Camel Snus MRTP Application

Tobacco Products Scientific Advisory Committee

September 13-14, 2018

Introduction and Overview

Michael Ogden, PhD

Senior Vice President, Scientific & Regulatory Affairs
RAI Services Company

Benefits of Advertising Camel Snus as an MRTP

- **Smokers who switch completely to Camel Snus can greatly reduce their risk for four smoking-related diseases:**
  - **Lung cancer**
  - **Oral cancer**
  - **Respiratory disease**
  - **Heart disease**
- **Authorization of the proposed modified risk advertising is highly likely to yield a net public health benefit**

An Important Consideration

- **There is no one-size-fits-all approach to dramatically reduce the harm from smoking**
  - Different types of reduced-risk products appeal to different people
- **Clearing the proposed MRTP advertising for Camel Snus is a scientifically sound step to reduce tobacco risk**

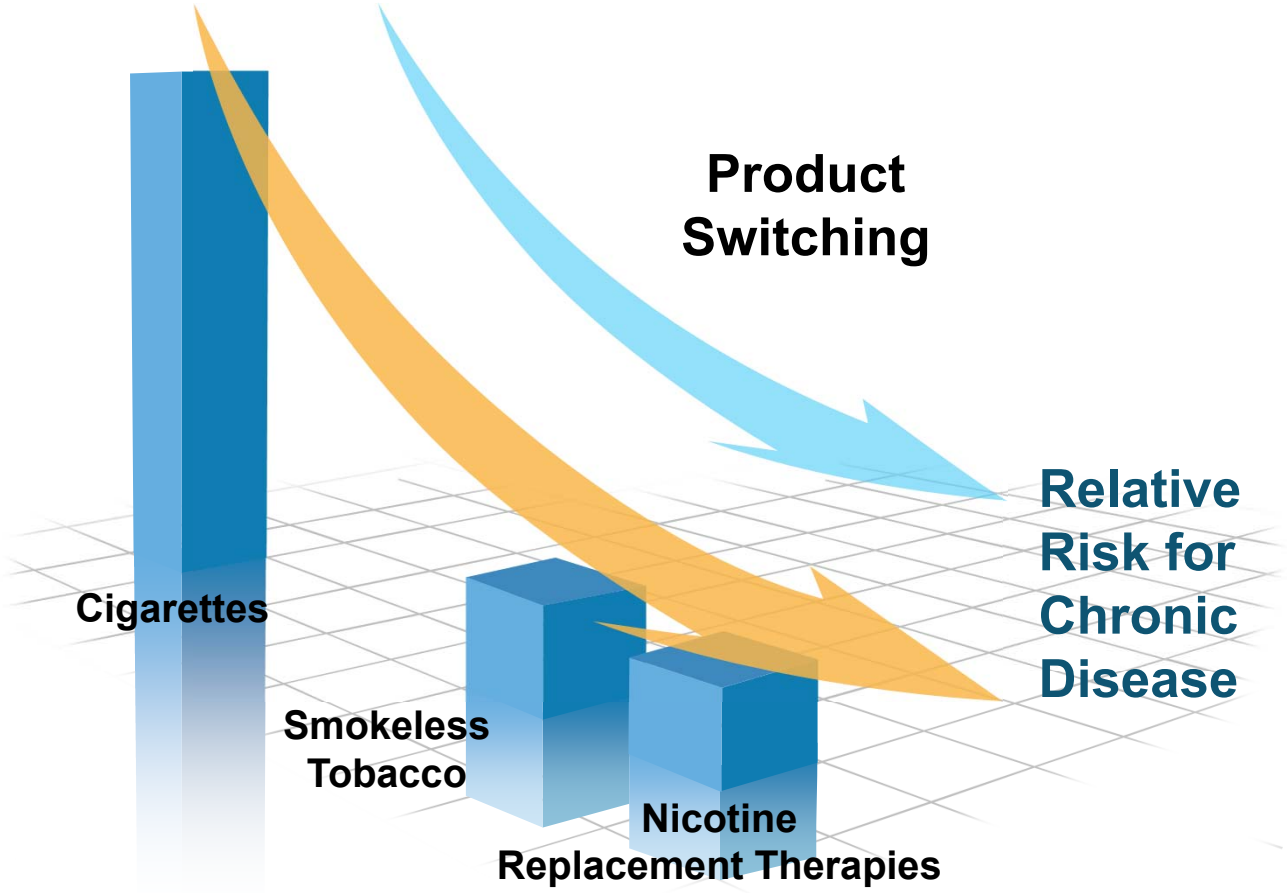
Presentation Topics

- Camel Snus history, product development and design
- Proposed modified risk advertising
- Scientific evidence that individual health risk is reduced when smokers switch to Camel Snus
- Consumer studies showing the proposed advertising will promote beneficial behavioral changes in smokers
- Statistical modeling indicating the population as a whole will benefit from the resulting risk reductions

Presenters

Michael Ogden, PhD Senior Vice President, Scientific & Regulatory Affairs, RAI Services Company	**Introduction and Conclusions**
Kristin Marano, MPH, PhD, CPH Director, Scientific & Regulatory Affairs, RAI Services Company	**Epidemiology**
Elaine Round, PhD Senior Director, Scientific & Regulatory Affairs, RAI Services Company	**Clinical and Preclinical Research**
Saul Shiffman, PhD Senior Scientific Advisor, Pinney Associates Professor of Psychology, Psychiatry, Pharmaceutical Sciences and Clinical Translational Science, University of Pittsburgh	**Risk Perceptions, Comprehension, and Likelihood of Use**
Geoffrey Curtin, PhD Senior Director, Scientific & Regulatory Affairs, RAI Services Company	**Population Health Benefit for Camel Snus with Modified Risk Advertising**

The Tobacco and Nicotine Product Risk Continuum



Consumers need accurate information about the relative risks of products to encourage them to migrate to less harmful products

Camel Snus Product Design

- **Camel Snus is a spitless, pouched, smokeless tobacco product**
- **Designed to have risk-reduction characteristics of Swedish snus**
  - Made with low-toxicant tobaccos
  - Has same basic formulation
  - Flavors adapted for American palate using common smokeless tobacco and food ingredients

Each tin contains 15 pouches

Camel Snus Production Process and Styles

- **Production Process**
  - Low toxicant, finely milled tobaccos
  - Mixed with water, salt and heat-treated
  - Buffered with pH-stabilizing solution, further heat-treated
  - Humectants and flavors added

Camel Snus Production Process and Styles

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  - Humectants and flavors added

600 mg

Frost

Mint

Mellow

1000 mg

Frost Large

Winterchill

Robust

Camel Snus MRTP Messaging Topline

- **Only seeking authorization for the specific modified risk messages and layouts submitted to the FDA**
- **Presents adult smokers with accurate, easily understood comparative risk information**
  - No change to current product label or government smokeless tobacco warnings
- **Subject to post-market surveillance**

Overview of Print Advertisement

- **Three versions/advertising executions developed through iterative process**
- **Important to present clear, accurate scientific information using appealing language and graphics easily understood by smokers**
- **The three versions are very similar, but there are some important differences**

Overview of Print Advertisement

Camel Snus MRTP Messages – 1st Panel

Introduces opportunity for adult smokers to reduce risk

Note cigarette crushed by snus tin

Maintains government warning

Camel Snus MRTP Messages – 2nd Panel

Describes product and use

Emphasizes that Camel Snus 'contains nicotine' and 'is addictive'

Describes ingredients, sizes, flavors, quantity, and use duration

Camel Snus MRTP Messages – 3rd Panel

Key modified risk statement (variations among executions)

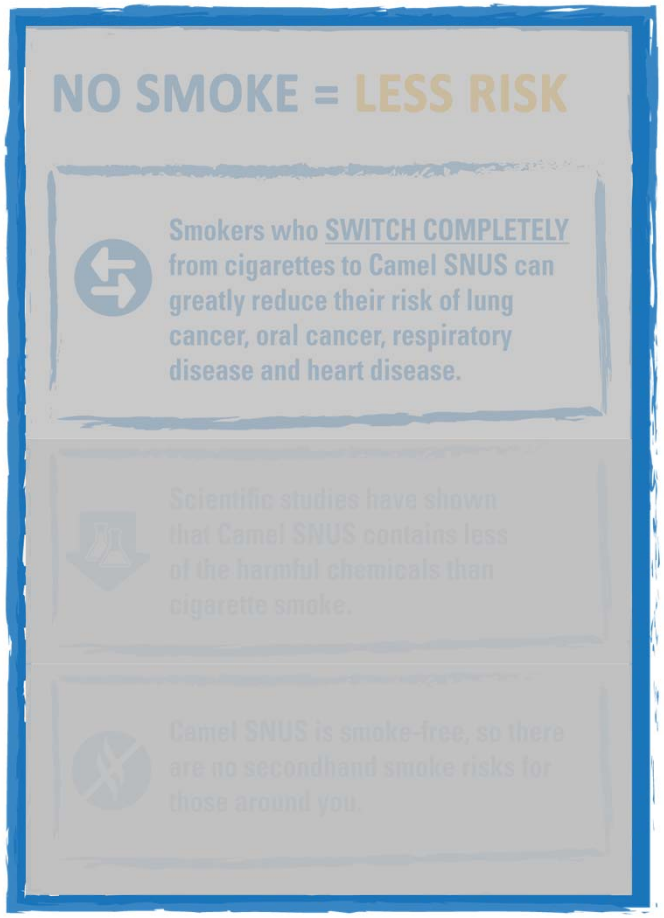
Additional benefits of switching

Balancing information

Camel Snus MRTP Messages – 3rd Panel

Advertising Execution 2

Variations in Key Modified Risk Statement – 3rd Panel



Key modified risk statement (variations among executions)

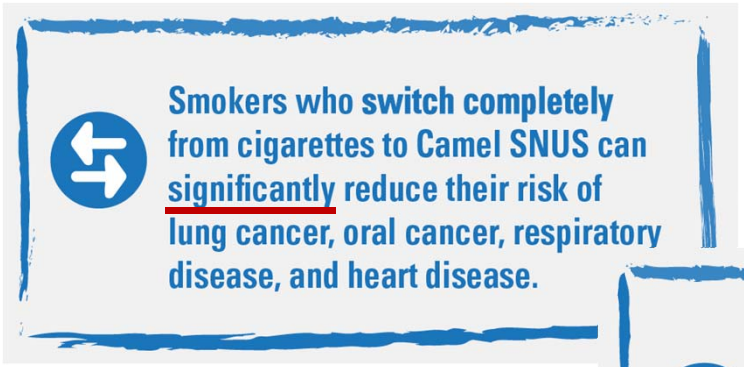
‘Less harmful chemicals’

‘Smoke-free’ statement

Advertising Execution 2

Variations in Key Modified Risk Statement – 3rd Panel

Execution 1



Execution 2

Execution 3

Camel Snus MRTP Messages – 3rd Panel

I'M A SMOKER.
WHY SHOULD I SWITCH?
Switching to SNUS means...
Less of the harmful chemicals found in cigarette smoke
Less risk for you and those around you
No lingering smoke smell
Hassle-free tobacco

Advertising Execution 2

Camel Snus MRTP Messages – 3rd Panel

NO TOBACCO PRODUCT IS SAFE

- Like all tobacco products, Camel SNUS **contains nicotine** and **is addictive**.
- Adults who do not use or have quit using tobacco products should not start.
- **Minors and pregnant women should never use tobacco products.**
- If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider.
- But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.

Advertising Execution 2

Proposed Camel Snus MRTP Print Advertisement

MRTP Advertising for Camel Snus

Epidemiology

Kristin Marano, MPH, PhD, CPH

Director, Scientific & Regulatory Affairs
RAI Services Company

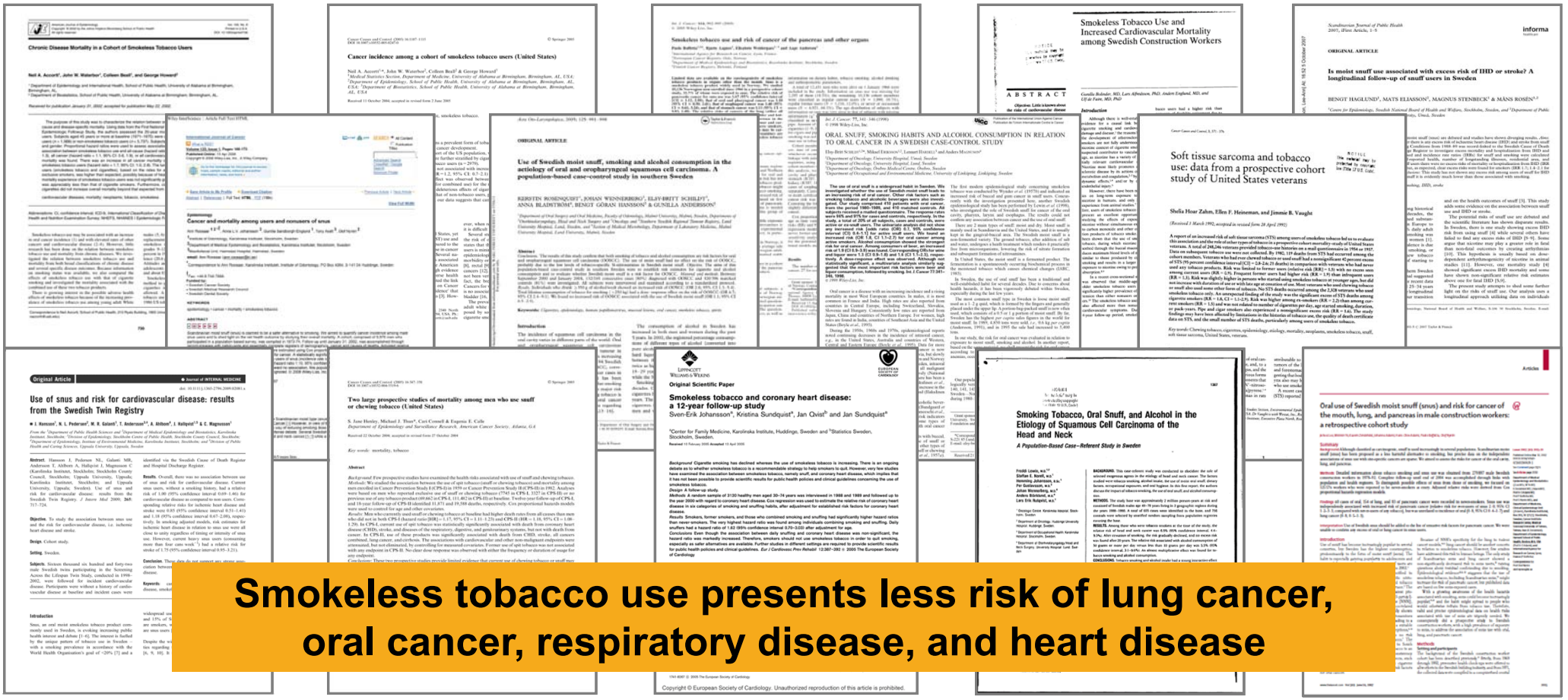
Smokers who Switch Completely to Camel Snus Can Reduce Risk

- **For smokers who switch completely, Camel Snus reduces risk:**
  - Lung cancer
  - Oral cancer
  - Respiratory disease
  - Heart disease

Epidemiology Confirms Significant Risk Reductions Compared to Smoking

- **Epidemiology is a scientific tool for assessing associations between exposure and disease risk**
- **Considerable epidemiological data exists regarding smokeless tobacco**
- **Scientific consensus that smokeless tobacco use presents significantly lower risks than cigarette smoking**
- **Data from U.S. and Sweden demonstrate lower risks for these four diseases**

Scientific Literature Confirms Risk Reduction



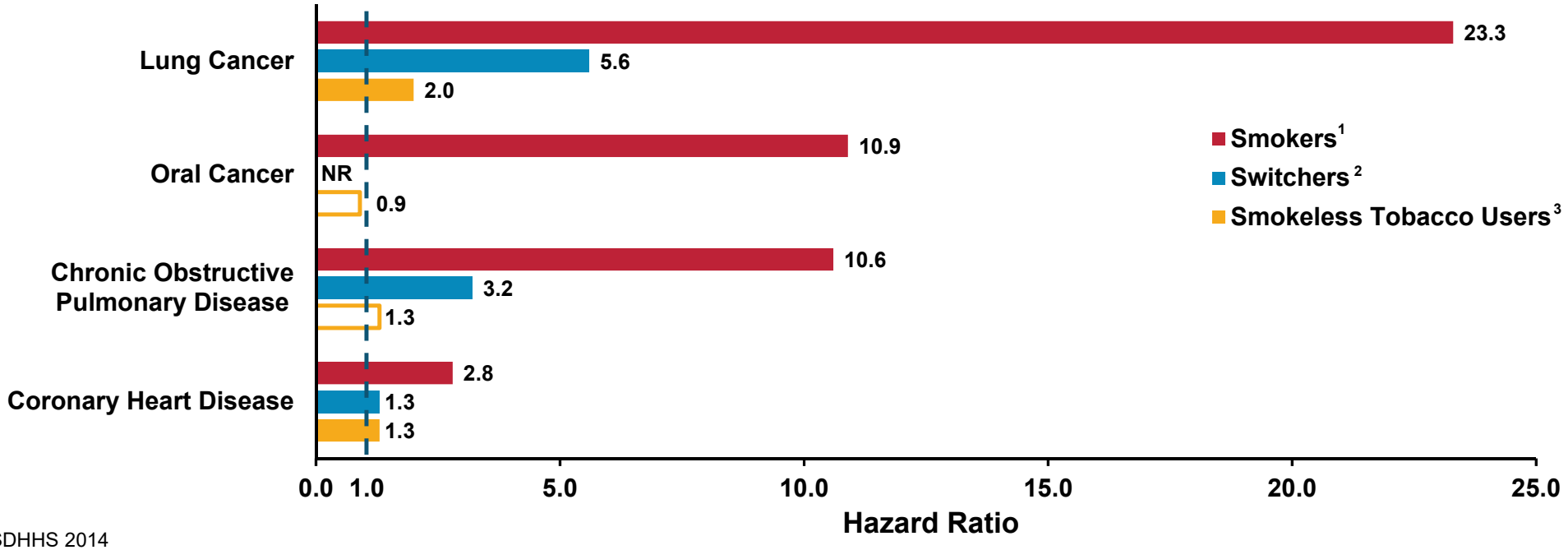
Smokeless tobacco use presents less risk of lung cancer, oral cancer, respiratory disease, and heart disease

Two Large Cohorts

- **U.S. Cancer Prevention Study II (CPS-II)**
  - American Cancer Society
  - Over 500,000 males
  - Enrollment and follow-up
    - 1982-1988 (smokers); 1982-2000 (smokeless tobacco users); 1982-2002 (switchers)
- **Swedish Construction Workers Cohort**
  - Over 250,000 males
  - Enrollment and follow-up
    - 1969-1992

U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

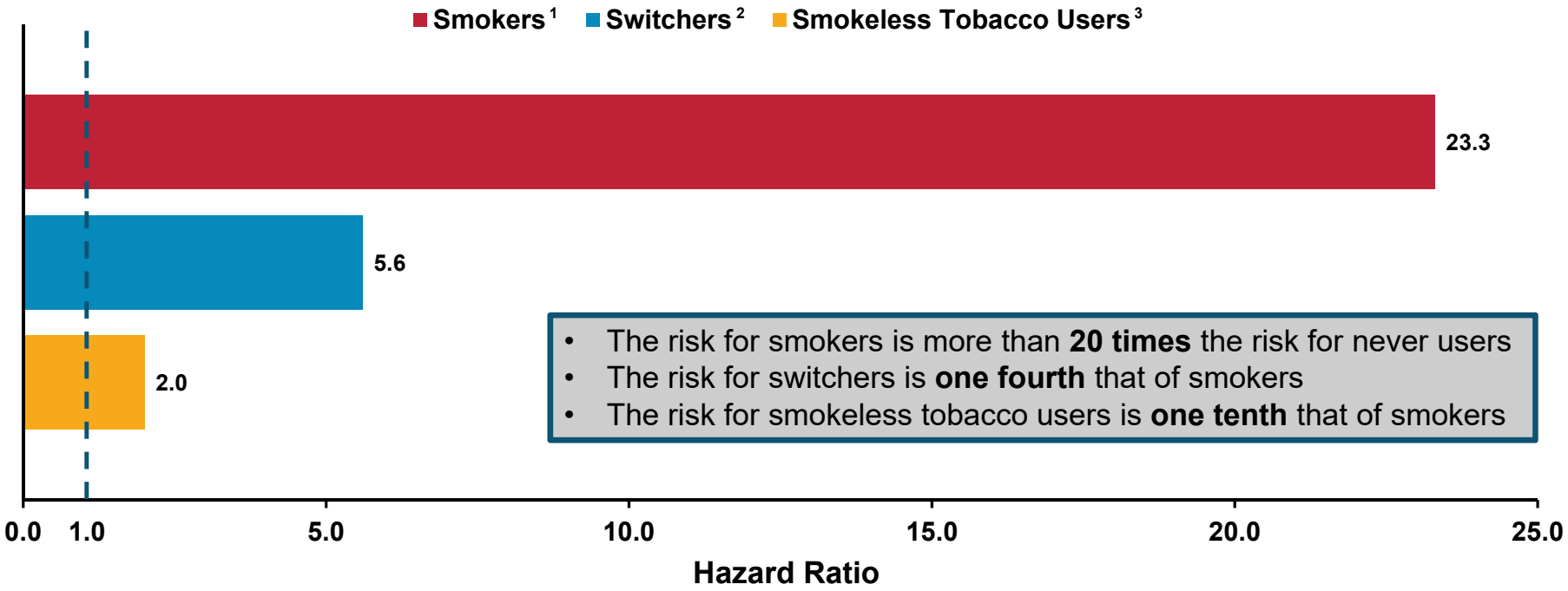
NR=Not Reported

Dashed line represents hazard ratio=1.0

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Lung Cancer

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



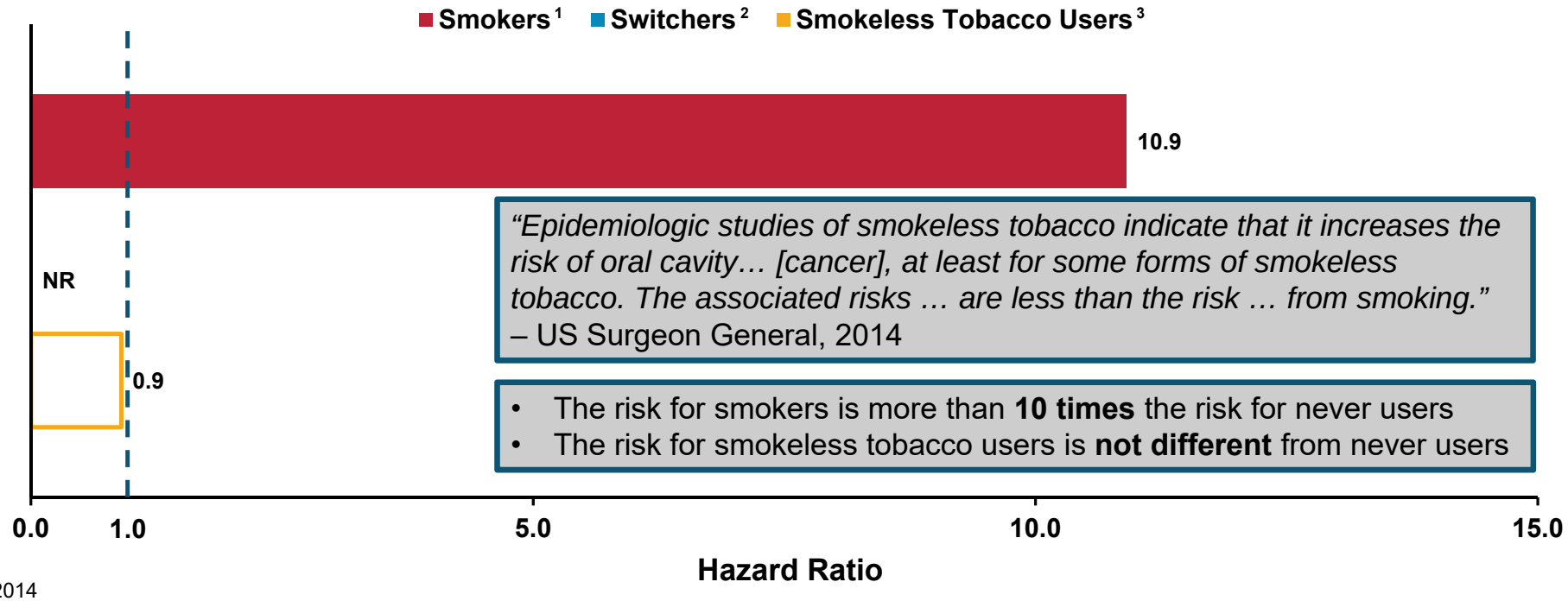
Solid bars = statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

Dashed line represents hazard ratio=1.0

U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Oral Cancer

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



"Epidemiologic studies of smokeless tobacco indicate that it increases the risk of oral cavity… [cancer], at least for some forms of smokeless tobacco. The associated risks … are less than the risk … from smoking."
– US Surgeon General, 2014

- The risk for smokers is more than **10 times** the risk for never users
- The risk for smokeless tobacco users is **not different** from never users

1. USDHHS 2014
2. Henley et al. 2007
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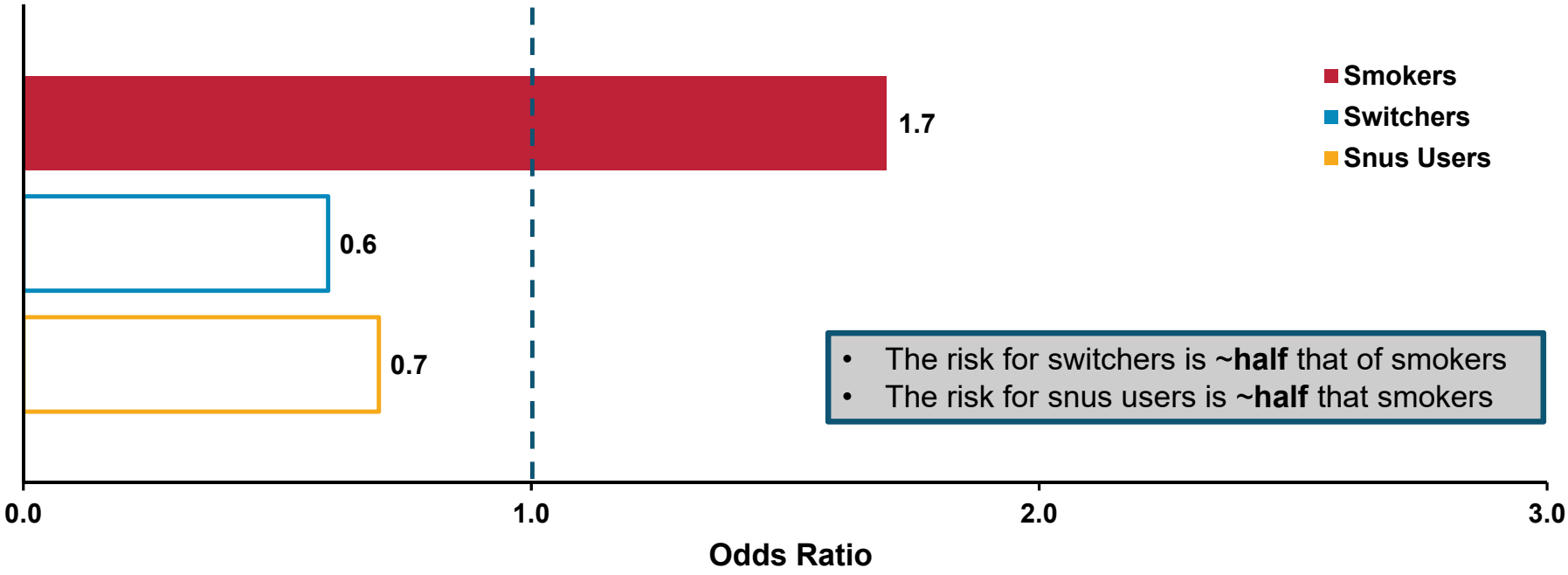
Swedish Epidemiology Data Confirm a Significant Reduction in Risk for Oral Cancer Including Switchers

Odds of Oral Cancer, Case-Control Study, Sweden
1980-1989, 354 incident cases



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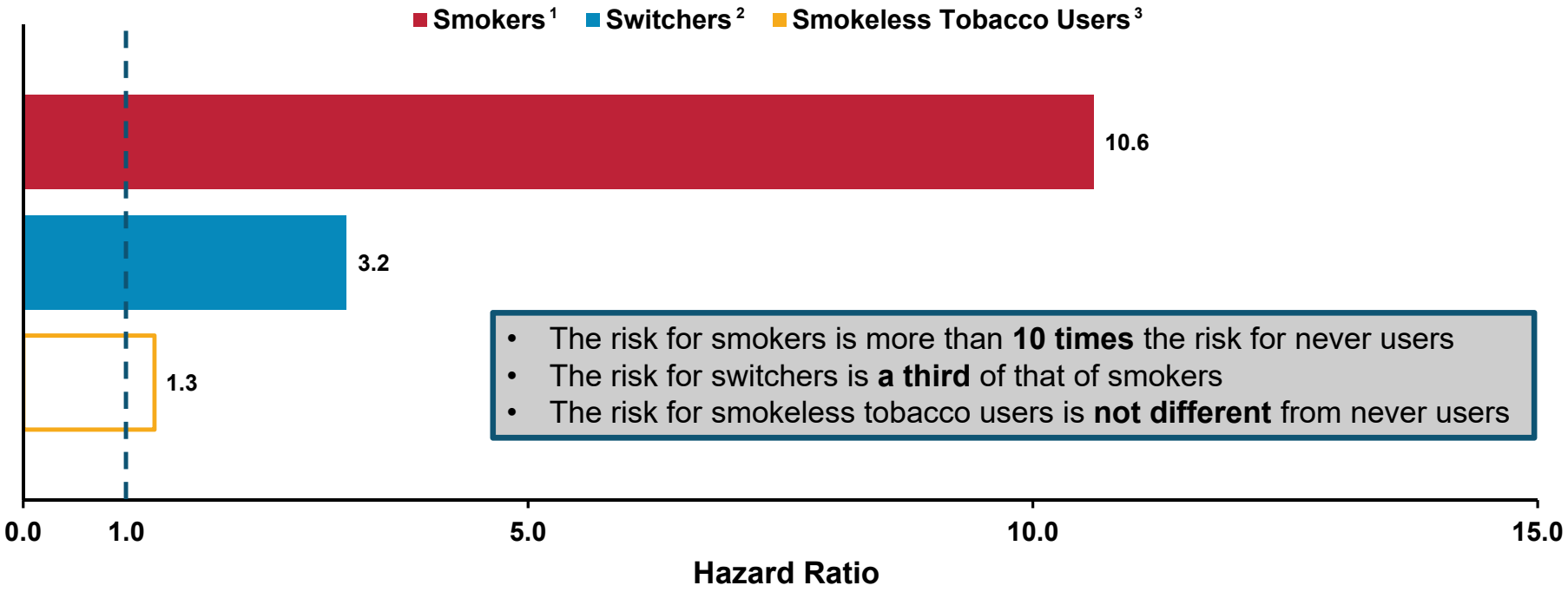
Open bars = not statistically significantly different versus never users of tobacco

Schildt et al. 1998
Dashed line represents odds ratio=1.0

U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Chronic Obstructive Pulmonary Disease

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



- The risk for smokers is more than **10 times** the risk for never users
- The risk for switchers is **a third** of that of smokers
- The risk for smokeless tobacco users is **not different** from never users

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

Dashed line represents hazard ratio=1.0

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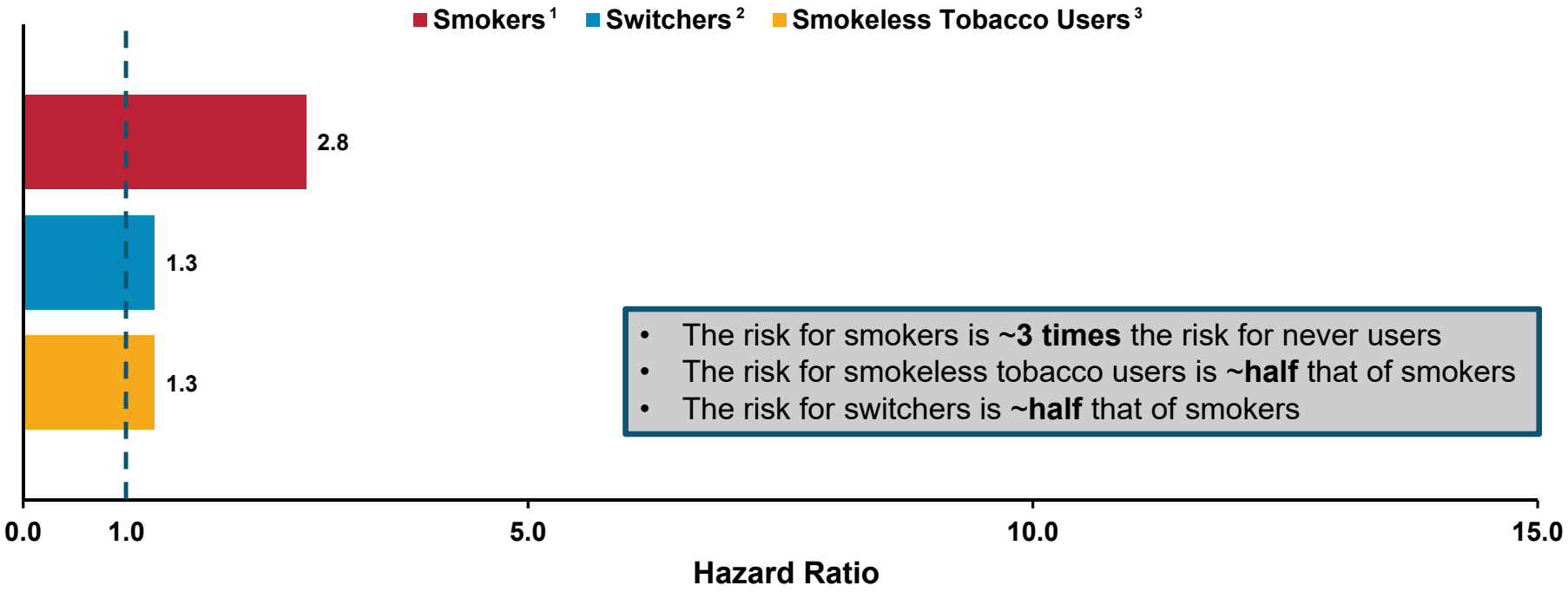
U.S. Epidemiology Data Confirm a Significant Reduction in Risk for Coronary Heart Disease

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



- The risk for smokers is ~**3 times** the risk for never users
- The risk for smokeless tobacco users is ~**half** that of smokers
- The risk for switchers is ~**half** that of smokers

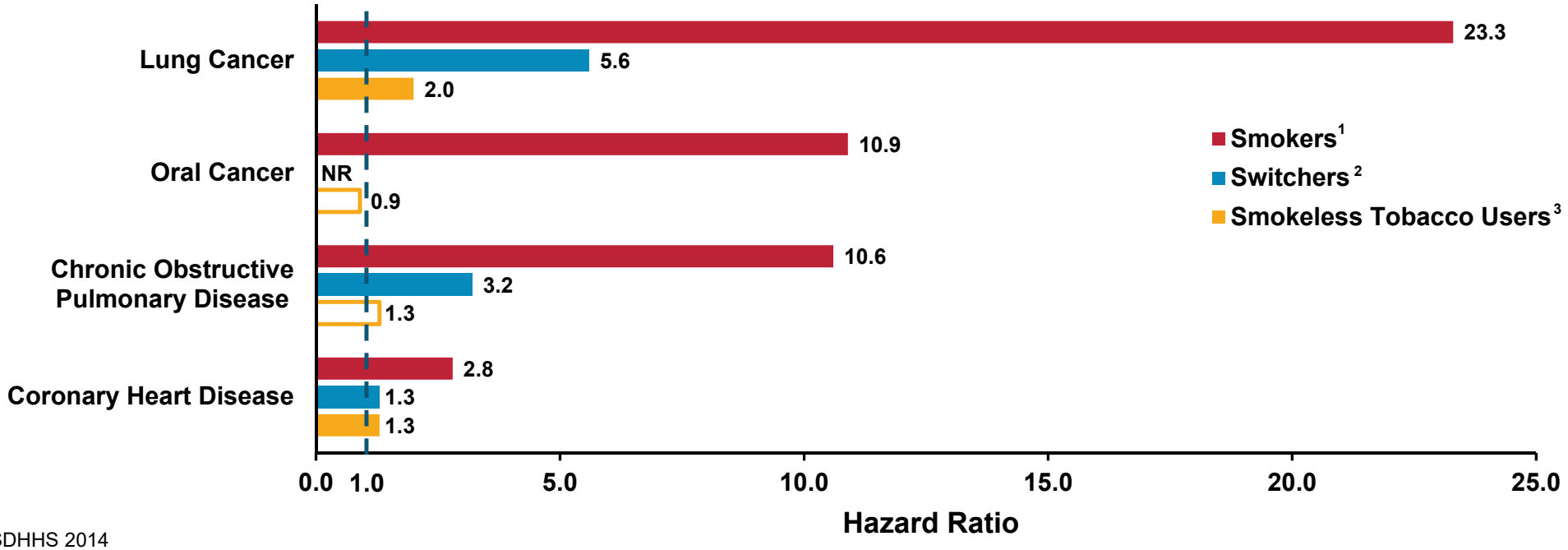
Solid bars = statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

Dashed line represents hazard ratio=1.0

U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

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Dashed line represents hazard ratio=1.0

