

Risk / Benefit Assessment for APPH Determination – Are We There Yet? NJOY® Case Study

Altria Client Services LLC
Regulatory Affairs



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Agenda



Overview of Evidence Supporting FDA Authorization of NJOY ACE Products: Assessing the Benefits and Risks for APPH

Kate Vergara PhD MPH
Sr. Principal Scientist

Framework for Evaluating “Added Benefit”

Ed Largo PhD
Associate Fellow



NJOY ACE® Portfolio

Marketing Granted Order



“...the FDA determined there was sufficient evidence to demonstrate that permitting marketing of the products would be **appropriate for the protection of the public health...**

Specifically, evidence submitted by the applicant showed that these menthol-flavored products **provided a benefit** for adults who smoke cigarettes relative to that of the applicant's previously authorized tobacco-flavored products—in terms of complete switching—that is sufficient to **outweigh the risks** of the product, including youth appeal.”



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Scientific Framework

CONSTITUENT REDUCTION



THE PRODUCT

- Chemistry Manufacturing and Controls
- Product Stability
- Chemical Characterization

INDIVIDUAL RISK REDUCTION



EXPOSURE and HEALTH RISK

- Toxicology & Risk Assessment
- Health Risk Assessment (Absolute and Relative)
- Biomarker Studies
- Abuse Liability Studies
- Human Factors Assessment

POPULATION HARM REDUCTION



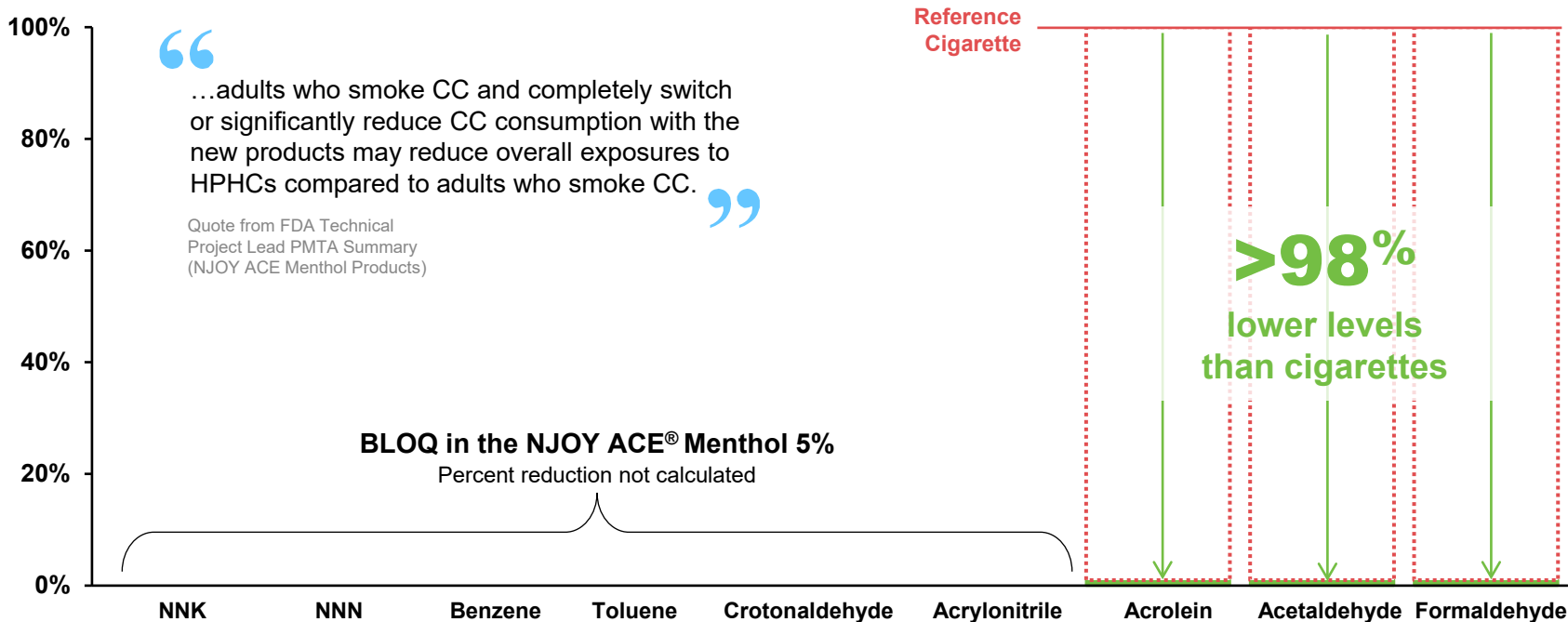
IMPACT on the POPULATION

- Risk Perceptions (Absolute and Relative)
- Impact of Product on Users
- Impact on Non-users
- Overall Impact on the Population
- Environmental Assessment





HPHCs in NJOY ACE® Menthol 5% are Not Detected or Substantially Reduced Compared to Cigarettes



CC=combustible cigarette; HPHC=harmful and potentially harmful constituents; NNK=4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN=N-nitrososonornicotine. BLOQ=below level of quantification

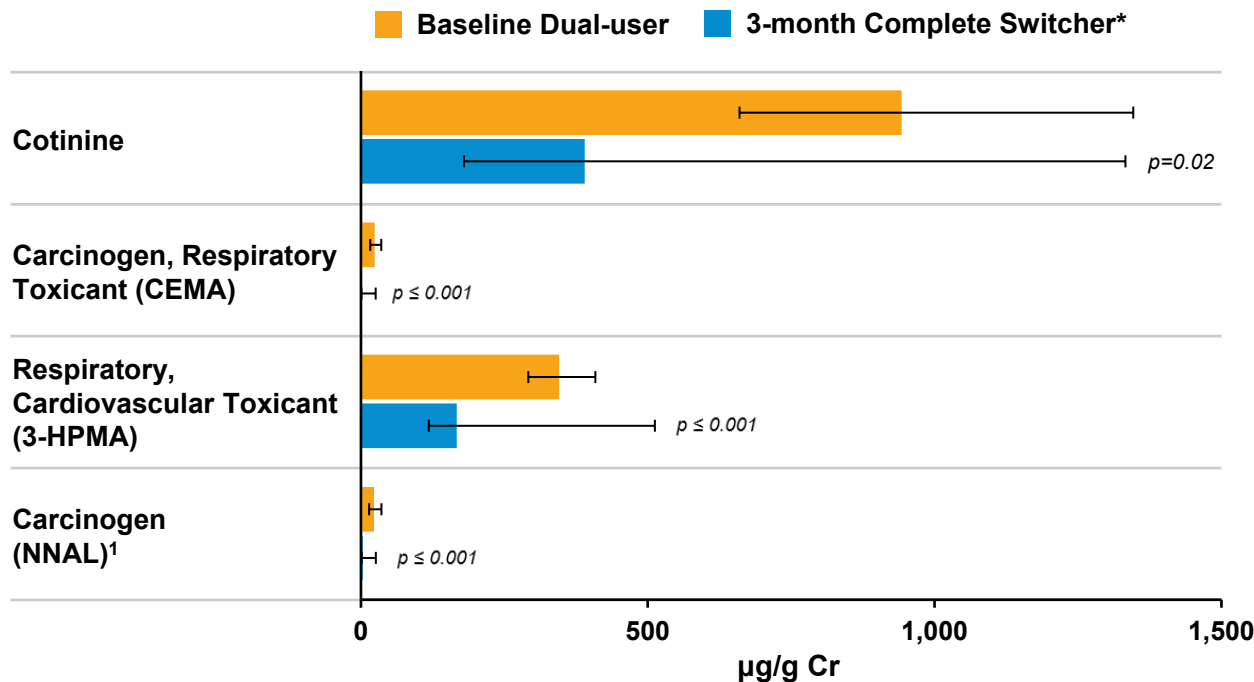
Source: Report Evaluation of HPHCs in NJOY ACE POD Aerosols after 6 to 9 months Storage; Percent reductions based on non-intense use scenarios and ambient storage conditions HPHC levels in Menthol 5% NJOY ACE products at 6 months compared to cigarette mainstream smoke levels measured under ISO conditions.



Biomarkers of Exposure are Significantly Reduced Among Switchers Based on Real World Evidence

“...biomarker data from the NJOY User Study suggests that adults who exclusively use the new products will have lower HPHC exposures compared to adults who dually use CC and the new products.”

