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TOBACCO HARM REDUCTION:

An Overview of PMI's Scientific Approach & Main Results for the Tobacco Heating System (THS) 2.2, a Candidate Modified Risk Tobacco Product

Tunis, Tunisia

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Philip Morris International
November 9th 2018

The Scientists

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Blaine Phillips


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Creating a New Category: Reduced-Risk Products

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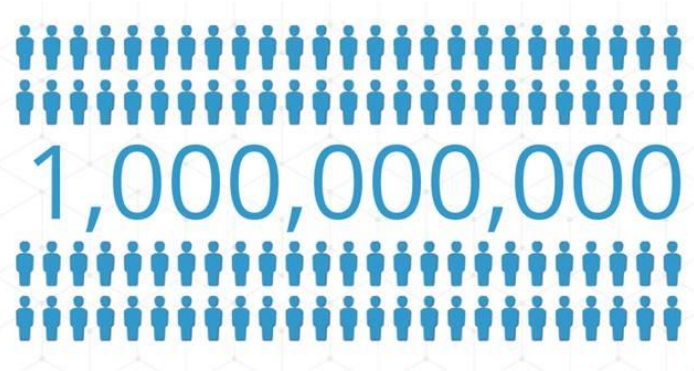
Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

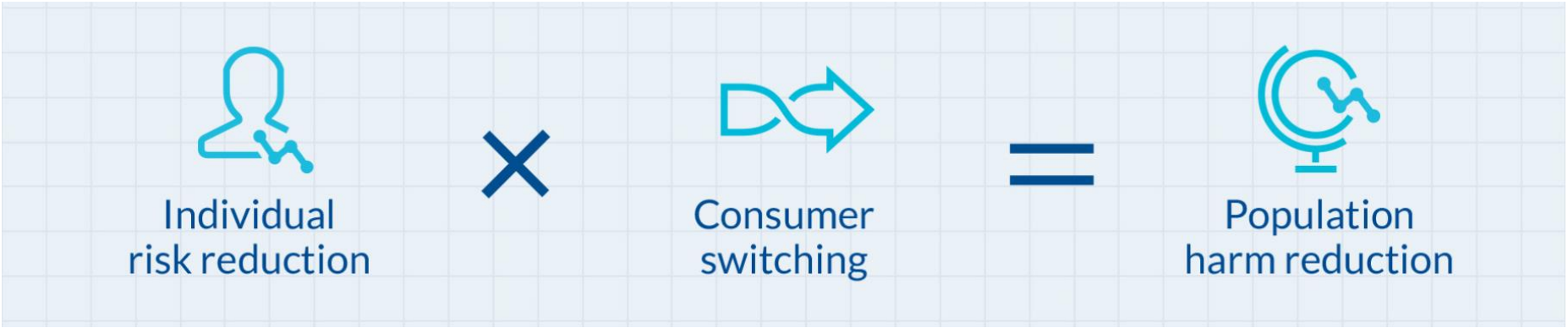
We have a range of RRPs in various stages of development, scientific assessment, and commercialization.

Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

The Objective Is Harm Reduction

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies





Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products to which they can fully switch, should they decide not to quit.

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

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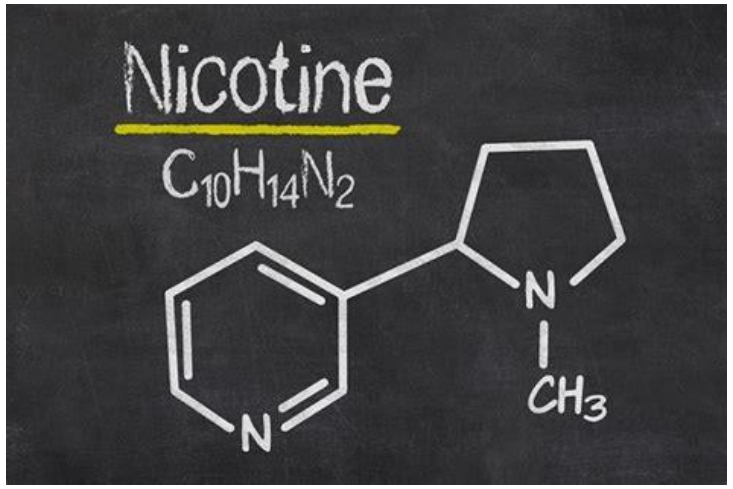
Nicotine Is Not the Primary Cause of Smoking-Related Diseases

"It is primarily the toxins and carcinogens in tobacco smoke–not the nicotine–that cause illness and death."

-NICE Public Health Guidance: Tobacco: Harm Reduction Approaches to Smoking (2013)



Nicotine, though addictive and not risk-free, is not the primary cause of smoking-related diseases

"Nicotine is the core of the problem but also the centerpiece of the solution."

-Mitch Zeller, director of US FDA's Center for Tobacco Products; Presentation at Food and Drug law Institute Conference (Washington 26 October 2017)

Public Health England

FDA

Royal College of Physicians

NICE National Institute for Health and Care Excellence

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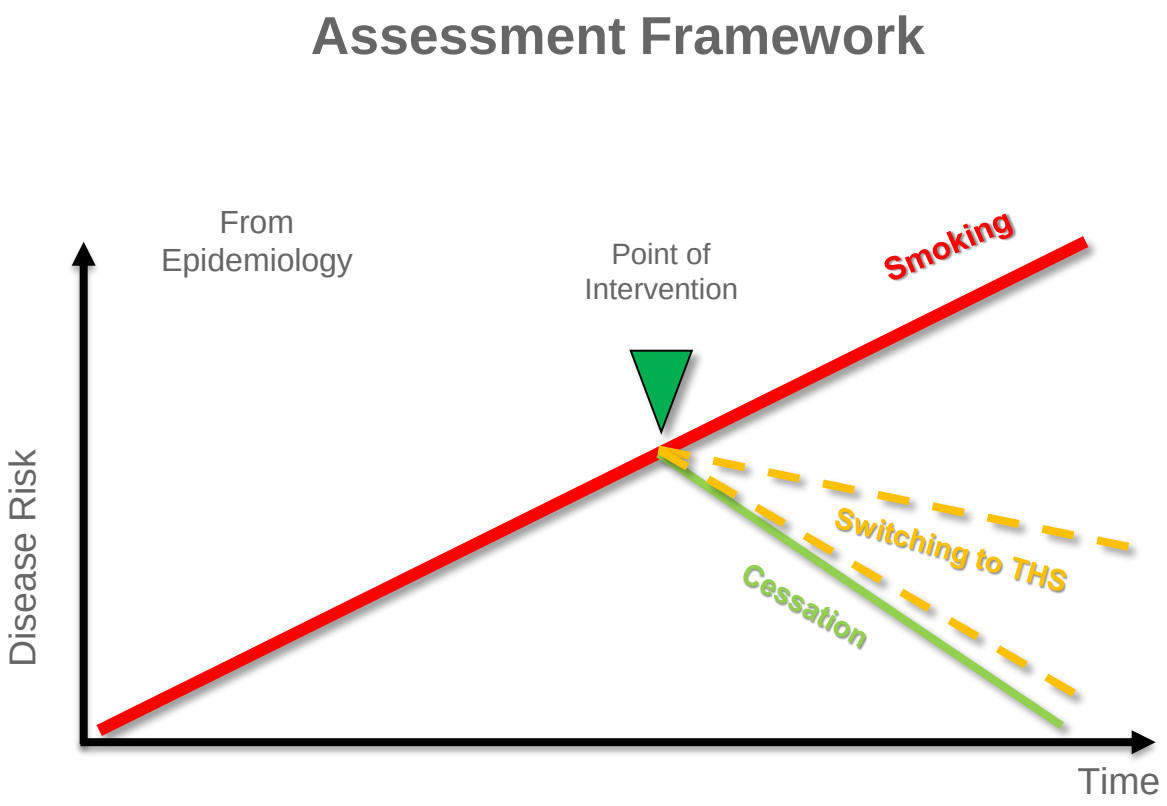
PMI's Scientific Assessment Approach