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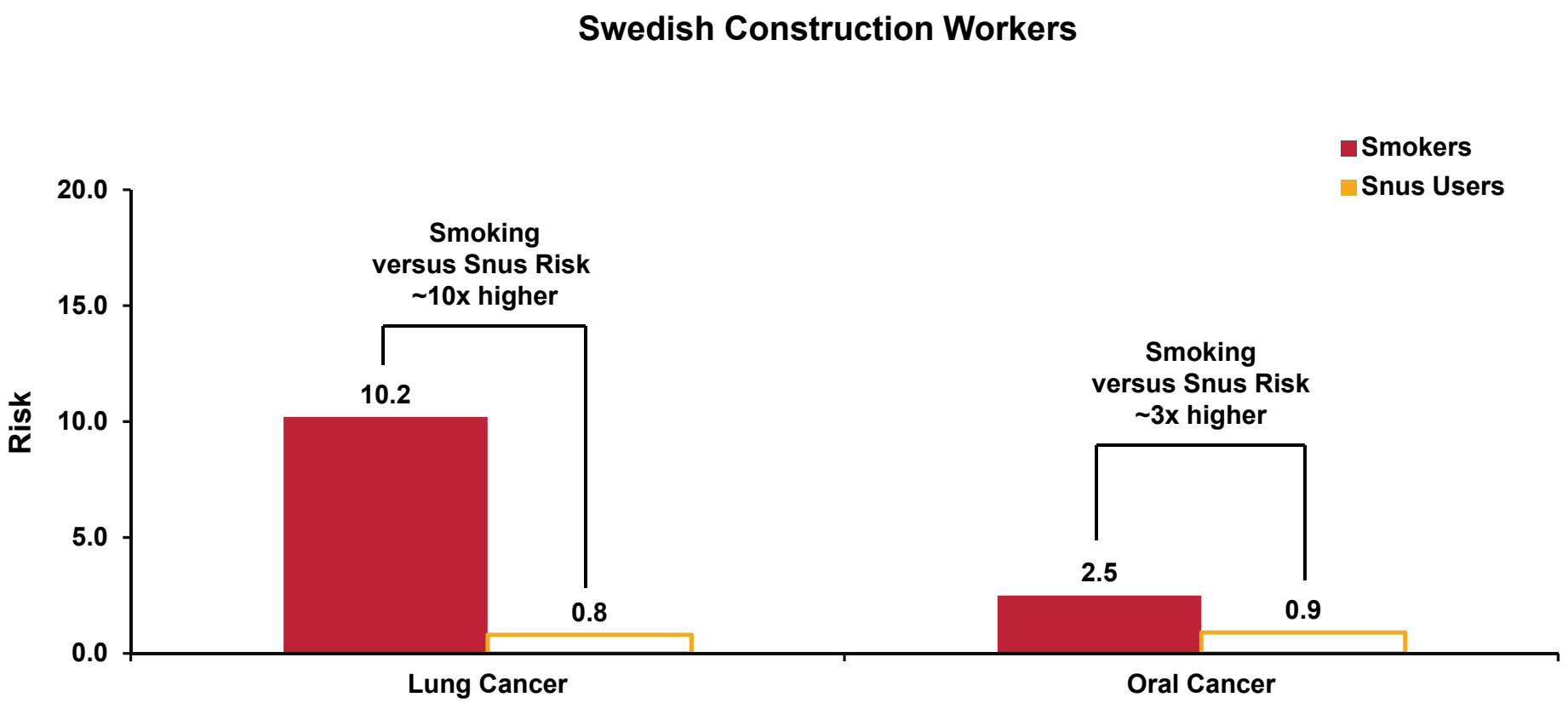
Swedish Epidemiology Data Confirm Significant Reductions in Risks for Lung Cancer and Oral Cancer



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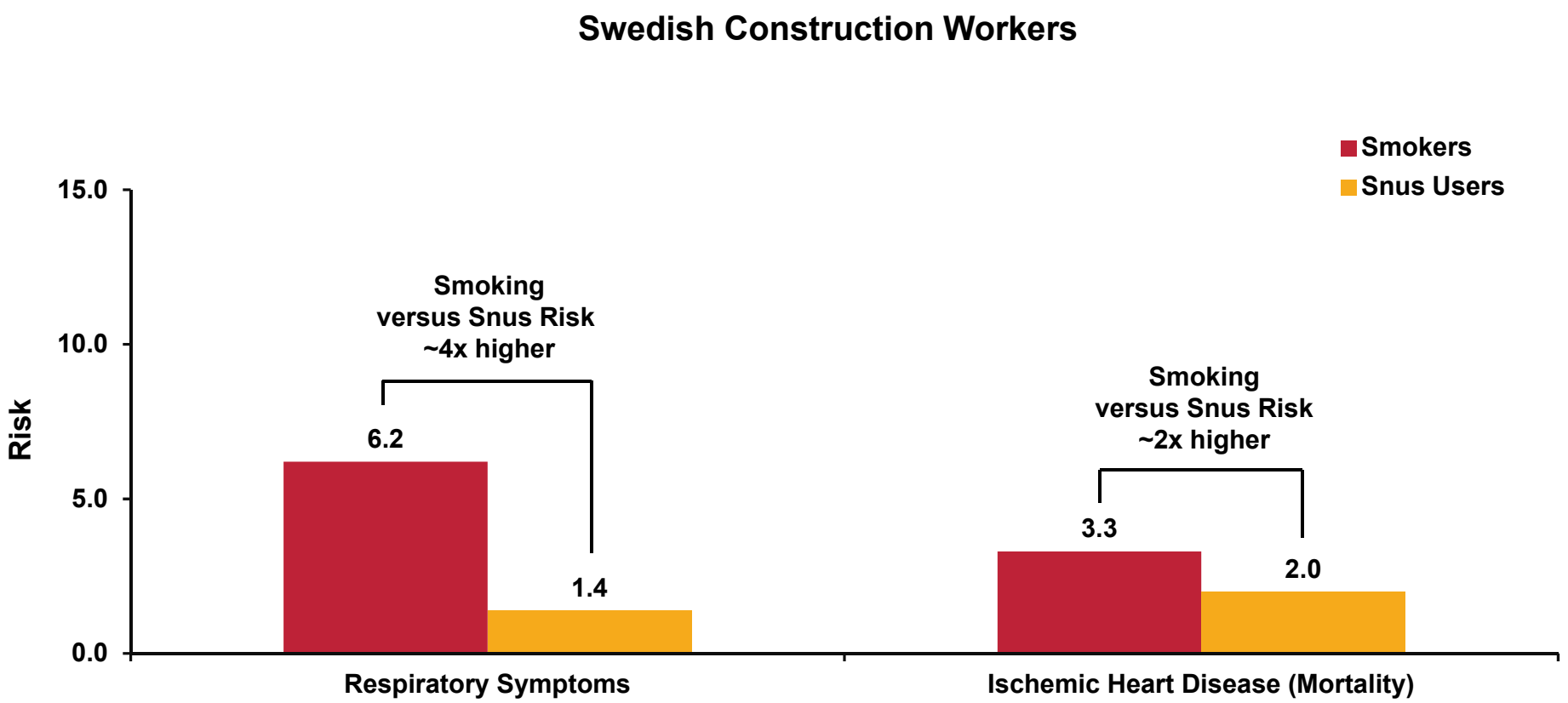
Open bars = not statistically significantly different versus never users of tobacco

Luo et al. 2007

Swedish Epidemiology Data Confirm Significant Reductions in Risks for Respiratory Disease and Heart Disease



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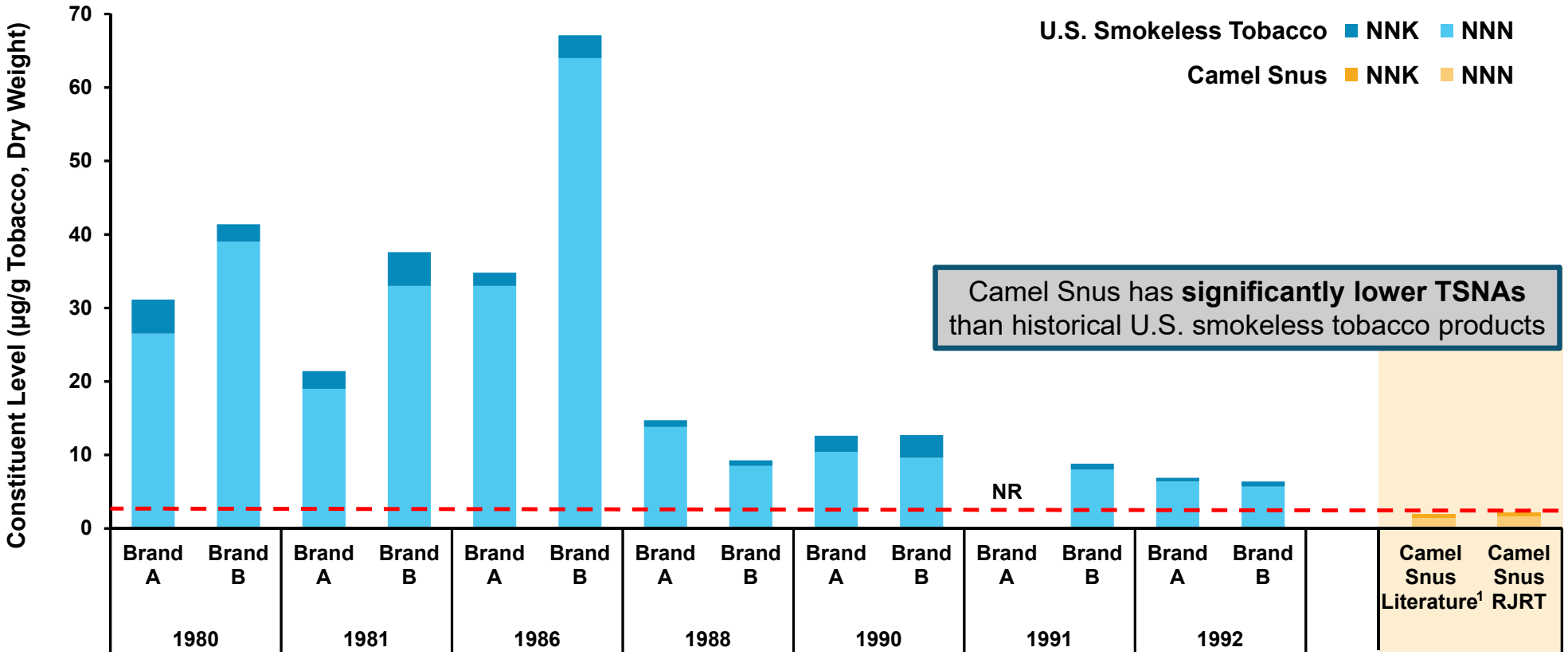
Bolinder et al. 1992
Bolinder et al. 1994

U.S. and Swedish Epidemiology Data are Relevant to Camel Snus

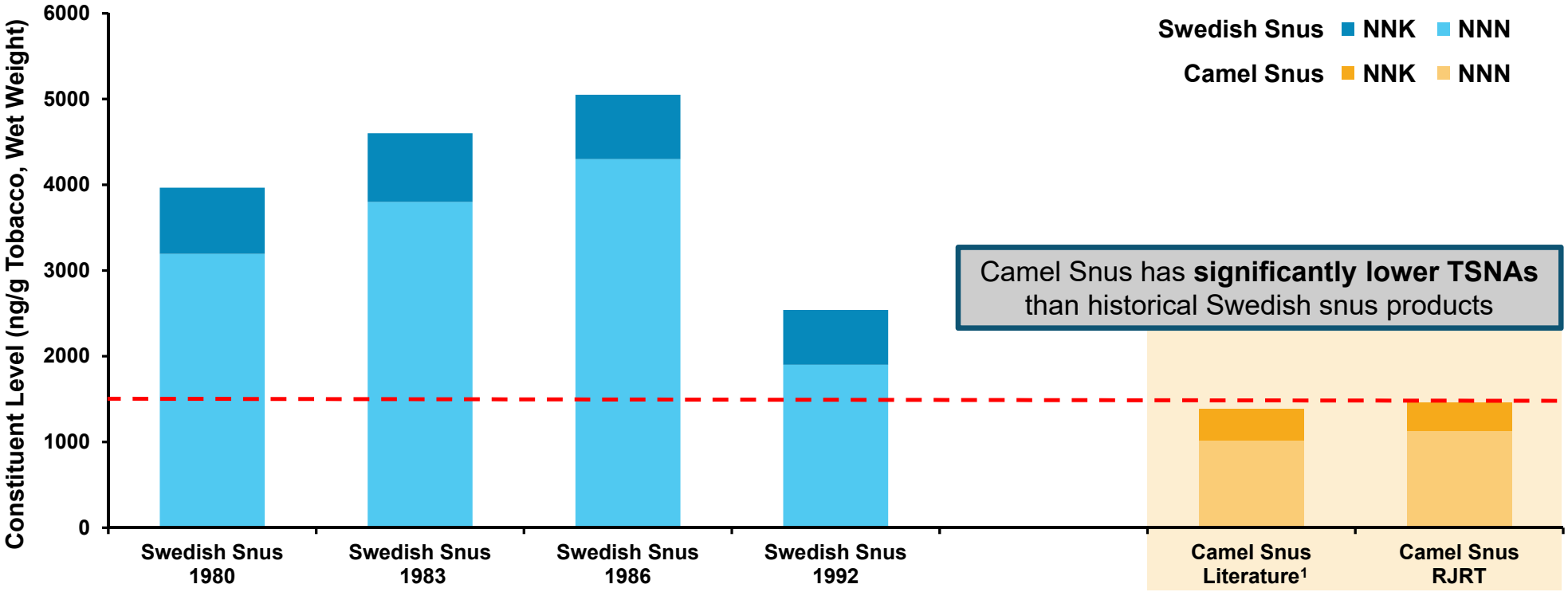
- **Lower exposure with Camel Snus than the smokeless tobacco products used during the epidemiology studies**
  - Toxicants
  - Consumption

Corrected: Camel Snus Has Lower Levels of TSNAs than U.S. Smokeless Tobacco Products Used in Epidemiology Studies



1. From Hatsukami et al. 2015, 2017; Hecht et al. 2011; Lawler et al. 2013; Song et al. 2016; Stepanov et al. 2008, 2012, 2013, 2014, and others
U.S. smokeless data from Djordjevic et al. 1993
NR=Not Reported

Camel Snus Has Lower Levels of TSNAs than Swedish Snus Products Used in Epidemiology Studies



1. Hatsukami et al. 2015, 2017; Hecht et al. 2011; Lawler et al. 2013; Song et al. 2016; Stepanov et al. 2008, 2012, 2013, 2014, and others
Swedish snus data from Österdahl et al. 2004

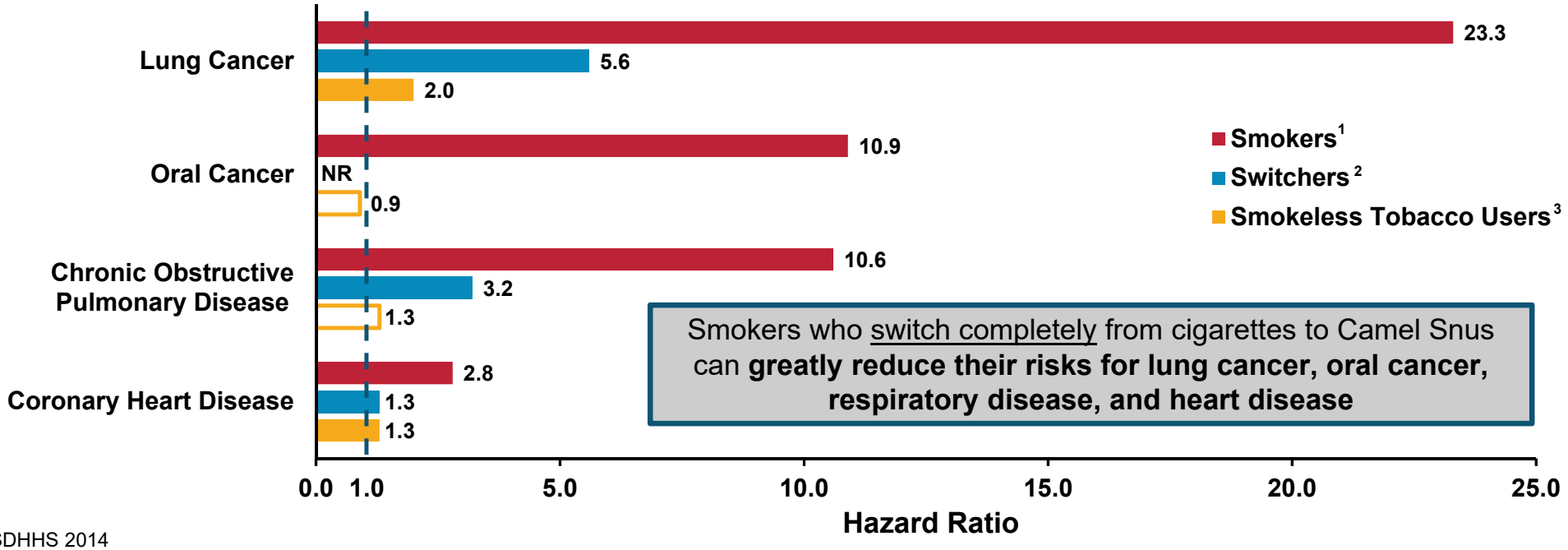
Usage of Camel Snus is Less than Historical Usage of U.S. Smokeless Tobacco Products

	Camel Snus[1]	Historical U.S. Smokeless Tobacco Products[2]
Average amount used/day	3 – 5 g	7 – 20 g

1. Blank and Eissenberg 2010; Burris et al., 2014; Burris et al. 2016; Hatsukami et al. 2011; Hatsukami et al. 2016; Kotlyar et al. 2011; O'Connor et al. 2011; PATH; RJRT Brand Tracker; RJRT Clinical Studies; RAIS NTBM
2. Hatsukami et al. 1988; Glover et al. 1981; IARC 1985

U.S. Epidemiology Data Confirm Significant Reductions in Risks for All Four Diseases

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



Smokers who switch completely from cigarettes to Camel Snus can **greatly reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease**

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1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

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Dashed line represents hazard ratio=1.0

Clinical and Preclinical Research

Elaine Round, PhD

Senior Director, Scientific & Regulatory Affairs
RAI Services Company

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Clinical and Preclinical Studies Fully Support the MRTP Advertising

- **Clinical studies examined human use and exposure**
- **Preclinical studies compared Camel Snus to cigarettes**
  - Cytotoxicity (lung cancer, oral cancer, respiratory disease, heart disease)
  - Mutagenicity (lung cancer, oral cancer)
  - Genotoxicity (lung cancer, oral cancer)
  - Animal studies (assess short and long-term effects for all four diseases)
- **The entire body of clinical and preclinical evidence**
  - Consistent with the epidemiological conclusions
  - Supports reduced health risks from Camel Snus compared to smoking

Several Clinical Trials Studied Camel Snus

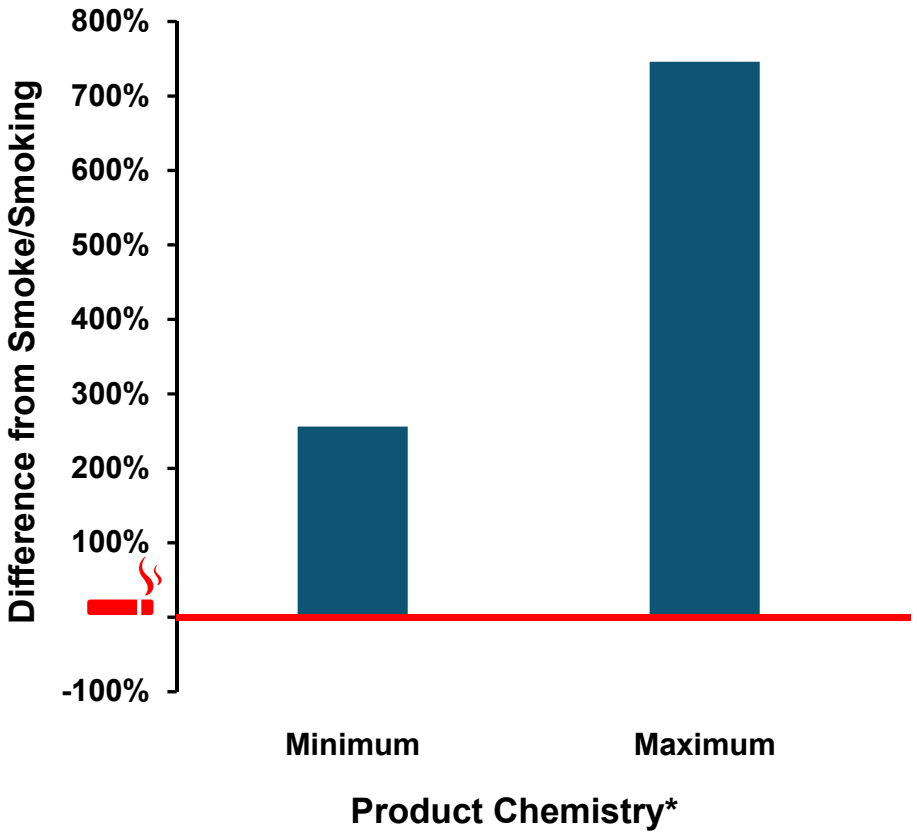
- **Eight RJRT studies with varying endpoint combinations**
- **Five additional published studies**
- **Endpoints included:**
  - Product use
  - Nicotine pharmacokinetics
  - Mouth-level exposure
  - Biomarkers

Blank MD and Eissenberg T. 2010. *Nicotine Tob Res.* 12(4):336-43.
Burris JL, et al. 2014. *Nicotine & Tob Res.* 16(4):397-405.
Carpenter MJ, et al. 2017. *Tob Control.* 26:202-209.
Hatsukami DK, et al. 2016. *Tob Control.* 25:267-274.
Kotlyar M, et al. 2011. *Cancer Epidemiol Biomarkers Prev.* 20(1), 91-100.

Biomarkers, Not Chemistry, Provide Definitive Information about Exposure to Toxicants

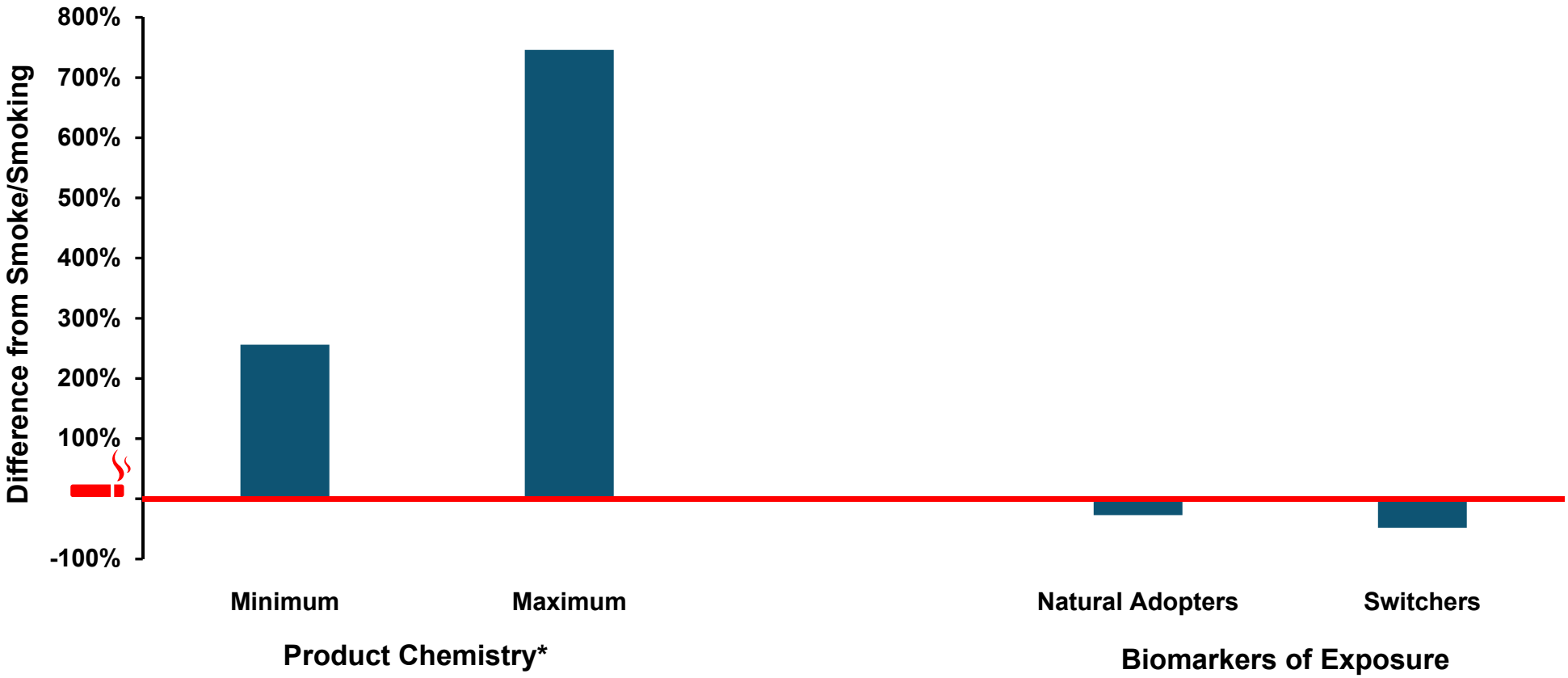
- **Biomarkers**
  - **Measure**
    - Actual exposure to HPHCs, accounting for HPHC content
  - **Integrate**
    - Product chemistry
    - Product use
      - Amount used per day
      - Time used per day
      - Route of exposure

Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine



*Values cited from FDA Briefing Document

Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine

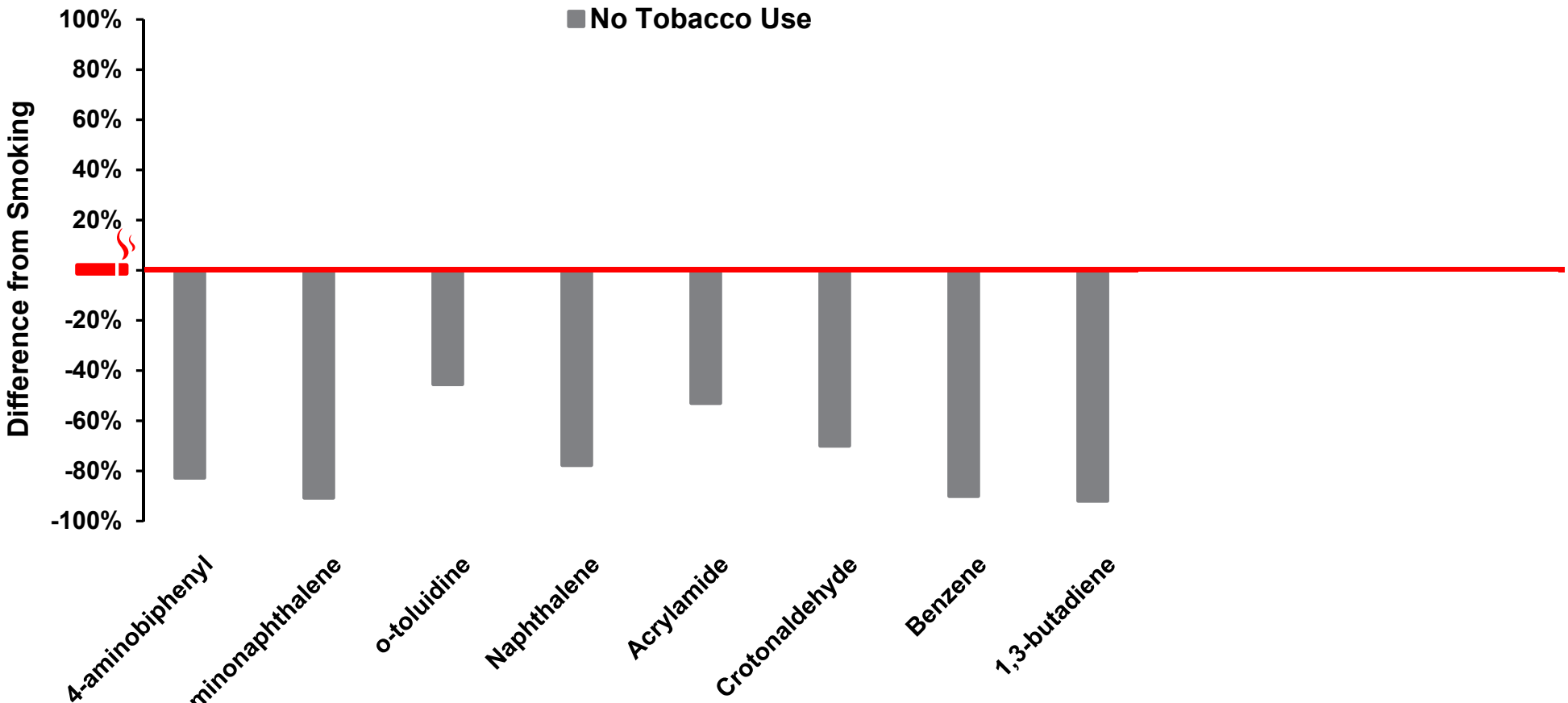


*Values cited from FDA Briefing Document

Comparison of Natural Adopters of Camel Snus to Exclusive Smokers

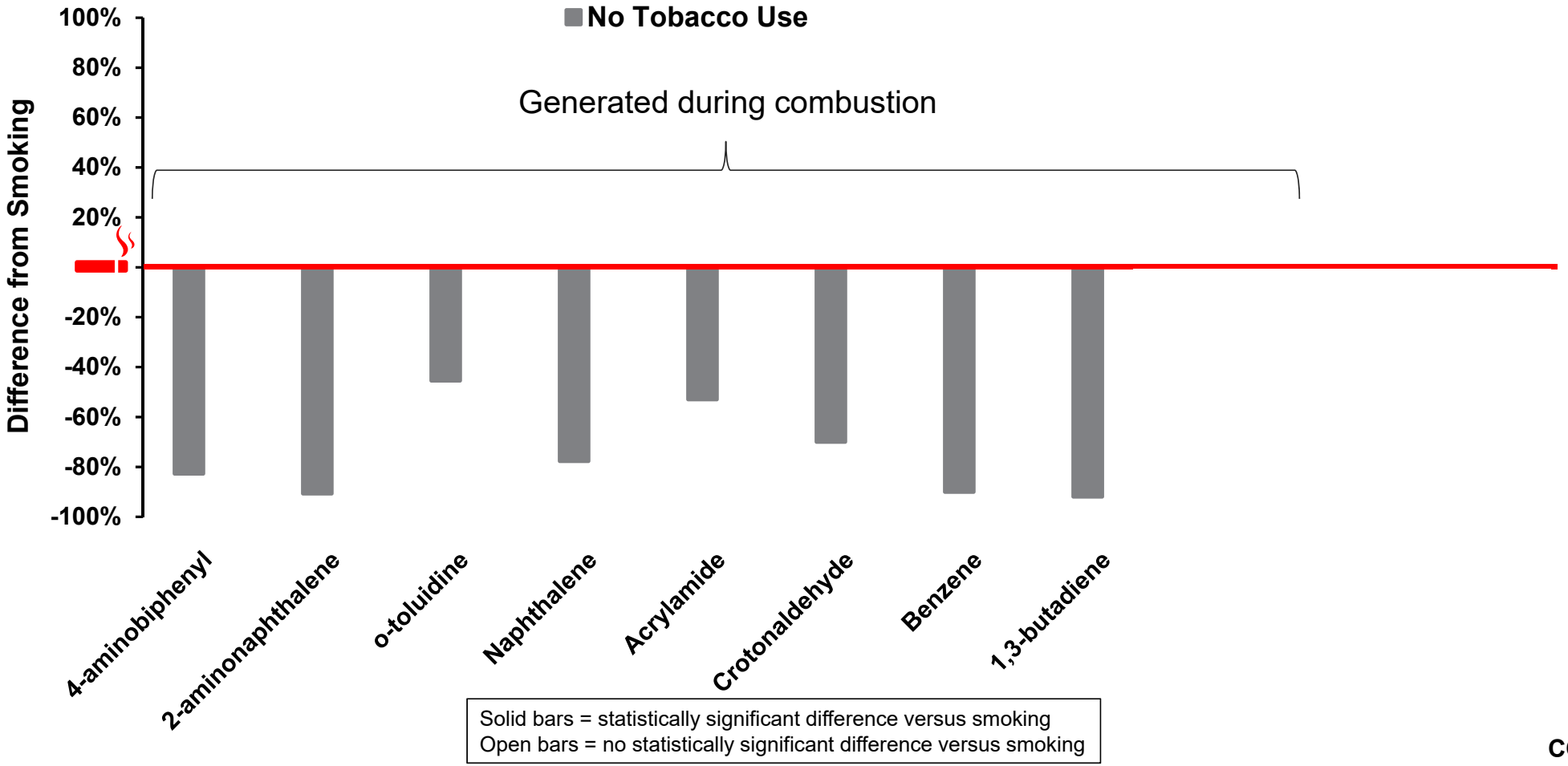
- **Relevant natural adopter study groups**
  - Cigarettes only, N=60
  - Camel Snus only, N=50
  - Non-tobacco users, N=59

Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use



Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use



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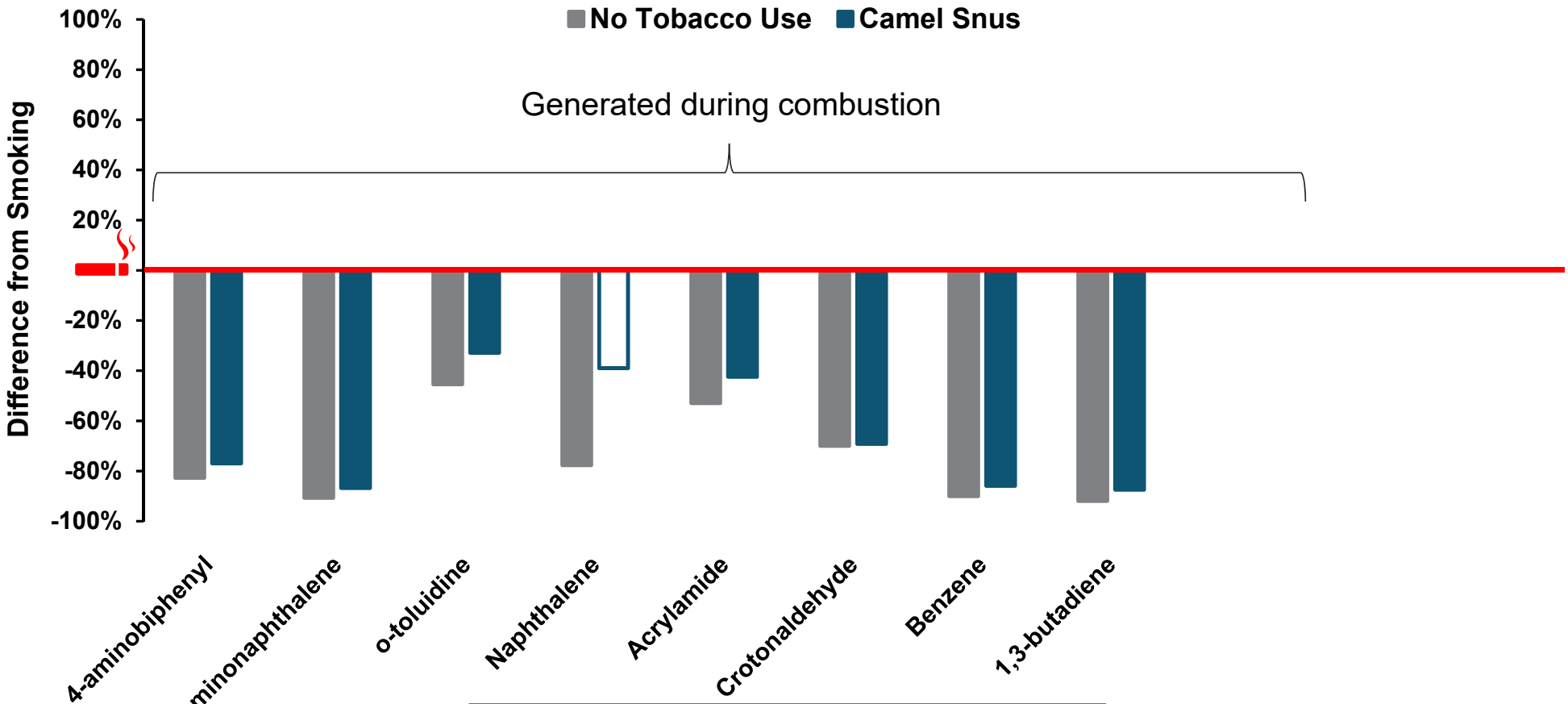

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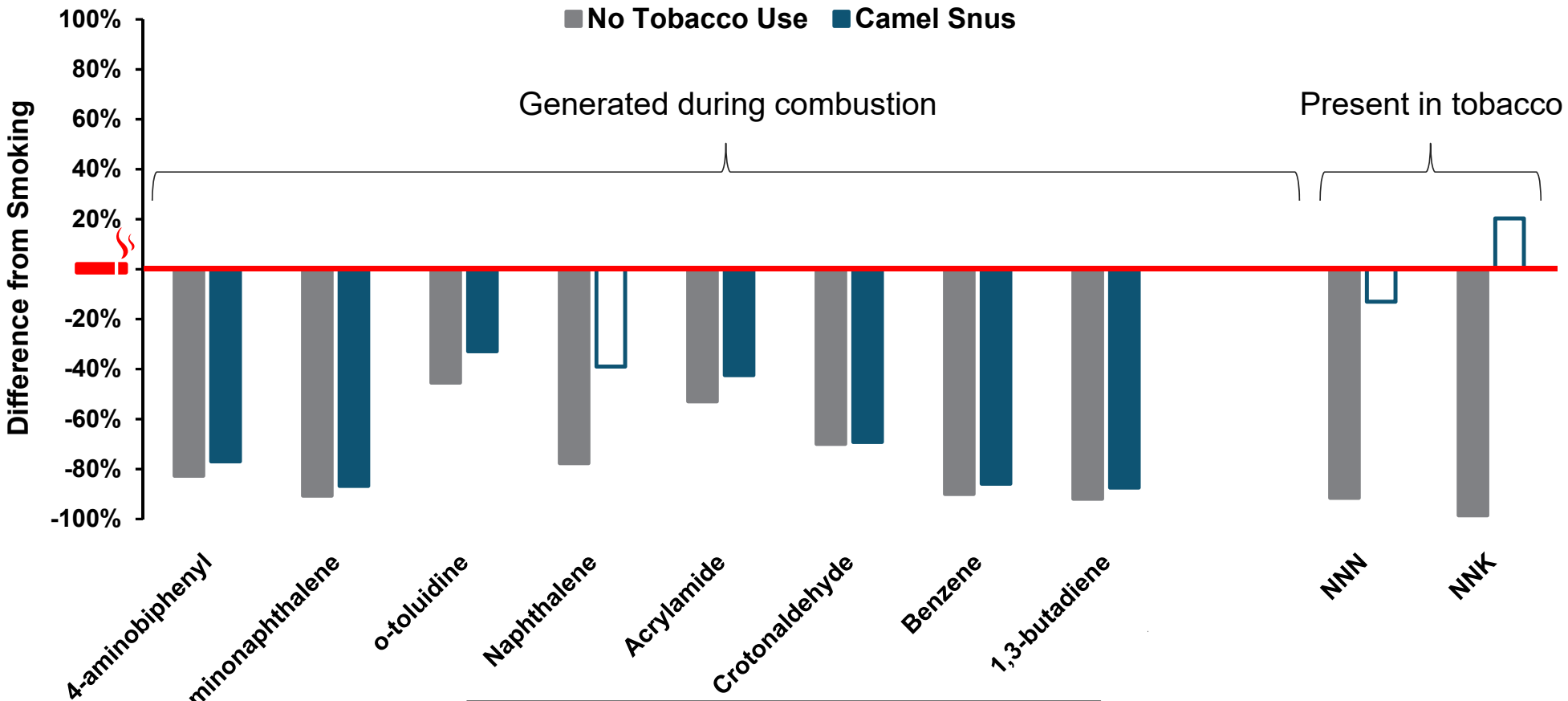

