H., Stephen J. Verzi, Ph.D., Eric D. Vugrin, Ph.D., Nancy S. Brodsky, Ph.D., and Brian L. Rostron, Ph.D., M.P.H.

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]

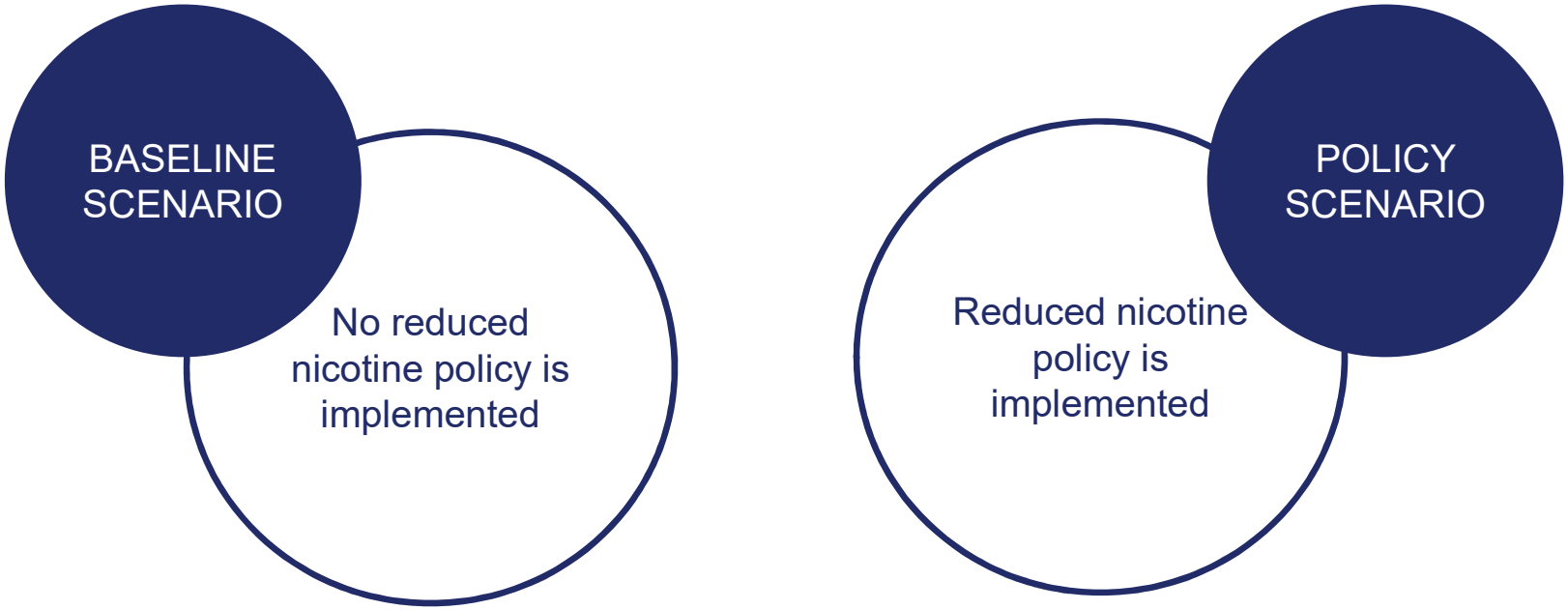
The majority of cigarette smokers in the United States began smoking during their youth,[4-6] which is a cause for concern. The age at which people begin smoking can greatly influence how much they smoke per day and how long they smoke, which ultimately influences their risks of tobacco-related disease and death.[7,8] Addiction to nicotine

