



CENTER FOR TOBACCO PRODUCTS | OFFICE OF SCIENCE



Tobacco Regulatory Science Research Program at FDA's Center for Tobacco Products: Summary and Highlights

FISCAL YEARS 2010-2017



June 2018

Dedication

DAVID L. ASHLEY, PH.D.

David L. Ashley, Ph.D., served as the Director of the Office of Science from July 2010 to May 2017. Throughout his tenure as the first Director of CTP-OS, he applied his valuable scientific and leadership expertise to implement a rigorous scientific program to review tobacco product applications, provide scientific input into development of regulations and guidance, improve the scientific knowledge base, and develop a tobacco regulatory research program.

Dr. Ashley's vision was for CTP-OS to be recognized nationally and internationally as the premier scientific organization for the regulation of tobacco products. There is no other tobacco regulatory organization in the world that has this responsibility and authority. Under his direction, several "firsts" were accomplished, such as preventing new tobacco products that did not meet the statutory standard from entering the market, finding new tobacco products appropriate for the protection of public health under the premarket tobacco application pathway, and launching the large, longitudinal Population Assessment of Tobacco and Health (PATH) Study. These "firsts" highlight Dr. Ashley's contribution to public health and tobacco control through science-based policy. We dedicate this report to Dr. Ashley in honor of his many accomplishments and his unwavering dedication to and leadership of the Office of Science.

Table of Contents

Introduction	1
Leadership Perspective: CTP’s Comprehensive Tobacco and Nicotine Regulation Plan	3
<i>Mitchell Zeller</i> , J.D., Director, Center for Tobacco Products	
Leadership Perspective: Tobacco Use and the Role of Tobacco Regulatory Science	4
<i>Matthew Holman</i> , Ph.D., Director, CTP Office of Science	
Leadership Perspective: CTP-OS’s Research Priorities	5
<i>Cathy L. Backinger</i> , Ph.D., M.P.H., Deputy Director for Research, CTP Office of Science	
Leadership Perspective: Science-Based Public Education Campaigns	7
<i>Kathy Crosby</i> , Director, CTP Office of Health Communication and Education	
FDA’s Tobacco Product Regulation	10
CTP-OS: Who We Are	13
OHCE’s Science-Based Approach to Communicating Public Health Messages	16
CTP’s Regulatory Research Program	18
Research Summary	18
CTP-Funded Projects by Research Domain	19
CTP-Funded Projects by Population	20
CTP-Funded Projects by Tobacco Product	21
Tobacco Product Research Summaries	23
Cigarettes and Cigarette Smoke	25
E-cigarettes	30
Cigars	37
Smokeless Tobacco and Snus	40
Hookah (Waterpipe)	46
Dissolvables	50
Low Nicotine	54
Flavors	57
Studies Examining Strategies and Impacts of CTP Public Education Campaigns	62
Research Partners	68
National Institutes of Health	68
Tobacco Regulatory Science Program	68
Tobacco Centers of Regulatory Science	68
Center for Evaluation and Coordination of Training and Research	71
Other Grants	71
NIH Intramural Projects	72
PhenX	72

Table of Contents (cont'd.)

- Research Partners (Cont'd.)**
- The Population Assessment of Tobacco and Health (PATH) Study 74
- Centers for Disease Control and Prevention..... 75
 - Division of Laboratory Science 75
 - Office on Smoking and Health 75
 - National Center for Health Statistics 75
 - Division of Reproductive Health..... 75
- National Center for Toxicological Research 77
- Other Federal Partners..... 77
- Contracts..... 77
- In-House Research 77
- Funded Publications**..... 79
- Training the Next Generation of Regulatory Scientists**..... 86
- Looking Toward the Future** 91
- References**..... 93



Introduction

Introduction

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), enacted on June 22, 2009, directed the U.S. Food and Drug Administration to create a Center for Tobacco Products (CTP) that works to protect Americans from tobacco-related death and disease by regulating the manufacture, distribution, and marketing of tobacco products, and by educating the public about tobacco products and the dangers their use poses. To carry out its regulation of tobacco products under the Federal Food, Drug, & Cosmetic Act (FD&C Act), CTP established an Office of Science (OS) to ensure that a robust science base informs the center's actions. To meet its mission, CTP-OS assesses existing scientific evidence and supports new research to inform regulatory actions intended to protect the public health by:

- Reducing the number of people who start to use tobacco products
- Encouraging more people to stop using these products
- Reducing the adverse health impact for those who continue to use these products

Focus on Regulatory Science

To make the most effective regulatory decisions, CTP must increase critical knowledge in evolving areas of regulatory science including the population health effect of the rapidly changing tobacco product market. Regulatory science research is critical to understanding the impact of manufacturing, marketing, and distribution of tobacco products on public health so that effective product review decisions can be made and other critical authorities granted by Congress to FDA can be used most effectively to reduce the death and disease resulting from tobacco use.

This is especially the case in adding to the science base to inform regulatory decisions. In general, noncigarette tobacco products have not been studied as extensively as cigarettes and smokeless products so additional research on these products is particularly important.

Regulatory science research is a critical component of all of FDA's programmatic activities and supports product review by adding to the knowledge the agency uses to effectively evaluate the premarket applications submitted for review.

Extending FDA's Authority to All Tobacco Products

Since 2009, FDA has regulated cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco. In May 2016, the agency finalized a rule—"Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act"—deeming all products that meet the statutory definition of a tobacco product, except accessories of deemed tobacco products, to be subject to FDA's tobacco product authority. This included electronic nicotine delivery systems (such as e-cigarettes and vape pens), all cigars, hookah (waterpipe) tobacco, pipe tobacco, and nicotine gels, among others. This action was a milestone in consumer protection. Going forward, CTP is now able to:

- Review submissions for tobacco products—including deemed products—not yet on the market
- Prevent misleading claims by tobacco product manufacturers
- Evaluate the ingredients of tobacco products and how these products are made
- Communicate the potential risks of tobacco products

In addition, the deeming rule means that certain requirements aimed at restricting youth access now apply to deemed tobacco products, such as e-cigarettes and vape pens; these requirements include:

- Prohibiting the sale of products to persons under the age of 18 years (in person and online)
- Requiring age verification by photo ID
- Prohibiting the sale of tobacco products in vending machines (unless in an adult-only facility)
- Prohibiting the distribution of free samples

This final rule went into effect on August 8, 2016.

LEADERSHIP PERSPECTIVE: CTP'S COMPREHENSIVE TOBACCO AND NICOTINE REGULATION PLAN

The historic Family Smoking Prevention and Tobacco Control Act gave FDA the unprecedented regulatory leadership role in reducing the toll of tobacco use on the nation's health. CTP is dedicated to taking regulatory actions that are grounded in science; thus, CTP-OS's research program is at the core of this historic mission.

CTP-OS is an integral part of FDA's comprehensive plan for tobacco and nicotine regulation that was announced by the FDA Commissioner on July 28, 2017. This comprehensive plan will serve as a multiyear roadmap to better protect kids and significantly reduce tobacco-related disease and death. The approach places nicotine, and the issue of addiction, at the center of the agency's tobacco regulatory efforts. FDA has begun a public dialogue about lowering nicotine levels in combustible cigarettes to nonaddictive levels through achievable product standards. The agency recently issued an advance notice of proposed rulemaking (ANPRM) to seek input on the potential public health benefits and any possible adverse effects of lowering nicotine in cigarettes. Because almost 90 percent of adult smokers started smoking before the age of 18 and more than 2,300 youth smoke their first cigarette every day in the United States, lowering nicotine levels could decrease the likelihood that future generations become addicted to cigarettes and allow more currently addicted smokers to quit. As part of the comprehensive regulatory plan to shift the trajectory of tobacco-related death and disease, FDA also issued an ANPRM on the role that flavors in tobacco products, including menthol, play in attracting youth, as well as the role that flavors may play in helping some smokers switch to potentially less harmful forms of nicotine delivery.

This comprehensive plan and sweeping approach to tobacco and nicotine allows FDA to apply the powerful tools given by Congress to achieve a significant public health impact. Public input on these complex issues will help ensure the agency has the proper science-based policies in place to meaningfully reduce the harms caused by tobacco use.



Mitchell Zeller, J.D., Director,
Center for Tobacco Products

LEADERSHIP PERSPECTIVE: TOBACCO USE AND THE ROLE OF TOBACCO REGULATORY SCIENCE

Tobacco use remains a top public health issue in the United States. In 2015, approximately 15 percent of adults aged 18 to 65 smoked,¹ and cigarette smoking kills more than 480,000 Americans annually.² An analysis of data from the 2013–2014 National Adult Tobacco Survey found that one-fifth (21.1 percent) of U.S. adults used any tobacco product daily or some days, 17.6 percent used any combustible tobacco product, and 3.9 percent used two or more tobacco products.³ Despite declines in cigarette smoking in recent years, tobacco use among adolescents remains significant: an analysis of National Youth Tobacco Survey data indicates that in 2016, 20.2 percent of high school students and 7.2 percent of middle school students reported current tobacco product use, and that 47.2 percent and 42.4 percent, respectively, of current users reported use of two or more tobacco products.⁴ Although combustible tobacco product use declined, current use of any tobacco product did not change significantly between 2011 and 2016.⁵



Matthew Holman, Ph.D., Director,
CTP Office of Science

Pursuing regulatory activities to reduce tobacco use and prevent initiation is a critical role of FDA as a regulatory agency—a role that is defined by decisions that are based on, and fall within the limits of, both the science and the law. Accordingly, tobacco regulatory science at CTP-OS is a key contributor to our tobacco-related decisionmaking. The goal of tobacco regulatory science is to generate research findings that have the potential to inform specific regulatory actions.

The CTP-OS research program has been key to our programmatic success to date and will continue to inform our regulatory activities. A vast and sound science base already exists for many areas of the Tobacco Control Act, and we are continually broadening that base of evidence with the research we conduct or sponsor. Research supported by CTP-OS informs policy development, product standards, and our review of new tobacco products seeking to enter or remain on the market. Details about the products themselves, how products are perceived and used (and by whom), labeling and advertising, and the impact on both individual and population health are some of the important areas we seek to better understand through research. In these and many other ways, CTP is enhancing tobacco regulatory science, thereby maximizing the tools Congress has given us to impact public health.

LEADERSHIP PERSPECTIVE: CTP-OS'S RESEARCH PRIORITIES

Rigorous, state-of-the-art science is at the cornerstone of FDA's efforts to regulate the manufacture, marketing, and distribution of tobacco products. Accordingly, CTP-OS is leading cutting-edge research to build a healthier future for all Americans.

A vast amount of research confirming tobacco's addictive and toxic properties, its negative impact on health, and knowledge, attitudes, perceptions, and behaviors about tobacco provides a solid scientific rationale for our regulatory actions. CTP-OS is continuing to develop the evidence base to inform regulation through its tobacco regulatory science research program. Since its inception in 2010, CTP-OS has honed its research priorities to include those that will make a positive impact on public health. The seven current research priorities include:



Cathy L. Backinger, Ph.D., M.P.H.,
Deputy Director for Research,
CTP Office of Science

1. **Toxicity**—Understanding how tobacco products and changes to tobacco product characteristics affect their potential to cause morbidity and mortality, including animal and cell culture models as well as novel alternative toxicology approaches that test the toxicity of tobacco smoke, aerosols, or specific constituents in tobacco.
2. **Addiction**—Understanding the effect of tobacco product characteristics on addiction and abuse liability.
3. **Health effects**—Understanding the short- and long-term health effects of tobacco products. Highest priority areas include cardiovascular or respiratory health effects, including inflammation.
4. **Behavior**—Understanding the knowledge, attitudes, and behaviors related to tobacco product use and changes in tobacco product characteristics.
5. **Communications**—Understanding how to communicate effectively to the public and vulnerable populations regarding nicotine and the health effects of tobacco products, including media campaigns and digital media.
6. **Marketing influences**—Understanding why people become susceptible to using tobacco products (both classes of products and products within classes) and transitions between experimentation and initiation to regular use and dual use. Topics may include tobacco industry marketing such as advertising, point-of-sale campaigns, digital media, and promotions.
7. **Impact analysis**—Understanding the impact of potential FDA regulatory actions.

Using these research priorities as a framework, CTP-OS is currently funding a range of research projects in collaboration with the National Institutes of Health, FDA's National Center for Toxicological Research, the Centers for Disease Control and Prevention, contract research organizations, and other partners, and continues to solicit and fund new research studies each year. By directing resources toward scientifically sound research projects that address these research priorities, CTP-OS is striving to ensure that tobacco use and tobacco-related death and disease can be reduced as rapidly as possible.

LEADERSHIP PERSPECTIVE: SCIENCE-BASED PUBLIC EDUCATION CAMPAIGNS

Achieving FDA’s mission of reducing the enormous public health burden of tobacco use requires a comprehensive, innovative approach. In direct support of this mission, the agency is investing in a number of science-based campaigns to educate the public, especially young people, about the harms from tobacco use.

CTP’s public education efforts, led by our Office of Health Communication and Education (OHCE), have been organized as four major efforts:

- **“The Real Cost.”** Launched in 2014, this campaign initially focused advertising on at-risk youth aged 12 to 17 who were open to smoking or already experimenting with cigarettes. In 2016, “The Real Cost” expanded to include advertising designed to reach male youth at risk of using smokeless tobacco. In fall 2017, the campaign released new digital materials focused on electronic nicotine delivery systems.
- **“Fresh Empire.”** The second CTP campaign to prevent youth tobacco use, launched in 2015, is designed to prevent and reduce tobacco use among at-risk multicultural youth aged 12 to 17, including African American, Hispanic, and Asian American/Pacific Islander youth. “Fresh Empire” specifically targets youth who identify with the hip-hop peer crowd—an innovative and promising segmentation approach that focuses on youth who share the same core ideals, have similar life experiences and common interests, and may be at higher risk for tobacco use.
- **“This Free Life.”** This campaign, launched in 2016, is targeted to lesbian, gay, bisexual, and transgender (LGBT) young adults aged 18 to 24 who are occasional smokers. LGBT young adults are nearly twice as likely to use tobacco as other young adults, resulting in tens of thousands of LGBT lives lost to tobacco use each year.
- **“Every Try Counts.”** This campaign, launched in 2017, is aimed at encouraging cigarette smokers to quit through messages of support that underscore the health benefits of quitting. These messages will be displayed in and around gas stations or convenience stores—retail locations where smokers face a multitude of triggers and that typically feature cigarette advertisements. The “Every Try Counts” campaign targets smokers aged 25 to 54 who have attempted to quit smoking in the last year but were unsuccessful.



Kathy Crosby, Director,
CTP Office of Health
Communication and Education

CTP is developing additional campaigns targeting other audiences, including American Indian/Alaska Native youth.

Using an Evidence-Based Approach

CTP's public education campaigns are based on a robust body of evidence that supports the use of mass media campaigns to prevent and reduce tobacco use. As part of an evidence-based approach, CTP conducts multiple rounds of research to develop effective strategies and messaging to reach discrete target audiences.

Measuring Success

Each campaign is evaluated to measure its effectiveness in changing relevant tobacco-related knowledge, attitudes, beliefs, or behaviors among the target audience. Some studies have been completed, as detailed later in this report, and other evaluations are under way. These studies show that these types of innovative, science-based campaigns can positively affect youth behaviors and have the potential to help free today's youth and future generations from tobacco addiction, disease, and death.



FDA's Tobacco Product Regulation

FDA's Tobacco Product Regulation

The Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act)—which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act)—gives FDA broad authority to regulate the manufacture, distribution, and marketing of tobacco products. Some of FDA's regulatory activities under the law include:

- Regulating tobacco products
- Regulating tobacco product advertising, marketing, promotion, distribution, and sales
- Setting product standards
- Reviewing premarket applications for new and modified risk tobacco products
- Requiring new health warnings on products and advertising
- Enforcing regulations
- Supporting regulatory science
- Providing public education

FDA's tobacco product authorities generally do not extend to the following: banning all tobacco products in certain categories; requiring the total elimination of nicotine from tobacco products; setting taxation rates; regulating therapeutic products (such as nicotine replacement therapies, which are regulated by FDA's Center for Drug Evaluation and Research); banning tobacco sales in broad types of sales outlets (such as a ban on tobacco sales in all pharmacies); setting clean indoor air policies; or regulating tobacco farming.⁶

FDA'S TOBACCO REGULATION IN ACTION

To reduce the public health burden of tobacco products, CTP has undertaken numerous actions, including:

- Using the best available science to develop and issue regulations to protect the nation's health
- Publishing numerous guidances to help industry comply with regulations for tobacco products
- Conducting retailer inspections across the United States and issuing warning letters, no-tobacco-sale orders, and civil monetary penalties for violations
- Requiring tobacco manufacturers to report the ingredients of their products
- Reviewing proposed modified risk tobacco product applications before such products can be authorized for marketing
- Restricting the access and attractiveness of tobacco products to youth
- Enforcing the ban on the manufacture and sale of flavored cigarettes, other than menthol and tobacco flavors
- Prohibiting the use of misleading claims such as "low," "light," and "mild" that imply products are safer
- Establishing new tobacco health warnings to communicate health risks
- Producing public information and education campaigns, including the award-winning "The Real Cost" campaign, about the dangers of tobacco products



CTP-OS: Who We Are

CTP-OS: Who We Are

CTP-OS has adopted a comprehensive, multifaceted approach toward reducing the negative health effects of tobacco use. This approach includes conducting research to provide the science that guides policy, establishes regulations, educates Americans on tobacco products, and informs decisions on whether new products and claims can be marketed—including reviewing and evaluating applications and claims before the products are allowed on the market.

This approach requires the expertise of scientists covering a wide variety of fields, including chemistry, engineering, microbiology, toxicology, environmental science, medicine, psychology, epidemiology, behavioral and social sciences, and statistics. These scientists work in concert to analyze tobacco products and related issues from a variety of perspectives.

CTP-OS MISSION AND VISION

Mission

The Office of Science develops, evaluates, and applies the science that informs and supports the regulatory and other public health goals and objectives of the Center for Tobacco Products.

Vision

The Office of Science is recognized nationally and internationally as the premier scientific organization for the regulation of tobacco products.

CTP-OS BY THE NUMBERS

- 23 employees as of the end of FY10—and 324 employees as of the end of FY17
- 3 active research projects at the end of FY10—and 226 active research projects at the end of FY17
- 398 total projects funded through FY17
- \$1.243 billion total funds supporting research through FY17
- \$53 million awarded in FY13 to establish 14 Tobacco Centers of Regulatory Science

CTP-OS research scientists are organized into four divisions that monitor and pursue research in defined areas. These divisions are the Division of Product Science, the Division of Nonclinical Science, the Division of Individual Health Science, and the Division of Population Health Science.

- The Division of Product Science evaluates product composition and design as related to marketing application review, scientific research, and guidance and regulation development.
- The Division of Nonclinical Science conducts analyses related to toxicology, pharmacology, risk assessment, and environmental assessment.
- The Division of Individual Health Science evaluates tobacco use behaviors, exposure-response relationships, and the health impact of various tobacco products.
- The Division of Population Health Science focuses on identifying, measuring, and evaluating factors associated with tobacco product use and the consequences of such use; assessing the impact of tobacco product marketing on perceptions, beliefs, and behaviors related to tobacco products; and developing and evaluating the communication of complex scientific and regulatory information.

Additional groups within CTP-OS support the research scientists in their work. These groups include the Research and Knowledge Management team, the Advisors and Consultants Staff, the Science and Policy Team, the Division of Regulatory Science Informatics, the Division of Regulatory Project Management, and the Management Office.

- The Research and Knowledge Management team oversees and provides support for the CTP-OS research program by facilitating and disseminating tobacco regulatory science, leading and coordinating research and knowledge management programs, and ensuring effective use of resources.
- The Advisors and Consultants Staff oversees the use of scientific advisors, consultants, and committees and coordinates workshops and symposia.
- The Science Policy Team provides independent input and scientific/regulatory policy direction during all stages of development, implementation, and operation of CTP-OS regulatory science programs.
- The Division of Regulatory Science Informatics develops, implements, and manages information systems that support CTP-OS's regulatory science programs.
- The Division of Regulatory Project Management provides direct project management support to scientists by offering input on study development, managing logistical and budgetary study activities, and supporting product reviews.
- The Program Management Team is responsible for handling all CTP-OS administrative functions.

OHCE's Science-Based Approach to Communicating Public Health Messages

OHCE's Science-Based Approach to Communicating Public Health Messages

CTP's Office of Health Communication and Education (OHCE) is responsible for conducting public education and regulatory communication programs designed to ensure FDA's success in implementing the Tobacco Control Act. These efforts include developing breakthrough communication strategies to reduce youth tobacco use, encouraging current tobacco users to quit, and building regulated industry understanding of and compliance with FDA tobacco product regulations.

OHCE communicates directly with a range of audiences—from regulated industry to at-risk youth—across a broad spectrum of channels that spans from traditional media to Twitter. Understanding the unique needs of each individual audience and how to identify the best channels, tactics, and messages to reach them requires an evidence-based, multidisciplinary communications approach. Developing such a complex approach requires an in-depth understanding of communication science and best practices, including applied behavior change theories and information dissemination models; detailed knowledge of the current state of tobacco science and tobacco control best practices; profound understanding of FDA's regulatory framework and policy goals; expertise in navigating a dynamic media environment, including adapting to new and emerging technologies; and careful evaluation of communications activities over time to identify new opportunities for improving the public's health.

Although OHCE's mission is inherently communications-focused, the office also contributes significantly to CTP's tobacco science knowledge base and to the broader field of public health by:

- Guiding the design, implementation, and analysis of foundational research used to develop and evaluate national public education campaigns, including conducting primary research with a range of target audiences.
- Applying secondary research insights from internal and external sources to further inform CTP communications and public education campaigns.
- Assisting in CTP-wide communications research that supports the development and implementation of regulatory initiatives.
- Sharing research and evaluation data with internal and external audiences through publication of peer-reviewed articles, presentations at relevant conferences, and participation in meetings with key stakeholders.

CTP's Regulatory Research Program



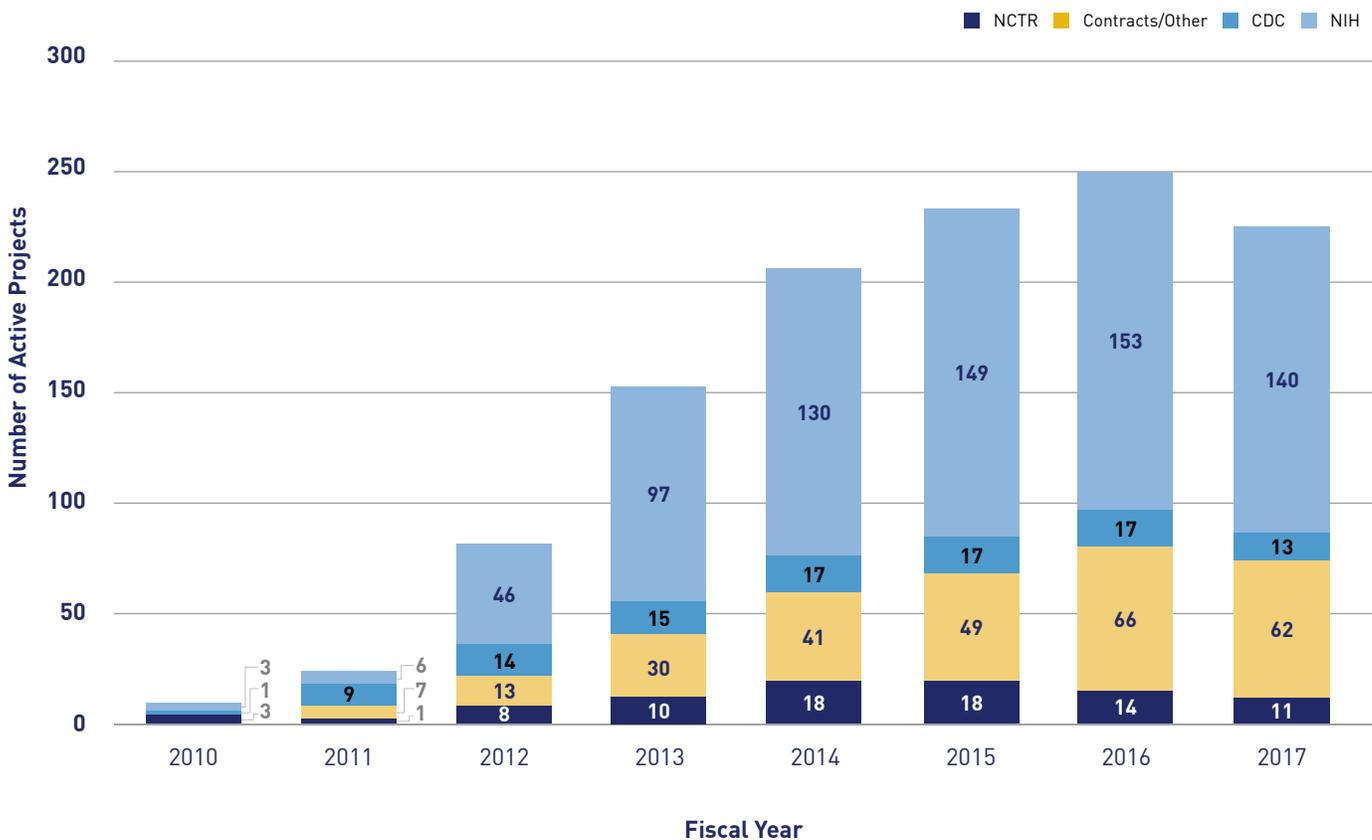
CTP's Regulatory Research Program

RESEARCH SUMMARY

CTP has funded a total of 398 projects from FY10 through FY17. Projects have been funded through NIH, CDC, FDA's National Center for Toxicological Research (NCTR), and contracts and other mechanisms. The program has grown from funding seven projects in FY10 to funding 226 projects in FY17.