Post-Market Studies and Surveillance

Consumer Perception and Behavior Assessment

Clinical Trials

Systems Toxicology Assessment

Standard Toxicology Assessment

Aerosol Chemistry and Physics

Product Design and Control Principles

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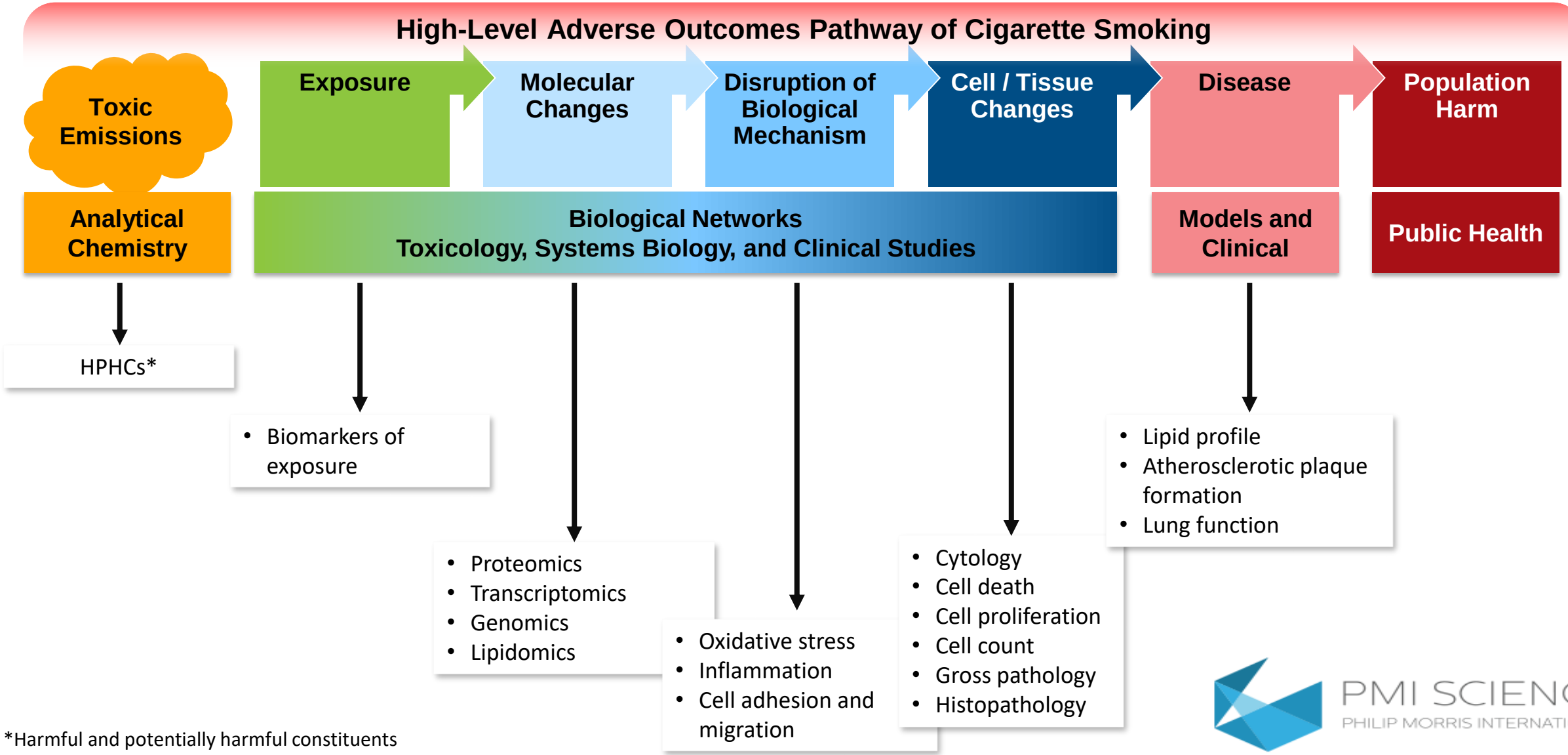
Source: Smith, M.R., et al., Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). http://dx.doi.org/10.1016/j.yrtph.2016.07.006

Assessment Framework: Informed by Epidemiology



*Harmful and potentially harmful constituents

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PMI's Reduced-Risk Product Portfolio

Heated Tobacco Products

PLATFORM 1

ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP) OR TOBACCO HEATING SYSTEM (THS)

PLATFORM 2

CARBON-HEATED TOBACCO PRODUCT (CHTP)

Products Without Tobacco

PLATFORM 3

NICOTINE DELIVERY SYSTEM

PLATFORM 4

E-VAPOR PRODUCTS

Note: The RRPs depicted are subject to ongoing development; therefore, the descriptions are illustrative and do not necessarily represent the latest stages of product development.