Quote from FDA Technical Project Lead PMTA Summary (NJOY ACE Menthol Products)



* Indicates that biomarker levels were significantly lower than dual-users ($p < 0.05$); Data represented as Least Square Means + 95% CI from Statistical Model. ¹NNAL is expressed as ng/g Cr. CC=combustible cigarette; 3-HPMA=3-Hydroxypropylmercapturic Acid; CEMA=Cyanoethyl mercapturic acid; NNAL=4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol). Source: NJOY ACE Biomarker Substudy Final Report



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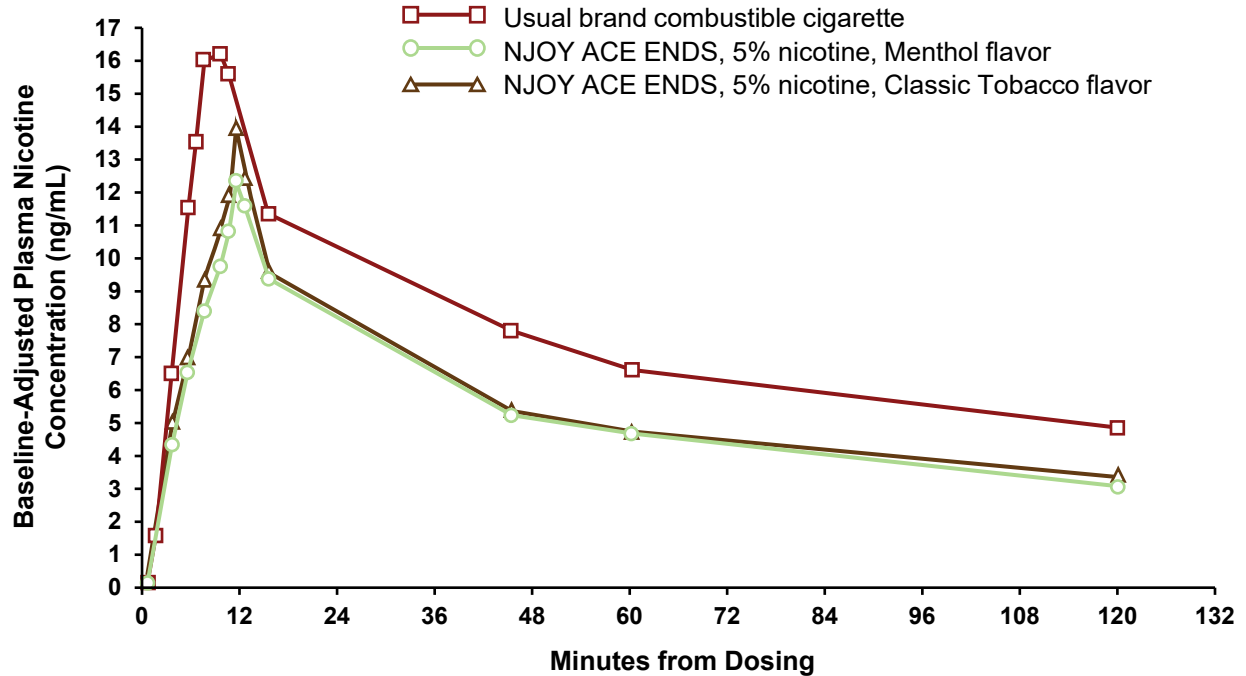
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Nicotine PK Indicates NJOY ACE® Abuse Liability Not Likely to be Higher Than Cigarettes

Abuse Liability

“...the new product's abuse liability is similar to CC among adults who are experienced with ENDS use, suggesting that the new product may be a suitable substitute for CC among adults who smoke CC and who want to quit.”

Quote from FDA Technical
Project Lead PMTA Summary
(NJOY ACE Menthol Products)



CC=combustible cigarette; ENDS=electronic nicotine delivery system.

Longitudinal Cohort Study Overview



POPULATION HARM REDUCTION

PROSPECTIVE LONGITUDINAL ONLINE OBSERVATIONAL SURVEY

Evaluating the Effectiveness of NJOY ACE ENDS on Reduction and Switching From CC Use



PURPOSE

Assesses relationship between the frequency of combustible cigarette smoking, switching from combustible cigarettes to ENDS, and the purchasing and use of NJOY ENDS products*

STUDY DESIGN

National purposive sample of 8,002 US adult subjects aged 21+ years who first used NJOY ACE® within the 12-month period prior to completing the baseline survey

COHORTS

Primary Outcomes Cohort

Baseline and 3-month timepoints

Secondary Outcomes Cohort

Baseline, 3-month and 6-month timepoints

*When the study began in 2019, the following NJOY ACE products were available: NJOY ACE Classic Tobacco 2.4% and 5%, Rich Tobacco 5%, Menthol 2.4% and 5%, Blueberry 2.4% and 5%, Watermelon 2.4% and 5%. The NJOY ACE Blueberry and Watermelon products were removed from the market pursuant to the FDA Enforcement announced in January 2020.
CC=combustible cigarette; ENDS=electronic nicotine delivery system.



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Real World Evidence Demonstrates Switching Success with NJOY ACE® (PPA)



POPULATION HARM REDUCTION

PRIMARY OUTCOMES COHORT

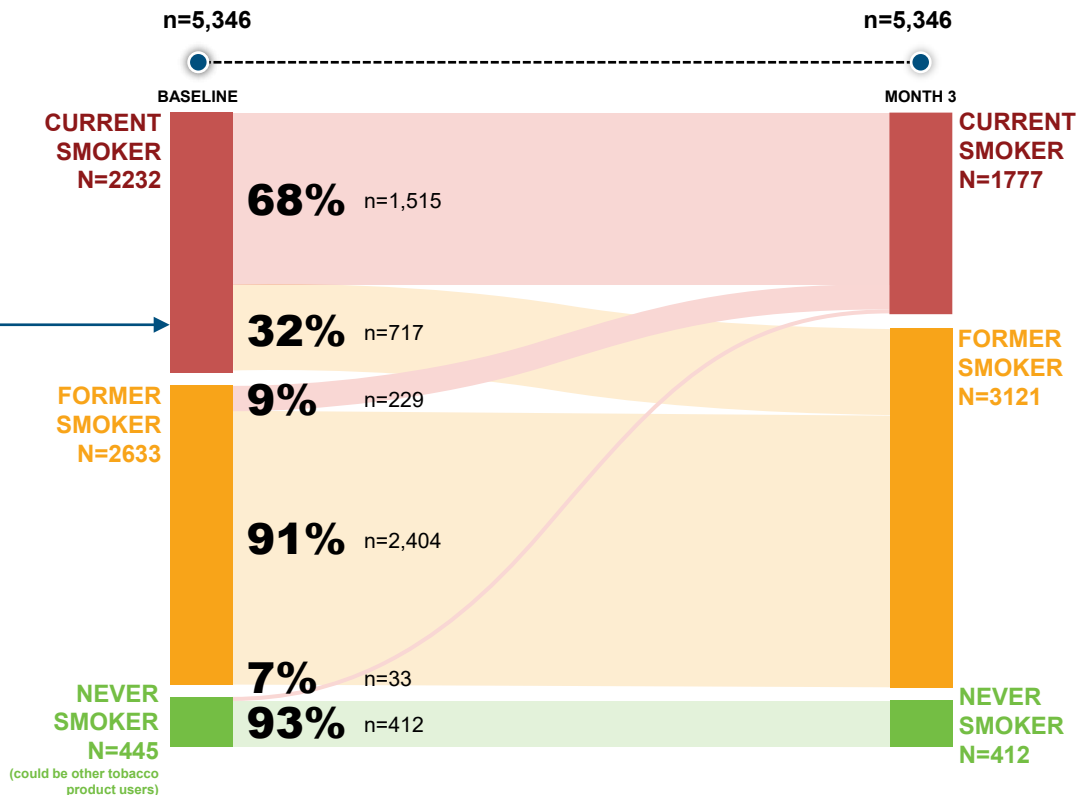
32%

of Adult Smokers

(21+ at Baseline)

transitioned to Former Smokers

by the primary outcomes time point*



* Indicates that switching rate calculated based on the number of participants initially using NJOY ACE at baseline and completing survey at three months (per protocol population).
Source: Prospective Longitudinal Cohort Study Figure 7-1. N=36 did not answer the smoking frequency question at the Primary Outcomes time point and are not included on this figure.



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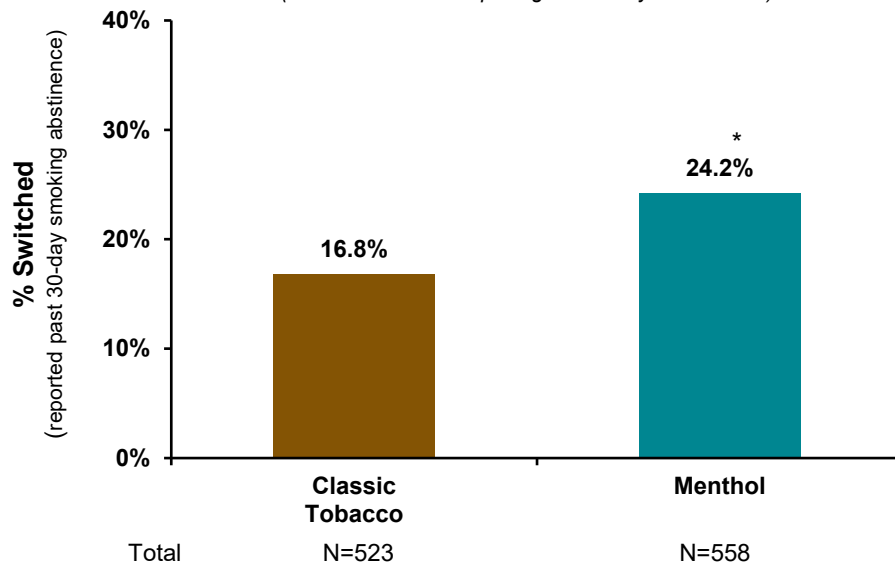
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NJOY ACE® Menthol More Effective in Promoting Complete Switching Relative to Tobacco-Flavored