dence 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

REVIEW OF THE NICOTINE MODEL



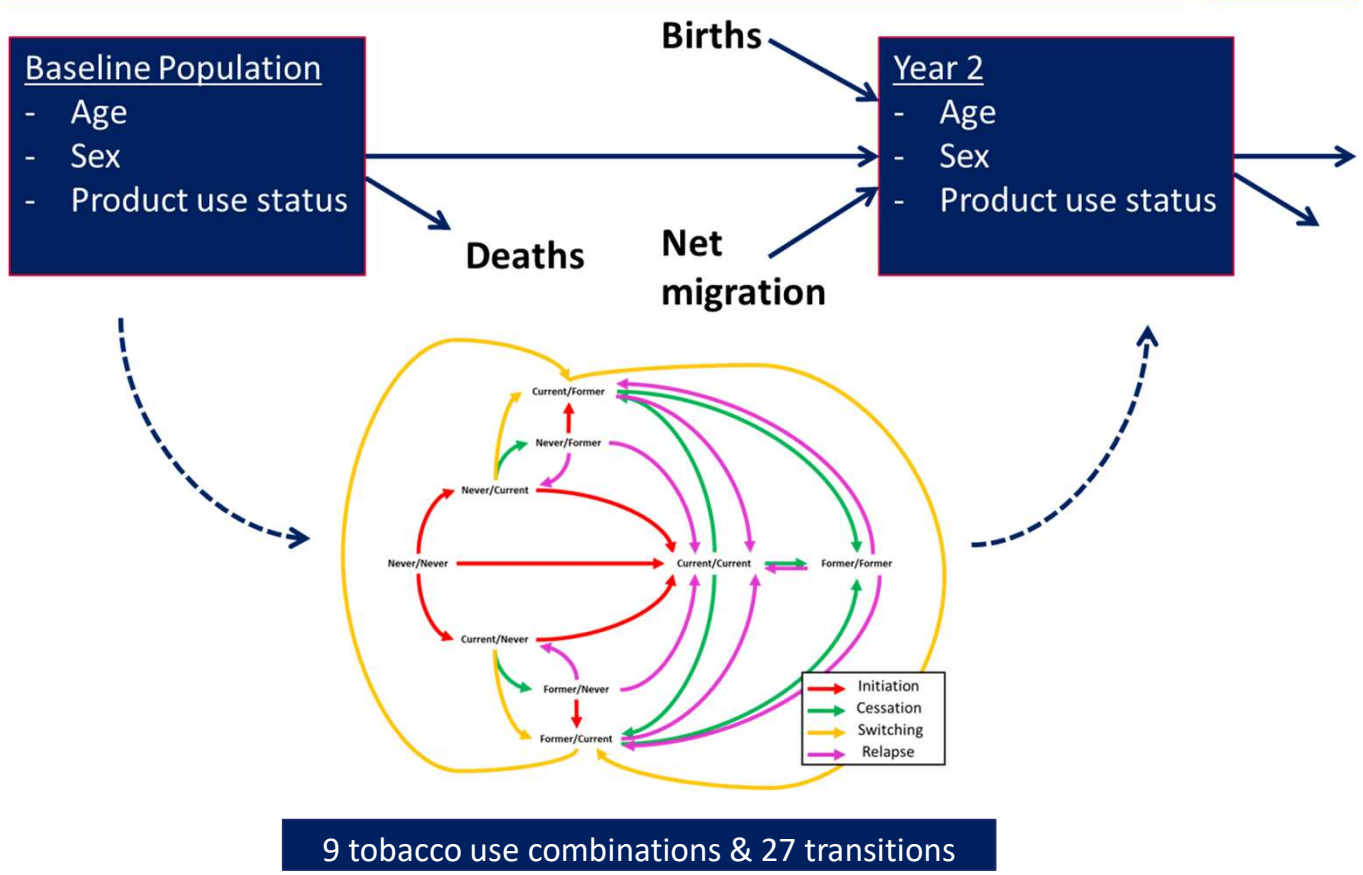
Projected tobacco use and public health effects through year 2100

REVIEW OF THE NICOTINE MODEL

Two-product model used to project impacts of the proposed standard on tobacco use, morbidity, and mortality in the U.S.

Product 1: combustible products (including low nicotine cigarettes)

Product 2: non-combustible products (including e-cigarettes)



9 tobacco use combinations & 27 transitions

NICOTINE MODEL: EXPERT ELICITATION

- To obtain inputs about the behavioral impacts of a reduced nicotine policy, we conducted an expert elicitation with Industrial Economics, Inc. (IEc)

- Panel of eight experts in tobacco science (6) and policy (2)

- Questions asked experts about the anticipated impact of the policy on:
  - Cigarette smoking cessation
  - Switching to products not covered by the policy
  - Dual use of cigarettes and products not covered
  - Cigarette smoking initiation
  - Initiation of products not covered