More than 95 percent of the research portfolio resides in CTP-OS. The following graphs also include projects led by CTP's Office of Health Communication and Education (OHCE); these projects relate to research informing CTP's public education activities.

Active CTP-Funded Projects by Fiscal Year

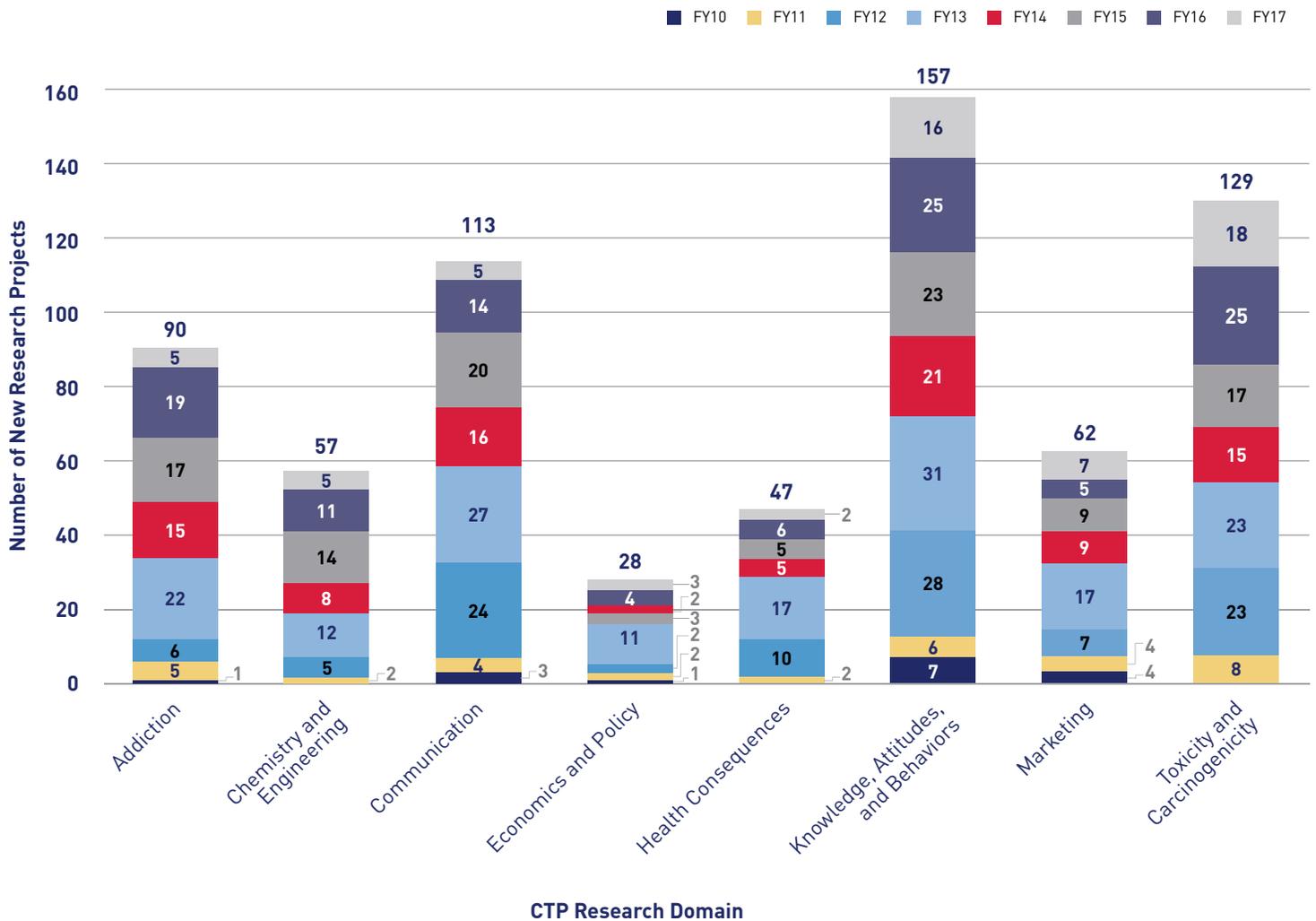


Note: Graph represents active CTP-funded projects by fiscal year; projects reflect federal collaborations and government and nongovernment contracts. Projects may be active in multiple fiscal years. Budget includes research infrastructure. FY17 budget numbers are preliminary.

CTP-FUNDED PROJECTS BY RESEARCH DOMAIN

CTP funding over 8 years has been spread across eight research domains, including (in order of number of projects): knowledge, attitudes, and behaviors (157 projects); toxicity and carcinogenicity (129 projects); communication (113 projects); addiction (90 projects); marketing (62 projects); chemistry and engineering (57 projects); health consequences (47 projects); and economics and policy (28 projects).

CTP-Funded Projects by Research Domain (FY10–FY17)

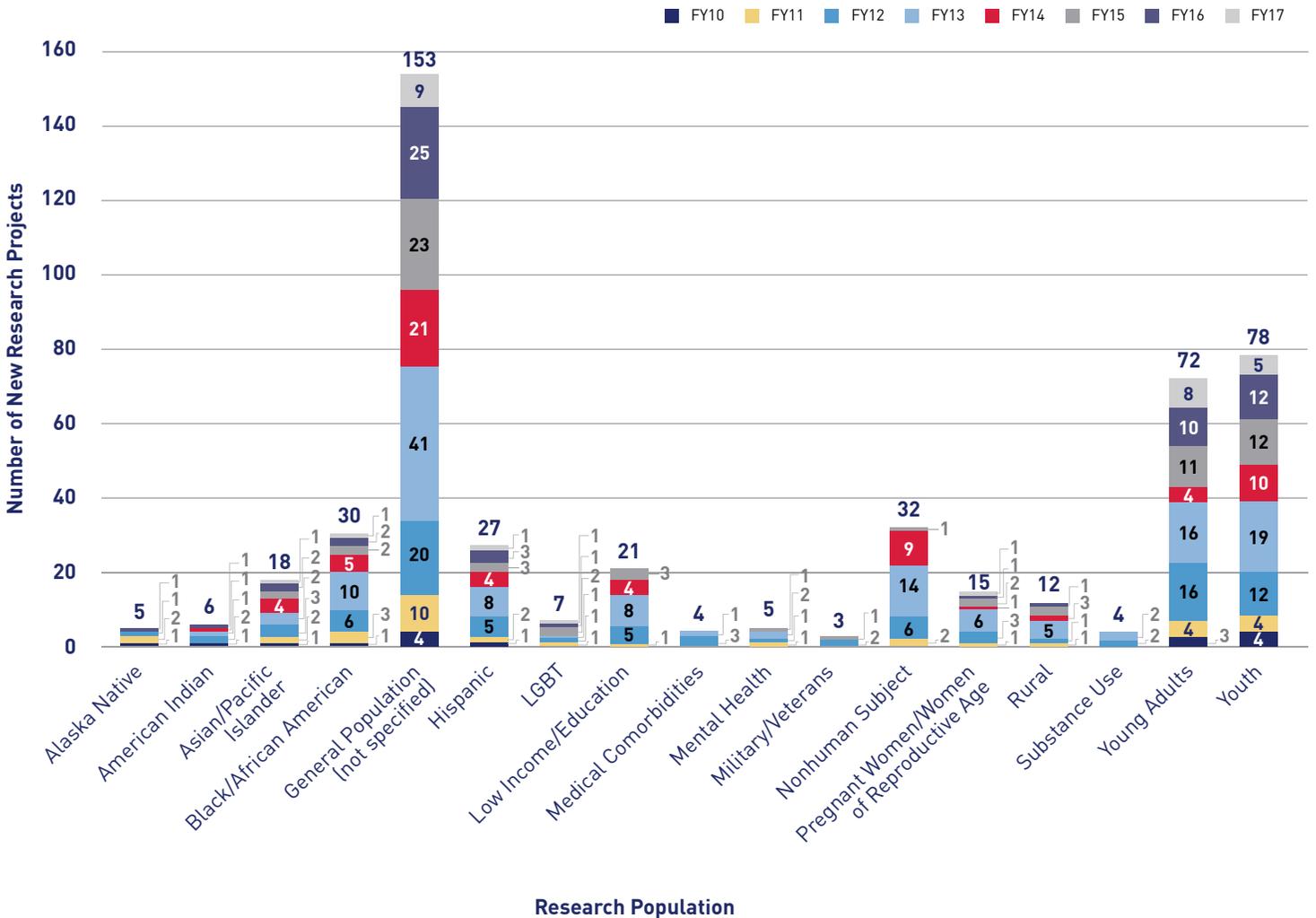


Note: Research categories are not mutually exclusive.

CTP-FUNDED PROJECTS BY POPULATION

The majority of CTP projects have focused on the general population (153 projects), although meaningful numbers of projects have focused on vulnerable populations such as youth (78 projects), young adults (72 projects), Blacks/African Americans (30 projects), Hispanics/Latinos (27 projects), low-income/low-education populations (21 projects), Asians/Pacific Islanders (18 projects), pregnant women/women of reproductive age (15 projects), and rural populations (12 projects). (*Note: Projects may include more than one population group.*)

CTP-Funded Research Projects by Population (FY10-FY17)

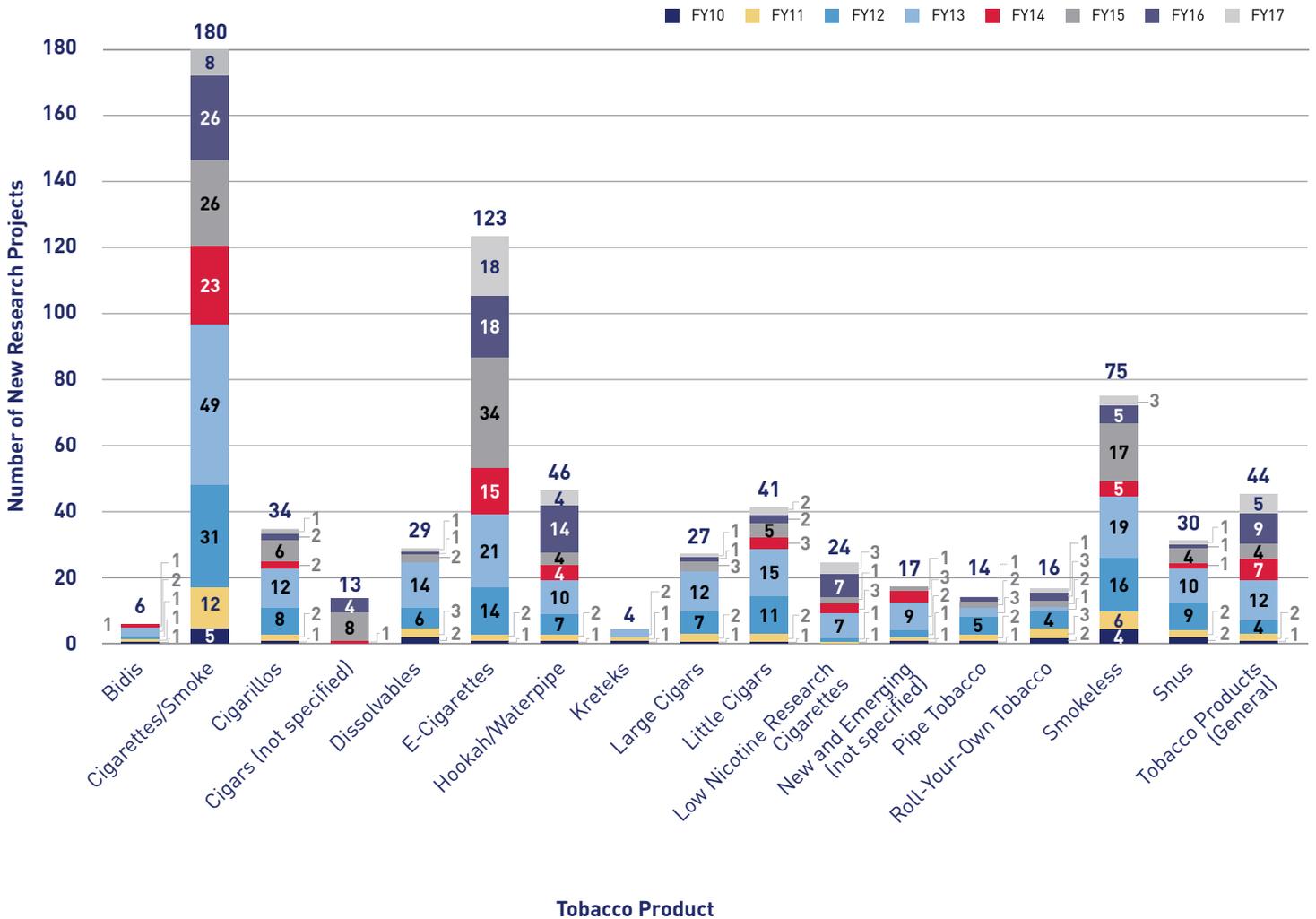


Note: Population categories are not mutually exclusive.

CTP-FUNDED PROJECTS BY TOBACCO PRODUCT

Although a large number of projects have focused on cigarettes and cigarette smoke (180 projects), CTP has funded projects on a wide array of tobacco products, including e-cigarettes (123 projects), smokeless tobacco (75 projects), little cigars (41 projects), hookah (waterpipe) tobacco (46 projects), cigarillos (34 projects), snus (30 projects), dissolvables (29 projects), large cigars (27 projects), roll-your-own tobacco (16 projects), and pipe tobacco (14 projects). (Note: Projects may include more than one product.)

CTP-Funded Research Projects by Tobacco Product (FY10-FY17)



Note: Product categories are not mutually exclusive.

Tobacco Product Research Summaries



Tobacco Product Research Summaries

CTP-supported research covers a wide range of tobacco products, including cigarettes, e-cigarettes, cigars (large cigars, little cigars, and cigarillos), smokeless tobacco, snus, dissolvables, hookah (waterpipe) tobacco, pipe tobacco, roll-your-own tobacco, and bidis, as well as low-nicotine research cigarettes.

Brief summaries of published research for seven selected products under CTP’s regulatory authority (cigarettes/smoke, e-cigarettes, cigars, smokeless tobacco, snus, hookah/waterpipe tobacco, and dissolvables) as well as research on two additional topics (low nicotine content cigarettes and flavors) are presented below. These summaries highlight published articles and research findings that have resulted from CTP-funded research. Findings have been or may be used to inform CTP’s regulatory activities, including conducting product reviews, developing product standards, developing public education campaigns, and executing compliance and enforcement actions. Taken together, these findings and the activities they inform are helping CTP achieve its mission of reducing the morbidity and mortality associated with tobacco use.

Note: The findings and conclusions of the research are those of the authors and do not necessarily represent the views of FDA.

Using the Research

In general, research findings have informed many important activities and actions at CTP. For example, CTP-funded studies helped inform the additional provisions that were in the deeming rule, which extended FDA’s authority to include the regulation of electronic nicotine delivery systems (such as e-cigarettes and vape pens), all cigars, hookah (waterpipe) tobacco, pipe tobacco and nicotine gels, among others. (See the next section for more information about how research informed the deeming rule.) In addition, research study findings support CTP review of premarket tobacco product applications. For example, research findings regarding the chemistry and engineering of the product—as well as the impact of the product at the individual and population levels regarding toxicity, addictiveness, use behavior, perceptions, and appeal—are informative in reviewing evidence provided by the applicant. Findings also have informed the development of CTP public education campaigns, including “The Real Cost” campaign directed toward youth, the “Fresh Empire” campaign targeted at multicultural youth, and the “This Free Life” campaign directed toward lesbian, gay, bisexual, and transgender youth; additional campaigns already developed or in development target American Indian/Alaska Native youth, tobacco product retailers, and tobacco users at the point of sale. Finally, general research can inform compliance and enforcement activities such as surveillance, inspection, and investigation of specific products.

Research findings are useful in informing more specific activities as well. For example, CTP-supported research on smokeless tobacco helped inform the development of a proposed product standard on N'-nitrosonornicotine (NNN).^{*} NNN is a potent carcinogenic agent found in smokeless tobacco products and is a major contributor to the elevated cancer risks associated with smokeless tobacco use. This proposed standard would establish a limit of NNN in finished smokeless tobacco products sold in the United States to decrease oral cancer deaths caused by smokeless tobacco.

In addition, CTP-supported research on very low nicotine content (VLNC) cigarettes helped inform the development of an advance notice of proposed rulemaking (ANPRM), “Tobacco Product Standard for Nicotine Level of Combusted Cigarettes” (March 16, 2018).⁷ The ANPRM provides a wide-ranging review of the current scientific understanding about the role nicotine plays in creating or sustaining addiction to cigarettes. It seeks comments on key areas, as well as additional research and data for public review, as we continue our consideration of developing a nicotine product standard. The goal is to lower nicotine in combustible cigarettes to minimally or nonaddictive levels, thereby making it harder for future generations to become addicted in the first place and allowing more currently addicted smokers to quit or switch to potentially less harmful products. CTP-supported research on flavors, including menthol, also was informative in the development of another ANPRM, “Regulation of Flavors in Tobacco Products” (March 21, 2018).⁸ This ANPRM calls upon all stakeholders to share data, research, and information that can inform our process for examining the role that flavors—including menthol—play in initiation, use, and cessation of tobacco products. This ANPRM may inform the most effective regulatory options FDA could pursue to address this issue. Finally, CTP-supported research on premium cigars informed the development of a third ANPRM, “Regulation of Premium Cigars” (March 26, 2018).⁹ This ANPRM seeks comments, data, research results, and other information that may inform regulatory actions FDA might take with respect to premium cigars.

^{*} Available at <https://www.federalregister.gov/documents/2017/01/23/2017-01030/tobacco-product-standard-for-n-nitrosonornicotine-level-in-finished-smokeless-tobacco-products>.

CIGARETTES AND CIGARETTE SMOKE

From FY10 to FY17, 365 articles based on CTP-funded research related to cigarettes and cigarette smoke were published in peer-reviewed journals. Topics fell within all eight CTP research domains (addiction; chemistry and engineering; communications; economics and policy; health consequences; knowledge, attitudes, and behaviors; marketing; and toxicity and carcinogenicity).

Examples of specific study topics include the impact of graphic health warnings, perceptions of cigarette package descriptors, menthol content in cigarettes, predictors of cigarette use, impact of tobacco marketing on tobacco use, impact of smoking on diseases such as cardiovascular disease and acute respiratory distress syndrome, and concentrations of toxic metals in cigarette smoke.

Research Summary:[◇] While rates of cigarette smoking have declined in recent years, cigarette smoking remains a major public health concern, particularly among certain population groups. In 2016, the National Youth Tobacco Survey (NYTS) found that 8.0 percent of high school students and 2.2 percent of middle school students reported current (past 30 days) use of cigarettes.¹⁰ Among adults, data from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) Study showed that more than a quarter (27.6 percent) of adults currently used at least one type of tobacco product in 2013 and 2014, and 8.9 percent of youths had used a tobacco product in the previous 30 days; cigarettes continue to be the most prevalent tobacco product used, with 22.5 percent of adults having smoked a cigarette in the past 30 days.¹¹

Despite declines in cigarette smoking rates, an analysis of PATH Study Wave 1 data found that the poly-tobacco use prevalence rate among U.S. adults was 37.8 percent among tobacco users; 76.2 percent of poly-users used cigarettes and at least one other product, with the most common combination being cigarettes plus e-cigarettes (22.5 percent). Factors associated with higher tobacco use included being non-Hispanic American Indian or Alaska Native, non-Hispanic of two or more races, and non-Hispanic black; identifying as bisexual, gay, or lesbian; having less education and lower incomes than their counterparts; and living in the South or Midwest compared to the Northeast or West.¹²

Research has confirmed the dangers of cigarette smoking. Research among more than 290,000 older adults found that low-intensity smoking over the lifetime was associated with elevated risk of all-cause mortality, as well as mortality related to lung cancer and cardiovascular disease.¹³ When exposed to cigarette smoke, airway basal cells undergo biological changes and disorders that lead to lung function loss and development of smoking-associated lung diseases.¹⁴ Studies found that smoking accelerates aging of small airway epithelium¹⁵ and that exposure to acrolein, which is present in tobacco smoke, is associated with an increased risk of cardiovascular disease.¹⁶ In addition, smoking intensity was associated with early biomarkers of cardiovascular disease, particularly markers of systemic inflammation.¹⁷

[◇] Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

A systematic review about how the public thinks about cigarette smoke chemicals found that people knew little about cigarette additives, assumed harmful chemicals are added during manufacturing, and perceived cigarettes without additives to be less harmful.¹⁸ A study to estimate differences in cigarette harm perceptions among smokers of the Natural American Spirit brand (which was marketed as “natural,” “organic,” and “additive-free” at the time of the study) compared to other smokers found that the majority of these smokers inaccurately believe that their cigarettes are less harmful than other brands.¹⁹

The Tobacco Control Act directed FDA to require graphic health warnings to accompany nine textual warning statements for cigarettes. This area of research is continuing and will inform FDA as it moves forward to propose revised graphic health warnings. For example, a 2015 study of 293 daily smokers found that graphic health warnings enhanced warning credibility, affected risk perceptions, and increased smoking risk knowledge.²⁰ In a systematic review of 32 longitudinal observation studies, strengthened warnings were associated with increased knowledge of the health effects of smoking.²¹ In another systemic review of 22 studies assessing attention and message processing found that strengthened warnings increased attention to warnings, recall of warnings, and thinking about the health risks of smoking.²²

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Byron MJ, Baig SA, Morocco KE, Brewer NT. Adolescents' and adults' perceptions of "natural," "organic" and "additive-free" cigarettes, and the required disclaimers. *Tob Control*. 2016;25:517-520.

Descriptors on cigarette packages may convey messages about relative health benefits that can impact users' beliefs and behavior. Researchers conducted nine focus groups with 59 participants aged 13–64 years to evaluate perceptions of an American Spirit cigarette advertisement that included "natural," "organic," and "additive-free" descriptors along with disclaimers stating that these cigarettes are not safer than other brands. Researchers found that many participants were skeptical or confused about the descriptors. Despite the disclaimers, many participants viewed American Spirit cigarettes as being less, or possibly less, harmful than other brands. Some participants said that people tend to ignore disclaimers; a few doubted that the disclaimers were completely true; some did not notice the disclaimers. A few participants said that they smoke American Spirit cigarettes because they think these cigarettes are not as harmful as other brands. The researchers concluded that disclaimers may be insufficient to prevent consumers from attributing a health benefit to cigarettes labeled with the above descriptors.

PUBLICATION HIGHLIGHT

DeJarnett N, Conklin DJ, Riggs DW, Myers JA, O'Toole TE, Hamzeh I. Acrolein exposure is associated with increased cardiovascular disease risk. *J Am Heart Assoc*. 2014;3(4).

Exposure to acrolein, a reactive aldehyde present in tobacco smoke, may be associated with increased cardiovascular disease (CVD) risk. Researchers assessed acrolein exposure in 211 Louisville Healthy Heart Study participants with moderate to high CVD risk by measuring urinary levels of the acrolein metabolite-3-hydroxypropylmercapturic acid (3-HPMA). Urinary 3-HPMA levels were higher in smokers than nonsmokers; were positively correlated with urinary cotinine levels; suppressed circulating angiogenic cells; and were positively associated with increased levels of platelet-leukocyte aggregates and the Framingham Risk Score. Researchers did not observe an association between 3-HPMA and plasma fibrinogen, and only found an association between 3-HPMA and C-reactive protein in nonsmokers. Findings indicate that acrolein exposure is associated with platelet activation, suppression of circulating angiogenic cell levels, and increased CVD risk.

