

# Reducing nicotine in cigarettes: the science

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# Establishing a Nicotine Threshold for Addiction

- **Goal:**

- To prevent nicotine addiction in youth.

- **Threshold for Addiction:**

- Dose to establish and maintain addiction  
~ 5 mg/day.

- **Proposal:**

- A gradual reduction of nicotine content of cigarettes over 10-15 years.



The NEW ENGLAND  
JOURNAL of MEDICINE

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. (1994). *N Engl J Med*, 331(2), 123-125.

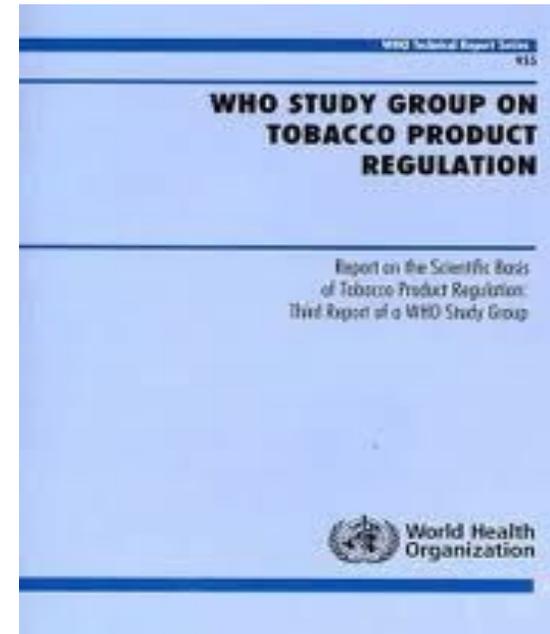


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## Family Smoking Prevention and Tobacco Control Act

## Framework Convention on Tobacco Control: Articles 9



# Nicotine reduction revisited: science and future directions

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Jack E Henningfield,<sup>5</sup> Neal L Benowitz,<sup>6</sup> Cathy L Backinger,<sup>7</sup> Mitch Zeller<sup>8</sup>

Nicotine & Tobacco Research, Volume 15, Number 6 (June 2013) 1003–1013

## REVIEW

### Nicotine Reduction: Strategic Research Plan

Dorothy K. Hatsukami PhD<sup>1</sup>, Neal L. Benowitz MD<sup>2</sup>, Eric Donny PhD<sup>3</sup>, Jack Henningfield PhD<sup>4</sup>,  
Mitch Zeller JD<sup>4</sup>

Nicotine & Tobacco Research, Volume 15, Number 6 (June 2013) 1113–1121

## ORIGINAL INVESTIGATION

### Dose–Response Effects of Spectrum Research Cigarettes

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Astia N. Roper-Batker BA<sup>1</sup>, Kristen M. Mackowick BS<sup>2</sup>, Joni Jensen MPH<sup>1</sup>, Sharon E. Murphy PhD<sup>3</sup>,  
Brian F. Thomas PhD<sup>5</sup>, Eric Donny PhD<sup>4</sup>



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# What dose of nicotine leads to reduced smoking

*The NEW ENGLAND JOURNAL of MEDICINE*

SPECIAL ARTICLE

## Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Eric C. Donny, Ph.D., Rachel L. Denlinger, B.S., Jennifer W. Tidey, Ph.D., Joseph S. Koopmeiners, Ph.D., Neal L. Benowitz, M.D., Ryan G. Vandrey, Ph.D., Mustafa al'Absi, Ph.D., Steven G. Carmella, B.A., Paul M. Cinciripini, Ph.D., Sarah S. Dermody, M.S., David J. Drobes, Ph.D., Stephen S. Hecht, Ph.D., Joni Jensen, M.P.H., Tonya Lane, M.Ed., Chap T. Le, Ph.D., F. Joseph McClernon, Ph.D., Ivan D. Montoya, M.D., M.P.H., Sharon E. Murphy, Ph.D., Jason D. Robinson, Ph.D., Maxine L. Stitzer, Ph.D., Andrew A. Strasser, Ph.D., Hilary Tindle, M.D., M.P.H., and Dorothy K. Hatsukami, Ph.D.