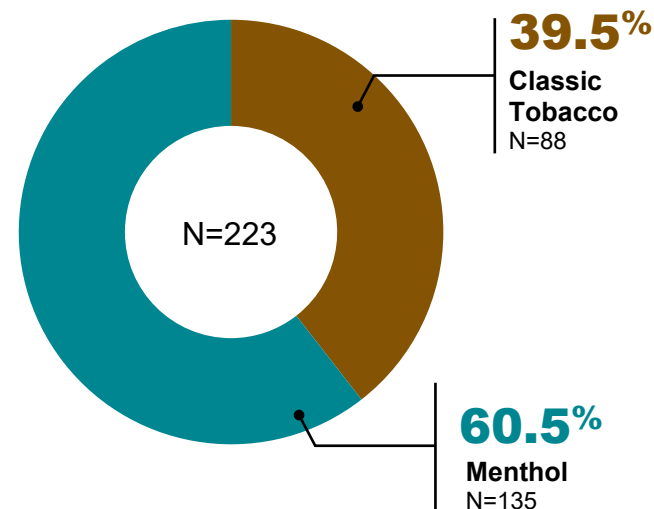
Complete Switching at 3 Months By Initial Flavor Used

(based on those completing the survey at 3 months)



Proportion of Complete Switchers at 3 Months By Initial Flavor Used

(based on those completing the survey at 3 months)



*Statistically significantly greater than Classic Tobacco-flavored NJOY ACE products
Analysis shows per protocol 30-day point prevalence abstinence for initially used NJOY ACE flavor.
Source: NJOY ACE User Survey Supplemental Blueberry and Watermelon Report; Initial Used NJOY Flavor.

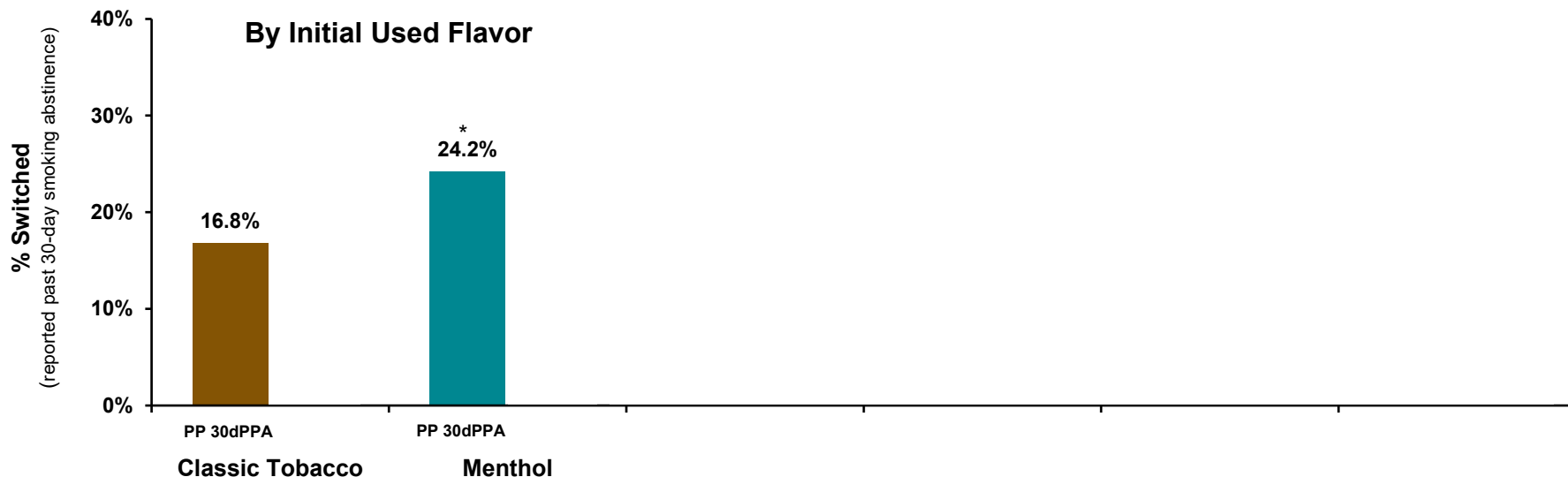


NJOY ACE® Menthol Associated with Greater Complete Switching Relative to Tobacco-Flavored



POPULATION HARM REDUCTION

Complete Switching at 3 Months (Per Protocol 30dPPA)



*Statistically significantly greater than Classic Tobacco-flavored NJOY ACE products

Analysis shows ITT 30-day point prevalence abstinence for initially used NJOY ACE flavor.

PPP 30dPPA=per protocol 30-day point prevalence abstinence; ITT=intent to treat.

Source: NJOY ACE User Survey Supplemental Blueberry and Watermelon Report; NJOY ACE User Survey Supplemental Menthol Report.



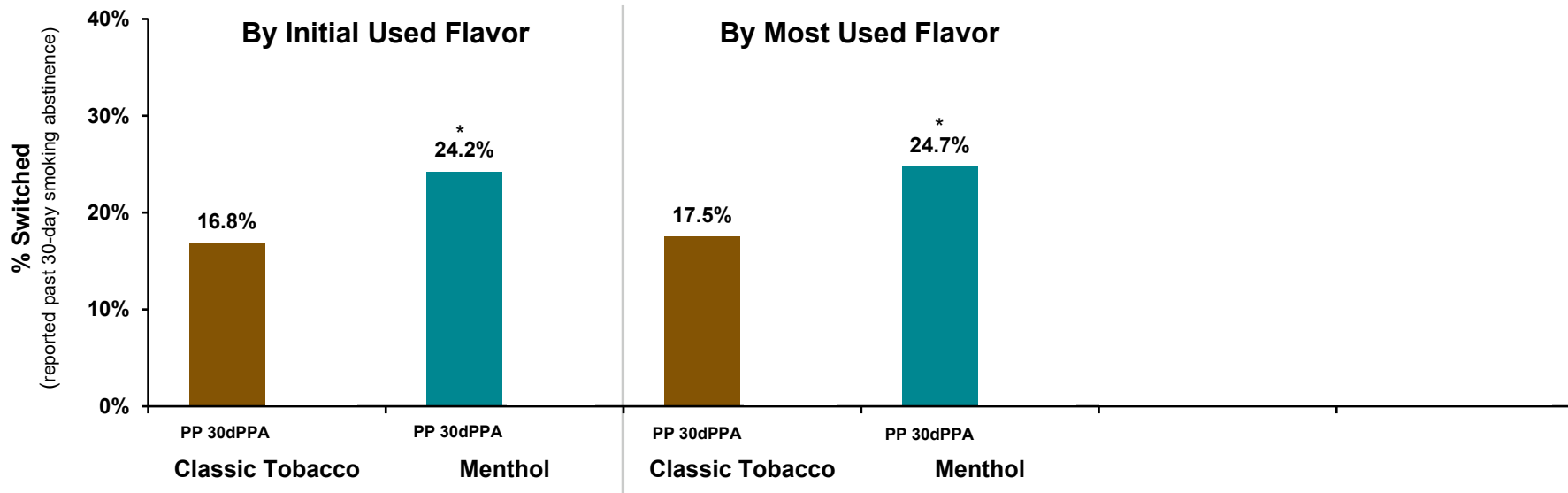
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Flavored NJOY ACE® Products Associated with Greater Complete Switching Relative to Tobacco-Flavored

Complete Switching at 3 Months (Per Protocol 30dPPA)



*Statistically significantly greater than Classic Tobacco-flavored NJOY ACE products

Analysis shows ITT 30-day point prevalence abstinence for initially used NJOY ACE flavor.

PPP 30dPPA=per protocol 30-day point prevalence abstinence; ITT=intent to treat.

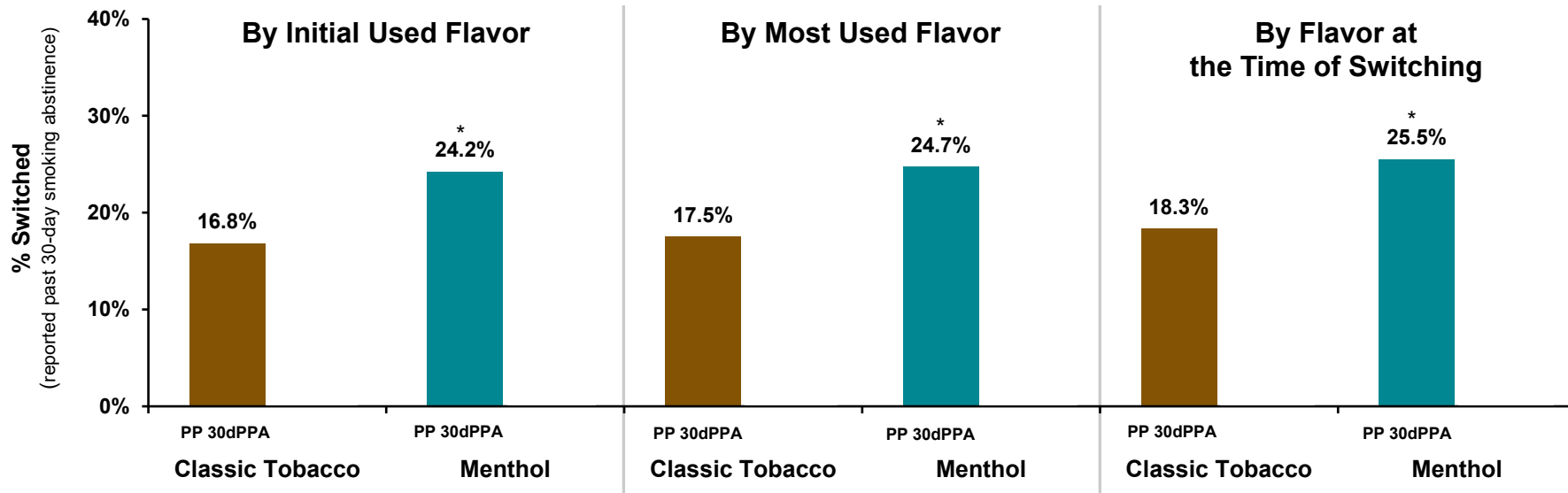
Source: NJOY ACE User Survey Supplemental Blueberry and Watermelon Report; NJOY ACE User Survey Supplemental Menthol Report.