PUBLICATION HIGHLIGHT

Evans AT, Peters E, Strasser AA, Emery LF, Sheerin KM, Romer D. Graphic warning labels elicit affective and thoughtful responses from smokers: results of a randomized clinical trial. *PLoS One*. 2015;10(12):e0142879.

Evidence suggests that graphic health warnings on cigarette packs are an effective way to educate consumers about the health risks of smoking. Researchers investigated the psychological impacts of exposure to graphic versus text-only cigarette pack warnings. In this study, 293 adults who smoked 5 to 40 cigarettes daily were randomly assigned to receive their own brand of cigarettes for 4 weeks in packs modified with one of three cigarette warnings: text only, graphic images plus text, or graphic images with elaborated text. Researchers examined participants' affect toward smoking, credibility of warning information, risk perceptions, quit intentions, warning label memory, and smoking risk knowledge. Compared to text-only warnings, graphic warnings caused more negative affect toward smoking and enhanced warning credibility, both of which indirectly influenced risk perceptions and quit intentions. In addition, graphic warnings increased warning information recall and indirectly increased smoking risk knowledge. Surprisingly, elaborated text reduced warning credibility. Findings indicated that, compared to text-only warnings, graphic warning labels more effectively encourage smokers to consider quitting and educate them about smoking risks.

PUBLICATION HIGHLIGHT

Noar SM, Francis DB, Bridges C, et al. The impact of strengthening cigarette pack warnings: systematic review of longitudinal observational studies. *Soc Sci Med*. 2016;164:118-129.

Researchers conducted a systematic review of longitudinal observational studies that examined national implementation of strengthened cigarette pack warnings to determine their impact on knowledge, beliefs, attitudes, intentions, and behavior. They analyzed 32 longitudinal observational studies conducted in 20 countries with 812,363 participants. About two-thirds (64 percent) studied changes from text to pictorial warnings, while the rest studied strengthened warnings (text or pictorial). Findings were as follows: (1) knowledge increased in 12 of 12 studies evaluating this variable; (2) results related to beliefs/attitudes and intentions were mixed; (3) quitline calls increased in four of six studies; (4) foregoing of cigarettes did not increase; (5) cigarette consumption decreased in three of eight studies; (6) quit attempts increased in four of seven studies; (7) short-term cessation increased in two of three studies; and (8) smoking prevalence decreased in six of nine studies.

PUBLICATION HIGHLIGHT

Wang H, Word B, Lyn-Cook L Jr, Yang M, Hammons G, Lyn-Cook B. Cytotoxicity of chronic exposure to 4 cigarette smoke condensates in 2 cell lines. *Int J Toxicol.* 2015;34(2):182-194.

The cytotoxicity of tobacco smoke is associated with a variety of conditions, including inflammation and oxidative stress, that lead to chronic tobacco-related diseases. Researchers assessed the cytotoxicity of cigarette smoke condensate (CSC) from two reference cigarettes using a primary human small airway epithelial (PSAE) cell line for 28 days. CSCs (0.3 to 10 µg/mL) promoted cell proliferation at 120 hours of exposure, but demonstrated cytotoxicity at days 14 and 28. CSCs (0.3 to 3 µg/mL) prompted cell death at day 14 but induced cell proliferation at day 28. Changes to cell form and structure began by day 14 and increased by day 28. Researchers also assessed CSC toxicity in a Barrett esophagus cell line; these cells demonstrated dose- and time-dependent cytotoxicity over 28 days, but were more resistant to CSCs than the PSAE cells. This study demonstrates that CSCs cause cytotoxicity as well as cell transformation.

E-CIGARETTES

From FY10 to FY17, 265 articles based on CTP-funded research related to e-cigarettes were published in peer-reviewed journals. Topics fell within all eight CTP research domains (addiction; chemistry and engineering; communications; economics and policy; health consequences; knowledge, attitudes, and behaviors; marketing; and toxicity and carcinogenicity).

Examples of specific study topics pertaining to e-cigarettes include use patterns, intention to smoke cigarettes among young e-cigarette users, reasons for use, flavors and appeal, marketing strategies, harm perceptions, chemical composition of e-liquids, nicotine delivery, and information about toxicity and potential health effects.

Research Summary: [◇] E-cigarettes are the most commonly used tobacco product among youth, surpassing cigarettes in 2014. The National Youth Tobacco Survey (NYTS) found that current (past 30 day) e-cigarette use rose from 1.5 percent of high school students in 2011 to 16.0 percent in 2015; however, use was 11.3 percent in 2016.²³ Despite the recent 1-year decrease, an estimated 2.2 million middle and high school students reported currently using e-cigarettes in 2016.²⁴ Among U.S. middle and high school students who have ever used e-cigarettes, the majority of students (53.4 percent) reported using only rechargeable/refillable e-cigarettes, 14.5 percent reported using only disposable e-cigarettes, and 32.1 percent reported using both types.²⁵ Data from the 2014 Southern California Children’s Health Study indicate that 40.5 percent of current e-cigarette users had never smoked a cigarette.²⁶ The 2014 NYTS found a high prevalence of poly-tobacco use among U.S. middle school and high school students currently using e-cigarettes: 63 percent of current e-cigarette users reported using at least one other tobacco product, with most of these other products being combustible tobacco products.²⁷ However, data from five consecutive NYTS surveys suggest that between 2011 and 2015, a greater proportion of adolescents who used e-cigarettes reported being exclusive e-cigarette users.²⁸

Researchers used data from the PATH Study to examine patterns of e-cigarette use among adult users. In 2013–2014, the majority of current adult e-cigarette users were nondaily users and current cigarette smokers. Cigarette smokers who quit in the past year were more likely to report daily e-cigarette use, compared with current smokers. Those who reported using rechargeable or refillable devices were more likely to report daily use compared with those who did not use these devices.²⁹ A study of a national sample of pregnant women in 2015 found that 6.5 percent of women used e-cigarettes during pregnancy as compared to 5.6 percent who used cigarettes. Of the e-cigarette users, 74.6 percent reported switching to e-cigarettes when they learned they were pregnant.³⁰

Studies have evaluated beliefs and attitudes about e-cigarettes, including reasons for trying e-cigarettes. Among adolescents and young adults, top reasons for e-cigarette experimentation are curiosity, appealing flavors, and peer influences.³¹ PATH Study Wave 1 data showed that youth (12–17 years) also reported using e-cigarettes because of their appealing flavors, but also because they may be less harmful than cigarettes to both themselves and to others.³² Longitudinal surveys from middle and high school students found that several reasons for trying

[◇] Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

e-cigarettes predicted continued use, including low cost, the ability to use e-cigarettes anywhere, and using e-cigarettes to quit smoking combustible cigarettes.³³ An online survey of experienced adult e-cigarette users found that their reasons for use were facilitation of smoking cessation, overall health improvement, and reduced cost.³⁴ Focus group research of current and former smokers found that older adults (1) use e-cigarettes for smoking cessation (although few were successful) and for use in no-smoking areas, (2) have false perceptions about the safety of e-cigarettes, and (3) believe that marketing efforts promote dual use with cigarettes and are renormalizing smoking through the presentation of socially desirable behaviors.³⁵ Other focus group research of adult e-cigarette users found that although participants expressed positive attitudes about e-cigarettes, including the belief that e-cigarettes were likely less harmful than conventional cigarettes, they also reported a lack of information and knowledge about e-cigarettes.³⁶

Researchers have studied e-cigarette flavors and appeal as well. Results from the 2014 NYTS on flavored tobacco product use in the past 30 days among middle and high school students show that an estimated 3.3 million youth tobacco users reported flavored tobacco product use in the past 30 days.³⁷ PATH Study Wave 1 data showed that 81 percent of youth (aged 12–17 years) who have ever used (i.e., ever tried even one or two times) electronic nicotine delivery systems (ENDS) reported that their first product used was flavored. Similarly, 79.8 percent of youth current tobacco users in the PATH Study reported using a flavored tobacco product in the past 30 days, including 85.3 percent of ENDS users.³⁸ E-cigarettes that have sweet flavors are most popular among adolescents.³⁹ Some flavors may appeal to youth more than others: researchers found that adolescents reported greater interest in trying e-cigarettes flavored like menthol, candy, or fruit compared with tobacco; adolescents also believed that fruit-flavored e-cigarettes are less harmful to their health than those flavored like tobacco.⁴⁰ Researchers examined how the use of flavored e-cigarettes varied between youth, young adults, and older adults. Compared to older adults, youth and young adults preferred flavors other than tobacco. Among adults, the use of tobacco flavor at initiation was common among dual users, while other flavors were more common among former cigarette smokers.⁴¹ Investigators who studied the reasons for flavored e-cigarette use among current adult e-cigarette users found that flavors may increase the rewarding and possible addictive effects of e-cigarettes.⁴²

Marketing strategies, advertisements, and perceptions about e-cigarettes also have been a research focus. PATH Study Wave 1 data showed that susceptibility levels among youth (12–17 years) were comparable for cigarettes and e-cigarettes (28.6 percent and 27.4 percent, respectively).⁴³ Youth were found to be receptive to e-cigarette advertising. PATH Study Wave 1 data showed that 28 percent to 33 percent of youth were found to be receptive to advertising for e-cigarettes. E-cigarette ads shown on television had the highest recall. Among cigarette-susceptible adolescents, receptivity to e-cigarette advertising was higher than for cigarette advertising.⁴⁴ Researchers examined marketing practices used to promote e-cigarettes. One study investigated point-of-sale marketing practices near alternative high schools in Southern California and found that 70 percent of stores sold e-cigarettes.⁴⁵ Researchers also examined adult susceptibility and receptivity to e-cigarette advertising and marketing.

Among nonsmokers, exposure to tobacco advertising and receipt of tobacco coupons were related to measures of e-cigarette susceptibility.⁴⁶ Communications about e-cigarettes, including those in advertisements and on social media, may inform health communication and education efforts. Researchers found that daily smokers who viewed e-cigarette commercials with vaping visuals reported a greater urge to smoke and a greater incidence of smoking a tobacco cigarette than those viewing ads with no vaping visuals.⁴⁷ Former smokers viewing ads with vaping visuals reported lower intentions to abstain from smoking. Investigators examined message content on Twitter from e-cigarette brands and found that flavor-related posts (as compared to non-flavor-related posts) were retweeted at significantly higher rates by e-cigarette brands and other Twitter users.⁴⁸ Researchers studied a sample of YouTube e-cigarette videos and found that 94 percent were positive, 4 percent were neutral, and only 2 percent were negative; of the positive videos, 84.3 percent contained web links for e-cigarette purchase and 71.4 percent claimed that e-cigarettes were healthier than conventional cigarettes.⁴⁹

Research also suggests that social interactions are a popular way smokers share information about e-cigarettes with others. Investigators analyzed data gathered as part of a graphic health warning study of adult smokers in North Carolina and California to describe smokers' social interactions related to e-cigarettes and recommendations for use; in the past 30 days, 45 percent reported talking to at least one person about e-cigarettes, and nearly one-third (27 percent) recommended them; smokers recommended e-cigarettes to cut back on smoking (57 percent), to quit smoking (48 percent), for health reasons (36 percent), and for fun (27 percent).⁵⁰

Research has been conducted with regard to study methodologies and e-cigarette chemistry. Methods have been developed to separate the free-base form of nicotine, which is more readily absorbed than the protonated form of nicotine in e-cigarette liquids and aerosols. Previous studies had measured total nicotine only and, therefore, had not accurately measured the concentration of nicotine that users would absorb.⁵¹ Another methodology study identified autofluorescence of e-liquids (350–402 nm) as a marker for e-cigarette aerosol, which can be used as a marker of e-cigarette aerosol deposition.⁵² Carbonyl compounds (acrolein) in e-cigarette aerosol generally have been detected using 2,4-dinitrophenylhydrazine (DNPH) trapping, which may yield low recoveries. Authors used nuclear magnetic spectroscopy, a method that eliminates aerosol processing for identification of the degradation products of propylene glycol (PG) and vegetable glycerin (VG). The authors identified several new compounds from PG and VG degradation, and proposed molecular degradation pathways.⁵³ This methodology further identified and characterized the formation of formaldehyde hemiacetal compounds from the degradation of PG and VG, for which the health effects are not yet known. Formaldehyde hemiacetal is formed from the reaction of formaldehyde under conditions found in DNPH trapping, which therefore underestimates the amount of formaldehyde present in e-cigarette aerosols.⁵⁴

Several studies evaluated topography and use behavior as well as nicotine pharmacokinetics, which are important for determining abuse liability. One study found differences in e-cigarette and cigarette topography during prescribed use: experienced e-cigarette users took larger, longer puffs with lower flow rates of the e-cigarette compared to combustible cigarette topography in smokers from a previous study.⁵⁵ Another study characterized e-cigarette use patterns during *ad libitum* use and found that e-cigarette use patterns differ from cigarette smoking, leading to differences in nicotine delivery. Although the plasma nicotine boost (peak) following e-cigarette use was similar to smoking a cigarette, longer time to reach the peak resulted in an overall nicotine delivery level similar to smoking three to four cigarettes.⁵⁶ Two studies investigated nicotine pharmacokinetics during prescribed use. Experienced e-cigarette users were found to achieve plasma nicotine concentrations that exceeded those of combustible cigarettes,⁵⁷ whereas e-cigarette-naive smokers were found to achieve plasma nicotine concentrations comparable to those obtained through use of combustible cigarettes.⁵⁸

Levels of ingredients and harmful and potentially harmful constituents (HPHCs) in e-cigarette refill solutions, cartridges, aerosols, and environmental emissions may vary considerably, and the nicotine level listed on e-cigarette cartridge and refill solution labels may be significantly different from measured values.⁵⁹ Studies have found that e-cigarette aerosol and some flavored e-liquids induce toxicity, oxidative stress, and inflammatory responses in human lung epithelial cells, in human fetal lung fibroblast cells, and in lungs of mice exposed to e-liquid aerosol.⁶⁰ Diacetyl and other flavor chemicals associated with toxicity have been detected in e-cigarette aerosol. When inhaled, these flavoring chemicals may lead to respiratory-related adverse effects.⁶¹ Toxicological studies of flavored e-liquids showed that three e-liquids containing cinnamaldehyde induced a dose-dependent immunosuppressive effect on respiratory immune cells, which can increase the susceptibility to respiratory-related adverse effects.⁶²

Researchers have examined the number and nature of e-cigarette overheating, fires, and explosions in the United States. One hundred reference sources identified 92 overheating, fires, and explosion events. Almost half (49 percent) of these events injured people, and some of the events resulted in life-threatening injury, permanent disfigurement, and disability.⁶³

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Barrington-Trimis JL, Urman R, Berhane K, et al. E-cigarettes and future cigarette use. *Pediatrics*. 2016 Jul;138(1).

Researchers used data from the Children's Health Study, a prospectively followed cohort in Southern California, to investigate whether e-cigarette use increases the risk of cigarette initiation among adolescents. Researchers collected initial data on 11th and 12th grade students and followed up with a subset of participants (146 never-smoking e-cigarette users and 152 never-smoking, never e-cigarette users) 16 months later. Cigarette initiation during follow-up was reported by 40.4 percent of e-cigarette users and 10.5 percent of never users. E-cigarette users were more than six times as likely to initiate cigarettes as never e-cigarette users. E-cigarette users also were five times more likely to initiate use of any combustible product, including hookah, cigars, or pipes. The researchers concluded that e-cigarette use in never-smoking youth may increase risk of subsequent initiation of cigarettes and other combustible products.

PUBLICATION HIGHLIGHT

El-Hellani A, El-Hage R, Salman R, Talih S, Shihadeh A, Saliba NA. Carboxylate counteranions in electronic cigarette liquids: influence on nicotine emissions. *Chem Res Toxicol*. 2017 Aug 21;30(8):1577-1581.

Authors measured e-cigarette aerosol to show that thermally unstable carboxylate ions such as citric acid decompose with higher power of e-cigarettes (4.6W) to yield aerosols that are enriched with the free-base form of nicotine that is more readily absorbed. Therefore, counteranions of protonated nicotine salts in e-liquids play a role in the delivery profile of nicotine in e-cigarette aerosols.

PUBLICATION HIGHLIGHT

Morean ME, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine concentration of e-cigarettes used by adolescents. *Drug Alcohol Depend.* 2016 Oct 1;167:224-227.

Investigators conducted cross-sectional surveys in four Connecticut high schools and two middle schools in spring 2014 and evaluated e-cigarette nicotine concentrations used by 513 past-30-day e-cigarette users. Among respondents, 37.4 percent reported using nicotine e-liquid, 28.5 percent reported using nicotine-free e-liquid, and 34.1 percent reported not knowing their e-liquid nicotine concentration. Nicotine users included more cigarette smokers and heavier e-cigarette users than those in the other two groups. Nicotine users also were more likely to be male and to purchase e-cigarettes online or from tobacco shops.

PUBLICATION HIGHLIGHT

Ramôa CP, Hiler MM, Spindle TR, et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. *Tob Control.* 2016 Apr;25(e1):e6-9.

Researchers examined nicotine delivery of ENDS in experienced e-cigarette users and found that nicotine delivery can exceed that of combustible cigarettes. Sixteen participants used e-cigarettes during four sessions, which differed by e-liquid nicotine concentration (0, 8, 18, or 36 mg/ml). In each session, participants completed two 10-puff sessions separated by 1 hour. Blood samples were obtained to determine plasma nicotine concentration. The study demonstrated a relationship between e-liquid nicotine concentration and plasma nicotine concentration in experienced users. Results showed that experienced users may achieve nicotine delivery from some e-cigarettes that may surpass that of combustible cigarettes.

PUBLICATION HIGHLIGHT

Soussy S, El-Hellani A, Baalbaki R, Salman R, Shihadeh A, Saliba NA. Detection of 5-hydroxymethylfurfural and furfural in the aerosol of electronic cigarettes. *Tob Control.* 2016 Nov;25(Suppl 2):ii88-ii93.

Sweet flavors are popular among ENDS users. The authors noted that thermal degradation of sugars has been reported to yield toxic furans including 5-hydroxymethylfurfural and furfural. Studies have indicated furans can act as respiratory irritants and possible carcinogens. Using a novel analytical gas chromatography-mass spectrometry (GC-MS) method, the authors tested in-house prepared e-liquids containing sucrose, glucose, and sorbitol for the presence of toxicants. The authors detected higher levels of 5-hydroxymethylfurfural and furfural when the e-liquid contained sucrose and glucose but not sorbitol, which could raise concerns for public health.

PUBLICATION HIGHLIGHT

Williams RS, Derrick J, Ribisl KM. Electronic cigarette sales to minors via the internet. *JAMA Pediatr.* 2015;169(3):e1563.

E-cigarettes are increasingly used by U.S. teenagers and may be easily accessible despite age restrictions on purchases. Researchers examined the extent to which minors are purchasing e-cigarettes online and assessed compliance with North Carolina's e-cigarette age verification law. Eleven nonsmoking teens (aged 14–17) attempted to purchase e-cigarettes from 98 online vendors. Eighteen purchase attempts failed for reasons other than age verification; of the 80 remaining attempts, only five were rejected following age verification by vendors. Minors received e-cigarette deliveries from more than three-quarters (76.5 percent) of purchase attempts. None of the delivery companies attempted to verify age upon delivery, and 95 percent of orders were left at the door. Findings indicate that minors are easily able to purchase e-cigarettes online.

CIGARS

From FY10 to FY17, 36 articles based on CTP-funded research related to large cigars, 55 articles related to little cigars, 39 articles related to cigarillos, and 23 articles related to cigars (unspecified) were published in peer-reviewed journals. (*Note:* These cigar product subcategories are not mutually exclusive, meaning that two or three types of cigar products might have been addressed in a single article.) Topics fell within seven CTP research domains (addiction; communications; economics and policy; health consequences; knowledge, attitudes, and behaviors; marketing; and toxicity and carcinogenicity).

Examples of specific study topics include mortality and economic costs associated with cigar use; impact of flavors on cigar use among youth and young adults; trends in the use of cigars, little cigars, and cigarillos; biomarkers of exposure among cigar smokers; impairment of endothelial function due to secondhand smoke from little cigars; nicotine and carbon monoxide exposure from inhalation of cigarillo smoke; and toxic metals in little cigar tobacco.

Research Summary:[◇] Studies have found that the health and economic burden of cigar smoking is significant; this burden may increase over time due to increasing trends in consumption of cigars, particularly little cigars and cigarillos.⁶⁴ Cigar smoking is associated with many of the same health risks as cigarette smoking, including all-cause mortality, several types of cancer (oral, esophageal, pancreatic, laryngeal, lung), and cardiac conditions (coronary heart disease, aortic aneurysm).⁶⁵ Cigar smokers have higher cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and lead concentrations than nontobacco users; NNAL concentrations in daily cigar smokers are comparable to those in daily cigarette smokers.⁶⁶ Furthermore, exposure to little cigar secondhand smoke impairs arterial flow-mediated dilation (a marker of cardiac risk) at least equal to that of cigarette secondhand smoke.⁶⁷ Research on the effects of little cigar smoking on bronchial epithelial cells has found that little cigars are more toxic than cigarettes, possibly because they produce more chemicals than cigarettes.⁶⁸ In another study, researchers characterized 20 large cigar and cigarillo products for physical properties (i.e., weight, length, diameter), filler nicotine content, and tobacco pH (for the determination of free nicotine).⁶⁹ The products exhibited wide variation in product size and nicotine content, but similar tobacco pH; when a subset of products was analyzed again, the researchers found considerable within-brand variance in nicotine content and concentration between the first and second analyses. This study highlights the challenges in cigar research as well as the need to characterize the nicotine and tobacco content of cigars before they are used in clinical studies.

Flavors may be contributing to the growth in cigar popularity in the United States, particularly among certain subpopulations.⁷⁰ The variety of sweet and fruit-flavored little cigars and cigarillos and packaging cues influence young adults' affect, susceptibility to, and initiation of little cigar and cigarillo use; flavored products also may prompt a switch from cigarettes to flavored little cigars and cigarillos.⁷¹

[◇] Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health*. 2015;15:390.

Researchers conducted a systematic literature review and identified 22 studies published prior to June 2014 that examined the association between cigar smoking and all-cause and smoking-related mortality. Primary cigar smoking—defined as current, exclusive cigar smoking with no history of smoking cigarettes or pipes—was associated with higher all-cause mortality, several types of cancer (oral, esophageal, pancreatic, laryngeal, lung), and cardiac conditions (coronary heart disease, aortic aneurysm). Primary cigar smoking also was associated with strong dose effects (as measured by cigars per day and inhalation level) for oral, esophageal, laryngeal, and lung cancers. Primary cigar smokers who reported no inhalation still exhibited higher elevated relative mortality risk for oral, esophageal, and laryngeal cancers. The researchers concluded that cigar smoking is associated with many of the same health risks as cigarette smoking.

PUBLICATION HIGHLIGHT

Klupinski TP, Strozier ED, Friedenber DA, Brinkman MC, Gordon SM, Clark PI. Identification of new and distinctive exposures from little cigars. *Chem Res Toxicol*. 2016 Feb 15;29(2):162-168.

Investigators compared four little cigar products and four cigarette products to identify chemical compounds that are either unique to (i.e., new exposures) or more abundant in (i.e., distinct exposures) little cigars. Total particulate matter samples were collected from machine-generated mainstream smoke, and extracts were analyzed using two-dimensional gas chromatography-time-of-flight mass spectrometry. More than 25,000 components were detected across the complete data set. Ambrox was found to be a new exposure, and 3-methylbutanenitrile and 4-methylimidazole were found to be distinctive exposures. Concentrations of these compounds in little cigar mainstream smoke were approximately 0.4, 0.7, and 12 µg/rod, respectively.

PUBLICATION HIGHLIGHT

Nasim A, Guy MC, Soule EK, Cobb CO, Blank MD, Eissenberg T. Characteristics and patterns of Black & Mild use among African American smokers. *Nicotine Tob Res.* 2016;18(5):842-849.