ABSTRACT



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**GROUPS (7 total)**

**1. Usual Brand**

**2. Normal Nicotine**

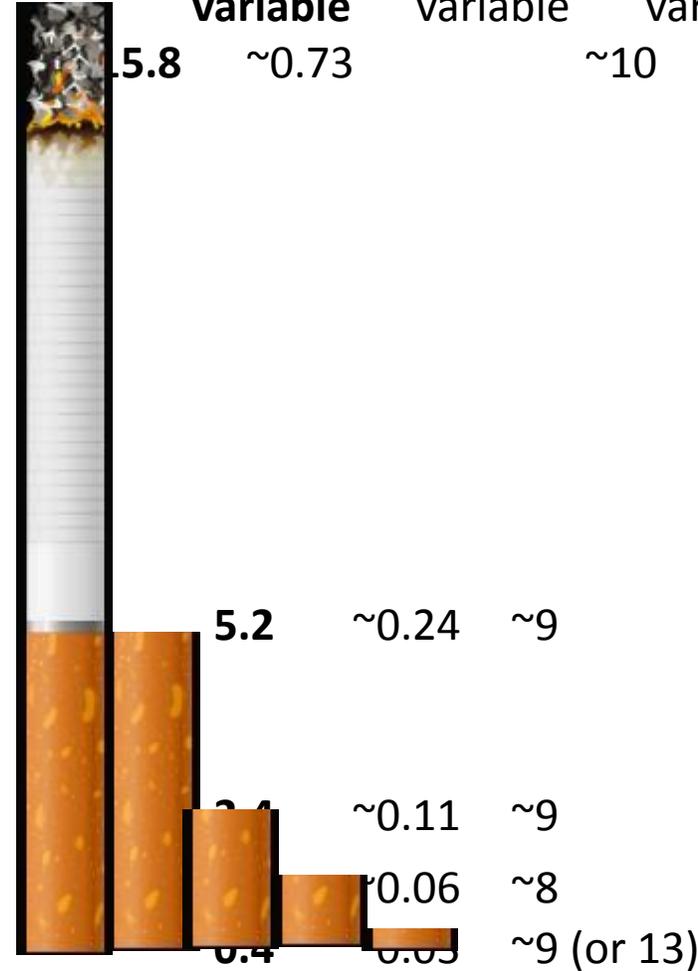
**3. Reduced Nicotine**

**4. Very Low Nicotine**

**5. Very Low Nicotine**

**6/7. Very Low Nicotine**

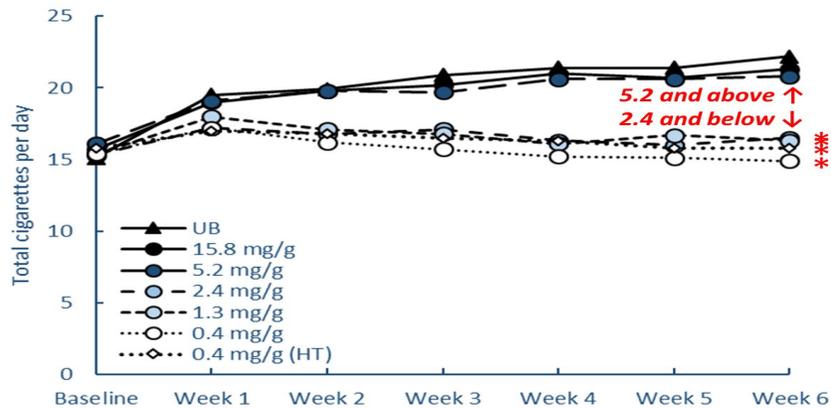
Nicotine Content	Nicotine Yield (ISO)	Tar Yield (ISO)
<i>(mg/g)</i>	<i>(mg/cig)</i>	<i>(mg/cig)</i>
variable	variable	variable
5.8	~0.73	~10



