

A photograph of three scientists in a laboratory setting, wearing white lab coats and safety glasses. They are gathered around a table, looking at something off-camera. The image is overlaid with a semi-transparent blue filter. The text 'Tobacco Harm Reduction' is written in large white letters across the middle of the image.

Tobacco Harm Reduction



Disclaimer

This material was prepared to facilitate discussion with policymakers and government officials regarding government policy and tobacco harm reduction. Without limitation, the topics, proposals, concepts and other matters discussed or described herein are not final, are subject to change and/or cancellation and may be for illustrative or theoretical purposes only. No definitive plans or commitments should be inferred from these materials, and any proposed plans or commitments are subject in all respects to applicable internal reviews and governance requirements.

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Agenda *Click any section for quick navigation, return to agenda from home button in right corner.

1. Tobacco Harm Reduction Overview

2. Reynolds' THR Approach

3. Reynolds' Scientific Assessment



4. Academic / Public Health Science

5. Acceleration of Smoker Migration

6. Public Health Opportunities



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1. Tobacco Harm Reduction Overview

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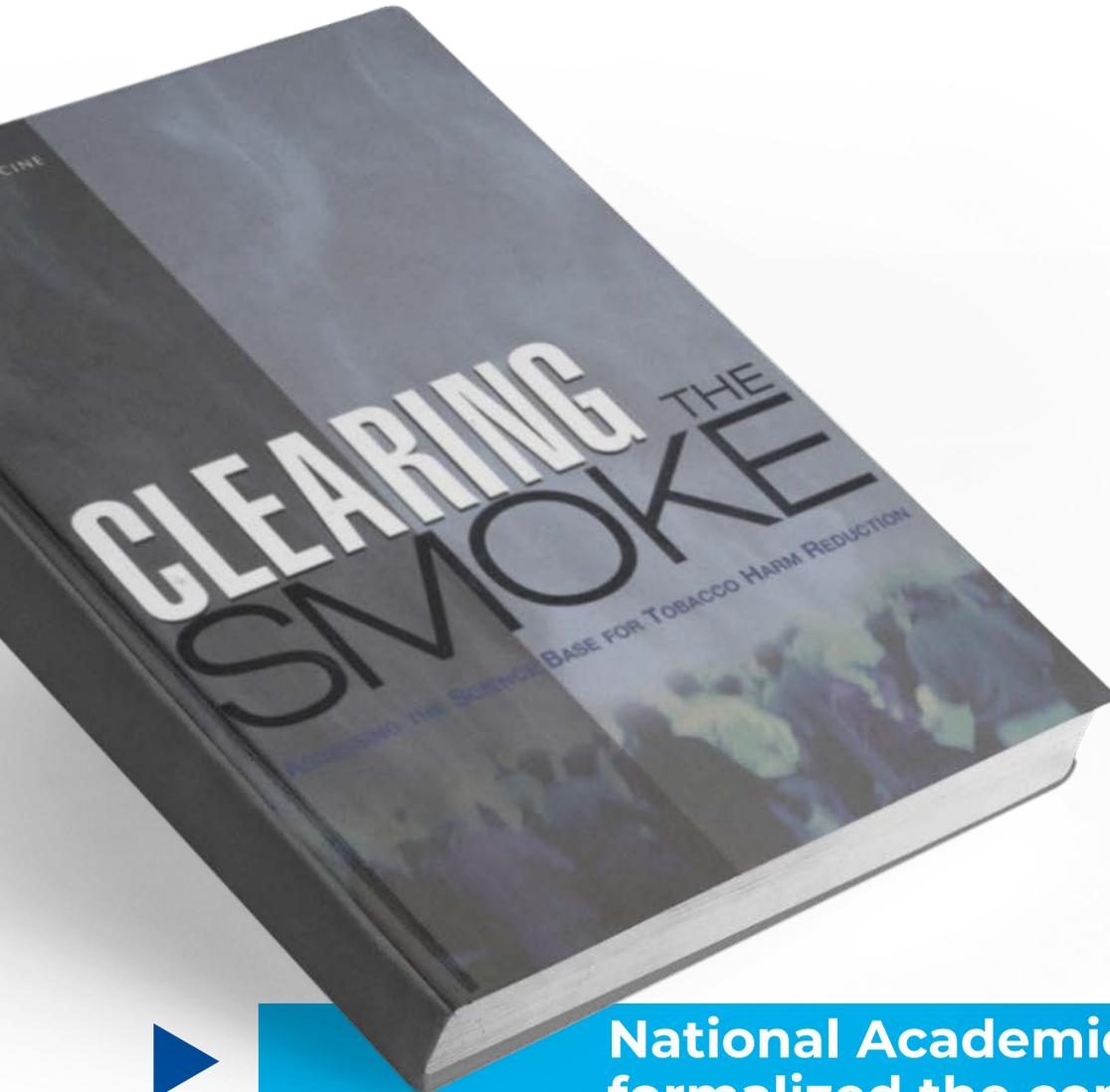


4. Academic / Public Health Science

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Core principles of Tobacco Harm Reduction (THR)

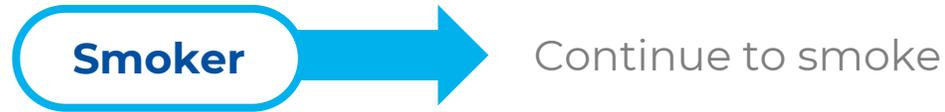


“...[tobacco] harm reduction refers to minimizing harms, decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use.”⁽ⁱ⁾

National Academies of Science, Engineering, & Medicine (formerly Institute of Medicine) formalized the concept of THR

Smoker transitions within Tobacco Harm Reduction

[Zero Tobacco Harm Reduction Benefit]



[Some Tobacco Harm Reduction benefit]



[Full Tobacco Harm Reduction benefit]



 **Smoker status and transitions underpin potential of Tobacco Harm Reduction**

Global perspectives on THR

“The **closer** the **risks** and **exposures** from the **Reduced Risk Products** are **to cessation** ...the more confident a regulator can be in the chances for net **public health benefit**”⁽ⁱⁱⁱ⁾



2001⁽ⁱ⁾

2007⁽ⁱⁱ⁾

2012⁽ⁱⁱⁱ⁾

Science is informing Policy and Regulation globally



Food and Drug Administration



Public Health England*



National institute for Public Health & the Environment

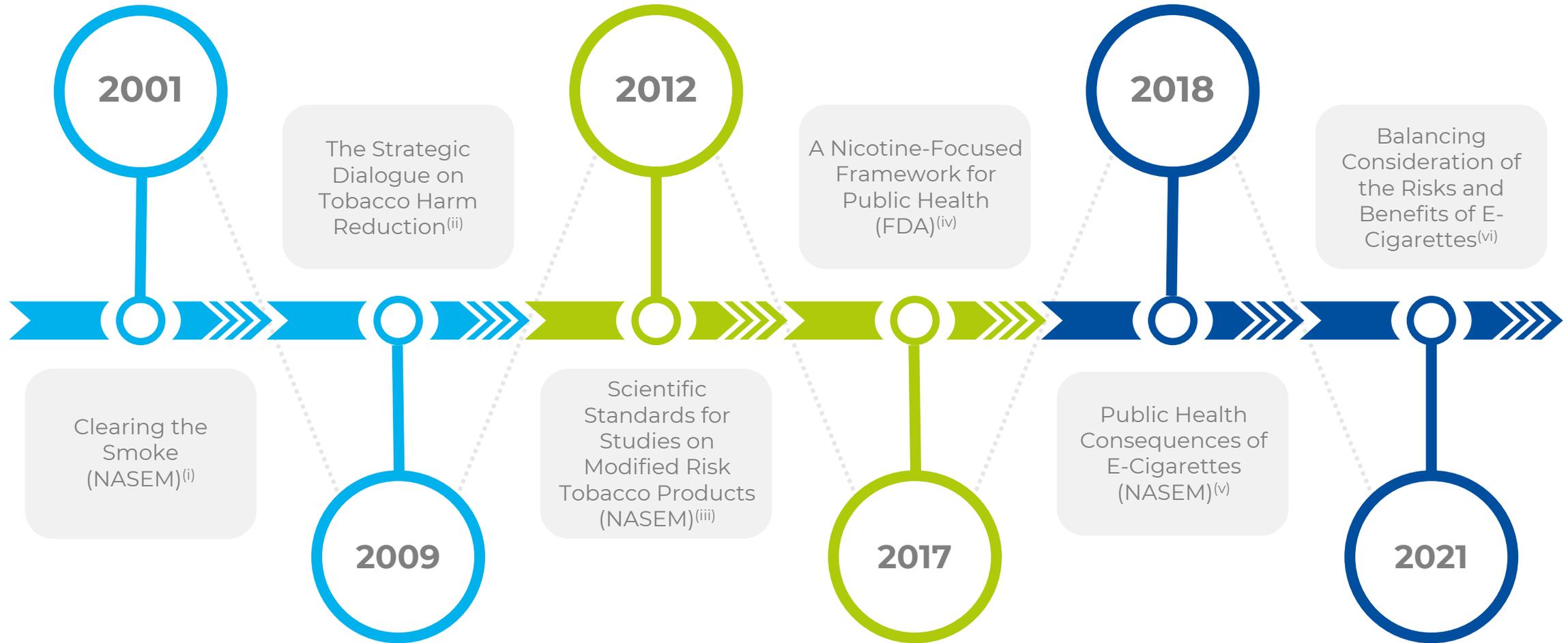


& others



THR globally recognized in Policy and Regulation

Tobacco Harm Reduction timeline



FDA and NASEM are critical stakeholders in THR

Potential THR benefit for the United States is profound



POPULATION:
330 M



SMOKING
PREVALENCE:
14%⁽ⁱ⁾



VAPING
PREVALENCE:
3%⁽ⁱⁱ⁾

“[Modeling] projects that under current patterns of ... use and substitution, [US] nicotine vaping product use will translate into

1.8 million premature... deaths avoided

38.9 million life-years gained^{”(iii)} from 2013-2060



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6. Public Health Opportunities



THR is central to our company's vision

Our Purpose

To reduce the health impact of our business



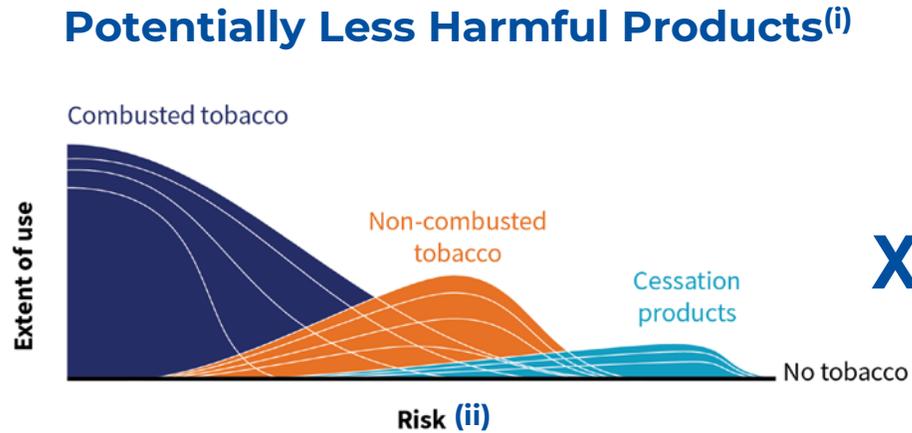
Our Commitment

To provide adult consumers with a wide range of enjoyable and potentially less risky products