Cigarillo smoking has increased in recent years, especially among smokers in vulnerable population groups. Researchers evaluated patterns of cigarillo use among 331 African American Black & Mild cigarillo smokers. Five classes of use patterns were identified. Three classes (daily-hypers, daily-flavored, and heavy-daily-hypers) exhibited average daily consumption rates of 2.7 to 8.9 cigarillos per day. Non-daily-hypers and non-daily-flavored classes smoked an average of less than one cigarillo per day. Both daily and non-daily users included smokers who indicated a preference for flavored tobacco and who modified products (e.g., hipping, blunting). Findings indicate that tailored interventions reflecting user differences should be developed to reduce cigarillo smoking prevalence.

PUBLICATION HIGHLIGHT

Sterling K, Fryer C, Pagano I, Jones D, Fagan P. Association between menthol-flavoured cigarette smoking and flavoured little cigar and cigarillo use among African-American, Hispanic, and white young and middle-aged adult smokers. *Tob Control.* 2016 Nov; 25(Suppl 2):ii21-ii31.

Flavor additives in tobacco products may influence dual use of flavored products. Investigators studied the association among mentholated cigarette use, risk perceptions of flavor additives in little cigars and cigarillos (LCCs), and flavored LCC smoking behavior in 964 adult current cigarette smokers. They found that compared to occasional non-menthol cigarette smokers, daily menthol smokers were nearly twice as likely to smoke flavored LCCs (odds ratio [OR]=1.75), a relationship that held for males, blacks/African Americans, and Hispanics/Latinos. Positive perceptions of menthol, clove, spice, and alcohol flavors in LCCs were associated with increased odds of flavored LCC use.

PUBLICATION HIGHLIGHT

Liu J, Wang X, Narayan S, Glantz S, Schick S, Springer M. Impairment of endothelial function by little cigar secondhand smoke. *Tob Regul Sci.* 2016 Jan;2(1):56-63.

Anesthetized, male Sprague-Dawley rats were exposed to cigarette or little cigar secondhand smoke. Swisher Sweets little cigars (100 mm) and Marlboro cigarettes (85 mm) were smoked to completion using ISO 3308 laboratory smoking conditions standardized for each product. Arterial flow-mediated dilation (FMD) was measured as a marker of cardiac risk; impairment of vascular endothelial function is one of the most acute health consequences of cigarette smoke. Exposure to little cigar secondhand smoke led to impairment of vascular function that is at least equal to that of cigarette secondhand smoke.

SMOKELESS TOBACCO AND SNUS

From FY10 to FY17, 74 articles related to smokeless tobacco (snuff, loose, and chew) and 28 articles related to snus based on CTP-funded research were published in peer-reviewed journals. Topics fell within all eight CTP research domains (addiction; chemistry and engineering; communications; economics and policy; health consequences; knowledge, attitudes, and behaviors; marketing; and toxicity and carcinogenicity).

Examples of specific study topics include patterns and trends in smokeless tobacco use, impact of smokeless tobacco packaging and labeling on perceptions and beliefs, smokeless tobacco abuse liability, awareness and perceptions of snus, snus availability and sales to minors, vulnerability to smokeless tobacco use in individuals with major depressive disorder, and measurement of aflatoxin B1 in smokeless tobacco products. Analyses of HPHC content of various smokeless products, biomarkers of exposure to smokeless products in the human population, and the role of the oral microbiome in tobacco-specific nitrosamine (TSNA) formation also have added to our understanding of the public health burden of smokeless tobacco use.

Research Summary:◊ Smokeless tobacco use is less prevalent in the U.S. population (5 percent) than use of combustible tobacco products; however, use patterns are not distributed evenly across subpopulations or geographic regions. An analysis of the nationally representative PATH Study Wave 1 data (n=32,320 adults) found that smokeless tobacco use was most common among men, younger adults, non-Hispanic whites, and nonurban respondents.⁷² Researchers compared urban/rural and regional differences in U.S. tobacco use using 2012–2013 data from the National Survey on Drug Use and Health; they found that cigarette, chew, and snuff use was higher in rural areas, with differences particularly pronounced in certain regions, such as the South Atlantic states.⁷³ Furthermore, use and poly-use patterns vary by type of smokeless product. In the PATH Study analysis, pouched snus users were more likely to report non-daily and poly-tobacco use than users of other smokeless products; compared to daily smokeless users, respondents who used smokeless tobacco on some days were more likely to be current cigarette smokers.⁷⁴ Several of these CTP-OS research activities have supported the center’s communication and outreach strategies, such as expanding its award-winning “The Real Cost” campaign to educate rural, white male teenagers about the negative health consequences associated with smokeless tobacco use.

Studies have found that, in general, smokeless tobacco product use is not associated with smoking reduction or cessation.⁷⁵ Switching from exclusive smoking to exclusive smokeless tobacco use is limited (adults: 0–1.4%, adolescents: 0.8–3.8%); switching from exclusive smokeless tobacco use to exclusive smoking is much more common (adults: 0.9–26.6%, adolescents: 16.6–25.5%).⁷⁶

◊ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

The harm perceptions and awareness and behaviors of individuals toward use of smokeless tobacco products significantly influences smokeless product use and, therefore, exposure to harmful constituents. An analysis of three cycles (2012, 2014, and 2015) of the Health Information National Trends Survey (HINTS) data found that a majority of adults do not believe that smokeless tobacco products are less harmful than cigarettes, although differences in relative harm perceptions existed for specific demographic subgroups; males, individuals with higher education or income, and tobacco users were more likely to believe that smokeless tobacco is less harmful than cigarettes.⁷⁷ However, an analysis of PATH Study Wave 1 data indicates that youth aged 12 to 17 were more likely to rate smokeless tobacco as less harmful than cigarettes on both indirect and direct measures of harm (29.7 percent and 11.7 percent, respectively).⁷⁸ Among young adults who are aware of snus, 16.3 percent believe that snus can facilitate smoking cessation, 17.3 percent believe that snus is less harmful than cigarettes, and 11.3 percent believe that snus is less addictive than cigarettes.⁷⁹ Current cigarette smokers are about four times more likely than nonsmokers to report snus awareness and use; correlates of snus awareness and use include male gender, full-time employment, and younger age.⁸⁰ Smokeless tobacco pack characteristics, including graphic warning labels and corporate branding, have a measurable effect on perceptions of health risk and product appeal.⁸¹ It is important to be aware that tobacco product users and nonusers have different perceptions, behaviors, and awareness of smokeless tobacco products.

Smokeless tobacco use results in nicotine exposure to users and is addictive.⁸² In addition to the harm of nicotine addiction, smokeless tobacco has dangerous levels of the (S)-enantiomer of N'-nitrosonornicotine (NNN), an esophageal and oral carcinogen.⁸³ Investigators measured the NNN levels and water content of 34 smokeless tobacco products sold in the United States in 2015. NNN levels ranged from 0.64 to 12.0 µg/g dry weight; dry snuff had the highest NNN levels (>5 µg/g dry weight). However, NNN levels for six moist snuff products decreased between 2004 and 2015.⁸⁴ Changes over time in smokeless tobacco product content are important when considering population health. Internal exposure provides a more accurate measuring of exposure in the population. Internal exposure refers to a measure of internal chemical loading—a measure of a tobacco constituent in urine, blood, or other biological matter such that there is certainty that the toxic constituent of the tobacco product was transferred to the user. Investigators analyzed tobacco exposure biomarkers for 23,684 adult participants in the National Health and Nutrition Examination Survey and found that, compared to exclusive cigarette smokers, exclusive smokeless tobacco users have higher observed levels of exposure to nicotine and carcinogenic TSNAs, as measured by cotinine and NNAL (a surrogate for the nicotine-derived nitrosamine ketone [NNK]) biomarker concentrations.⁸⁵ These data demonstrate that measures of both external (smokeless tobacco product) and internal (biomarker) exposure are necessary to understand the population health impact of smokeless tobacco product use.

Researchers are learning that the innate oral microbiome, which may be influenced by age, diet, and tobacco product use, influences nicotine and HPHC/TSNA metabolism and, therefore, affects individual (internal) exposures to these constituents.⁸⁶ The impact of smokeless tobacco use on the health and stability of the oral microbiome is also an active area of study. In an experimental setting (an in vitro study), investigators analyzed metabolic alterations in the oral bacterium *Capnocytophaga sputigena* resulting from smokeless tobacco exposure and assessed the bacterium's capability to metabolize nicotine; they found that smokeless tobacco extracts caused oxidative stress in the bacterium and that nicotine and TSNA metabolism is influenced by innate oral microbes.⁸⁷ In another study, investigators created a baseline microbiological profile of smokeless tobacco products by analyzing 90 samples representing 15 common smokeless tobacco products. Compared to snus and some chewing tobacco products, moist snuff products exhibited higher levels of bacteria and greater diversity of bacterial populations representing greater potential for external exposure (the toxic chemical constituents or microbial constituents of tobacco products themselves, measured prior to consumption); several identified species have the potential to cause opportunistic infections and reportedly convert nitrates to nitrites, a step in TSNA formation.⁸⁸

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Klein EG, Quisenberry AJ, Shoben AB, et al. Health warning labels for smokeless tobacco: the impact of graphic images on attention, recall, and craving. *Nicotine Tob Res.* 2017 Oct 1; 19(10):1172-1177. [Epub 2017 Jan 28]

More research can help clarify the impact of graphic health warnings (GHWs) on smokeless tobacco product users. Researchers asked 142 rural male smokeless tobacco users to view a smokeless tobacco advertisement with a GHW or a text-only warning. Eye-tracking equipment measured viewing time, and participants were asked to report craving and recall health warning content. The researchers found that GHW viewers spent a greater proportion of viewing time on the health warning compared to text-only warning viewers (30 percent vs. 24 percent, respectively). Although significant differences in total advertisement viewing duration did not exist, GHW viewers had increased recall of health warning messages compared to the text-only warning viewers (76 percent vs. 53 percent, respectively, had any warning message recall). Craving after advertisement exposure was lower for GHW viewers compared to text-only warning viewers, but this difference was not statistically significant.

PUBLICATION HIGHLIGHT

Mays D, Moran MB, Levy DT, Niaura RS. The impact of health warning labels for Swedish snus advertisements on young adults' snus perceptions and behavioral intentions. *Nicotine Tob Res.* 2015;18(5):1371-1375.

Researchers examined the impact of five Swedish snus warning labels on 517 U.S. young adult nonsmokers and smokers aged 18–30. Participants were randomized to one of five experimental advertisement and warning label conditions: (1) control (no warning); (2) addiction (warning conveying the addictiveness of snus); (3) harm (warning conveying the potential harms of snus); (4) harm reduction (warning conveying the potential reduced harms of snus compared to cigarettes); and (5) harm reduction switch (warning communicating the potential reduced harms of snus when switching completely from cigarettes to snus). Participants in the two harm reduction conditions perceived that snus was less harmful than cigarettes compared to participants in the other three conditions. Nonsmokers in the harm reduction condition reported fewer thoughts about not using snus compared to nonsmokers in the harm condition. Intentions to use snus were low overall. Findings suggest that warnings about the reduced harm of snus compared to cigarettes may affect harm perceptions in both smokers and nonsmokers. Additional research is needed to understand the impact on use intentions.

PUBLICATION HIGHLIGHT

Persoskie A, Nguyen AB, Kaufman AR, Tworek C. Criterion validity of measures of perceived relative harm of e-cigarettes and smokeless tobacco compared to cigarettes. *Addict Behav.* 2017 Apr;67:100-105.

Researchers evaluated the validity of direct and indirect measures of perceived harm of two products—e-cigarettes and smokeless tobacco—compared to cigarettes. Direct measures allow participants to explicitly compare the harmfulness of each product (e.g., people rate the harm of using e-cigarettes as lower or higher than the harm of using cigarettes in a single question). Indirect measures require participants to rate the harmfulness of each product separately, after which ratings are compared (e.g., people rate the harms of using e-cigarettes and cigarettes on two separate questions, and then ratings are compared to determine whether the harm for one product was rated lower than the other). Logistic regression analysis assessed whether measures were associated with variables including ever trying e-cigarettes, ever trying snus, and smokeless tobacco use status. The direct measures of harm were more consistently associated with the variables than were the indirect measures. On the direct measures, 11 percent of adults rated smokeless tobacco as less harmful than cigarettes. These findings suggest that direct measures provide valid information about individuals' harm beliefs.

PUBLICATION HIGHLIGHT

Song MA, Marian C, Brasky TM, Reisinger S, Djordjevic M, Shields PG. Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products. *Toxicol Lett.* 2016 Mar 14;245:68-77.

Analyses of chemical composition and toxicity are helpful to compare conventional and newer smokeless tobacco products (STPs) and their tobacco-specific nitrosamine (TSNA) yields. Researchers analyzed seven conventional and 12 low-TSNA moist snuff products purchased in the United States, Sweden, and South Africa for 18 chemical constituents (classified by the International Agency for Research on Cancer as carcinogens), pH, nicotine, and free nicotine. Compared to low-TSNA moist snuff products, conventional products had higher ammonia, benzo[a]pyrene, cadmium, nickel, nicotine, nitrate, and TSNA levels. However, the conventional products had lower arsenic in dry weight content and per mg nicotine and lower levels of lead and chromium. Differences among products were reduced when they were analyzed on a per mg nicotine basis. Estimated probabilistic cancer risks were 3.77-fold or 3-fold higher in conventional products compared to low-TSNA products under dry weight and per mg nicotine content analyses, respectively. In vitro testing indicated that low-TSNA products in South Africa and the United States had lower toxicity than conventional products, and low-TSNA and conventional products in Sweden had similar toxicity.

PUBLICATION HIGHLIGHT

Stepanov I, Yershova K, Carmella S, Upadhyaya P, Hecht SS. Levels of (S)-N'-nitrosonornicotine in U.S. tobacco products. *Nicotine Tob Res.* 2013;15(7):1305-1310.

N'-nitrosonornicotine (NNN) is an esophageal and oral carcinogen present in tobacco products. In particular, the (S)-enantiomer of NNN is a highly potent carcinogen, but data on (S)-NNN content and its contribution to measured NNN levels in tobacco products would be useful. Using chiral gas chromatography analysis, researchers analyzed levels of the (S)-NNN in 37 tobacco products (conventional smokeless tobacco/moist snuff, novel smokeless tobacco products, and cigarette tobacco filler) currently marketed in the United States. Among all products, (S)-NNN averaged 62.9 ± 6.3 percent of NNN. The absolute amount of (S)-NNN averaged 1.26 ± 0.5 $\mu\text{g/g}$ tobacco in conventional moist snuff, 0.70 ± 0.2 $\mu\text{g/g}$ tobacco in novel smokeless products, and 1.36 ± 0.6 $\mu\text{g/g}$ tobacco in cigarette filler. Results indicate that (S)-NNN is the predominant NNN enantiomer in these products, supporting the importance of NNN reduction or elimination in tobacco products.

HOOKAH (WATERPIPE)

From FY10 to FY17, 56 articles related to CTP-funded research on waterpipe (hookah) were published in peer-reviewed journals. Topics fell within six CTP research domains (addiction; communications; economics and policy; health consequences; knowledge, attitudes, and behaviors; and marketing).

Examples of specific study topics include trends in and prevalence and intensity of waterpipe use, young adults' risk perceptions of waterpipe relative to cigarettes, waterpipe use among sexual minority adults, prevalence and predictors of waterpipe use, nicotine/tobacco dependence associated with waterpipe use, and air quality in New York City hookah bars.

Research Summary:◇ An analysis of data from the most recent National Adult Tobacco Survey (2013–2014) indicates that approximately 10.0 million adults aged 18 and older reported using hookah.⁸⁹ Young adults aged 18–24 years reported much higher prevalence of using hookah every day, some days, or rarely (20.2%; 95% confidence interval [CR], 18.7–21.6) compared to the prevalence among individuals aged 25–44 years (5.0%; 95% CI, 4.6–5.4) and those aged 45–64 years (0.4%; 95% CI, 0.3–0.5).⁹⁰ PATH Study Wave 1 data indicate that 16.4 percent of adults reported ever smoking tobacco from a hookah; of those, 31.9 percent reported smoking hookah within the past year, nearly a quarter of whom were daily, weekly, or monthly users.⁹¹ PATH Study Wave 1 data also indicate that among adolescents (aged 12–17 years) who had used hookah, 19.0 percent were exclusive hookah users, 61.1 percent were susceptible to using e-cigarettes, 51.7 percent were susceptible to using cigarettes, 40.1 percent were susceptible to using cigars, and 17.8 percent were susceptible to using smokeless tobacco.⁹² In the 2015 National Youth Tobacco Survey, hookah was used by 7.2 percent of high school students and 2.0 percent of middle school students, indicating that an estimated 1.2 million middle and high school students used hookah.⁹³ The Southern California Children's Health Study of alternative tobacco product use found that hookah/waterpipe tobacco use had the highest current use (10.7 percent) among 11th and 12th graders.⁹⁴ Nationally, approximately 18.2 percent of young adults use hookah, and openness among all young adults to using non-cigarette tobacco products is greatest for hookah (28.2 percent).⁹⁵ PATH Study Wave 1 data on 388 pregnant women (aged 18 years and older) indicate that prevalence of current and prior use of hookah was 2.5 percent, compared to a prevalence for cigarette smoking of 13.8 percent, followed by e-cigarettes (4.9 percent), cigars (2.3 percent), and below 1 percent for all other tobacco products.⁹⁶

Among U.S. adults, research indicates variation in the prevalence of hookah use, factors associated with hookah smoking, and harm perceptions.⁹⁷ Adults who used non-cigarette tobacco products, such as cigars, little cigars, cigarillos, and e-cigarettes, had higher odds of hookah smoking than those who did not. Adults with some college education, those with a college degree or more, and those identified as non-Hispanic other were more likely to be ever hookah smokers.

◇ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

Being a young adult, college-educated, a never smoker, and an ever hookah smoker were factors associated with lower perceptions of harm compared to combustible cigarettes. An analysis of PATH Study Wave 1 data found evidence of co-occurring hookah use, substance use, and mental health problems among youth; among ever hookah users, 84.6 percent reported alcohol or any drug use with 71.4 percent alcohol use, 65.5 percent marijuana use, 12.5 percent Ritalin/Adderall use, 17.0 percent painkiller/sedative use, and 9.9 percent other drug use.⁹⁸

The availability of flavored products seems to be an appealing feature of hookah smoking. Data from the 2014 National Youth Tobacco Survey show that 60.6 percent of respondents (1.02 million youth) had used flavored hookah tobacco;⁹⁹ 88.7 percent of youth ever hookah users reported that the first hookah product they had used was flavored; and 78.9 percent of youth reported product flavoring as a reason for use.¹⁰⁰ Data from the 2013 to 2014 National Adult Tobacco Survey found that an estimated 6.1 million hookah users (82.3 percent) used flavored products in the past 30 days; the most prevalent hookah flavors used were fruit flavors (74.0 percent).¹⁰¹

Study findings indicate that most waterpipe smokers are unaware of the potential risks of use,¹⁰² suggesting that users may not see a reason to quit. For example, an analysis of the 2012 National Youth Tobacco Survey data indicates that, compared to users of other tobacco products, current hookah users had the lowest prevalence of quit intentions (41.5 percent) and past-year quit attempts (43.7 percent).¹⁰³ Focus groups of hookah and little cigar and cigarillo users reveal that users do not perceive that health effects associated with the use of these products are serious or likely to happen, given their low use frequency and perceptions that they are less harmful than cigarettes.¹⁰⁴

However, research suggests health risks associated with hookah (waterpipe) use. Waterpipe smoking may support tobacco dependence through nicotine delivery; some smokers experience withdrawal when they abstain from waterpipe, alter their behavior to access a waterpipe, and have difficulty quitting.¹⁰⁵ Other health effects exist as well. A literature review revealed that waterpipe smoke contains significant concentrations of toxicants linked to dependence, heart disease, lung disease, and cancer in cigarette smokers; substances identified included nitric oxide, carbonylic compounds, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, heavy metals, primary aromatic amines, furanic compounds, volatile organic compounds, phenolic compounds, and 27 known or suspected carcinogens.¹⁰⁶ One study that evaluated toxicant exposure (carbon monoxide, nitric oxide, nicotine, volatile aldehydes, polycyclic aromatic hydrocarbons, and total particulate matter) in 22 pairs of waterpipe smokers who used a waterpipe individually and as a pair found that dyad smoking was associated with greater exposure to carbon monoxide, tar, nicotine, propionaldehyde, butyraldehyde, and anthracene.¹⁰⁷ Toxicant levels were measured in indoor air in hookah bars; a study of New York City hookah bars found that mean indoor air levels of air pollutants were as follows: black carbon, 4.1 $\mu\text{g}/\text{m}^3$; organic carbon, 237.9 $\mu\text{g}/\text{m}^3$; and carbon monoxide, 32 ppm.¹⁰⁸ Graphic health warning labels may mitigate hookah use: compared to daily cigarette smokers, hookah users were more than twice as likely to report that graphic labels would prompt them to consider not smoking.¹⁰⁹

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Ramo CP, Shihadeh A, Salman R, Eissenberg T. Group waterpipe tobacco smoking increases smoke toxicant concentration. *Nicotine Tob Res.* 2016 May;18(5):770-776.

Although laboratory research on waterpipe use has focused on individual users, group use is common. Researchers investigated the differences in toxicant exposure and smoke toxicant yield between individual and group waterpipe smoking. In this study, 22 pairs of waterpipe smokers used a waterpipe individually and as a pair. Compared to individual smokers, paired smokers expired less carbon monoxide, but nicotine exposure as measured by mean plasma nicotine concentration did not differ. However, smoking behaviors differed: when participants smoked in pairs, they took more puffs and had shorter interpuff intervals. Smoke produced by pairs yielded higher concentrations of several toxicants, which is possibly attributable to the differences in puffing behavior.

PUBLICATION HIGHLIGHT

Robinson J, Wang B, Jackson K, Donaldson E, Ryant C. Characteristics of hookah tobacco smoking sessions and correlates of use frequency among US adults: findings from Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine Tob Res.* 2017 Mar 9. [Epub ahead of print]

PATH Study Wave 1 data indicate that 16.4 percent of adults (aged 18 years and older) reported ever smoking tobacco from a hookah. Of those, 31.9 percent reported smoking hookah within the past year. Among 3,947 past-year hookah tobacco smokers, 10.7 percent were daily/weekly users, 13.7 percent were monthly users, 42.1 percent smoked every couple of months, and 33.5 percent smoked about once a year. Among daily/weekly hookah users, 66 percent were young adults (aged 18–24 years).

PUBLICATION HIGHLIGHT

Shihadeh A, Schubert J, Klaiany J, El Sabban M, Luch A, Saliba NA. Toxicant content, physical properties and biological activity of waterpipe tobacco smoke and its tobacco-free alternatives. *Tob Control*. 2015;24 Suppl 1:i22-i30.

The health effects of waterpipe use are not fully understood. Researchers analyzed the peer-reviewed literature published between 1991 and 2014 to review the chemical, physical, and biological properties of waterpipe smoke. The review revealed that waterpipe smoke contains approximately 300 chemicals, including significant concentrations of toxicants linked to dependence, heart disease, lung disease, and cancer in cigarette smokers. Substances identified in the literature include nitric oxide, carbonylic compounds, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, heavy metals, primary aromatic amines, furanic compounds, volatile organic compounds, phenolic compounds, and others; 27 known or suspected carcinogens were identified. When inhaled, waterpipe smoke produces cellular responses associated with pulmonary and arterial diseases. Waterpipe smoke generated by tobacco-free preparations contain equivalent or higher doses of toxicants (except for nicotine) and causes the same cellular effects as conventional products. Researchers concluded that this evidence base is sufficient to support public health interventions addressing waterpipe tobacco smoke as a serious inhalation hazard.

PUBLICATION HIGHLIGHT

Wackowski OA, Delnevo CD. Young adults' risk perceptions of various tobacco products relative to cigarettes: results from the National Young Adult Health Survey. *Health Educ Behav*. 2015;43(3):328-336.

This study explored risk perceptions of various tobacco products relative to traditional cigarettes with young adults. Researchers analyzed data from a nationally representative sample of young adults (aged 18–34 years; n=2,871 tobacco users and nonusers) participating in the 2011 National Young Adult Health Survey. Nearly one-quarter of the respondents (24.5 percent) believed that smoking from a hookah was less risky compared to cigarette smoking. Ever or current users of e-cigarettes, smokeless tobacco, and hookah were significantly more likely to have beliefs of lower risk than never product users. Compared to older young adults, younger young adults were more likely to rate e-cigarettes and hookah as being less risky and cigars and smokeless tobacco as being more risky.

