Characterizing Biomarkers of Exposure Among Dual Users of Cigarettes and E-cigarettes Stratified by Product Use Behavior Patterns

Pavel (Paul) N. Lizhnyak, Ph.D.
Principal Scientist, Regulatory Affairs - Population Sciences
Altria Client Services LLC, Richmond, VA 23219
Center for Research and Technology
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Outline

Introduction

Characterization of Adult Dual User Subgroups

- Cross-sectional Assessment of Biomarkers of Exposure Based on Frequency of Smoking
- Longitudinal Assessment of Biomarkers of Exposure Based on Cigarette Consumption

Key Takeaways

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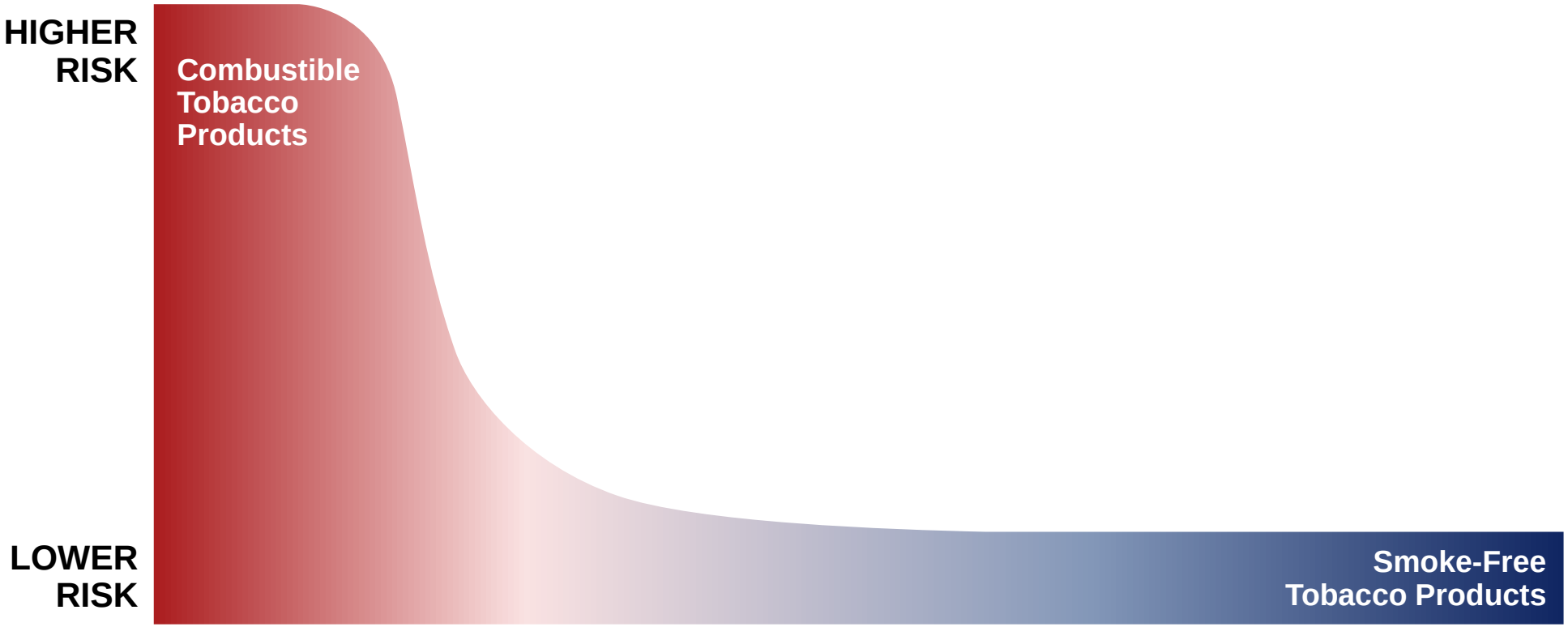
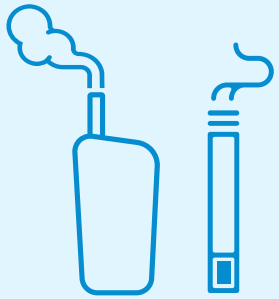
Risk Differential – Combustible vs. Smoke-free Products

Risk Cliff Between Combustible & Smoke-Free Tobacco[1]



[1]Adapted from Nutt, et. al Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach. *Eur. Addict Res* 2014; 20:218-225.

