Challenges to Tobacco Regulation: How Alterations in Tobacco Products Influence Use Behaviors

Alayna P. Tackett, PhD

Associate Professor

Department of Internal Medicine

Division of Medical Oncology

The James Comprehensive Cancer Center

The Center for Tobacco Research

OSU TCORS

Disclosures + Conflicts of Interest

- Research reported in this presentation support by the NIH, FDA, AHA, or Internal funds provided by the Center for Tobacco Research/The James Comprehensive Cancer Center.
- No conflicts of interests to report.
- The views and opinions expressed in this presentation are mine and do not necessarily represent the official position of The Ohio State University, the NIH, AHA or the FDA.

Presentation Overview

1. Flavor Manipulation

2. Nicotine Analogues

What is Tobacco Regulatory Science?

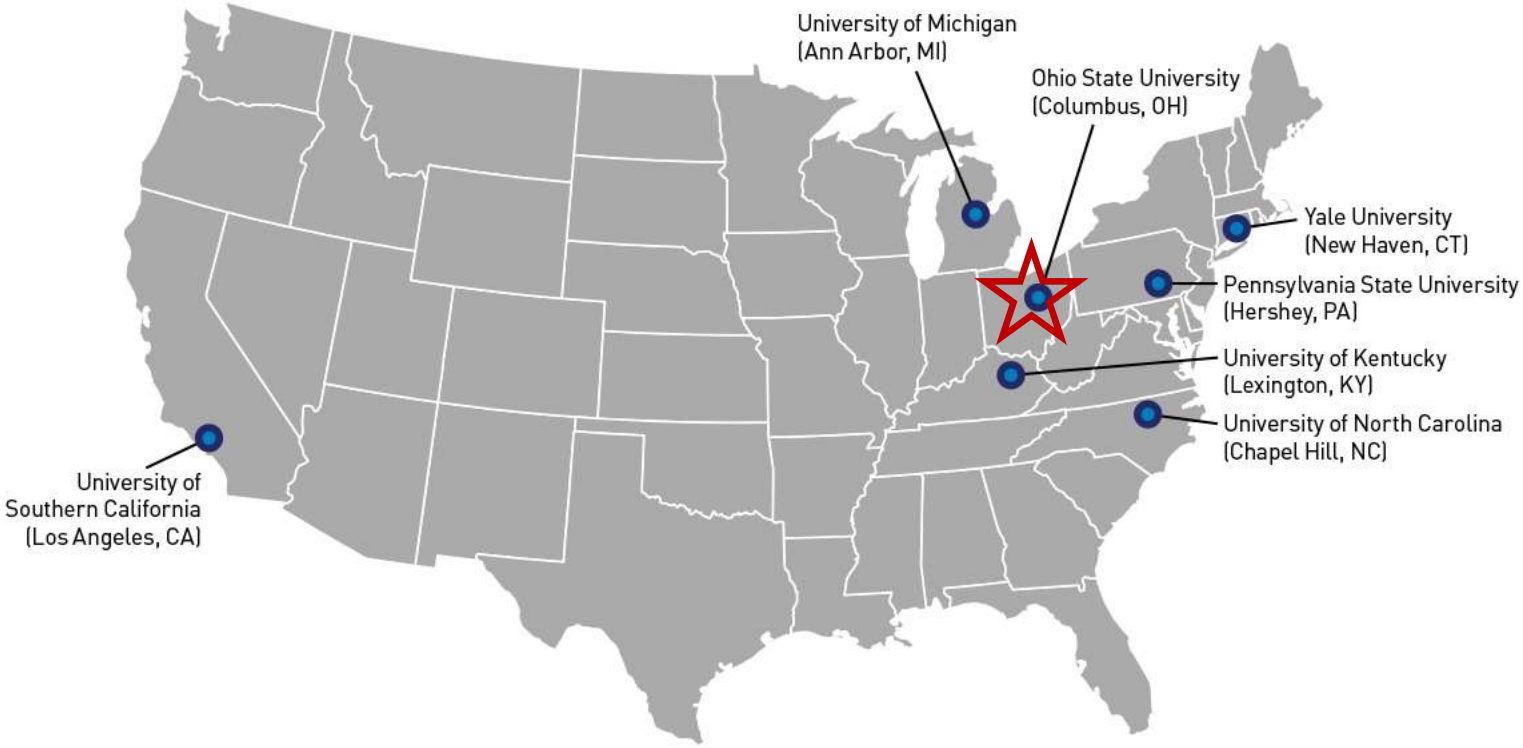
Family Smoking Prevention and Tobacco Control Act, 2009

Granted the FDA the authority to regulate the marketing and sale of tobacco products

"Deeming Rule," 2016

Brought all tobacco products under this regulatory umbrella, including e-cigarettes

Tobacco Centers for Regulatory Science in the United States



Classifying E-Cigarettes, or Vaping, Products

How to Classify the User's E-Cigarette, or Vaping, Product

For an accessible explanation of schematic below on how to classify e-cigarettes, go to Appendix, page 25.