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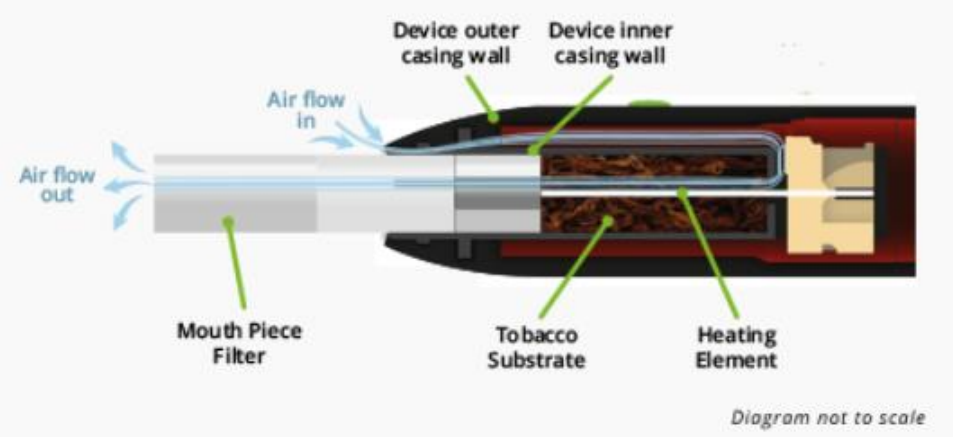
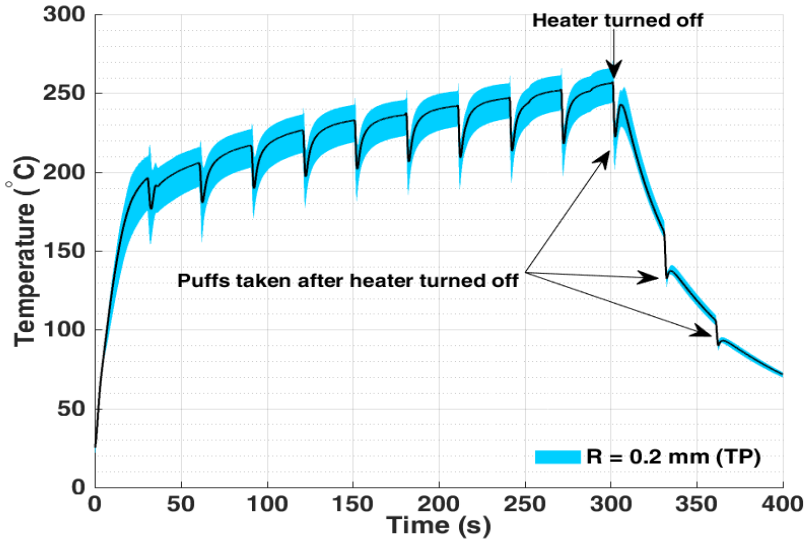
Why Heat Tobacco Rather than Burn It?

The Tobacco Heating System (THS) (currently commercialized as *IQOS* in > 40 countries) is designed and has been demonstrated to:

- Heat tobacco <u>without</u> combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile, and ritual characteristics of cigarettes





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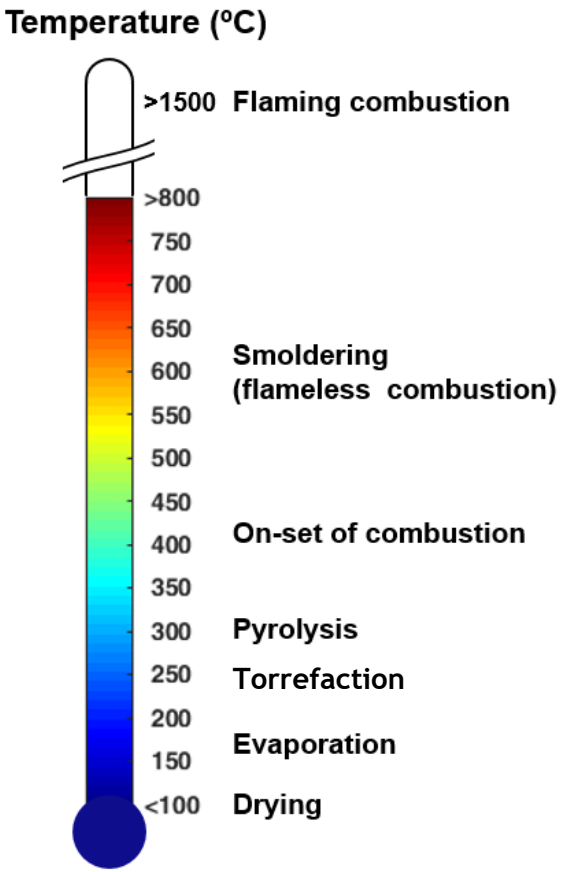
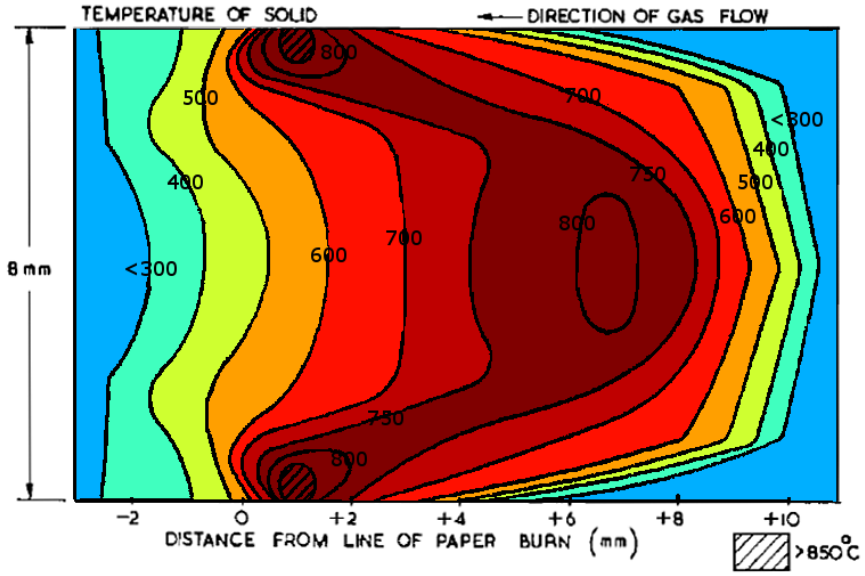
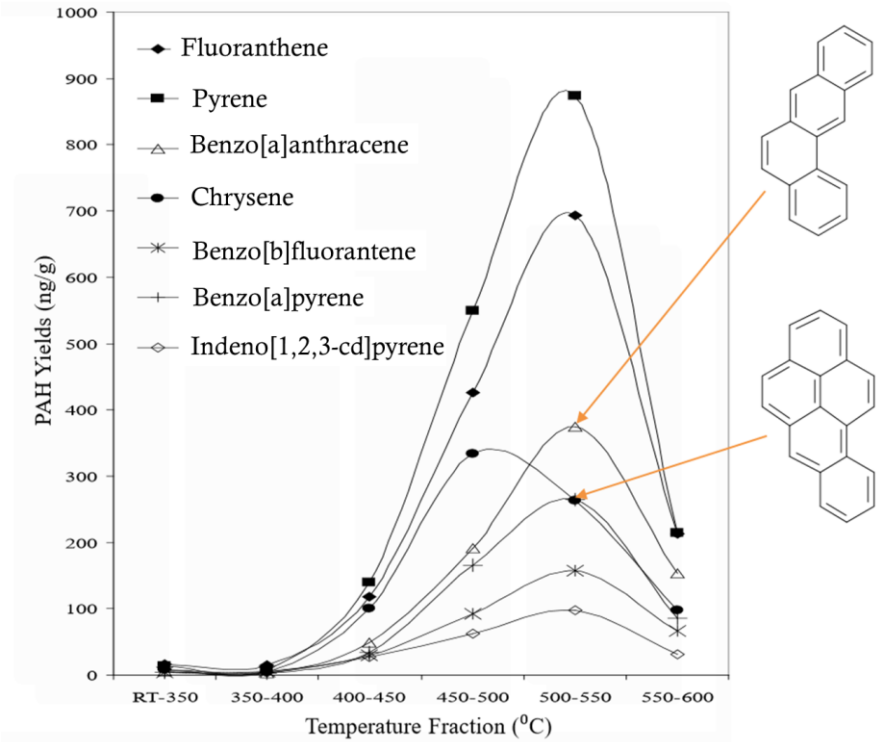
Elimination of Combustion Is Key

Scientific studies have shown that as the temperature of tobacco increases, the levels of harmful chemicals formed increase





Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.



Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

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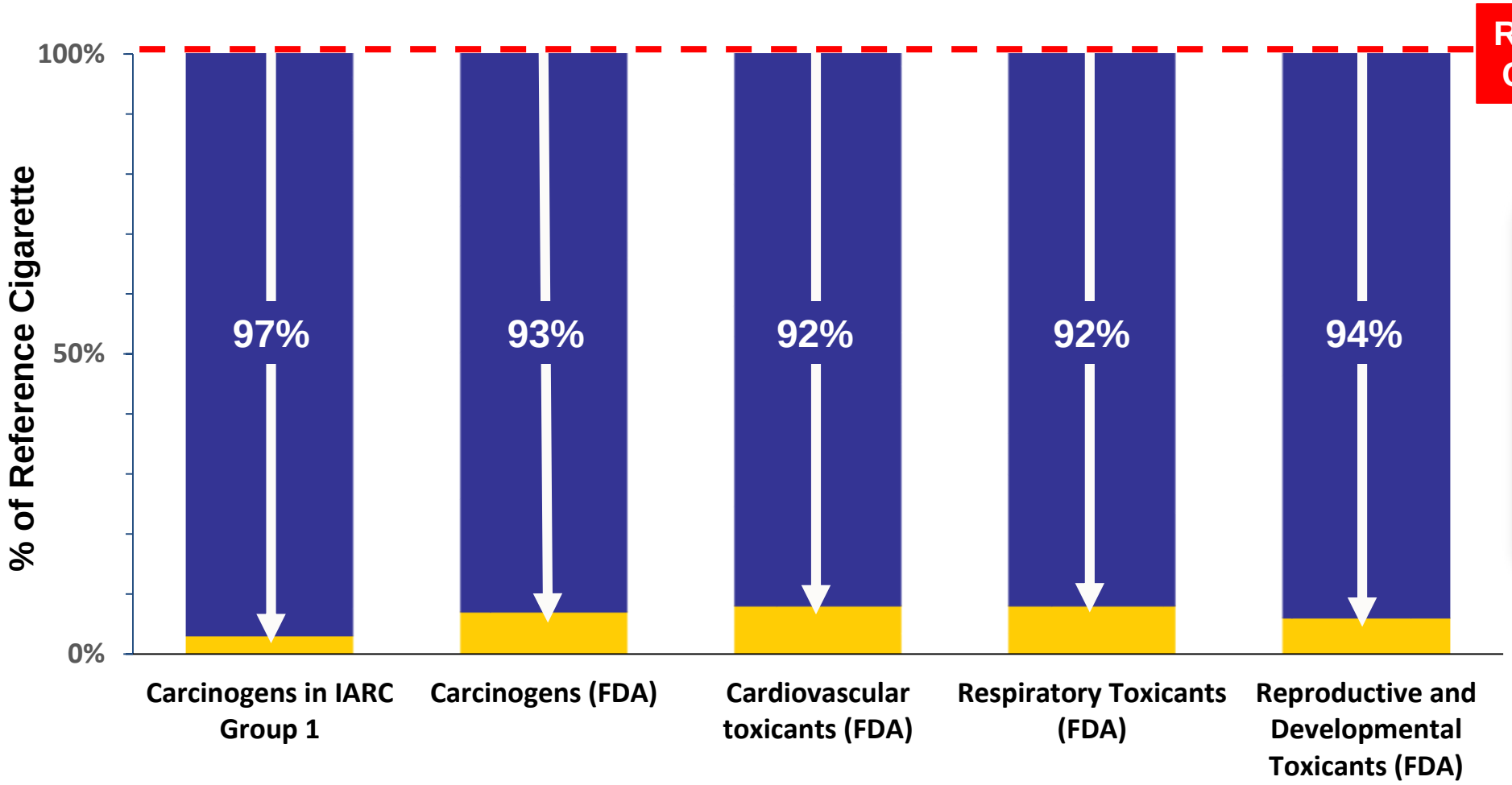
Reduced Formation of HPHCs by Disease Categories



No. of toxicants	**12**	**29**	**8**	**18**	**7**

THS 2.2 produces an aerosol that contains **on average 90-95% lower levels of harmful and potentially harmful chemicals than a reference cigarette**

Note: Health Canada Intense Smoking Regime; comparison on a per-stick basis; excludes nicotine

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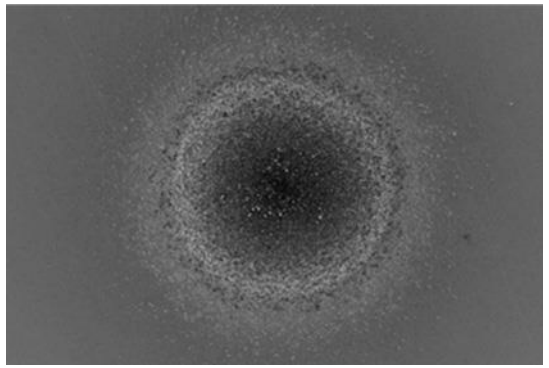
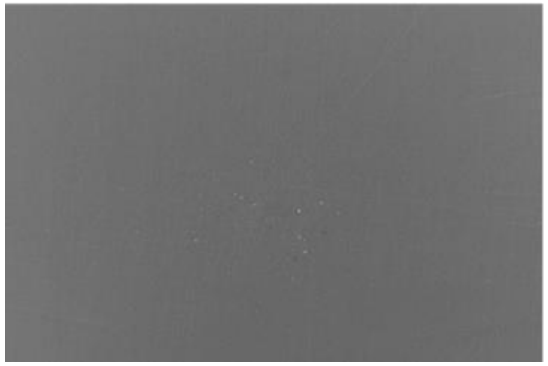
Reduced Formation of HPHCs by Disease Categories

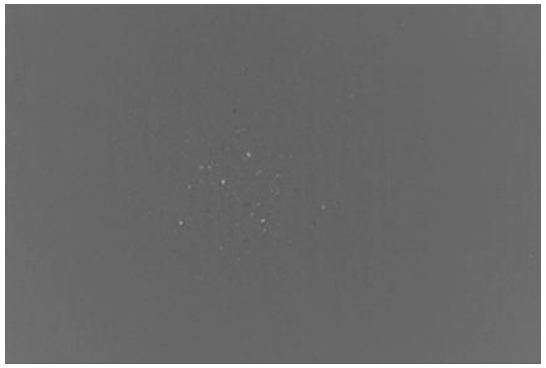


Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm
Amount: $6x10^{11}$ particles ~= 0.7 mg*



Blank (Air)



THS aerosol

No solid particles

Scanning electron microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300ºC to remove the volatile portion/collected material characterized by electron diffusive X-ray.