Adults Who Smoke Cigarettes and Use Smoke-free Products (Dual Users) – Harm Reduction



APPROXIMATELY

30% of adult e-cigarette users also smoke cigarettes

(NHIS 2021 MMWR)

> For adults who smoke, switching completely from cigarettes to e-cigarettes may reduce exposure to many harmful chemicals… **However, it is important that they switch completely… to get the full health benefit.**
>
> – FDA

> Long periods of dual use … **can result in harms similar to**, or in addition to, **the harms from exclusive use of cigarettes.**
>
> – FDA

Dual-use behavior is not homogeneous
(Jackson 2025)

Source: The Relative Risks of Tobacco Products | FDA

Lack of Standardization in Dual Use Characterization

Any use of both products	• Current cigarette and ever e-cigarette use[1,2] • Everyday or some days use of both[3,4,5,6,7,8] • Weekly use of both products[9]
Daily and non-daily use of both products	• Daily cigarette use and everyday or some days e-cigarette use[10] • Daily e-cigarette use with cigarette smoking[11] • Daily and non-daily use of both products[12]
Frequent and infrequent use of both products	• Light, predominant, and heavy use of both products[13] • Frequent and infrequent use of both products[14]
Consumption	• Reducers, maintainers, increasers[15] • Low and High CPD[16] • Reductions in CPD[17]

1. Christensen 2014; 2. Cheng 2022; 3. Simonavicius 2017; 4. Goniewicz 2018; 5. Coleman 2019; 6. Chang 2021; 7. Strong 2022; 8. Chen 2024; 9. Levy 2016; 10. Rostron 2019; 11. Biener 2015; 12. Smith 2021; 13. Buu 2022; 14. Lizhnyak 2022; 15. Anic 2022; 16. Xue 2025; 17. *Forthcoming* Lizhnyak 2025.

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Cross-Sectional Assessment of Adult Dual User Subgroups

The Population Assessment of Tobacco and Health (PATH) Study

Wave 1 Adult Questionnaire Restricted-Use Files and Biomarker Restricted-Use Files (2013-2014)

STUDY GROUPS:

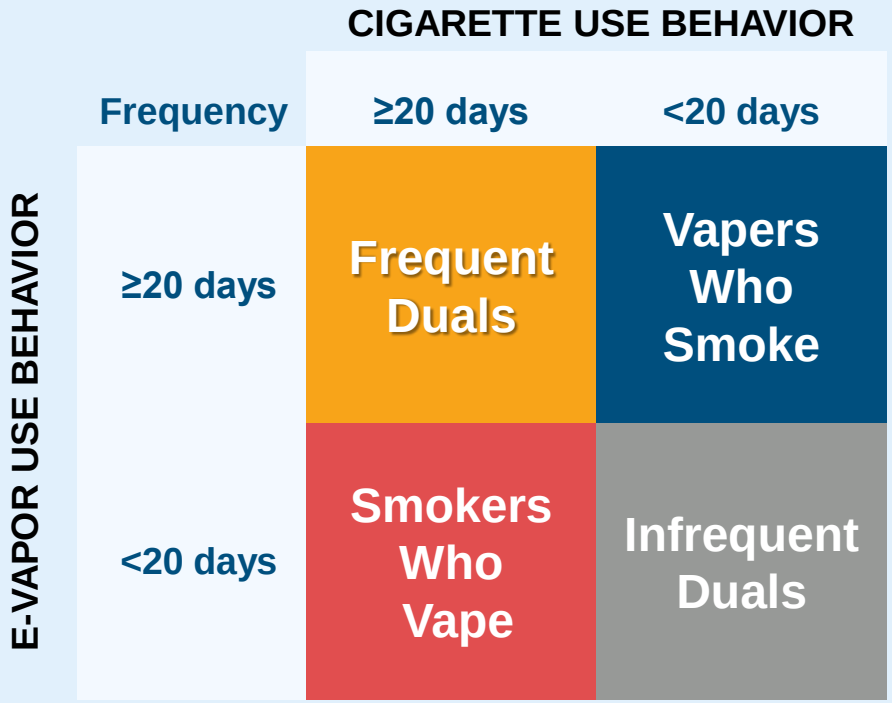
- Four Dual User Subgroups
- Exclusive Daily Cigarette Smokers
- Exclusive Daily E-Cigarette Users
- Never Tobacco Users