Important notes:

1. E-liquids can contain nicotine, THC, CBD, flavors, or other solvents.
2. Marijuana herb, hash oil, dab wax are used with vaporizers.

QUESTION 1: Is the e-liquid contained in a disposable e-cigarette, cartridge, tank, or pod?

Disposable e-cigarette (no cartridge, tank or pod) → **1st GENERATION** (Cigalike)

Cartridge (Prefilled or refillable)

QUESTION 2: Is the cartridge also called a pod cartridge or contains nicotine salts?

NO → **2nd GENERATION** (Battery Pen)

YES

Tank/ Sub-Ohm (Refillable)

→ **3rd GENERATION** (Modifiable—allows variable voltage/watts)

Pod (Prefilled or refillable)

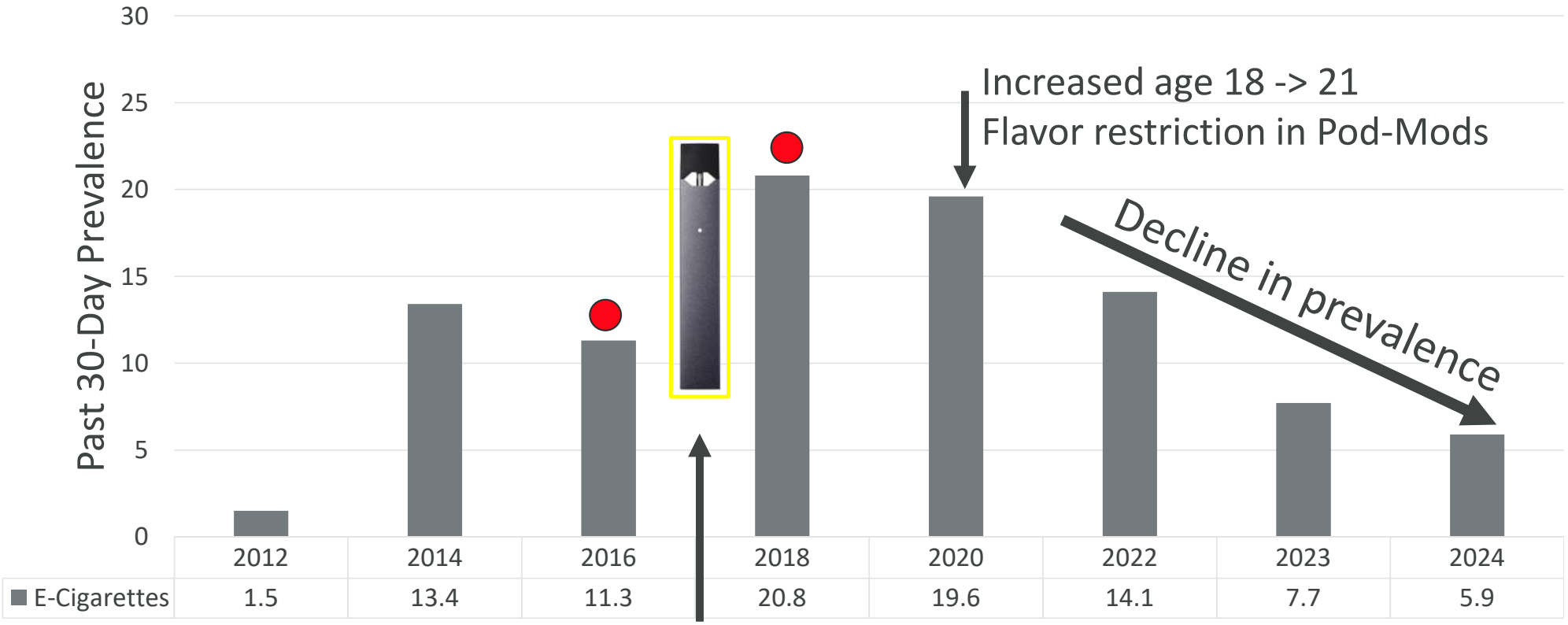
→ **4th GENERATION** (Pod Mod)

5th Generation?