DISSOLVABLES

Dissolvable tobacco products dissolve in the user's mouth and do not require spitting or discarding of the product. Dissolvables can be sold as lozenges, strips, or sticks, and some may look like candy. Like other tobacco products, dissolvable tobacco products contain nicotine and other harmful and potentially harmful constituents (HPHCs). Relatively few studies focused on dissolvables because they represent a small portion of the total tobacco market. From FY10 to FY17, 17 articles based on CTP-funded research related to dissolvables were published in peer reviewed journals. Topics fell within five CTP research domains (chemistry and engineering; economics and policy; health consequences; knowledge, attitudes, and behaviors; and marketing).

Examples of specific study topics include the prevalence, harm perceptions, and reasons for use; dissolvable use among middle and high school students; young adults' perceptions of dissolvable products; marketing of dissolvable products; pharmacokinetic characteristics and pharmacodynamic effects of dissolvable products; poison events associated with ingestion by young children; and use of electrophysiology to measure brain responses associated with dissolvable use.

Research Summary: ♦ Limited information exists regarding the characteristics of individuals who use dissolvables. In general, evidence suggests low appeal of dissolvables, although there is a concern that their candy-like form makes them attractive to young children (accidental exposure) as well as youth (experimentation) and that marketing of dissolvables may prompt tobacco initiation.¹¹⁰ A small survey of 22 rural male high school students found that dissolvables were not commonly used.¹¹¹ An analysis of National Adult Tobacco Survey data on openness to using non-cigarette tobacco products found that only 0.1 percent of respondents were current dissolvable users and only 1.5 percent of respondents were open to using dissolvables.¹¹² However, a focus group study on perceptions of emerging tobacco products among pregnant women and women planning a pregnancy found that participants thought dissolvable tobacco products offered a way to use tobacco during pregnancy discreetly and without stigma.¹¹³

Given dissolvables' small size, concerns exist about the risk of accidental ingestion by small children. A study of tobacco-related poison events involving young children in the United States found that, between January 2001 and October 2016, 36 calls to poison control centers involved dissolvable tobacco products.¹¹⁴ The number of these calls declined from 11 in 2009 to seven in 2015 and two in 2016; 27 (75 percent) were for children aged 2 and younger. Although risks do exist, the low uptake and use of dissolvables mitigates the population-level risk of accidental ingestion.

♦ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

A study published in 2016 found that high levels of sweeteners (including sucralose and sorbitol) are found in dissolvable products and are up to 25 times higher than those in confectionery products; the authors note that high sweetener levels are likely necessary to improve user tolerance of the unpleasant flavor of tobacco ingredients.¹¹⁵ Data on the pharmacokinetic characteristics and pharmacodynamic effects of dissolvable tobacco products are limited and inconclusive;¹¹⁶ several animal and human clinical studies are under way to evaluate the role of sweeteners, menthol, and other flavors on nicotine absorption and product use to address this question.

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Richardson A, Pearson J, Xiao H, Stalgaitis C, Vallone D. Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. *Am J Public Health.* 2014;104(8):1437-1444.

Researchers assessed awareness of, prevalence of, purchase of, harm perceptions of, and reasons for using noncombustible tobacco products (electronic nicotine delivery systems; snus; chewing tobacco, dip, or snuff; and dissolvables) among 1,487 current and former smokers from eight U.S. market areas. Findings indicated that although most respondents (96 percent) were aware of at least one noncombustible tobacco product, only 33 percent had used and 21 percent had purchased a noncombustible product. Respondents reported using noncombustible products to cut down on or quit cigarette use. However, noncombustible tobacco product use was not associated with smoking reduction or cessation, and snus was the only product associated with a higher likelihood of a quit attempt. Noncombustible tobacco product users were likely to endorse the product as being less harmful than cigarettes.

PUBLICATION HIGHLIGHT

Southwell BG, Kim AE, Tessman GK, MacMonegle AJ, Choiniere CJ, Evans SE. The marketing of dissolvable tobacco: social science and public policy research needs. *Am J Health Promot.* 2012;26(6):331-332.

Dissolvable tobacco products in the form of strips, orbs, sticks, and lozenges deliver nicotine by dissolving or disintegrating in a user's mouth. Researchers conducted a literature review and identified knowledge gaps regarding dissolvable tobacco products and developed associated public policy research questions. They found limited clinical data regarding the health effects of dissolvable tobacco use. Limited information exists regarding who uses dissolvables, although evidence suggests low appeal. Nevertheless, concerns exist that their similarity to candies makes them attractive to youth and that enhanced marketing efforts may prompt tobacco initiation. Given U.S. consumers' limited awareness of these products, consumer perceptions of their risks and benefits remain unclear. Potential future research topics include how real-world use of dissolvable products affects health; whether product design and marketing increase their social acceptability; the impact of packaging on use behaviors; and whether dissolvables encourage tobacco use among nonusers and youth and/or dual use among users of other tobacco products.

PUBLICATION HIGHLIGHT

Wang B, King BA, Corey CG, Arrazola RA, Johnson SE. Awareness and use of nonconventional tobacco products among U.S. students, 2012. *Am J Prev Med.* 2014;47(2 Suppl 1):S36-52.

Researchers assessed awareness and use of nonconventional tobacco products among U.S. students by analyzing data from the 2012 National Youth Tobacco Survey. Prevalence of awareness, ever use, and current use of e-cigarettes, hookah, snus, and dissolvables were calculated overall and by sex, school level, race/ethnicity, and use of conventional tobacco products (i.e., cigarettes, cigars, smokeless tobacco). Researchers found that about half (50.3 percent) of students were aware of e-cigarettes; prevalence of ever and current use of e-cigarettes was 6.8 percent and 2.1 percent, respectively. Awareness of hookah was 41.2 percent, and ever use and current use were 8.9 percent and 3.6 percent, respectively. Awareness, ever use, and current use of snus (32 percent, 5.3 percent, 1.7 percent, respectively) and dissolvables (19.3 percent, 2.0 percent, 0.7 percent, respectively) were generally lower than those of e-cigarettes or hookah. Awareness and use of nonconventional tobacco products were more common among conventional tobacco product users.

LOW NICOTINE

From FY10 to FY17, 39 articles based on CTP-funded research related to low nicotine were published in peer-reviewed journals. Topics fell within three CTP research domains (addiction; health consequences; and toxicity and carcinogenicity).

Examples of specific study topics include the effects of gradual vs. immediate implementation of nicotine reduction in cigarettes, methods to identify noncompliance in very low nicotine content (VLNC) cigarette trials, sex differences in the ability of VLNC cigarettes to reduce nicotine withdrawal, impact of low nicotine cigarettes on alcohol use and on smokers with conditions such as cardiovascular disease and affective disorders, the ability of individuals to discriminate between cigarettes with differing nicotine contents, and the smoking characteristics (e.g., topography) of VLNC cigarettes in schizophrenic patients and controls.

Research Summary: ♦ Study findings indicate that cigarettes with lower nicotine content result in reduced nicotine exposure, dependence, and number of cigarettes smoked compared to standard-nicotine cigarettes, with minimal compensatory smoking behavior.¹¹⁷ Data also suggest that by reducing nicotine in cigarettes, individuals who try smoking for the first time are less likely to initiate regular smoking, resulting in lower smoking rates and a lower smoking prevalence relative to individuals with a history of smoking cigarettes with regular nicotine content.¹¹⁸ The combination of VLNC cigarettes and nicotine patch is more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males, whereas females smoked the same number of VLNC cigarettes regardless of nicotine patch use.¹¹⁹ One study of VLNC cigarettes found that smokers with schizophrenia, a vulnerable population of cigarette smokers, altered their smoking behaviors in ways that indicated compensatory smoking to a greater degree than smokers without psychiatric illness (including more puffs per session, more puffs per cigarette, higher puff volumes, and shorter interpuff intervals). However, both groups of smokers showed an increase in puff duration and a decrease in time between puffs, but took fewer puffs, of VLNC cigarettes compared to their usual brand. This led to a net decrease in cigarette and total smoking session volume and no change in carbon monoxide boost, indicating that smokers with schizophrenia as well as smokers without psychiatric illness did not increase their VLNC cigarette use.¹²⁰ Evidence also suggests that reducing cigarette nicotine content may reduce alcohol use and problem drinking due to reduced exposure to nicotine and the smoking cues associated with alcohol use.¹²¹

♦ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Denlinger-Apte RL, Joel DL, Strasser AA, Donny EC. Low nicotine content descriptors reduce perceived health risks and positive cigarette ratings in participants using very low nicotine content cigarettes. *Nicotine Tob Res.* 2016 Dec 21; doi: 10.1093/ntr/ntw320. [Epub ahead of print]

Consumers may misunderstand health risks of reduced nicotine content cigarettes. In this study, 68 adult daily smokers smoked two identical VLNC cigarettes. Investigators told subjects that one cigarette contained “average” nicotine content, while the other contained “very low” nicotine content. Subjects rated the “very low” nicotine cigarette as less harmful to their health overall, as well as less harmful with regard to specific smoking-related diseases, compared to the “average” nicotine cigarette. Smokers also stated that the “very low” nicotine cigarette had less desirable subjective effects than the “average” nicotine cigarette. Finally, smokers said that they would be more interested in quitting smoking in the future if only the “very low” nicotine cigarette was available. Thus, knowing that a cigarette had very low nicotine content changed the smokers’ perceptions of the cigarette.

PUBLICATION HIGHLIGHT

Dermody SS, Tidey JW, Denlinger RL, et al. The impact of smoking very low nicotine content cigarettes on alcohol use. *Alcohol Clin Exp Res.* 2016 Mar;40(3):606-615.

Researchers assessed whether reducing the nicotine content in cigarettes had unintended consequences related to alcohol use. Researchers conducted a double-blind randomized clinical trial at 10 U.S.-based sites. They assigned 839 daily smokers (403 of whom were current alcohol drinkers) to smoke cigarettes containing either normal nicotine content (NNC; 15.8 mg/g, 9 mg tar), moderate nicotine content (5.2 mg/g nicotine, 9 mg tar), or very low nicotine content (VLNC; 0.4–2.4 mg/g, 9–13 mg tar) for 6 weeks. The researchers found no evidence of compensatory drinking in response to nicotine reduction or nicotine withdrawal, even among heavier drinkers and highly nicotine-dependent individuals.

PUBLICATION HIGHLIGHT

Donny E, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med.* 2015;373(14):1340-1349.

In a 10-site, 6-week clinical trial of reduced nicotine cigarettes, 840 participants (780 study completers) were randomly assigned to smoke either their usual brand of cigarettes or one of six investigational cigarettes with nicotine content ranging from 15.8 mg per gram of tobacco (typical of commercial brands) to 0.4 mg per gram. During week 6, the average number of cigarettes smoked per day was lower for participants assigned to cigarettes with 2.4, 1.3, or 0.4 mg of nicotine per gram of tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants assigned to their usual brand or to cigarettes containing 15.8 mg of nicotine per gram (22.2 and 21.3 cigarettes, respectively). Researchers found that cigarettes with lower nicotine content reduced exposure to nicotine, dependence on nicotine, and craving during smoking abstinence, without significantly increasing expired carbon monoxide level or total puff volume.

FLAVORS

From FY10 to FY17, 54 articles based on CTP-funded research related to flavors (including menthol) were published in peer-reviewed journals. Topics fell within seven CTP research domains (addiction; chemistry and engineering; economics and policy; health consequences; knowledge, attitudes, and behaviors; marketing; and toxicity and carcinogenicity).

Examples of specific study topics include the menthol content in cigarettes marketed in the United States, flavored tobacco product use among adolescents, patterns of transitions in menthol use among young adults, preferences for flavored cigar brands, flavored e-cigarette use among youth, flavoring chemicals in e-cigarettes, menthol cigarette smoking and nicotine dependence, spreading the appeal of flavors through social media, health effects of exposure to aerosol from flavored e-cigarettes, and appeal of small cigar flavors on young adult small cigar use.

Research Summary: ♦ Research suggests that many youth and young adults use flavored tobacco products and report flavors as a reason for use. Data from the 2014 National Youth Tobacco Survey show that more than 3 million U.S. middle and high school students reported using flavored tobacco products.¹²² PATH Study Wave 1 data show that most youth reported the first product they used was a flavored product and endorse flavor as a reason for use.¹²³ PATH Study data also show a significant association between youth and adult reports that their first tobacco product used was flavored and current tobacco use.¹²⁴ Additionally, a systematic review of 40 quantitative studies found that individuals report taste and variety of flavors as factors influencing use, including experimentation, initiation, continued use, and cessation.¹²⁵

A review of 59 flavor articles revealed general differences in youth and adult flavor preferences. Specifically, sweet flavor preference is higher in youth and young adults compared to adults.¹²⁶ Regarding tobacco products, data from the 2013–2014 National Adult Tobacco Survey show that adults report using a variety of flavor types (e.g., fruit), with flavor type use varying by tobacco product type; for example, most flavored hookah users reported using fruit-flavored hookah, and most flavored smokeless tobacco users reported using menthol or mint smokeless tobacco.¹²⁷

Research also suggests that individuals perceive non-menthol flavored tobacco products as less harmful to one's health. A systematic literature review of 40 studies about perceptions of and experiences with flavored non-menthol tobacco products found that, in six studies specifically assessing harm perceptions of non-menthol tobacco products, participants believed flavored tobacco products were less harmful than cigarettes.¹²⁸ However, researchers found that some e-cigarette liquids and aerosols containing flavoring chemicals such as acetoin (butter), diacetyl, pentanedione, maltol (malt), ortho-vanillin (vanilla), coumarin, and cinnamaldehyde can cause inflammatory response and significant loss of epithelial barrier function in lung cells.¹²⁹ Another study found that flavorings in e-cigarettes and other electronic nicotine delivery systems can lead to decreased cellular metabolic activity, reduced cell viability, and increased inhalation toxicity.¹³⁰ Lastly, research on the cytotoxic effects of little cigar smoke exposure on pulmonary epithelia shows that both non-flavored and flavored little cigars similarly increased apoptosis, suggesting equal harm.¹³¹

♦ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

By masking the aversive taste of nicotine, menthol may increase the appeal of tobacco products, thereby facilitating initiation. Researchers found that menthol cigarette smoke suppressed the irritation response in mice even at very high smoke concentrations, and that including menthol in smoke resulted in an increase in plasma cotinine levels, suggesting that menthol may promote smoking initiation and nicotine addiction.¹³² Among young adult smokers, significant predictors of current menthol cigarette use included initiation with menthol, African American race, and higher scores on the Allen menthol taste subscale.¹³³ Chemosensory experiments with 14 e-cigarette users aged 16 to 20 found that even at low doses, menthol was an independent factor in enhancing liking/wanting of e-cigarettes, indicating that menthol increases e-cigarette appeal among youth and young adults.¹³⁴ A randomized trial involving 1,504 adult smokers interested in cessation found that smoking menthol cigarettes was associated with a lower likelihood of smoking cessation success compared to smoking non-menthol cigarettes; African American women were at particular risk of cessation failure.¹³⁵ A study in which rats could press a lever for intravenous nicotine self-administration found that menthol facilitated nicotine self-administration in a dose-dependent fashion.¹³⁶ An analysis of menthol content in 45 cigarettes marketed in the United States found that menthol was present in 22 cigarette products not labeled to contain menthol.¹³⁷

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Ai J, Taylor KM, Lisko JG, Tran H, Watson CH, Holman MR. Menthol content in US marketed cigarettes. *Nicotine Tob Res.* 2016;18(7):1575-1580.

Researchers measured the menthol levels in 45 cigarettes using a gas chromatography/mass spectrometry. They found that menthol levels ranged from 2.9 to 19.6 mg/cigarette in 23 cigarette brands labeled as menthol products; menthol also was present in 22 cigarette products not labeled to contain menthol, ranging from 0.002 to 0.07 mg/cigarette. The type of packaging (soft vs. hard pack) did not appear to affect menthol levels.

PUBLICATION HIGHLIGHT

Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among U.S. youth ages 12–17 years: 2013–2014. *JAMA.* 2015;314(17):1871-1873.

Researchers analyzed flavored tobacco use by the 13,651 youth respondents (aged 12–17) in the PATH Study, a household-based, nationally representative, longitudinal cohort study of 45,971 adults and youth in the United States. Most ever-users reported that the first product they used was a flavored product (88.7 percent of ever hookah users; 81.0 percent of ever e-cigarette users; 65.4 percent of ever users of any cigar type; and 50.1 percent of ever cigarette smokers). For past 30-day use, four-fifths (79.8 percent) of tobacco users had used a flavored product; flavored product use by product type was 89.0 percent among hookah users, 85.3 percent among e-cigarette users, 71.7 percent among users of any cigar type, and 59.5 percent among cigarette smokers. This study confirms that flavored products have widespread appeal among youth tobacco users.

PUBLICATION HIGHLIGHT

Bonhomme MG, Holder-Hayes E, Ambrose BK, Tworek C, Feirman SP, King BA, Apelberg B. Flavoured non-cigarette tobacco product use among US adults: 2013-2014. *Tob Control*. 2016 Nov;25(Suppl 2):ii4-ii13.

Researchers analyzed data from the 2013–2014 National Adult Tobacco Survey on past 30-day non-cigarette tobacco product (NCTP) use, flavored NCTP use, and flavor types. The analysis revealed that an estimated 10.2 million e-cigarette users (68.2 percent), 6.1 million hookah users (82.3 percent), 4.1 million cigar smokers (36.2 percent), and 4.0 million smokeless tobacco users (50.6 percent) used flavored products in the past 30 days. The most prevalent flavors reported by product were: (1) menthol/mint for smokeless tobacco; (2) fruit for hookah; (3) fruit, candy/chocolate/other sweet flavors, and alcohol for cigars/cigarillos/filtered little cigars; (4) fruit, menthol/mint, and candy/chocolate/other sweet flavors for e-cigarettes; and (5) fruit, candy/chocolate/other sweet flavors, and menthol/mint for pipes. Except for hookahs and pipes, past 30-day flavored product use was highest among young adults aged 18–24 years. Never smoking e-cigarette users (84.8 percent) were more likely to report flavored e-cigarette use, followed by recent former smokers (78.1 percent), long-term former smokers (70.4 percent), and current smokers (63.2 percent).

PUBLICATION HIGHLIGHT

Delnevo CD, Giovenco DP, Ambrose BK, Corey CG, Conway KP. Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tob Control*. 2015;24:389-394.

Use of flavors in tobacco products may increase their palatability and appeal. Researchers used the 2010–2011 National Survey on Drug Use and Health and Nielsen market scanner data to analyze flavored cigar use among 6,678 past-30-day cigar smokers. Researchers found that flavored cigars were responsible for 75 percent of the increase in U.S. cigar sales between 2008 and 2011. Certain population groups—including youth, young adults, females, African Americans, cigarette smokers, blunt users, and daily cigar smokers—had a preference for flavored cigars. Findings suggest that flavors may be contributing to the growth in cigar popularity in the United States, particularly among certain subpopulations.

PUBLICATION HIGHLIGHT

Rosbrook K, Green BG. Sensory effects of menthol and nicotine in an e-cigarette. *Nicotine Tob Res.* 2016 July;18(7):1588-1595.

Investigators measured users' perception of menthol in an e-cigarette with the primary goal of assessing its analgesic effect on irritation produced by inhaled nicotine. In this study, 32 adult cigarette smokers sampled aerosolized e-liquids containing five different concentrations of nicotine with 0 percent, 0.5 percent, or 3.5 percent menthol, as well as two commercial menthol flavors with and without nicotine. Participants rated overall sensation intensity, coolness/cold, irritation/harshness, and flavor like/dislike. The researchers found that: (1) perceived irritation/harshness was unaffected by low menthol concentration (0.5 percent), while high menthol concentration (3.5 percent) led to higher perceived irritation/harshness at low nicotine concentrations but to lower irritation/harshness at a high nicotine concentration (24 mg/ml); (2) nicotine enhanced the coolness/cold sensation; and (3) menthol slightly increased liking regardless of nicotine concentration. Thus, the researchers concluded that menthol may improve e-cigarette appeal not only through its coolness and minty flavor, but also by reducing harshness from high nicotine concentrations.

STUDIES EXAMINING STRATEGIES AND IMPACTS OF CTP PUBLIC EDUCATION CAMPAIGNS

From FY10 to FY17, five articles based on CTP-funded research related to public education campaigns were published in peer-reviewed journals. Specific study topics included youth receptivity to “The Real Cost” campaign messages, the effect of “The Real Cost” on risk perceptions and beliefs about smoking among youth, impact on behavior change, and peer crowd segmentation as a strategy for culturally targeting health behavior interventions to youth.

Research Summary:◇ Research findings demonstrate that “The Real Cost” campaign has attained high levels of ad awareness and that the campaign has achieved positive changes in population-level perceptions of tobacco-related harms among youth. A scientific assessment found that approximately 350,000 youth aged 11 to 18 were prevented from smoking nationwide between 2014 and 2016 as a result of “The Real Cost” campaign; ultimately, exposure to “The Real Cost” ads was associated with a 30 percent decrease in the risk of smoking initiation from 2014 to 2016, demonstrating that carefully developed evidence-based campaigns promise to reduce addiction, disease, and death from tobacco.¹³⁸

In the specific area of segmenting and targeting at-risk youth for public education campaigns, peer crowd targeting has been shown to be a useful strategy. The “Fresh Empire” campaign has demonstrated how peer crowd targeting can be implemented in multiple cities across the country to create and disseminate tobacco prevention messages to youth.¹³⁹ By replacing unhealthy behavioral norms with certain desirable lifestyles, peer crowd-targeted interventions can potentially transcend race, ethnicity, and geography to create a lasting impact.

◇ Research findings are reported by study authors; they are not a formal dissemination of information by FDA and do not represent agency position or policy.

Note: The following publications are highlighted for illustrative purposes only. The information in these Publication Highlights is not a formal dissemination of information by FDA and does not represent agency position or policy. The contents of the publications are the responsibility of the authors alone; findings and conclusions are those of the authors and do not necessarily represent the views of FDA.

PUBLICATION HIGHLIGHT

Duke JC, Alexander TN, Zhao X, et al. Youth's awareness of and reactions to The Real Cost national tobacco public education campaign. *PLoS One*. 2015;10(12).

In 2014, FDA launched its first tobacco-focused public education campaign, "The Real Cost," aimed at reducing tobacco use among 12- to 17-year-olds in the United States. This study describes "The Real Cost" message strategy, implementation, and initial evaluation findings. The campaign is designed to encourage youth who have never smoked but are susceptible to trying cigarettes (susceptible nonsmokers) and youth who have previously experimented with smoking (experimenters) to reassess what they know about the "costs" of tobacco use to their body and mind. Overall, 89.0 percent of U.S. youth were aware of at least one advertisement 6 to 8 months after campaign launch, and high levels of awareness were attained within the campaign's two targeted audiences: susceptible nonsmokers (90.5 percent) and experimenters (94.6 percent). Most youth considered "The Real Cost" advertising to be effective, based on assessments of ad perceived effectiveness (mean=4.0 on a scale from 1.0 to 5.0). High levels of awareness and positive reactions to advertisements are requisite proximal indicators of health behavioral change. The findings of this analysis demonstrate that "The Real Cost" attained high levels of ad awareness during the study period, which is a critical first step in achieving positive changes in tobacco-related attitudes and behaviors.

PUBLICATION HIGHLIGHT

Duke JC, Farrelly MC, Alexander TN, et al. Effect of a national tobacco public education campaign on youth's risk perceptions and beliefs about smoking. *Am J Health Promot.* 2018 Jun;32(5):1248-1256. [Epub 2017 Jul 31]

This study assessed the relationship between youth exposure to FDA's national tobacco public education campaign, "The Real Cost," and changes in campaign-targeted beliefs. The study shows results from a longitudinal design with baseline survey and two post-campaign follow-up surveys. The study sample included youth from 75 U.S. media markets (n=1,680) who completed all three surveys and had experimented with or were susceptible to future cigarette smoking. Exposure to "The Real Cost" was measured by self-reported frequency of ad exposure and media market-level target rating points. Agreement with 30 self-reported tobacco-related beliefs was assessed. Descriptive analyses of aggregate changes in beliefs and logistic regressions were conducted to examine the association between campaign exposure and beliefs. Agreement with campaign-targeted beliefs increased from baseline to first and second follow-ups, with a mean relative increase of 10.4 percent and 11.5 percent, respectively. Nontargeted beliefs did not change substantially. This study shows how a sustained national tobacco public education campaign can change population-level perceptions of tobacco-related harms among youth.