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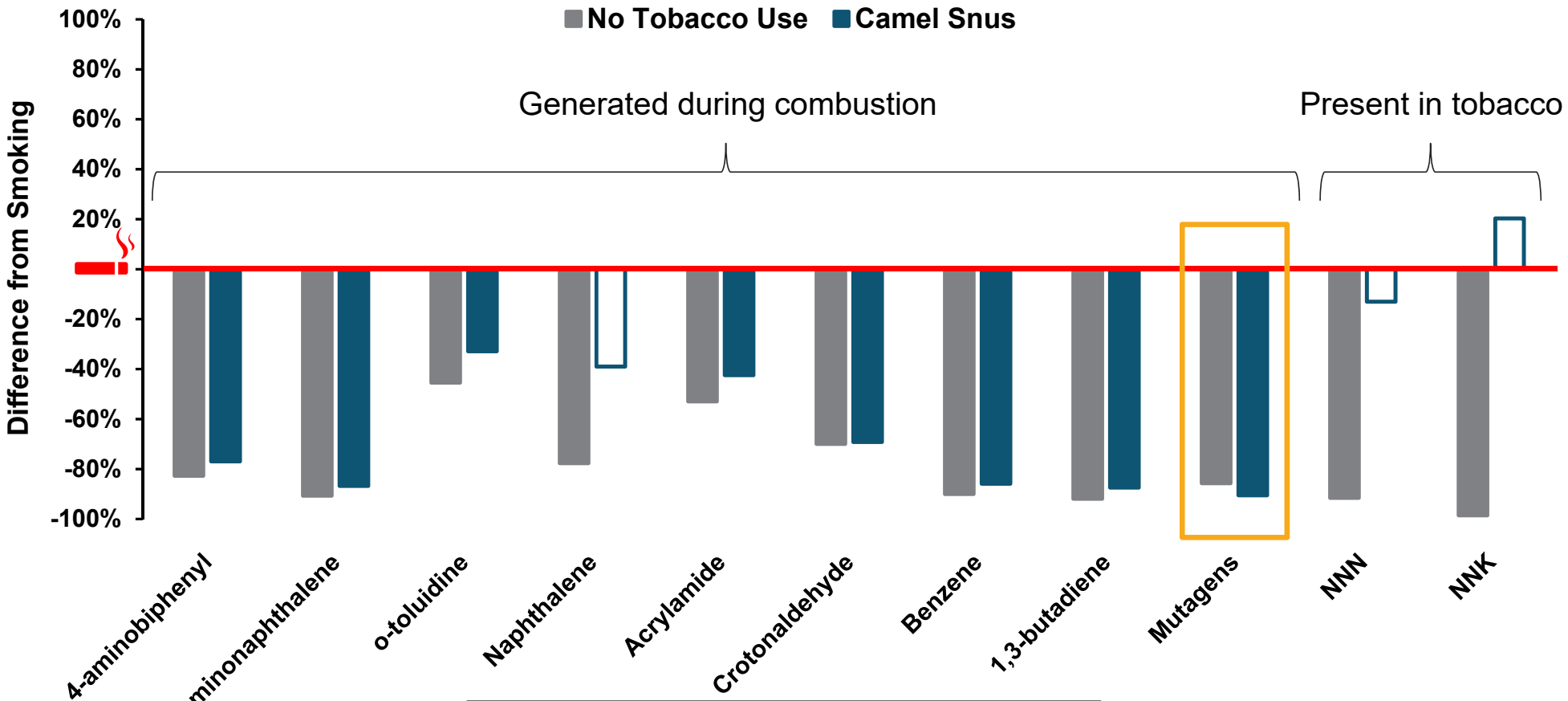
Carcinogens: Camel Snus Use Results in Lower Exposure, Generally Similar to No Tobacco Use



Solid bars = statistically significant difference versus smoking
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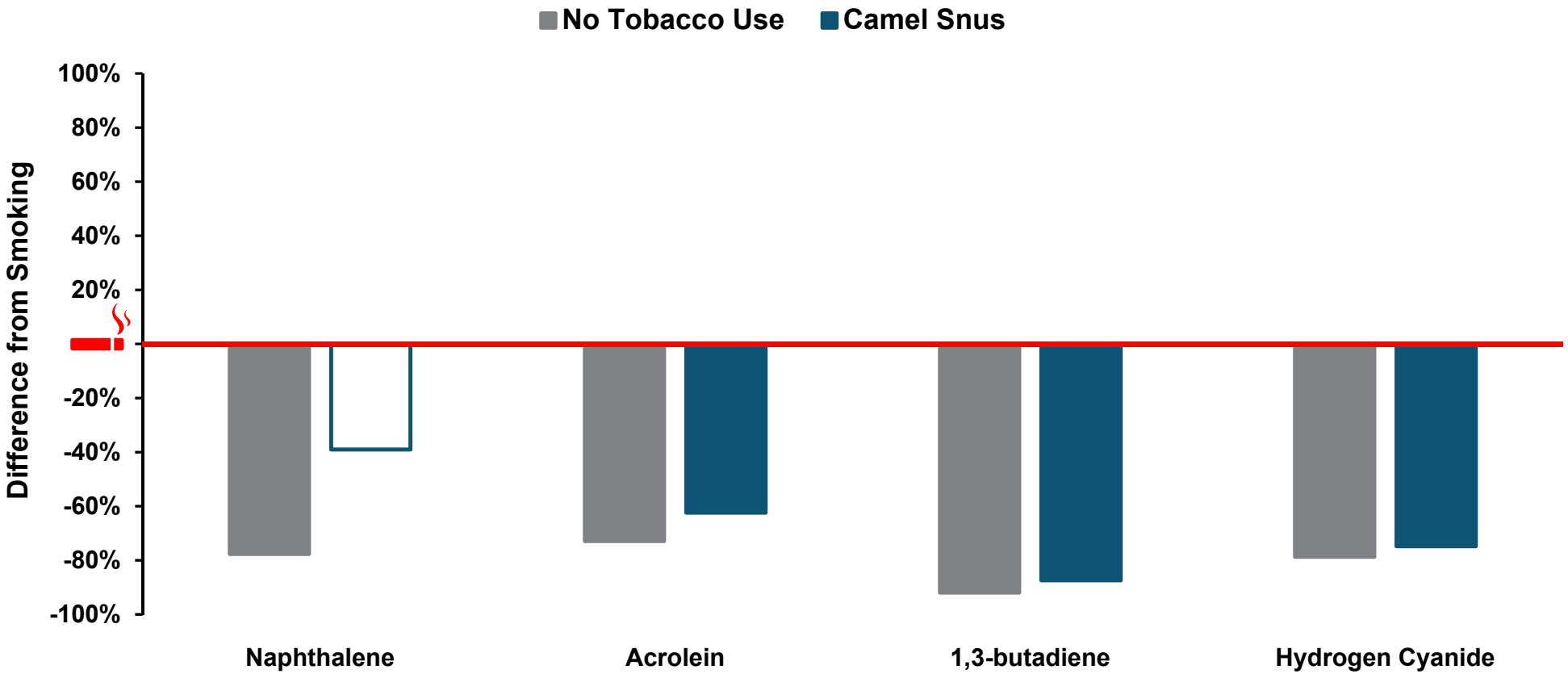
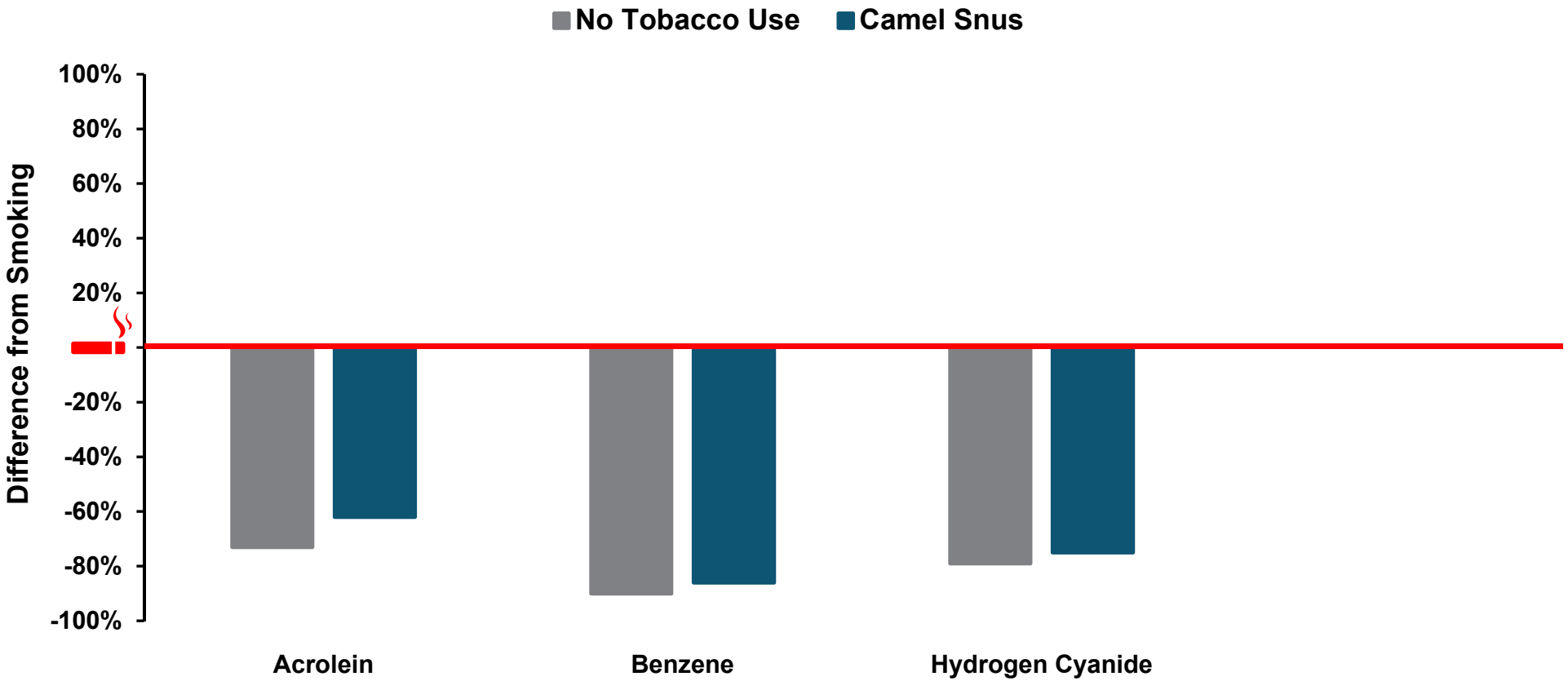
Respiratory Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use



Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Cardiovascular Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use



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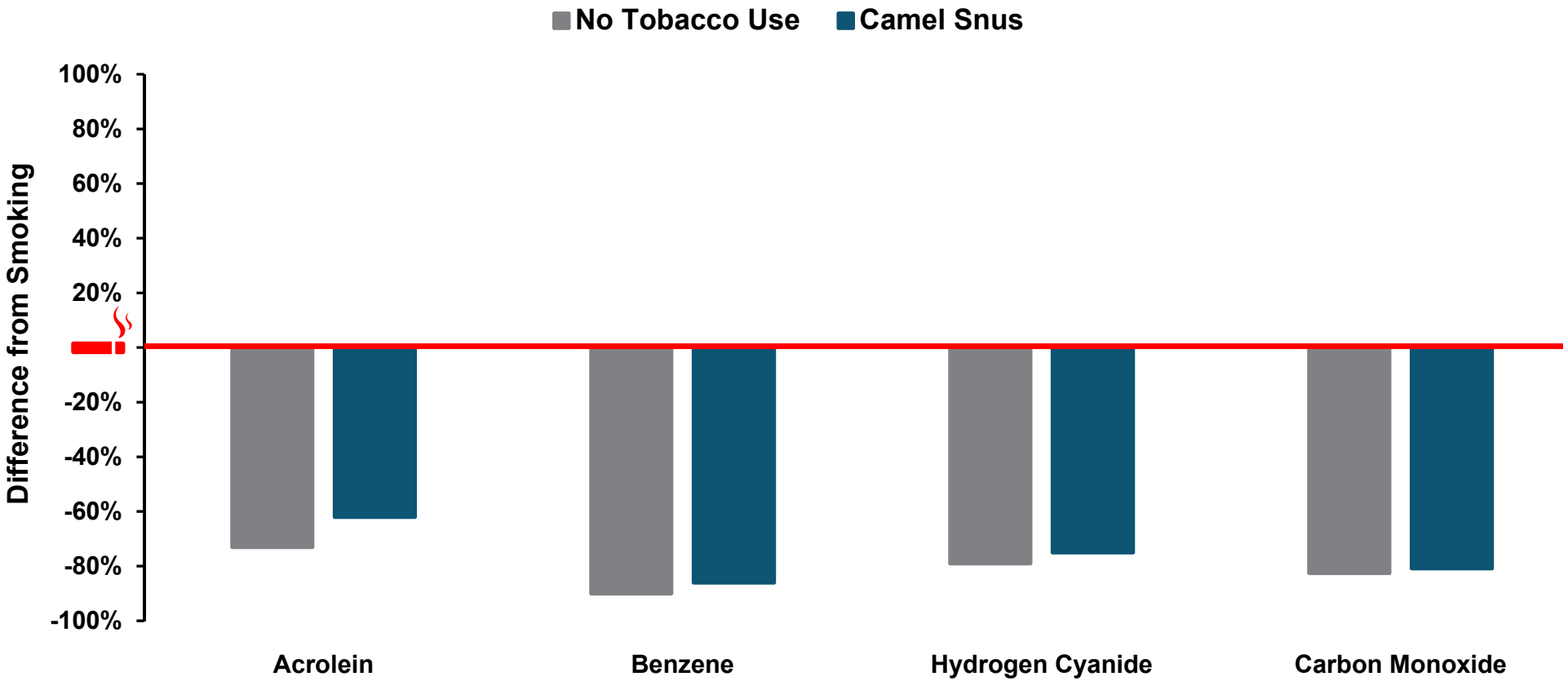
Cardiovascular Toxicants: Camel Snus Use Results in Lower Exposure, Similar to No Tobacco Use

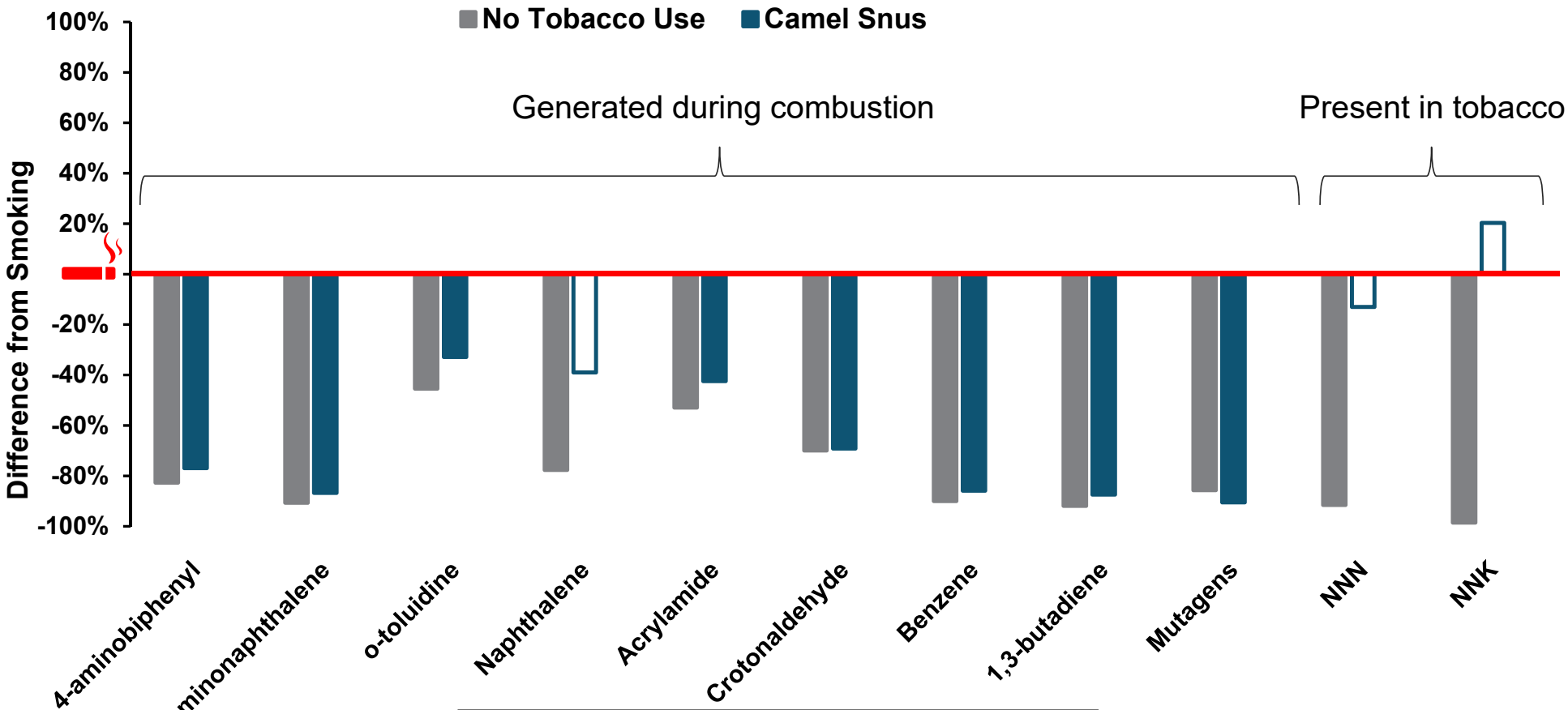


Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Comparison of Natural Adopters of Camel Snus to Exclusive Smokers and Users of Camel Snus and Cigarettes

- **Natural adopter relevant study groups**
  - Cigarettes, N=60
  - Camel Snus only, N=50
  - Non-tobacco users, N=59
  - Cigarettes and Camel Snus, N=50

Carcinogens: Dual Use of Camel Snus and Cigarettes Does Not Increase Exposure



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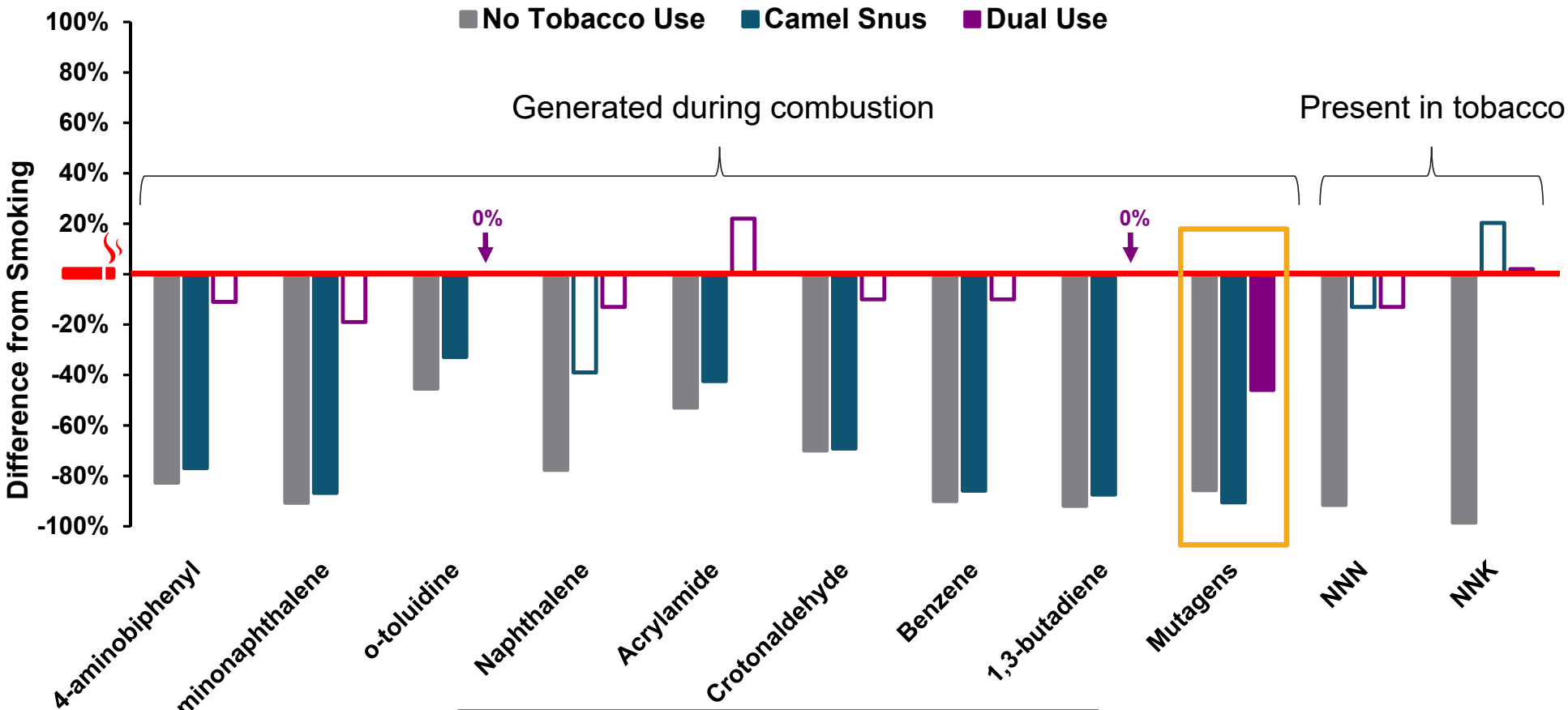
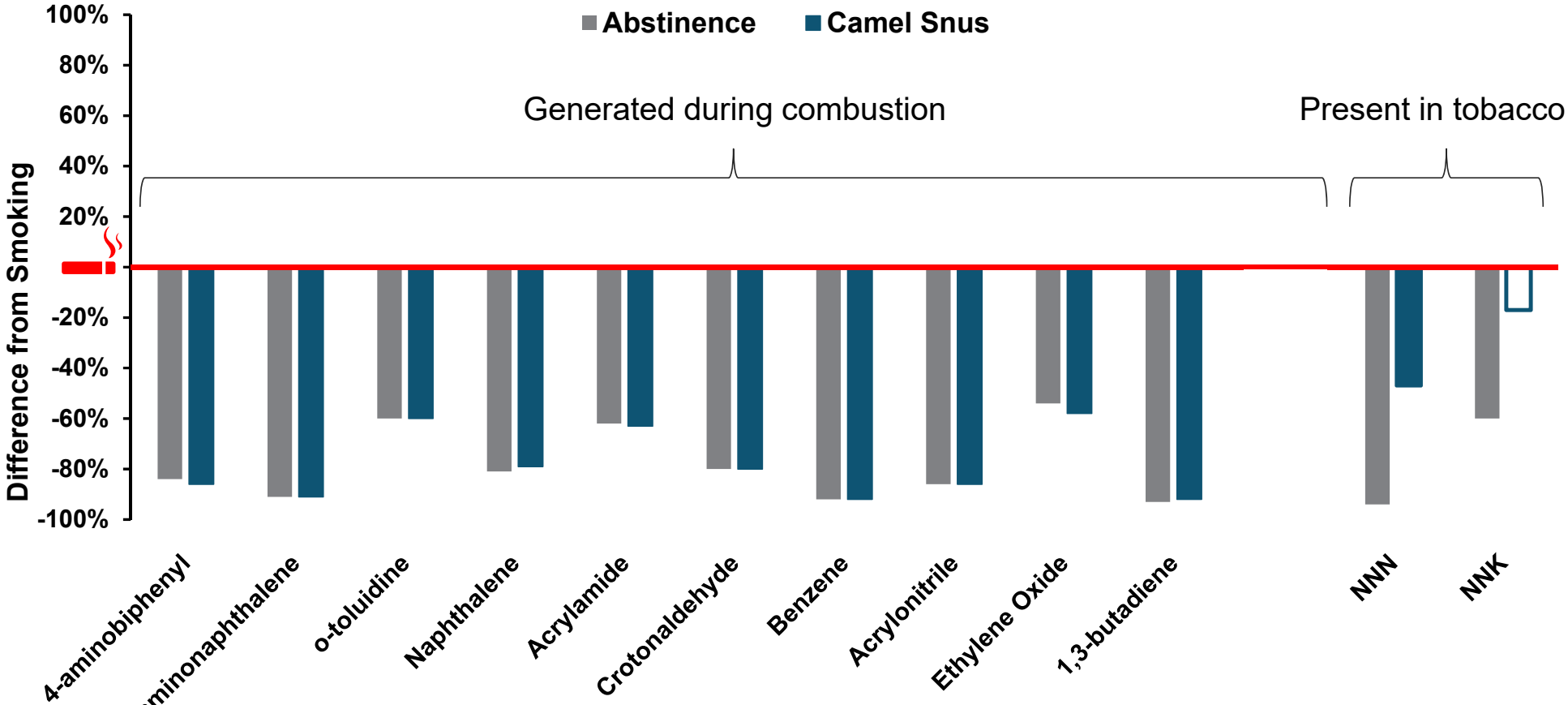


Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Clinical Biomarker Results Show Reduced Toxicant Exposure When Cigarette Smokers Switch to Camel Snus

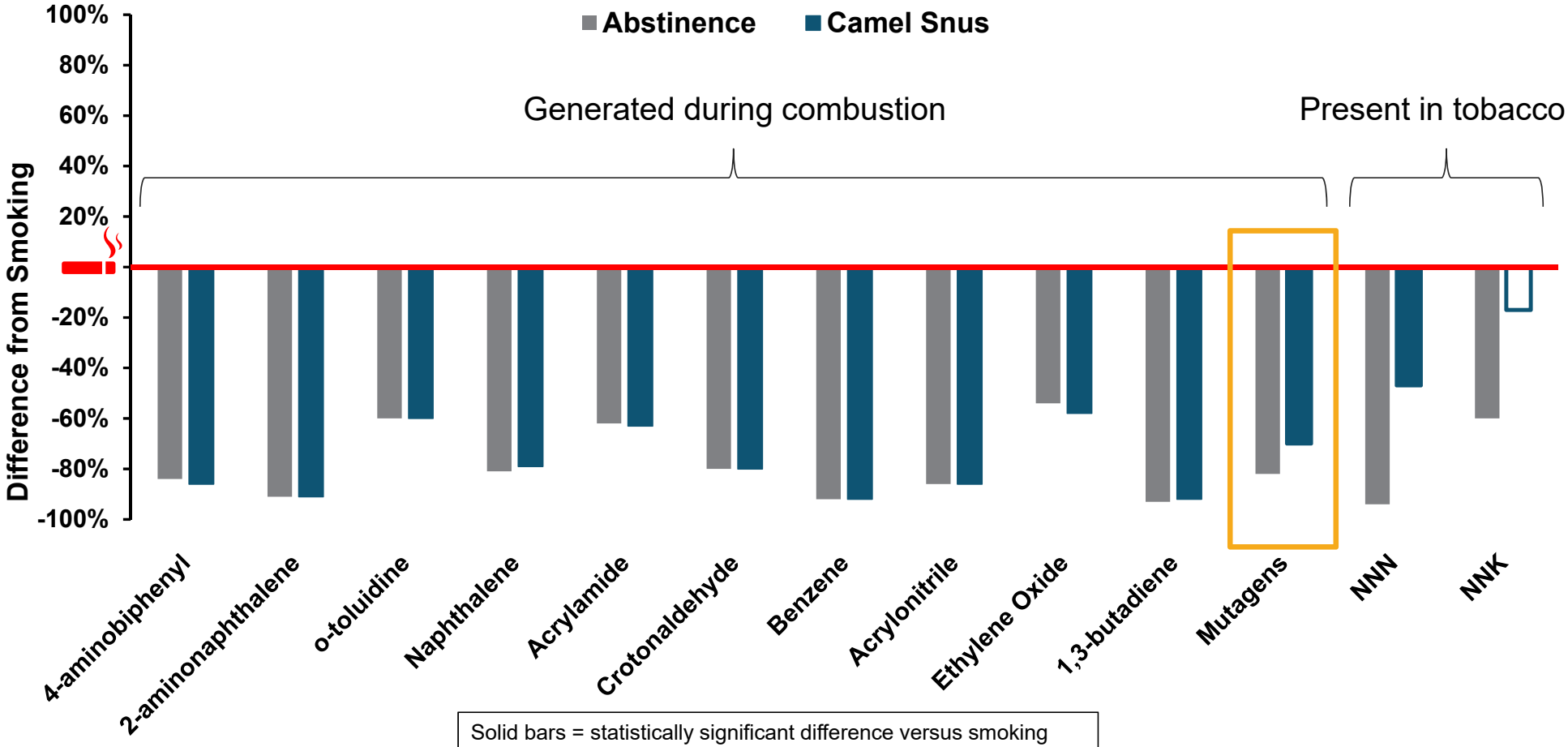
- **Participants resided in clinic for the duration of 1-week study**
  - Baseline smoking – 2 days
  - Product switch – 5 days
- **Smokers were <u>switched completely</u> from cigarettes to:**
  - Exclusive Camel Snus use, N=30
  - Abstinence from all tobacco and nicotine products, N=25

Carcinogens: Camel Snus Use Decreases Exposure, Similar to Abstinence



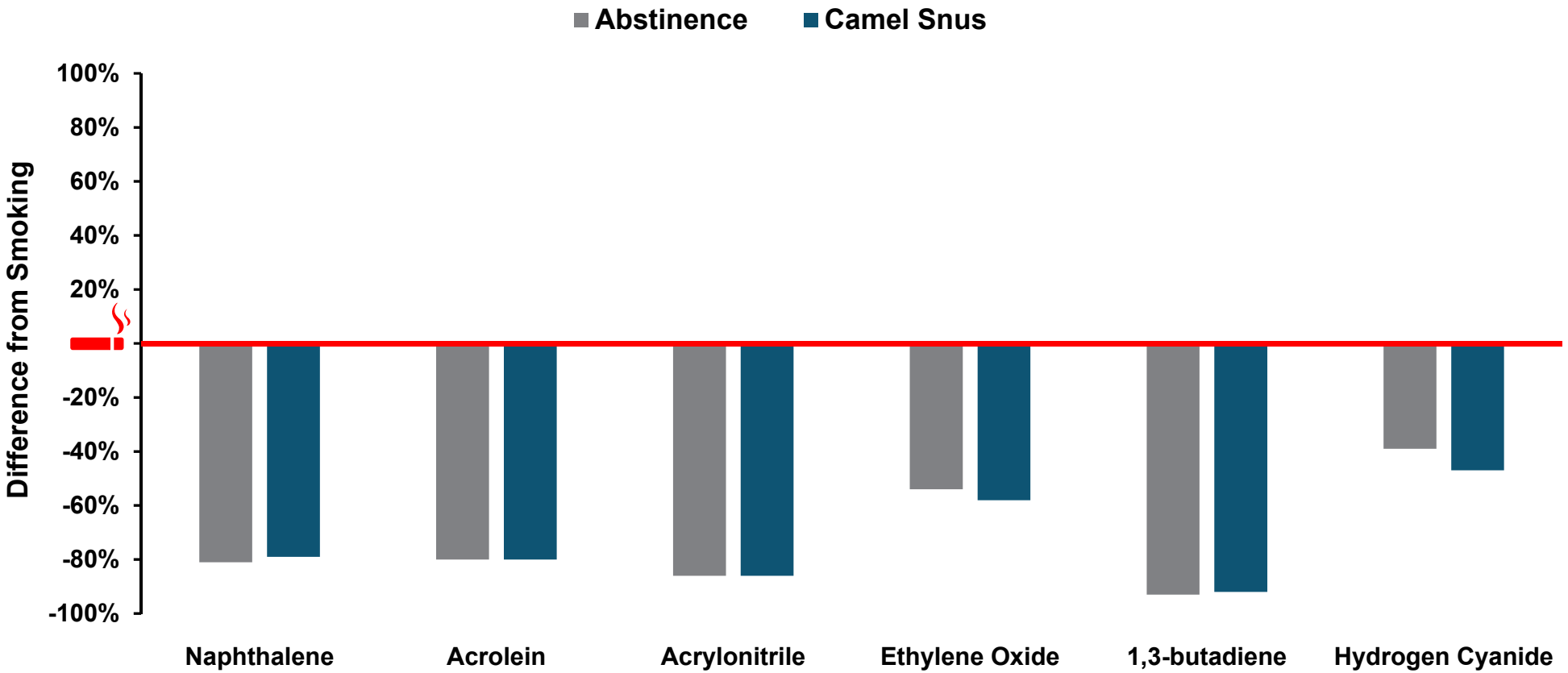
Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Carcinogens: Camel Snus Use Decreases Exposure, Similar to Abstinence



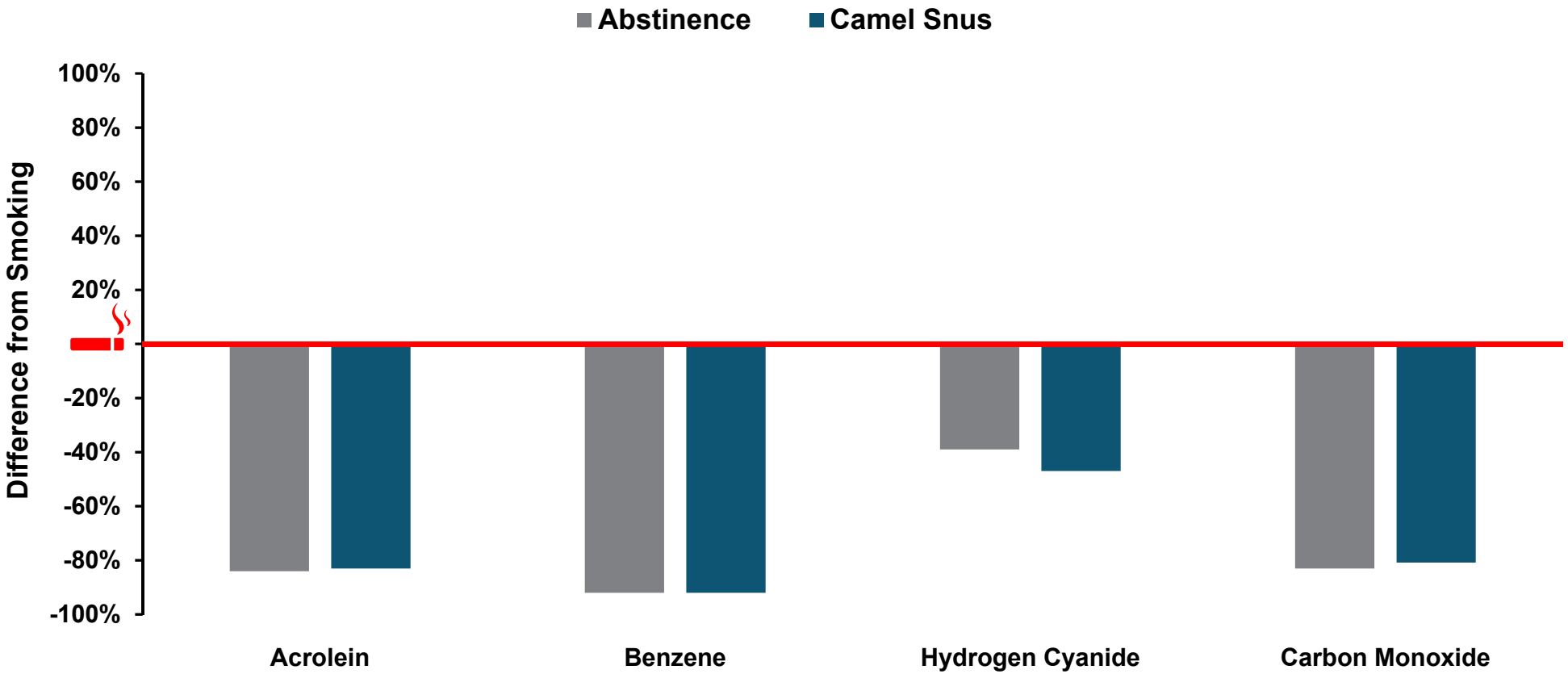
Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Respiratory Toxicants: Camel Snus Use Decreases Exposure, Similar to Abstinence



Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Cardiovascular Toxicants: Camel Snus Use Decreases Exposure, Similar to Abstinence



Solid bars = statistically significant difference versus smoking
Open bars = no statistically significant difference versus smoking

Results of Clinical Studies

Exclusive Camel Snus use exposes individuals to significantly lower levels of carcinogens, respiratory toxicants, and cardiovascular toxicants than cigarettes.