POPULATION:

Adults aged 18 or older[1]

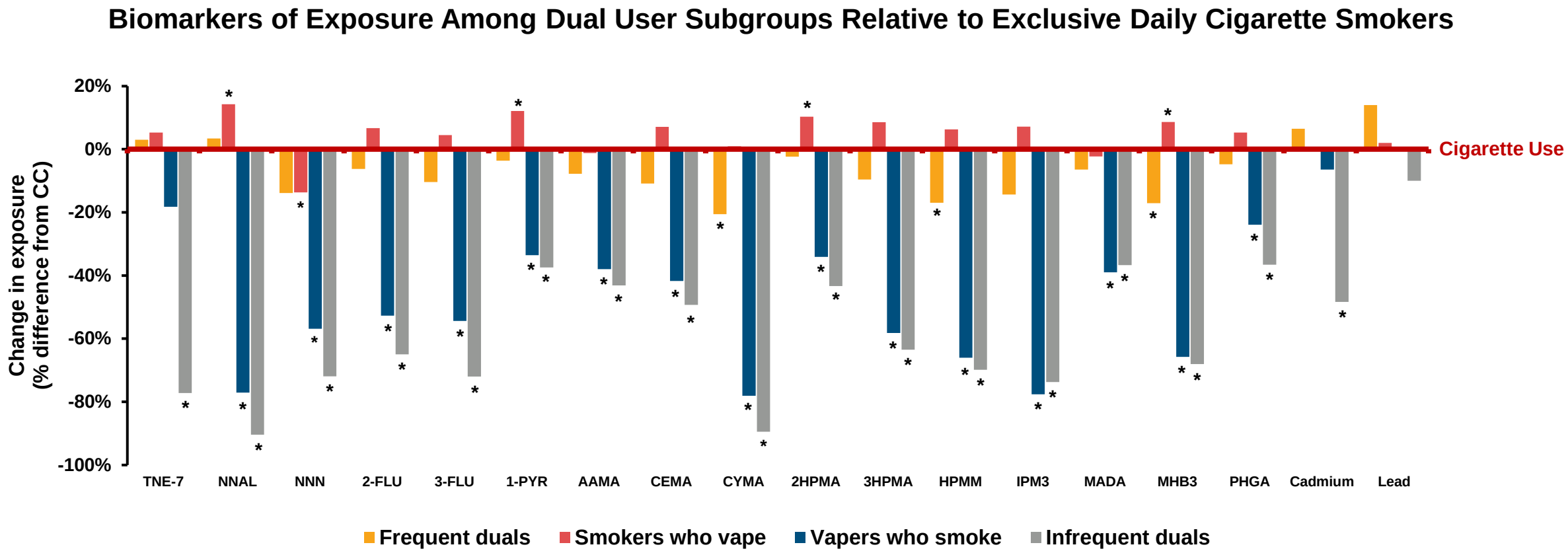
OUTCOMES

Biomarkers of exposure (BOE)



[1]The analysis was not restricted to 21+ because, at the time data were collected, the federal minimum legal age to purchase tobacco products was 18.