Tobacco Harm Reduction strategy

**Tobacco
Harm
Reduction**

=



Number of adult smokers who switch⁽ⁱⁱⁱ⁾

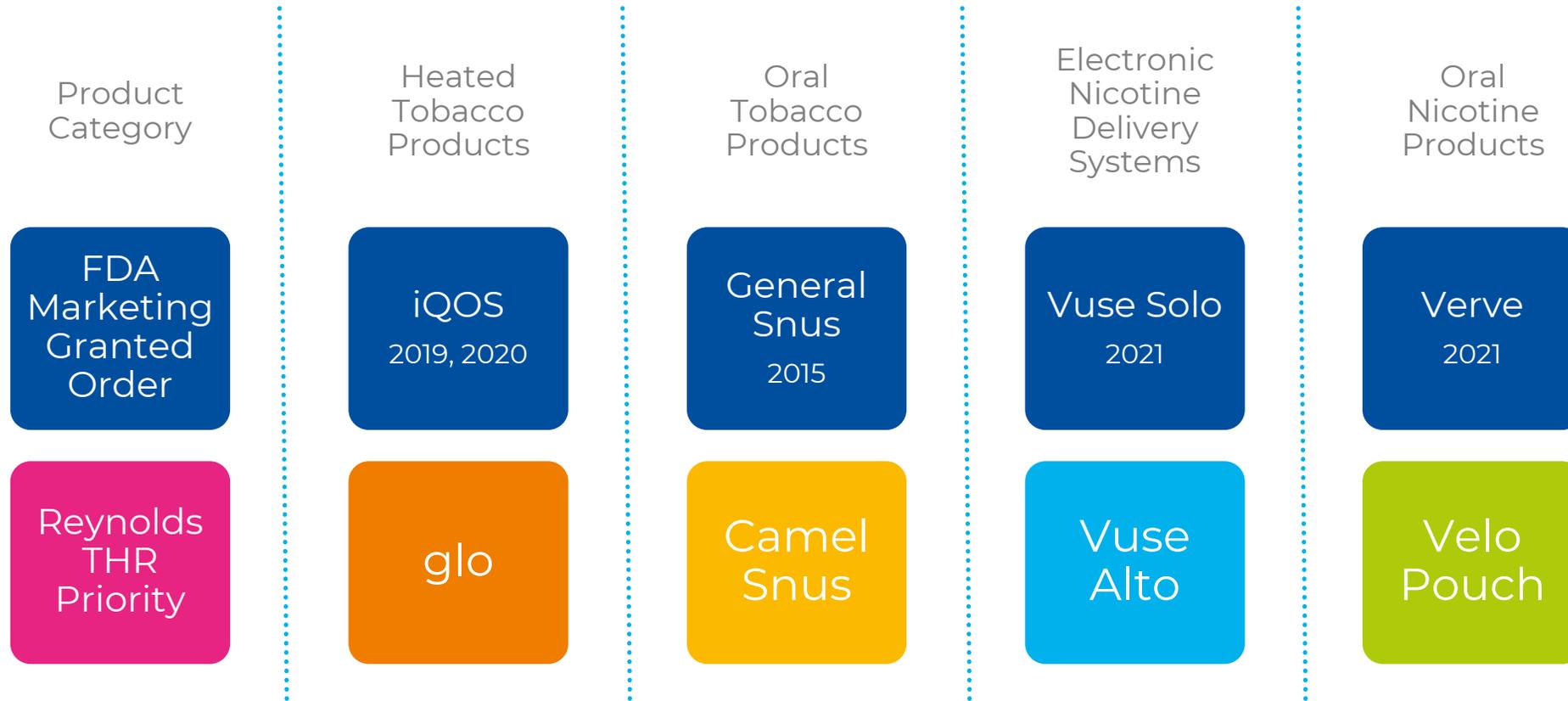


Inflection point when
Adult Smokers =
Adult PLHP users



Reynolds' THR strategy is focused on the mass migration of adult smokers to PLHPs

Potentially Less Harmful Product Platforms⁽ⁱ⁾

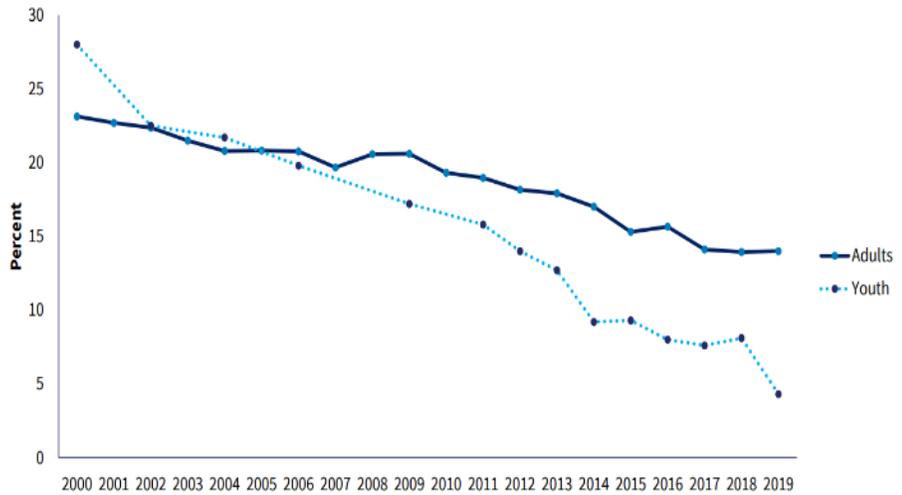


FDA Marketing Granted Orders build adult smokers' confidence to switch to PLHPs

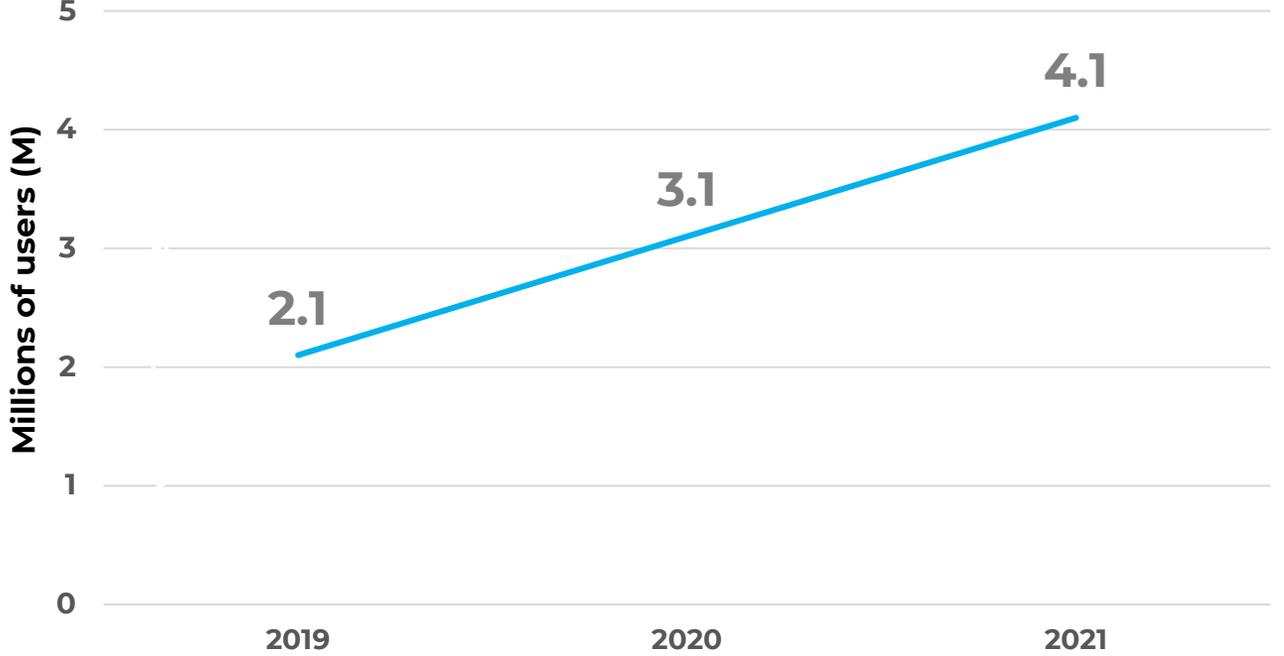
Reynolds' progress on migrating adult smokers down the risk continuum

Decline in cigarette smoking⁽ⁱ⁾

TRENDS IN U.S. ADULT & YOUTH CIGARETTE SMOKING FDA



Adult smokers migrating to Vuse⁽ⁱⁱ⁾



Declining cigarette usage corresponds to increasing adult vapor usage that should contribute to a public health benefit



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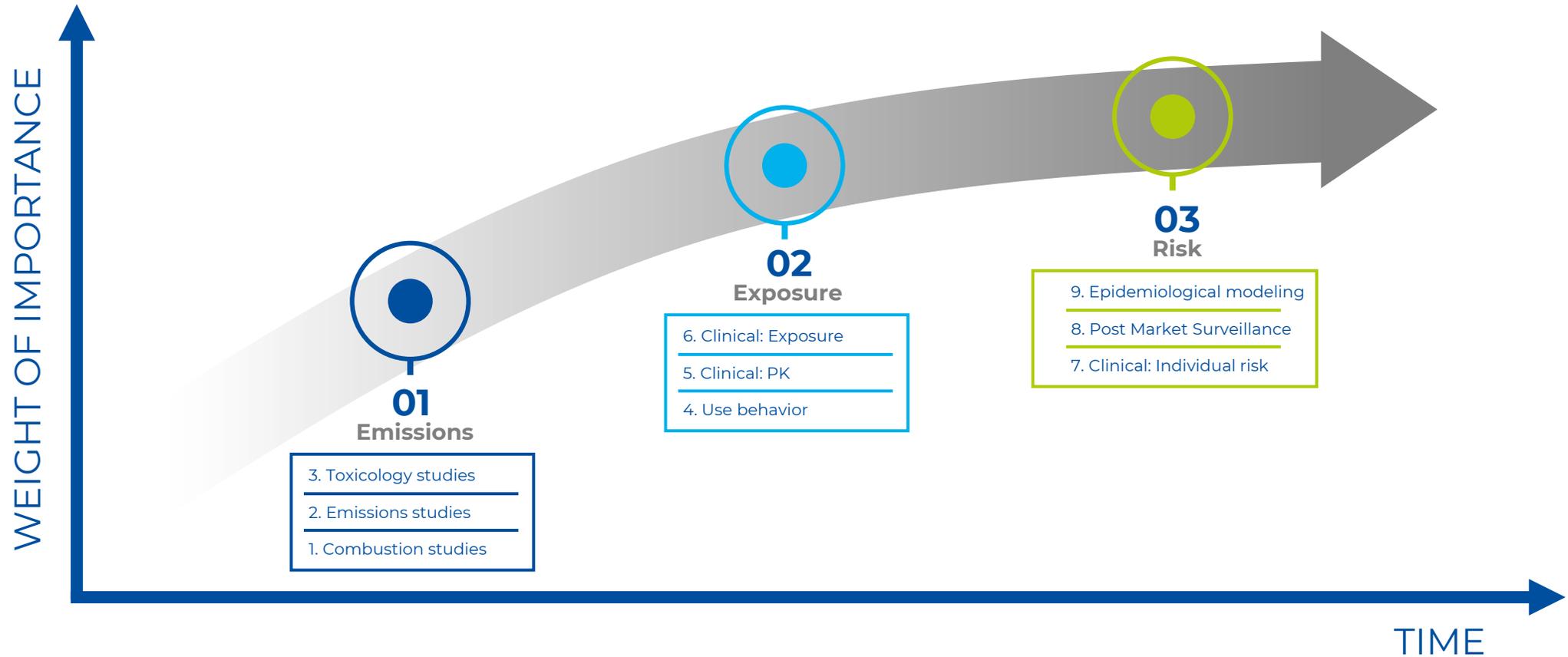