NICOTINE MODEL: RESULTS

Approximately 5 million additional adult smokers would quit smoking within just one year after implementation, compared to the baseline scenario

More than 134 million years of life gained among the U.S. population by the year 2100

Only about 1.4 percent of the U.S. adult population would smoke cigarettes by 2100, in part, because more than 33 million people would avoid becoming regular smokers

By the year 2100, more than 8 million premature deaths from tobacco could be avoided

LOOKING FORWARD: PRODUCT STANDARDS TO REDUCE THE APPEAL OF COMBUSTED TOBACCO

FDA NEWS RELEASE

FDA Commits to Evidence-Based Actions Aimed at Saving Lives and Preventing Future Generations of Smokers

Efforts to ban menthol cigarettes, ban flavored cigars build on previous flavor ban and mark significant steps to reduce addiction and youth experimentation, improve quitting, and address health disparities

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For Immediate Release: April 29, 2021

Today, the U.S. Food and Drug Administration announced it is committing to advancing two tobacco product standards to significantly reduce disease and death from using combusted tobacco products, the leading cause of preventable death in the U.S. The FDA is working toward issuing proposed product standards within the next year to ban menthol as a characterizing flavor in cigarettes and ban all characterizing flavors (including menthol) in cigars; the authority to adopt product standards is one of the most powerful tobacco regulatory tools Congress gave the agency. This decision is based on clear science and evidence establishing the addictiveness and harm of these products and builds on important, previous actions that banned other flavored cigarettes in 2009.

MENTHOL CIGARETTES: MODELING STUDIES

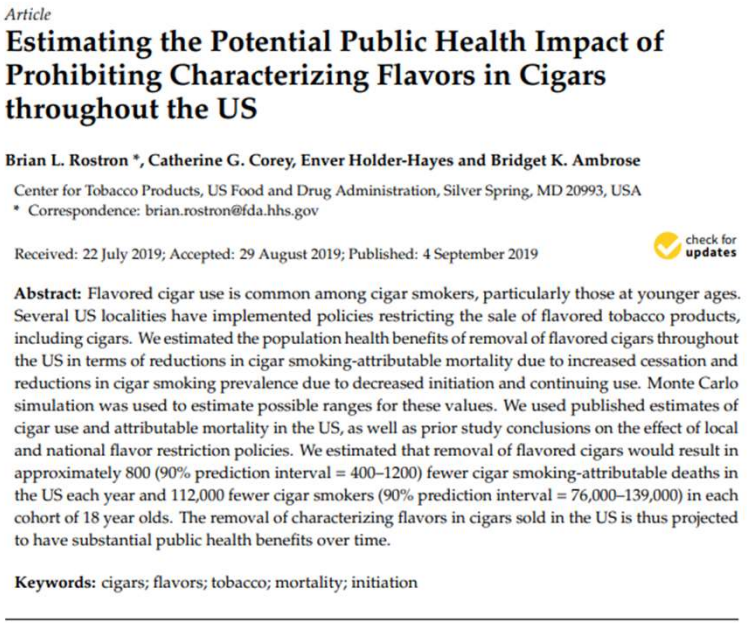
- Computational modeling can play an important role in characterizing the public health burden due to tobacco products and assessing the potential public health impact of a regulatory action.

- Examples of modeling studies related to menthol cigarettes:
  - Le and Mendez, 2021: Researchers estimate that menthol cigarettes were responsible for ~378,000 smoking-related premature deaths, 3 million life years lost and 10.1 million new smokers from 1980-2018.
  - Levy, 2011: Over a 40-year period, between 323,000 and 633,000 deaths could be avoided under a menthol cigarette ban, almost one third of which would be among African-Americans.

MODELING THE POTENTIAL IMPACT OF A FLAVORED CIGAR PRODUCT STANDARD

- A 2019 study estimated the population health impact of prohibiting characterizing flavors in cigars using:
  - Data on U.S. cigar use, cigar-attributable mortality, and evaluations of the effect of local and national flavor restriction policies.