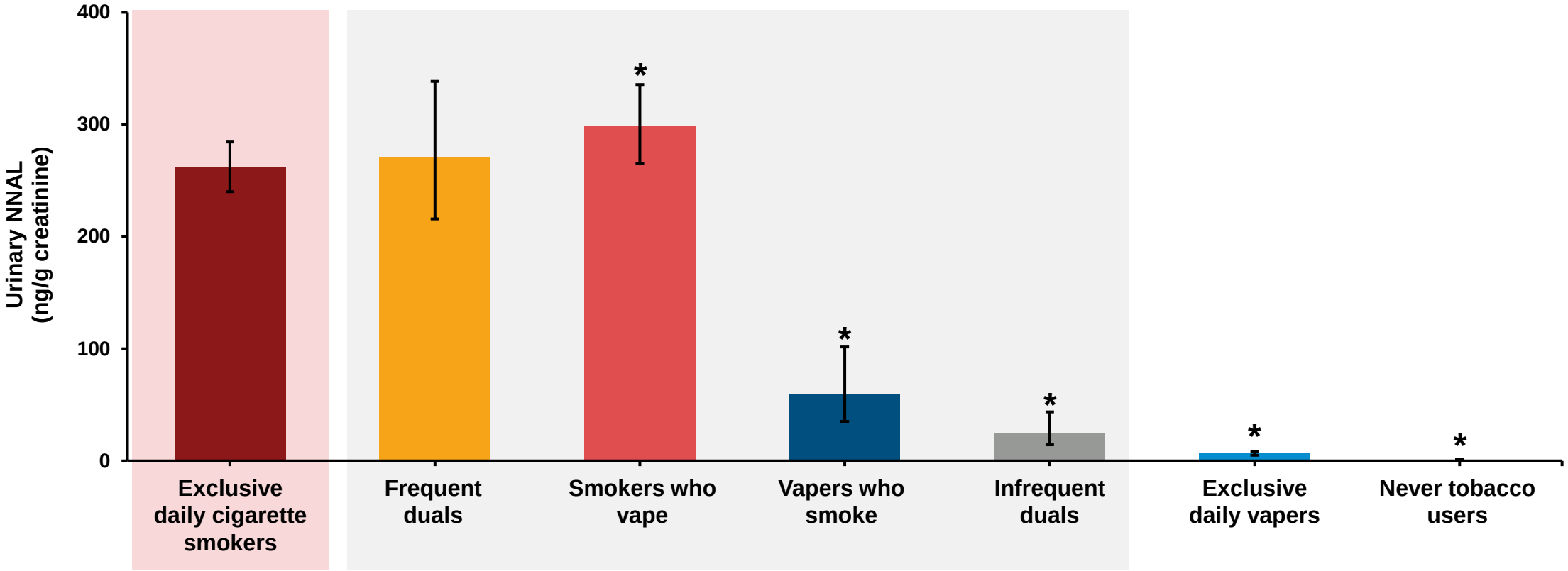
Substantially Lower BOEs in Some Adult Dual User Subgroups



Abbreviations: TNE-7: Total Nicotine Equivalents -7; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN: N'-Nitrosonornicotine; 2-FLU: 2-hydroxyfluorene; 3-FLU: 3-hydroxyfluorene; 1-PYR: 1-hydroxypyrene; AAMA: N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; CEMA: N-Acetyl-S-(2-carboxyethyl)-L-cysteine; CYMA: N-Acetyl-S-(2-cyanoethyl)-L-cysteine; 2HPMA: N-Acetyl-S-(2-hydroxypropyl)-L-cysteine; 3HPMA: N-Acetyl-S-(3-hydroxypropyl)-L-cysteine; HPMM: N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; IPM3: N-Acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine; MADA - Mandelic acid; MHB3: N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine; PHGA - Phenylglyoxylic acid
Note: * - denotes statistically significant difference ($p<0.05$) when compared to exclusive cigarette smokers.

Evaluating the Impact of Dual Use Requires Differentiating Subgroups

Exposure to NNK (NNAL) Among Exclusive Daily Cigarette Smokers, Dual User Subgroups, Exclusive Daily E-cigarette Users, and Never Tobacco Users



Abbreviation: NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
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Longitudinal Assessment of Adult Cigarette Smokers Who Transition to ENDS

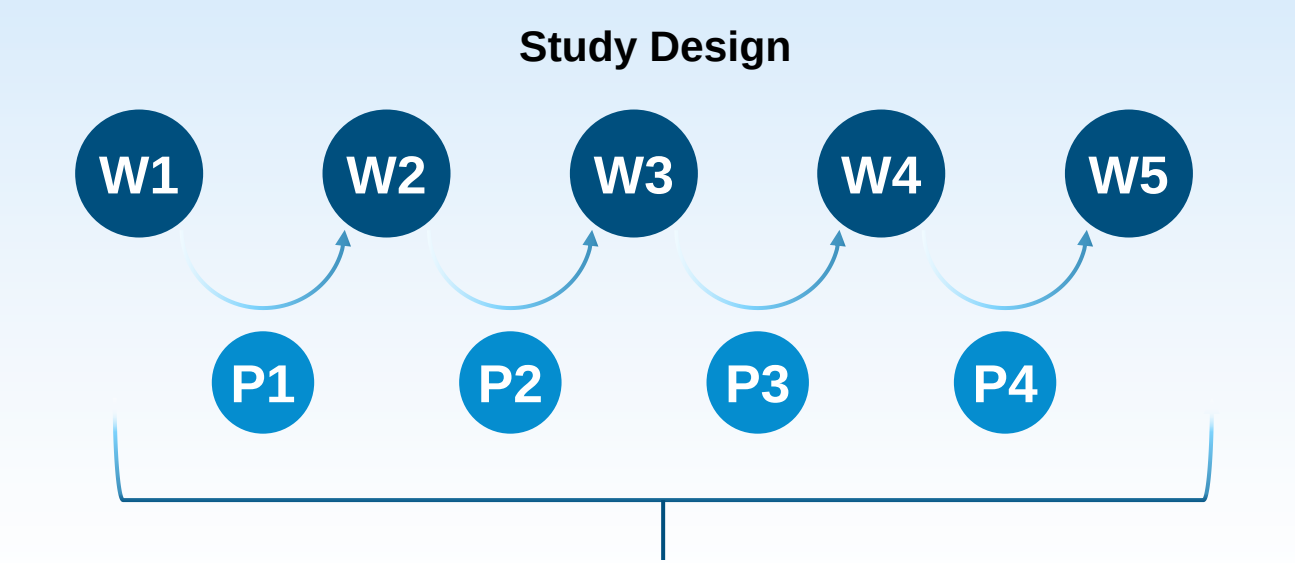
DATA SOURCE
PATH Waves 1-5 RUF Biomarker Core