Flavored NJOY ACE® Products Associated with Greater Complete Switching Relative to Tobacco-Flavored

Complete Switching at 3 Months (Per Protocol 30dPPA)



*Statistically significantly greater than Classic Tobacco-flavored NJOY ACE products
Analysis shows ITT 30-day point prevalence abstinence for initially used NJOY ACE flavor.
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Source: NJOY ACE User Survey Supplemental Blueberry and Watermelon Report; NJOY ACE User Survey Supplemental Menthol Report.

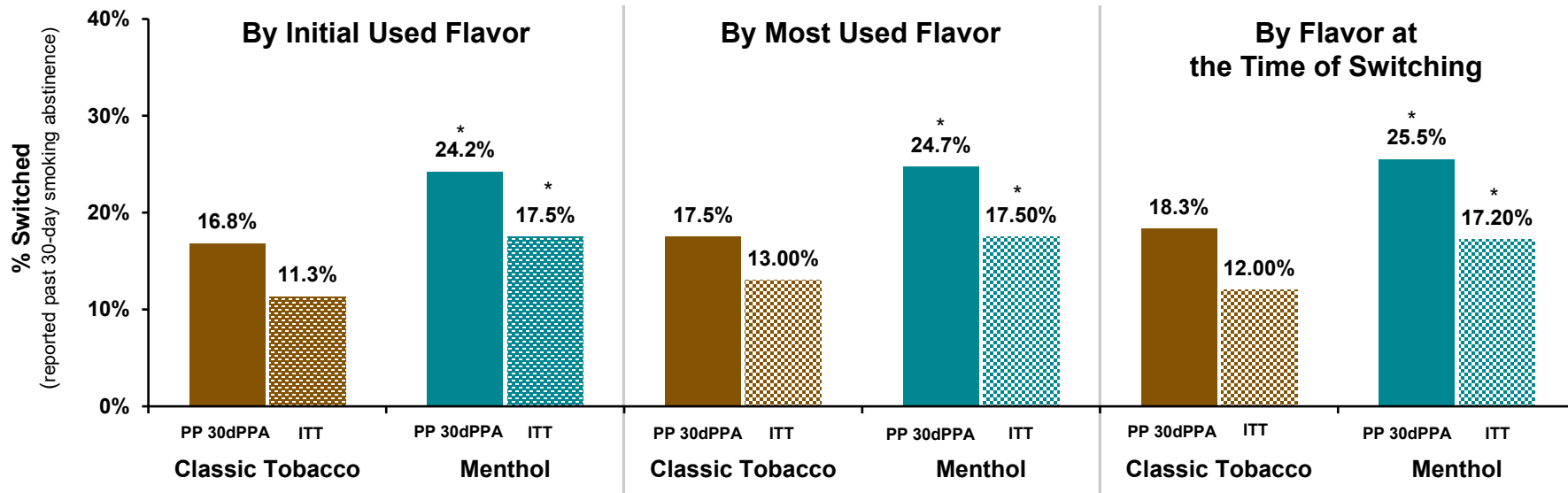




Flavored NJOY ACE® Products Associated with Greater Complete Switching Relative to Tobacco-Flavored

Complete Switching at 3 Months

(Per Protocol 30dPPA and Intent to Treat Analysis)



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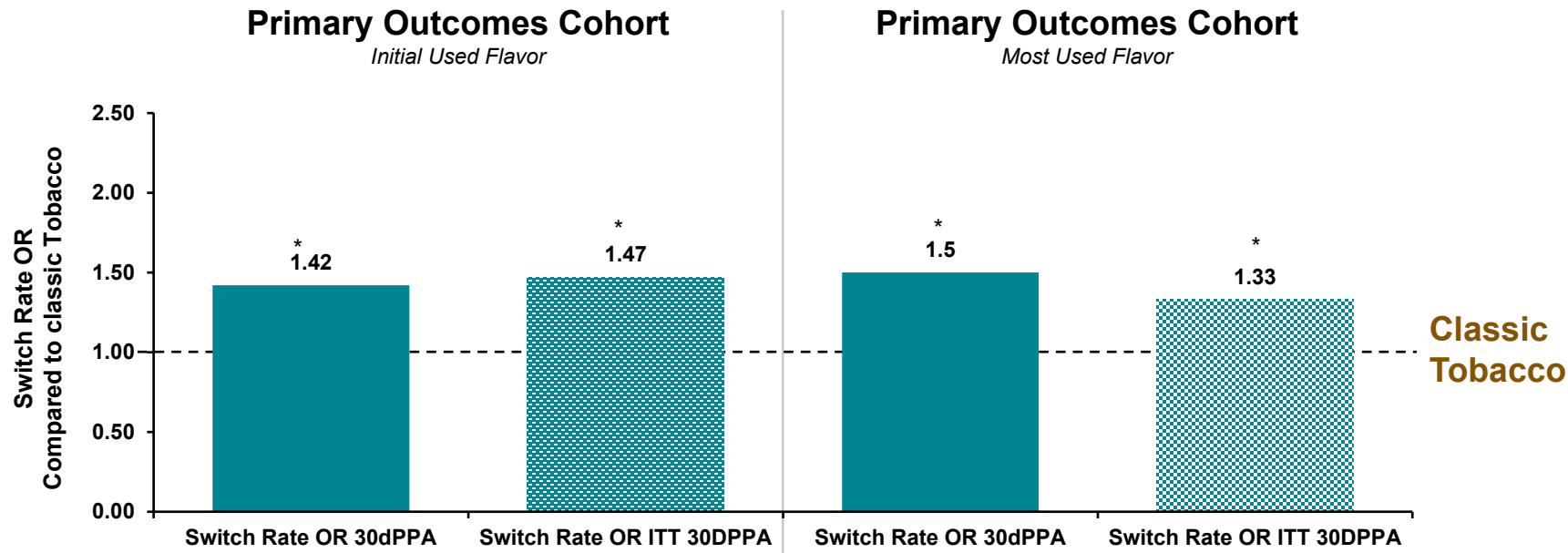
Source: NJOY ACE User Survey Supplemental Blueberry and Watermelon Report; NJOY ACE User Survey Supplemental Menthol Report.



Higher Adjusted Odds of Complete Switching for NJOY ACE® Menthol vs. NJOY ACE® Classic Tobacco



POPULATION HARM REDUCTION



*Statistically significantly greater than Classic Tobacco-flavored NJOY ACE products.

PPP 30dPPA=per protocol 30-day point prevalence abstinence; ITT=intent to treat.

Source: NJOY ACE User Survey Supplemental Menthol Report; Analysis shows Switch Rate Adjusted Odds Ratios for Per Protocol 30-Day Point Prevalence Abstinence for Initially Used NJOY ACE Flavor.