All Preclinical Study Results Support Proposed MRTP Advertising

Endpoint		Camel Snus	Cigarette Smoke
Subchronic animal studies		No toxicity	Histopathologic and inflammatory respiratory changes[1]
Chronic animal studies	1 year	No toxicity	Epidermal tumors[1]
	2 year	No tumors	
in vitro cytotoxicity		Substantial reduction	Significant cytotoxicity
in vitro mutagenicity		Substantial reduction	Significant mutagenicity
in vitro genotoxicity		Substantial reduction	Significant genotoxicity

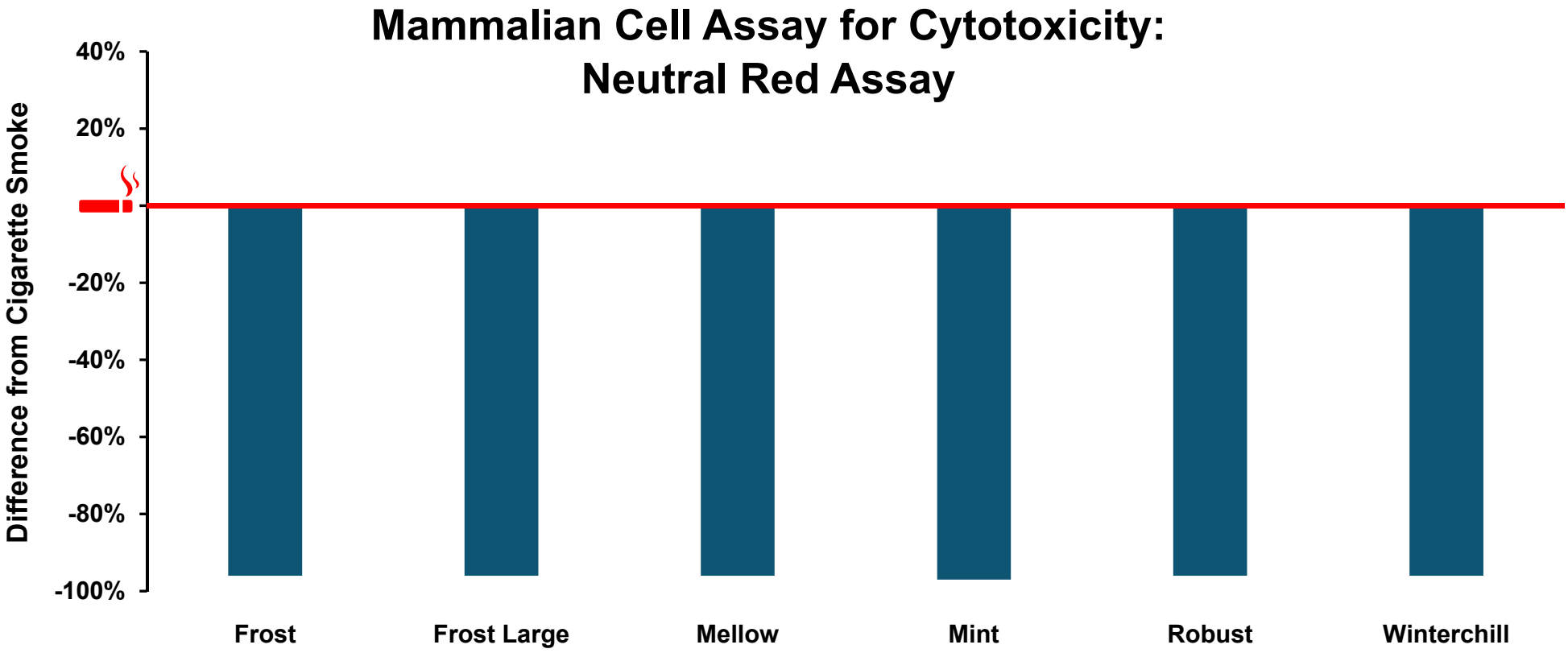
1. Historical data; literature review

Camel Snus Does Not Manifest Systemic or Organ-Specific Toxicity or Carcinogenicity in Rodent Studies

Rodent Studies		Camel Snus	Cigarette Smoke
Subchronic (90-day)		No significant organ or system toxicity	Significant histopathologic and inflammatory respiratory changes[1]
Chronic	1 year	No significant toxicity	Significant malignant epidermal tumors[1]
	2 year	No significant tumor occurrences due to snus	

1. Historical data; literature review

Camel Snus Extracts Are Less Cytotoxic than Cigarette Smoke

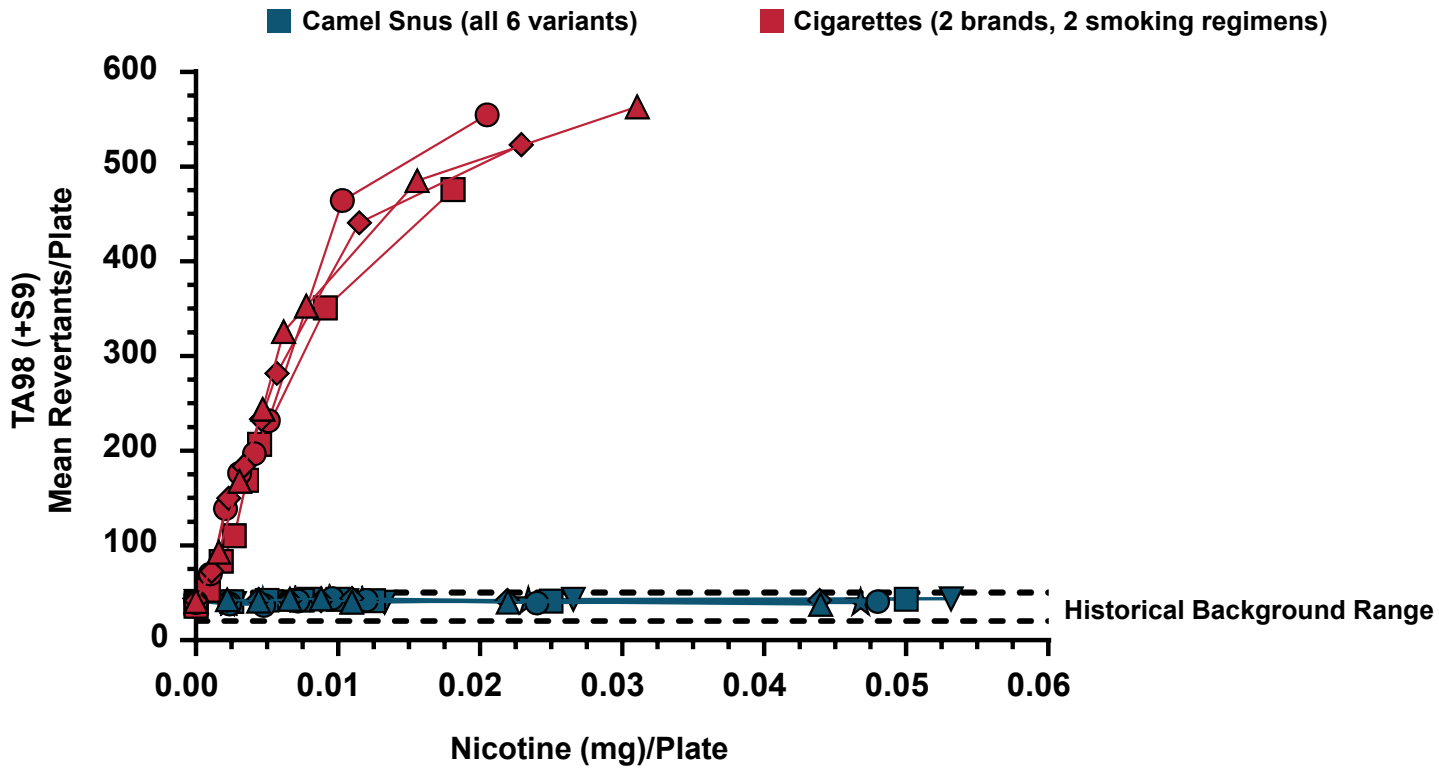


Reduction in cytotoxicity observed for Camel Snus relative to commercial cigarette comparators, normalized per mg of nicotine

RJRT Study Data

Camel Snus Extracts are Less Mutagenic than Cigarette Smoke

Bacterial Cell Assays for DNA Damage at the Gene Level: Ames Assay (Mutagenicity)



RJRT Study Data

All Preclinical Study Results Support Proposed MRTP Advertising

Endpoint		Camel Snus	Cigarette Smoke
Subchronic animal studies		No toxicity	Histopathologic and inflammatory respiratory changes[1]
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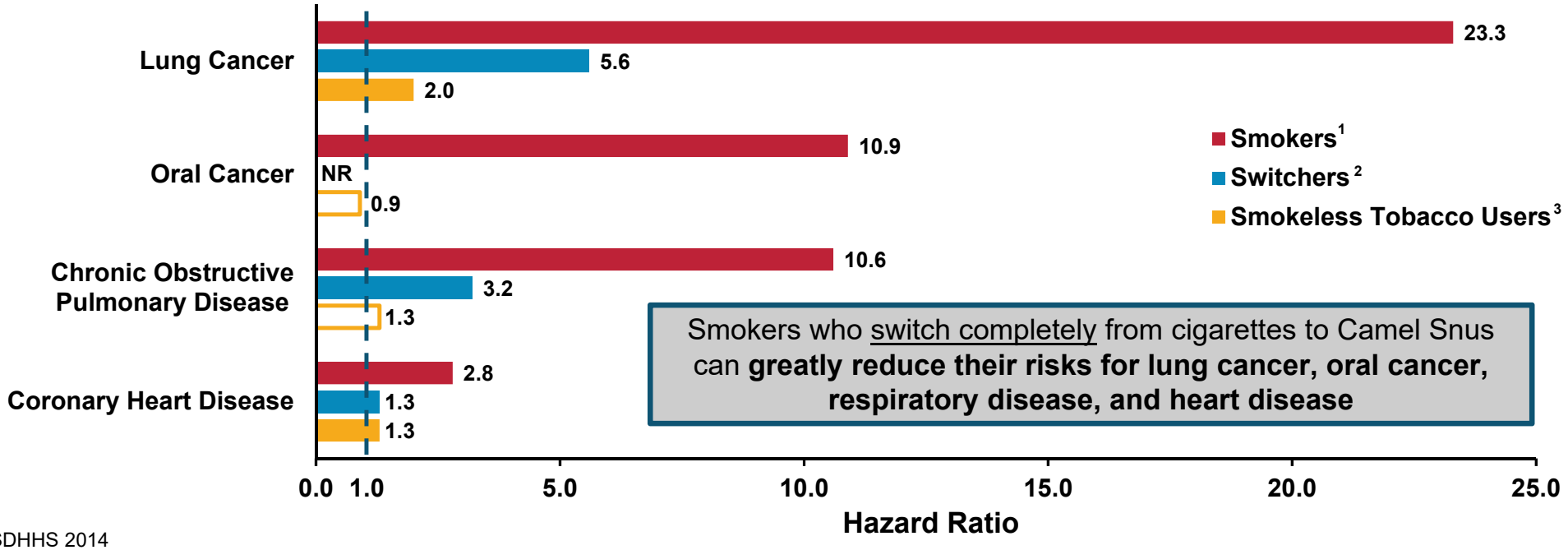
	2 year	No tumors	
in vitro cytotoxicity		Substantial reduction	Significant cytotoxicity
in vitro mutagenicity		Substantial reduction	Significant mutagenicity
in vitro genotoxicity		Substantial reduction	Significant genotoxicity

1. Historical data; literature review

Clinical and Preclinical Results are Consistent with the Epidemiology

Mortality Risk Estimates, U.S. Males, Cancer Prevention Study II



Smokers who switch completely from cigarettes to Camel Snus can **greatly reduce their risks for lung cancer, oral cancer, respiratory disease, and heart disease**

Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

1. USDHHS 2014
2. Henley et al. 2007
3. Henley et al. 2005

NR=Not Reported
Dashed line represents hazard ratio=1.0

Risk Perceptions, Comprehension, and Likelihood of Use

Saul Shiffman, PhD

Senior Scientific Advisor, Pinney Associates, Inc.

Professor of Psychology, Psychiatry, Pharmaceutical Sciences & Clinical Translational Science, University of Pittsburgh

CC-73

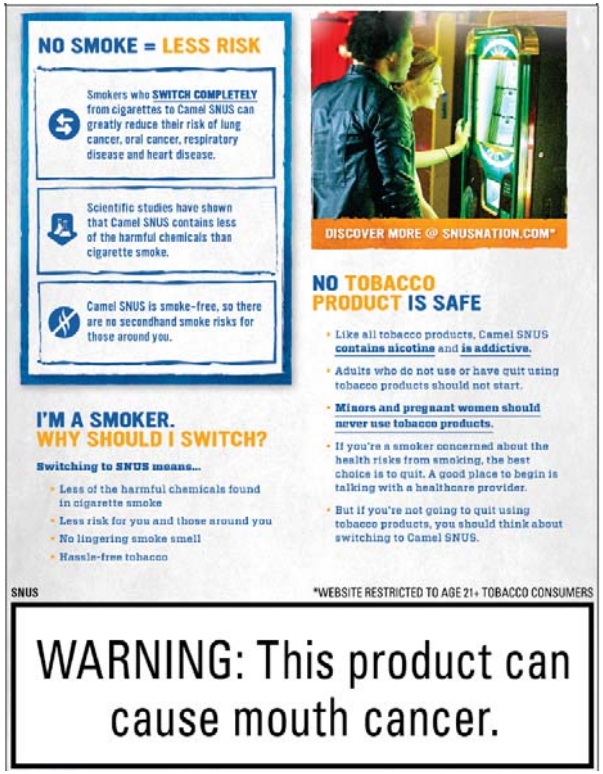
Disclosure

Through Pinney Associates, Dr. Shiffman consults on tobacco cessation and harm reduction products to RAI Services Company and other subsidiaries of Reynolds American, Inc. and British American Tobacco

Behavioral Research

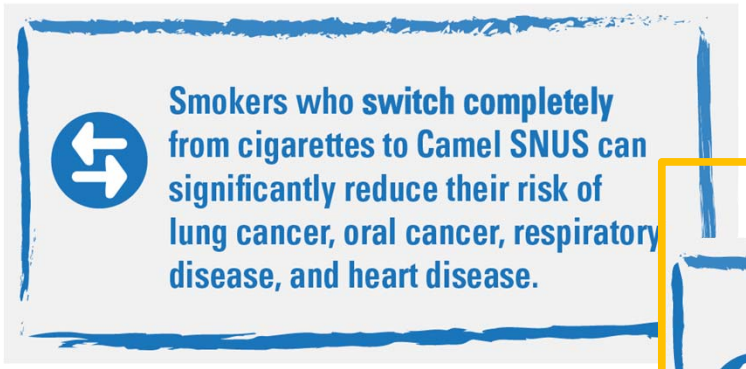
- **Risk perceptions**
- **Message comprehension**
- **Likelihood of use**

Modified Risk Advertisement

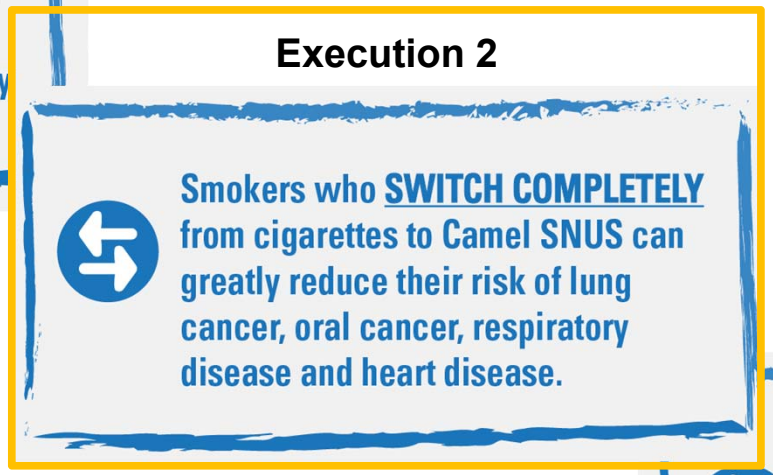


Three Executions: Variations in Key Modified Risk Text

Execution 1



Execution 2



Execution 3

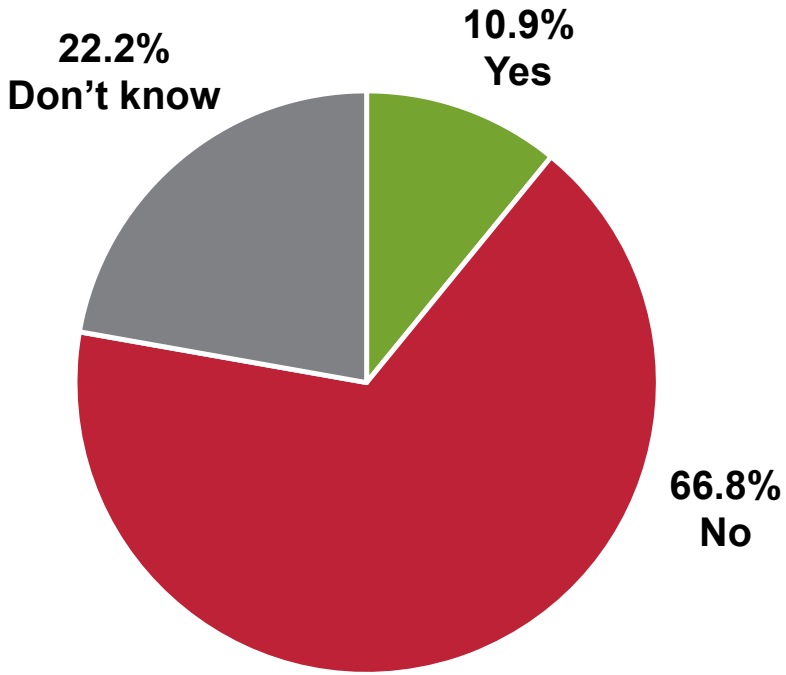
Research Questions for Population Testing

- **Do people viewing the advertising understand that switching to Camel Snus carries less risk than smoking, but still has risk?**

Widespread Misperceptions of Relative Risks: Most Adults Believe Smokeless at Least as Risky as Cigarettes

Health Information National Trends Survey (HINTS)-FDA 2015
N=3,738 U.S. Adults

Do you think that some smokeless tobacco products, such as chewing tobacco, snus, and snuff are less harmful to a person's health than cigarettes?



Feirman SP, et al. 2018. *Addictive Behaviors.* 77:7-15.

Study to Assess Risk Perceptions and Comprehension of Balancing Information

- **Sample: 4,924 adults from online research panels**
  - 3 equal strata: current, former, never tobacco users
  - Diverse sample, balanced and weighted to U.S. population
- **Viewed Camel Snus modified risk advertisement**
  - 4 statutory smokeless tobacco warnings rotated randomly
- **Assessment**
  - Online quantitative assessment
  - Absolute and relative risk perceptions; Camel Snus vs. cigarettes
  - Comprehension of balancing information regarding Camel Snus

Indirect and Direct Comparisons[1] of Risk: Snus vs. Cigarette Smoking

- **Indirect comparison: Camel Snus and cigarette smoking each rated independently**
  - Assessed for each disease in modified risk advertisement
    - Absolute risk on 1-7 scale ('no risk' to 'substantial risk')
    - Compare numerically

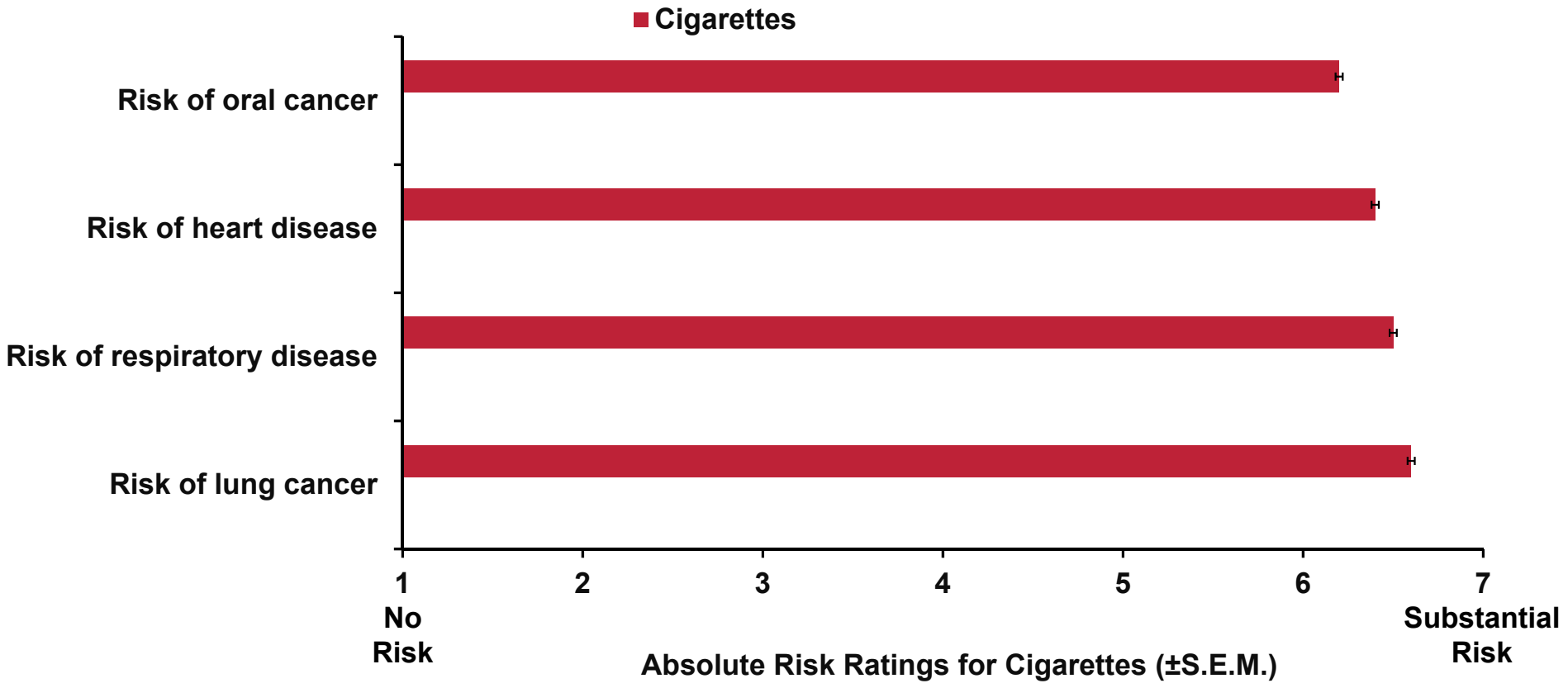
No Risk ⇩						Substantial Risk ⇩
1	2	3	4	5	6	7
❍	❍	❍	❍	❍	❍	❍

- **Direct comparison: Camel Snus relative to cigarette smoking**
  - Assessed for each disease in modified risk advertisement

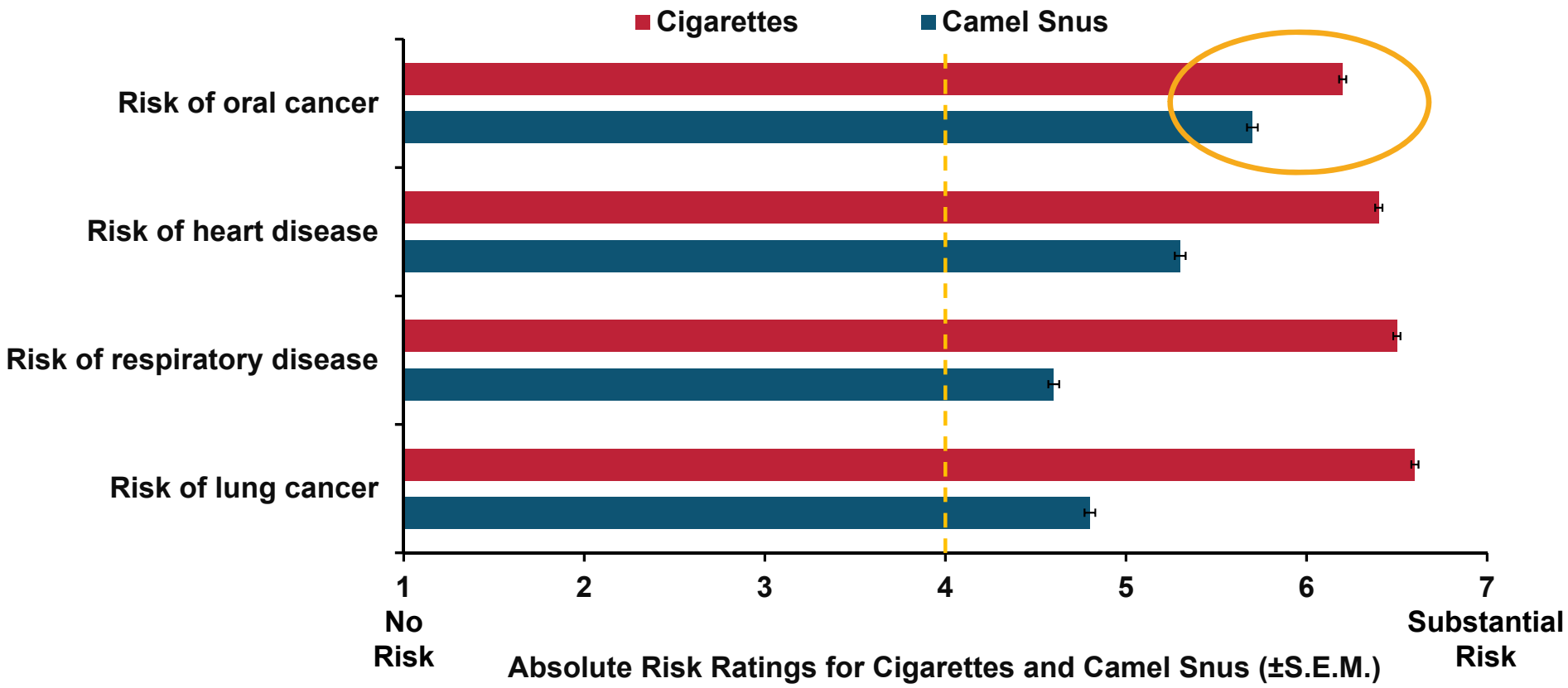
Camel SNUS has…			
Same level of health risk as continuing to smoke	Less health risk than continuing to smoke, but has some risk	No health risk at all	I don't know/not sure
o	o	o	o

1. e.g., Persoskie A, Nguyen AB, Kaufman AR, Tworek C. *Addict Behav* 2017;67:100-105.

People Understand that Cigarette Smoking Carries Substantial Risk

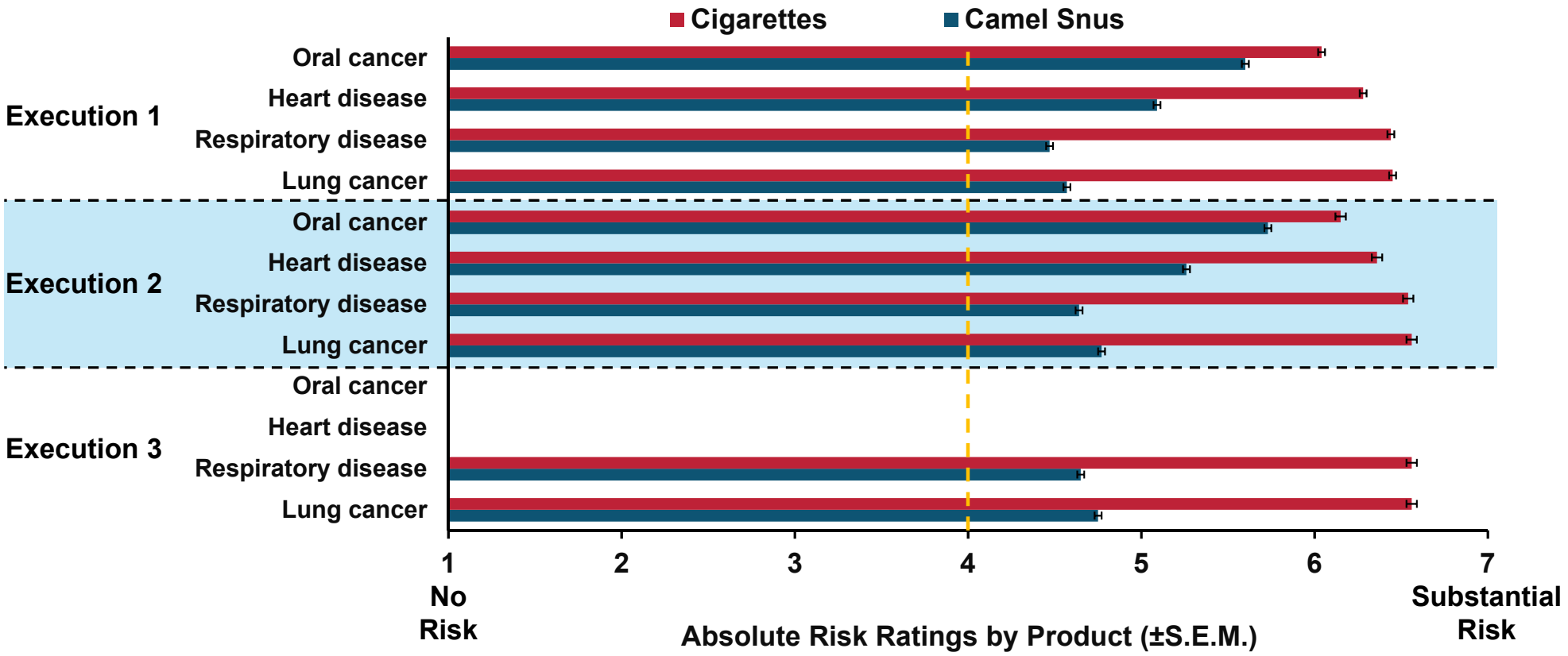


Indirect Comparison: People Understand Camel Snus has Less Risk, but Still Some Risk



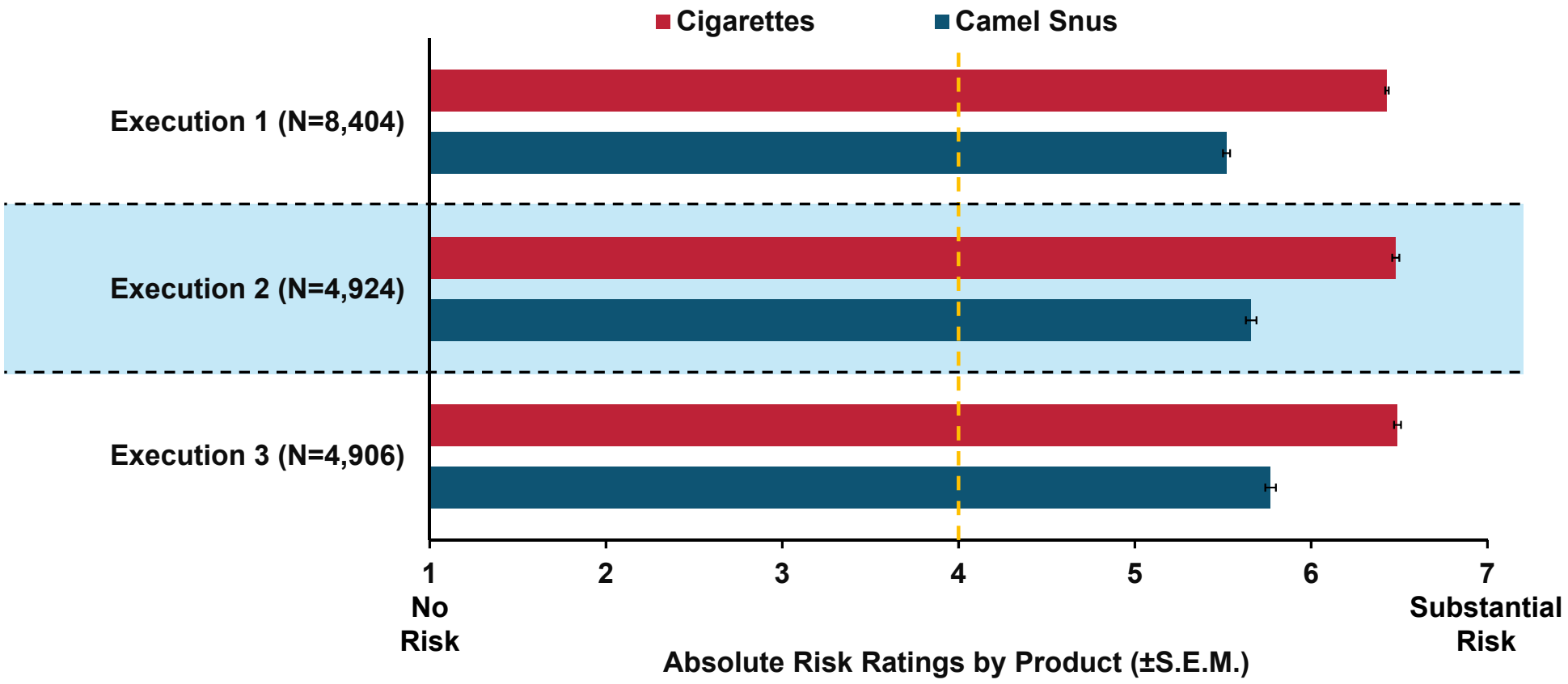
CC-83

Camel Snus has Less Risk, but Still Some Risk, Understood in All Three Executions



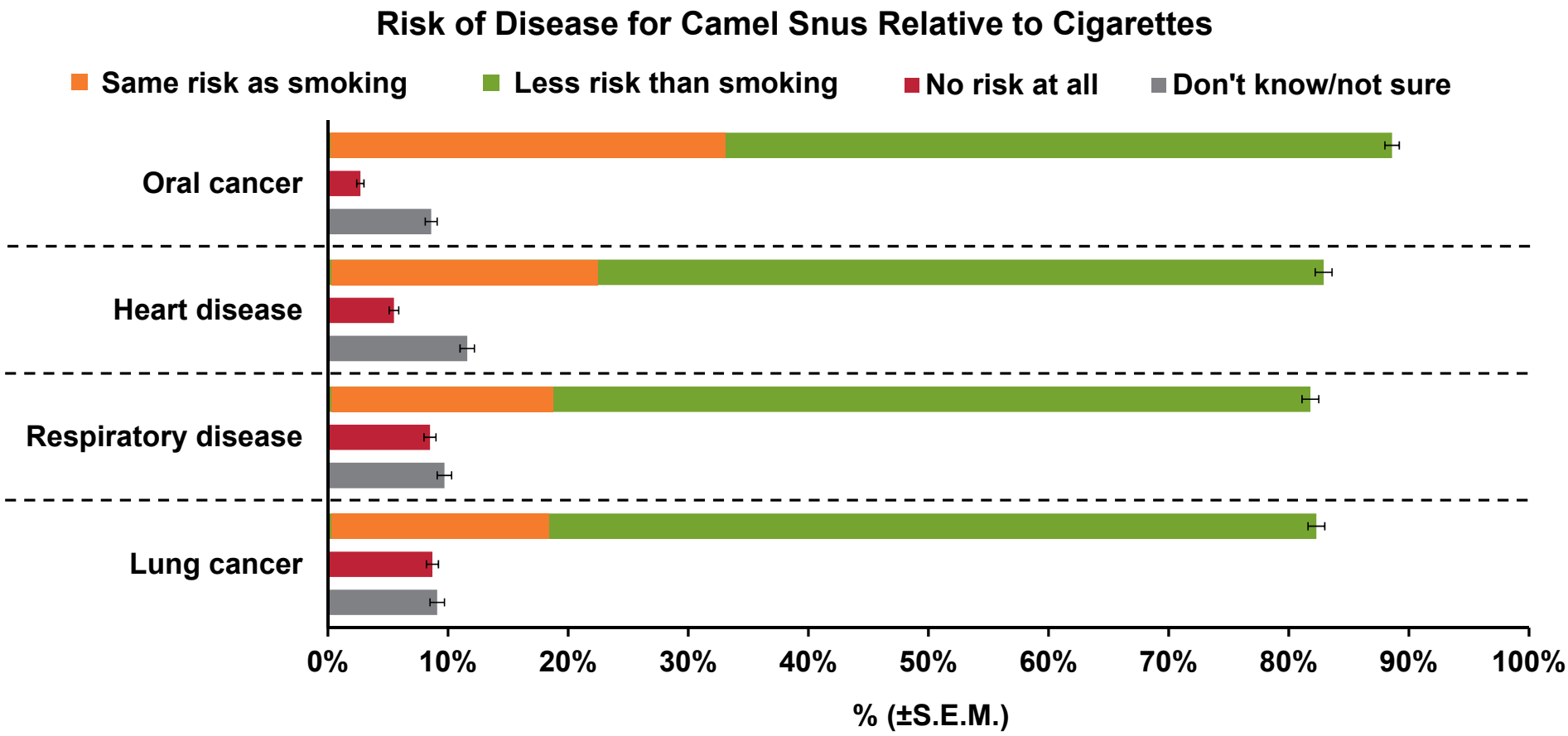
CC-84

Snus Presents Lower Risk of *Generally Poorer Health* Understood in All Executions



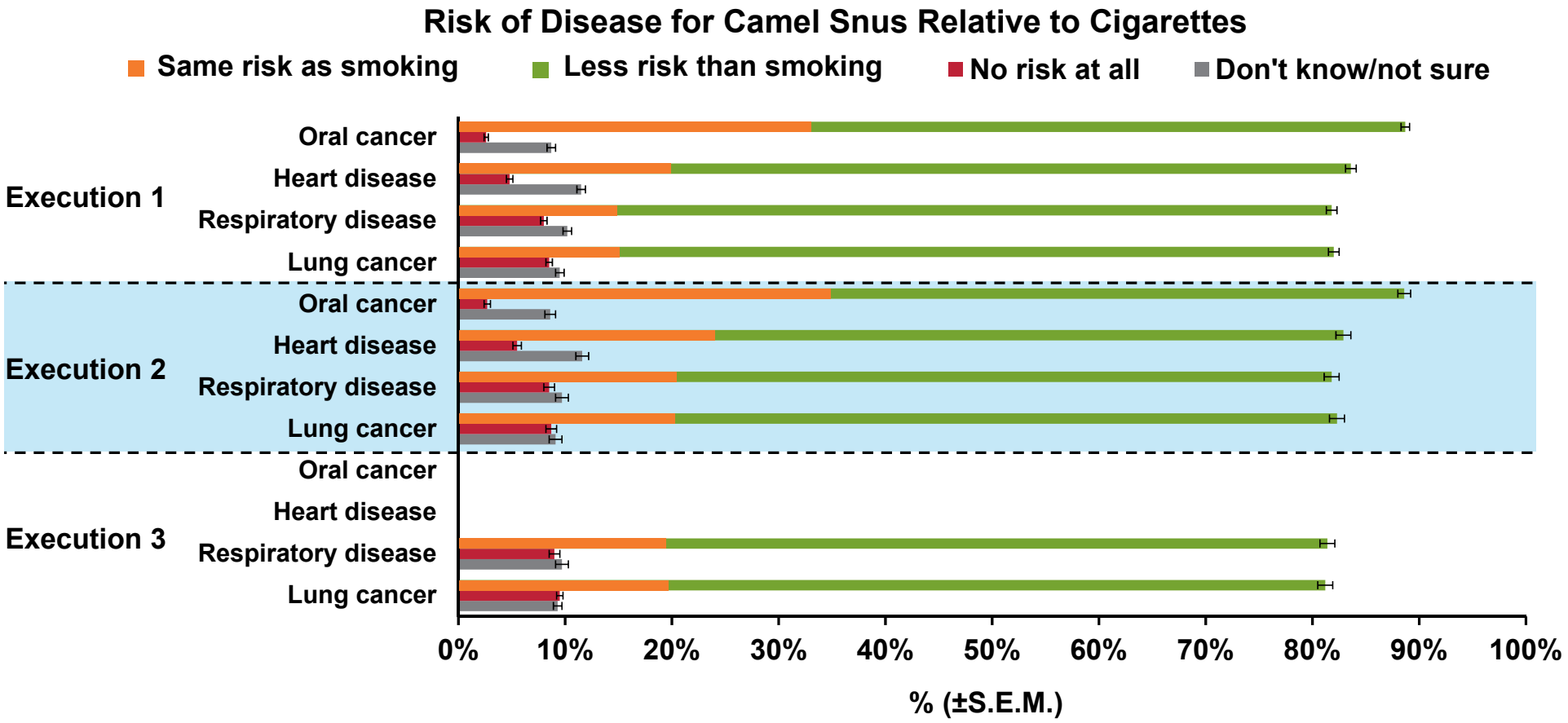
CC-85

Direct Comparison: Large Majorities Understand Camel Snus Presents Some Risk; Few Believe it has No Risk at All



CC-86

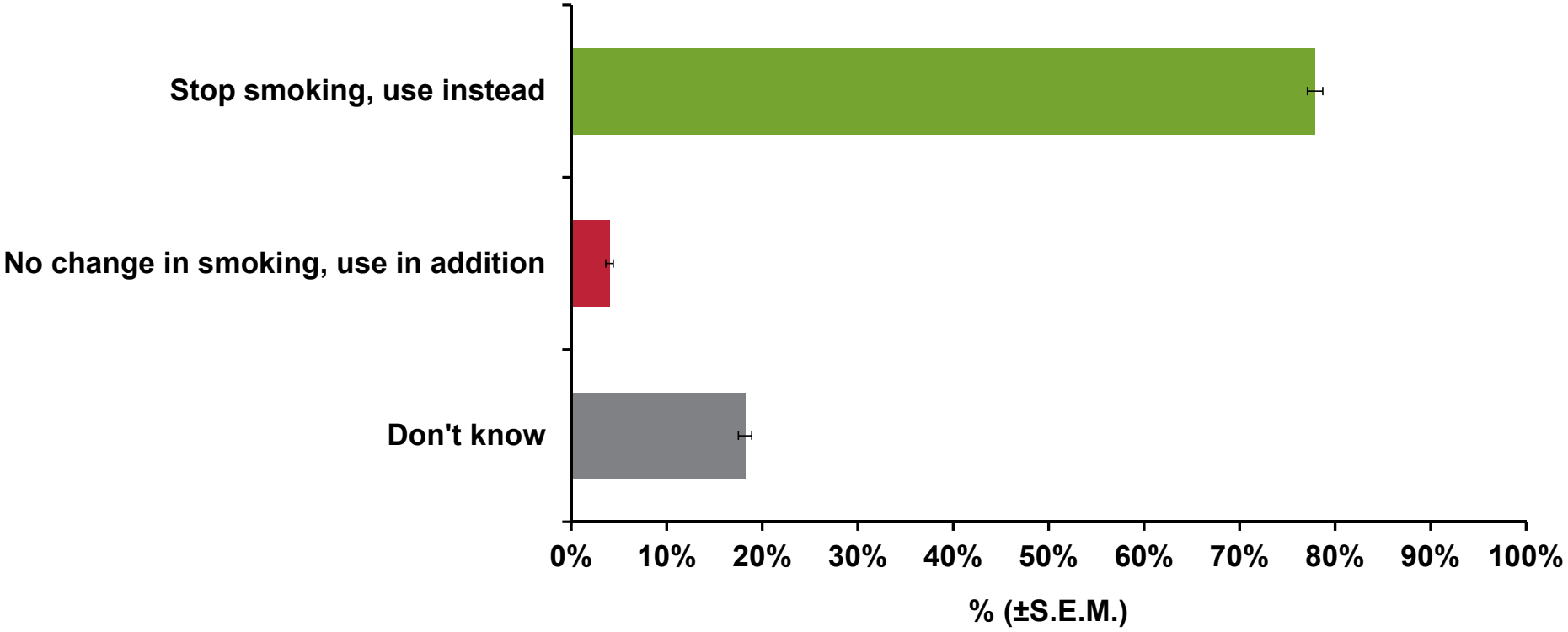
Camel Snus Presents Some Risk; Few Believe No Risk at All, in All Three Executions



CC-87

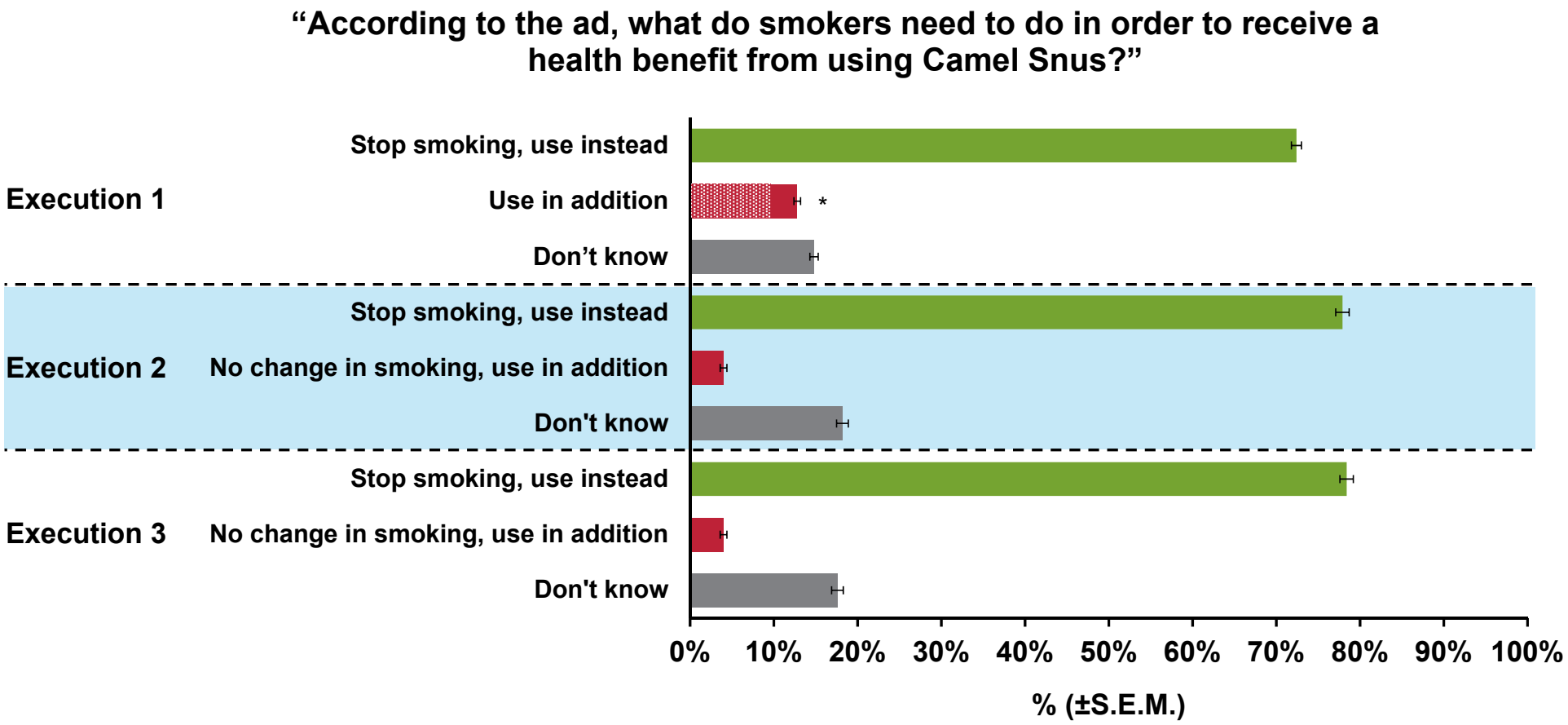
Large Majority Comprehends Need to Switch Completely to Capture Reduction in Risk

"According to the ad, what do smokers need to do in order to receive a health benefit from using Camel Snus?"