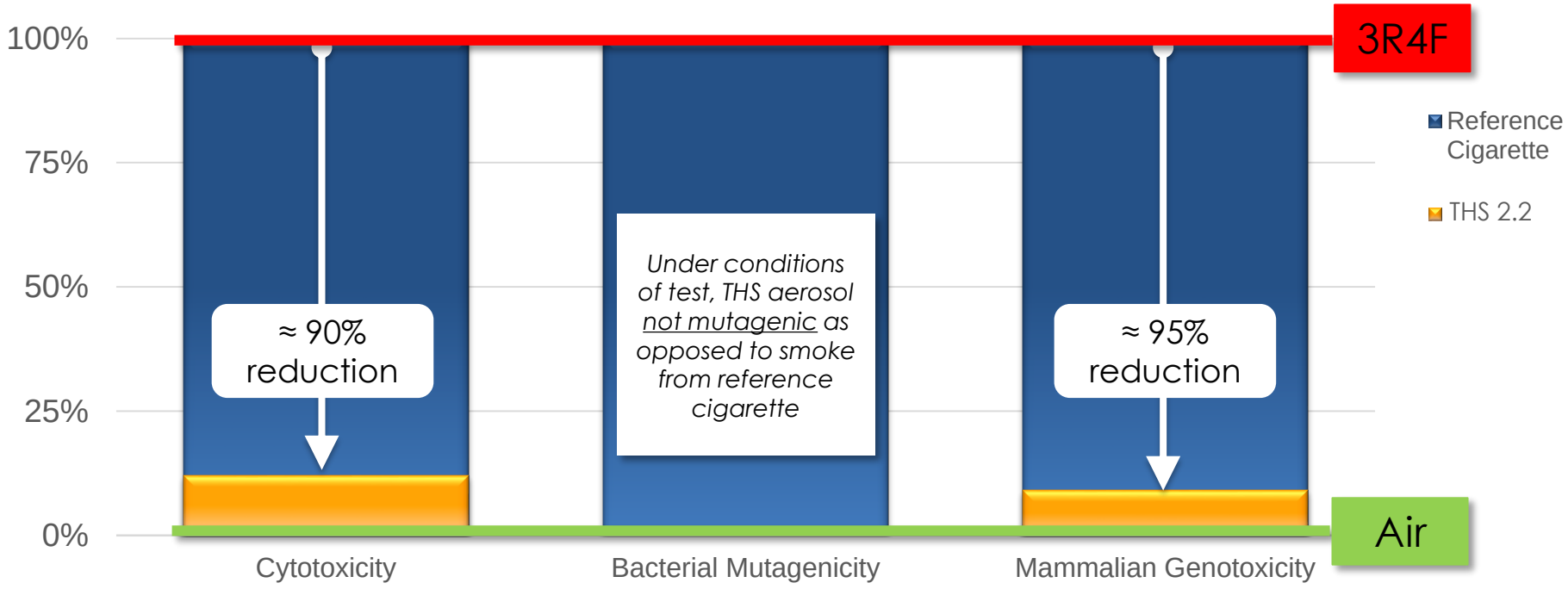
* Under the Health Canada Intense Smoking Regime.

Pratte et al. Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. *Hum. Exp. Toxicol*, 2017; 36:1115-1120.

Cohen et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; 1907-1918.

Reduced Toxicity *In Vitro*

Average reductions in **toxicity** compared with levels measured for the 3R4F reference cigarette. Measured using Neutral Red Uptake, AMES, and Mouse Lymphoma Assays



Comparison on a per-nicotine basis
Note: These data alone do not represent a claim of reduced exposure or reduced risk.
Source: PMI Research and Development

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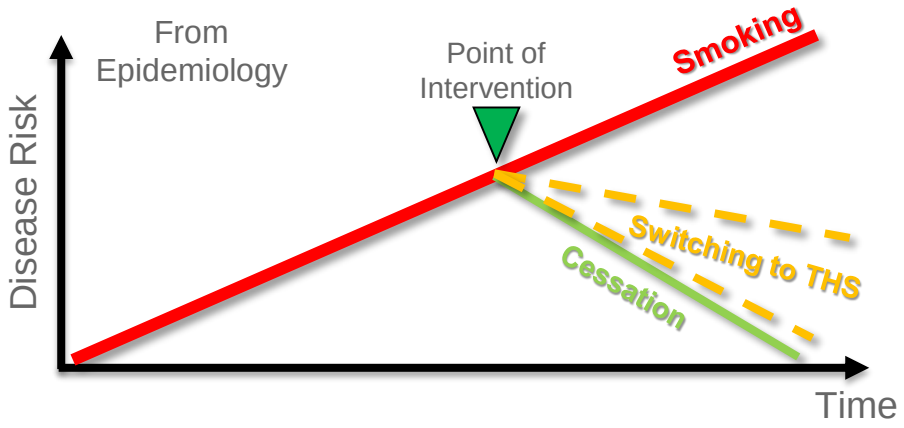
From Risk Assessment Framework to *In Vivo* Study Design