4. Academic / Public Health Science

5. Acceleration of Smoker Migration

6. Public Health Opportunities

Scientific framework for assessing PLHPs in the absence of epidemiology⁽ⁱ⁾



▶ **Reynolds' priority is to uncover science through rigorous assessment of PLHPs**

Scientific Assessment – Thermochemical Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

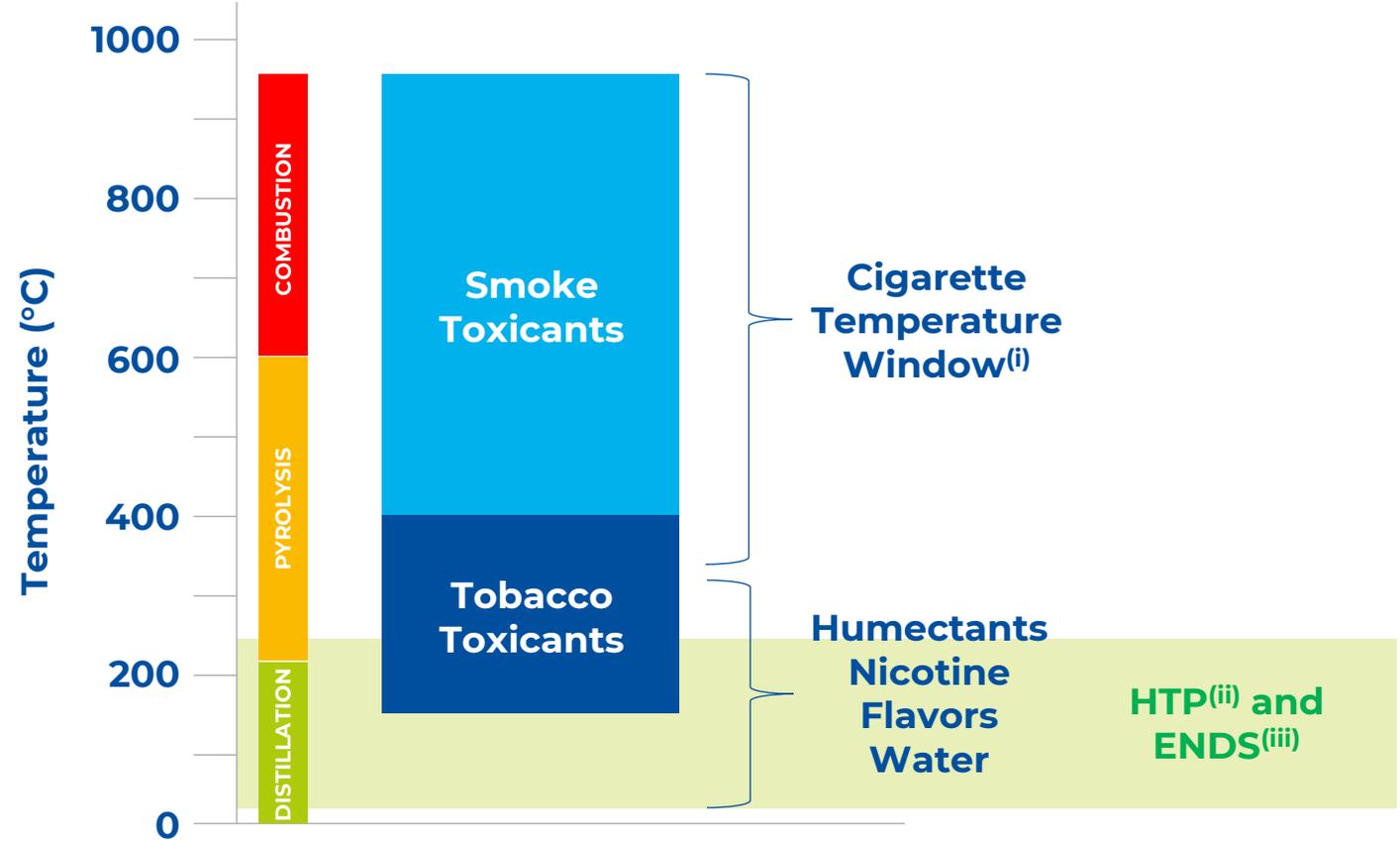
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Thermochemical Analysis of Tobacco and Nicotine Products

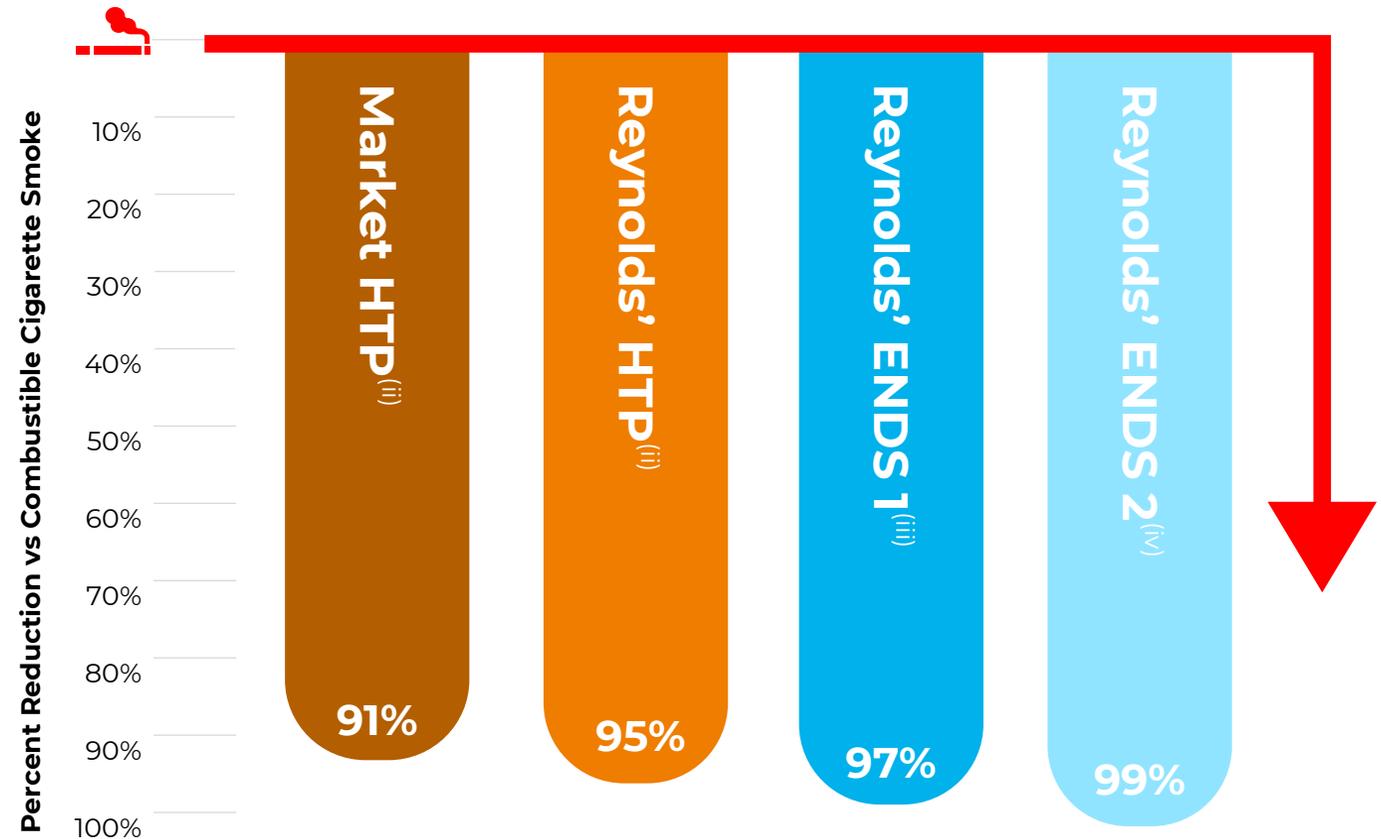


There is no combustion in PLHPs

Scientific Assessment – Chemistry Studies

- Thermochemical Studies
- Chemistry Studies**
- Toxicological Studies
- Exposure Studies
- Abuse Liability Assessments
- Individual Risk Studies
- Population Risk Studies

HTP and ENDS Chemistry Relative to Combustible Cigarette⁽ⁱ⁾



▶ Inhaled PLHPs have lower harmful and potentially harmful constituent (HPHC) yields compared to cigarette smoke

(i) Figure represents reduction in TobReg9 constituents (minus CO) per puff from Burns et al., 2008; (ii) Reynolds' HTP PMTA, STN pending; (iii) Reynolds' ENDS PMTA, STN PM0000973; (iv) Reynolds' ENDS PMTA, STN PM0000551/PM0000560

Scientific Assessment – Chemistry Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