- 1 week baseline
- 6 weeks intervention

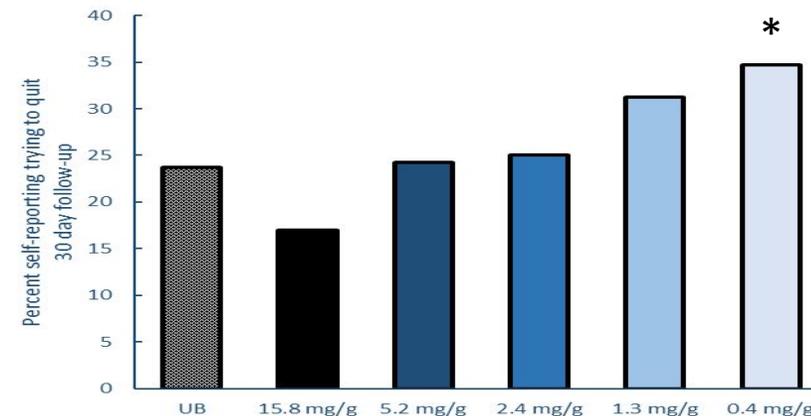
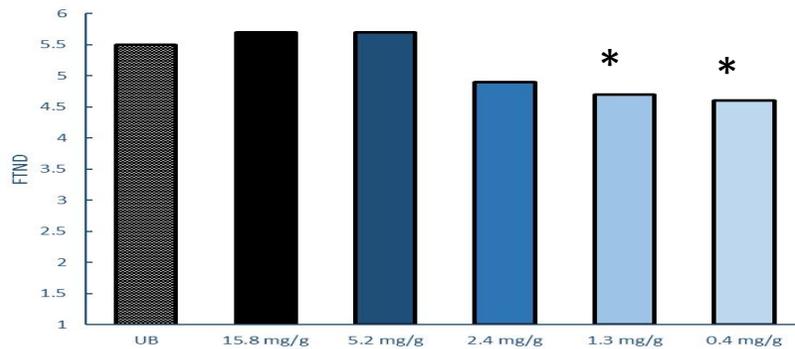


# Minimally-addictive nicotine dose: $\leq .4$ mg/g tobacco



**Relative to NNC cigarettes,  
 RNC cigarettes significantly:**

- Reduced cigarettes smoked ( $\leq 2.4$ )
- Reduced dependence ( $\leq 1.3$ ) and urges
- Increased quit attempts (only 0.4 mg)
- No compensatory smoking



# Reducing nicotine in cigarettes reduces smoking in different populations

**YOUTH**

**SERIOUS MENTAL ILLNESS**

**AFFECTIVE DISORDER**

**PEOPLE OF LOWER SES**

**INTERMITTENT SMOKERS**

**AFRICAN AMERICANS**

**MENTHOL SMOKERS**

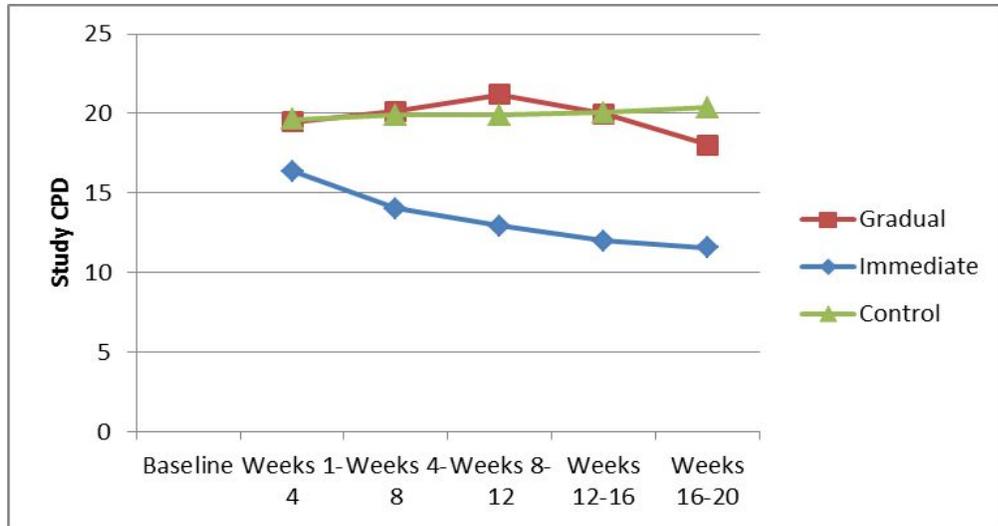
**SUBSTANCE USERS**

*Reviews see WHO 2019, Hatsukami et al., NTR 2021, Donny and White 2021.*



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# Do we gradually or immediately reduce nicotine?