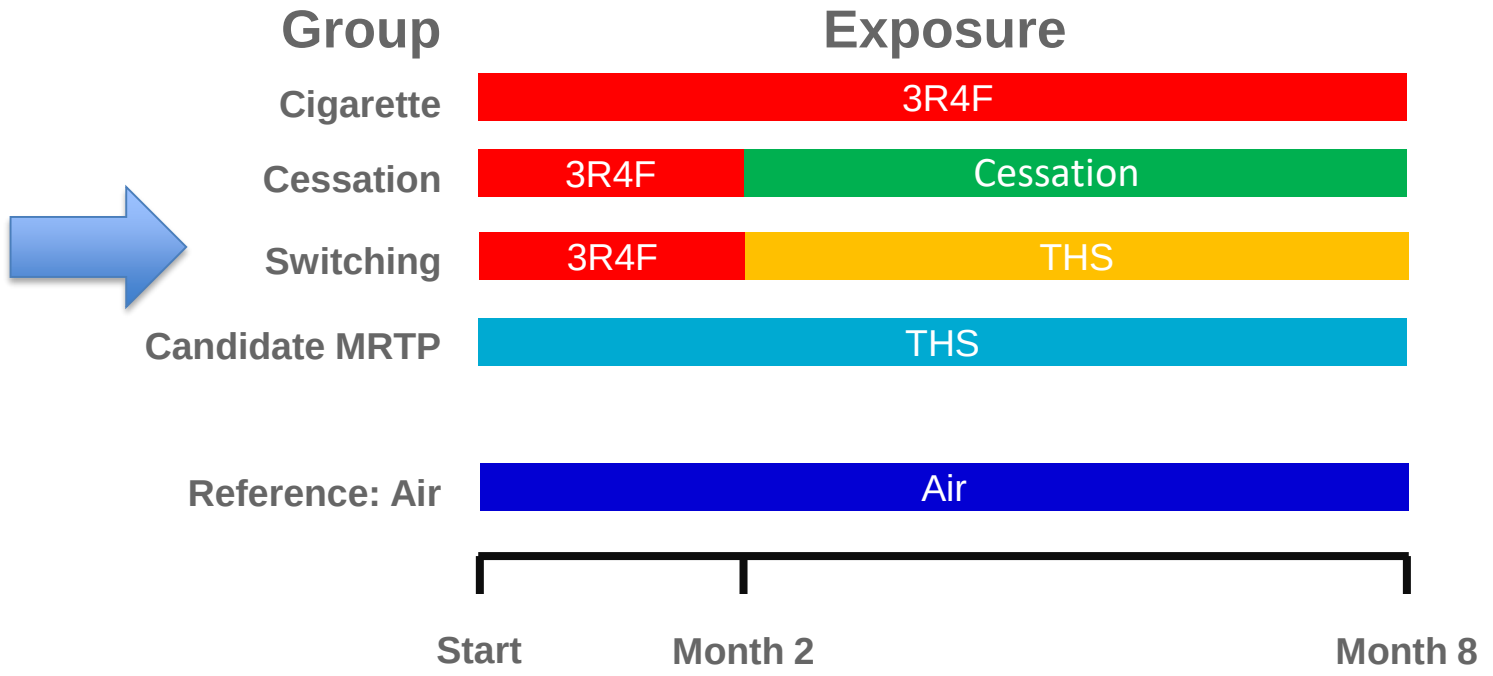
Animal Model: ApoE$^{-/-}$ Mouse – Concomitant Analysis of CVD and COPD Endpoints

- 8 months duration (approximately 40% of lifetime)
- Concomitant analysis of CVD and COPD endpoints
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison

Assessment Framework



Note: The descriptions in the chart are for illustrative purposes only



Phillips et al. (2015) An 8-Month Systems Toxicology Inhalation/Cessation Study in ApoE-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared with Conventional Cigarettes. Toxicological Sciences, in press

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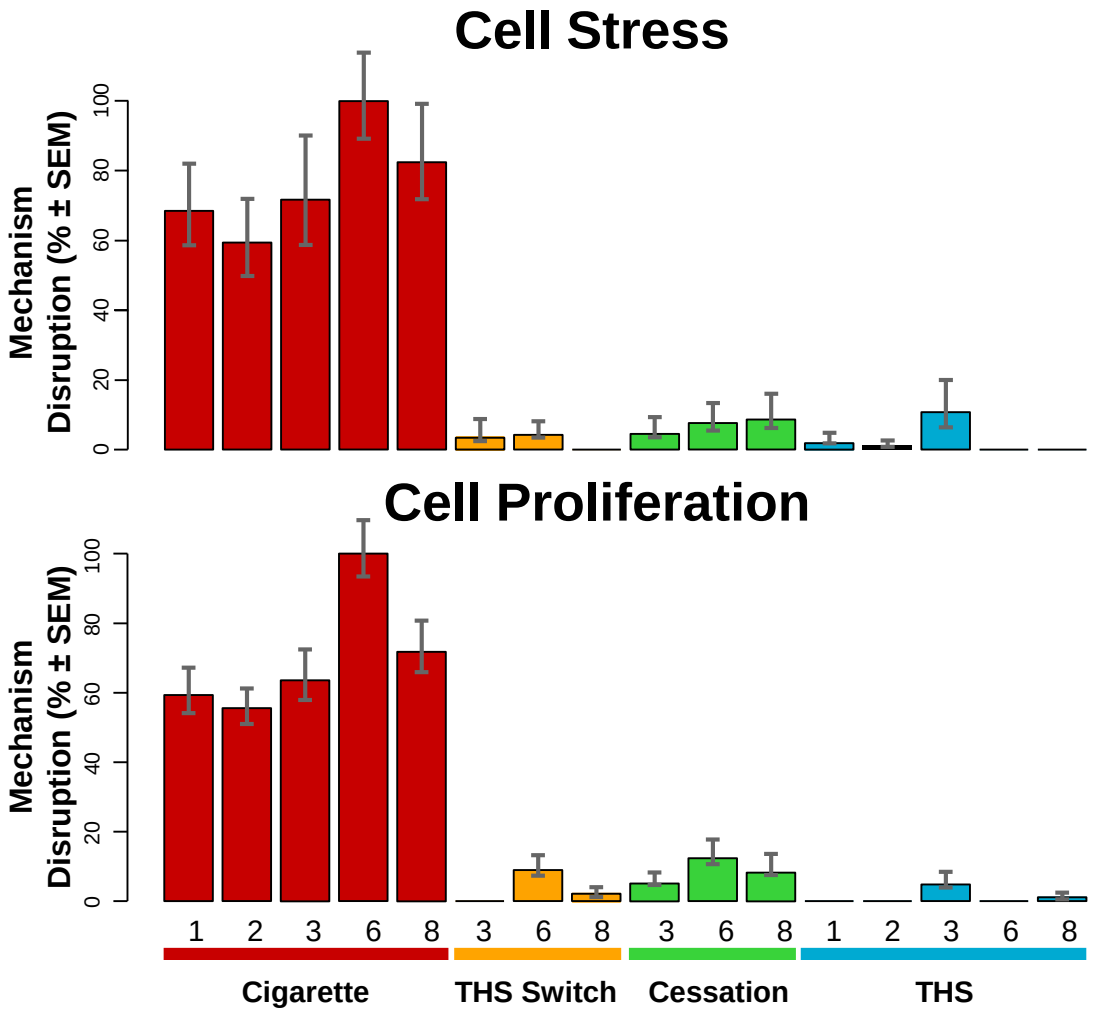
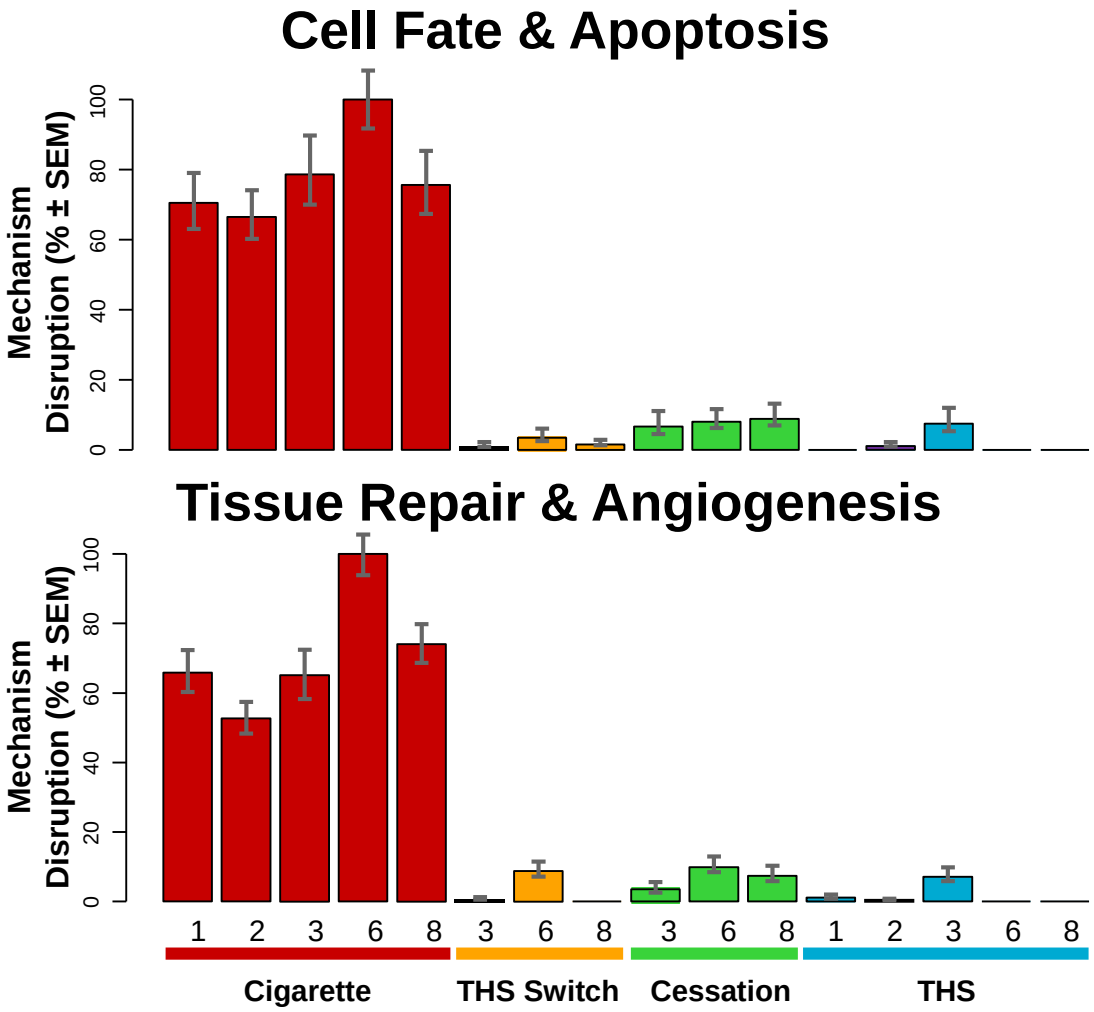
Reduced Effects on Disease Mechanisms