STUDY GROUPS
Adults 18+ Exclusive Established Cigarette Smokers who switched to ENDS, dual used, or quit smoking

OUTCOME MEASURES
Biomarkers of Exposure (BOE)

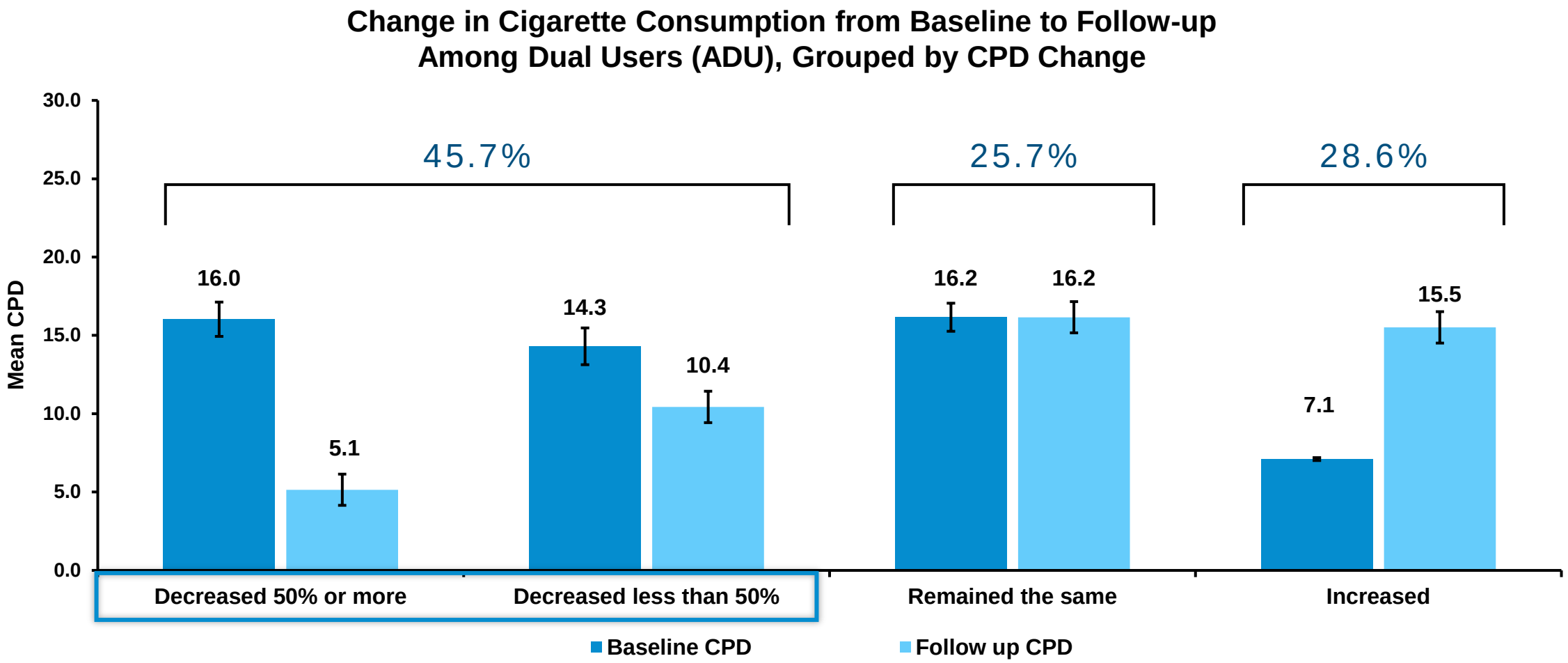
MODEL
Generalized Estimating Equations (GEE)