CC-88

Majority Comprehends Need to Switch Completely, in All Three Executions



*Bar combines "reduce smoking by half, use in addition" (hatched area) and "no change in smoking, use in addition."

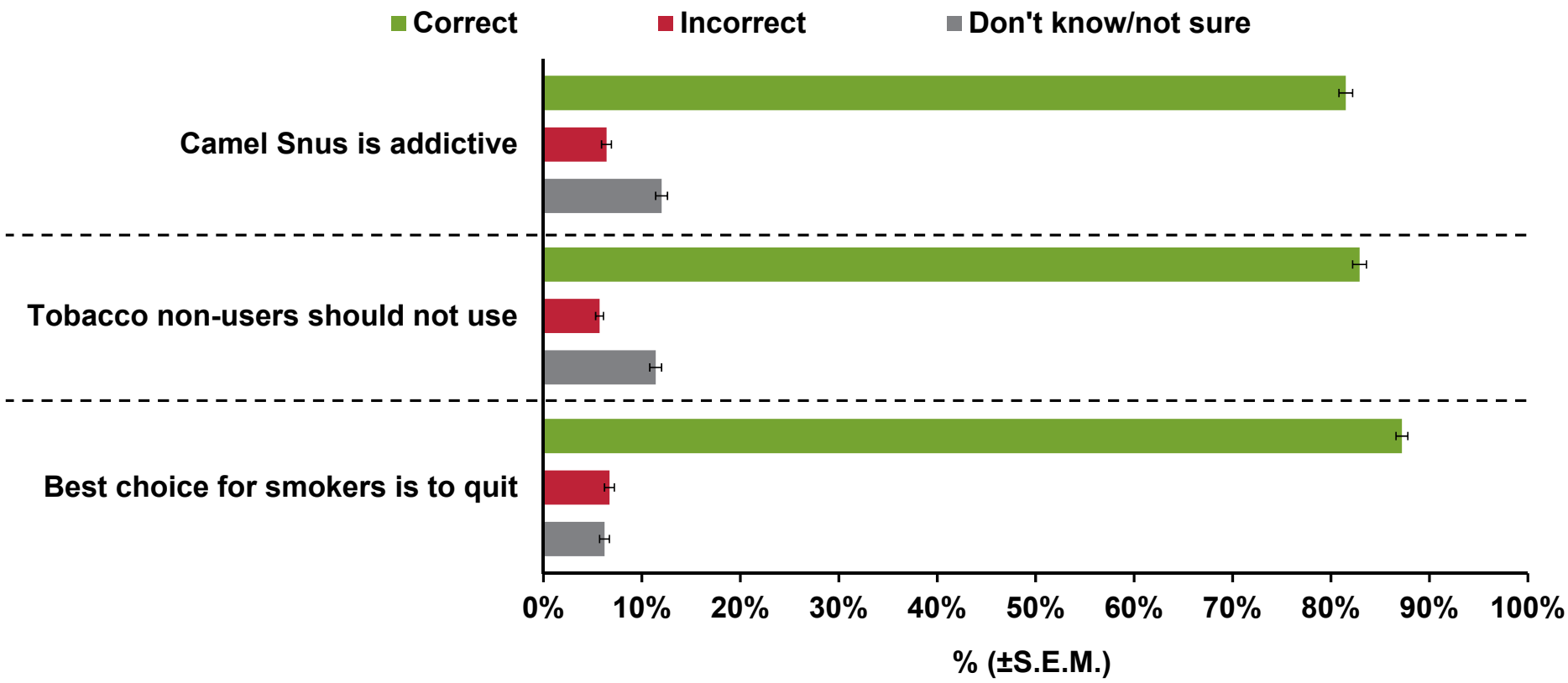
Research Findings from Population Testing

- **People understand that Camel Snus carries less risk, but still has risk**
  - Strong majority understands need to switch completely to benefit

Research Questions for Population Testing

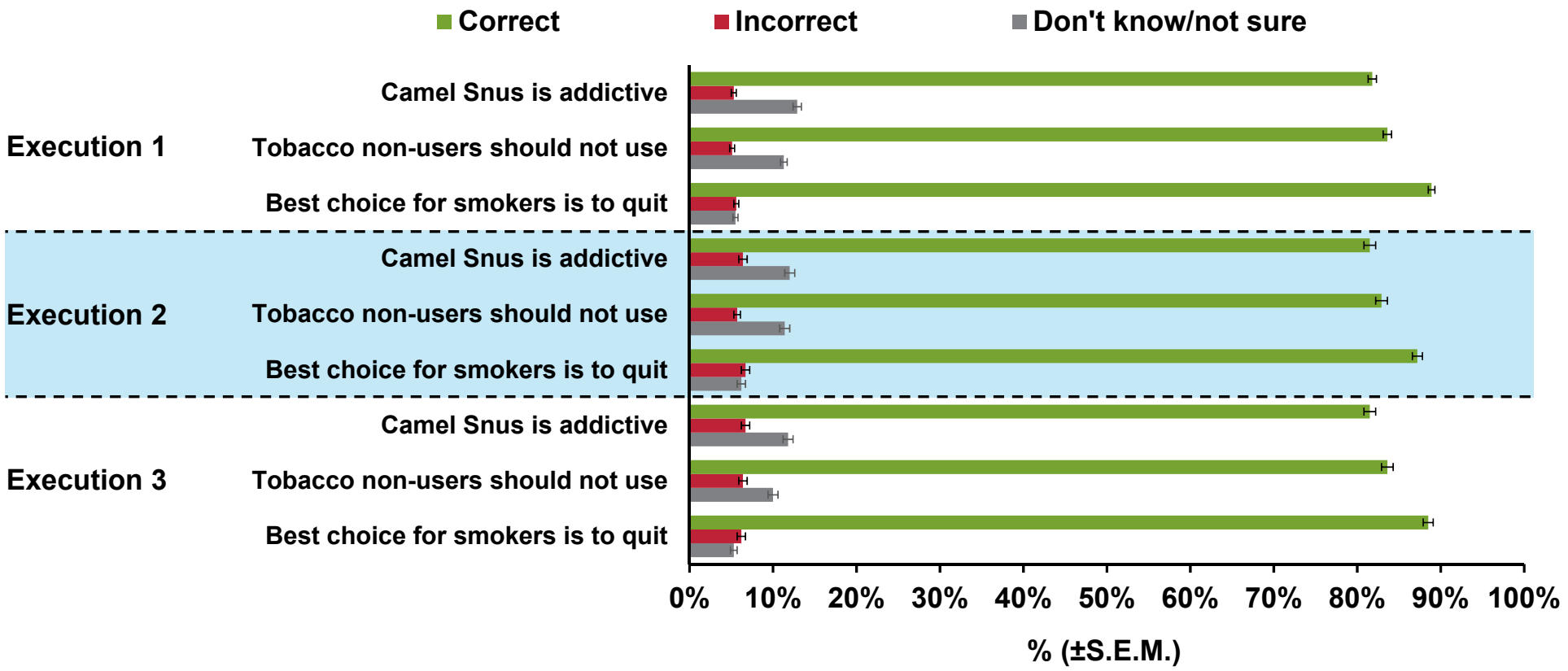
- **People understand that Camel Snus carries less risk, but still has risk**
  - Strong majority understands need to switch completely to benefit
- **Do people seeing the advertising understand that:**
  - Camel Snus is addictive
  - Non-users of tobacco should not use Camel Snus
  - The best choice for health-concerned smokers is to quit

Large Majorities Understand Balancing Information



CC-92

Large Majorities Understand Balancing Information, in All Three Executions



CC-93

Research Findings from Population Testing

- People understand that switching to Camel Snus carries less risk than smoking, but still has some risk
- **People understand the balancing statements convey that:**
  - Camel Snus is addictive
  - Non-users of tobacco should not use Camel Snus
  - The best choice for health-concerned smokers is to quit

Camel Snus Impact on Population Health Depends on Who Uses Camel Snus

- **Adoption by continuing smokers benefits population health**
- **Adoption by non-users of tobacco conveys harm**
  - Current non-users (never and former users)
  - *Expected* non-users (smokers likely to quit otherwise)
- **"Likelihood of Use" study projected use by relevant populations**

Research Questions for Population Testing

- **People understand that switching to Camel Snus carries less risk than smoking, but still has some risk**
- **People understand the balancing statements convey that:**
  - The best choice for smokers is to quit
  - Non-tobacco users should not use Camel Snus
  - Camel Snus is addictive
- **Who is likely to use Camel Snus?**

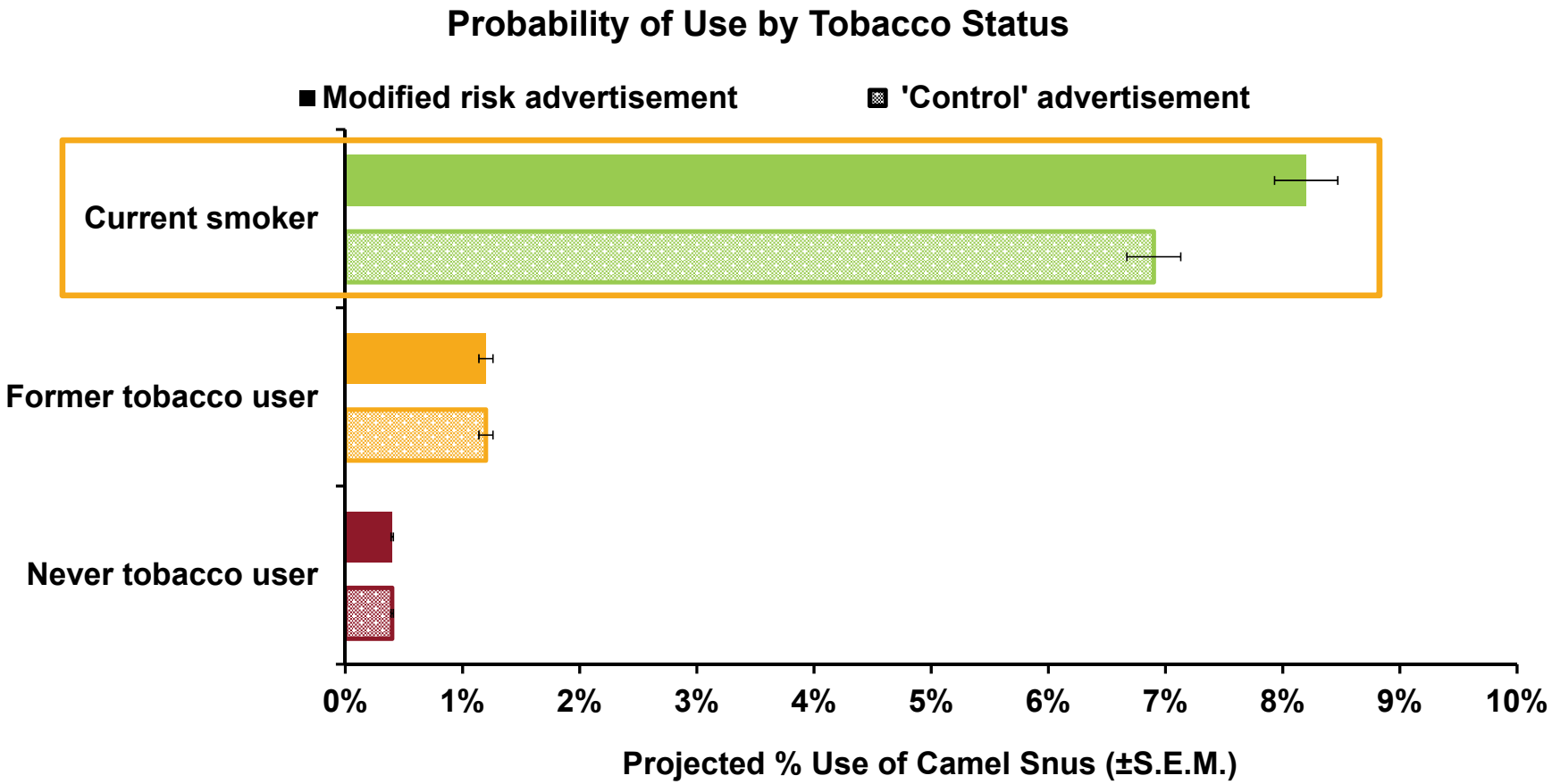
Likelihood of Use Study

- **Sample: 11,302 adults from online research panels**
  - Tobacco user status (current, former, never tobacco user) per population proportions
  - Balanced and weighted to U.S. population
- **Viewed a Camel Snus advertisement, randomized to either:**
  - Advertisement with modified risk information and balancing statements
  - Control advertisement with neither
- **Assessment**
  - Online quantitative assessment
  - Rated likelihood to purchase/use (1-10 rating)

Estimating Likelihood of Use

- **Respondents rated likelihood to purchase/use (1-10 rating)**
- **Ratings used to project probability of purchase/use, using empirically derived logistic regression algorithm**
  - Derived from prior longitudinal study connecting ratings to actual tobacco product purchase/use 9 months later
  - Algorithm includes moderators of rating→likelihood relationship

Projected Use Substantially Highest Among Current Smokers, Who are Also Differentially Attracted by Modified Risk Information



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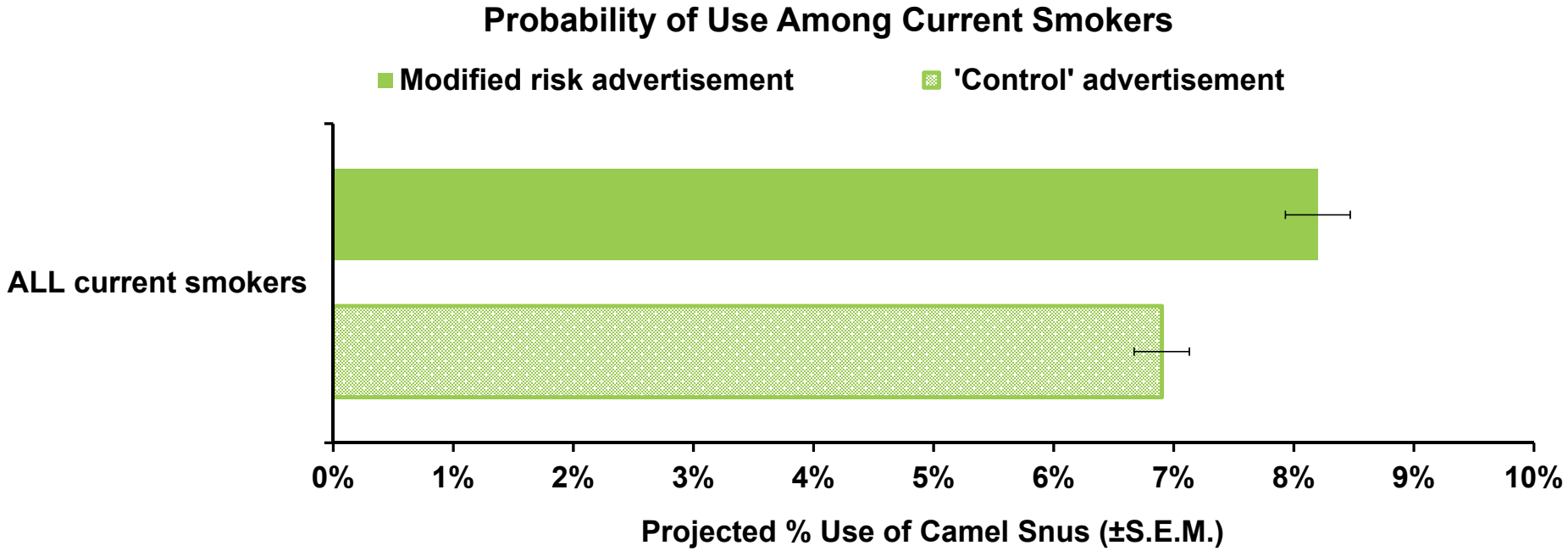
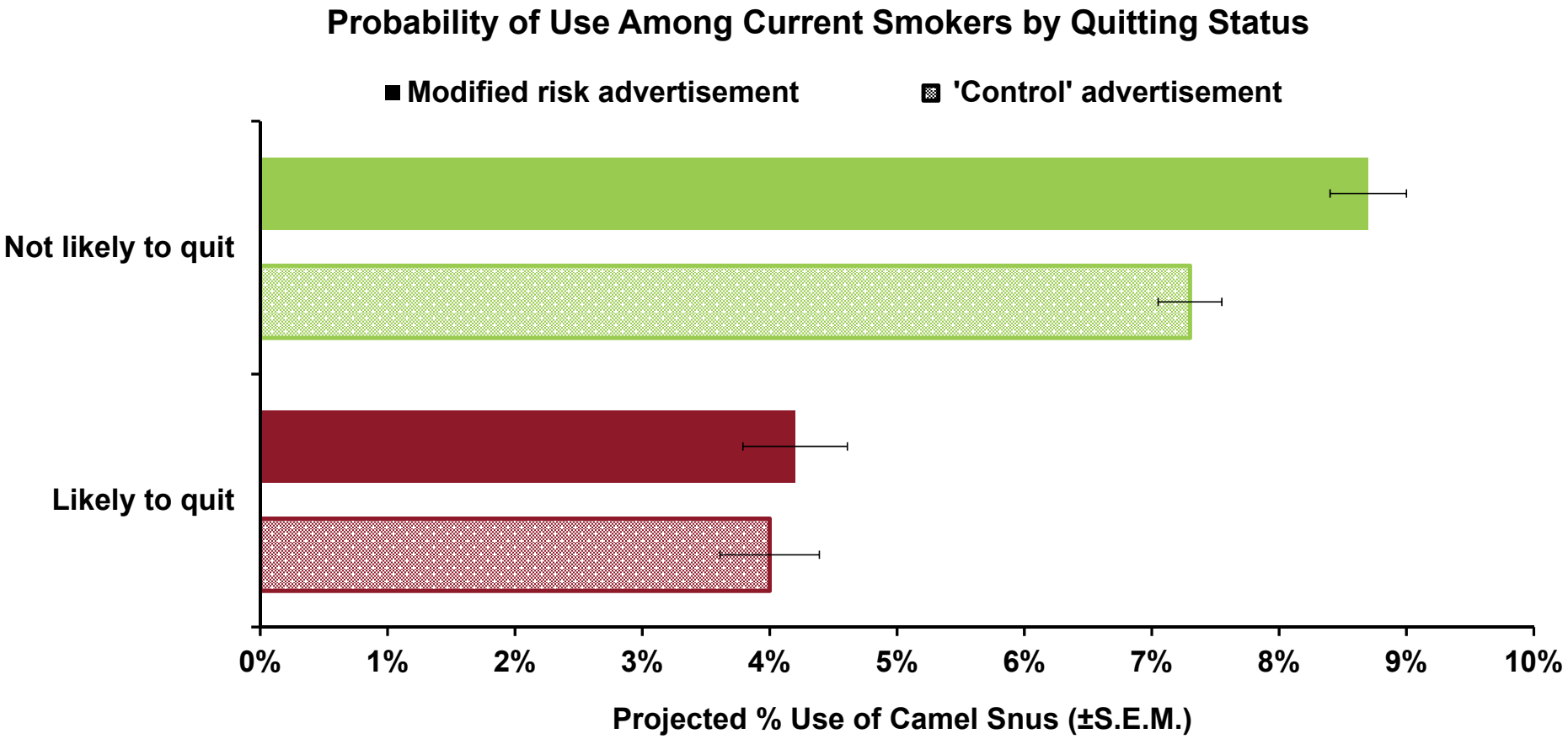
Projected Use Highest Among Current Smokers, Who are Also Differentially Attracted by Modified Risk Information



- Need to differentiate those NOT likely to quit
- Based on expected abstinence in 9 months

CC-100

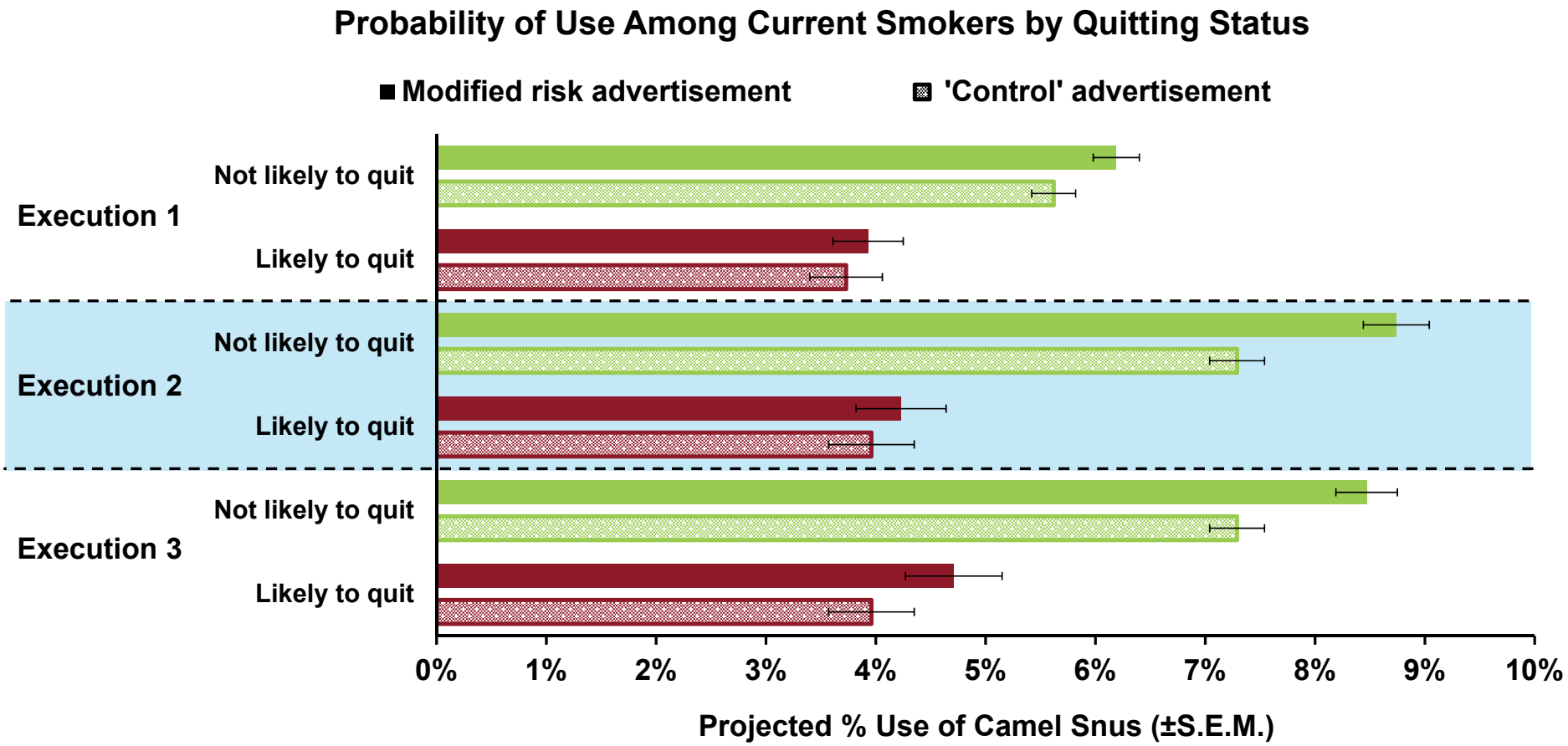
Among Current Smokers, Projected Use Highest Among Those Not Likely to Quit



'Likely to quit' = expect to be tobacco-free in 9 months

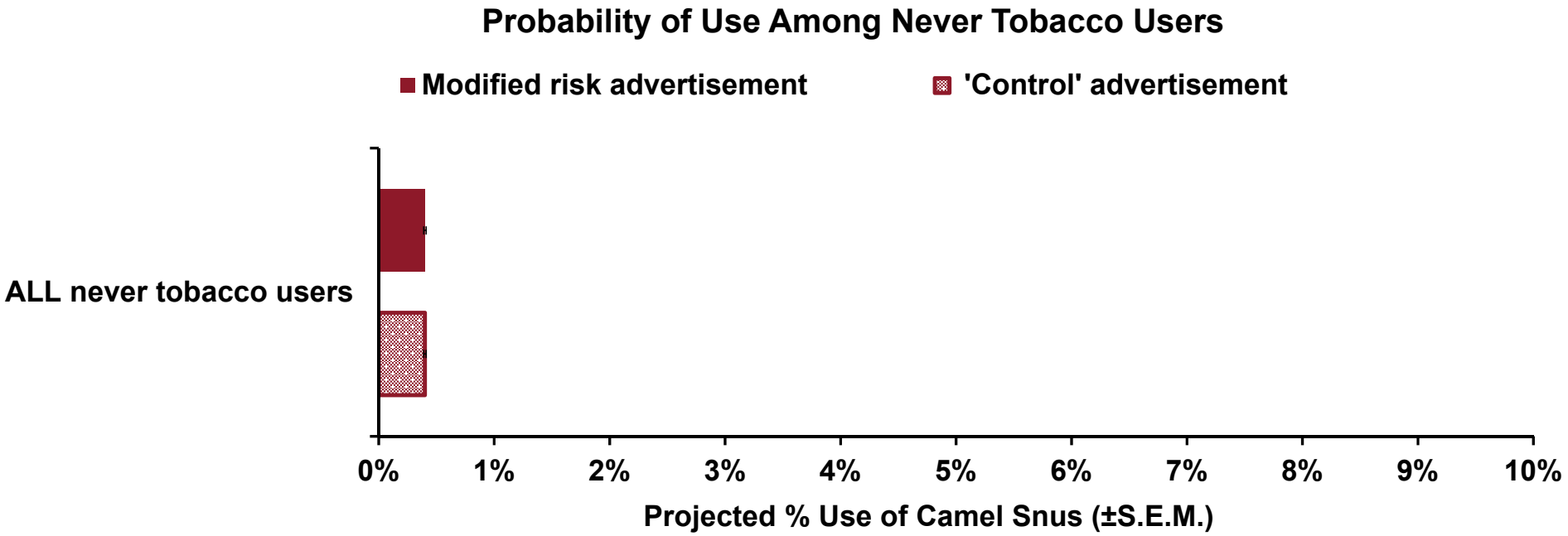
CC-101

Projected Use Highest in Current Smokers Not Likely to Quit, in All Three Executions



CC-102

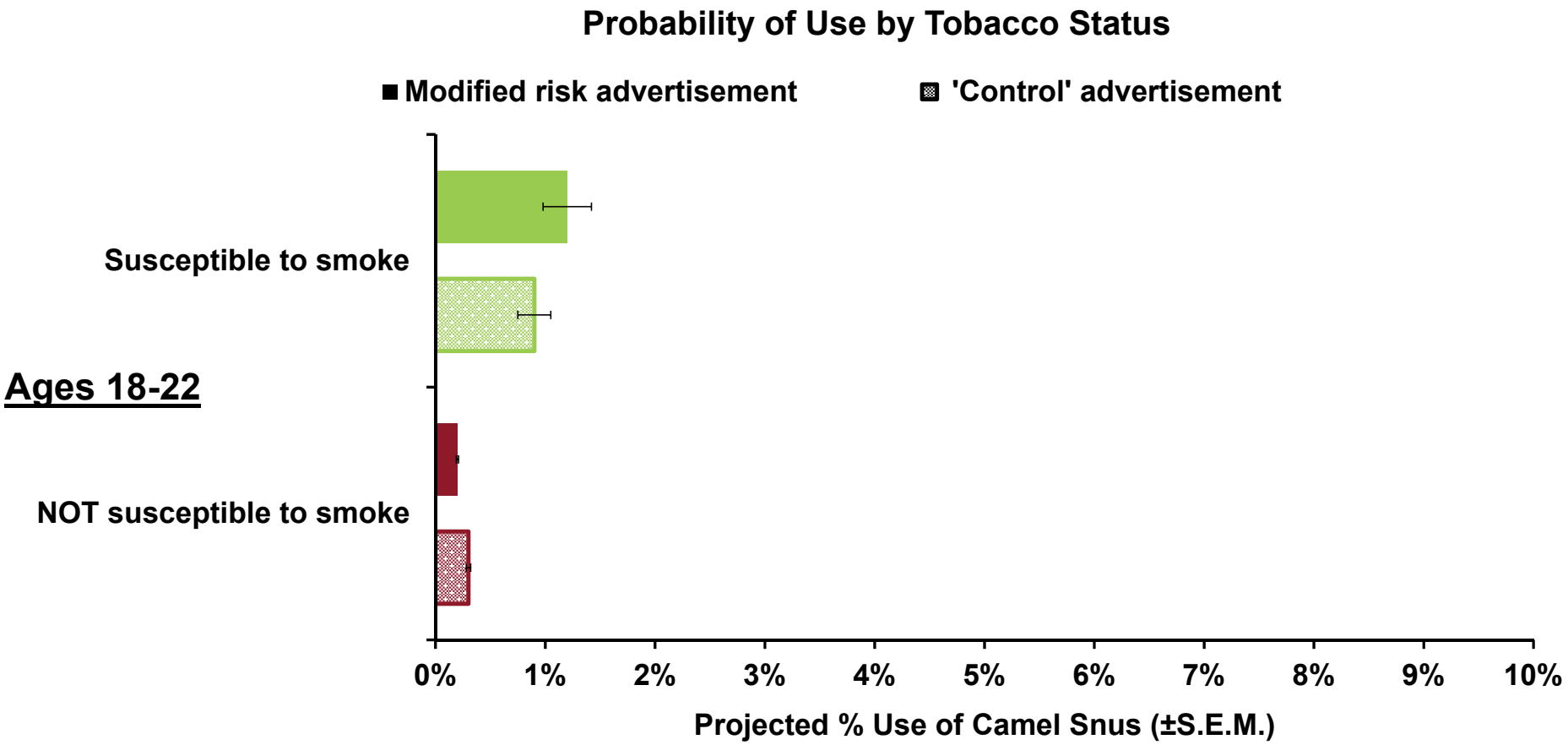
Very Low Projected Use Among Never Tobacco Users Across All Ages



- **Consider susceptibility to smoking**
  - Pierce et al.[1] measure, predicts subsequent smoking initiation

1. Pierce JP, Choi WS, Gilpin EA, Farkas AJ, Merritt RK. *Health Psychol* 1996;15(5):355-361

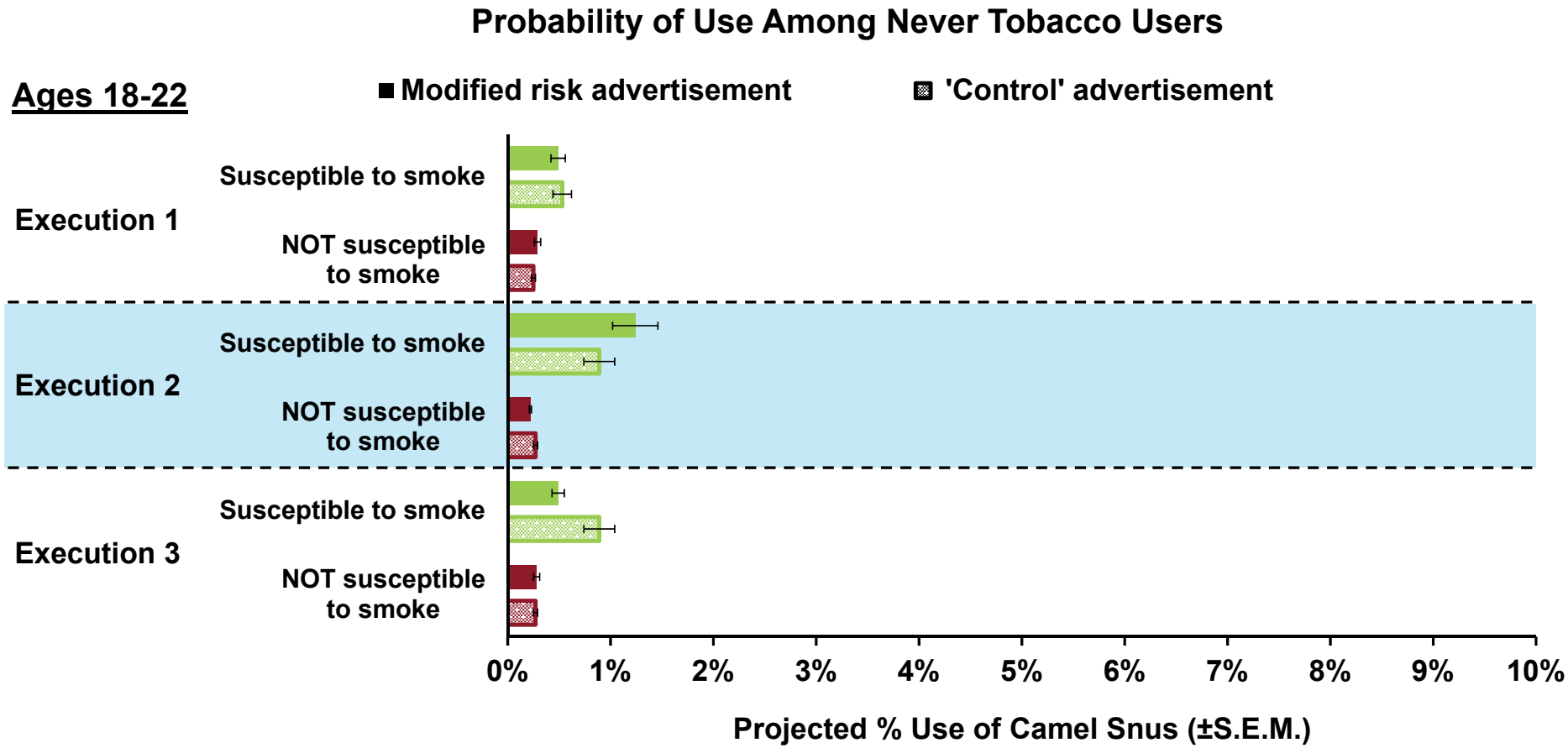
Very Low Projected Use Among Young Adult (18-22) Never Tobacco Users, Especially Those Not Susceptible to Smoking