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf

Wagener, 2018; Tackett et al., 2020; *Hammond et al., 2021; Kechter et al., 2021, Mantey et al., 2021, Sargent et al., 2022, Tackett et al., 2021, Boykan et al., 2019; Y. Wang et al., 2022*

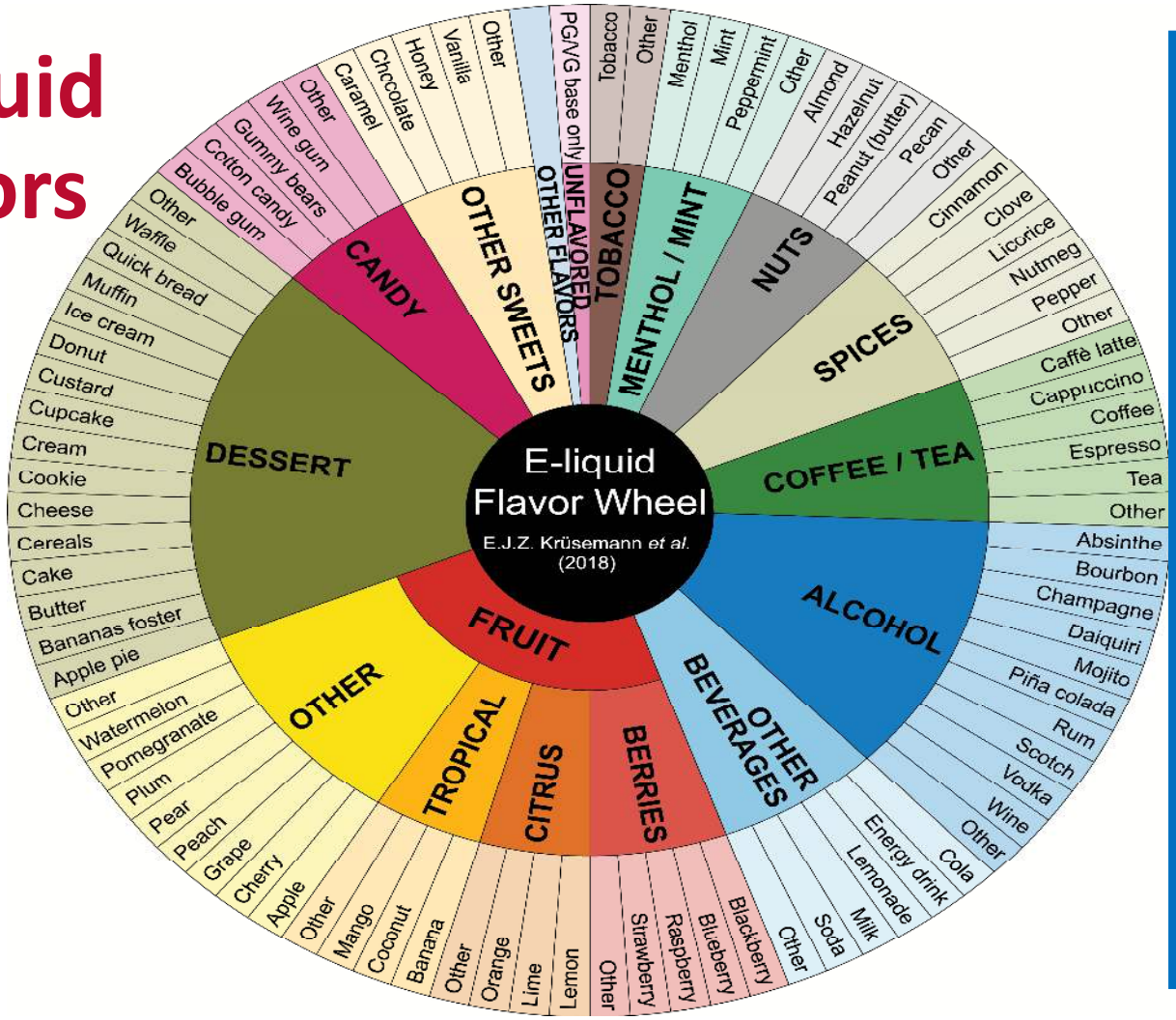
National Youth Tobacco Survey (NYTS)
E-Cigarette Use Among High Schoolers



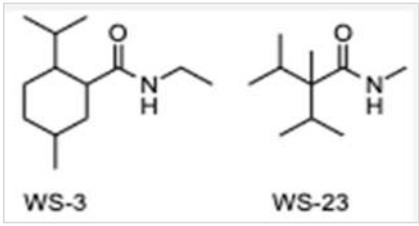
	2012	2014	2016	2018	2020	2022	2023	2024
E-Cigarettes	1.5	13.4	11.3	20.8	19.6	14.1	7.7	5.9

Jamal, A., et al. (2017). Tobacco use among middle and high school students—United States, 2011–2016. *Morbidity and Mortality Weekly Report*, *66*(23), 597.
Gentzke, A. S., et al. (2020). Tobacco product use among middle and high school students—United States, 2020. *Morbidity and Mortality Weekly Report*, *69*(50), 1881.
Gentzke AS, et al. Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018. MMWR Morb Mortal Wkly Rep. 2019 Feb 15;68(6):157-164.
Park-Lee, E et al. (2022). Tobacco product use among middle and high school students—United States, 2022. *Morbidity and Mortality Weekly Report*, *71*(45), 1429-1435.
Birdsey J, Cornelius M, Jamal A, et al. Tobacco Product Use Among U.S. Middle and High School Students — National Youth Tobacco Survey, 2023. MMWR Morb Mortal Wkly Rep 2023
Park-Lee E, et al. Notes from the Field: E-Cigarette and Nicotine Pouch Use Among Middle and High School Students — United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:774–778.