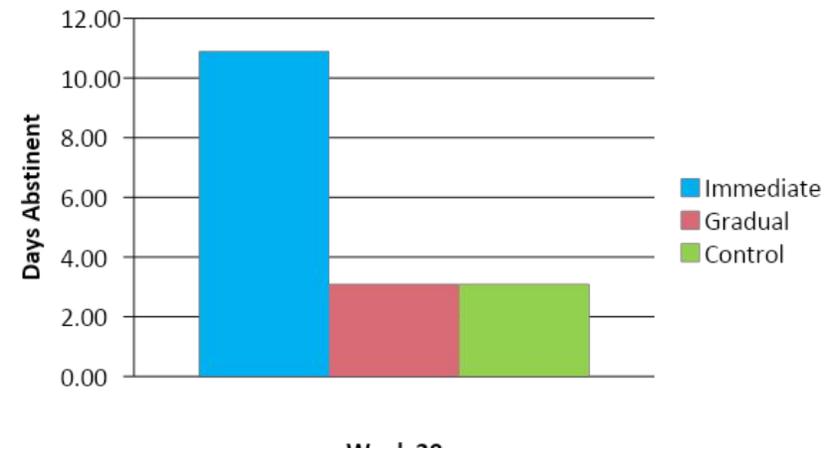
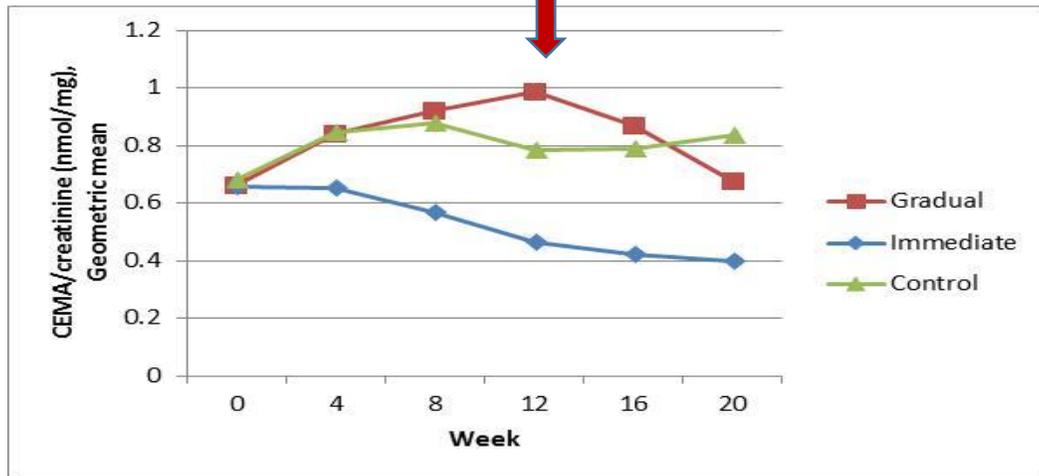
Area under the curve (AUC) analysis, adjusting for baseline level:

Overall  $p < 0.0001$

Immediate vs. Control  $p < 0.0001$

Gradual vs. Control = NS

Gradual vs. Immediate  $p < 0.0001$



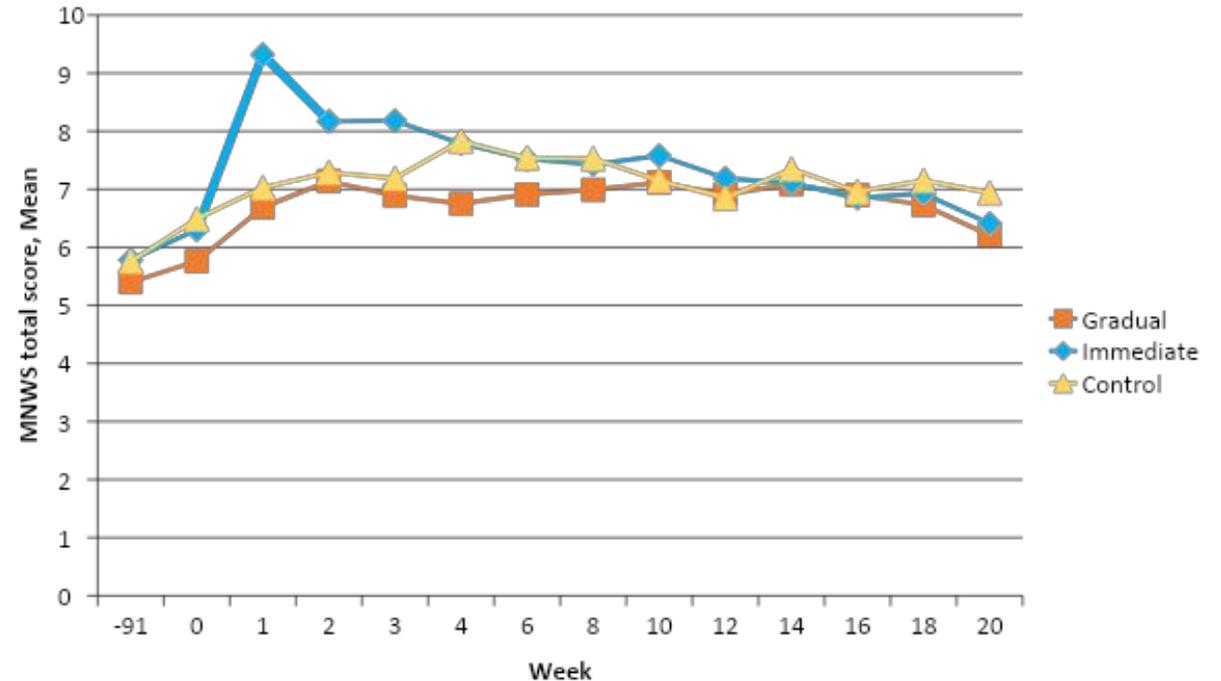
Hatsukami et al., JAMA, 2018



# Concerns about immediate nicotine reduction

Immediate nicotine reduction is associated with:

- Greater withdrawal symptoms
- Higher drop-out rates
- Higher non-compliance with only study cigarette use



***Some smokers may need other nicotine products.***



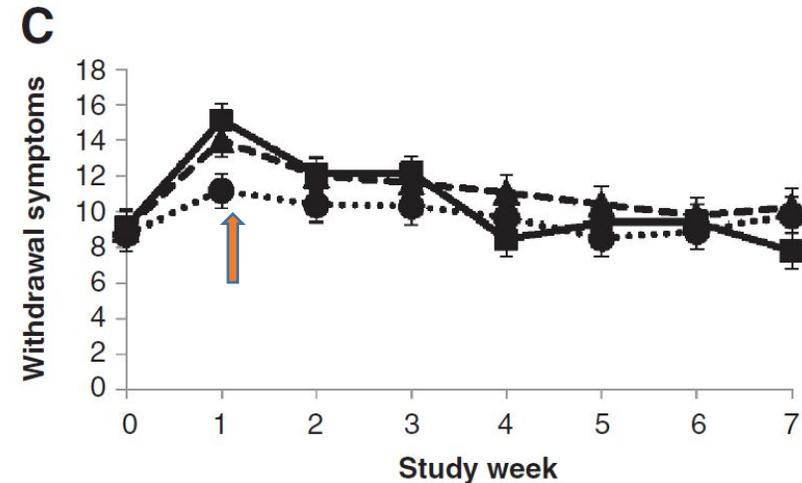
# Reducing unintended consequences



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# Access to pharmacological treatments and smoking cessation services

- Pharmacological treatments can reduce withdrawal discomfort.