PUBLICATION HIGHLIGHT

Farrelly MC, Duke JC, Nonnemaker J, et al. Association between The Real Cost media campaign and smoking initiation among youths - United States, 2014-2016. *MMWR Morb Mortal Wkly Rep.* 2017;66(2):47-50.

In the United States, approximately 900,000 youths smoke their first cigarette each year. Health communication interventions are evidence-based strategies for preventing the initiation of tobacco use, promoting and facilitating cessation, and changing beliefs and attitudes about tobacco use. This article describes the association between FDA's national tobacco public education campaign, "The Real Cost," and rates of smoking initiation among U.S. youths from 2014 to 2016. A nationally representative cohort study of youths (n=5,185) was conducted from November 2013 to March 2016. Results from a discrete-time survival model indicate that, among youths who reported never having smoked a cigarette in the baseline survey, the odds of reporting smoking initiation at follow-up were lower among youths with frequent exposure to campaign advertisements than among those with little or no exposure (adjusted odds ratio [aOR]=0.70, 95% CI=0.55-0.91). Based on the results of the model, "The Real Cost" is associated with an estimated 348,398 U.S. youths aged 11-18 years who did not initiate smoking between February 2014 and March 2016. Sustained youth-focused tobacco education campaigns, such as "The Real Cost," can help speed progress toward preventing tobacco use among youths in the United States.

PUBLICATION HIGHLIGHT

Moran MB, Walker MW, Alexander TN, Wagner DE. Why peer crowds matter: incorporating youth subcultures and values in health education campaigns. *Am J Public Health.* 2017;107:389-395.

Grounded in research showing that health risk behaviors vary by peer crowd, FDA's "Fresh Empire" campaign targeted youth influenced by hip-hop, a peer crowd at higher risk of tobacco use. Peer crowd targeting supports aligning health behavior messaging with youth peer crowd culture and values. Using "Fresh Empire" as an example, researchers illustrated the benefits and limitations of this approach. By replacing unhealthy behavioral norms with desirable, healthy lifestyles, peer crowd-targeted interventions potentially can create a lasting impact among the target audience.

PUBLICATION HIGHLIGHT

Zhao X, Alexander TN, Hoffman L, et al. Youth receptivity to FDA's The Real Cost tobacco prevention campaign: evidence from message pretesting. *J Health Commun.* 2016;21(11):1153-1160.

Researchers examined youth receptivity to 14 potential ads for “The Real Cost” campaign using data from three message pretesting studies. A total of 3,258 adolescents aged 13 to 17 were randomized to either an ad-viewing condition or a no-exposure control condition. Perceived ad effectiveness, smoking-related beliefs, and attitudes were measured as outcome variables. The sample consisted of both experimental smokers (58 percent) and current nonsmokers at risk for cigarette initiation (42 percent). Participants who viewed the ads generally considered them to be effective (with a mean perceived ad effectiveness score of 3.66 on a scale from 1 to 5). Compared to those in the control condition, participants in the ad-viewing condition reported stronger beliefs about the health risks of smoking ($p < .001$), a greater likelihood that smoking would lead to loss of control in life ($p < .001$), and more negative attitudes toward smoking ($p < .001$). Responses to campaign ads were largely consistent between experimenters and at-risk nonsmokers.



Research Partners

Research Partners

CTP-OS is fortunate to work with several research partners to support FDA's regulatory science research.

NATIONAL INSTITUTES OF HEALTH

Tobacco Regulatory Science Program

CTP and NIH jointly established a Tobacco Regulatory Science Program (TRSP), a unique collaboration that supports the expansion of the regulatory science base related to tobacco products. TRSP has stimulated investigator-initiated research and released targeted funding opportunity announcements to study:

- The impact of marketing and communications on tobacco use behavior
- Perceptions, knowledge, attitudes, and beliefs regarding tobacco products
- Toxicity, carcinogenicity, and health risks of tobacco products
- Varying nicotine levels and other constituents' effects on initiation, dependence, and quitting

FDA has continued to invest in scientific research to gain a better understanding of all tobacco products and patterns of tobacco use. From FY10 through FY17, FDA and NIH have funded 231 research projects through TRSP. These research projects include grants and cooperative agreements that address important FDA research priorities. Funding through FY17 totaled \$542.3 million.¹⁴⁰

Tobacco Centers of Regulatory Science

In conjunction with NIH under TRSP, CTP established the Tobacco Centers of Regulatory Science (TCORS), a first-of-its-kind program designed to generate research to inform the regulation of tobacco products to protect public health. The program was initially funded in September 2013 and will run for up to 5 years. TCORS were funded at the following 14 institutions:

- American Heart Association
- Georgia State University
- Ohio State University
- Pennsylvania State University
- University of California, San Francisco
- University of Maryland
- University of North Carolina at Chapel Hill, School of Medicine
- University of North Carolina, School of Public Health
- University of Pennsylvania
- University of Southern California
- University of Texas
- University of Vermont and State Agriculture College
- Virginia Commonwealth University
- Yale University

The overall objective of the 14 TCORS is to conduct multidisciplinary research that will inform FDA's regulatory actions related to the manufacture, distribution, and marketing of tobacco products. Essential elements of these centers include three or more theoretically grounded research projects with an integrated theme, the ability to respond quickly to emerging research questions through pilot projects, and a program for career development to train future generations of researchers in tobacco regulatory science.

In addition, 10 currently active workgroups (behavioral pharmacology, biomarkers, economics, eye tracking research, health communication, measures, nicotine, training, vape shops, and vulnerable populations) with cross-TCORS representation bring together subject matter experts to discuss challenges in the field, identify best practices, determine how to best disseminate knowledge, and synthesize information about study design and future research. The workgroups—which are coordinated through the Center for Evaluation and Coordination of Training and Research (CECTR) and meet monthly by telephone and annually in person—pursue a variety of activities, including producing manuscripts and white papers and conducting workshops. The workgroups provide a mechanism that allows TCORS to coordinate their activities to maximize their public health impact.

Note: These views do not necessarily represent FDA policy or position.

We know that while nicotine has adverse consequences, nicotine isn't all that toxic when delivered at relatively safe low doses. If we can make products that are safer than cigarettes, we could potentially encourage people who are currently smoking to move to these products. We could set nicotine levels in cigarettes low enough so that young people, should they try them, will not become addicted.

– Stephen Higgins, Ph.D., Professor of Psychiatry and Psychology, University of Vermont, and Principal Investigator, University of Vermont TCORS

We are entering an age where different disciplines need to come together and work as a team. What is particularly satisfying about working in tobacco is that ... we have the opportunity to work with experts and bright young people in a variety of fields.

– Mary Ellen Wewers, Ph.D., M.P.H., Division of Epidemiology and Division of Health Behavior and Health Promotion, Ohio State University, and Co-Principal Investigator, Ohio State University TCORS

Our TCORS is focused on tobacco product messaging in a complex communication environment. There is a ton of misinformation out there in social media about tobacco products that are under FDA's tobacco regulatory authority. We're concerned that some of that misinformation can actually undermine some of FDA's efforts ... It's incredibly exciting to be part of this pioneering effort, and one of the things that's particularly exciting about it is the team science approach. We can examine the issue of communication from individual brain neuroscience out to society.

– Caryn Lerman, Ph.D., Deputy Director, Abramson Cancer Center, University of Pennsylvania, and Principal Investigator, University of Pennsylvania TCORS

We are interested in doing a better job of warning consumers about the dangers of constituents... We are doing research studies that will guide the way FDA communicates to consumers and tobacco product users. FDA must communicate about the harmful and potentially harmful constituents in tobacco products. Not a lot is known about what consumers think about these. We are trying to understand which constituents consumers are aware of and which discourage them from smoking. Those will be the best ones to use in warning label projects.

– Kurt Ribisl, Ph.D., Professor, University of North Carolina, Gillings School of Global Public Health, and Principal Investigator, University of North Carolina TCORS

Many emerging tobacco products are available in a wide variety of flavors ... The overall goal of the Yale TCORS is to understand the role of flavors in tobacco products and how flavors may alter initiation of and addiction to these products.

– Suchitra Krishnan-Sarin, Ph.D., Associate Professor of Psychiatry, Yale University School of Medicine, and Principal Investigator, Yale TCORS

The popularity of little cigars and cigarillos is quite high among young adults, particularly young adults from ethnic minority communities. My research will give the FDA data that helps them understand the pattern of usage among young adults, particularly young adults from ethnic communities.

– Kymberle Sterling, Dr.P.H., Associate Professor, Health Promotion and Behavior, Georgia State University, and Co-Investigator, Georgia State University TCORS

Center for Evaluation and Coordination of Training and Research

In September 2014, FDA funded the Center for Evaluation and Coordination of Training and Research (CECTR) via the TRSP partnership. CECTR is an NIH cooperative agreement to support and conduct an evaluation of the tobacco-related scientific programs funded by FDA and to facilitate coordination and communications of research and scientific training within those programs. CECTR—which is staffed by tobacco scientists, evaluators, training developers, epidemiologists, analysts, and statisticians—serves as an efficient infrastructure for providing scientific leadership and technical research expertise. CECTR’s goals are (1) to accelerate knowledge sharing and innovation by facilitating collaboration and communication; (2) to increase the timely availability of tobacco regulatory science conceptual models, common measures, and other policy-relevant research tools; and (3) to enhance the capacity of the research community to conduct more rapid and impactful tobacco regulatory science research by coordinating cross-disciplinary training of CTP-funded scientists and facilitating data sharing, analysis, and synthesis. CECTR activities will result in coordinated tobacco regulatory science methods, measures, and applications; development of a shared conceptual multidisciplinary framework; and training of the next generation of tobacco regulatory scientists.

Other Grants

In addition to TCORS and CECTR, CTP and NIH use a variety of funding mechanisms to support a large number of research opportunities that cover myriad topics. Examples of topics studied since FY10 include those related to particular products (e.g., cigarettes and cigarette smoke, smokeless tobacco, snus, cigars/little cigars/cigarillos, pipes, waterpipes, dissolvables) as well as other topics, including:

- Assessment of user perceptions, beliefs, attitudes, and behaviors
- Patterns of new product adoption, including dual and poly-use
- Evaluation of harmful and potentially harmful constituents (including nicotine and metals)
- Effects of menthol and other tobacco product flavorings
- Use and impact of low nicotine content cigarettes
- Evaluation of addiction and abuse liability
- Evaluation of toxicant and carcinogen exposure
- Impact of tobacco product use on human health, including cardiac, respiratory, and oral health consequences
- Impact on vulnerable population groups including youth/young adults, pregnant women/women of reproductive age, members of the U.S. military, and individuals with mental health disorders
- Identification of biomarkers of harm
- Impact of marketing, advertising, and packaging/labeling on the general population and on vulnerable population groups
- Provision and impact of public information on tobacco product constituents
- Economic assessment of tobacco use
- Impact of tobacco regulatory actions

Note: These views do not necessarily represent FDA policy or position.

The thing about addiction I find most disturbing is that people lose the sense of control and freedom that should be part of making the decision about whether to use a product. I hope our research helps FDA figure out ways to help people make more informed, more personal decisions about product use that aren't constrained by whether the product is addictive.

– Eric Donny, Ph.D., Director, Center for the Evaluation of Nicotine in Cigarettes, University of Pittsburgh

NIH Intramural Projects

Through an interagency agreement with NIH, FDA provides funds to NIH to conduct intramural research projects on a variety of tobacco-related subjects. This research will help further the scientific knowledge base regarding tobacco products. Sample topics include the impact of tobacco use on oral health; the development of biomarkers of tobacco smoke exposure and of nicotine addiction; cellular sensitivity to tobacco compounds; genetic factors in taste perception and tobacco use; toxicant exposure in dual users of cigarettes and e-cigarettes; the impact of tobacco product marketing and advertising exposure; low nicotine cigarette use in adolescents; the effects of waterpipe smoke on the respiratory system; and the effects of tobacco use on vulnerable populations, including adolescents, women of reproductive age, people with mental health disorders, and members of the U.S. military.

There is a lot of focus on death due to tobacco use, but oral health is a very important part of tobacco-induced poor health. Understanding the degree to which tobacco causes poor oral health will help inform the full burden of tobacco's impact on the American population. ... My hope is that by the time I am done with my career, this isn't an issue anymore, and that we know enough that we can eliminate tobacco as a major cause of death and disability in the United States.

– Christian Abnet, Ph.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute

PhenX

PhenX (consensus measures for Phenotypes and eXposures), led by RTI International and funded by the National Human Genome Research Institute, facilitates integration and collaboration in genetics and epidemiologic research. Toward this end, PhenX has established a web-based toolkit of standard measures for use in genome-wide association studies and other population-based studies. The PhenX toolkit is intended to help researchers easily expand their study design by providing high-quality, standard measures across a wide range of research domains.

TRSP and CTP supplemented PhenX to provide a set of expert-recommended, prioritized common measures as a resource to investigators conducting tobacco regulatory research. This newest collection, completed in August 2016, added 77 measures to the PhenX Toolkit. Research measures are organized into two cores, which are deemed relevant across all areas of tobacco regulatory research, and five specialty collections based on the HAVE (Host, Agent, Vector, and Environment) model:

- Social/Cognitive (Host)—intrapersonal factors influencing tobacco use
- Biobehavioral (Host)—product use, exposure, and outcomes
- Agent—assessment of tobacco products
- Vector—industry and retailer activities
- Environment—environmental factors influencing tobacco use

The PhenX Toolkit currently includes about 480 measures from 23 research domains and four collections that each provide greater depth in a particular field. The measures included in each collection are chosen by domain experts who recommend measures for inclusion that are suitable for a variety of study designs, using a consensus-based process, which includes input from the scientific community.

THE POPULATION ASSESSMENT OF TOBACCO AND HEALTH (PATH) STUDY

In FY11, in collaboration with NIH's National Institute on Drug Abuse, FDA funded the PATH Study, which will help scientists learn how and why people start using tobacco, switch products, quit using tobacco, and start using it again after they've quit. The PATH Study is a nationally representative, longitudinal cohort study of 45,971 U.S. adults and youth (aged 12 years and older); the study oversamples tobacco users, young adults (aged 18–24 years), and African Americans. PATH Study Wave 1 was conducted from September 12, 2013, to December 15, 2014, using audio computer-assisted self-interviewing technology to collect information on tobacco use patterns, risk perceptions and attitudes toward current and newly emerging tobacco products, tobacco initiation, cessation, relapse behaviors, and health outcomes. Additionally, the PATH Study collects blood and urine specimens from consenting adults (aged 18 years and older) and measures biomarkers of exposure and potential harm related to tobacco use.¹⁴¹ This study will provide:

- Research on tobacco product-related harm, evaluating patterns of tobacco use such as switching products and using multiple products
- An understanding of perceptions and knowledge of, attitudes toward, and use of various tobacco products

By monitoring and assessing the behavioral and adverse health impacts of tobacco use in the United States, the PATH Study will add to the evidence base to inform regulatory decisions about the marketing, manufacture, and distribution of tobacco products. The PATH Study completed baseline data collection in December 2014 with a sample size of approximately 46,000. Wave 2 of the PATH Study began data collection in October 2014 and was completed in September 2015. A new 10-year contract was awarded in January 2016.

Note: These views do not necessarily represent FDA policy or position.

The PATH Study is critical to creating a foundational evidence base upon which future regulations will be implemented. The work that's being done here, not just the PATH Study but across the FDA-funded projects, will be looked upon in the future as a groundbreaking, necessary endeavor in order to save lives.

– Andrew Hyland, Ph.D., Chair, Department of Health Behavior, Roswell Park Cancer Institute, and Principal Investigator, PATH Study

CENTERS FOR DISEASE CONTROL AND PREVENTION

Division of Laboratory Science

FDA is partnering with CDC's Division of Laboratory Science on projects that use laboratory-based approaches to expand our knowledge of how best to regulate tobacco products. These include analyses of tobacco products and mainstream smoke, method development for biomarkers, exposure assessments under actual use conditions, and further method development for harmful and potentially harmful constituents (HPHCs). CDC also is providing the analyses of tobacco exposure biomarkers as part of the PATH Study.

Office on Smoking and Health

To provide critical data on the impact of tobacco regulation on populations, CTP-OS has provided funding to expand the scope and increase the frequency of data collection for the National Youth Tobacco Survey conducted by CDC. This large, annual, nationally representative survey of middle and high school students focuses exclusively on tobacco. Data from this survey allow CTP-OS to monitor awareness of, susceptibility to, and experimentation with and use of a wide range of tobacco products.

National Center for Health Statistics

The National Health Interview Survey (NHIS), conducted annually by the National Center for Health Statistics (NCHS), is the principal source of information on the health of the U.S. civilian noninstitutionalized household population. The NHIS has been conducted continuously since its inception in 1957 with the goal of monitoring the health of the nation. CTP-OS worked with NCHS and other federal partners to develop and include noncigarette tobacco use questions in the 2015 NHIS; specifically, new survey questions will assess ever and current use of e-cigarettes, noncigarette combustible products, and noncombustible tobacco products to complement annual NHIS data on cigarette use prevalence.

Division of Reproductive Health

CTP-OS added e-cigarette measures to the Pregnancy Risk Assessment Monitoring System (PRAMS), a surveillance project of CDC and state health departments. PRAMS collects state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy. PRAMS enrolls women who have had a recent live birth, with each participating state sampling 1,300 to 3,400 women per year. Topics addressed in the PRAMS questionnaire include barriers to and content of prenatal care, obstetric history, maternal use of alcohol and cigarettes, physical abuse, contraception, economic status, maternal stress, and early infant development and health status. New questions about e-cigarette and waterpipe use address frequency of use, use behaviors, and dual use of e-cigarettes and traditional cigarettes.

Note: These views do not necessarily represent FDA policy or position.

We have lost a generation of senior members of our family because of tobacco addiction. It's my hope that I can be part of a change such that tobacco products are no longer as addictive and as harmful, so that in future generations, grandmothers and grandfathers can be around for their grandkids. Our goal is to characterize tobacco products, tobacco smoke, and vapor ... and the health effects that result. We are using gold-standard analytical methods ... We hope to share that information so that it can be used by the public health community and FDA as a basis for appropriate regulatory decisions.

– Ben Blount, Ph.D., Chief, Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, CDC

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

CTP-OS has been working with FDA's National Center for Toxicological Research (NCTR) since 2010 to establish and conduct research in the following areas: toxicological characterization of compounds in cigarette smoke, biomarker discovery, characterization of toxic and addictive potential of tobacco products, and developmental bioinformatics projects. Starting in FY14 and continuing in FY17, CTP-OS focused on inhalation toxicology and behavioral pharmacology research projects and bioinformatics projects including the Tobacco Constituents Knowledge Base—the scientific enclave for information and data exchange between CTP and research collaborators—and text mining and topic modeling of data.

OTHER FEDERAL PARTNERS

CTP-OS is working with other partners to build scientific knowledge to inform tobacco product regulation. CTP-OS works with the National Institute of Standards and Technology on developing reference standards for nicotine and tobacco-specific nitrosamines. With Sandia National Laboratories, CTP-OS scientists have developed a modeling framework for FDA to use in understanding the impact of certain potential policy and marketing authorization decisions on population health. Along with NIH's National Cancer Institute, CTP-OS cosponsored the 2014–2015 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), administered by the U.S. Census Bureau. The TUS-CPS is a key source of national, state, and substate level data from U.S. households regarding smoking, use of tobacco products, and tobacco-related norms, attitudes, and policies. Results from this survey will provide CTP-OS with data on the impact of tobacco regulation on populations.

CONTRACTS

CTP-OS is working with several contract research organizations to address priority research needs. Examples include assessment of tobacco product pharmacology and behavior in clinical and nonclinical models; development of and use of a screening tool designed to rapidly identify tobacco product constituents with selective nicotine receptor subtype modulation properties; in vitro and in vivo research to conduct acute and subchronic studies of tobacco products; laboratory research to conduct chemical analysis of tobacco products; behavioral and social science research addressing consumer knowledge, attitudes, beliefs, perceptions, and behaviors regarding tobacco products; and development and testing of new graphic health warnings for cigarettes. In addition, two contracts access tobacco control policies: one on rapid assessment of state and local tobacco control policies and the other on research to expand the evidence base for CTP policy options.

IN-HOUSE RESEARCH

CTP-OS scientists conduct a significant amount of research in house, including literature searches, focus groups, and secondary data analyses.

For example, to clarify and contribute to the knowledge base about e-cigarettes and their impact on health, CTP scientists undertook a major literature review that evaluated the state of the science from multiple perspectives, including engineering/design considerations, chemistry, toxicology, abuse liability and subjective effects, nicotine clinical pharmacology, human health effects, human factors, pediatrics, and environmental impact. Findings were published in a *Tobacco Control* special supplement in March 2014.



Funded Publications

Funded Publications

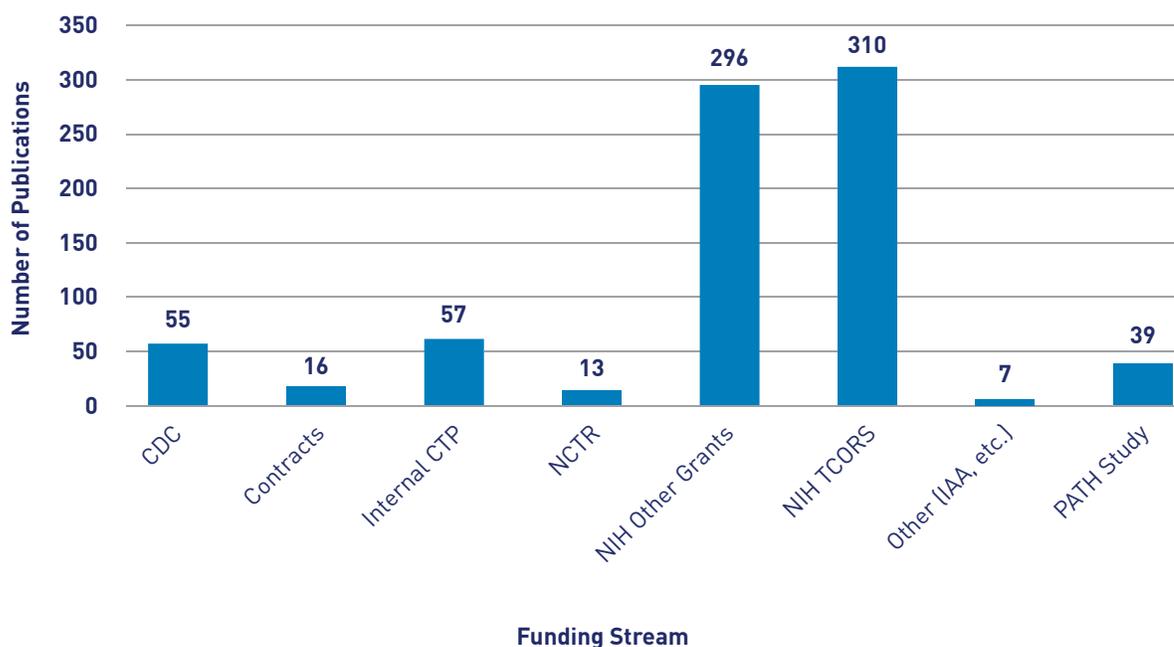
Through FY17, there were 794 publications resulting from CTP-funded research, of which 151 had a CTP author; 86 had a CTP staff member as the lead author, and 65 had one or more CTP staff members as coauthors. Publications have covered a wide variety of products, populations, and topics.

The following graphs reflect the best estimate of CTP-funded tobacco research publications (analysis date: October 23, 2017) through the end of FY17. Publications were included in the analysis if they were published at least 6 months after the project start date (i.e., publication date between April 1, 2010, and September 30, 2017).

PUBLICATIONS BASED ON CTP-FUNDED RESEARCH

Publications were produced by researchers funded through all funding mechanisms, including NIH TCORS (310 publications), NIH—other grants (296 publications), internal CTP (57 publications), CDC (55 publications), the PATH Study (39 publications), contracts (16 publications), NCTR (13 publications), and other funding mechanisms (7 publications).

Publications Based on CTP-Funded Research (FY10–FY17)



Note: Graph represents active CTP-funded projects that reflect federal collaborations and government and nongovernment contracts.