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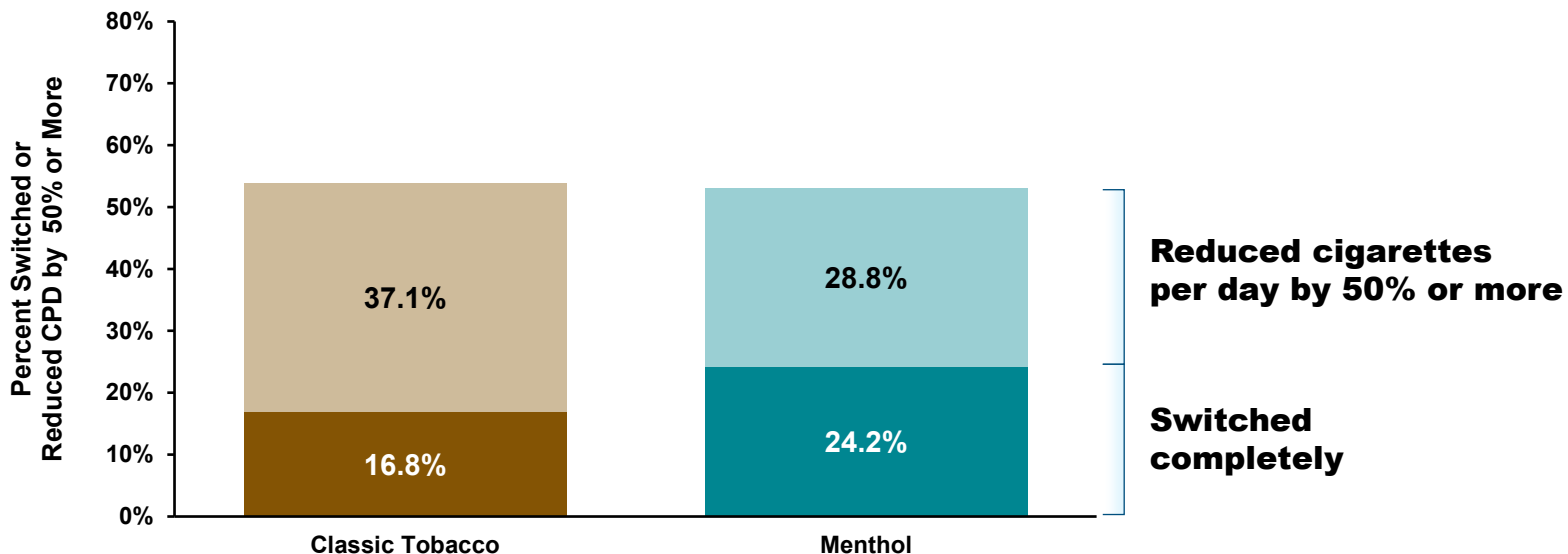
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NJOY ACE® Complete Switching and CPD Reduction at Three Months



POPULATION HARM REDUCTION

Complete Switching and CPD 50% Reduction by Initial Flavor Used



CPD=cigarettes per day

Source: Aggregated results include PP30dayPPA complete switch for Initial Flavor Used at 3mth timepoint, and CPD \geq 50% reduction for Initial Flavor Used at the 3mth timepoint; NJOY ACE User Survey 6mth Report.



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NJOY ACE® ENDS Youth Prevalence is Rare



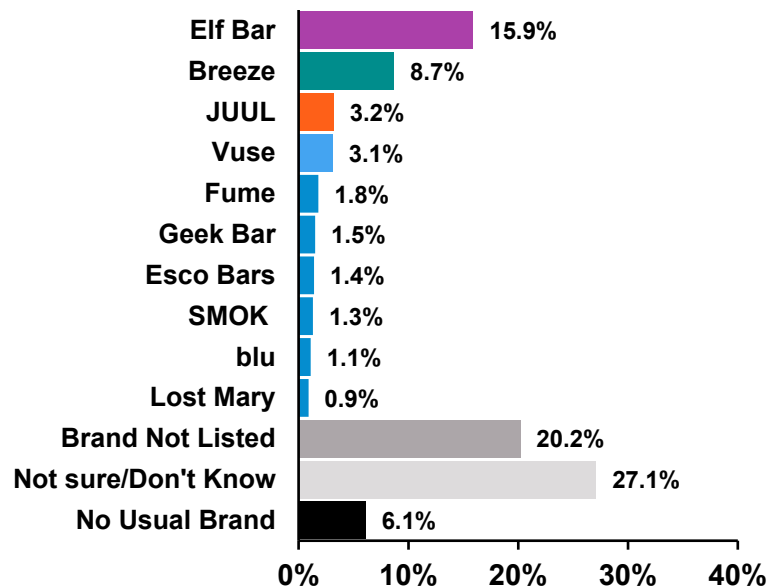
POPULATION HARM REDUCTION

NJOY Brand Detection Trends in NYTS

NYTS	NJOY Usual Brand Used Among Middle and High School E-Cigarette Users	Past 30-Day ENDS Use % (95% CI)
2021	NA ^a	7.6 (6.6-8.7)
2022	NA ^a	9.4 (8.0-11.1)
2023	NA ^a	7.7 (6.8–8.6)
2024	NA ^a	5.9 (5.3-6.6)

^aData not reported because responses were too low to determine statistically reliable estimates

2024 Usual Brand Used Among Middle and High School Current E-Cigarette Users



CI=confidence interval; ENDS=electronic nicotine delivery system; NA=not applicable; NYTS=National Youth Tobacco Survey.

Sources: MMWR Park-Lee et al., 2021; Cooper et al., 2022; Birdsey et al., 2023; Park-Lee et al., 2024

National Youth Tobacco Survey, 2024. *MMWR Morb Mortal Wkly Rep* 2024;73:774–778.
DOI: <http://dx.doi.org/10.15585/mmwr.mm7335a3>



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Integration of Multiple Lines of Evidence to Demonstrate APPH*

- ✓ HPHCs eliminated or substantially reduced
- ✓ Abuse liability is not likely to be higher than CC
- ✓ Real-world evidence demonstrated substantial switching to NJOY ACE
- ✓ Across multiple flavor variables and analyses, Menthol provided a significant benefit beyond Classic Tobacco
- ✓ Many AS who did not switch reduced cigs $\geq 50\%$
- ✓ Additional evidence submitted demonstrated low risk to nonusers



Net Population Benefit

APPH

*Appropriate for the Protection of Public Health

AS=adult smokers; Cig=cigarette; CC=combustible cigarette; HPHC=harmful and potentially harmful constituents.

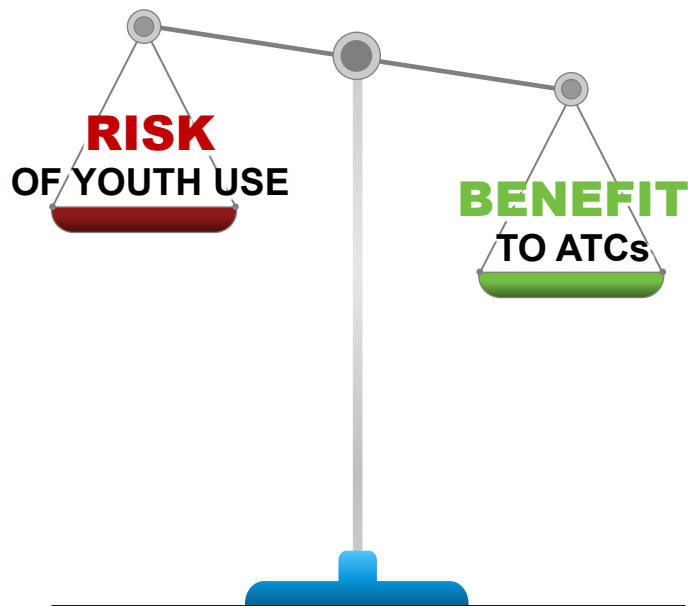


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FDA Has Set Higher Standards for Flavored E-vapor Products

“ Given the known and substantial risk to youth posed by flavored ENDS,...a demonstration with sufficiently reliable and robust evidence that **the FLAVORED ENDS have an ADDED BENEFIT relative to tobacco-flavored ENDS** in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS. ”



Source: FDA. 2021 Sample MDO TPL; emphasis added.



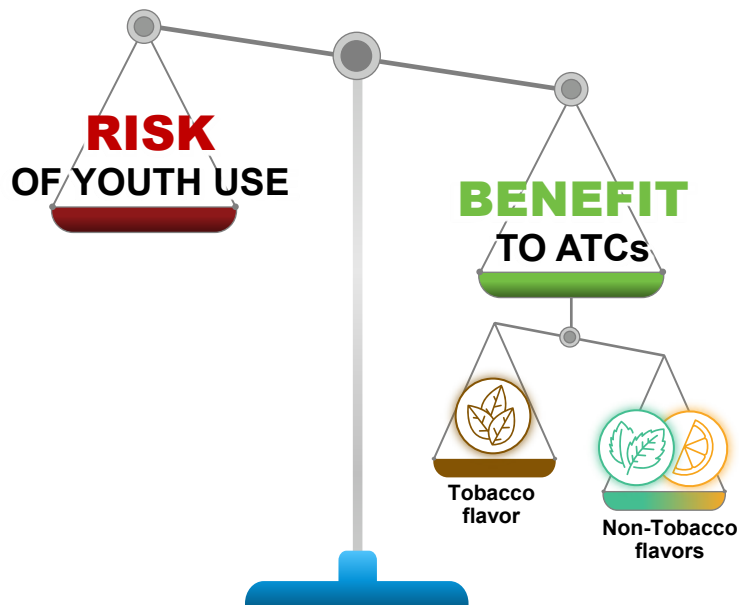
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“ Data from one of these studies could support a benefit to adult users if the findings show that, compared to the new tobacco-flavored product, **use of (each) new flavored product is associated with GREATER LIKELIHOOD** of either of these behavioral outcomes for adult smokers.... ”