Hatsukami, CEBP, 2013

- About a third of smokers may make a quit attempt and smoking cessation services will provide tools and ensure success.



# Experimental Marketplace

**CENIC** Center for the Evaluation of Nicotine in Cigarettes

Search



0 item(s) - 0 Points

## Browse By Category



Cigarettes



Nicotine Replacement Therapy



Vaping devices (e-cigarettes)



Moist Snuff ("dip")



Snus

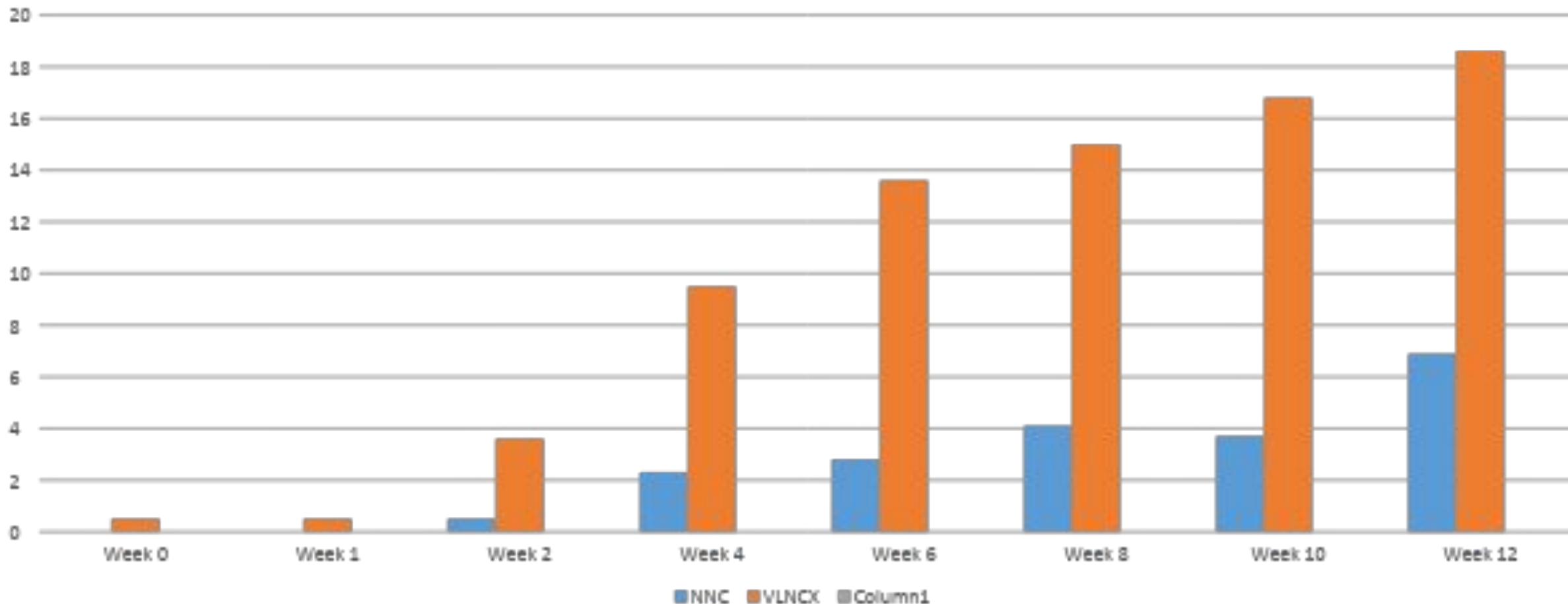


Nicotine Pouch

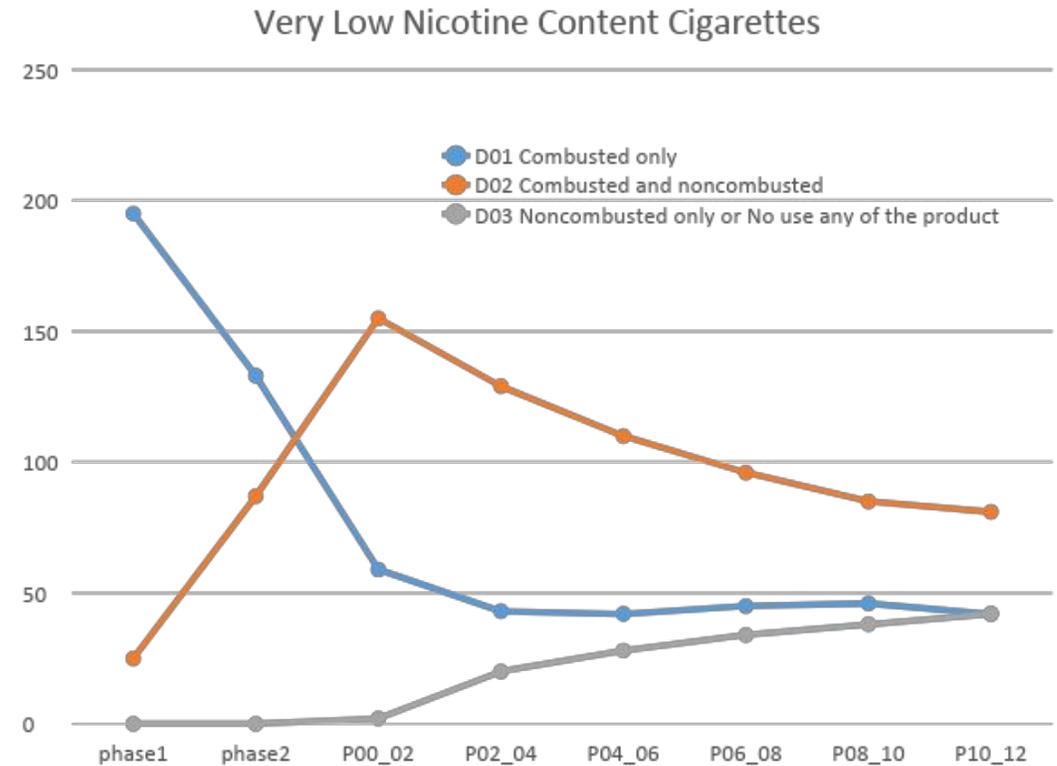
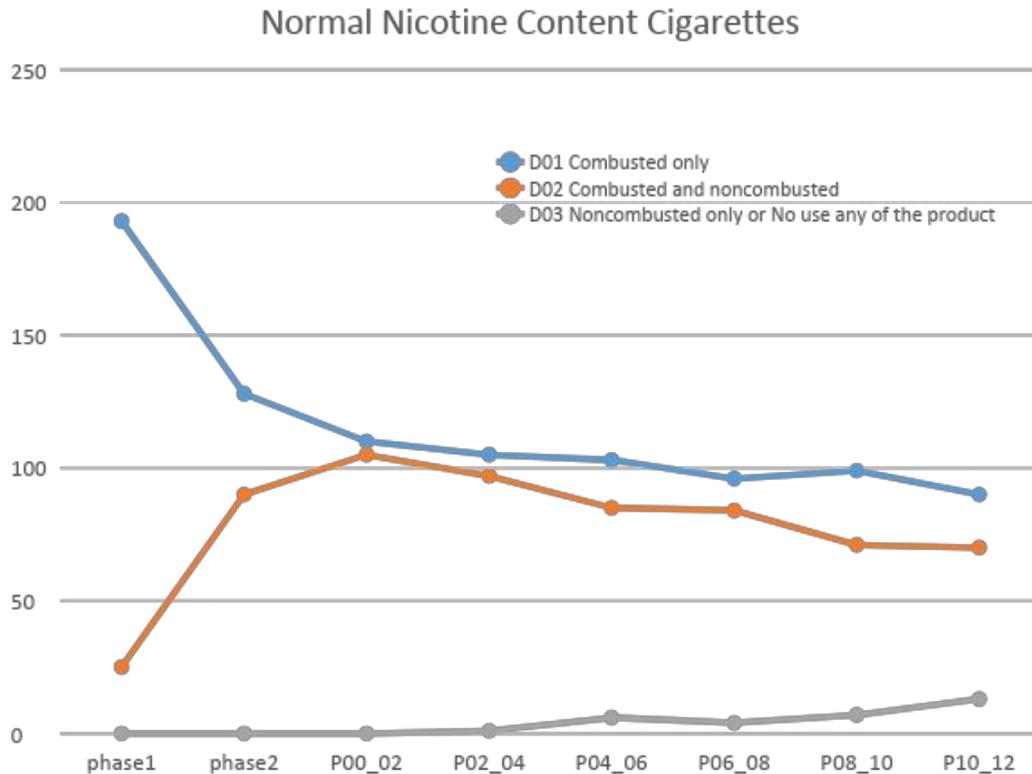
Your Store Credit