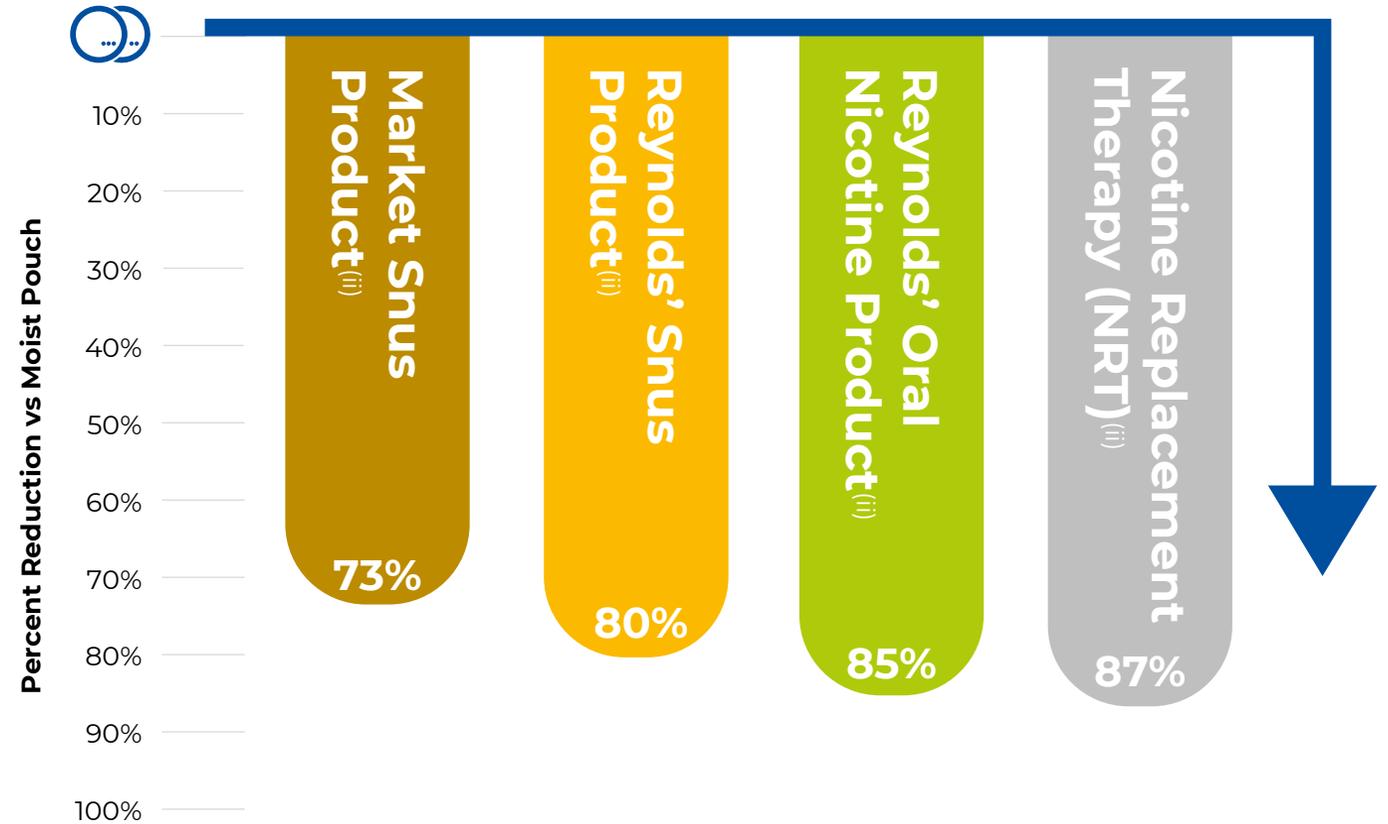
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Snus and Oral Nicotine Product Chemistry Relative to Moist Pouch⁽ⁱ⁾



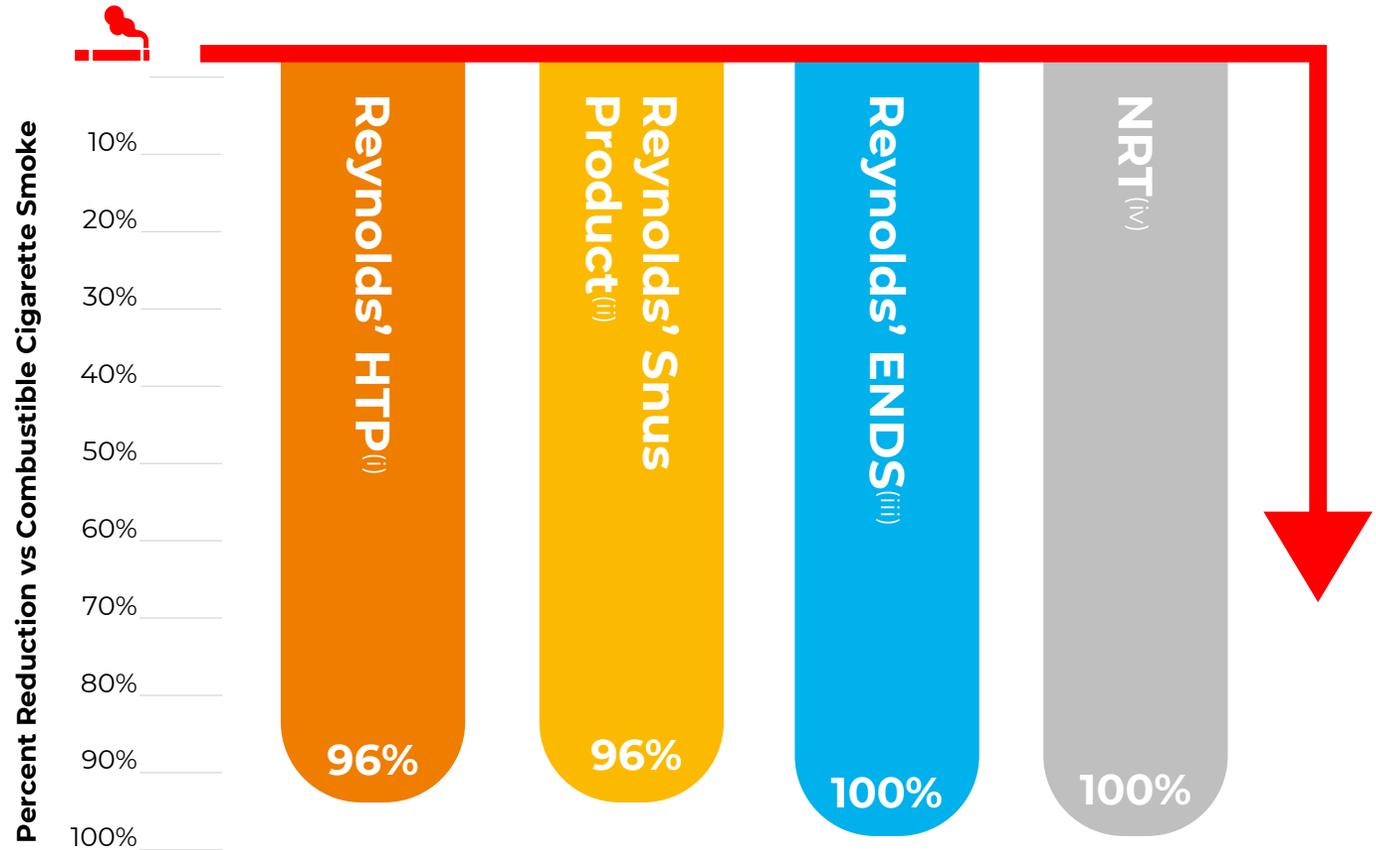
▶ **Oral PLHPs have lower HPHC yields compared to moist pouch**
Moist snuff products are supported by US epidemiology to be PLHPs⁽ⁱⁱⁱ⁾

⁽ⁱ⁾ Figure represents reduction in non-nicotine reportable smokeless tobacco harmful and potentially harmful constituents (HPHCs) per pouch from FDA, 2012;
⁽ⁱⁱ⁾ Reynolds' Oral Nicotine Product PMTA, STN PM0000902; ⁽ⁱⁱⁱ⁾ Henley et al., 2005

Scientific Assessment – Toxicological Studies

- Thermochemical Studies
- Chemistry Studies
- Toxicological Studies**
- Exposure Studies
- Abuse Liability Assessments
- Individual Risk Studies
- Population Risk Studies

PLHP Cytotoxicity Compared with Combustible Cigarettes*



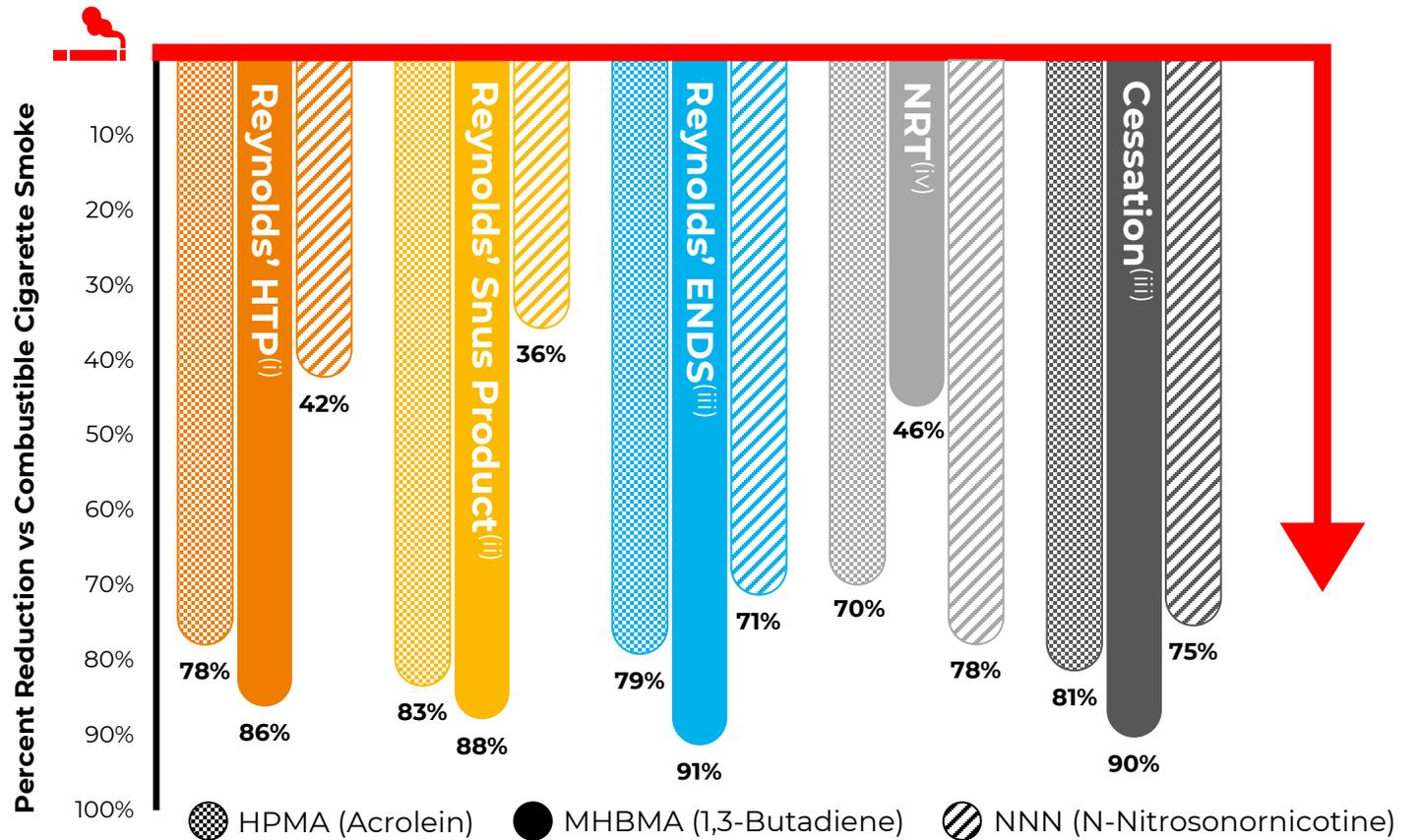
Reduced toxicity across PLHPs relative to cigarette smoke

* Figure represents results from Neutral Red Uptake (NRU) assay. Cytotoxicity shown for illustration purpose, full toxicological evaluation comprised mutagenicity, cytotoxicity and genotoxicity. All studies and publications from which data is presented had concurrently assessed combustible comparators: percent reductions based on assay conditions and doses analyzed. (i) Jaunky et al., 2018; Reynolds' HTP PMTA, STN pending; (ii) Reynolds' Snus Product MRTPA, STN MR000068/MR000069; (iii) Reynolds' Internal ENDS Data, Publication pending; (iv) Misra et al., 2014