- Study estimated that prohibiting characterizing flavors would result in:
  - ~800 fewer deaths per year due to increased cigar cessation among adults
  - ~112,000 fewer cigar smokers among each cohort of 18-year-olds



Article

Estimating the Potential Public Health Impact of Prohibiting Characterizing Flavors in Cigars throughout the US

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Abstract: Flavored cigar use is common among cigar smokers, particularly those at younger ages. Several US localities have implemented policies restricting the sale of flavored tobacco products, including cigars. We estimated the population health benefits of removal of flavored cigars throughout the US in terms of reductions in cigar smoking-attributable mortality due to increased cessation and reductions in cigar smoking prevalence due to decreased initiation and continuing use. Monte Carlo simulation was used to estimate possible ranges for these values. We used published estimates of cigar use and attributable mortality in the US, as well as prior study conclusions on the effect of local and national flavor restriction policies. We estimated that removal of flavored cigars would result in approximately 800 (90% prediction interval = 400–1200) fewer cigar smoking-attributable deaths in the US each year and 112,000 fewer cigar smokers (90% prediction interval = 76,000–139,000) in each cohort of 18 year olds. The removal of characterizing flavors in cigars sold in the US is thus projected to have substantial public health benefits over time.

Keywords: cigars; flavors; tobacco; mortality; initiation

COMPUTATIONAL MODELING TO INFORM PREMARKET AND POSTMARKET REVIEW

IOM REPORT: SCIENTIFIC STANDARDS FOR STUDIES ON MODIFIED RISK TOBACCO PRODUCTS

Utility of Modeling in MRTPs

- Synthesize information from empirical studies
- Explore complex interactions and systems that may be impractical to study empirically
- Explore “what if” scenarios
- Project short- and long-term effects of MRTP introduction

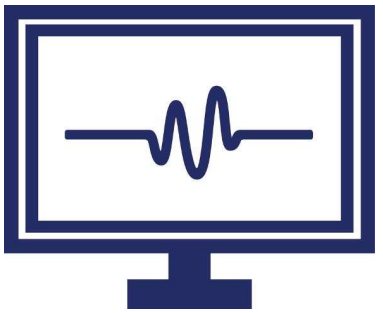
Considerations in the Conduct and Reporting of Model-Based Analyses

- Transparency
- Validation
- Uncertainty

Source: http://www.nationalacademies.org/hmd/Reports/2011/Scientific-Standards-for-Studies-on-Modified-Risk-Tobacco-Products.aspx

MRTP DRAFT GUIDANCE TO INDUSTRY: MODELING

In the draft guidance, FDA suggested that applicants could provide the following if they submit modeling:



- Explanations and justification of the technique used
- Assumptions used in the development of any models and parameters
- A listing of the parameters used in the analyses and/or models
- Data used to derive parameters or estimates and a rationale for the applicability of the data for the given parameter
- The results of various scenarios, including worst-case scenarios

MODELING TO INFORM POSTMARKET REVIEW

- On July 7, 2020, FDA authorized the IQOS System and Heatsticks to be marketed with reduced exposure claims.
  - Authorization includes requirements for postmarket surveillance and studies to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based…"

- The postmarket surveillance and studies requirement includes:
  - Studies of youth and adult use behavior, along with consumer understanding and perceptions
  - Computational toxicology study
  - Monitoring and reporting of serious and unexpected adverse events
  - Surveillance of new research study findings on the MRTPs
  - **Modeling the impact of the MRTP on population health**

MODELING REQUIREMENTS IN IQOS ORDER

- Model must incorporate data and information collected through postmarket surveillance and studies, e.g.:
  - Percentage of current smokers who switch completely to IQOS or become dual users
  - Percentage of former smokers who take up the use of IQOS
  - Percentage of youth and young adults who initiate the use of IQOS

- Model must incorporate the latest information on acute and long-term health effects of IQOS, including relative to cigarette smoking