E-Liquid Flavors



Synthetic Cooling Agents



Krüsemann, Erna JZ, et al. (2019): 1310-1319. https://doi.org/10.1093/ntr/nty101

Do AYAs use “ice” flavors?

- Cross-section survey data among **young adults**:
  - Ice-flavors preferred, commonly used:
    - 48% (vs 17% mint/menthol)
  - Ice flavor use associated with:
    - greater odds of past 30- day combustible tobacco
    - Vaping initiation at younger age
    - Increased number of days vaped + vaping episodes per day
- Cross-sectional survey data among **youth**:
  - 51.6% endorse vaping cooling flavors
  - Vaping initiation at younger age
  - vaping more frequently

Leventhal, A., Dai, H., Barrington-Trimis, J., & Sussman, S. (2023). ‘Ice’flavoured e-cigarette use among young adults. *Tobacco control*, *32*(1), 114-117; **Davis** DR, Morean ME, Bold KW, Camenga D, Kong G, et al. (2021) Cooling e-cigarette flavors and the association with e-cigarette use among a sample of high school students. PLOS ONE 16(9): https://doi.org/10.1371/journal.pone.0256844 ; **Talhout**, R., & Leventhal, A. M. (2024). Coolants, organic acids, flavourings and other additives that facilitate inhalation of tobacco and nicotine products: implications for regulation.; **Li, W**., Davis, D. R., Kong, G., Bold, K. W., Morean, M. E., Camenga, D., ... & Krishnan-Sarin, S. (2024). E-cigarette dependence and cooling flavor use are linked among youth. *Drug and alcohol dependence*, *260*, 111325.

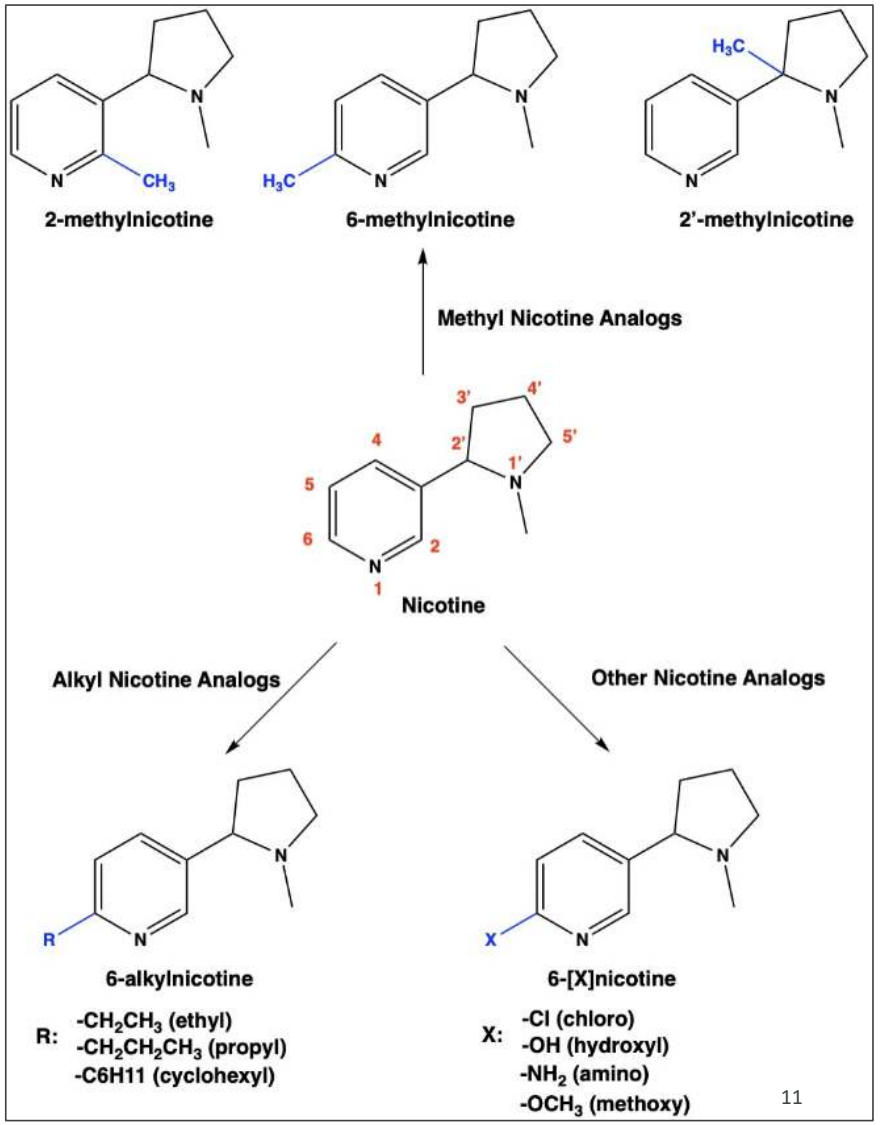
Why is this important?