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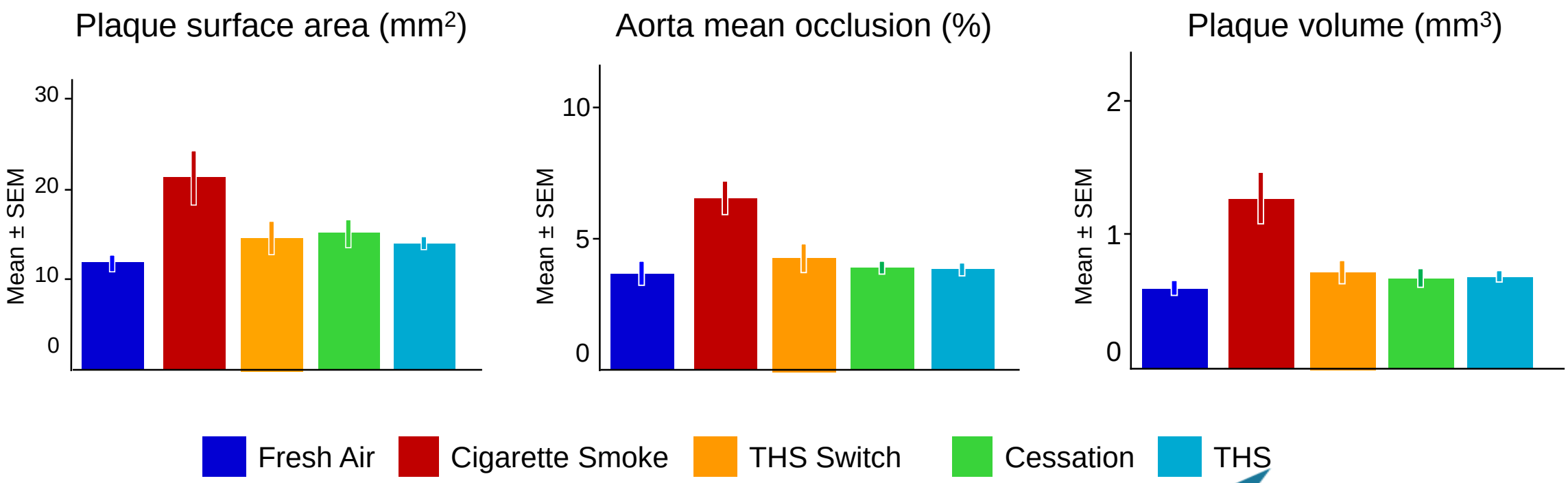
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at Month 7

Disease Endpoint for CVD

Atherosclerotic Plaque in the Aortic Arch

Data from µCT at Month 7



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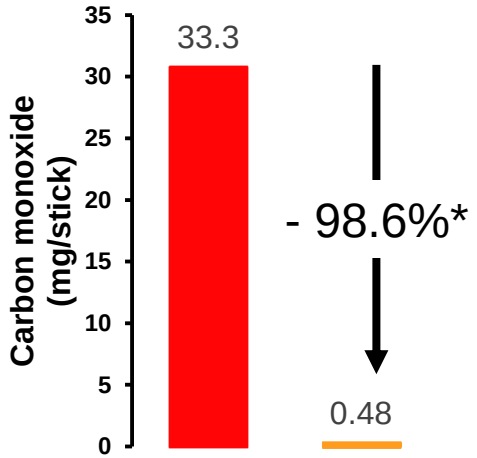
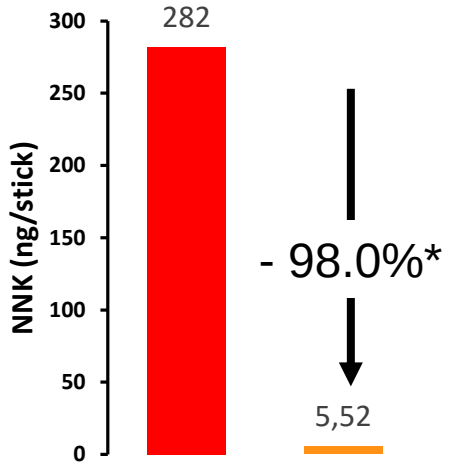
Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences **149(2): 411-432.**