Susceptible to smoke = potentially would smoke in next year or if offered by friend (Pierce et al., 1996)

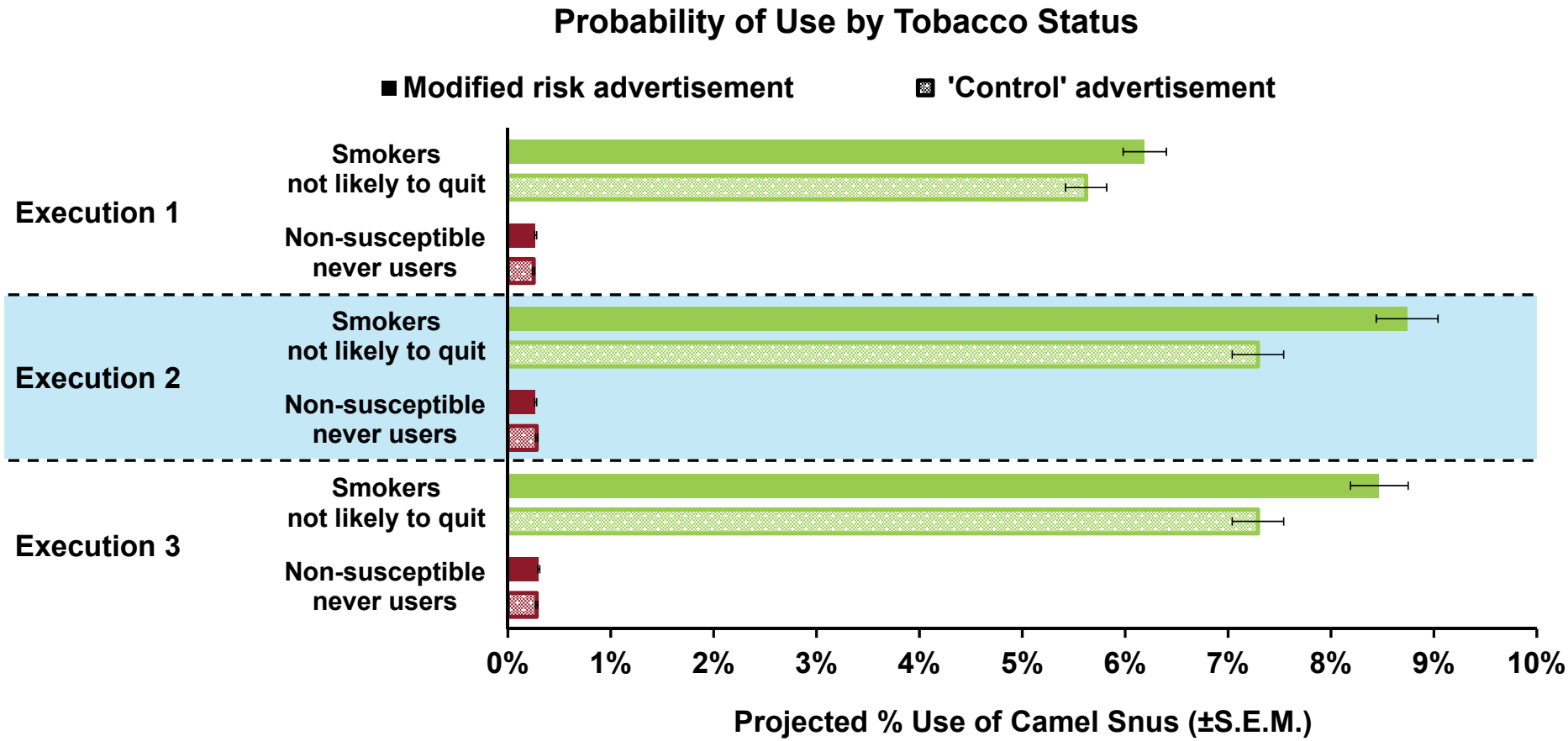
CC-104

Very Low Projected Use Among Young Adult (18-22) Never Tobacco Users Not Susceptible to Smoking, All Three Executions



CC-105

Projected Use Highest Among Continuing Smokers, Lowest Among Non-Susceptible Never Users, All Executions



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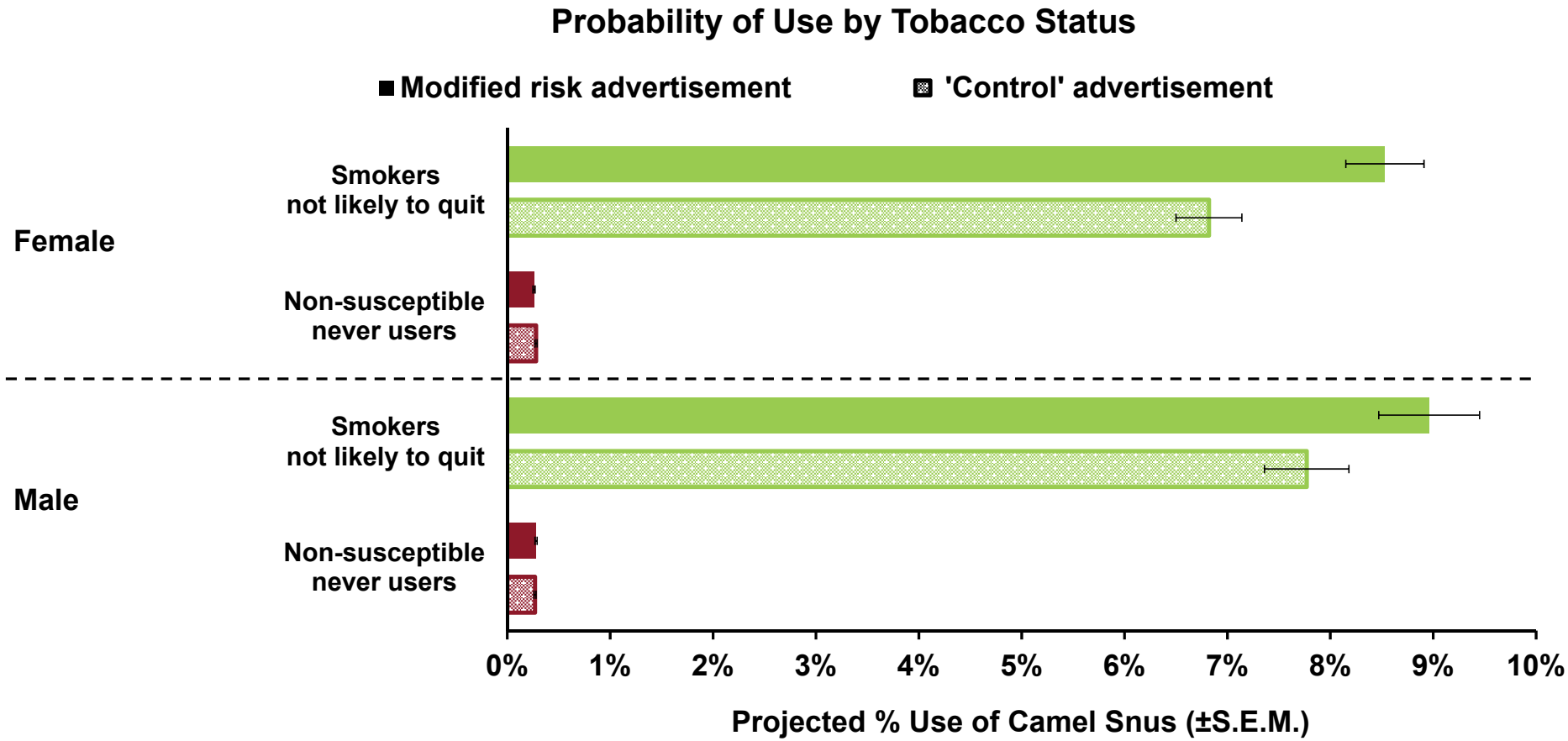
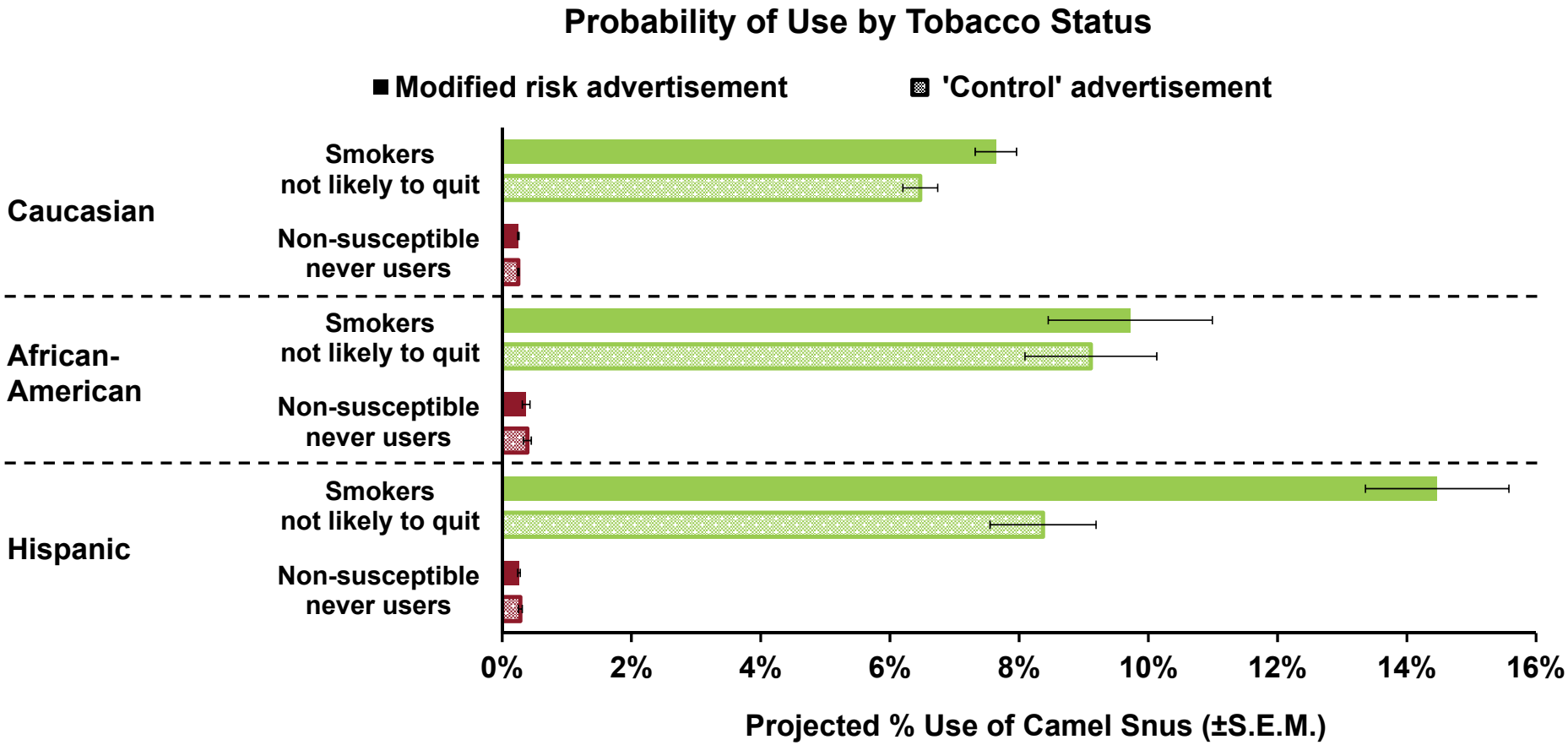
Projected Use: Continuing Smokers vs. Non-Susceptible Never Users; Women and Men



CC-107

Projected Use: Continuing Smokers vs. Non-Susceptible Never Users; Caucasian, African-American, Hispanic Individuals



CC-108

Research Findings from Population Testing

- **People understand that switching to Camel Snus carries less risk than smoking, but still has some risk**
- **People understand the balancing statements convey that:**
  - The best choice for smokers is to quit
  - Non-tobacco users should not use Camel Snus
  - Camel Snus is addictive
- **Camel Snus most likely to be used by smokers not likely to quit, who would benefit from switching**
  - Lower projected use among smokers likely to quit
  - Much lower projected use among former tobacco users
  - Almost no projected use among never tobacco users

Proposed Camel Snus Modified Risk Advertisements

- **Relative risk information is understood**
  - Reduced risk, but not *no* risk

Proposed Camel Snus Modified Risk Advertisements

- **Relative risk information is understood**
- **Balancing information is understood**
  - Snus contains nicotine and is addictive
  - Non-users of tobacco should not use snus
  - The best option for smokers is to quit

Proposed Camel Snus Modified Risk Advertisements

- **Relative risk information is understood**
- **Balancing information is understood**
- **Appeal to those who can benefit from switching to Camel Snus**
  - Smokers who would continue to smoke, more than smokers likely to quit
  - Very low appeal to those not using tobacco

Proposed Camel Snus Modified Risk Advertisements

- **Relative risk information is understood**
- **Balancing information is understood**
- **Appeal to those who can benefit from switching to Camel Snus**
- **Statistical modeling integrates rates of projected use by relevant populations**

Proposed Camel Snus Modified Risk Advertisements

- Relative risk information is understood
- Balancing information is understood
- Appeal to those who can benefit from switching to Camel Snus
- Statistical modeling integrates rates of projected use by relevant populations
- Camel Snus with modified risk information is likely to benefit population health

Population Health Benefit Projected for Camel Snus with Modified Risk Advertising

Results from Statistical Modeling

Geoffrey Curtin, PhD

Senior Director, Scientific & Regulatory Affairs
RAI Services Company

CC-115

Modeling Camel Snus as Modified Risk Product

- **Modeling estimates overall health effect for full population by following multiple cohorts over time**
  - Accounts for both beneficial and harmful changes in use patterns by tobacco users and non-users
  - Integrates evidence on changes in use and health consequences of those changes to estimate effect on population mortality

Camel Snus Modeling Projects Overall Benefit

- **Projects ~350,000 to ~450,000 additional survivors for population as a whole**
- **Direction and magnitude of population effect provides high confidence in benefit**

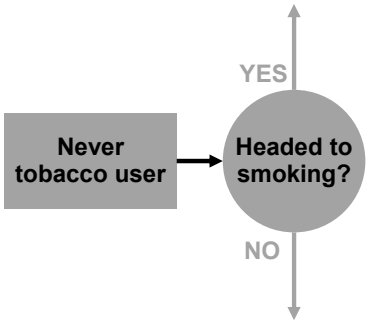
High Confidence in Population Health Benefit

- **Modeling projects population health benefit for Camel Snus with modified risk advertising**
  - Uses validated model
  - Accounts for all unintended, harmful changes in tobacco use
  - Relies on empirically derived model inputs
  - Includes sensitivity testing

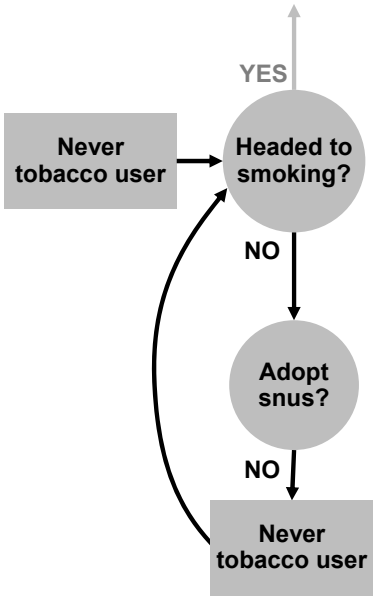
Modeling Based on Cohort Framework

- **Dynamic Population Modeler uses cohort framework to compare projected number of survivors for two scenarios**
  - 'What currently is' (simplified base case; cigarette use only)
  - 'What could be' (counterfactual; cigarette and/or Camel Snus use)
- **Mortality tracked across 5-year age intervals through age 102, then contrasted through age 72 to project differences**
  - Changes in tobacco use may occur for scenarios at each 5-year age interval

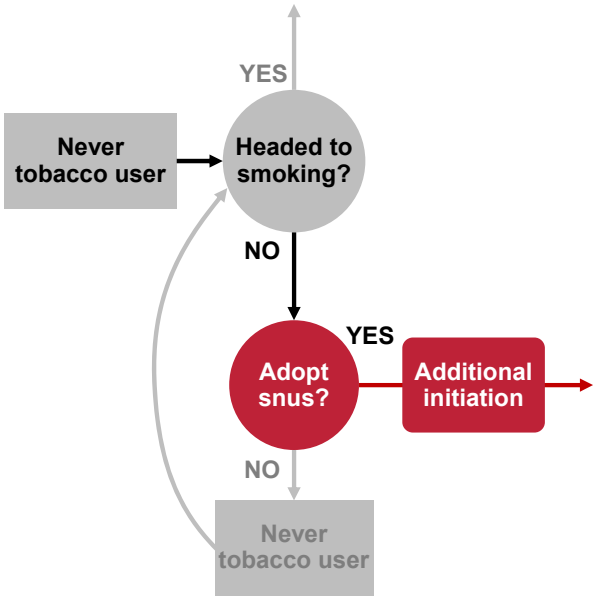
Full Accounting of Behaviors for Never Users



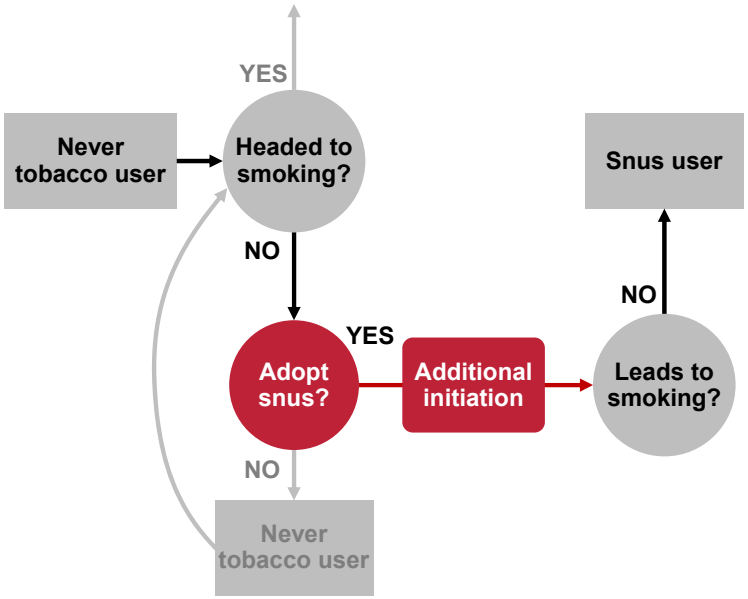
Full Accounting of Behaviors for Never Users



Full Accounting of Behaviors for Never Users



Full Accounting of Behaviors for Never Users



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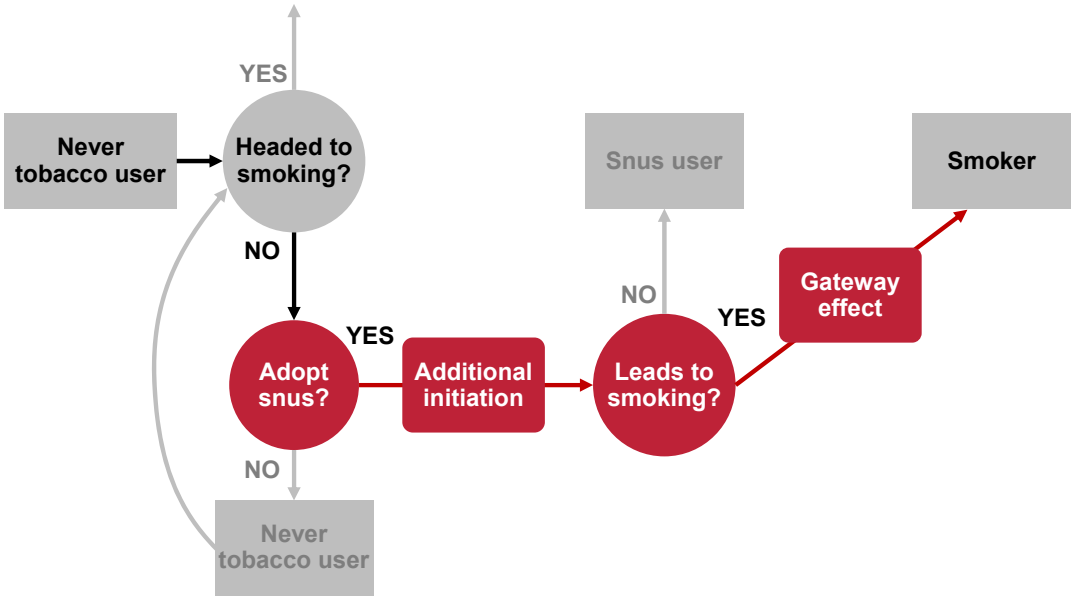

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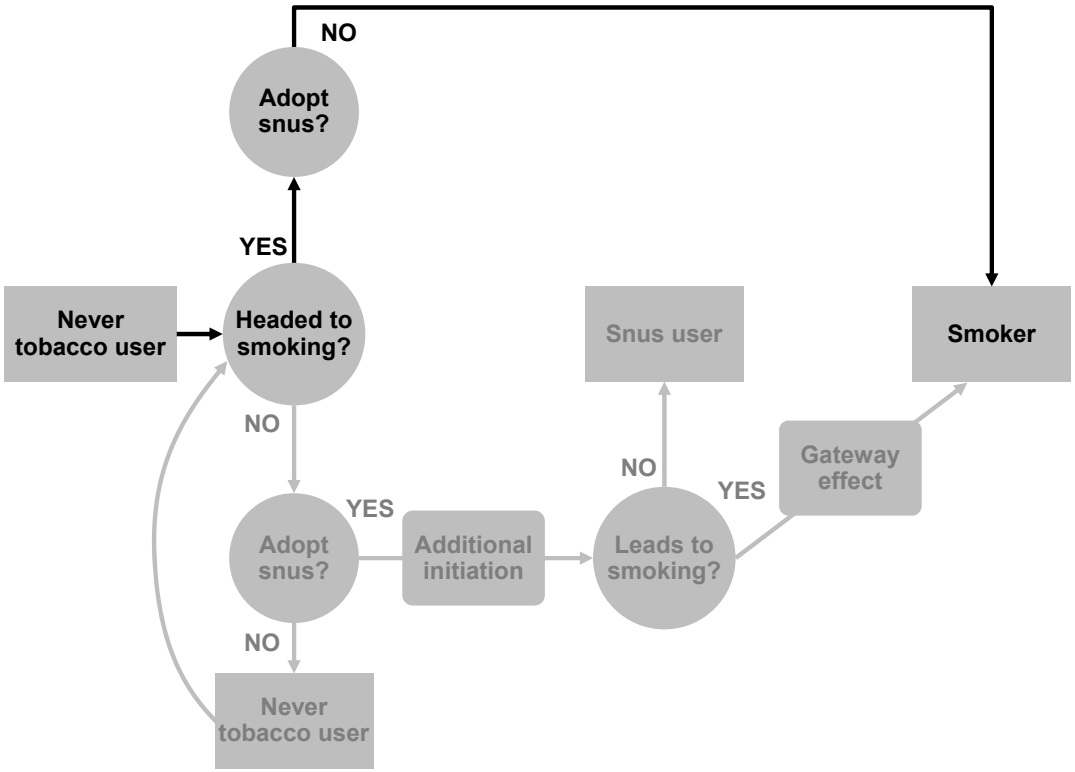

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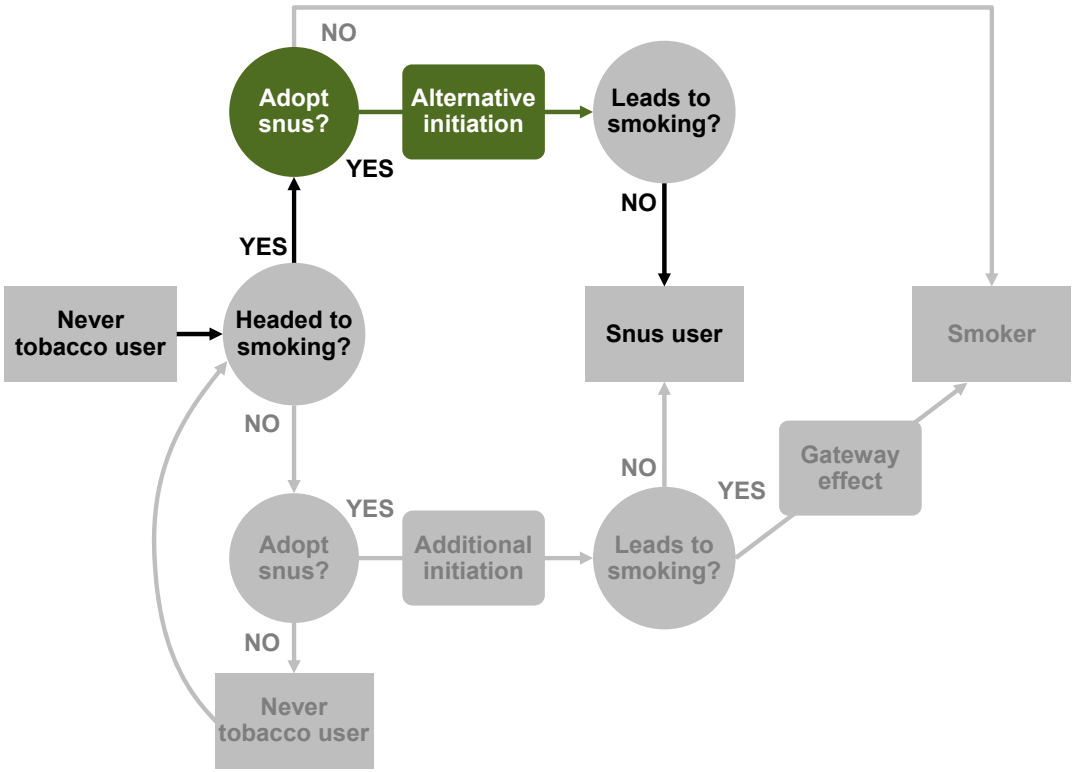
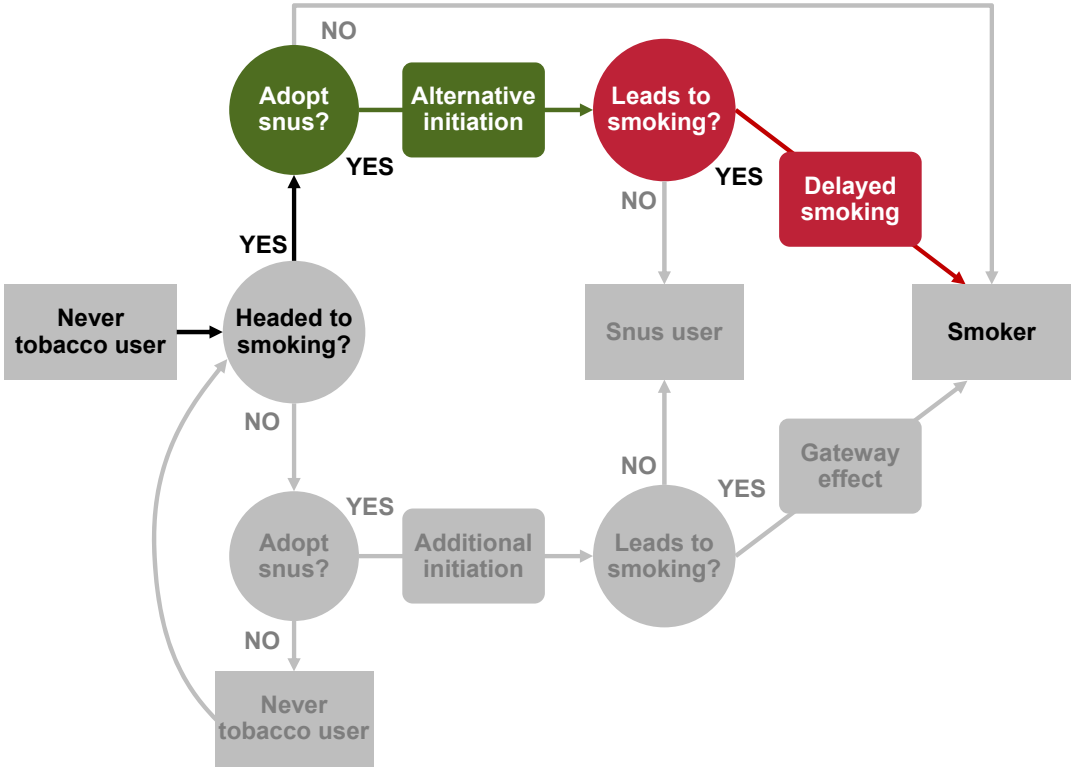
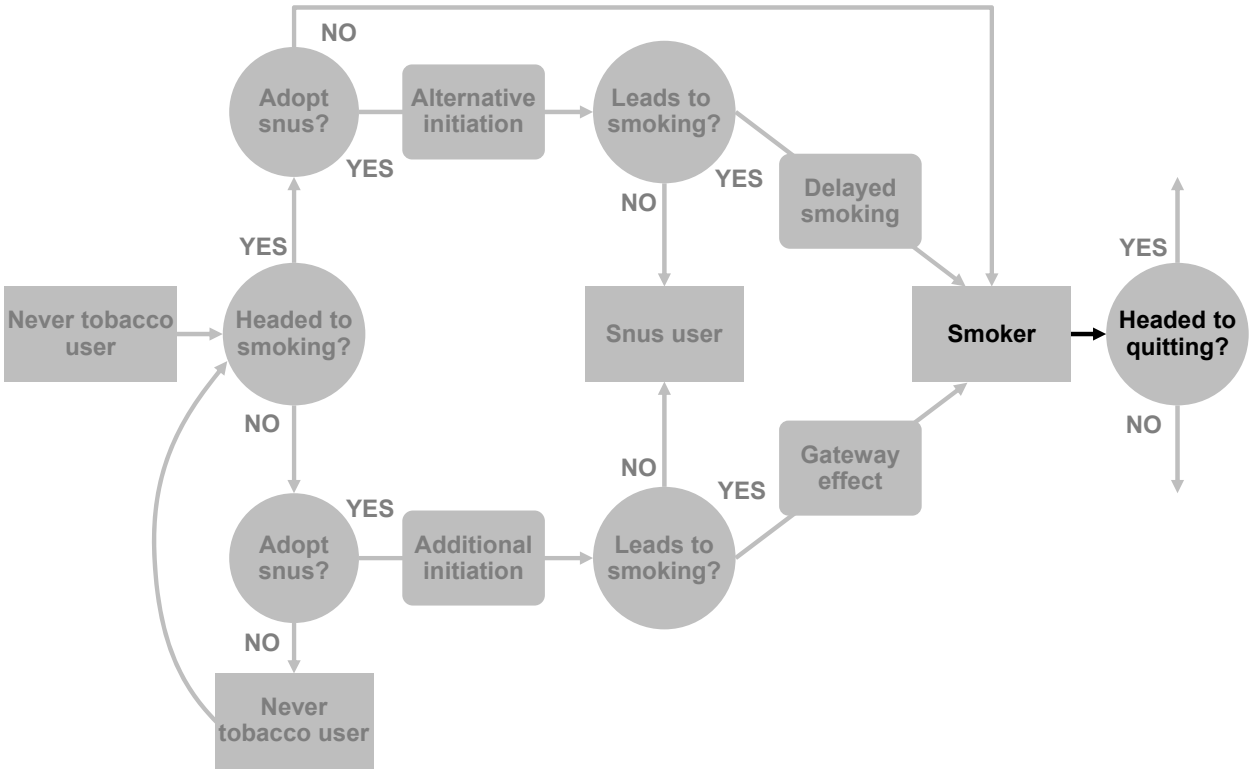


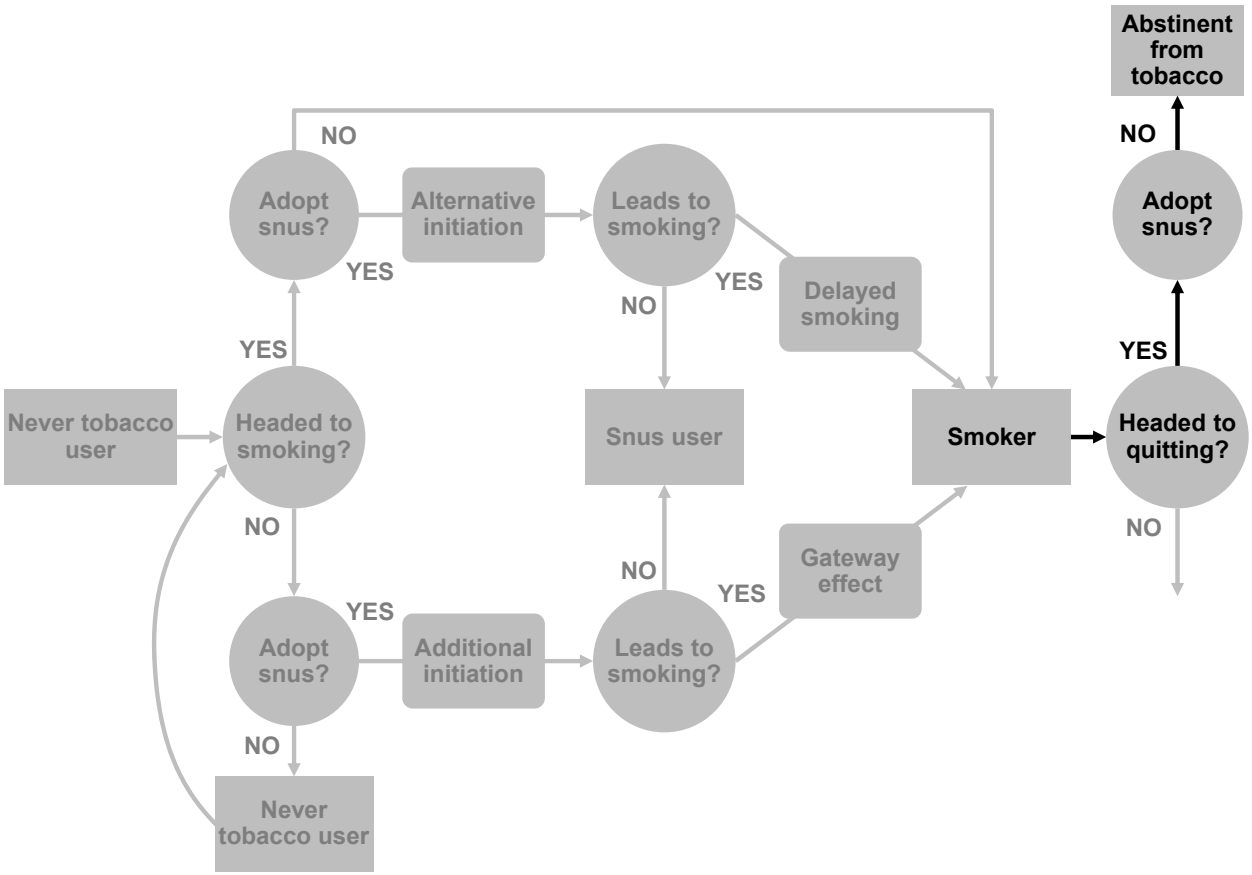
Full Accounting of Behaviors for Never Users



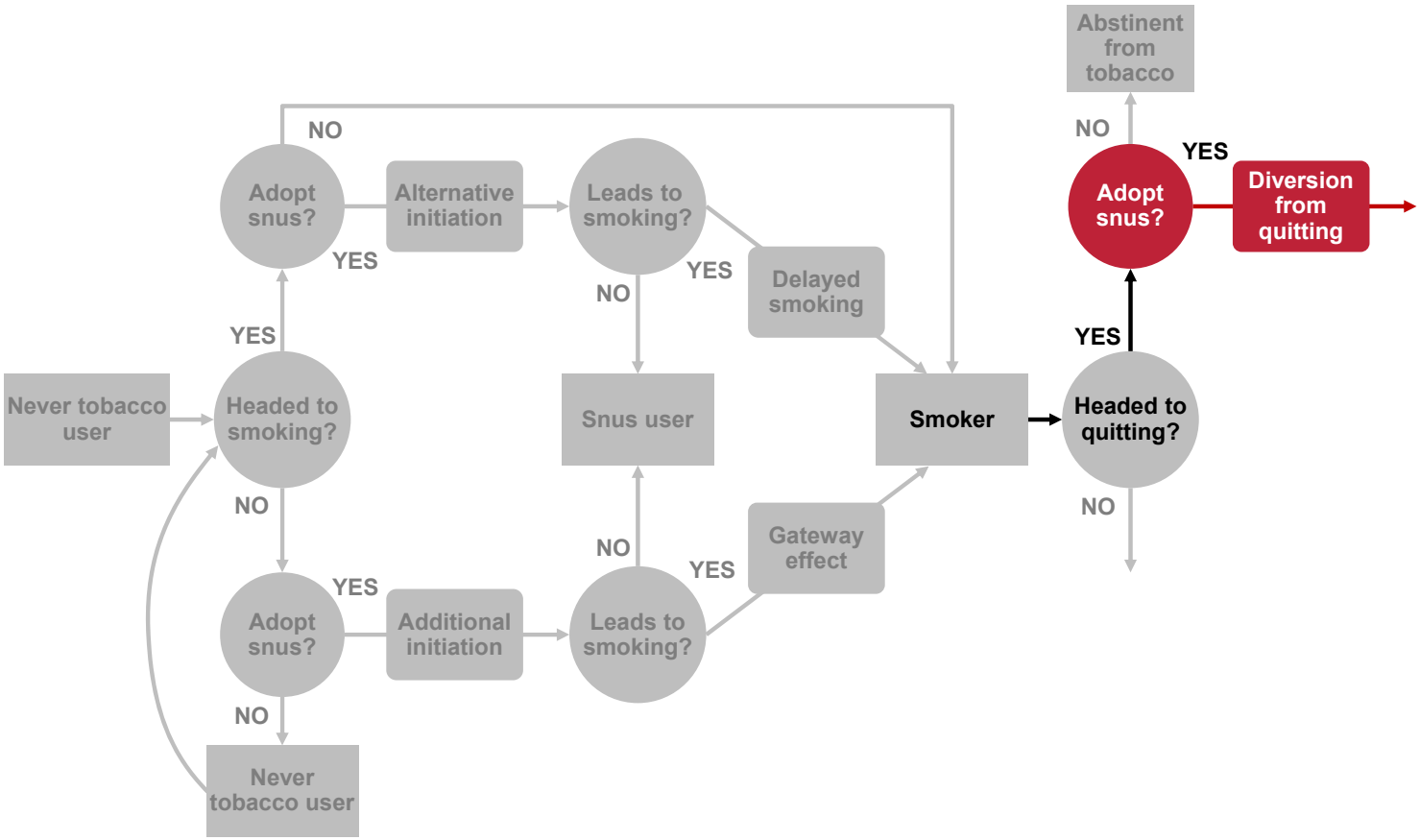
Full Accounting of Behaviors for Smokers