- **These additives may be present, even if AYAs do not use "ice" flavored EC products.**
  - In EC products at high concentrations (> 10 mg/mL), even without a "cool" or "icy" label (tobacco cream, mango peach).
- **Little is known about the respiratory and long-term effects of vaping WS-3 and/or WS-23 individually and in combination**.
  - In-vitro studies suggest WS-23 may impact airway epithelial cells.
- **Synthetic coolant WS-23 added to e-cigarettes enhances the vaping experience.**
  - More appealing, generalized across base flavor (e.g., tobacco, fruit).

Wong, M., Martinez, T., Tran, M. et al. A synthetic coolant (WS-23) in disposable electronic cigarettes impairs cytoskeletal function in EpiAirway microtissues exposedS at the air liquid interface. Sci Rep 13, 16906 (2023). https://doi.org/10.1038/s41598-023-43948-4 ; **Yogeswaran**, S. et al. (2022). The role of synthetic coolants, WS-3 and WS-23, in modulating E-cigarette-induced reactive oxygen species (ROS) in lung epithelial cells.; **Manevski**, M., et al. (2022). E-cigarette synthetic cooling agent WS-23 and nicotine aerosols differentially modulate airway epithelial cell responses.; **Tackett, A. P.,** et al.. (2025). Effects of 'Ice'flavoured e-cigarettes with synthetic cooling agent WS-23 or menthol on user-reported appeal and sensory attributes. Tobacco control, 34(2), 175-182.

What are nicotine analogues?

- A nicotine analogue is a synthetic chemical that has structural similarity to nicotine.
- There are at least 20 known nicotine analogues.
- **6-methyl nicotine (6-MN) is the only one that has been detected in several electronic vaping product brands.**



- Pankow, J. F., Luo, W., McWhirter, K. J., Sengupta, M., & Strongin, R. M. (2025). Levels of the nicotine analog 6-methyl nicotine as a naturally formed tobacco alkaloid in tobacco and tobacco products. *Scientific Reports*, *15*(1), 17945.
- Glennon RA, Dukat M. Nicotine Analogs: Structure-Affinity Relationships For Central Nicotinic Acetylcholinergic Receptor Binding. In: Yamamoto I, Casida JE, editors. Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor. Tokyo: Springer Japan; 1999. p. 237-52

Spree Bar: One Commercial Nicotine Analogue Product

- Flavors target the **mint, fruit-ice, and fruit categories** that are preferred by youth.
- E-liquids contain the high-potency artificial sweetener **neotame** and synthetic cooling agent **WS-23**.
- Advertised as “nicotine free,” and indicates that it does not fall under the FDA’s regulatory authority.

- Jordt, S. E., Caceres, A., Silinski, P., & Jabba, S. V. (2025). 6-methyl Nicotine in Electronic Cigarettes: Chemical Analysis and Toxicological Properties. *American Journal of Respiratory and Critical Care Medicine*, *211*(Abstracts), A7552-A7552.
- Pankow, J. F., Luo, W., McWhirter, K. J., Sengupta, M., & Strongin, R. M. (2025). Levels of the nicotine analog 6-methyl nicotine as a naturally formed tobacco alkaloid in tobacco and tobacco products. *Scientific Reports*, *15*(1), 17945.
- Erythropel HC, Jabba SV, Silinski P, Anastas PT, Krishnan-Sarin S, Zimmerman JB, Jordt SE. High Variability in Nicotine Analog Contents, Misleading Labeling, and Artificial Sweetener in New E-Cigarette Products Marketed as "FDA-Exempt". JAMA. 2024

Is this even a problem? What do we know?