COVARIATES
Age, sex, race and ethnicity, education, cigarettes per day, time (survey wave), and subject-specific correlations



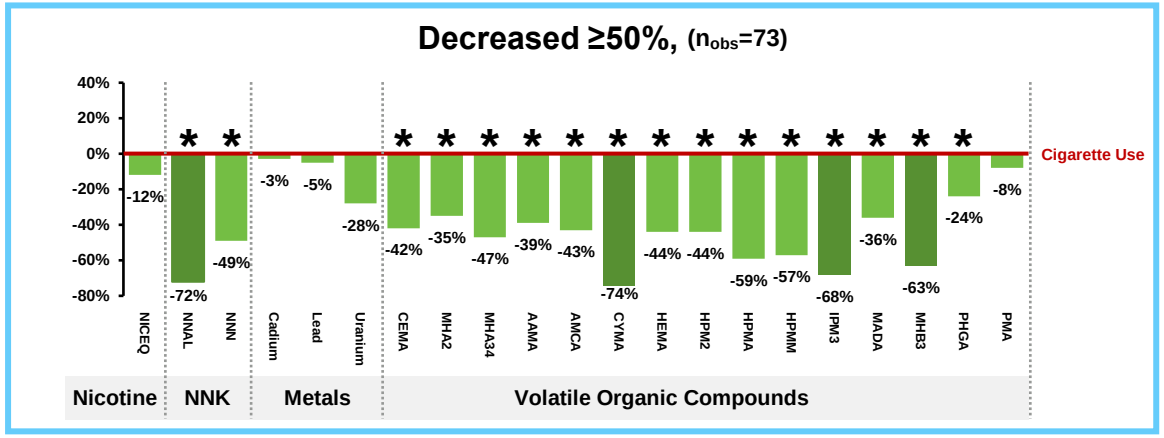
Tobacco User Group	Abbr.	Number of Observations
Exclusive Established Cigarette Smokers	CS	5,178
Exclusive Established ENDS Users	AE	79
Exclusive Established Dual Users	**ADU**	**311**
Former Smokers (no past 30-day tobacco use)	AQ	544

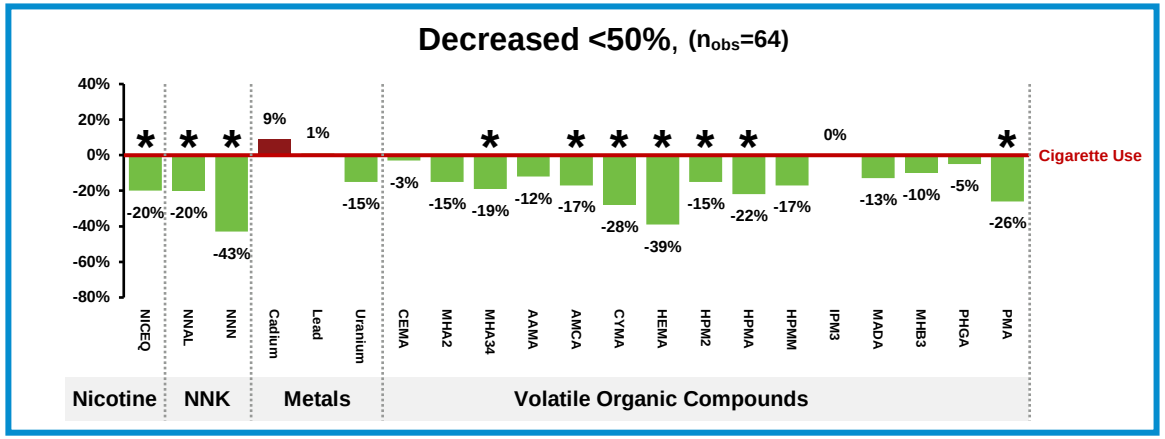
About Half of Adult Cigarette Smokers Who Transitioned to Dual Use Reduced Their Cigarette Consumption