Scientific Assessment – Exposure Studies

- Thermochemical Studies
- Chemistry Studies
- Toxicological Studies
- Exposure Studies**
- Abuse Liability Assessments
- Individual Risk Studies
- Population Risk Studies

Biomarkers of Exposure Responses* for PLHPs vs Cessation



Reduced exposure across all PLHPs relative to cigarette smoke

Scientific Assessment – Exposure Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

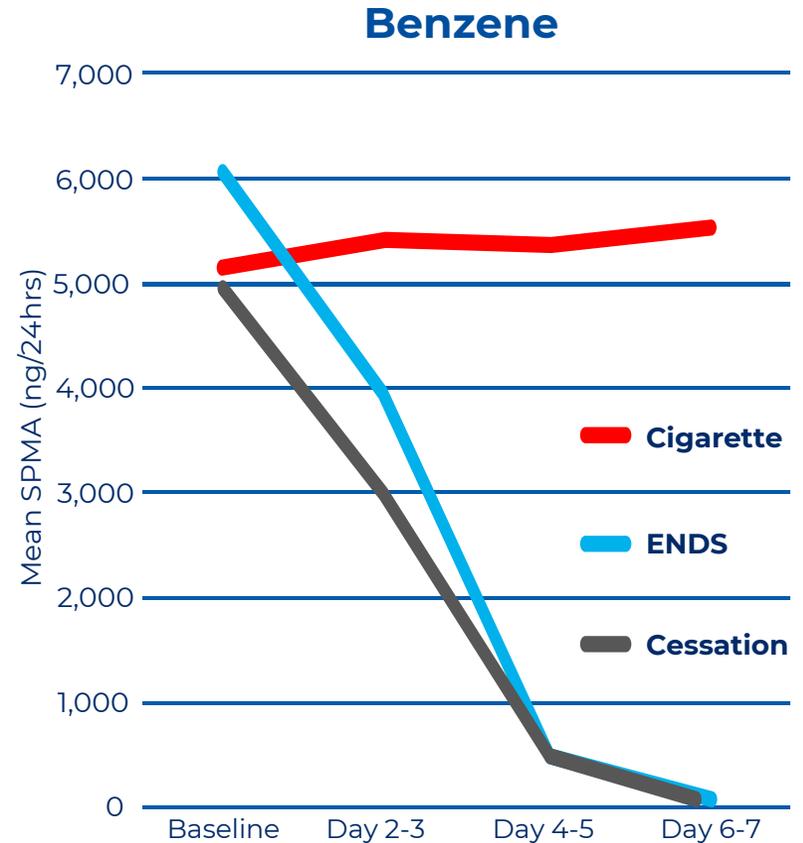
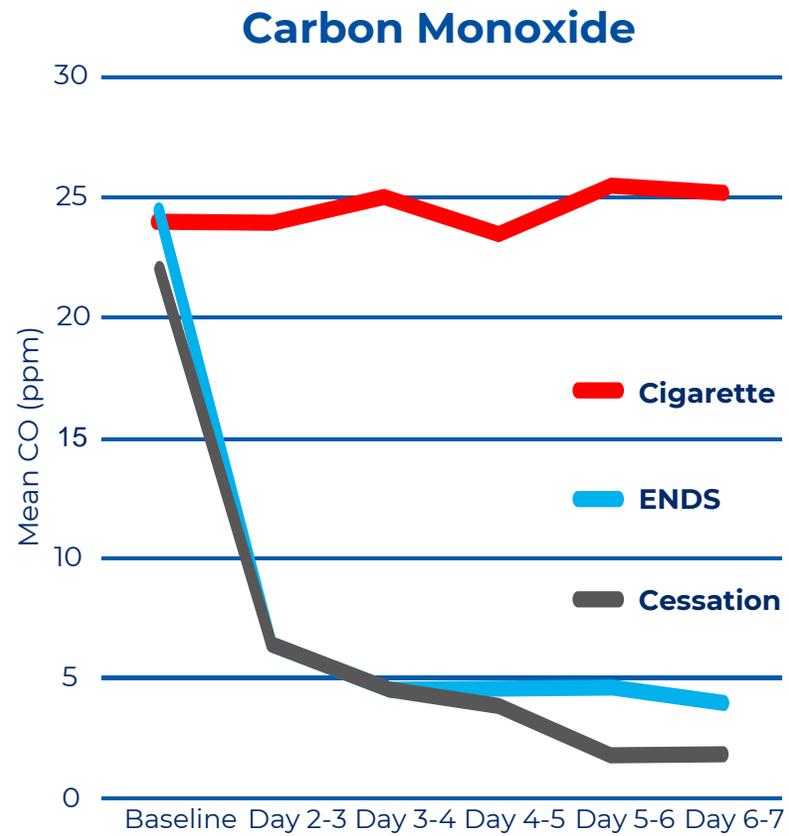
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Biomarkers of Exposure Responses* for ENDS vs Cessation⁽ⁱ⁾



Rapid reduction in exposure when smokers switch to ENDS to similar levels as cessation

Scientific Assessment – Abuse Liability Assessments

Thermochemical Studies

Chemistry Studies

Toxicological Studies

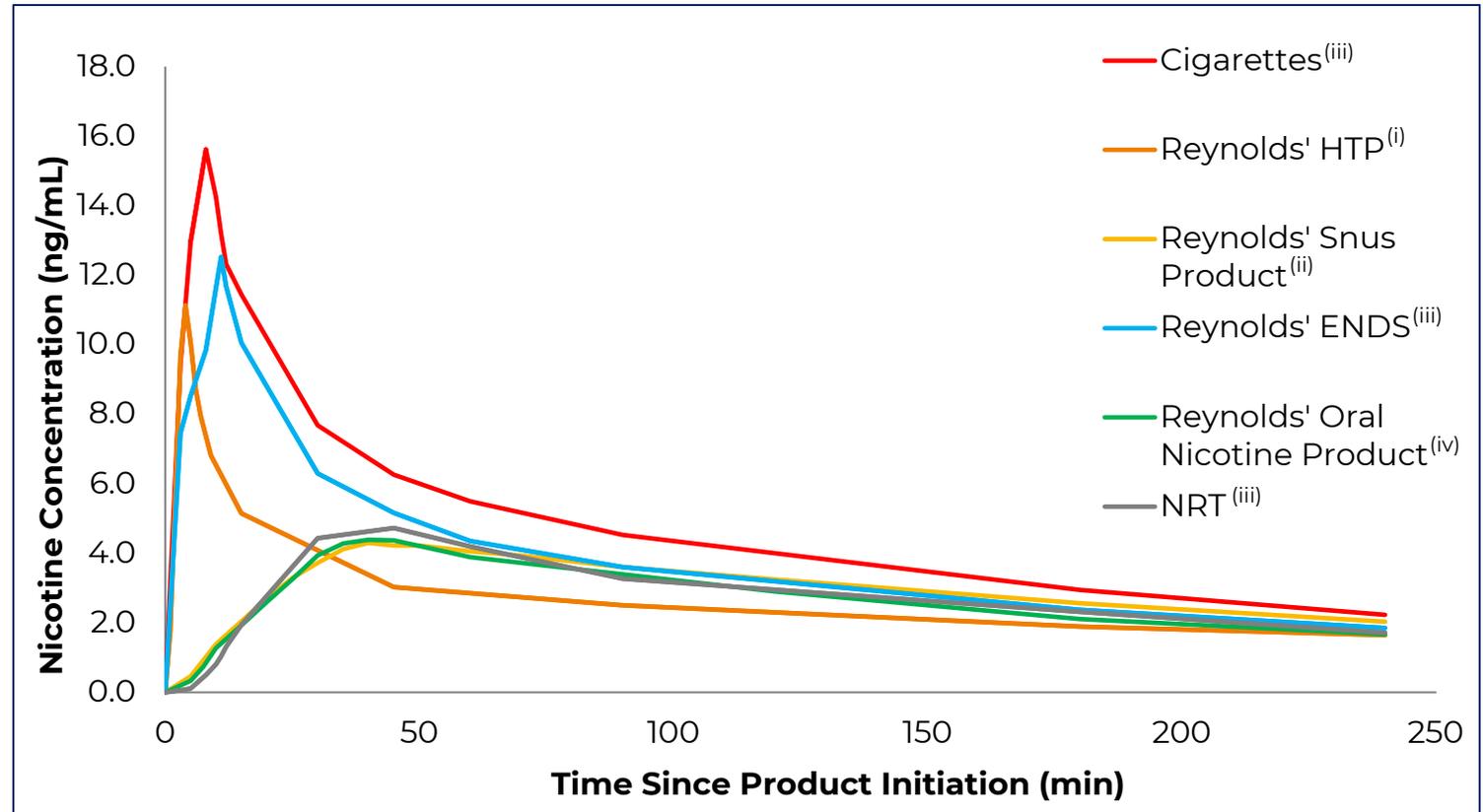
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Nicotine Pharmacokinetic (PK) Profiles of PLHPs

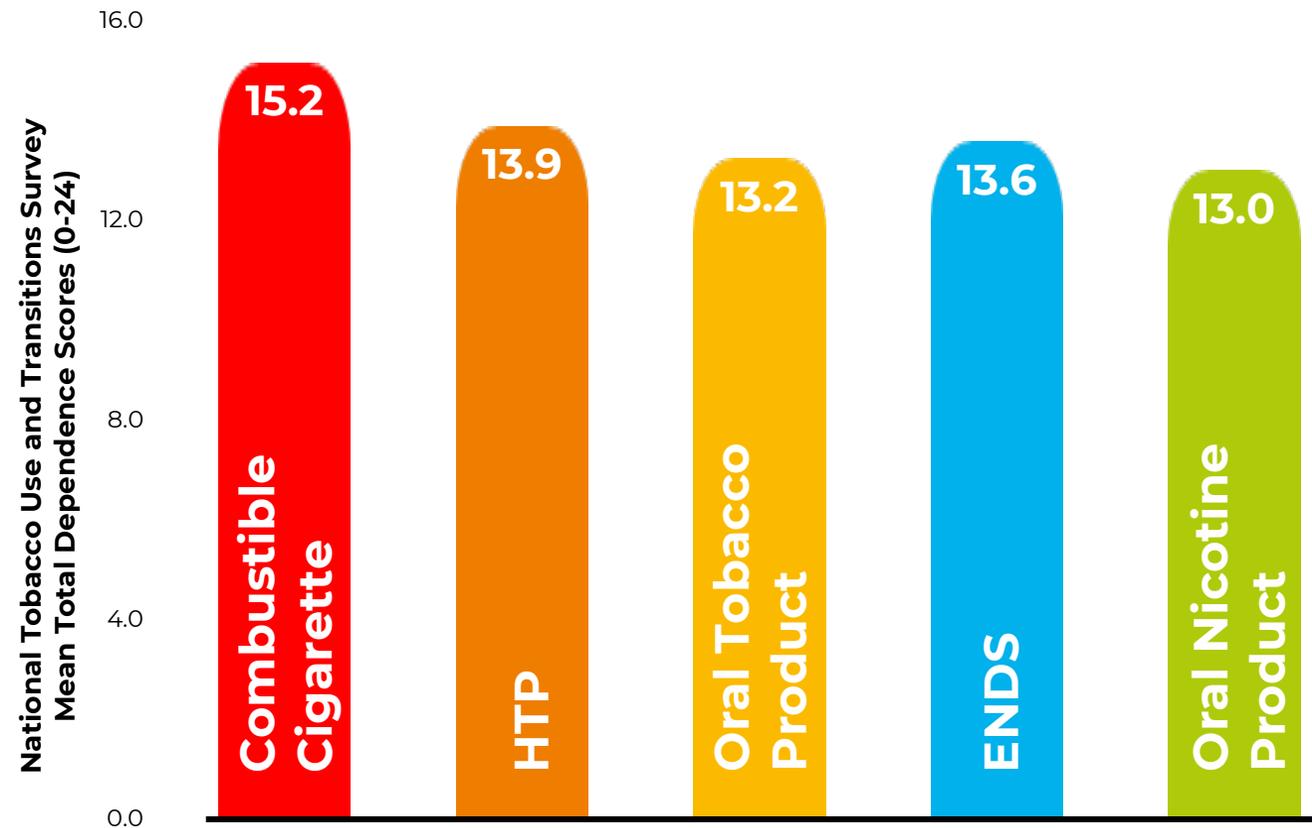


PK profile of PLHPs suggests reduced abuse liability relative to smoking

Scientific Assessment – Dependence Studies

- Thermochemical Studies
- Chemistry Studies
- Toxicological Studies
- Exposure Studies
- Abuse Liability Assessments**
- Individual Risk Studies
- Population Risk Studies