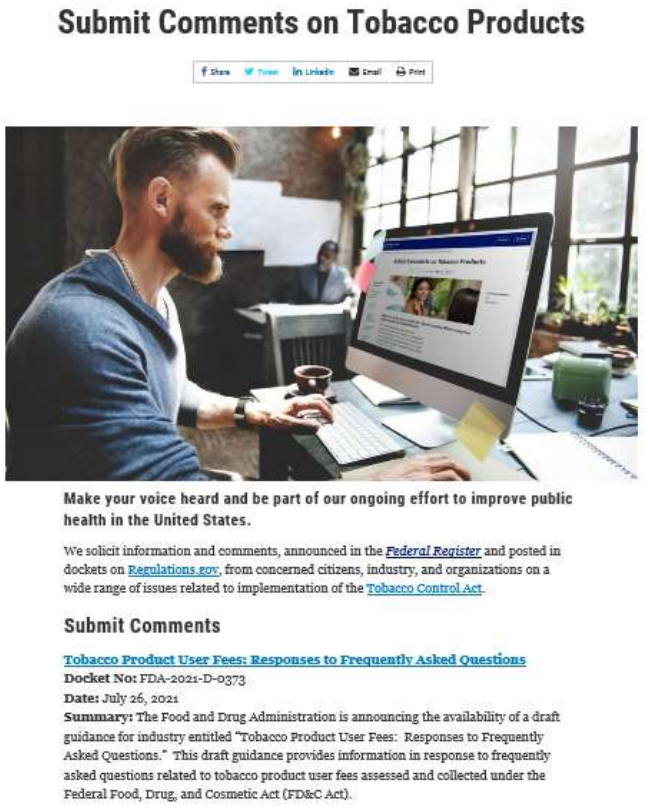
- Annual reporting must include:
  - Description of methodology, copy of the model or its code, description of all inputs and how they were derived, summary of results and implications for whether the MRTPs continue to be appropriate to promote the public health.

HOW MODELERS CAN INFORM TOBACCO REGULATION AND REVIEW

1. Publish studies that evaluate the potential impact of proposed regulations

2. Submit comments in public dockets at www.regulations.gov
   - Notice of Proposed Rule-Making (NPRM)
   - Modified Risk Tobacco Product Applications (MRTPs)

*All open comment opportunities are available on FDA's **Submit Comments on Tobacco Products** webpage*



Submit Comments on Tobacco Products

Make your voice heard and be part of our ongoing effort to improve public health in the United States.

We solicit information and comments, announced in the *Federal Register* and posted in dockets on Regulations.gov, from concerned citizens, industry, and organizations on a wide range of issues related to implementation of the Tobacco Control Act.

Submit Comments

Tobacco Product User Fees: Responses to Frequently Asked Questions
Docket No: FDA-2021-D-0373
Date: July 26, 2021
Summary: The Food and Drug Administration is announcing the availability of a draft guidance for industry entitled "Tobacco Product User Fees: Responses to Frequently Asked Questions." This draft guidance provides information in response to frequently asked questions related to tobacco product user fees assessed and collected under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

CHALLENGES AND FUTURE DIRECTIONS

ADDRESSING UNCERTAINTY

- Important sources of uncertainty may include: (1) structural assumptions of the model, (2) parameter inputs, and (3) variability among individuals in the population. (Source: IOM, 2011)
  - Difficult to accurately assess the “real-world” impact of a new product or new marketing in a pre-market setting
  - Uncertainty about the risk of a new product in the absence of long-term epidemiological evidence
  - Uncertainty about the impact of policies that have never been implemented before

- Approaches to help address model uncertainty include:
  - Transparency and documentation of model inputs and assumptions
  - Comparisons of results across different modeling approaches
  - Quantifying how uncertainty in inputs translates into uncertainty in outputs

CLOSING THOUGHTS

- FDA regulates tobacco products using a population health standard, which requires the consideration of individual risks and the impact of an action on the U.S. population.
- Computational modeling can be a useful tool to inform regulatory actions by incorporating product risks and use behaviors to project the potential impacts of different regulatory decisions.
- Useful features of models to inform tobacco product regulation include the ability to model the uptake of new tobacco products, the relative impact of different regulatory options, and potential countervailing effects, such as tobacco product substitution.
- Challenges include identifying relevant inputs for new policies or new tobacco products and appropriately characterizing the uncertainty associated with projected estimates.
- FDA decision-making provides opportunities for public input and comment, including the submission of new data or analyses for FDA consideration.

CONTACTING/FOLLOWING CTP

- **Report adverse experiences with tobacco products at: https://www.safetyreporting.hhs.gov**
- Call us: (877) CTP-1373
- Email us: AskCTP@fda.hhs.gov
- Follow us on Twitter: @FDATOBACCO