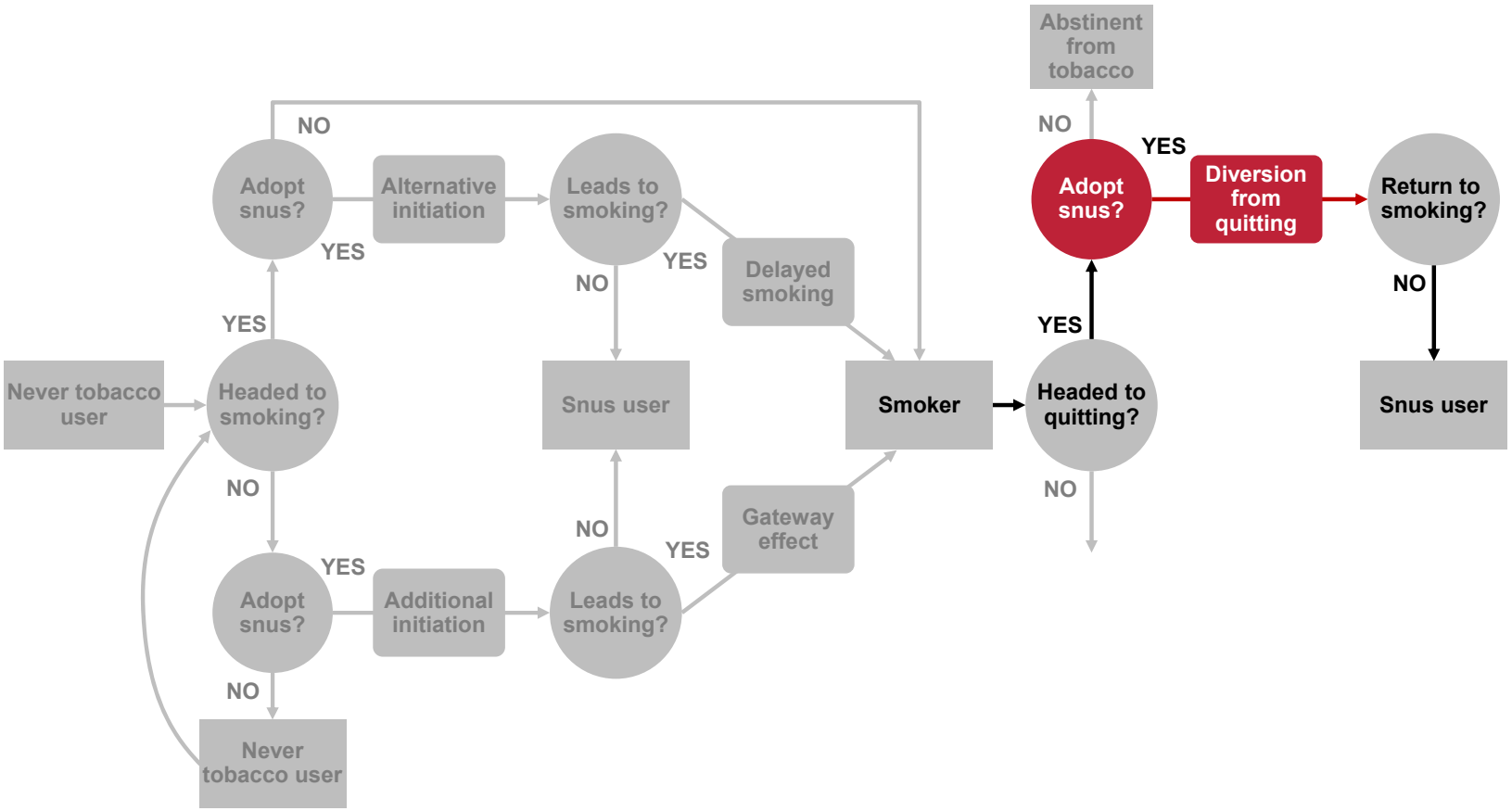
Full Accounting of Behaviors for Smokers



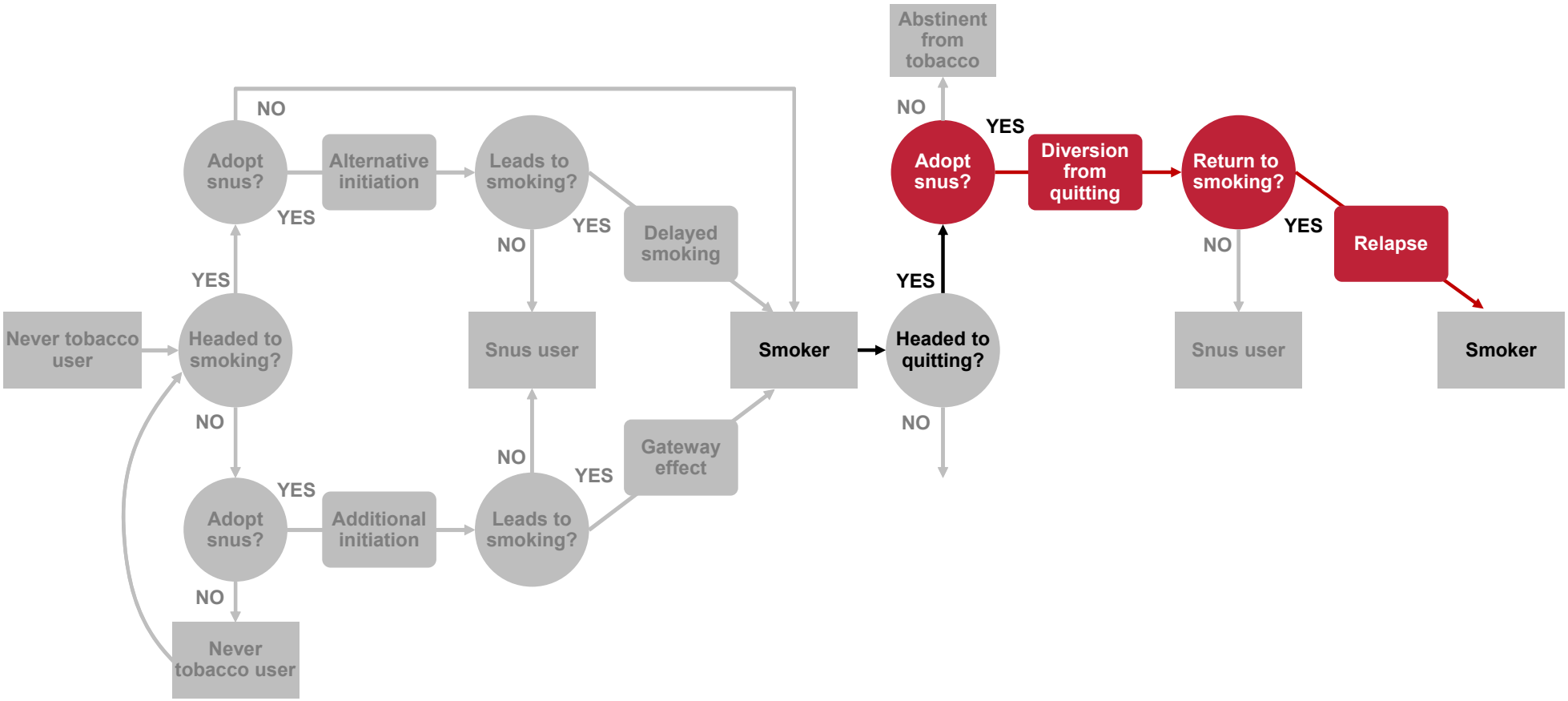
Full Accounting of Behaviors for Smokers



Full Accounting of Behaviors for Smokers

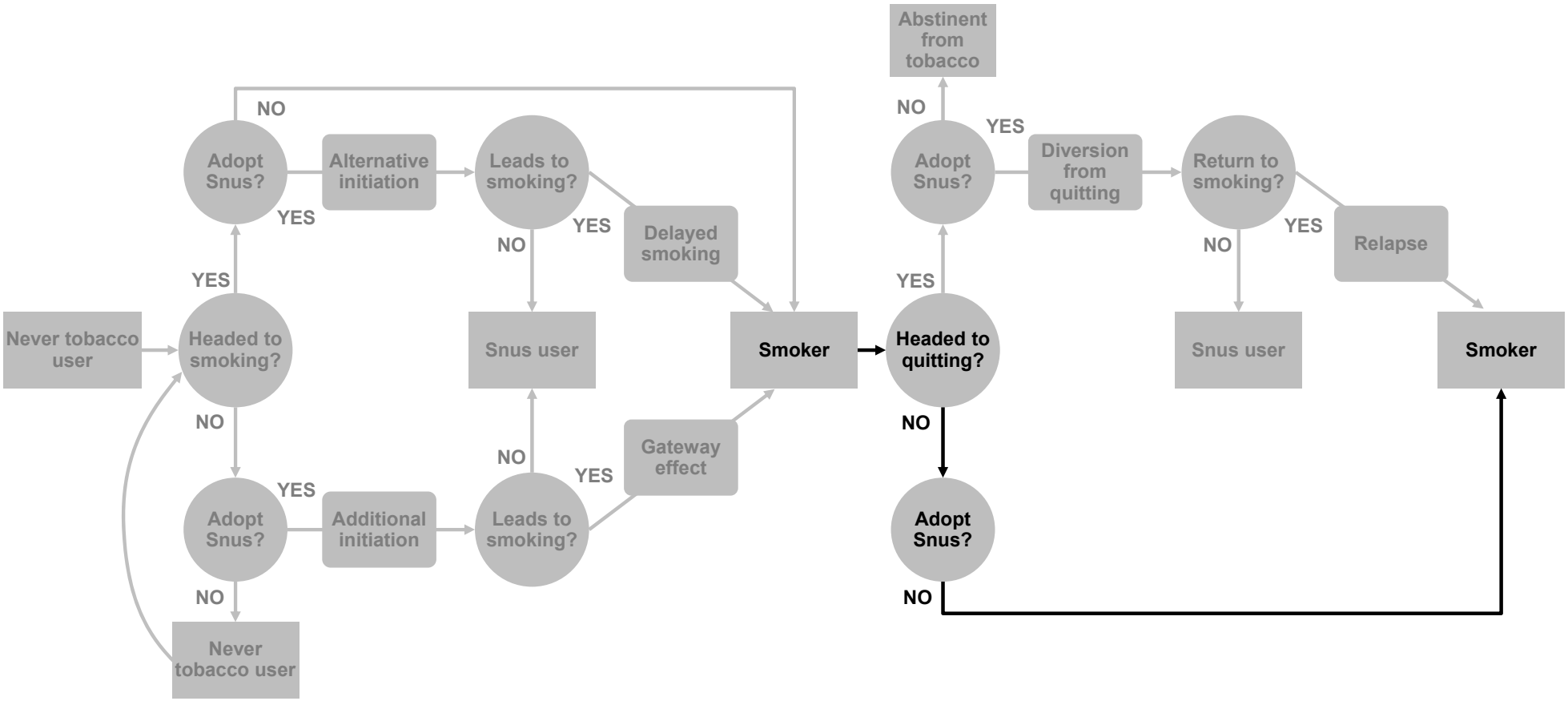


Full Accounting of Behaviors for Smokers



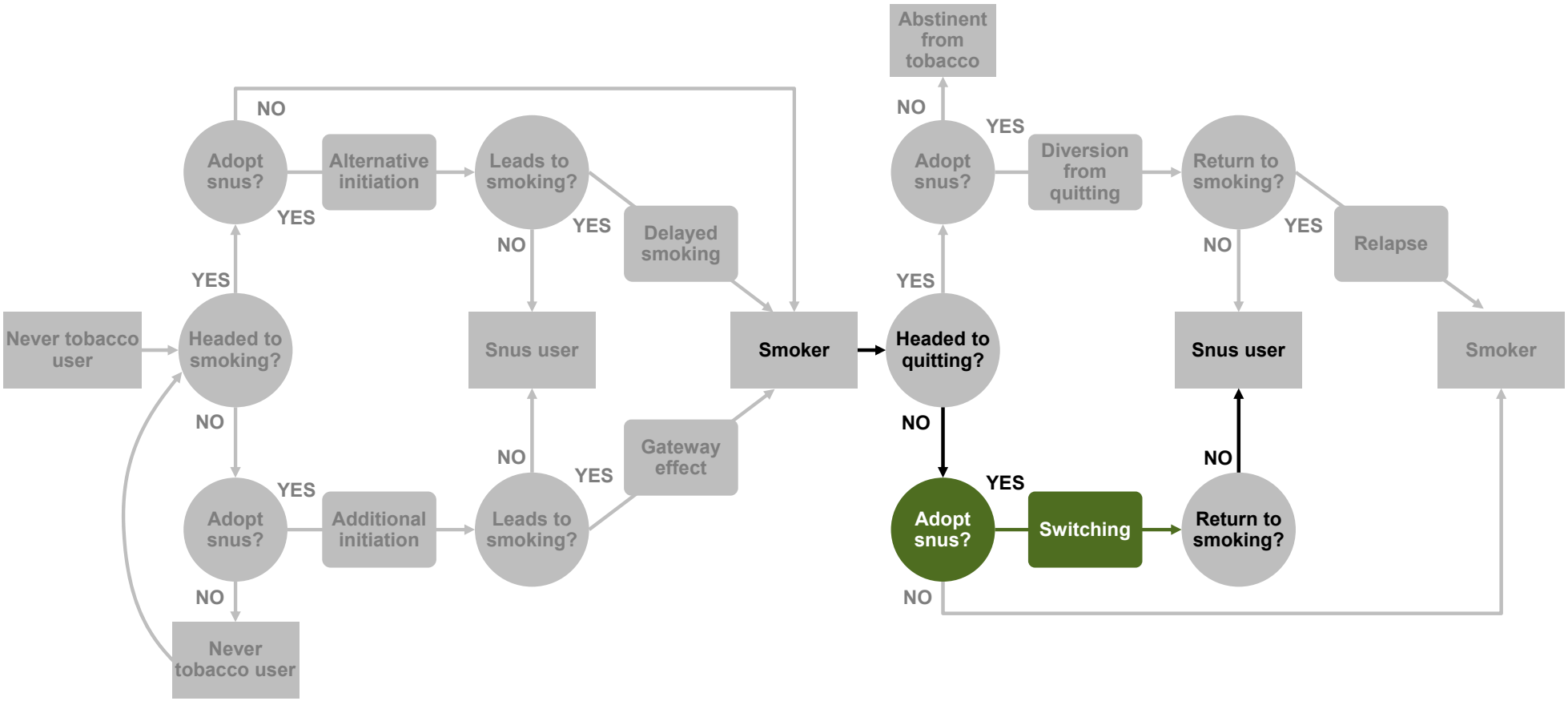
CC-132

Full Accounting of Behaviors for Smokers



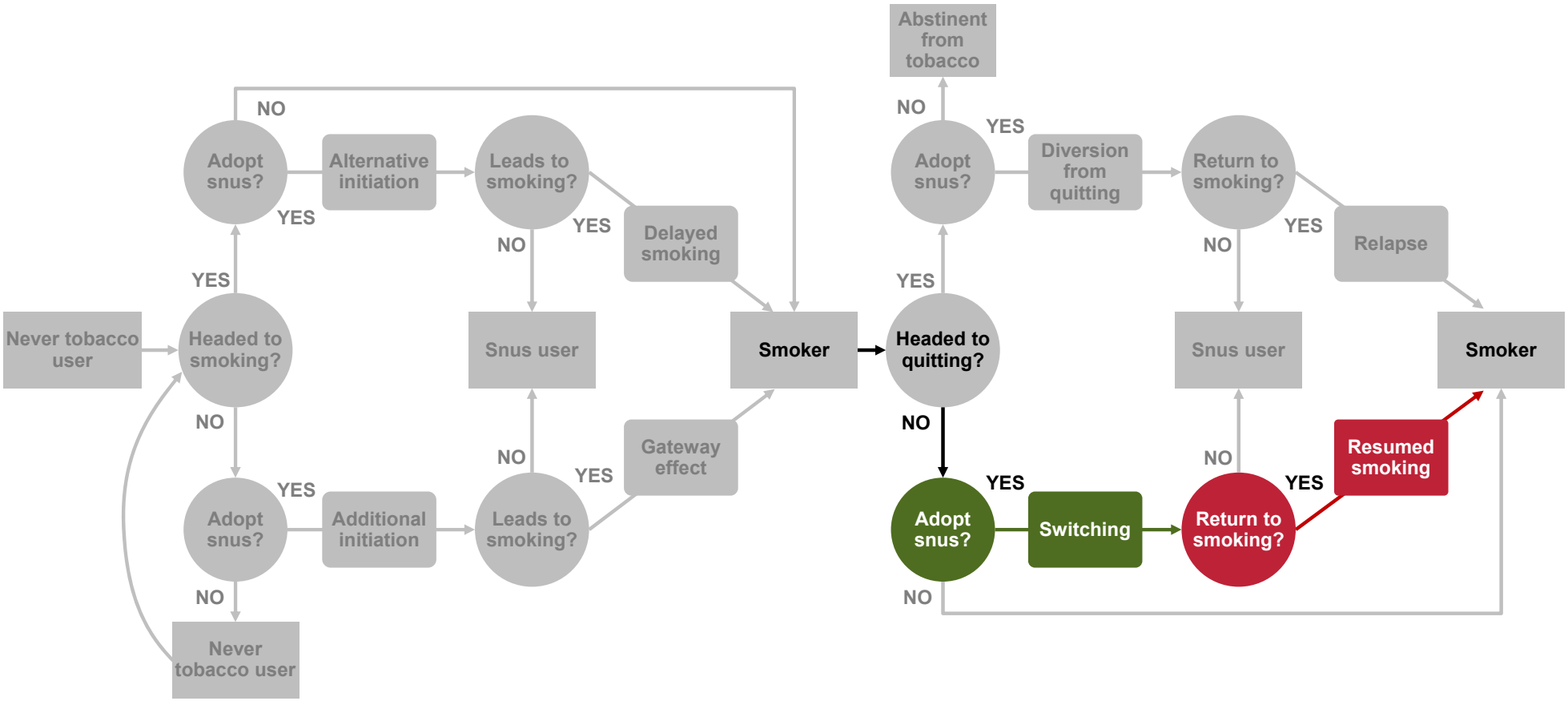
CC-133

Full Accounting of Behaviors for Smokers



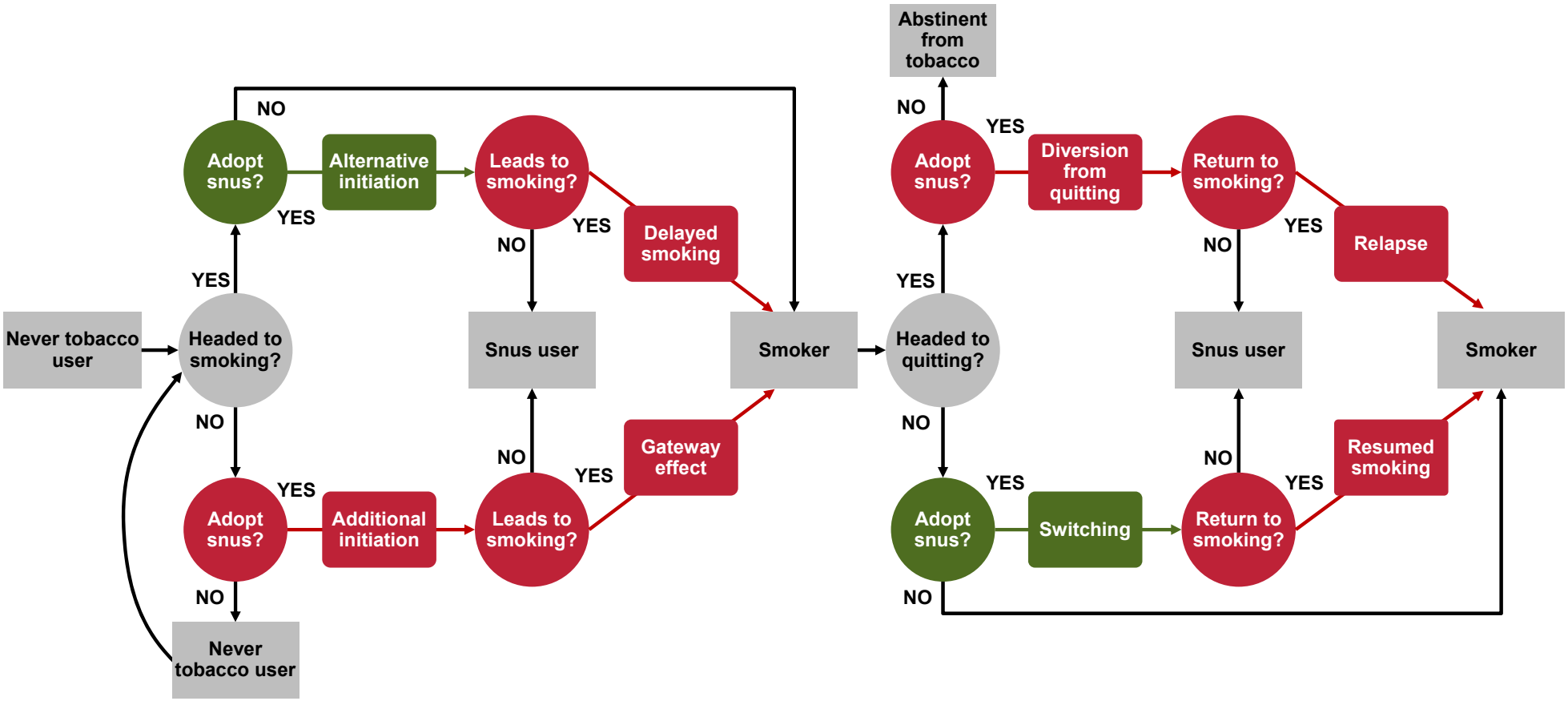
CC-134

Full Accounting of Behaviors for Smokers



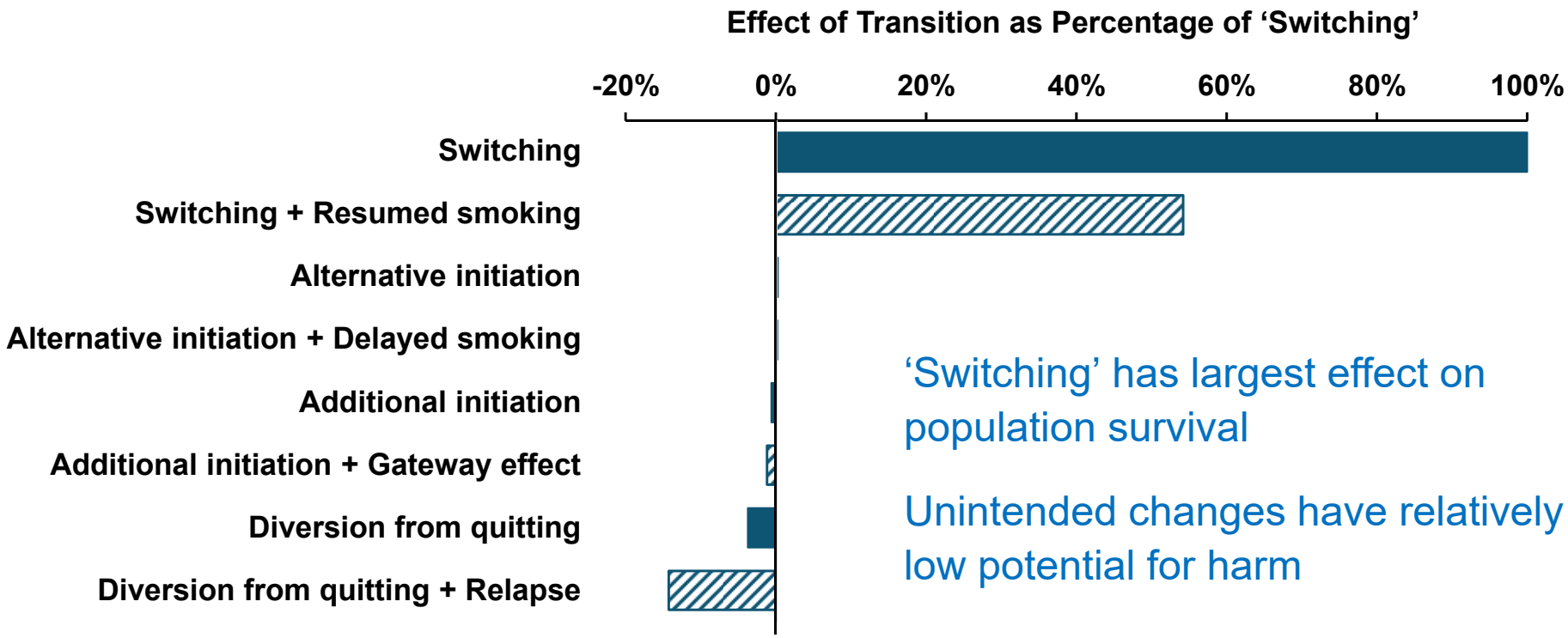
CC-135

Full Accounting of All Harmful Behaviors



CC-136

Key Driver of Population Effect is Switching



'Switching' has largest effect on population survival

Unintended changes have relatively low potential for harm

Empirically Derived Model Inputs

	Model Inputs	Supporting Source Data
Mortality rates Each 5-year interval (current age, duration of tobacco use, duration of quit)	Cigarette smoking	Kaiser-Permanente Cohort Study
	Camel Snus use	Levy et al. (2004) evidence synthesis (89% and 92% risk reduction)
Transition probabilities Changes in tobacco use may occur at each 5-year age interval	Cigarette smoking	U.S. initiation/cessation rates (NSDUH)
	Camel Snus use	Age-interval-specific probabilities from 'likelihood of use' testing
	Camel Snus use to smoking	*Hypothetical* probabilities (50% of snus users)

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Sensitivity Testing of Primary Inputs

- **Projected benefit of ~350,000 to ~450,000 additional survivors sensitive to model inputs**
  - Reducing empirical projections for use of Camel Snus by 75% still provides benefit of ~95,000 to ~120,000 additional survivors

Sensitivity Testing of Primary Inputs

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  - Reducing empirical projections for use of Camel Snus by 75% still provides benefit of ~95,000 to ~120,000 additional survivors
  - Risk reduction for snus of ≥53% compared to smoking still provides benefit

Overall Population Health Benefit for Camel Snus

- **High confidence in modeling that projects overall population health benefit**
  - Uses validated model
  - Accounts for unintended, harmful changes in tobacco use
  - Relies heavily on empirically derived model inputs
  - Includes sensitivity testing

Overall Population Health Benefit for Camel Snus

- **Multiple cohort modeling based on empirical probabilities of use projects ~350,000 to ~450,000 additional survivors**
- **Projected benefit makes it highly likely that Camel Snus with modified risk advertising will benefit public health**

Conclusions

Michael Ogden, PhD

Senior Vice President, Scientific & Regulatory Affairs
RAI Services Company

CC-145

Benefits of Advertising Camel Snus as an MRTP

- **Smokers who switch completely can greatly reduce their risk for four smoking-related diseases:**
  - **Lung cancer**
  - **Oral cancer**
  - **Respiratory disease**
  - **Heart disease**
- **Authorization of the proposed advertising is highly likely to yield a significant net public health benefit**

Risk Perception and Likelihood of Use

- **'Balancing information' in the ads effective, with majority of subjects understanding that:**
  - No tobacco product is safe
  - Camel Snus still presents some risk
  - Camel Snus is addictive
  - The best option for smokers is to quit completely
- **Ads appealed most to smokers who are not likely to quit**
  - Comparatively low likelihood of use among former smokers and never smokers

Postmarket Surveillance

- **We will work with FDA to develop and implement a robust postmarket surveillance program**
- **We will immediately share information of concern with the Agency and will file mandated annual reports**
- **There are strong safeguards built into the MRTP process**
  - FDA has authority to rescind authorization if warranted
  - MRTP order must be renewed after FDA-designated time frame

Camel Snus Meets MRTP Requirements

Epidemiologic data
Human biomarker data
Preclinical toxicology
Product analyses
Marketing impact
Projected behavior
Population modeling
Postmarket surveillance

- **Significantly reduces individual risk of:**
  - Lung cancer
  - Respiratory disease
  - Oral cancer
  - Heart disease
- **Overall population benefit**

Overall Conclusion

Authorizing the modified risk messaging for Camel Snus is a scientifically sound step toward significantly reducing the harm caused by cigarettes for individuals and the population as a whole.

Additional Experts

Michael Borgerding, PhD

Vice President, Scientific & Regulatory Affairs,
RAI Services Company

Camel Snus

Michael Polster, PhD

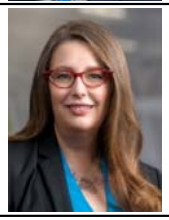
Senior Vice President, Health & Life Sciences
Naxion Research Consulting

Consumer research

Rachael Claxton

Vice President, Consumer Marketing
Reynolds Brands Inc.

Marketing



Sandra Sulsky, MPH, PhD

Principal
Ramboll US

Population modeling

Dan Heck, PhD, DABT, ATS

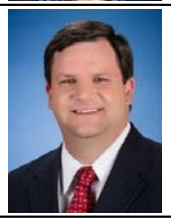
Principal Scientist, Scientific & Regulatory Affairs,
RAI Services Company

Clinical and pre-clinical research

Aaron Williams, PhD

Senior Vice President, Research & Development
RJ Reynolds Tobacco Company

Camel Snus product development



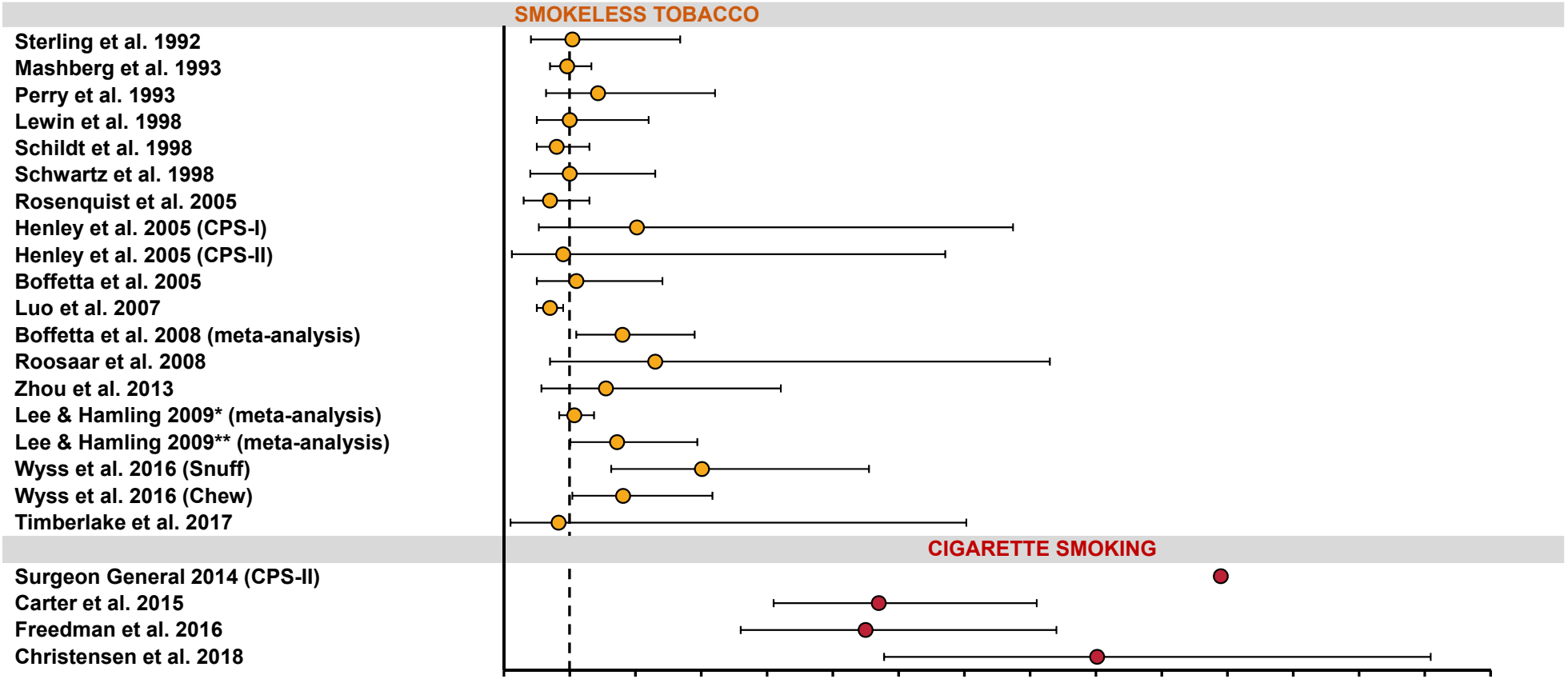
Jack Henningfield, PhD

- Vice President, Research, Health Policy, and Abuse Liability, Pinney Associates
- Professor (Adjunct), Behavioral Biology, The Johns Hopkins University School of Medicine

Abuse liability

Sponsor slides shown during Q&A: September 13, 2018

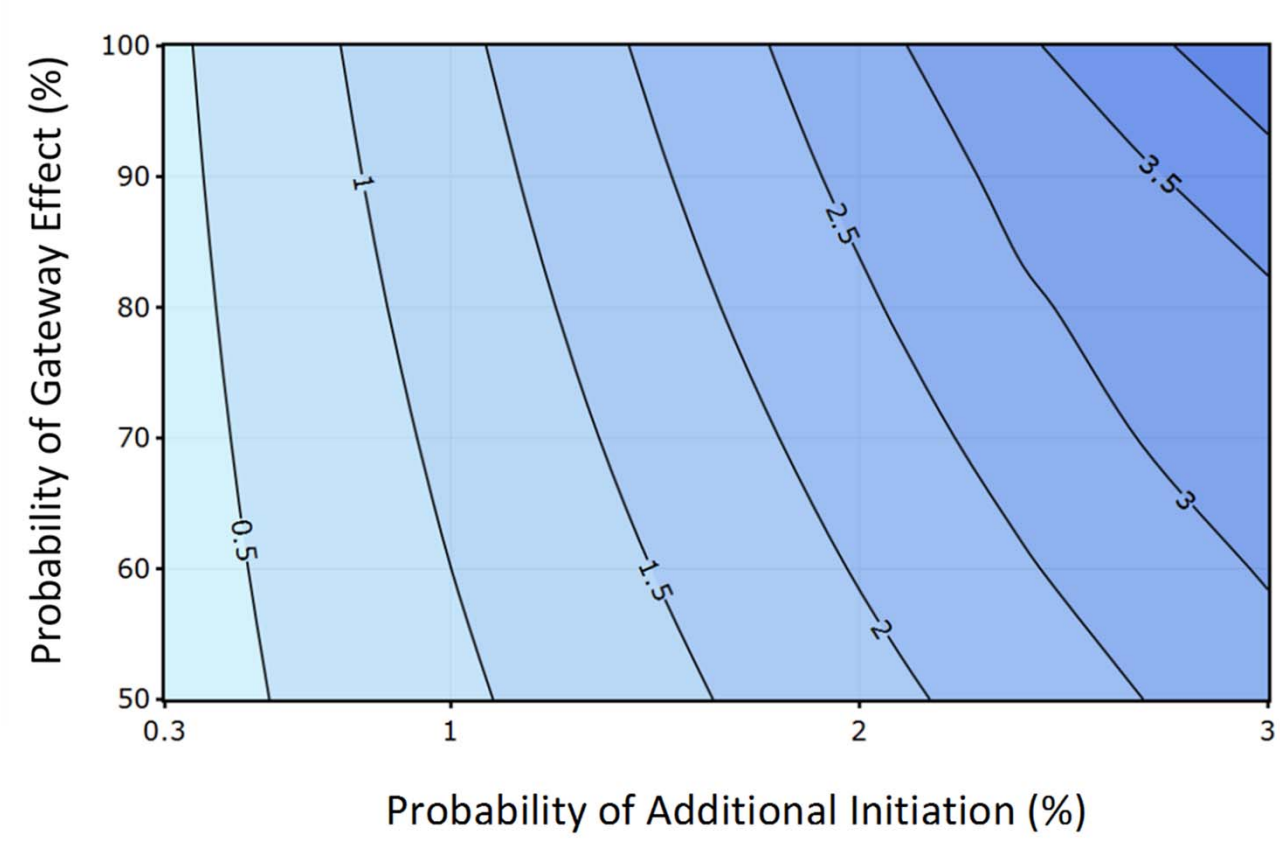
Oral Cancer:
Smokeless Tobacco vs. Cigarette Smoking



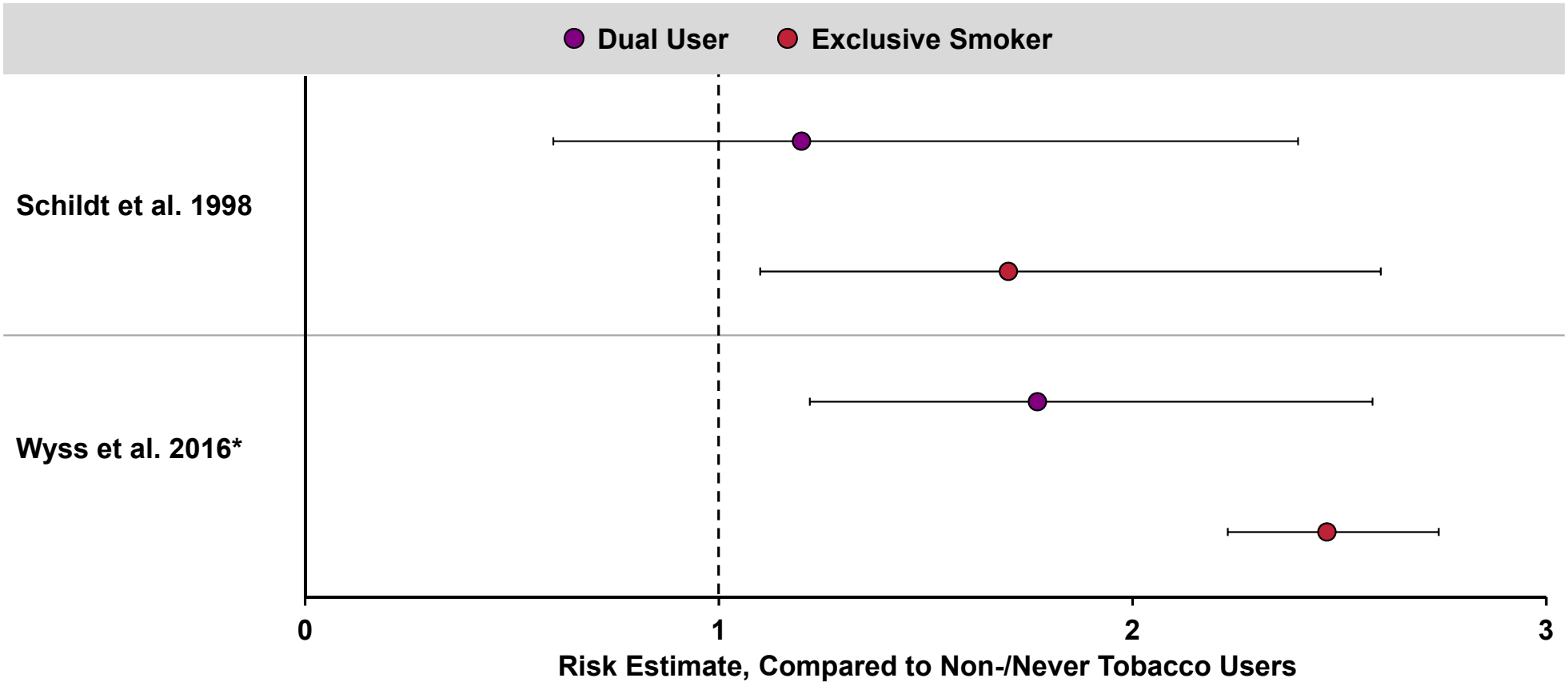
Smokeless tobacco values control for alcohol consumption
*adjusted for smoking, n=10
**never smokers, n=9