Measures of Dependence in Solus Smokers vs Solus PLHP Users⁽ⁱ⁾



Dependence is lower for PLHPs relative to smoking in US Market

Scientific Assessment – Individual Risk Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

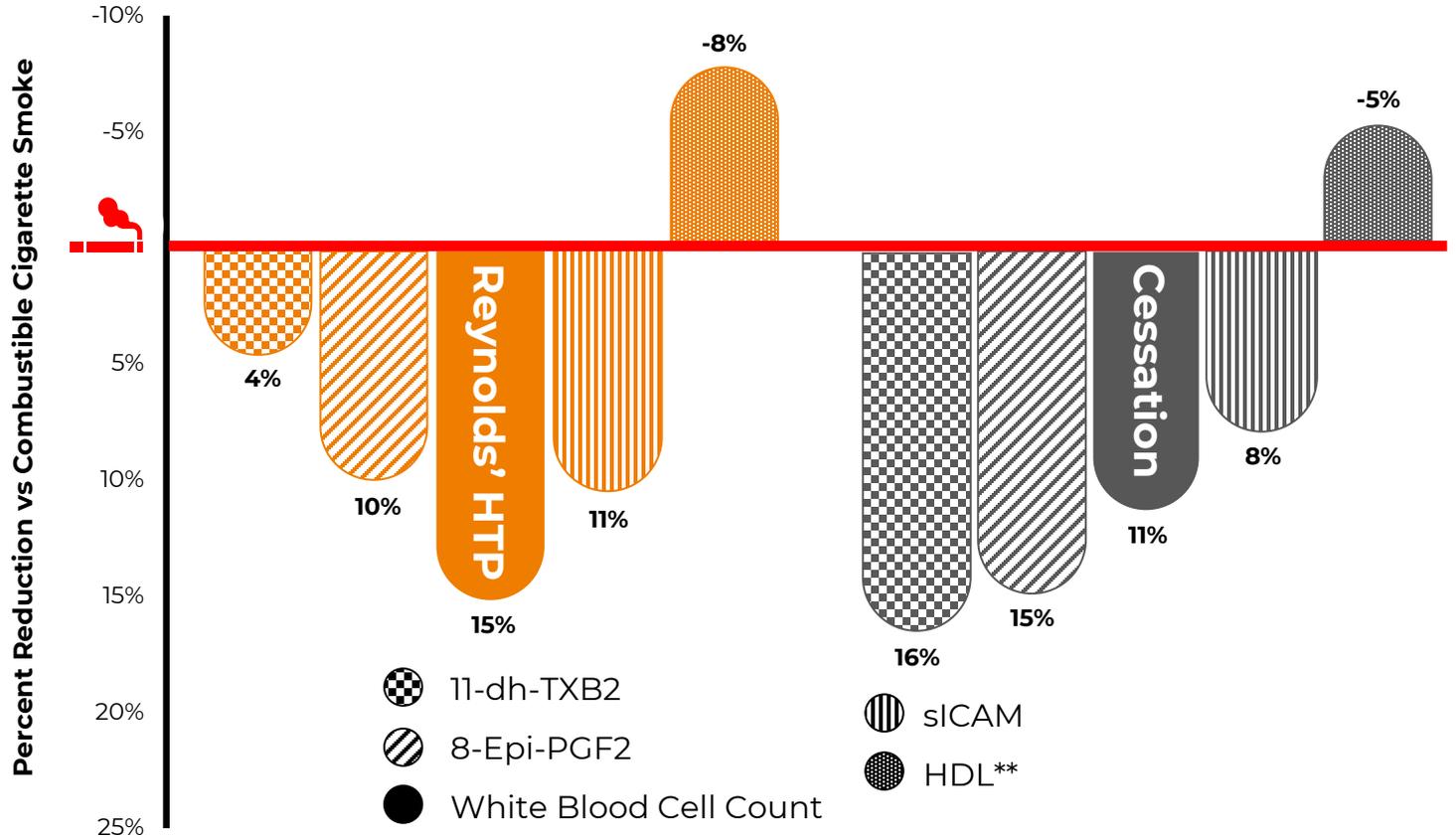
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Biomarkers of Potential Harm Responses* for HTP vs Cessation⁽ⁱ⁾



Biomarkers of potential harm responses for HTP users similar to cessation

Scientific Assessment – Individual Risk Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

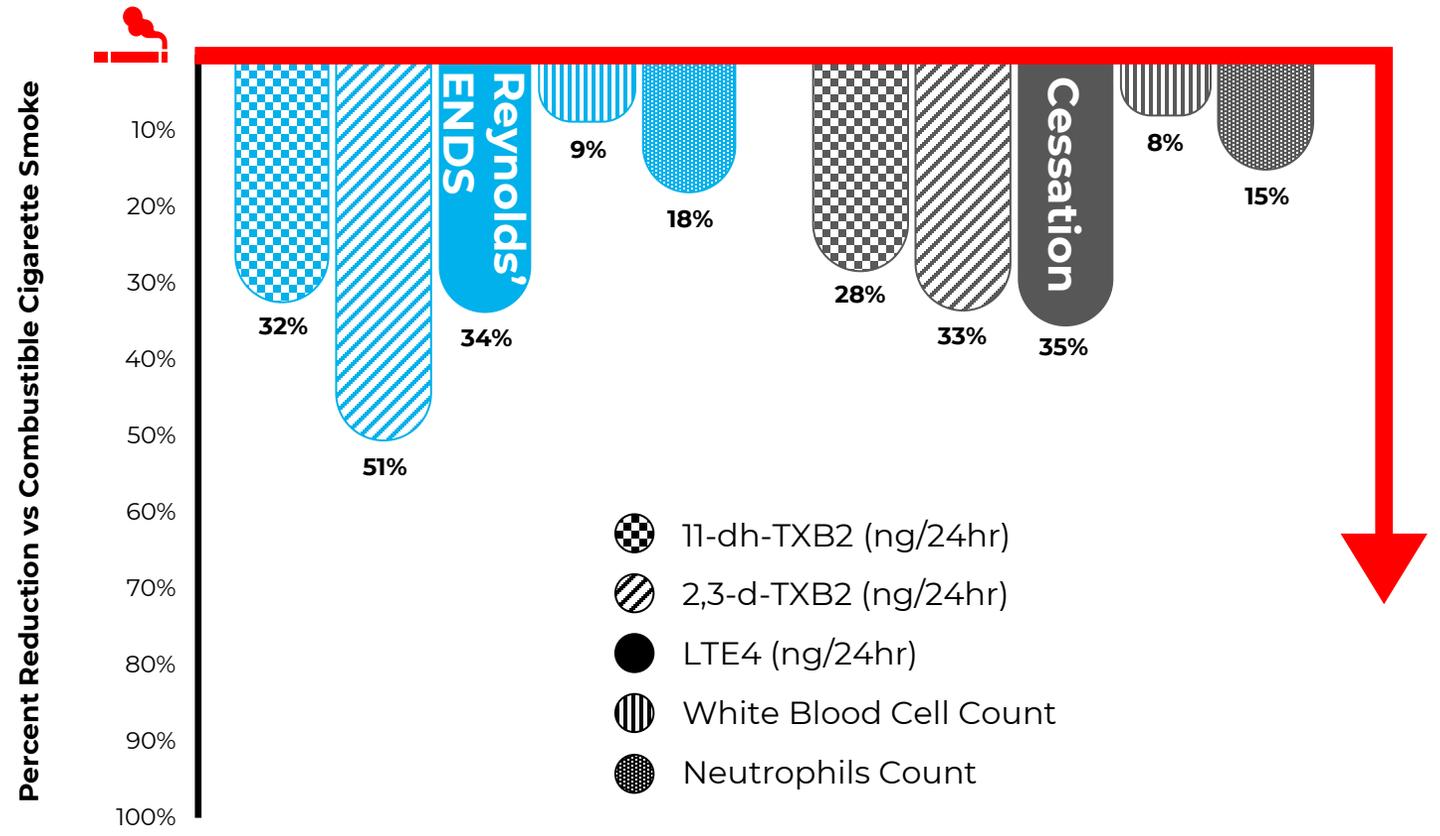
Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

Biomarkers of Potential Harm Responses* for ENDS vs Cessation⁽ⁱ⁾



Biomarkers of potential harm responses for ENDS users similar to cessation

Scientific Assessments – Population Risk Studies

Thermochemical Studies

Chemistry Studies

Toxicological Studies

Exposure Studies

Abuse Liability Assessments

Individual Risk Studies

Population Risk Studies

“[Modeling] projects that under current patterns of ... use and substitution, [US] nicotine vaping product use will translate into

1.8 million

premature...
deaths
avoided

38.9 million

life-years
gained”⁽ⁱ⁾

from 2013-2060

THR has a significant potential to benefit Public Health



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Public Health statements on THR



To truly protect the public, the FDA's approach must take into account the continuum of risk for nicotine-containing products.



S GOTTLIEB & M ZELLER

A Nicotine-Focused Framework for Public Health (2017)



Provision of the nicotine that smokers are addicted to without the harmful components of tobacco smoke can prevent most of the harm from smoking.