KEY:

CDC: Interagency agreements with CDC

Contracts: Contracts with external organizations

Internal CTP: Internal CTP staff

NCTR: Joint collaboration with NCTR

NIH Other Grants: Grants with NIH Institutes/Centers

NIH TCORS: Grants with NIH TCORS

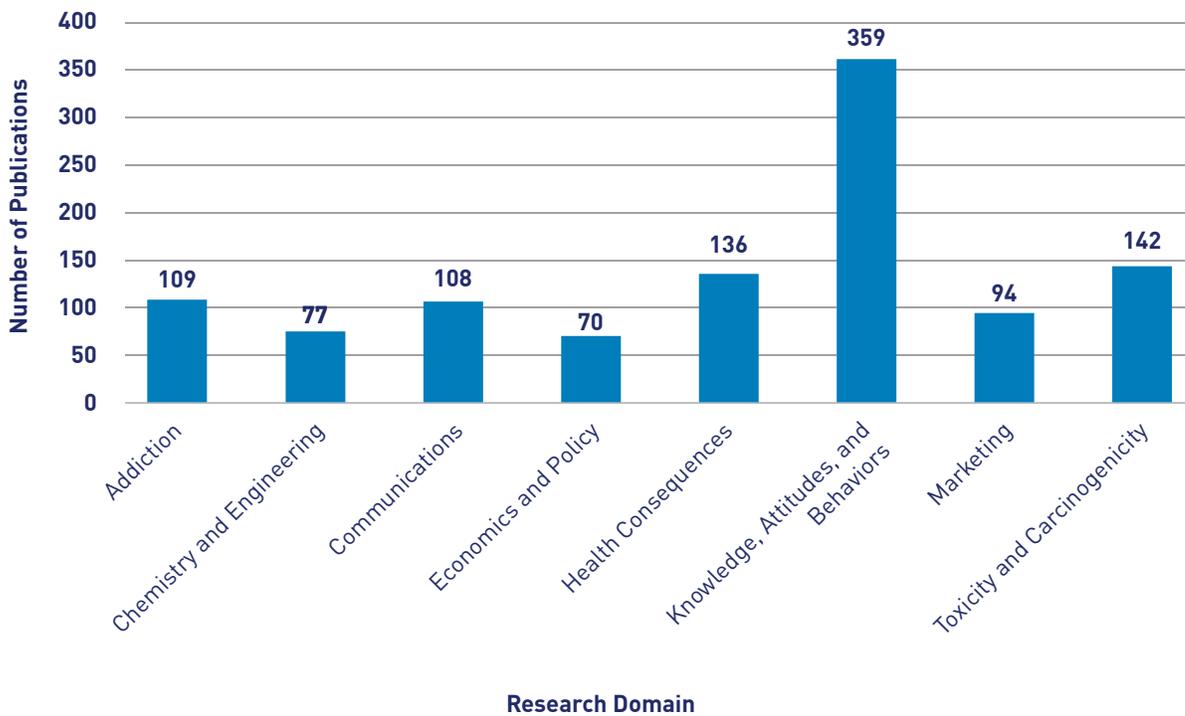
Other: Non-CDC Interagency Agreements (IAAs), FDA agreements

PATH Study: Collaborative publications under the PATH contract

PUBLICATIONS BY RESEARCH DOMAIN

Publications covered all eight CTP research domains, including knowledge, attitudes, and behaviors (359 publications), followed by toxicity and carcinogenicity (142 publications), health consequences (136 publications), addiction (109 publications), communications (108 publications), marketing (94 publications), chemistry and engineering (77 publications), and economics and policy (70 publications).

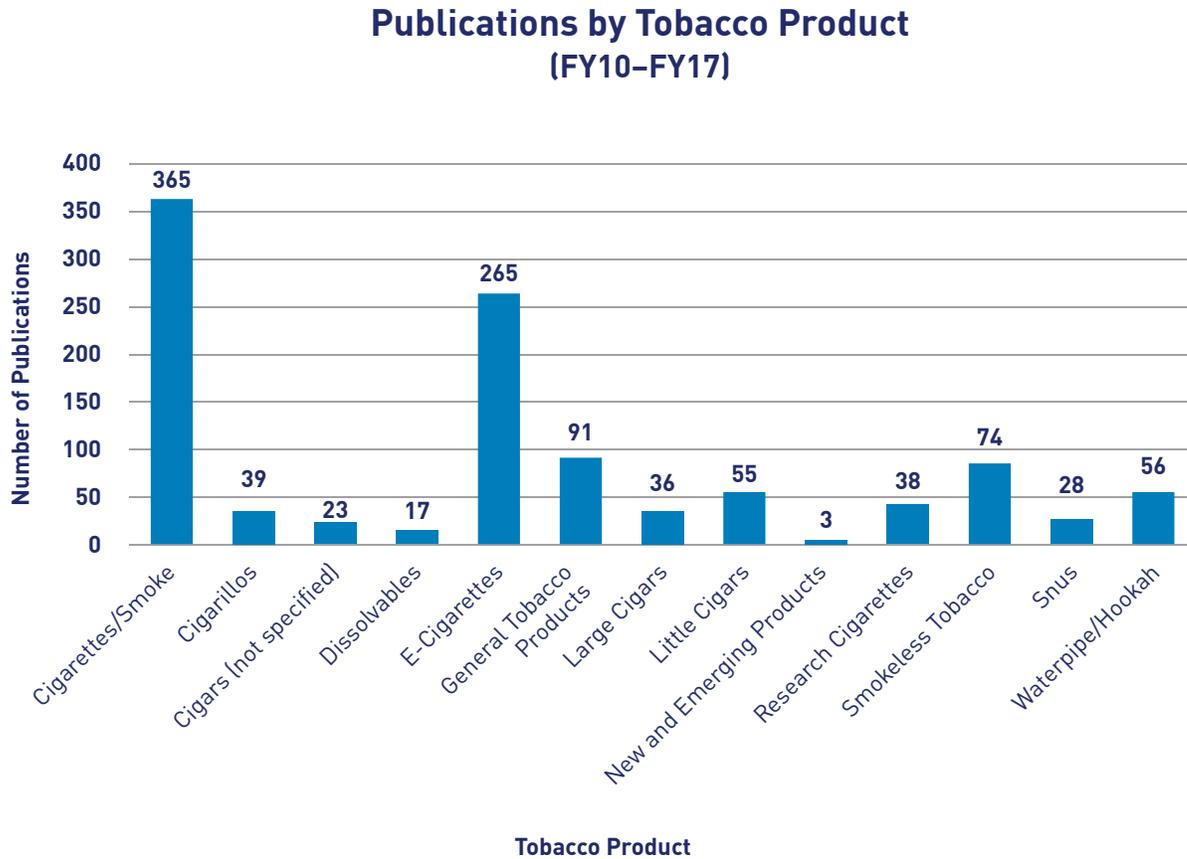
**Publications by Research Domain
(FY10–FY17)**



Note: Publications may address more than one research domain.

PUBLICATIONS BY TOBACCO PRODUCT

Publications addressed a wide variety of tobacco products. Approximately half of all publications addressed cigarettes/smoke (365 publications), and about one-third addressed e-cigarettes (265 publications); other products studied included smokeless tobacco, waterpipe/hookah, cigars and cigarillos, snus, dissolvables, research cigarettes, and new and emerging products. Ninety-one publications addressed tobacco products generally.

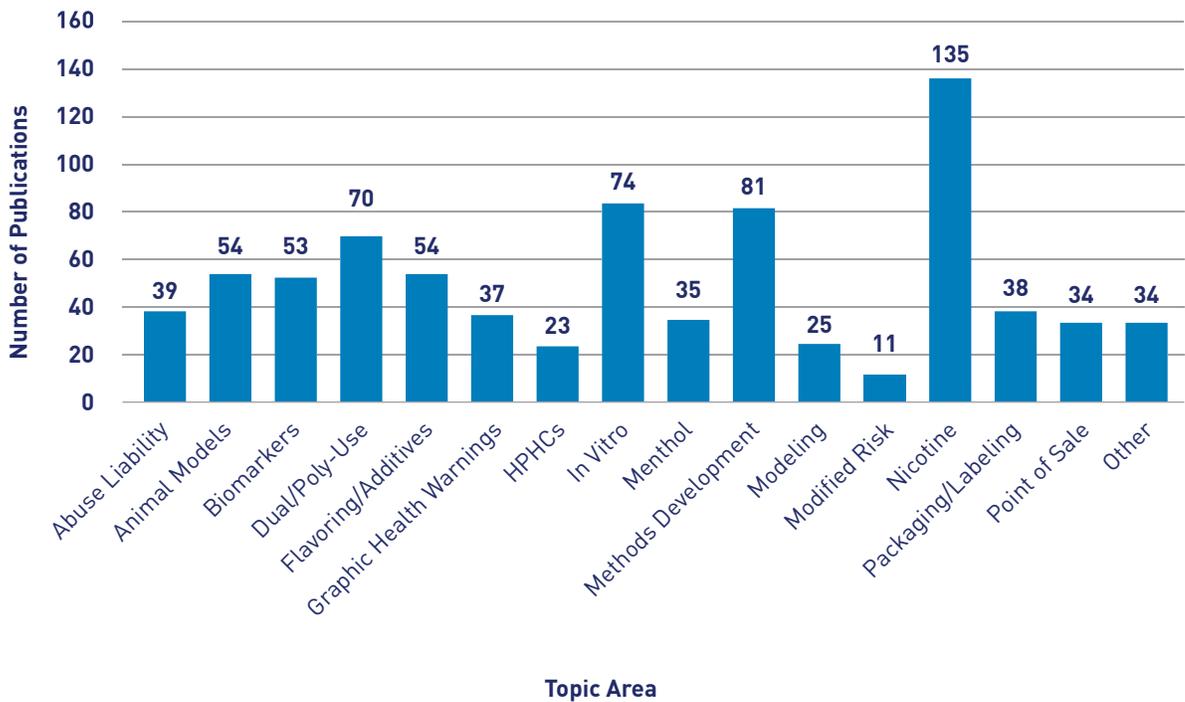


Note: Publications may address more than one tobacco product.

PUBLICATIONS BY TOPIC AREA

Publications covered a large number of defined topic areas. Nicotine was the most common (135 publications), followed by methods development (81 publications), in vitro (74 publications), and dual/poly-use (70 publications). Other topic areas included animal models, flavors/additives, biomarkers, abuse liability, packaging/labeling, graphic health warnings, menthol, point-of-sale campaigns, modeling, HPHCs, and modified risk. These numbers reflect only those publications that specified a defined topic area; 24 publications covered other topics.

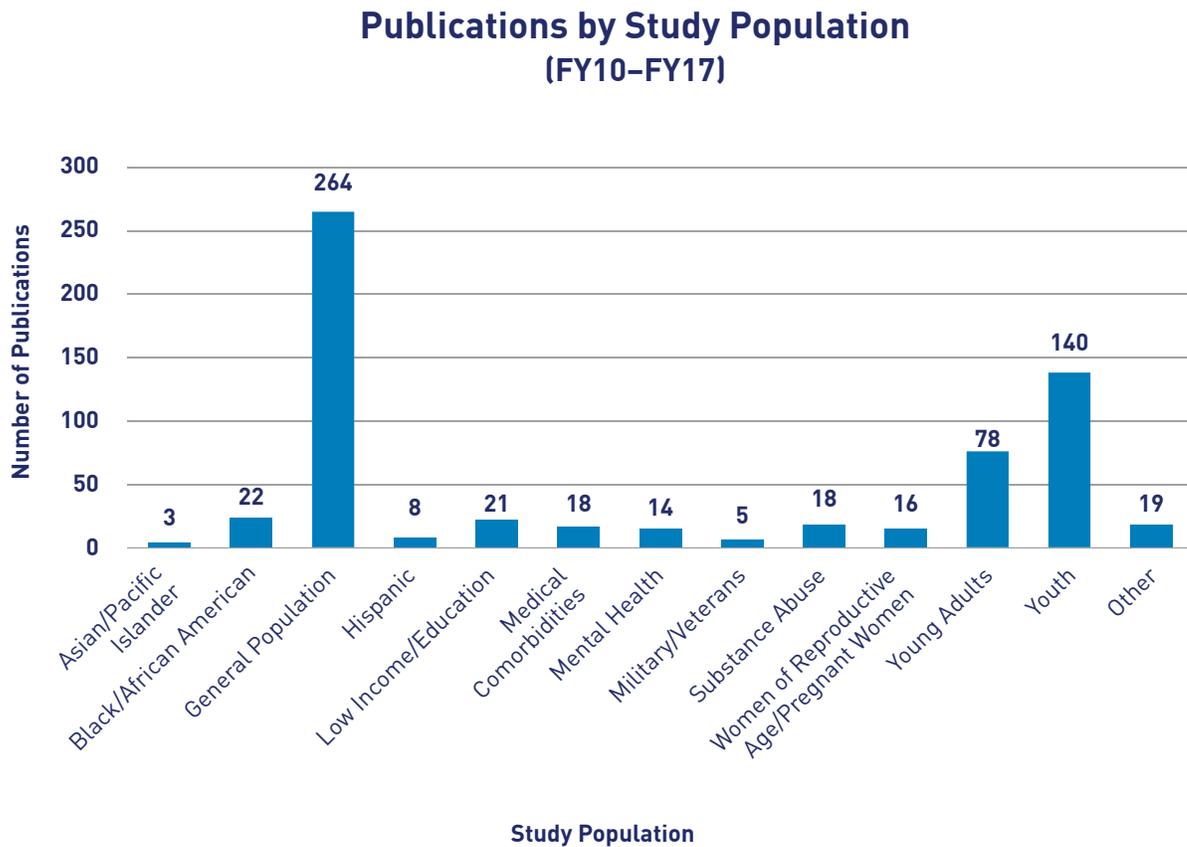
**Publications by Topic Area
(FY10-FY17)**



Note: Publications may include more than one topic area.

PUBLICATIONS BY STUDY POPULATION

Although many publications (264 publications) addressed the general population, many more addressed a defined subpopulation, including youth (140 publications) and young adults (78 publications). Other subpopulation categories studied included African Americans, Hispanics, Asians/Pacific Islanders, people with low income/education, people with medical comorbidities, people with mental health disorders, military personnel/veterans, pregnant women/women of reproductive age, and substance abusers. (*Note: These numbers reflect only those publications that specified a defined population.*)



Note: Publications may include more than one study population.

Training the Next Generation of Regulatory Scientists



Training the Next Generation of Regulatory Scientists

Regulatory science is a relatively new field, one that requires a shift in thinking for many scientific researchers. Given its unique mission and role, CTP is ideally placed to take a leadership role in building and nurturing a robust stable of researchers who can advance the important work of tobacco regulatory science. Accordingly, CTP-OS funds several training opportunities that prompt scientific investigators to pursue their research interests within a regulatory context. The goal is to encourage researchers to consider how their research could be designed and conducted in a purposeful way to inform regulatory activities, as opposed to evaluating treatment outcomes or enhancing scientific knowledge generally. These researchers are being trained on a common language and scientific approaches that apply to the types of research and information needed to help support regulatory policies and activities.

Toward that end, CTP has focused on engaging scientists who traditionally do not work on tobacco-related topics. The work of chemists, microbiologists, toxicologists, epidemiologists, social scientists, and others might not be specific to tobacco, but their skills and investigative models could be applied to tobacco regulatory science. Furthermore, CTP has been purposeful in creating funding opportunities for investigators at all different levels of their careers—graduate students (through grants and TCORS), postdoctoral researchers, and early career investigators or transitioning researchers who have a Ph.D. in one science but are now applying that scientific background to tobacco-related research.

Training Requirements in TCORS Funding Opportunities

CTP's funding opportunities have incorporated training as part of funding requirements. For example, as part of the TCORS Funding Opportunity Announcement and award, each TCORS was required to include a training "core"—an education plan to train new investigators to conduct cutting-edge research related to regulatory science. TCORS have been given the flexibility to design and enhance their training cores to meet their institutional capabilities and interests. Accordingly, TCORS training cores might include the development of complete multidisciplinary fellowship programs and/or intensive individualized researcher training and mentoring opportunities, in-person and online courses, external workshops, researcher exchange programs, and laboratory, classroom, and field work. TCORS programs are offered to undergraduates, graduate (master's and doctoral) students, postdoctoral students, and more experienced scientists.

In addition, a TCORS Training Workgroup that draws participation from across the 14 TCORS provides the opportunity for information exchange and a collegial environment for the interchange of ideas and knowledge. During the first 2 years, the Training Workgroup divided into four subcommittees: Life Course, Evaluation, Cross-TCORS Collaborations, and Competencies. Each subgroup addressed a variety of training-related topics; these topics are now housed together as training resources in the online Center for Evaluation and Coordination of Training and Research (CECTR) Knowledge Center. Here, mentors and trainees can access information such as recommended core reading lists for tobacco regulatory science trainees, online learning opportunities, recorded lectures from across the TCORS, and information on current fellowship and other career opportunities. The Training Workgroup also hosts monthly presentations—some made by senior scientists to educate the trainees and others made by the trainees themselves; recent topics have included how science informs policy and how to communicate findings through dockets. Finally, the Training Workgroup has developed networking opportunities that coincide with professional meetings (such as the Society for Research on Nicotine and Tobacco [SRNT] annual meeting) to ensure that young regulatory science investigators can meet face to face and build a community.

Career Development Awards

Aside from TCORS training opportunities, CTP also offers Career Development Awards through our collaboration with TRSP (K awards) to young doctoral-level investigators to give them an opportunity to develop a small research project with a view toward building a research portfolio. These awards include the following:

- **Mentored Clinical Scientist Research Career Development Award in Tobacco Control Regulatory Research (K08):** To prepare qualified individuals for careers that have a significant impact on and will inform the development and evaluation of regulations on tobacco product manufacture, distribution, and marketing.
- **Mentored Research Scientist Career Development Award in Tobacco Control Regulatory Research (K01):** To provide support and protected time (3, 4, or 5 years) for an intensive, supervised career development experience in biomedical, behavioral, and social science research that will inform the development and evaluation of regulations on tobacco product manufacturing, distribution, and marketing and that will lead to research independence.
- **Transition Career Development Award in Tobacco Control Regulatory Research (K22):** To facilitate the transition of investigators in mentored, nonindependent research positions in biomedical, behavioral, and social sciences to independent faculty research positions conducting research that will inform the development and evaluation of regulations on tobacco product manufacture, distribution, and marketing.
- **Pathway to Independence Award in Tobacco Control Regulatory Research (K99/ROO):** To facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position conducting research that will inform the development and evaluation of regulations on tobacco product manufacture, distribution, and marketing.

To date, six Career Development Awards have been awarded through the CTP-TRSP partnership:

- Evaluation of Very Low Nicotine Content Cigarettes in Adolescent Smokers (Rachel Cassidy, Brown University)
- Optimizing Graphic Warning Labels to Promote Cessation Among Young Adult Smokers (Darren Mays, Georgetown University)
- Unjust Targeting: How Marketing Features Impact Consumer Response and Tobacco Use (Meghan B. Moran, San Diego State University)
- EMA [ecological momentary assessment] and Lab Assessment of Nicotine Dependence Among Dual ENDS Users (Jennifer L. Pearson, The Truth Initiative)
- Communicating Harm of New Tobacco Products (Lyudmila Popova, University of California, San Francisco)
- Developing and Testing Warning Statements About E-Cigarettes (Olivia Wackowski, Rutgers University)

Small Grants for New Investigators

Through NIH, CTP also funds Tobacco Regulatory Science Small Grants for New Investigators (RO3) for young researchers who have not successfully competed for an independent research award (such as an NIH RO1 award). The purpose of the RO3 grants is to support new investigators in the biomedical, behavioral, and social sciences who are in the early stages of establishing independent careers in tobacco regulatory research. In FY14, an RO3 funding opportunity was included as part of a larger funding opportunity announcement (FOA); two RO3 grants were awarded: Dual Cigarette and Smokeless Tobacco Use: Behavior Patterns and Toxicant Exposure (Melissa D. Blank, West Virginia University), and Emerging Product Perceptions and Use Among African Americans (Kari-Lyn Kobayakawa Sakuma, Oregon State University). In FY15, an FOA was published specifically for RO3 grants; this FOA funded 24 grants with four receipt dates through FY17.

CTP Internships and Fellowships

CTP facilitates various opportunities that allow external scientists and students to obtain training related to regulatory science.

- The **Oak Ridge Institute for Science and Education (ORISE) Fellowship** is an educational and training program designed to provide students, recent graduates, and university faculty with opportunities to participate in project-specific research and developmental activities. The program provides educational experiences and training in public health to introduce participants to potential public health careers. Appointments are generally for 1 year, but can be extended for up to a total of 5 years.

- The **FDA Tobacco Regulatory Science Fellowship**, a collaborative effort between CTP and the National Academy of Medicine, is a 1-year multidisciplinary program held onsite at CTP. This fellowship allows mid-career professionals to experience and further define and develop the field of regulatory science as it relates to the regulation of tobacco products and the Tobacco Control Act. This is an excellent opportunity for professionals to actively participate in the development of science-based public health strategies, serve as the lead for defined projects, meet with policy leaders, and acquire new knowledge related to tobacco products and their use.
- The 2-year **FDA Commissioner’s Fellowship Program** provides intensive training on FDA regulatory science to health professionals and scientists working in fields such as medical devices, drugs, biologics, foods, tobacco, and cosmetics. Fellows take rigorous graduate-level coursework and develop a regulatory science research project under the mentorship and guidance of an FDA senior scientist.
- **FDA Pathways Internships** expose students enrolled in high school, home-school programs, vocational and technical schools, undergraduate programs, and graduate programs to careers in federal civil service by providing meaningful career development work. Interns may work temporarily for up to 1 year for an initial period, or for an indefinite period, to complete the educational requirement; interns may be full time, part time, or seasonal.
- The **CTP Student Volunteer Program** offers unpaid educational training opportunities and work experience to students enrolled in an accredited educational institution. There is no limit on the number of times students may volunteer as long as they do not exceed 6 months in a calendar year, except when their academic program requires 1 year of volunteer service to satisfy academic requirements.

Internal Training

CTP-OS is committed to providing ongoing training opportunities to its employees as well. CTP-OS scientists may avail themselves of many educational opportunities to enhance their knowledge of a subject. Such opportunities include “lunch and learn” events, scientific seminars, and workshops at FDA, as well as external conferences, presentations, and meetings.

Investment in training tobacco regulatory scientists is a worthwhile pursuit. Although tobacco control research is well established, CTP-OS will continue to require new and different types of tobacco research. Given the ever-changing tobacco marketplace environment and the opportunity for regulation to preserve and protect the public health, tobacco regulatory science will be an essential scientific competency for the foreseeable future.



Looking Toward the Future

Looking Toward the Future

In the 8 years since the Tobacco Control Act was enacted, FDA has created a new center and undertaken numerous activities to regulate a previously unregulated product using a public health standard.

The CTP research program has been and will continue to be a critical contributor to the center's wide-ranging accomplishments. Stated simply, research informs all pursuits that are central to CTP's mission: creating regulations and guidance, developing product standards, reviewing tobacco applications, overseeing compliance and enforcement, and providing public education.

TCORS and the PATH Study—as well as grants funded via NIH and research contracts and our work with CDC and NCTR—remain central to our research portfolio, and new projects and initiatives are continually being proposed and evaluated for funding. We continue to pursue focused research projects that will allow us to expand the body of knowledge by filling specific gaps in information related to the use and health effects of the growing number of tobacco products available in the United States. CTP is committed to ensuring that our research program remains strong well into the future in pursuit of our goal of reducing the toll of tobacco use on the nation's health.