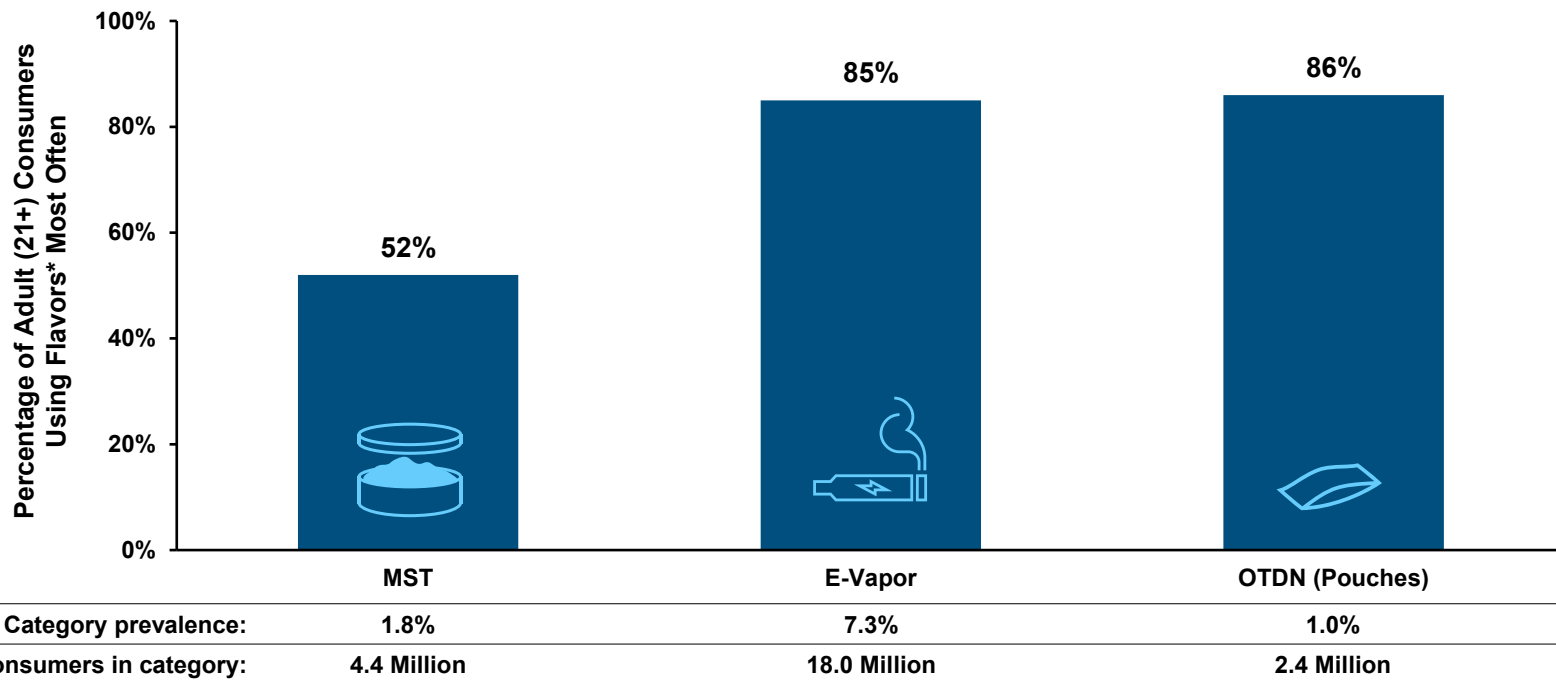
Source: FDA. 2021 Sample MDO TPL; emphasis added.



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Many Adults Who Use Smoke-free Tobacco Products Use Flavors



MST=moist smokeless tobacco; OTDN=oral tobacco-derived nicotine.

Source: ALCS Adult Tobacco Consumer Tracker, July 2023 to June 2024 (Internal docket 2024-AH-60). Estimates are calculated based on past 30-day product usage and flavor used most often. *Flavors: MST includes wintergreen, mint; E-Vapor includes menthol, mint, coffee/mocha crème/chai, fruit, blend of different flavors; OTDN includes mint, wintergreen, cinnamon, coffee/cream, citrus, berry, blend of different flavors.



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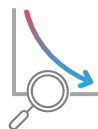
“Added Benefit” Needs to Consider Reach, Not Just Switch Rates

$$\text{\# OF ATCs USING THE PRODUCT} \times \text{SWITCH RATE} = \text{\# OF SWITCHERS}$$



SWITCH RATES ALONE provide an incomplete view

Impact depends on how many and who the ATCs are that use the product



ADDED BENEFIT should assess product's ability to move more ATCs down the risk continuum

Increased # of
Switchers & CPD Reducers

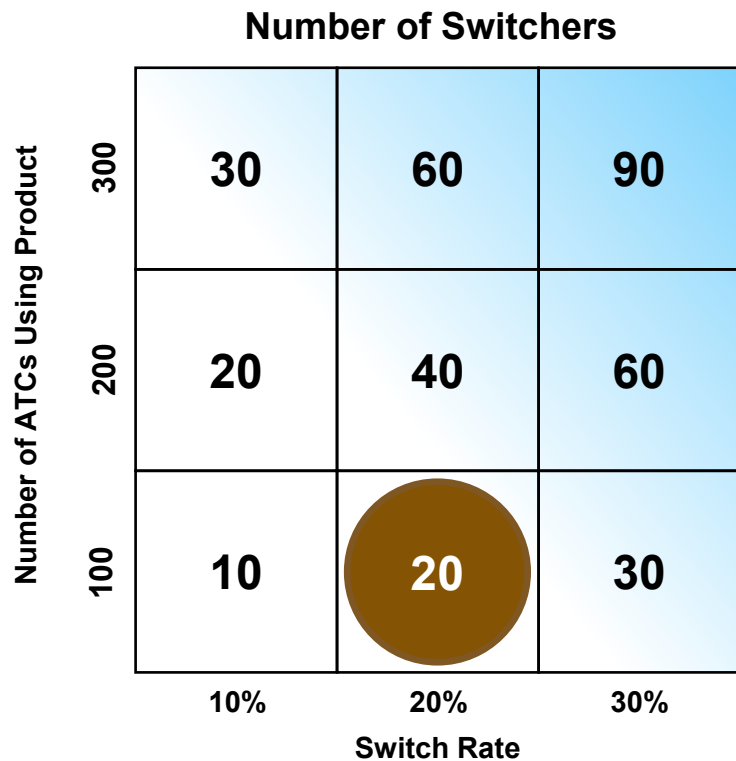
ATCs=adult tobacco consumers; CPD=cigarettes per day.



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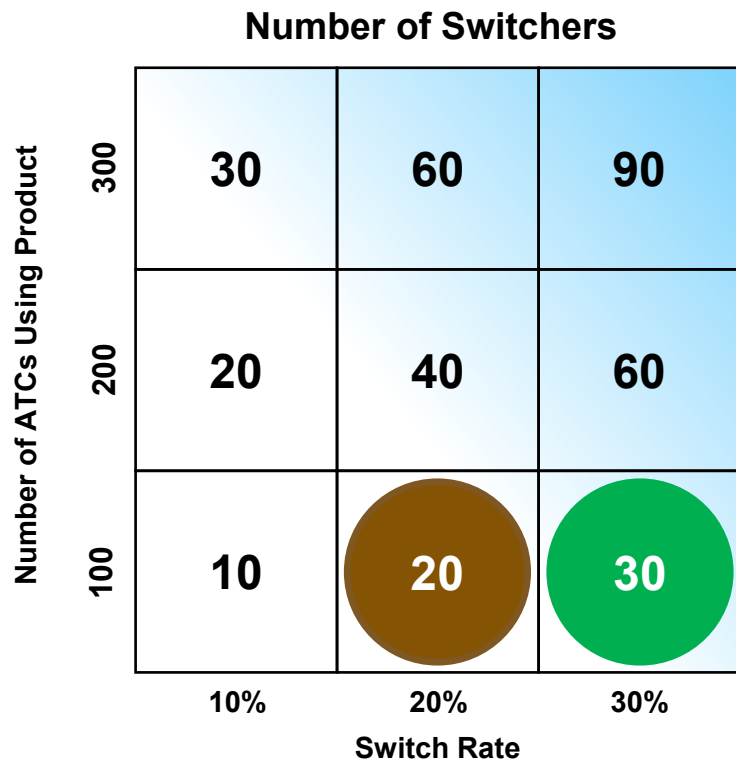
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Increasing Reach Can Increase Public Health Benefit