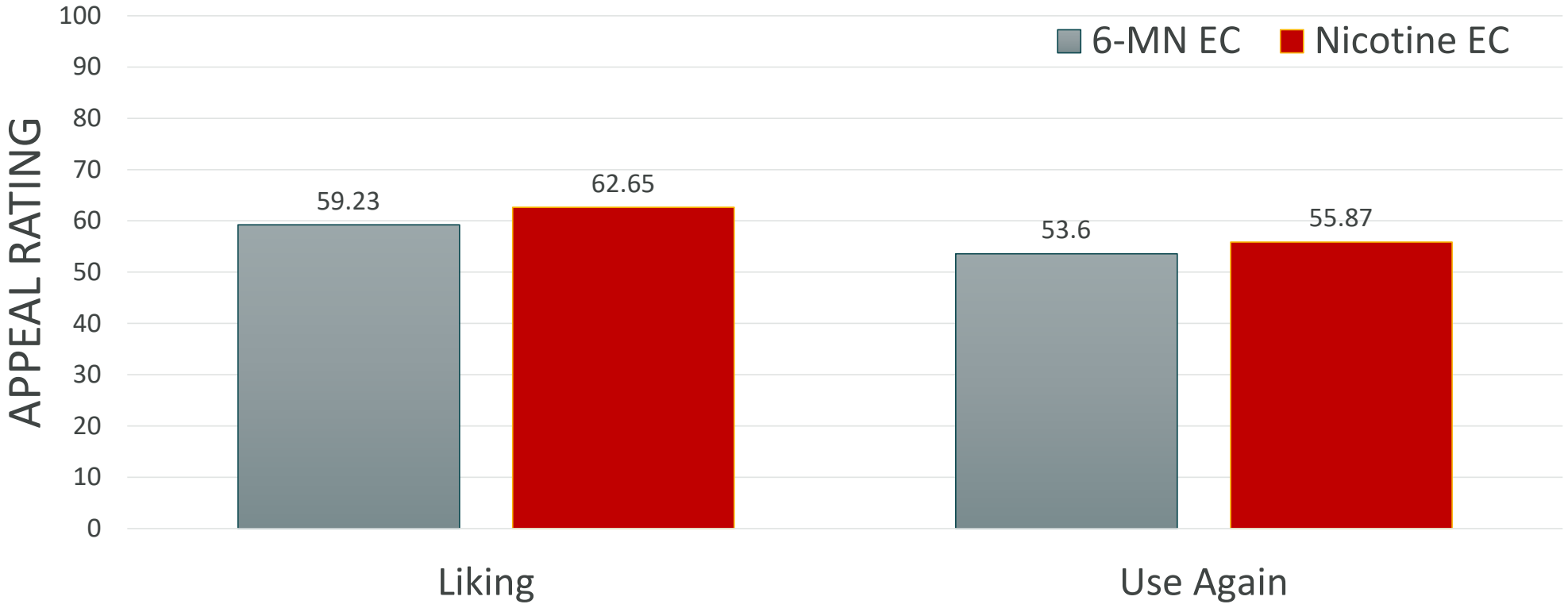
How big is the problem?

- 6-MN is just the first analogue to be successfully used in commercial products, and given the current lack of restrictions, more are expected in the US market.
- Products are available in vaping devices and oral nicotine pouches.
- Available industry data on nicotine analogues is sparse. Some data indicate these may be just as psychoactive and addictive, if not more so, than nicotine.

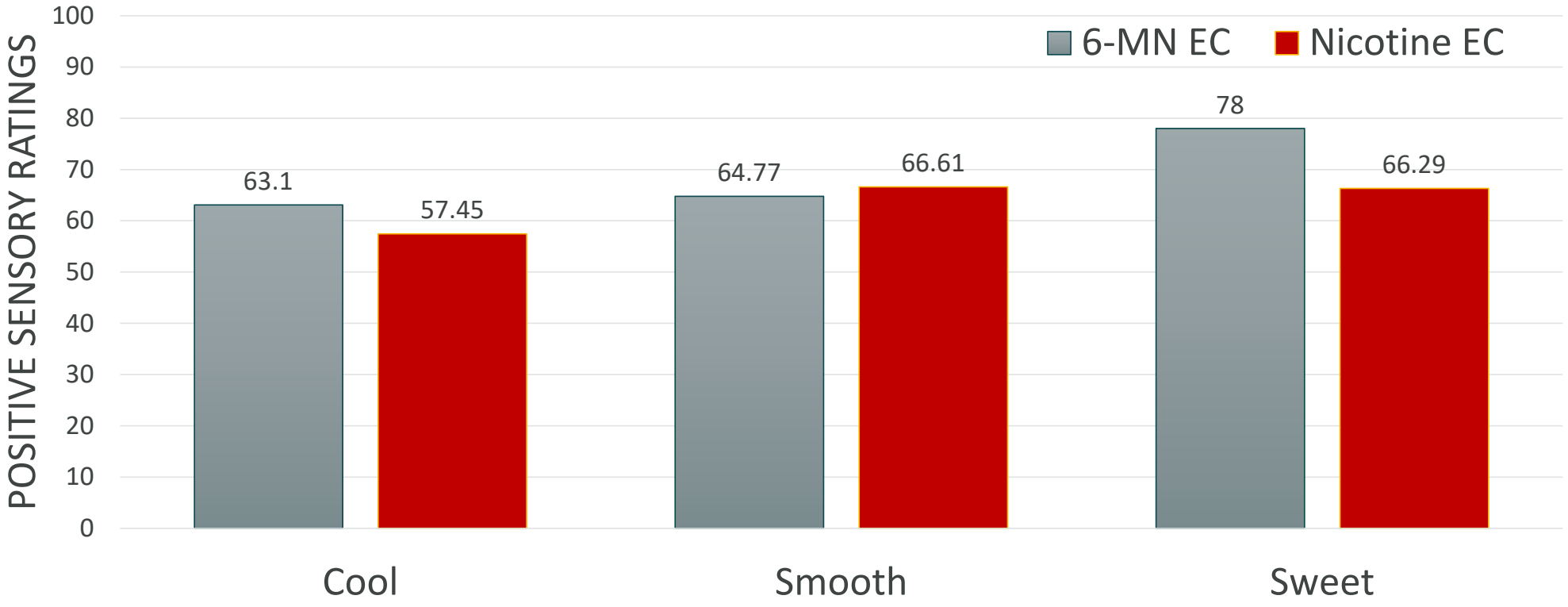
What do we know? Our pilot data (N = 30) among young adults (21-34) who currently used ECs shows…