References

REFERENCES

1. U.S. Centers for Disease Control and Prevention, National Center for Health Statistics. *Early Release of Selected Estimates Based on Data From the 2015 National Health Interview Survey*. May 2016. <https://www.cdc.gov/nchs/fastats/smoking.htm>. Accessed February 9, 2017.
2. U.S. Centers for Disease Control and Prevention. *Cigarette Smoking in the United States*. March 13, 2015. <http://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html>. Accessed June 22, 2015.
3. Phillips E, Wang T, Husten C, et al. Tobacco product use among adults - United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017 Nov 10;66(44):1209-1215.
4. Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students - United States, 2011-2016. *MMWR Morb Mortal Wkly Rep*. 2017 Jun 16; 66(23):597-603.
5. Ibid.
6. Husten CG, Deyton LR. Understanding the Tobacco Control Act: Efforts by the U.S. Food and Drug Administration to make tobacco-related morbidity part of the USA's past, not its future. *Lancet*. 2013 May 4;381(9877):1570-1580.
7. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on pivotal public health step to dramatically reduce smoking rates by lowering nicotine in combustible cigarettes to minimally or non-addictive levels. March 15, 2018. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601039.htm>. Accessed April 4, 2018.
8. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors—including menthol—in tobacco products. March 20, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM601690.htm?utm_source=CTPEblast&utm_medium=email&utm_term=sro&utm_content=pressrelease&utm_campaign=ctp-flavanprm. Accessed April 4, 2018.
9. *Federal Register*. Regulation of premium cigars. March 26, 2018. <https://www.federalregister.gov/documents/2018/03/26/2018-06047/regulation-of-premium-cigars>. Accessed April 4, 2018.
10. Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students—United States, 2011–2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:597-603.
11. Kasza KA, Ambrose BA, Conway KP, et al. Tobacco product use by adults and youths in the United States in 2013 and 2014. *N Engl J Med*. 2017;376:342-353.
12. Ibid.
13. Inoue-Choi M, Liao LM, Reyes-Guzman C, et al. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health–AARP Diet and Health Study. *JAMA Intern Med*. 2017;177(1):87-95.
14. Crystal RG. Airway basal cells: the “smoking gun” of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2014 Dec 15;190(12):1355-1362.
15. Walters MS, De BP, Salit J, et al. Smoking accelerates aging of the small airway epithelium. *Respir Res*. 2014 Sep 24;15(1):94.
16. DeJarnett N, Conklin DJ, Riggs DW, Myers JA, O’Toole TE, Hamzeh I. Acrolein exposure is associated with increased cardiovascular disease risk. *J Am Heart Assoc*. 2014 Aug 6;3(4).
17. Al Rifai M, DeFilippis AP, McEvoy JW, et al. The relationship between smoking intensity and subclinical cardiovascular injury: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2017 Mar;258:119-130.
18. Morgan JC, Byron MJ, Baig SA, et al. How people think about the chemicals in cigarette smoke: a systematic review. *J Behav Med*. 2017;40(4):553-564.
19. Pearson JL, Johnson A, Villanti A, et al. Misperceptions of harm among Natural American Spirit smokers: results from wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Tob Control*. 2017 Mar;26(e1):e61-67.
20. Evans AT, Peters E, Strasser AA, Emery LF, Sheerin KM, Romer D. Graphic warning labels elicit affective and thoughtful responses from smokers: results of a randomized clinical trial. *PLoS One*. 2015 Dec 16;10(12):e0142879.
21. Noar SM, Francis DB, Bridges C, et al. The impact of strengthening cigarette pack warnings: systematic review of longitudinal observational studies. *Soc Sci Med*. 2016;164:118-129.

22. Noar SM, Francis DB, Bridges C, et al. Effects of strengthening cigarette pack warnings on attention and message processing: a systematic review. *Journal Mass Commun Q.* 2017;94(2):416-442.
23. Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students - United States, 2011-2016. *MMWR Morb Mortal Wkly Rep.* 2017 Jun 16;66(23):597-603.
24. Ibid.
25. Singh T, Kennedy S, Marynak K, et al. Characteristics of electronic cigarette use among middle and high school students - United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(5051):1425-1429.
26. Barrington-Trimis JL, Berhane K, et al. Psychosocial factors associated with adolescent electronic cigarette and cigarette use. *Pediatrics.* 2015;136(2):308-317.
27. Villanti AC, Pearson JL, Glasser AM, et al. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: measurement precision is critical to inform public health. *Nicotine Tob Res.* 2016 Dec 24.
28. Chaffee BW, Couch ET, Gansky SA. Trends in characteristics and multi-product use among adolescents who use electronic cigarettes, United States 2011-2015. *PLoS ONE* 2017;12(5): e0177073.
29. Coleman BN, Rostron B, Johnson SE, et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Tob Control.* [Epub ahead of print: 17 June 2017].
30. Wagner NJ, Camerota M, Propper C. Prevalence and perceptions of electronic cigarette use during pregnancy. *Matern Child Health J.* 2017;21:1655.
31. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res.* 2015 Jul;17(7):847-854.
32. Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among US youth aged 12-17 years, 2013-2014. *JAMA.* 2015;314(17):1871-1873.
33. Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for trying e-cigarettes and risk of continued use. *Pediatrics.* 2016 Sep;138(3).
34. Baweja R, Curci KM, Yingst J, et al. Views of experienced electronic cigarette users. *Addict Res Theory.* 2016; 24(1):80-88.
35. Cataldo JK, Petersen AB, Hunter M, Wang J, Sheon N. E-cigarette marketing and older smokers: road to renormalization. *Am J Health Behav.* 2015 May;39(3):361-371.
36. Coleman BN, Johnson SE, Tessman GK, et al. “It’s not smoke. It’s not tar. It’s not 4000 chemicals. Case closed”: exploring attitudes, beliefs, and perceived social norms of e-cigarette use among adult users. *Drug Alcohol Depend.* 2016 Feb 1;159:80-85.
37. Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored tobacco product use among middle and high school students - United States, 2014. *MMWR Morbid Mortal Wkly Rep.* 2015;64(38):1066-1070.
38. Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among US youth aged 12-17 years, 2013-2014. *JAMA.* 2015;314(17):1871-1873.
39. Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. E-cigarette use among high school and middle school adolescents in Connecticut. *Nicotine Tob Res.* 2015 Jul;17(7):810-818.
40. Pepper JK, Ribisl KM, Brewer NT. Adolescents’ interest in trying flavoured e-cigarettes. *Tob Control.* 2016;25(2):ii103-ii105.
41. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: characterizing youth, young adult, and adult users. *Prev Med Rep.* 2016;5:33-40.
42. Soule EK, Lopez AA, Guy MC, Cobb CO. Reasons for using flavored liquids among electronic cigarette users: a concept mapping study. *Drug Alcohol Depend.* 2016 Sep 1;166:168-176.
43. Trinidad DR, Pierce JP, Sargent JD, et al. Susceptibility to tobacco product use among youth in Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Prev Med.* 2017 Aug;101:8-14.
44. Pierce JP, Sargent JC, White MM, et al. Receptivity to tobacco advertising and susceptibility to tobacco products. *Pediatrics.* 2017 Jun;139(6).
45. Miller S, Pike J, Chapman J, et al. The prevalence and marketing of electronic cigarettes in proximity to at-risk youths: an investigation of point-of-sale practices near alternative high schools. *J Child Adolesc Subst Abuse.* 2017;26(2):119-124. [Epub 2016 Oct 19]

46. Nicksic NE, Snell LM, Rudy AK, Cobb CO, Barnes AJ. Tobacco marketing, e-cigarette susceptibility, and perceptions among adults. *Am J Health Behav.* 2017 Sep 1;41(5):579-590. doi: 10.5993/AJHB.41.5.7.
47. Maloney EK, Cappella JN. Does vaping in e-cigarette advertisements affect tobacco smoking urge, intentions, and perceptions in daily, intermittent, and former smokers? *Health Commun.* 2016;31(1):129-138.
48. Chu KH, Unger JB, Cruz TB, Soto DW. Electronic cigarettes on Twitter—spreading the appeal of flavors. *Tob Regul Sci.* 2015 Apr;1(1):36-41.
49. Luo C, Zheng X, Zeng DD, Leischow S. Portrayal of electronic cigarettes on YouTube. *BMC Public Health.* 2014 Oct 3;14:1028.
50. Hall MG, Pepper JK, Morgan JC, Brewer NT. Social Interactions as a source of information about e-cigarettes: a study of US adult smokers. *Int J Environ Res Public Health.* 2016 Aug 5;13(8).
51. El-Hellani A, El-Hage R, Baalbaki R, et al. Free-base and protonated nicotine in electronic cigarette liquids and aerosols. *Chem Res Toxicol.* 2015;28:1532-1537.
52. Davis ES, Sassano MF, Goodell H, Tarran R. E-liquid autofluorescence can be used as a marker of vaping deposition and third-hand vape exposure. *Sci Reports.* 2017;7:7459.
53. Jensen RP, Strongin RM, Peyton DH. Solvent chemistry in the electronic cigarette reaction vessel. *Sci Reports.* 2017;7:42549.
54. Salamanca, JC, Munhehza I, Escobedo JO, et al. Formaldehyde hemiacetal sampling, recovery, and quantification from electronic cigarette aerosols. *Sci Reports.* 2017;7:11044
55. Spindle TR, Breland AB, Karaoghlanian NV, et al. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. *Nicotine Tob Res.* 2015 Feb;17(2):142-149.
56. St Helen G, Ross KC, Dempsey DA, et al. Nicotine delivery and vaping behavior during ad libitum e-cigarette access. *Tob Regul Sci.* 2016 Oct;2(4):363-376.
57. Ramôa CP, Hiler MM, Spindle TR, et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. *Tob Control.* 2016 Apr;25(e1):e6-9.
58. Lopez AA, Hiler MM, Soule EK, et al. Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: a preliminary report. *Nicotine Tob Res.* 2016 May;18(5):720-723.
59. Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control.* 2014 May;23 Suppl 2:ii11-17.
60. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One.* 2015 Feb 6;10(2):e0116732.
61. Allen JG, Flanigan SS, LeBlanc M, et al. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environ Health Perspect.* 2016 Jun;124(6):733-739.
62. Clapp PW, Pawlak EA, Lackey JT, et al. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am J Physiol Lung Cell Mol Physiol.* 2017 Aug 1;313(2):L278-L292.
63. Rudy SF, Durmowicz EL. Electronic nicotine delivery systems: overheating, fires and explosions. *Tob Control.* 2017;26:10-18.
64. Nonnemaker J, Rostron B, Hall P, MacMonegle A, Apelberg B. Mortality and economic costs from regular cigar use in the United States, 2010. *Am J Public Health.* 2014 Sep;104(9):e86-91.
65. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health.* 2015 Apr 24;15:390.
66. Chen J, Kettermann A, Rostron B, Day H. Biomarkers of exposure among U.S. cigar smokers: an analysis of 1999-2012 National Health and Nutrition Examination Survey (NHANES) data. *Cancer Epidemiol Biomarkers Prev.* 2014 Dec;23(12):2906-2915.
67. Liu J, Wang X, Narayan S, Glantz S, Schick S, Springer M. Impairment of endothelial function by little cigar secondhand smoke. *Tob Regul Sci.* 2016 Jan;2(1):56-63.
68. Ghosh A, Abdelwahab SH, Reeber SL, et al. Little cigars are more toxic than cigarettes and uniquely change the airway gene and protein expression. *Sci Rep.* 2017 Apr 27;7:46239.
69. Koszowski B, Thanner MH, Pickworth WB, Taylor KM, Hull LC, Schroeder MJ. Nicotine content and physical properties of large cigars and cigarillos in the United States. *Nicotine Tob Res.* 2018 Feb 7;20(3):393-398. [Epub 2017 Mar 4]

70. Delnevo CD, Giovenco DP, Ambrose BK, Corey CG, Conway KP. Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tob Control*. 2015 Jul;24(4):389-394. [Epub 2014 Apr 10]
71. Sterling KL, Fryer CS, Nix M, Fagan P. Appeal and impact of characterizing flavors on young adult small cigar use. *Tob Regul Sci*. 2015 Apr;1:42-53.
72. Cheng YC, Rostron BL, Day HR, et al. Patterns of use of smokeless tobacco in US adults, 2013-2014. *Am J Public Health*. 2017 Sep;107(9):1508-1514.
73. Roberts ME, Doogan NJ, Kurti AN, et al. Rural tobacco use across the United States: how rural and urban areas differ, broken down by census regions and divisions. *Health Place*. 2016 May;39:153-159.
74. Cheng YC, Rostron BL, Day HR, et al. Patterns of use of smokeless tobacco in US adults, 2013-2014. *Am J Public Health*. 2017 Sep;107(9):1508-1514.
75. Richardson A, Pearson J, Xiao H, Stalgaitis C, Vallone D. Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. *Am J Public Health*. 2014 Aug;104(8):1437-1444.
76. Tam J, Day HR, Rostron BL, Apelberg BJ. A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. *BMC Public Health*. 2015 Mar 18;15:258.
77. Feirman SP, Donaldson EA, Parascandola M, Snyder K, Tworek C. Monitoring harm perceptions of smokeless tobacco products among U.S. adults: Health Information National Trends Survey 2012, 2014, 2015. *Addict Behav*. 2017 Sep 9;77:7-15.
78. Persoskie A, O'Brien EK, Nguyen AB, Tworek C. Measuring youth beliefs about the harms of e-cigarettes and smokeless tobacco compared to cigarettes. *Addict Behav*. 2017 Jul;70:7-13.
79. Choi K, Forster JL. Awareness, perceptions, and use of snus among young adults from the upper Midwest region of the U.S.A. *Tob Control*. 2013 Nov;22(6):412-417.
80. Kaufman A, Mays D, Koblitz A, Portnoy D. Judgments, awareness, and the use of snus among adults in the United States. *Nicotine Tob Res*. 2014 Oct;16(10):1404-1408.
81. Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the U.S: findings from an internet-based cross-sectional survey. *Harm Reduct J*. 2014 Jan 17;11:2.
82. Harris A, Tally L, Schmidt C, Muelken P, Stepanov I, Saha S. Animal models to assess the abuse liability of tobacco products: effects of smokeless tobacco extracts on intracranial self-stimulation. *Drug Alcohol Depend*. 2015 Feb 1;147:60-67.
83. Stepanov I, Yershova K, Carmella S, Upadhyaya P, Hecht SS. Levels of (S)-N'-nitrosornicotine in U.S. tobacco products. *Nicotine Tob Res*. 2013 Jul;15(7):1305-1310.
84. Ammann JR, Lovejoy KS, Walters MJ, Holman MR. A survey of N'-nitrosornicotine (NNN) and total water content in select smokeless tobacco products purchased in the United States in 2015. *J Agric Food Chem*. 2016 Jun 1;64(21):4400-4406.
85. Rostron BL, Chang, CM, van Bommel, DM, Yang, X, Blount, BC. Nicotine and toxicant exposure among U.S. smokeless tobacco users: results from 1999 to 2012 National Health and Nutrition Examination Survey data. *Cancer Epidemiol Biomarkers Prev*. 2015 Dec;24(12):1829-1837.
86. Sun J, Jin J, Beger RD, Cerniglia CE, Yang M, Chen H. Metabolomics evaluation of the impact of smokeless tobacco exposure on the oral bacterium *Capnocytophaga sputigena*. *Toxicol In Vitro*. 2016 Oct;36:133-141.
87. Ibid.
88. Han J, Sanad YM, Deck J, et al. Bacterial populations associated with smokeless tobacco products. *Appl Environ Microbiol*. 2016 Sep 30;82(20):6273-6283.
89. Hu SS, Neff L, Agaku IT, et al. Tobacco product use among adults - United States, 2013-2014. *MMWR Morb Mortal Wkly Rep*. 2016 Jul 15;65(27):685-691.
90. Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students - United States, 2011-2016. *MMWR Morb Mortal Wkly Rep*. 2017 Jun 16; 66(23):597-603.
91. Robinson J, Wang B, Jackson K, Donaldson E, Ryant C. Characteristics of hookah tobacco smoking sessions and correlates of use frequency among US adults: findings from Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine Tob Res*. 2018 May 3;20(6):731-740. [Epub 2017 Mar 4]
92. Trinidad DR, Pierce JP, Sargent JD, et al. Susceptibility to tobacco product use among youth in wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Prev Med*. 2017 Aug;101:8-14.

93. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students - United States, 2011-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(14):361-367.
94. Gilreath TD, Leventhal A, Barrington-Trimis JL, et al. Patterns of alternative tobacco product use: emergence of hookah and e-cigarettes as preferred products amongst youth. *J Adolesc Health.* 2016 Feb;58(2):181-185.
95. Mays D, Arrazola RA, Tworek C, Rolle IV, Neff LJ, Portnoy DP. Openness to using non-cigarette tobacco products among US young adults. *Am J Prev Med.* 2016 Apr;50(4):528-534.
96. Kurti AN, Redner R, Lopez AA, et al. Tobacco and nicotine delivery product use in a national sample of pregnant women. *Prev Med.* 2017 Nov;104:50-56. [Epub 2017 Aug 5]
97. Majeed BA, Sterling KL, Weaver SR, Pechacek TF, Eriksen MP. Prevalence and harm perceptions of hookah smoking among U.S. adults, 2014-2015. *Addict Behav.* 2017 Jun;69:78-86.
98. Conway KP, Green VR, Kasza KA, et al. Co-occurrence of tobacco product use, substance use, and mental health problems among youth: findings from Wave 1 (2013-2014) of the Population Assessment of Tobacco and Health (PATH) Study. *Addict Behav.* 2018 Jan;76:208-217. [Epub 2017 Aug 18]
99. Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored tobacco product use among middle and high school students - United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015 Oct 2;64(38):1066-1070.
100. Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among U.S. youth aged 12-17 years: 2013-2014. *JAMA.* 2015 Nov 3;314(17):1871-1873.
101. Bonhomme MG, Holder-Hayes E, Ambrose BK, et al. Flavoured non-cigarette tobacco product use among US adults: 2013-2014. *Tob Control.* 2016 Nov;25(Suppl 2):ii4-ii13.
102. Haddad L, El-Shahawy O, Ghadban R, Barnett TE, Johnson E. Waterpipe smoking and regulation in the United States: a comprehensive review of the literature. *Int J Environ Res Public Health.* 2015 May 29;12(6):6115-6135.
103. Tworek C, Schauer GL, Wu CC, Malarcher AM, Jackson KJ, Hoffman AC. Youth tobacco cessation: quitting intentions and past-year quit attempts. *Am J Prev Med.* 2014 Aug;47(2 Suppl 1):S15-27.
104. Cornacchione J, Wagoner KG, Wiseman KD, et al. Adolescent and young adult perceptions of hookah and little cigars/cigarillos: implications for risk messages. *J Health Commun.* 2016 Jul;21(7):818-825.
105. Abouziza E, Eissenberg T. Waterpipe tobacco smoking: what is the evidence that it supports nicotine/tobacco dependence? *Tob Control.* 2015 Mar;24 Suppl 1:i44-i53.
106. Shihadeh A, Schubert J, Klaiany J, El Sabban M, Luch A, Saliba NA. Toxicant content, physical properties and biological activity of waterpipe tobacco smoke and its tobacco-free alternatives. *Tob Control.* 2015;24 Suppl 1:i22-i30.
107. Ramoa CP, Shihadeh A, Salman R, Eissenberg T. Group waterpipe tobacco smoking increases smoke toxicant concentration. *Nicotine Tob Res.* 2016 May;18(5):770-776.
108. Zhou S, Weitzman M, Vilcassim R, Wilson J, Legrand N, Saunders E. Air quality in New York City hookah bars. *Tob Control.* 2015 Oct;24(e3):e193-198. [Epub 2015 Sept 16]
109. Villanti AC, Pearson JL, Cantrell J, Vallone DM, Rath JM. Patterns of combustible tobacco use in U.S. young adults and potential response to graphic cigarette health warning labels. *Addict Behav.* 2015 Mar;42:119-125.
110. Southwell BG, Kim AE, Tessman GK, MacMonegle AJ, Choiniere CJ, Evans SE. The marketing of dissolvable tobacco: social science and public policy research needs. *Am J Health Promot.* 2012 Jul-Aug;26(6):331-332.
111. Chaffee B, Couch E, Essex G, Walsh M. Smoking: tobacco trends. *Br Dent J.* 2014 Mar;216(6):266.
112. Mays D, Arrazola RA, Tworek C, Rolle IV, Neff LJ, Portnoy DP. Openness to using non-cigarette tobacco products among US young adults. *Am J Prev Med.* 2016 Apr;50(4):528-534.
113. England LI, Tong VT, Koblitz A, Kish-Doto J, Lynch MM, Southwell BG. Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Prev Med Rep.* 2016 Sep 7;4:481-485.
114. Wang B, Rostron B. Tobacco-related poison events involving young children in the US, 2001-2016. *Tob Reg Sci.* 2017;3(4):525-535.
115. Miao S, Beach ES, Sommer TJ, Zimmerman JB, Jordt SE. High-intensity sweeteners in alternative tobacco products. *Nicotine Tob Res.* 2016 Nov;18(11):2169-2173.
116. Mishina EV, Hoffman AC. Clinical pharmacology research strategy for dissolvable tobacco products. *Nicotine Tob Res.* 2014 Mar;16(3):253-262.
117. Donny E, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med.* 2015 Oct 1;373(14):1340-1349.

118. Smith T, Schassburger R, Buffalari D, Sved A, Donny E. Low-dose nicotine self-administration is reduced in adult male rats naive to high doses of nicotine: implications for nicotine product standards. *Exp Clin Psychopharmacol*. 2014 Oct;22(5):453-459.
119. Vogel R, Hertzgaard L, Dermody S, Luo X, Moua L, Allen S. Sex differences in response to reduced nicotine content cigarettes. *Addict Behav*. 2014 Jul;39(7):1197-1204.
120. Tidey JW, Cassidy RN, Miller ME. Smoking topography characteristics of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. *Nicotine Tob Res*. 2016;18(9):1807-1812.
121. Dermody S, Donny E. The predicted impact of reducing the nicotine content in cigarettes on alcohol use. *Nicotine Tob Res*. 2014 Aug;16(8):1033-1044.
122. Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored tobacco product use among middle and high school students—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015 Oct 2;64(38):1066-1070.
123. Villanti AC, Johnson AL, Ambrose BK, et al. Flavored tobacco product use in youth and adults: findings from the first wave of the PATH Study (2013-2014). *Am J Prev Med*. 2017 Aug;53(2):139-151.
124. Ibid.
125. Huang LL, Baker HM, Meernik C, Ranney LM, Richardson A, Goldstein AO. Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: a systematic review. *Tob Control*. 2017 Nov;26(6):709-719. [Epub 2016 Nov 21]
126. Hoffman AC, Salgado RV, Dresler C, Faller RW, Bartlett C. Flavour preferences in youth versus adults: a review. *Tob Control*. 2016 Nov;25(Suppl 2):ii32-ii39.
127. Bonhomme MG, Holder-Hayes E, Ambrose BK, et al. Flavoured non-cigarette tobacco product use among US adults: 2013-2014. *Tob Control*. 2016 Nov;25(Suppl 2):ii4-ii13.
128. Kowitz SD, Meernik C, Baker HM, Osman A, Huang Li-Ling, Goldstein AO. Perceptions and experiences with flavored non-menthol tobacco products: a systematic review of qualitative studies. *Int J Environ Res Public Health*. 2017 Mar 23;14(4).
129. Gerloff J, Sundar IK, Freter R, et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. *Appl In Vitro Toxicol*. 2017 Mar 1;3(1):28-40.
130. Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). *Tob Control*. 2016 Nov;25(Suppl 2):ii81-ii87.
131. Ghosh A, Nethery RC, Herring AH, Tarran R. Flavored little cigar smoke induces cytotoxicity and apoptosis in airway epithelia. *Cell Death Discov*. 2017 Apr 24;3:17019.
132. Ha MA, Smith GJ, Cichocki JA, Fan L, Liu YS, Caceres AI. Menthol attenuates respiratory irritation and elevates blood cotinine in cigarette smoke exposed mice. *PLoS One*. 2015 Feb 13;10(2):e0117128.
133. Rath JM, Villanti AC, Williams VF, Richardson A, Pearson JL, Vallone DM. Patterns of longitudinal transitions in menthol use among US young adult smokers. *Nicotine Tob Res*. 2015 Jul;17(7):839-846.
134. Krishnan-Sarin S, Green BG, Kong G, et al. Studying the interactive effects of menthol and nicotine among youth: an examination using e-cigarettes. *Drug Alcohol Depend*. 2017 Aug 31;180:193-199.
135. Smith SS, Fiore MC, Baker TB. Smoking cessation in smokers who smoke menthol and non-menthol cigarettes. *Addiction*. 2014 Dec;109(12):2107-2117.
136. Biswas L, Harrison E, Gong Y, et al. Enhancing effect of menthol on nicotine self-administration in rats. *Psychopharmacology (Berl)*. 2016 Sept;233(18):3417-3427.
137. Ai J, Taylor KM, Lisko JG, Tran H, Watson CH, Holman MR. Menthol content in US marketed cigarettes. *Nicotine Tob Res*. 2016 Jul;18(7):1575-1580.
138. Farrelly MC, Duke JC, Nonnemaker J, et al. Association between The Real Cost media campaign and smoking initiation among youths - United States, 2014-2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(2):47-50.
139. Moran MB, Walker MW, Alexander TN, Wagner DE. Why peer crowds matter: incorporating youth subcultures and values in health education campaigns. *Am J Public Health*. 2017;107:389-395.
140. National Cancer Institute, Division of Cancer Control and Population Sciences. NIH-FDA Tobacco Regulatory Science Program (TRSP) Funded Grants. <https://maps.cancer.gov/overview/fda/index.jsp#> Accessed November 20, 2017.
141. Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tob Control*. 2017 Jul;26(4):371-378.