ROYAL COLLEGE OF PHYSICIANS

Nicotine without smoke: Tobacco harm reduction (2016)



Leading regulatory and public health agencies agree on the need for THR

Academic and Public Health Science on THR

Laboratory Studies

Learning: Consumer relevant puffing parameters used in studies ensures that findings show neither false negatives nor false positives



(i)

Clinical Studies

Learning: Comparison of users of different nicotine products enables an accurate comparison of exposures from cigarettes and PLHPs



(ii)

Population Studies

Learning: Accurate nicotine status at time of survey is critical to assessing Population Health Impact



(iii)

Rigorous methodology with representative products and exposures should be the gold standard for assessing the potential for THR



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Product Variety

Product Innovation

Nicotine Levels

Adult Flavors

Quality and Safety

Relative Risk

Nicotine Misperception



Adult smokers use a variety of products to facilitate their migration down the risk continuum

- Product Variety
- Product Innovation**
- Nicotine Levels
- Adult Flavors
- Quality and Safety
- Relative Risk
- Nicotine Misperception



▶ **FDA's Marketing Granted Orders are critical to continued product innovation, which in turn facilitates adult smoker migration down the risk continuum**

Product Variety

Product Innovation

Nicotine Levels

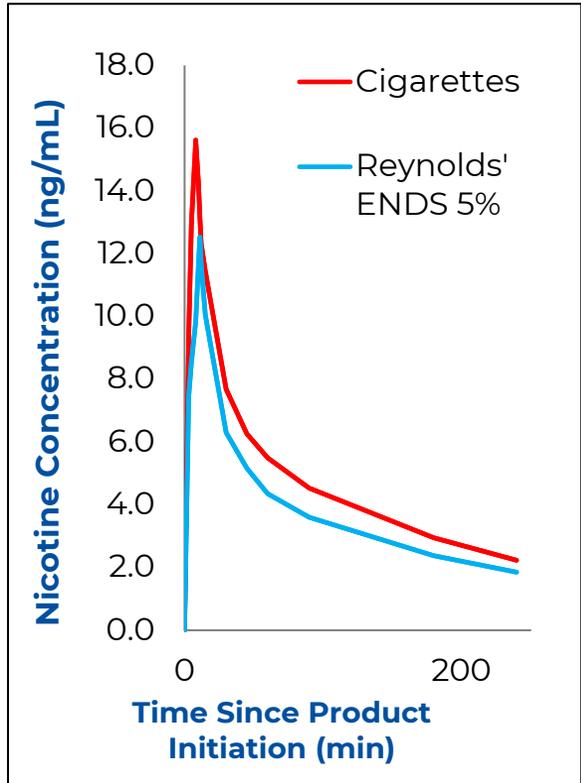
Adult Flavors

Quality and Safety

Relative Risk

Nicotine Misperception

PK Assessment⁽ⁱ⁾ and 2021 Sales⁽ⁱⁱ⁾ of 5% Nicotine ENDS



~73% of Current Closed ENDS Cartridge Sales in the US are 5% Nicotine Concentration E-Liquids

▶ Range of nicotine levels is important to facilitate adult smokers migrating to PLHPs

Product Variety

Product Innovation

Nicotine Levels

Adult Flavors

Quality and Safety

Relative Risk

Nicotine Misperception

Impact of Flavors on Adult Smoking Cessation



JAMA Network Open

Original Investigation | Substance Use and Addiction

Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation

Abigail S. Friedman, PhD, Siqiang Xu, BS

Abstract

IMPORTANCE Several states have banned sales of flavored e-cigarettes, but evidence on the association between vaping flavors and subsequent smoking initiation and cessation is limited.

OBJECTIVE To evaluate whether new uptake of flavored e-cigarettes is more strongly associated with subsequent smoking initiation and cessation than uptake of unflavored e-cigarettes, separately for youths (12-17 years), emerging adults (18-24 years), and prime-age adults (25-54 years).

DESIGN, SETTING, AND PARTICIPANTS This cohort study conducted secondary data analyses of longitudinal survey data from waves 1 to 4 of the Population Assessment of Tobacco and Health Study (collected from 2013 to 2018). The analytic sample was limited to 17 929 respondents aged 12 to 54 years at wave 1 who completed at least 3 consecutive waves of the survey and did not use e-cigarettes at baseline. Data were collected from 2013 to 2018 and analyzed in February 2020.

EXPOSURES Flavored vs unflavored e-cigarette use reported in wave 2 of the Population Assessment of Tobacco and Health Study.

MAIN RESULTS AND MEASURES Binary indicators captured wave 3 smoking among 7311 youths and 4634 emerging adults who did not smoke at baseline (ie, initiation) and not smoking at wave 3 among 1503 emerging adults and 4481 prime-age adults who smoked at baseline (ie, cessation). Smoking status was based on having smoked in the past 30 days for youths and established smoking (ie, current smoking among those who smoked at least 100 cigarettes in their lifetime) for emerging and prime-age adults.

RESULTS The youths who did not smoke at baseline, emerging adults who smoked at baseline, and prime-age adults who smoked at baseline consisted of 51.4% to 58.0% male participants and 66.9% to 77.0% white individuals. Vaping uptake was positively associated with smoking initiation in youth (adjusted odds ratio [AOR], 6.75; 95% CI, 3.93-11.57; $P < .001$) and in emerging adults (AOR, 3.20; 95% CI, 1.70-6.02; $P < .001$). Vaping uptake was associated with cessation in adults (AOR, 1.34; 95% CI, 1.02-1.75; $P = .03$). Vaping nontobacco flavors was no more associated with youth smoking initiation than vaping tobacco flavors (AOR in youth, 0.66; 95% CI, 0.16-2.76; $P = .56$) but was associated with increased adult smoking cessation (AOR in adults, 2.28; 95% CI, 1.04-5.01; $P = .04$).

CONCLUSIONS AND RELEVANCE In this study, adults who began vaping nontobacco-flavored e-cigarettes were more likely to quit smoking than those who vaped tobacco flavors. More research is needed to establish the relationship between e-cigarette flavors and smoking and to guide related policy.

JAMA Network Open. 2020;3(6):e200826.
Corrected on June 26, 2020. doi:10.1001/jamanetworkopen.2020.3836

Key Points

Question Does the association between vaping uptake and subsequent smoking differ between individuals favoring tobacco- vs nontobacco-flavored e-cigarettes?

Findings In this cohort study with 17 929 participants, multi-variable analyses of nationally representative, longitudinal survey data evaluated differences in smoking initiation and cessation subsequent to vaping uptake among those who used flavored vs unflavored e-cigarettes, separately by age group. Relative to vaping tobacco flavors, vaping nontobacco-flavored e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation.

Meaning In this study, adults who vaped flavored e-cigarettes were more likely to subsequently quit smoking than those who used unflavored e-cigarettes.

Editorial

Supplemental content

Author affiliations and article information are listed at the end of this article.

“ In this study, adults who vaped flavored e-cigarettes were more likely to subsequently quit smoking than those who used unflavored e-cigarettes.⁽ⁱ⁾ ”

▶ Flavors are important to facilitate adult smokers switching to PLHPs with appropriate market controls to protect vulnerable populations

Product Variety

Product Innovation

Nicotine Levels

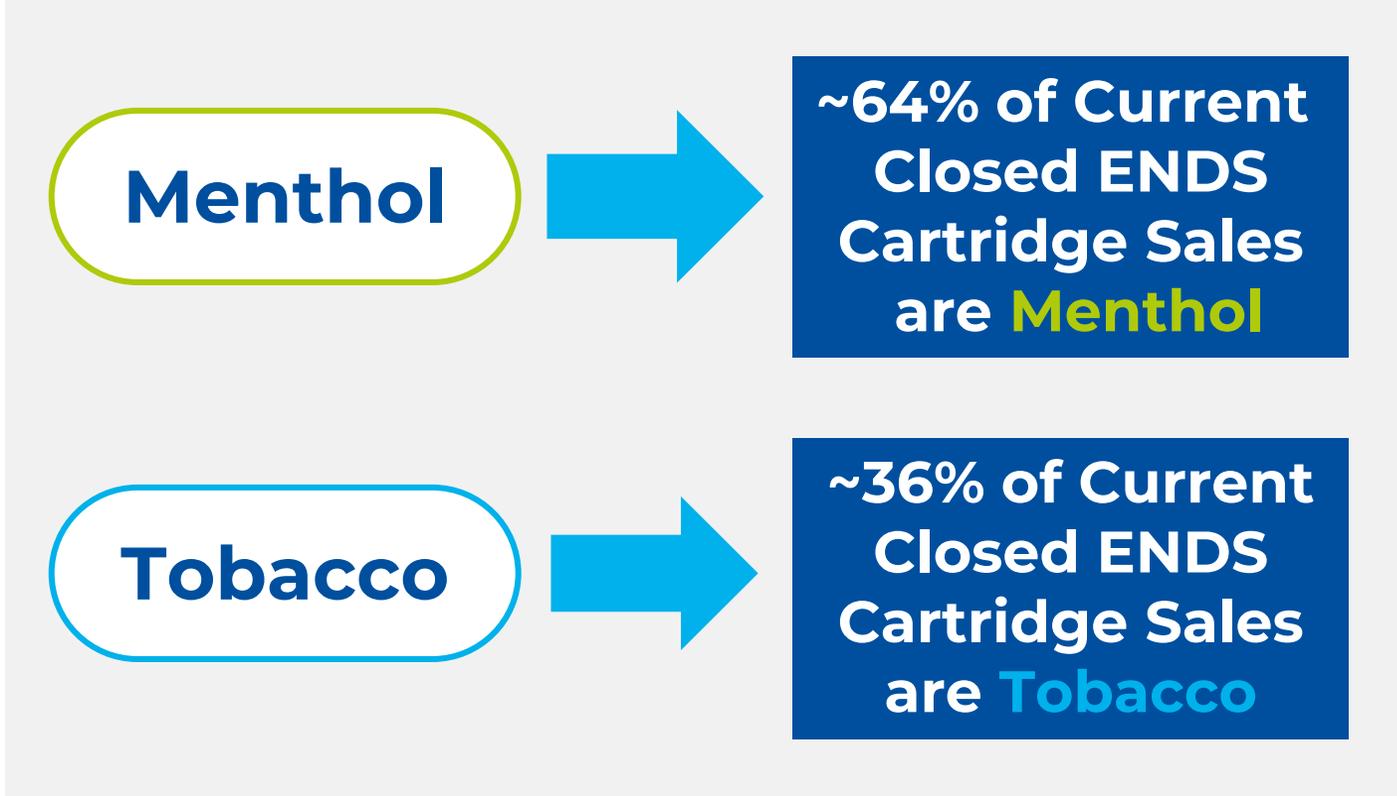
Adult Flavors

Quality and Safety

Relative Risk

Nicotine Misperception

2021 Sales⁽ⁱ⁾ of Menthol and Tobacco ENDS



▶ **Menthol in ENDS is important to facilitate adult smokers migrating to PLHPs in the US**

- Product Variety
- Product Innovation
- Nicotine Levels
- Adult Flavors
- Quality and Safety**
- Relative Risk
- Nicotine Misperception

Comprehensive Product Stewardship Process⁽ⁱ⁾

- 1. eLiquid safety assessment**
 - Negative list: CMRs*, respiratory sensitizers
 - Thermal degradants
- 2. Device safety assessment**
 - Battery safety
 - Thermal degradants
- 3. Aerosol safety assessment**
 - Toxicant levels



Comprehensive Quality program

- 1. Quality Management System**
 - Supplier and material qualification
 - Incoming material inspection
 - In-process quality testing
 - Finished goods quality release
 - World class quality culture
- 2. Quality Compliance Program**
 - Non-conformance Management
 - CAPA
 - Consumer Complaints Management
 - Document & Data Management System
 - Change Control Process
 - Internal Audit Process