59 Points

# CO-verified 7-day point prevalence



# Pattern of use: Number of participants using combusted only, combusted plus non-combusted and non-combusted only



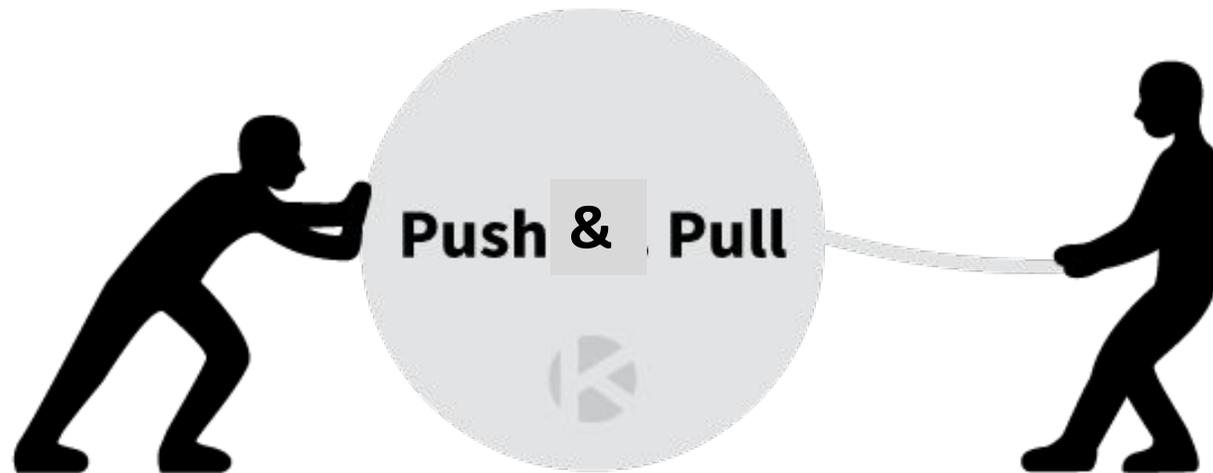
# Continuum of Risk

- There is a continuum of risk for nicotine-containing products
- Optimal goal is abstinence from all nicotine products
- But for people unable or unwilling to quit, the goal is to shift them to lower risk products

COMBUSTIBLES

NON-COMBUSTED PRODUCTS

NR  
T



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# Aggressive measures against illegal marketplace

- Track and trace system from growers, manufacturers, distributors to retailers
- Penalties imposed for infractions (not on consumers)
- Laboratory testing for compliance and surveillance
- Sufficient resources for strong enforcement



National Research Council. Understanding the U.S. Illicit Tobacco Market: Characteristics, Policy Context, and Lessons from International Experiences. 2015.



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# Summary

- Abundance of concordant evidence that shows that the reduction of nicotine in cigarettes is likely to have beneficial public health impact.
- Important to also include other selected combusted tobacco products
  - Similar PK
  - Similar toxicity
  - Similar patterns of use



# **FDA Announces Plans for Proposed Rule to Reduce Addictiveness of Cigarettes and Other Combusted Tobacco Products—June 21, 2022**

*Historic step could help millions quit smoking and prevent millions more from starting*

AHA



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