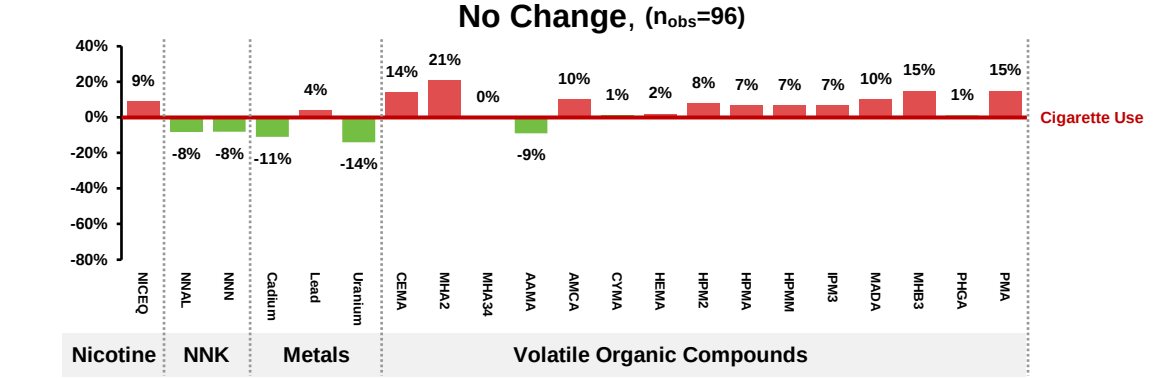


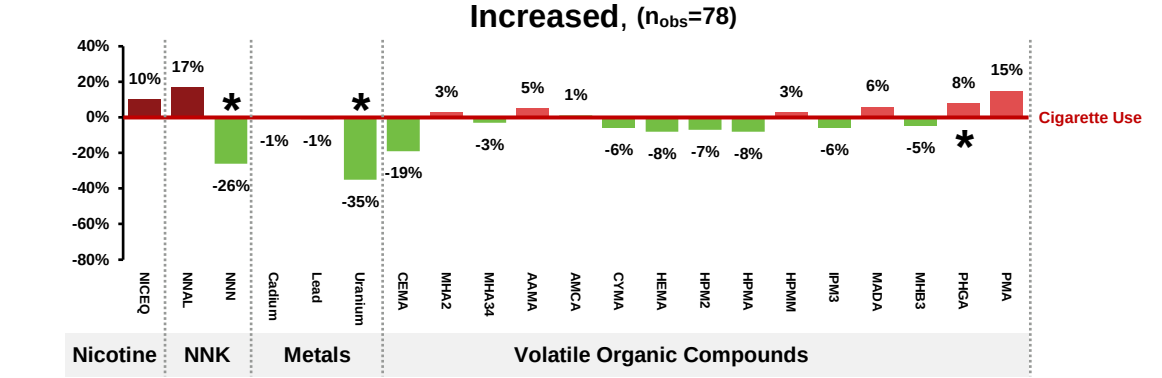
Significant Reductions in BOEs Among Adults Cigarette Smokers Who Transitioned to Dual Use and Reduced Cigarette Consumption

Changes in BOEs Among Adult Dual User Subgroups by Cigarette Consumption Compared to Continued Smokers