Vagg R, Chapman S. Nicotine analogues: a review of tobacco industry research interests. Addiction. 2005;100(5):701-12. doi: https://doi.org/10.1111/j.1360-0443.2005.01014.x. ; Pankow JF, Luo W, McWhirter KJ, Sengupta M, Strongin RM. Levels of the nicotine analog 6-methyl nicotine as a naturally formed tobacco alkaloid in tobacco and tobacco products. Scientific Reports.2025;15(1):17945. doi: 10.1038/s41598-025-01392-6. ; Xing H, Andrud KW, Soti F, Rouchaud A, Jahn SC, Lu Z, Cho YH, Habibi S, Corsino P, Slavov S, Rocca JR, Lindstrom JM, Lukas RJ, Kem WR. A Methyl Scan of the Pyrrolidinium Ring of Nicotine Reveals Significant Differences in Its Interactions with α7 and α4β2 Nicotinic Acetylcholine Receptors. Mol Pharmacol. 2020;98(2):168-80. doi: 10.1124/mol.119.118786. PMC7377336

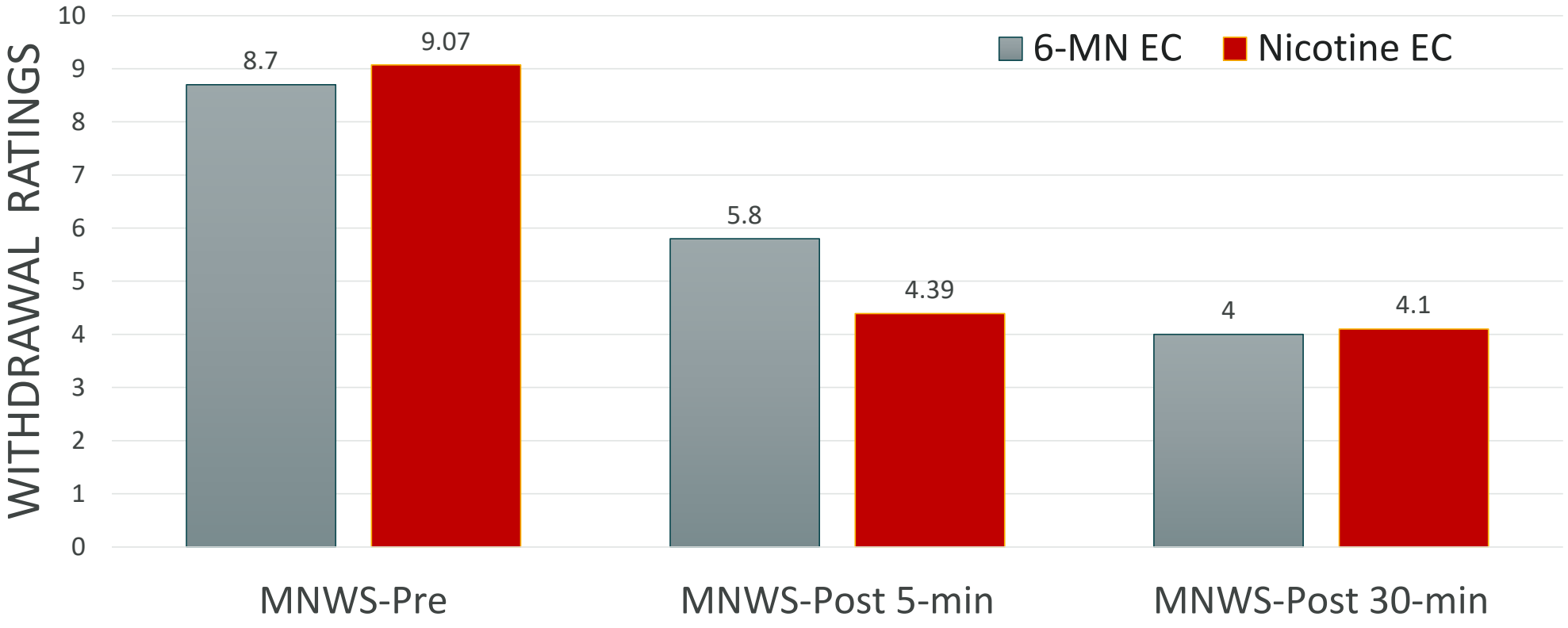
Appeal: 6-MN and Nicotine EC rated similarly.