EP-160

Tipping Point Analyses for Additional Initiation



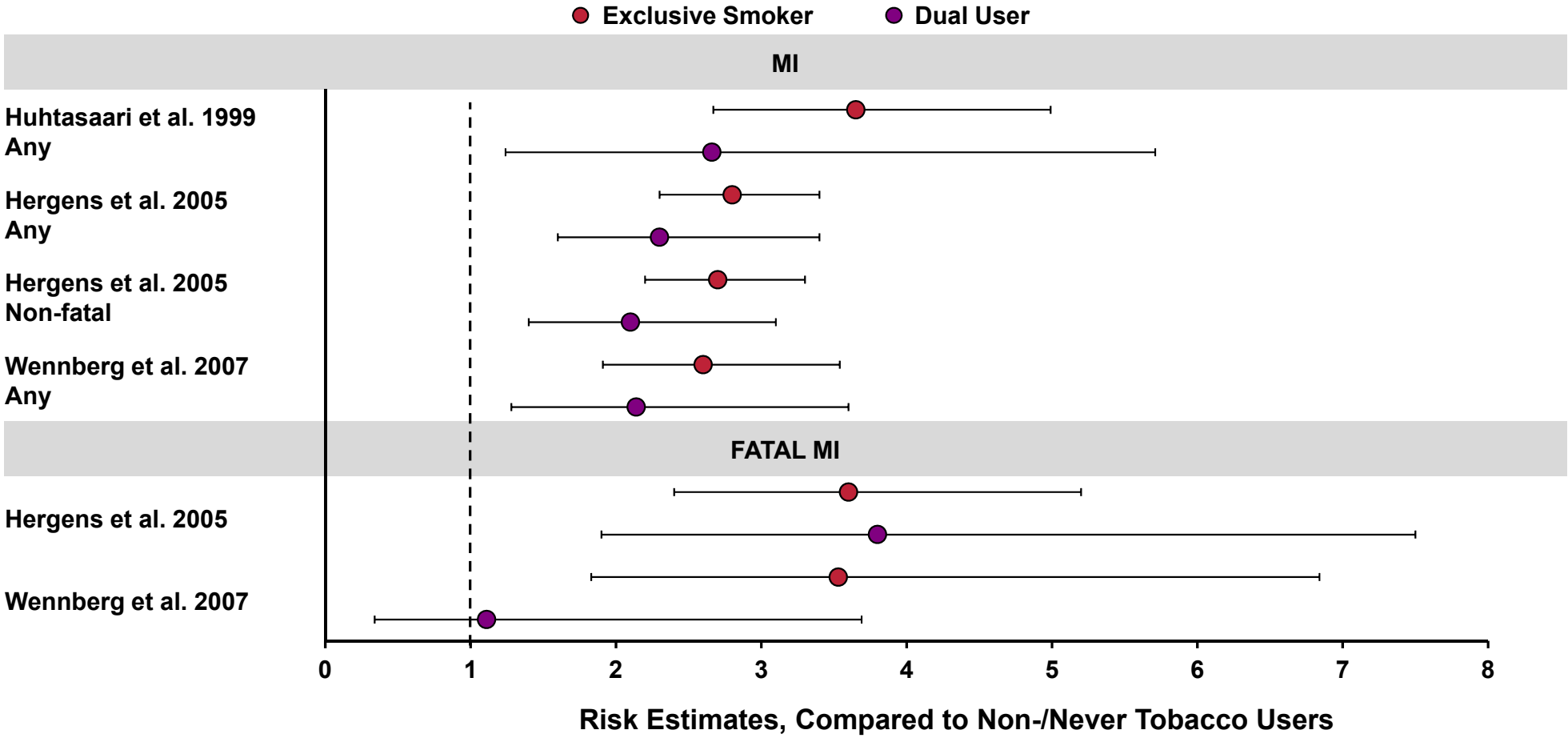
Oral Cancer:
Dual Use vs. Exclusive Smoking



*Head and neck cancer; includes poly use - smoking includes cigarettes, cigars, pipes; smokeless includes chewing tobacco and/or snuff

EP-133

Myocardial Infarction (MI):
Dual Use vs. Exclusive Smoking



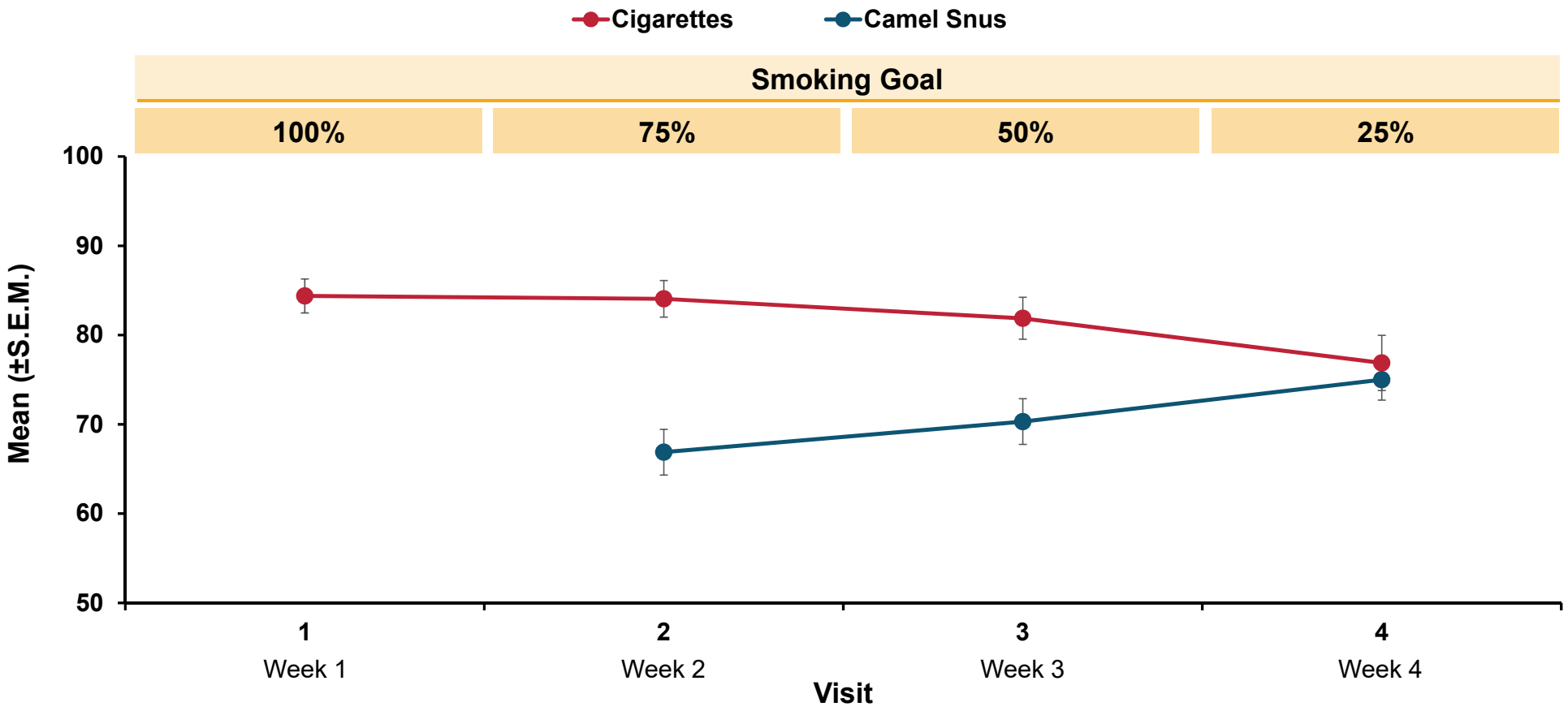
EP-166

Dual Use (Smokeless Tobacco & Smoking) as a Transitional State

- **Most switching from smoking to smokeless is through dual use**
  - Zhu et al. (2009): 16 x (compared to rate from exclusive smoking)
  - Wetter et al. (2002): 12 x
  - Tomar (2003): 42 x (adolescents)
- **Dual users more likely to make quit attempts**
  - Zhu et al. (2013): snus ~ 62% vs. 33%
  - Richardson et al. (2014): SLT 50% vs 38% (snus OR 2.92)
  - Jones et al. (2018): SLT 63% vs. 47%

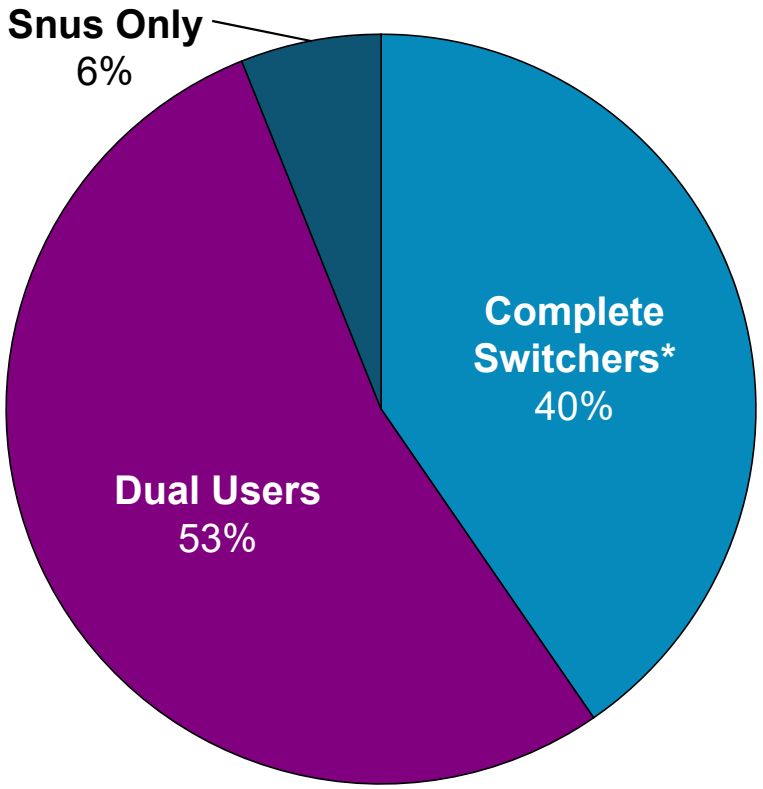
Jones DM, et al. *Nicotine Tob Res* 2018;S62–S70.
Richardson A, et al. *Amer J Public Health* 2014;104:1437-1444.
Tomar SL. *Nicotine Tob Res* 2003;5:561-569.
Wetter DW, et al. *Prev Med* 2002;34:638-648.
Zhu SH, et al. *Tob Control* 2009;18:82-87.
Zhu SH, et al. *PloS ONE* 2013;8(10):e79332.

CSD0905 – Mean Product Acceptability Ratings



CL-150

Snus Use Patterns in Current Snus Users



* Former smokers, now exclusive snus
Zhu et al. (2013); N=80

TCA Mandated Warnings

- **WARNING: This product can cause mouth cancer.**
- **WARNING: This product can cause gum disease and tooth loss.**
- **WARNING: This product is not a safe alternative to cigarettes.**
- **WARNING: Smokeless tobacco is addictive.**

Product Use Rates by Smokers and Dual Users of Camel Snus and Cigarettes (CSD0904 – Natural Adopters Study)

User Group	Pouches/Day (Mean ± SD)	Cigarettes/Day (Mean ± SD)
Exclusive Cigarettes	NA[a]	18 ± 7 cigarettes
Dual Use Camel Snus + Cigarettes	2 ± 2 pouches	15 ± 8 cigarettes

a. Not Applicable

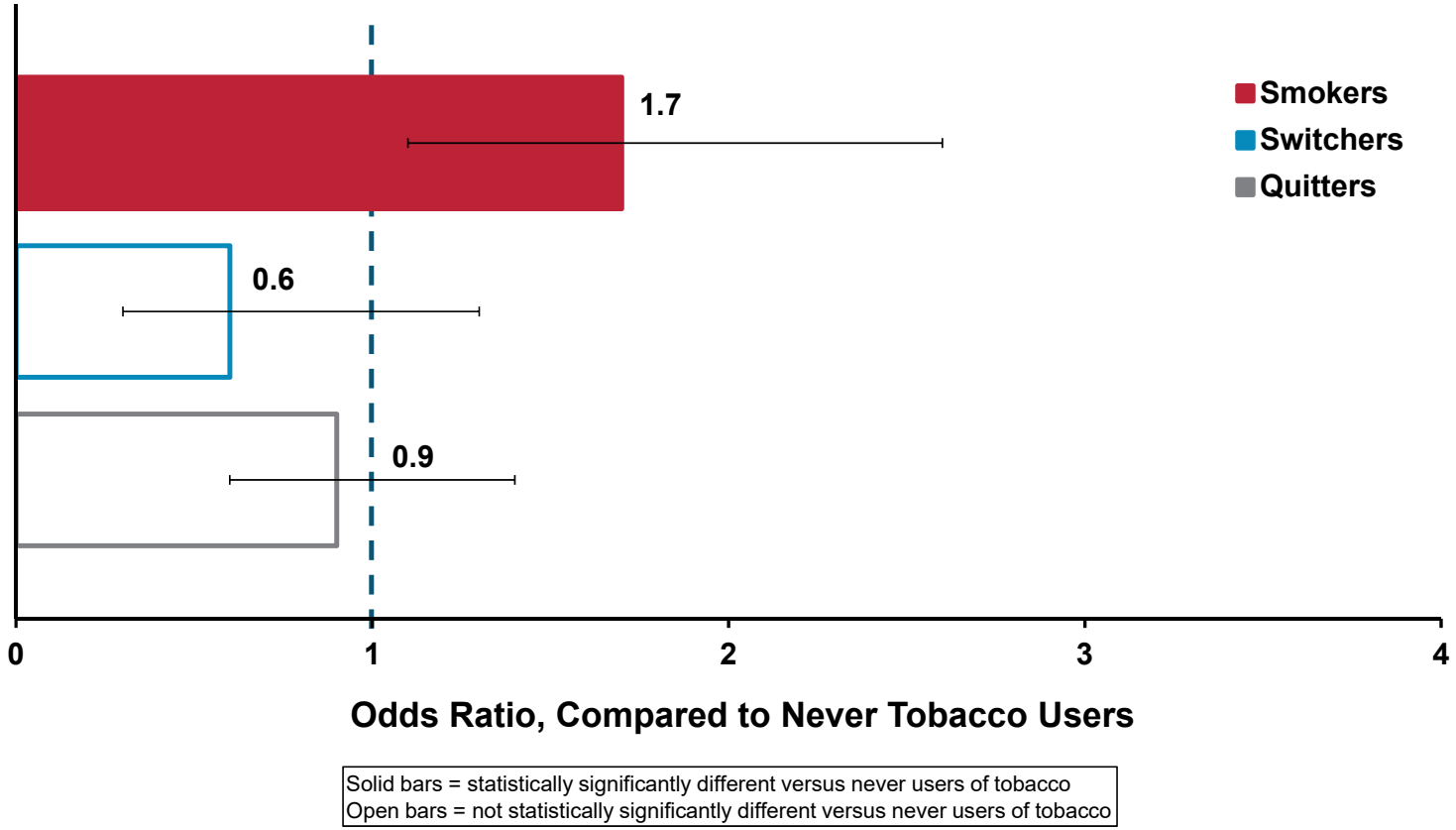
Snus and Cigarette Use Patterns: Exclusive Snus Users, Exclusive Smokers, and Dual Users

	Current Exclusive Snus Users n=373	Current Exclusive Smokers n=41,179	Current Dual Users n=4,127
Mean uses/day			
Snus	3.6	—	1.3
Cigarettes	—	12.7	7.8
Mean days/month			
Snus	15.9	—	7.9
Cigarettes	—	25.0	15.9
Mean uses/day on days used			
Snus	4.8	—	3.6
Cigarettes	—	13.4	9.4

National Tobacco Behavior Monitor: Q1 2013-Q4 2017

Oral Cancer:
Risks of Smokers, Switchers, and Quitters

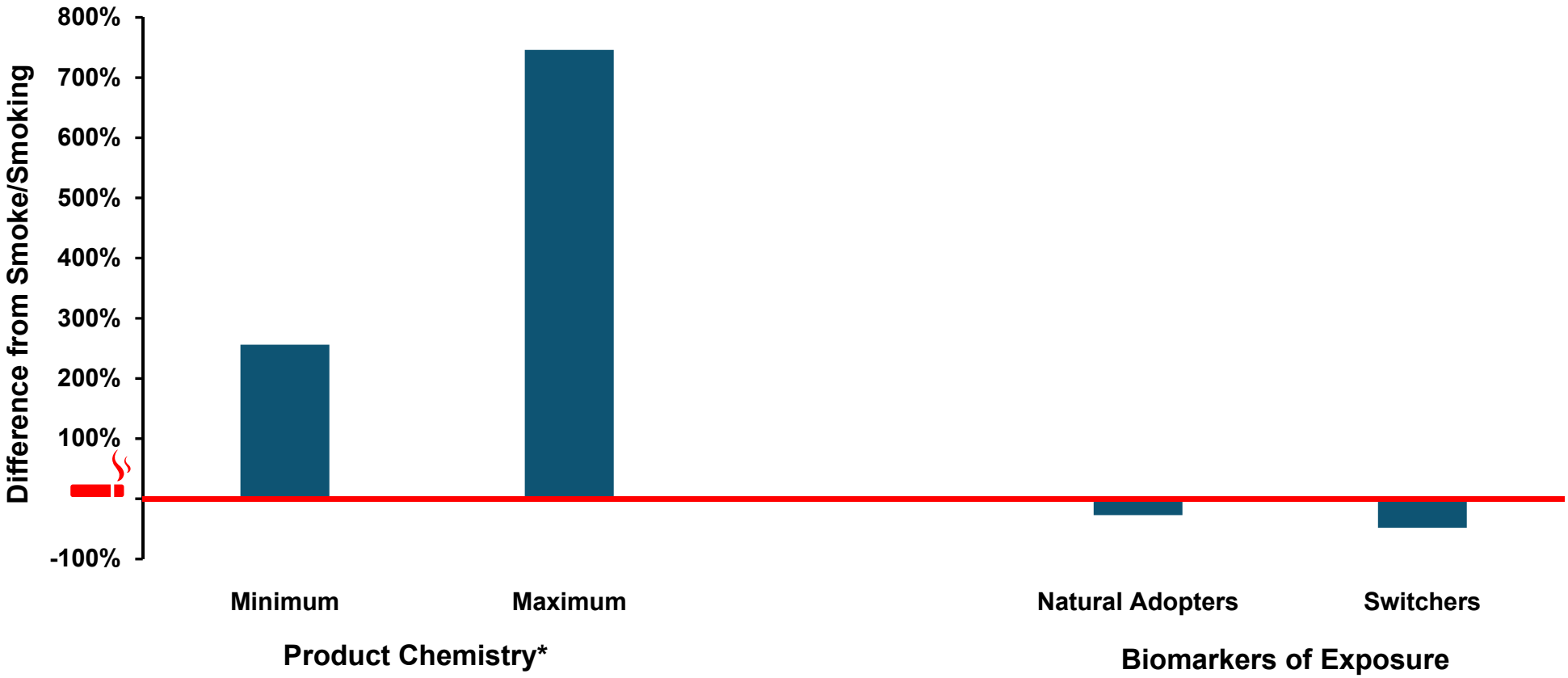
Schildt et al. 1998



Solid bars = statistically significantly different versus never users of tobacco
Open bars = not statistically significantly different versus never users of tobacco

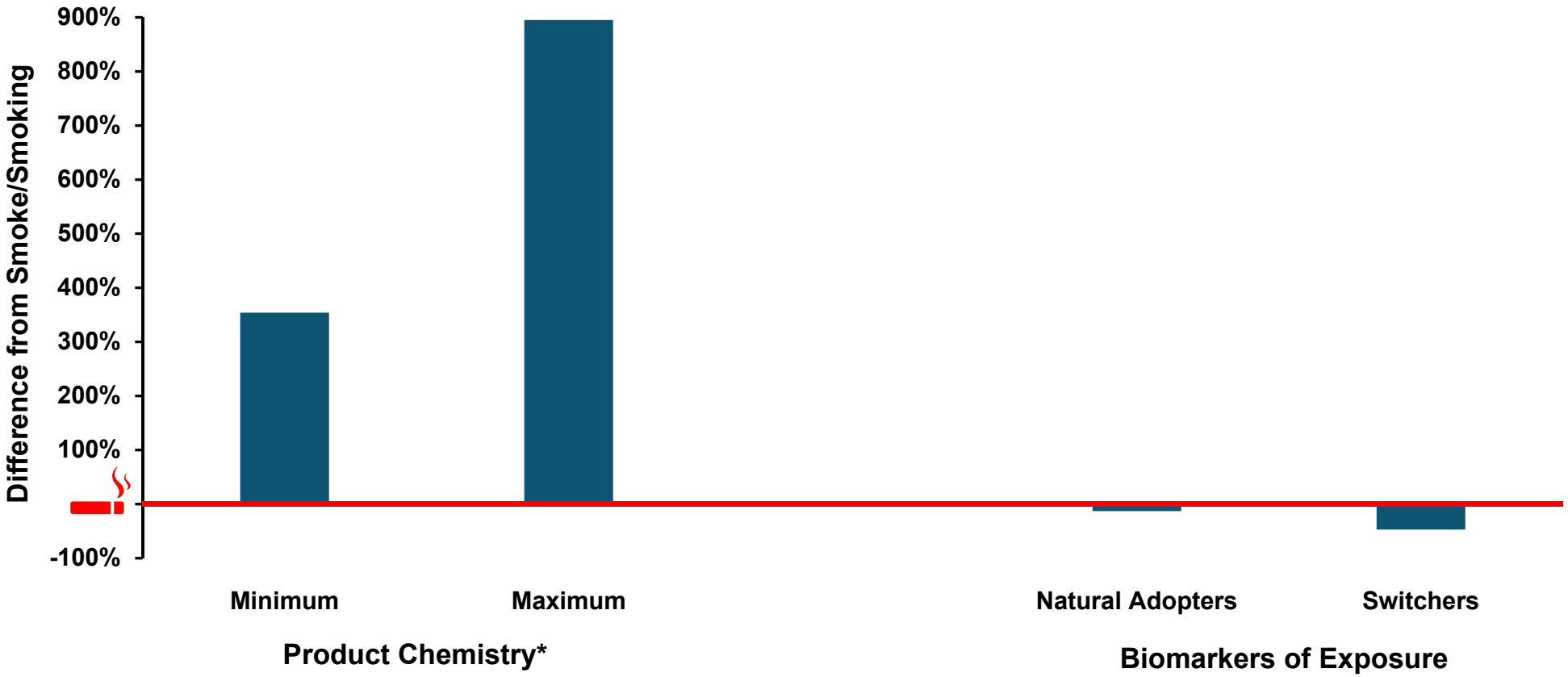
EP-175

Increases in Product Content Do Not Translate Into Increased Exposure – Nicotine



*Values cited from FDA Briefing Document

Increases In Product Content Do Not Translate Into Increased Exposure – NNN



*Values cited from FDA Briefing Document

Arsenic Exposure

- **Evaluation of biomonitoring data, NHANES, 2003-2008[1]**

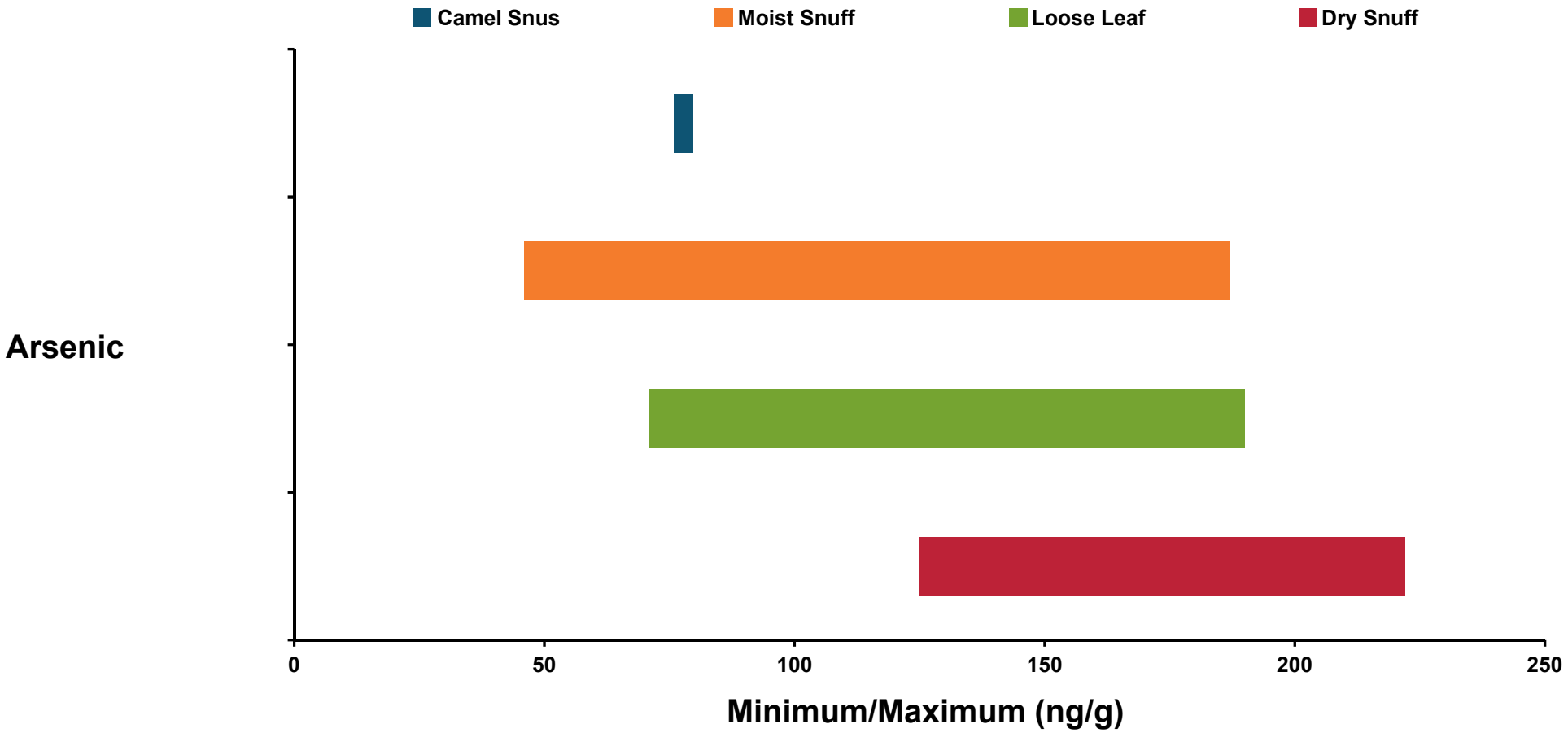
Arsenic	Cigarette Smokers	Smokeless Tobacco Users	Non-users
Urine (µg/g Creatinine)	**7.98 (7.08, 9.00)**	**6.14 (4.86, 7.74)**	**9.56 (8.92, 10.27)**

Values are geometric means adjusted for age, gender, race/ethnicity, body mass index, survey year, arsenobetaine, tobacco consumption category

- **Regression of serum cotinine and urine arsenic**
  - No significant associations among cigarette smokers, smokeless tobacco users, or nonusers[2]

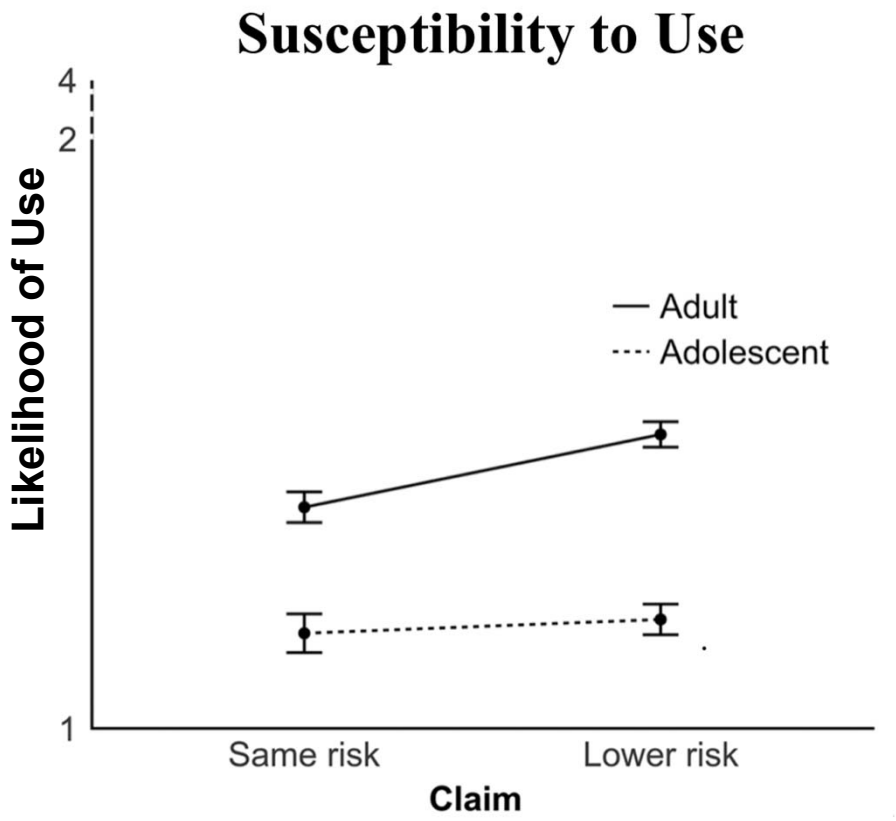
1. Marano et al. 2012b
2. Naufal et al. 2011

HPHCs in Camel Snus vs. Moist Snuff, Loose Leaf, and Dry Snuff – Arsenic



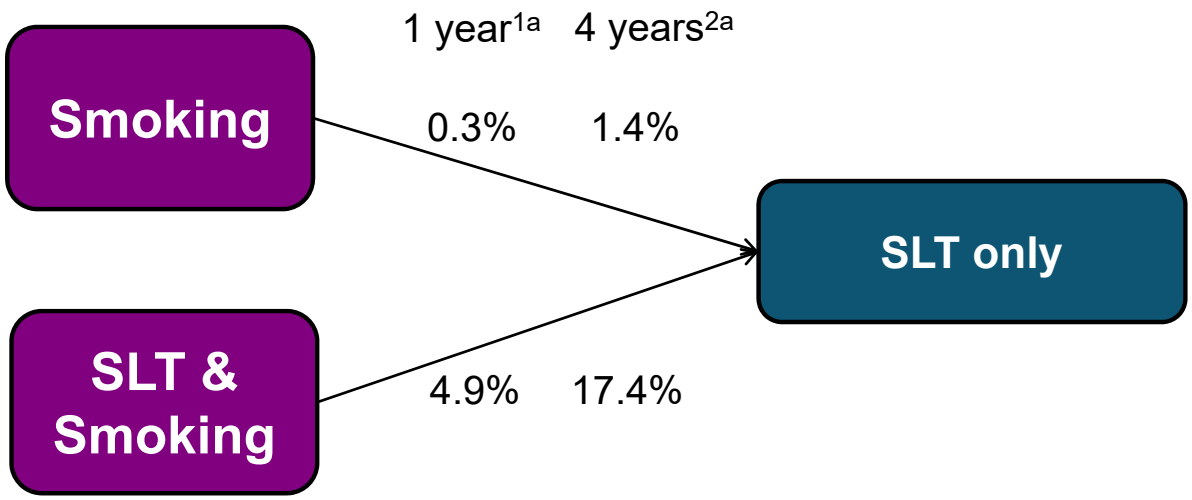
CH-84

Unlike Adults, Adolescents' Likelihood of Use is Not Increased by Modified-Risk Claims



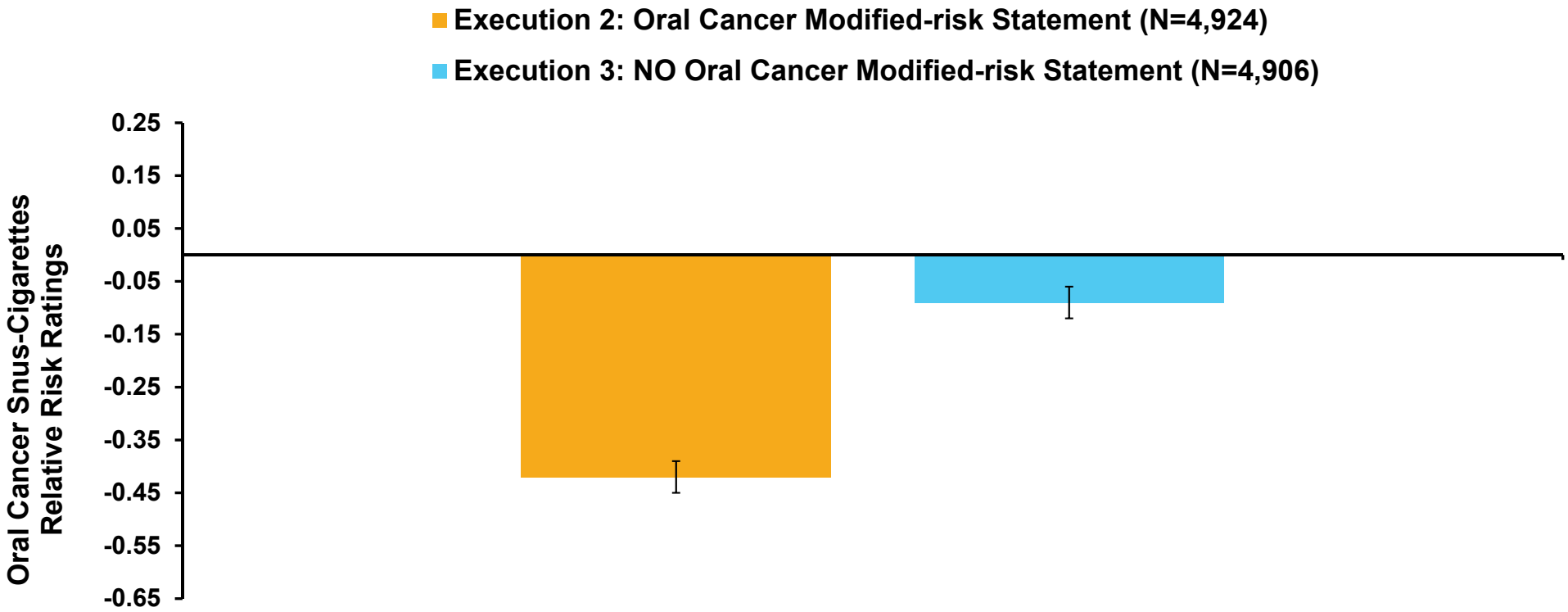
El –Toukhy S, et al. Tob Control 2018;0:1-8. doi:10:1136/tobaccocontrol-2018-054315.

Adults: Switching from Smoking to Smokeless Tobacco Occurs Primarily Through Dual Use



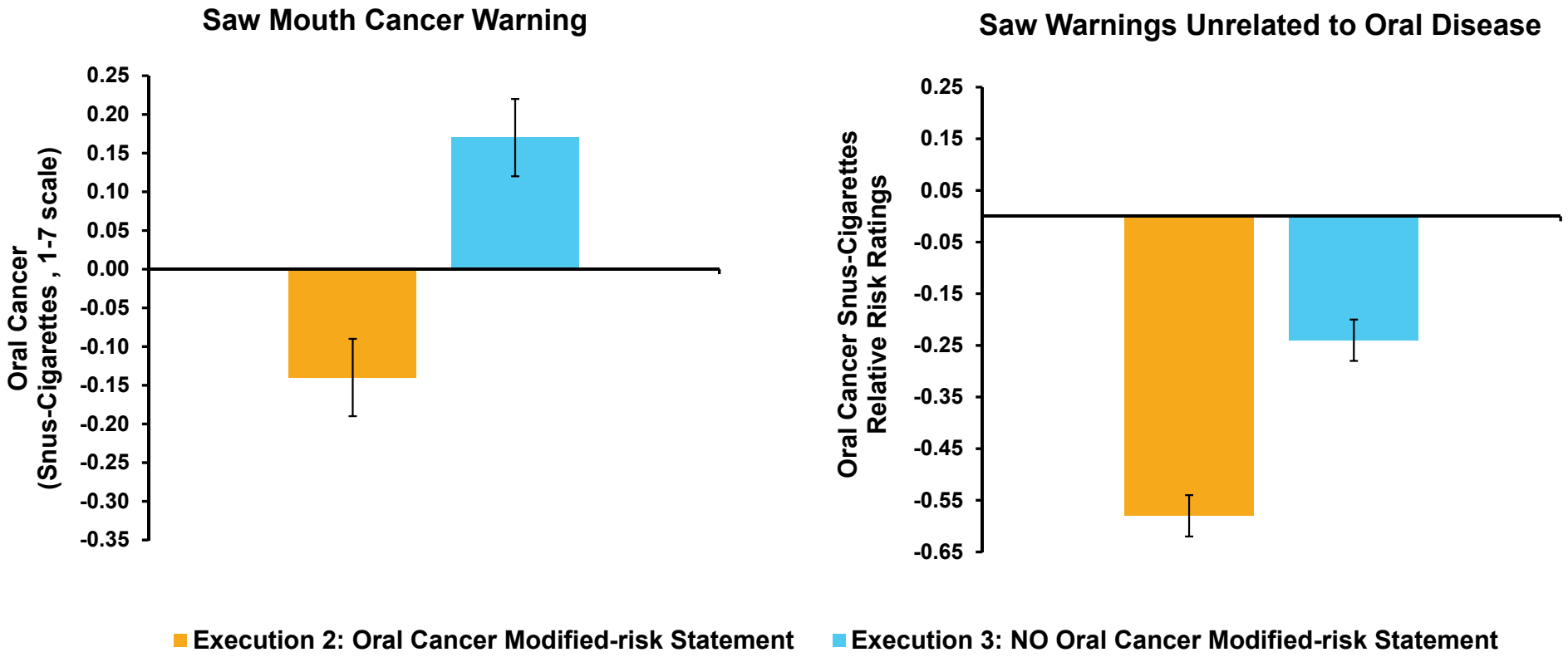
a. Males only
1. Zhu et al. (2009); Tobacco Use Supplement to the Current Population Survey
2. Wetter et al. (2002); Working Well Trial

Modified-Risk Statement Regarding Oral Cancer Informs Risk Perceptions



PB-161

Modified-Risk Statement on Oral Cancer Interacts with Warnings to Affect Relative Risk Perceptions



PB-165