 **Product safety and quality are imperative to facilitate adult smokers switching to PLHPs**

* Carcinogens, Mutagens, and Reproductive Toxins (CMRs); (i) Costigan and Meredith, 2015

Product Variety

Product Innovation

Nicotine Levels

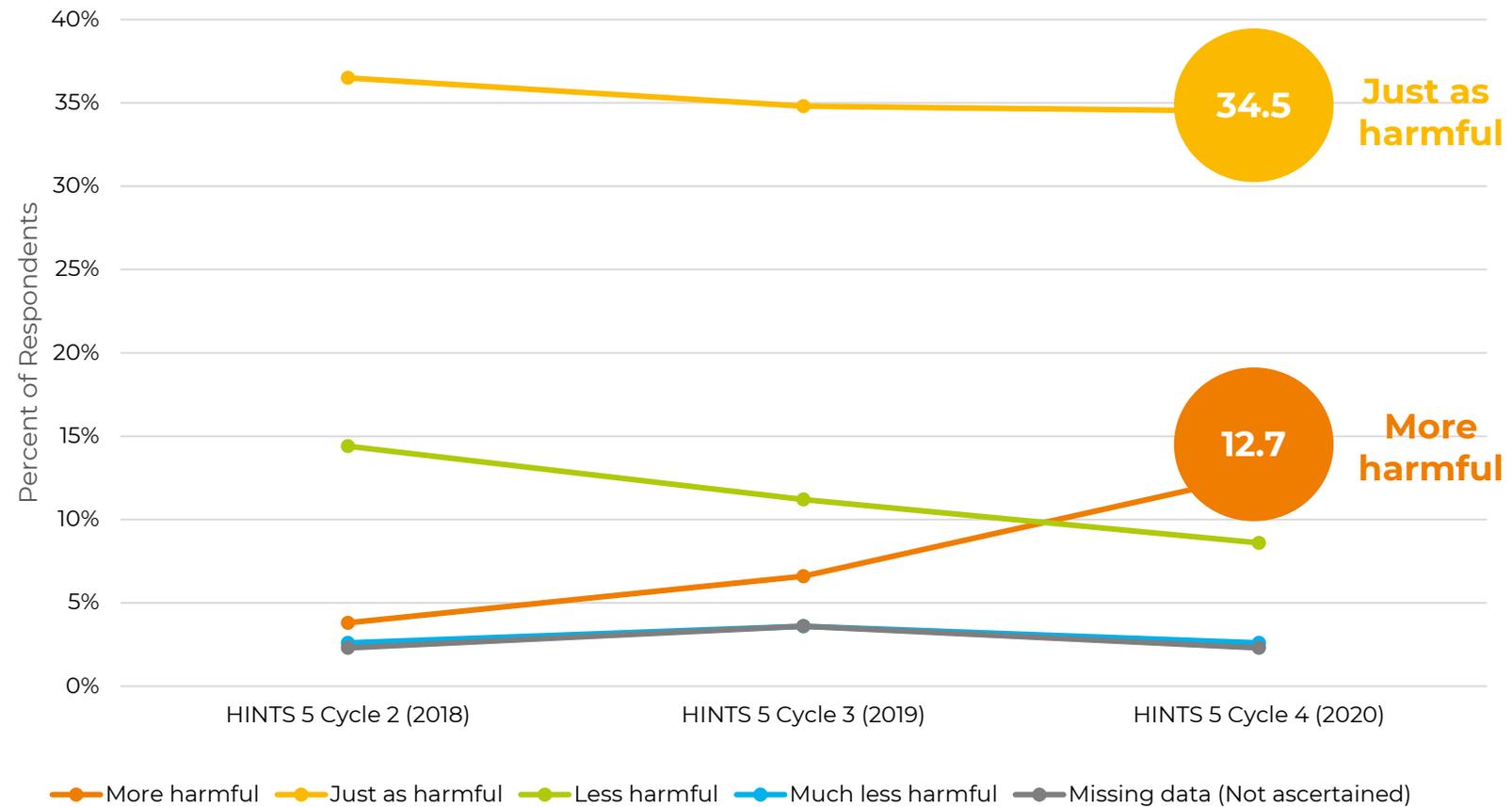
Adult Flavors

Quality and Safety

Relative Risk

Nicotine Misperception

“Compared to smoking cigarettes, would you say that electronic cigarettes are...”⁽ⁱ⁾



Misperceptions of the risk of ENDS relative to smoking have doubled since 2019

Product Variety

Product Innovation

Nicotine Levels

Adult Flavors

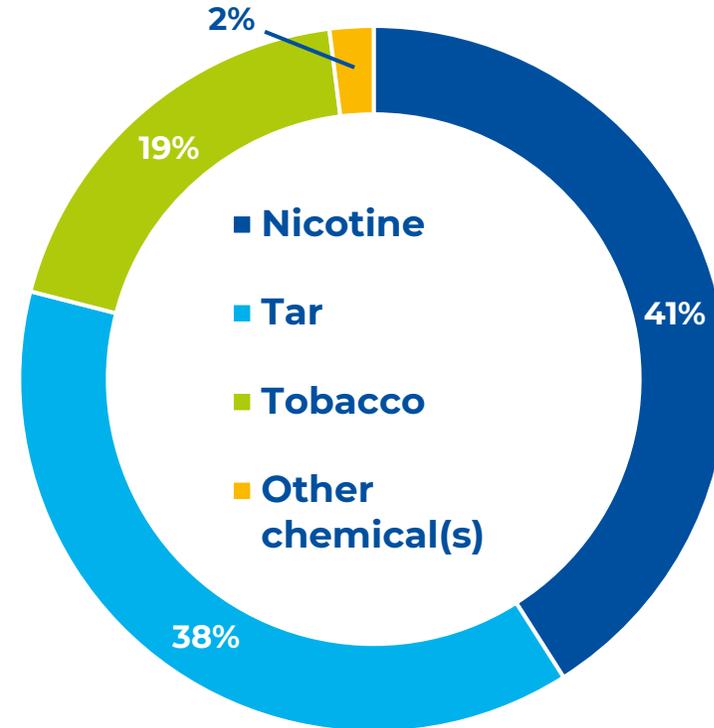
Quality and Safety

Relative Risk

Nicotine Misperception

Misperceptions of negative health impact associated with nicotine⁽ⁱ⁾

In your opinion, which ingredient is the primary cause of the negative health impacts associated with cigarettes?



Misperceptions of the harms of nicotine continue to be pervasive

Public health views on nicotine



80%

of **US physicians** surveyed “Strongly agreed” that **nicotine directly contributes** to:
Cardiovascular Disease – COPD – Cancer⁽ⁱ⁾



“Current evidence does not support the idea that nicotine is a human carcinogen”

National Academies of Sciences, Engineering, and Medicine⁽ⁱⁱ⁾

“There is insufficient data to conclude that nicotine causes or contributes to cancer in humans”

US Surgeon General⁽ⁱⁱⁱ⁾



Accurate communication around nicotine is paramount for public health



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Transparency of our science via Science Engagement

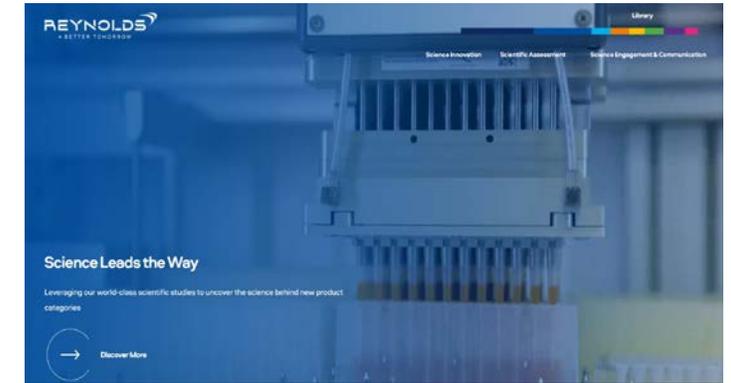
Conference Proceedings



Papers Published in Scientific Journals



Access to Science



Dedicated science website (reynoldscience.com)

Science engagement is fundamental to accelerating THR

Opportunities for FDA to enhance Public Health benefit

Increase accurate information on the relative risks of nicotine

1. Nicotine Misperception



2. Stakeholder Workshops

Create forums for constructive dialogue among all stakeholders

4. Post Market Surveillance

Increase reliance on Post Market Surveillance and Reporting for continued assessment of impact to public health

3. Prioritize PMTAs

Per FDA, "focus resources on products where scientific review will have the greatest public health impact, based on their market share"⁽ⁱ⁾



FDA is the center piece of a successful THR agenda



TOBACCO HARM REDUCTION

=

FDA + Adult Consumers +
Public Health + Industry



All stakeholder collaboration and
dialogue critical to THR success





FDA Stakeholder Engagement



Thank You

Tobacco Harm Reduction

Visit us at
ReynoldsScience.com





References

Slide 1: NA

Slide 2: NA

Slide 3: NA

Slide 4: NA

Slide 5: (i) Clearing the Smoke, US Institute of Medicine, Washington (DC): National Academies Press (US); 2001

Slide 6: (i) Gottlieb, S. and M. Zeller (2017). "A Nicotine-Focused Framework for Public Health." *New England Journal of Medicine* 377(12): 1111-1114.

Slide 7: (i) Clearing the Smoke, US Institute of Medicine, Washington (DC): National Academies Press (US); 2001 (ii) Evidence-Based Medicine and the Changing Nature of Healthcare: 2007 IOM Annual Meeting Summary. Washington (DC). (iii) Institute of Medicine (U.S.). Committee on Scientific Standards for Studies on Modified Risk Tobacco Products. (2012). *Scientific standards for studies on modified risk tobacco products*. Washington, DC, National Academies Press.

Slide 8: (i) Clearing the Smoke, US Institute of Medicine, Washington (DC): National Academies Press (US); 2001 (ii) Zeller, M., et al. (2009). "The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US." *Tobacco Control* 18(4): 324-332. (iii) Institute of Medicine (U.S.). Committee on Scientific Standards for Studies on Modified Risk Tobacco Products. (2012). *Scientific standards for studies on modified risk tobacco products*. Washington, DC, National Academies Press. (iv) Gottlieb, S. and M. Zeller (2017). "A Nicotine-Focused Framework for Public Health." *New England Journal of Medicine* 377(12): 1111-1114. (v) National Academies of Sciences, Engineering, and Medicine. (2018). In K. Stratton, L. Y. Kwan, & D. L. Eaton (Eds.), *Public Health Consequences of E-Cigarettes*. Washington (DC). (vi) Balfour, D. J. K., et al. (2021). "Balancing Consideration of the Risks and Benefits of E-Cigarettes." *American Journal of Public Health* 111(9): 1661-1672.

Slide 9: (i) CDC. "Current Cigarette Smoking Among Adults in the United States." National Center for Chronic Disease Prevention and Health Promotion. 2020. (ii) Villarroel, M. A., et al. "Electronic cigarette use among U.S. adults, 2018." NCHS Data Brief, No. 365. Hyattsville, MD: National Center for Health Statistics. 2020. (iii) Levy, D. T., et al. (2021). "Public health implications of vaping in the USA: the smoking and vaping simulation model." *Population Health Metrics* 19(1): 19.

Slide 10: NA

Slide 11: NA

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