Positive Sensory: Similar ratings for Coolness and Smoothness. 6-MN rated sweeter than Study EC.

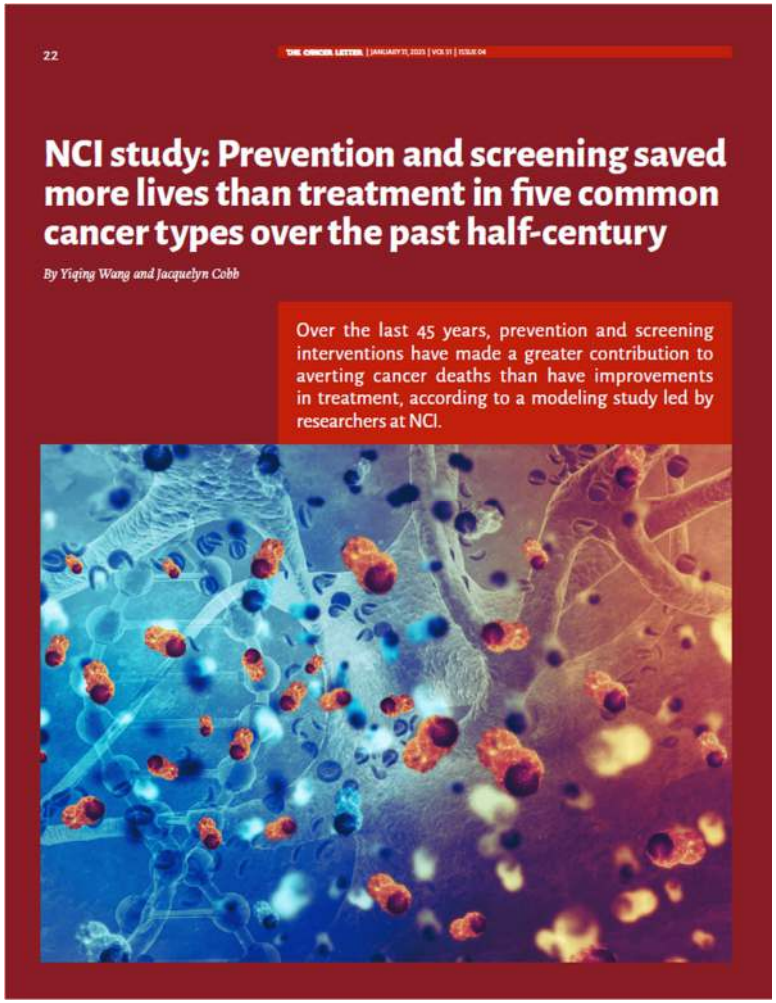


Withdrawal Relief (MNWS): Similar ratings for nicotine withdrawal relief.



Summary/Conclusions

1. **Product changes and constituent manipulations can impact future products.**
   - Spree Bar using synthetic cooling agent WS-23 and ice-flavor profiles.
2. **Flavors impact use behaviors among AYAs.**
   - Frequency of use, nicotine dependence, product initiation
   - Long-term impacts of vaping synthetic cooling agents?
3. **Nicotine analogues may change the US tobacco/nicotine landscape.**
   - No FDA regulation? More emergence of nicotine analogues? Safety of constituents used in vapes/pouches?
4. **Very little known about the addiction profile of nicotine analogues and long-term health effects are unknown.**



Why Tobacco Control for Cancer Prevention Matters

"Prevention and screening accounted for 80% of averted cancer deaths between 1975 and 2020, while improvements in cancer treatment accounted for 20%. **A single prevention intervention—tobacco control—was responsible for more than half of all averted cancer deaths."**

Wang & Coob (Jan 31 2025). *NCI study: Prevention and screening saved more lives than treatment in five common cancer types over the past half-century . The Cancer Letter.*

Thank You!

- OSU Center for Tobacco Research Team
  - Tackett Lab
    - Logan Miller
    - Ray Niu
    - Natalie Noblie
    - Chukwudi Keke
- The James Comprehensive Cancer Center
- OSU TCORS
- American Heart Association
- NIH, NHLBI, NCI, FDA CTP

The James
Center for Tobacco Research
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Questions?

Alayna.Tackett@osumc.edu