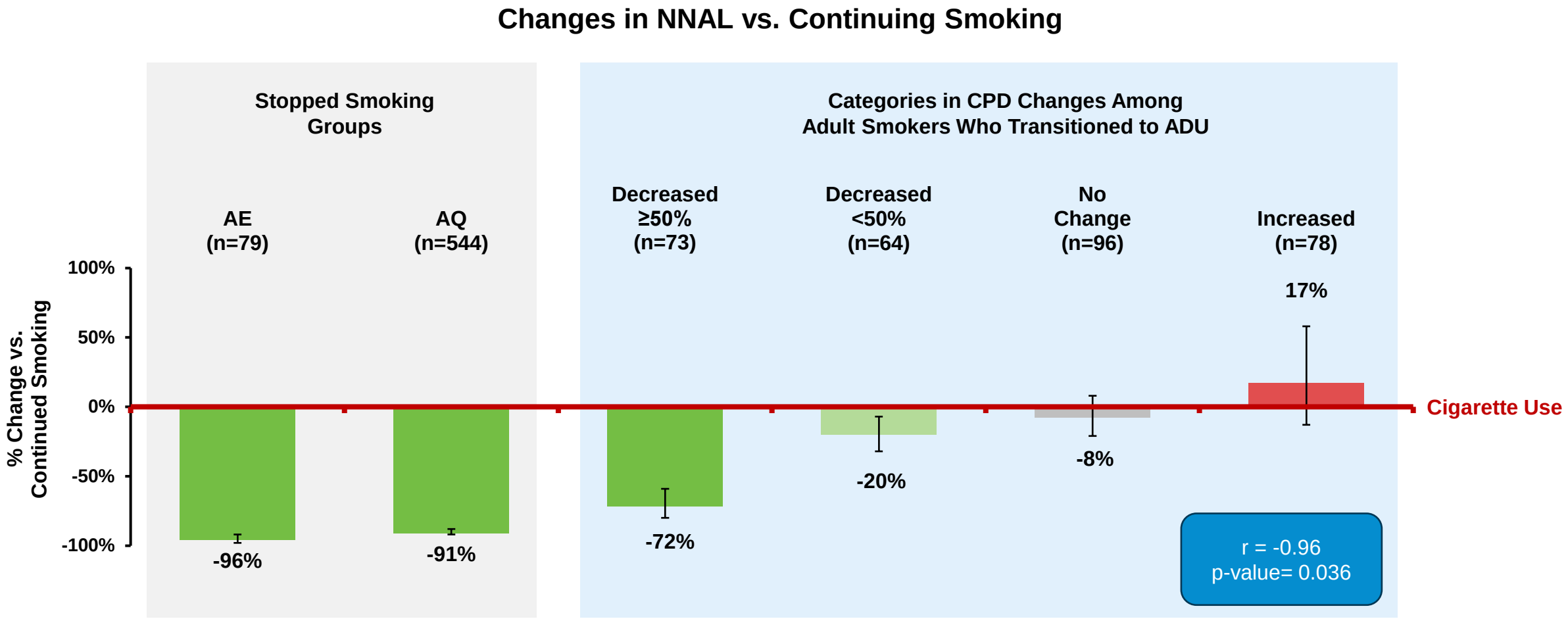






Abbreviations: **NICEQ**: Nicotine Equivalents - 3; **NNAL**: 4-(methylnitrosamino)-1-1(3-pyridyl)-1-butanol; **NNN**: N'-Nitrosonornicotine; **CEMA**: N-Acetyl-S-(2-carboxyethyl)-L-cysteine; **MHA2**: 2_methylhippuric_acid; **MHA34**: 3-4-Methylhippuric acid**; AAMA**: N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; **AMCA**: Aminocabonyl Mercapturic Acid; **CYMA**: N-Acetyl-S-(2-cyanoethyl)-L-cysteine; **HEMA**: Mercapturic acid; **HPM2**: N-Acetyl-S-(2-hydroxypropyl)-L-cysteine; **HPMA**: N-Acetyl-S-(3-hydroxypropyl)-L-cysteine; **HPMM**: N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; **IPM3**: N-Acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine; **MADA**: Mandelic acid; **MHB3**: N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine; **PHGA**: Phenylglyoxylic acid; **PMA**: Phenylmercapturic acid.
* - denotes statistically significant difference ($p<0.05$) when compared to continued smoking.

Using Cigarette Consumption Patterns to Differentiate Dual Use Subgroups



Abbreviations: **NNAL**: 4-(methylnitrosamino)-1-1(3-pyridyl)-1-butanol; AE – Exclusive Established ENDS Users; AQ – Former Smokers (no past 30-day tobacco use); ADU – Exclusive Established Cigarette Smoking and ENDS Users; CPD – Cigarettes Per Day

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- **Characterizing adult dual user subgroups by frequency and amount of product use is important for accurate exposure assessment**
  - Differences in BOEs are influenced by the frequency of cigarette smoking.
  - BOE differences are also driven by cigarette consumption levels.
  - More frequent ENDS use is accompanied by decreased cigarette smoking, resulting in lower levels of BOEs.
- **Dual users should not be treated as a homogeneous group and should be deconstructed into subgroups**
- **Some subgroups will experience reduction in exposure which can lead to reduced risk of smoking-related diseases**

Thank You

Please contact us if you have any questions.

Paul Lizhnyak (Pavel.N.Lizhnyak@altria.com)
Principal Scientist at Altria Client Services, LLC
601 E. Jackson St., Richmond, VA, 23219

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