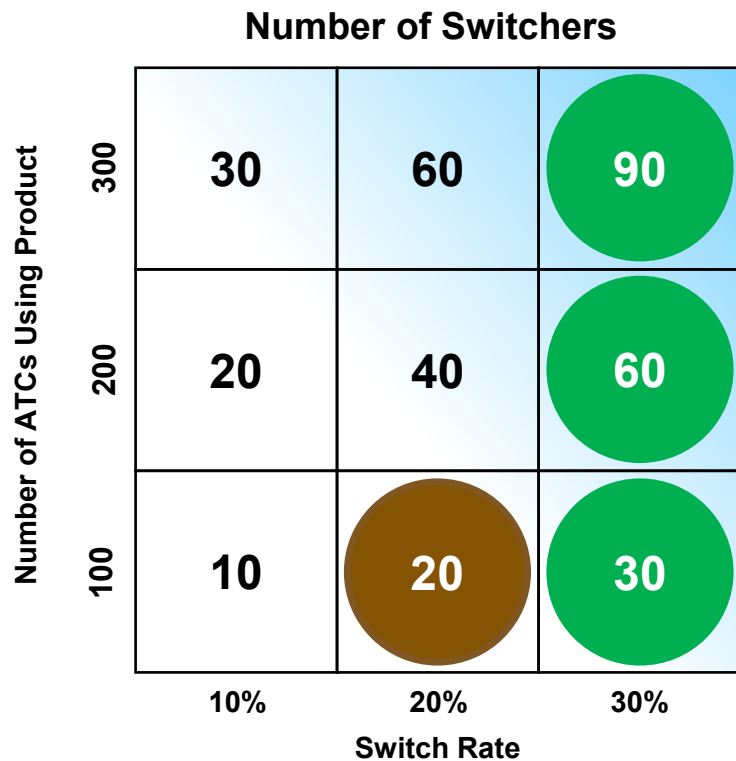
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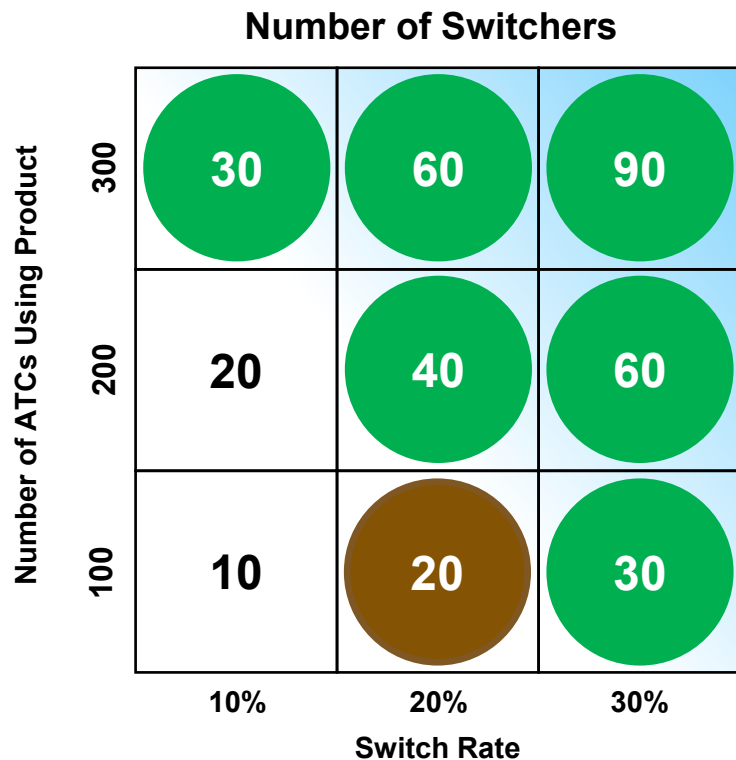
ATCs=adult tobacco consumers.

Increasing Reach Can Increase Public Health Benefit



ATCs=adult tobacco consumers.

Increasing Reach Can Increase Public Health Benefit



MORE ADULT TOBACCO CONSUMER SWITCHING

is possible in scenarios in which switch rates for **flavored products** are comparable to or even lower than **tobacco flavor**

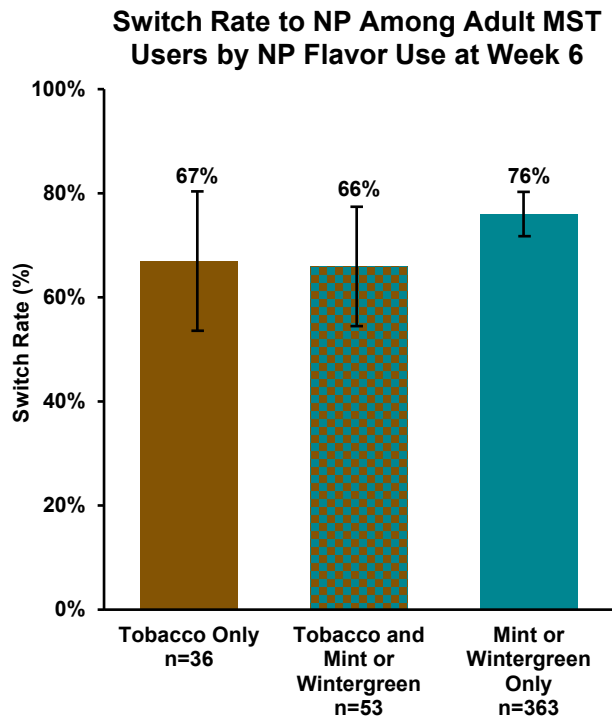
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While Switching Rates Were Similar across Varieties, the Vast Majority Switched with Mint or Wintergreen

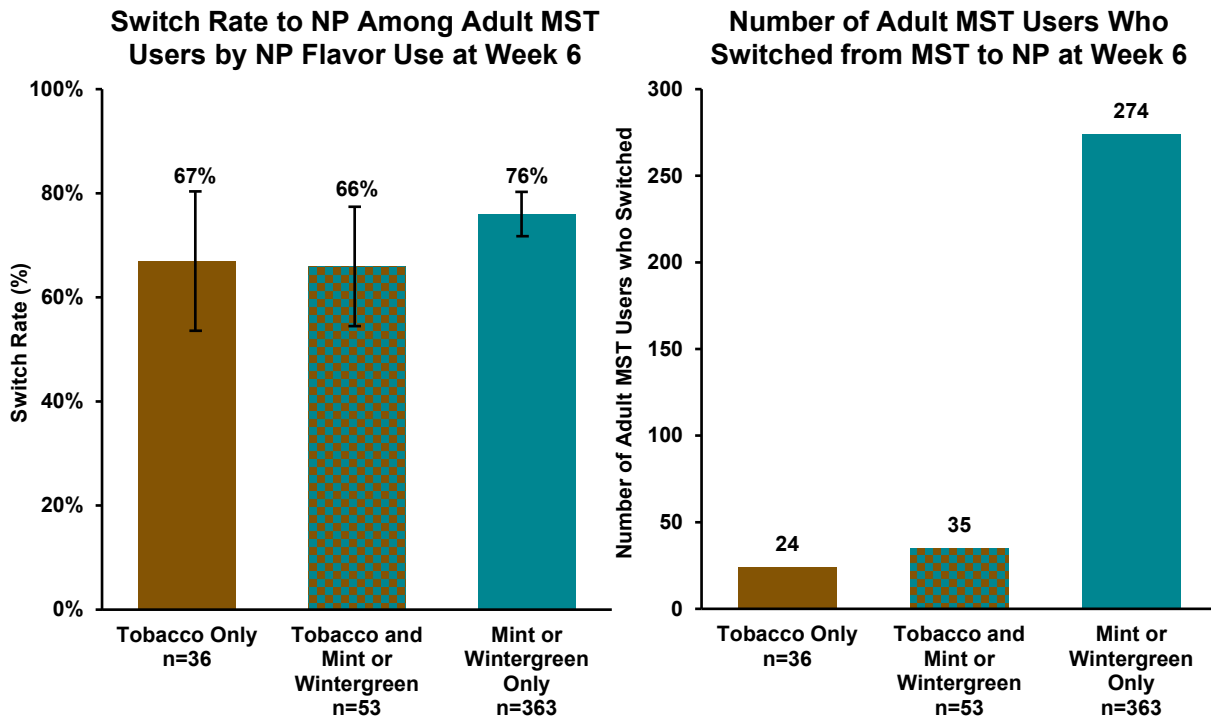


MST= moist smokeless tobacco, NP=nicotine pouch.

Source: ALCS on! Plus Actual Use Study, 2023 (internal docket 2023-AH-61).



While Switching Rates Were Similar across Varieties, the Vast Majority Switched with Mint or Wintergreen



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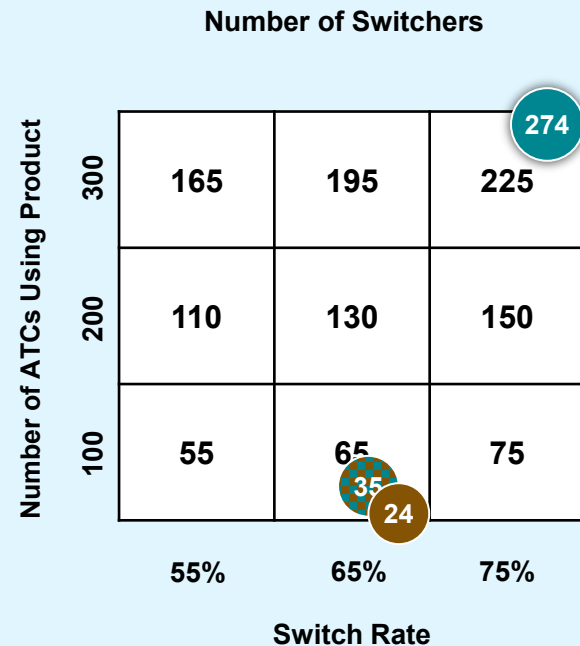
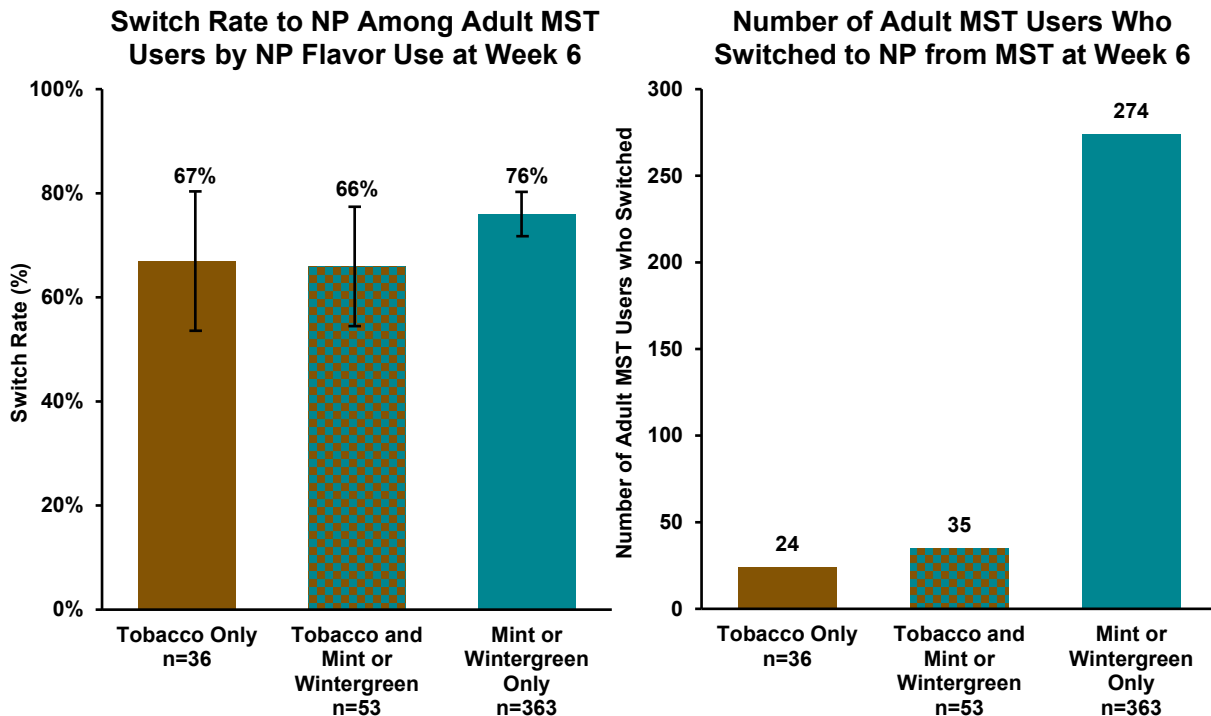
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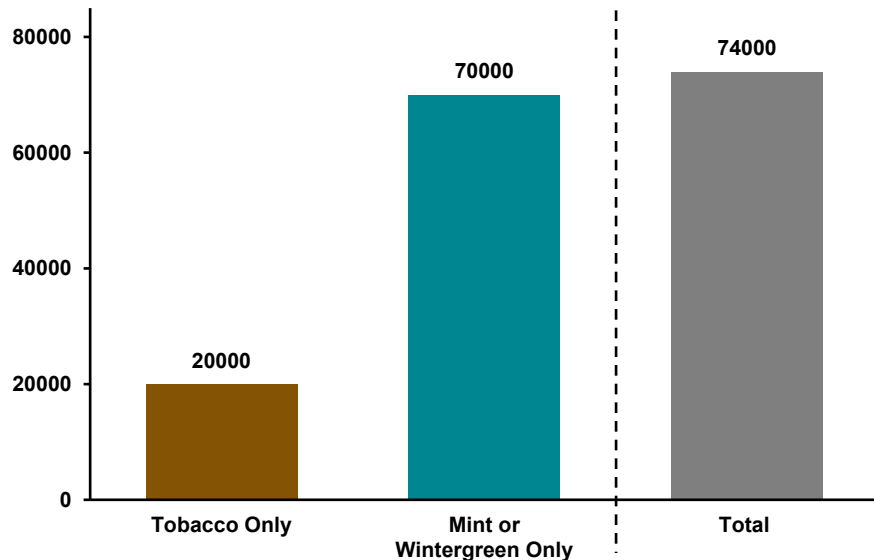
ATCs=adult tobacco consumers, MST= moist smokeless tobacco, NP=nicotine pouch.

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Flavor Accounts for Large Share of Public Health Benefit

**Population Health Impact Overall and by Flavor Usage
All-Cause Premature Death Prevented by 2100**



**Switching adjusted based on flavor used in week 6
of actual use study**

Source: Hannel, T.; Wei, L.; He, Y.; Muhammad-Kah, R.; Largo, E.; Sarkar, M., "Modeling the Population Health Impact of Flavor Variety and Potential Risk of Youth Initiation Resulting from the Marketing of an Oral Nicotine Pouch Product". Poster presented at the 77th Tobacco Science Research Conference, September 8-11, 2024.



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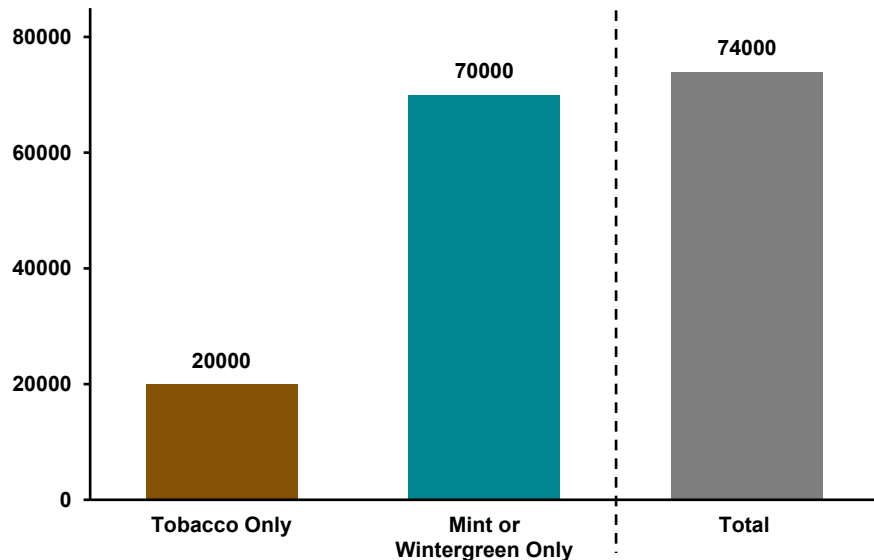
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Flavor Accounts for Large Share of Public Health Benefit

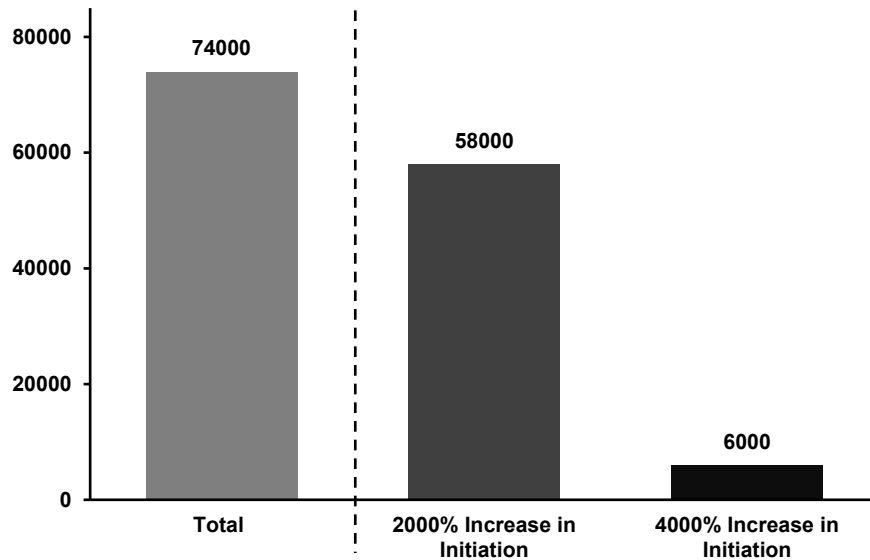
Tipping Point Analysis Shows the Underage Initiation Would Need to Increase Substantially to Shift Balance

Population Health Impact Overall and by Flavor Usage
All-Cause Premature Death Prevented by 2100



Switching adjusted based on flavor used in week 6 of actual use study

Population Health Impact Overall and by Varying Underage Initiation Rates
All-Cause Premature Death Prevented by 2100



Candidate product initiation rate increased among underage (12-20) population

Source: Hannel, T.; Wei, L.; He, Y.; Muhammad-Kah, R.; Largo, E.; Sarkar, M., "Modeling the Population Health Impact of Flavor Variety and Potential Risk of Youth Initiation Resulting from the Marketing of an Oral Nicotine Pouch Product". Poster presented at the 77th Tobacco Science Research Conference, September 8-11, 2024.



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Conclusions



Evidence for NJOY menthol e-vapor products, including switching relative to tobacco-flavored products, **supported an APPH determination**

“Switching superiority”

RUNS RISK OF PROVIDING incomplete view of potential benefit of flavored products to adult tobacco consumers

“Added benefit”

SHOULD INCORPORATE assessment of how flavored products facilitate switching *AND* extend reach to move more adult tobacco consumers down the risk continuum

Taking a consumer-centric approach



recognizing the value of preferences and importance of availability



can accelerate tobacco harm reduction

APPH=appropriate for the protection of public health.



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