Changes in Exposure to HPHCs

Reduced Exposure in Healthy Human Subjects

Levels of HPHCs Are Drastically Reduced in THS Aerosol





Leads to

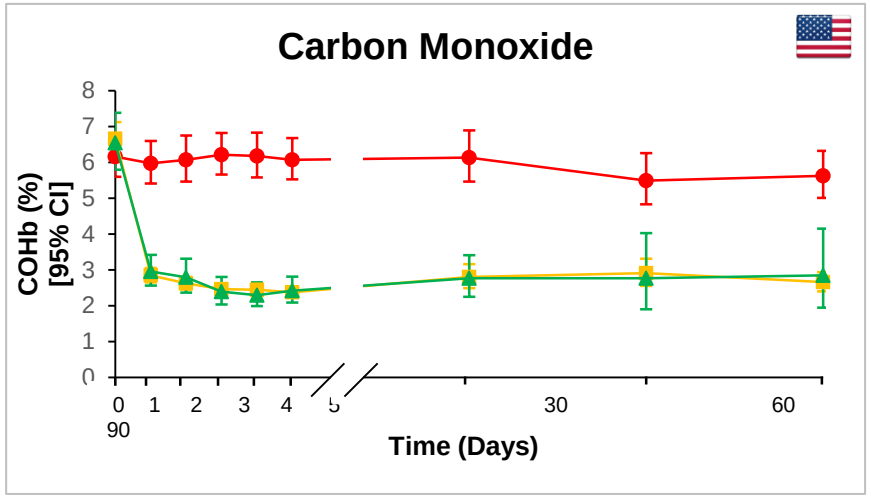
Cigarette

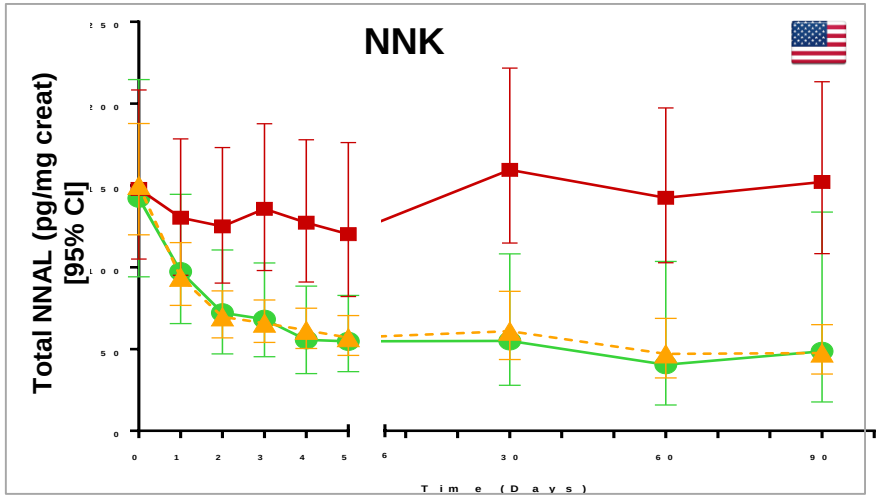
THS

Smoking Abstinence

Leads to

Exposure Is Significantly Reduced After Switching to THS

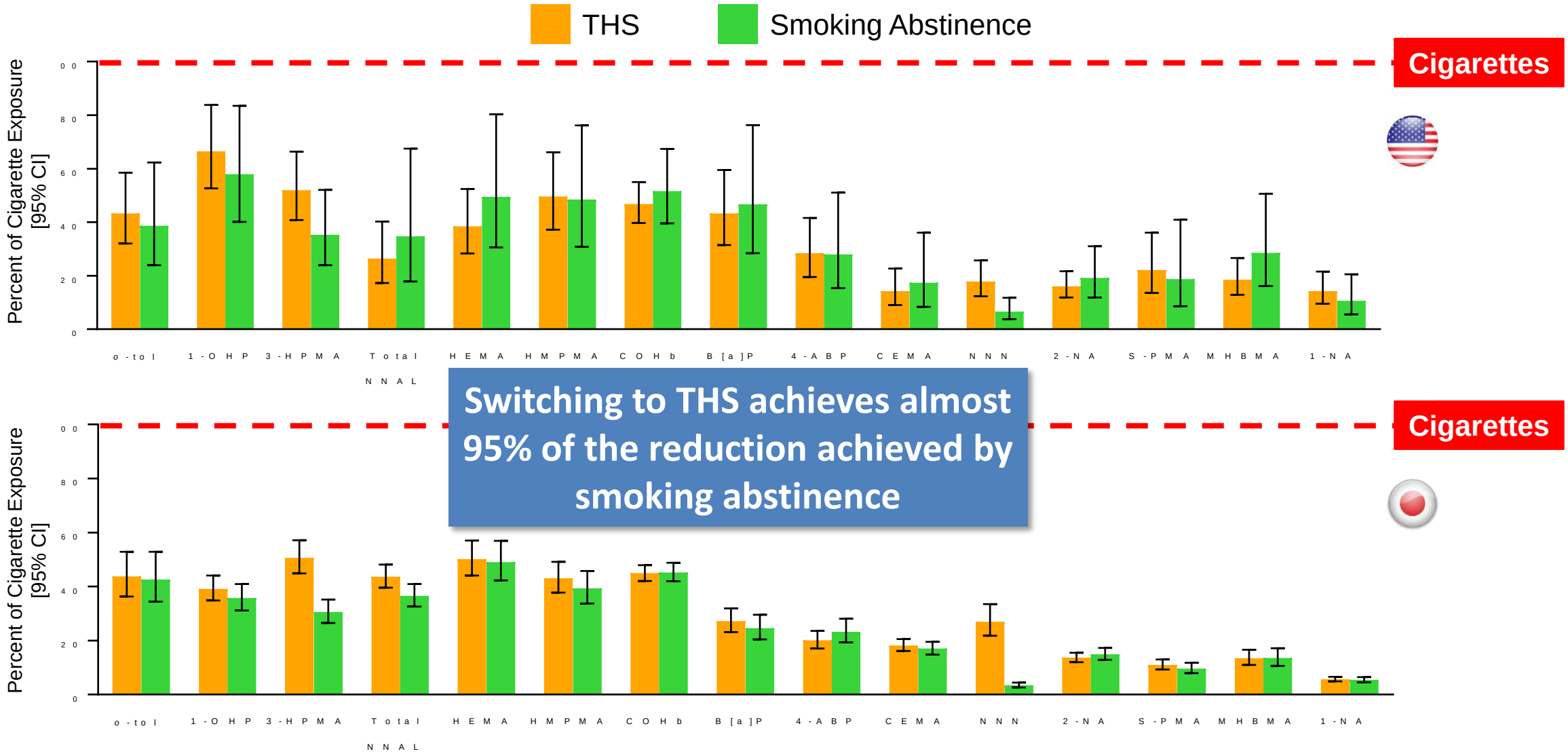




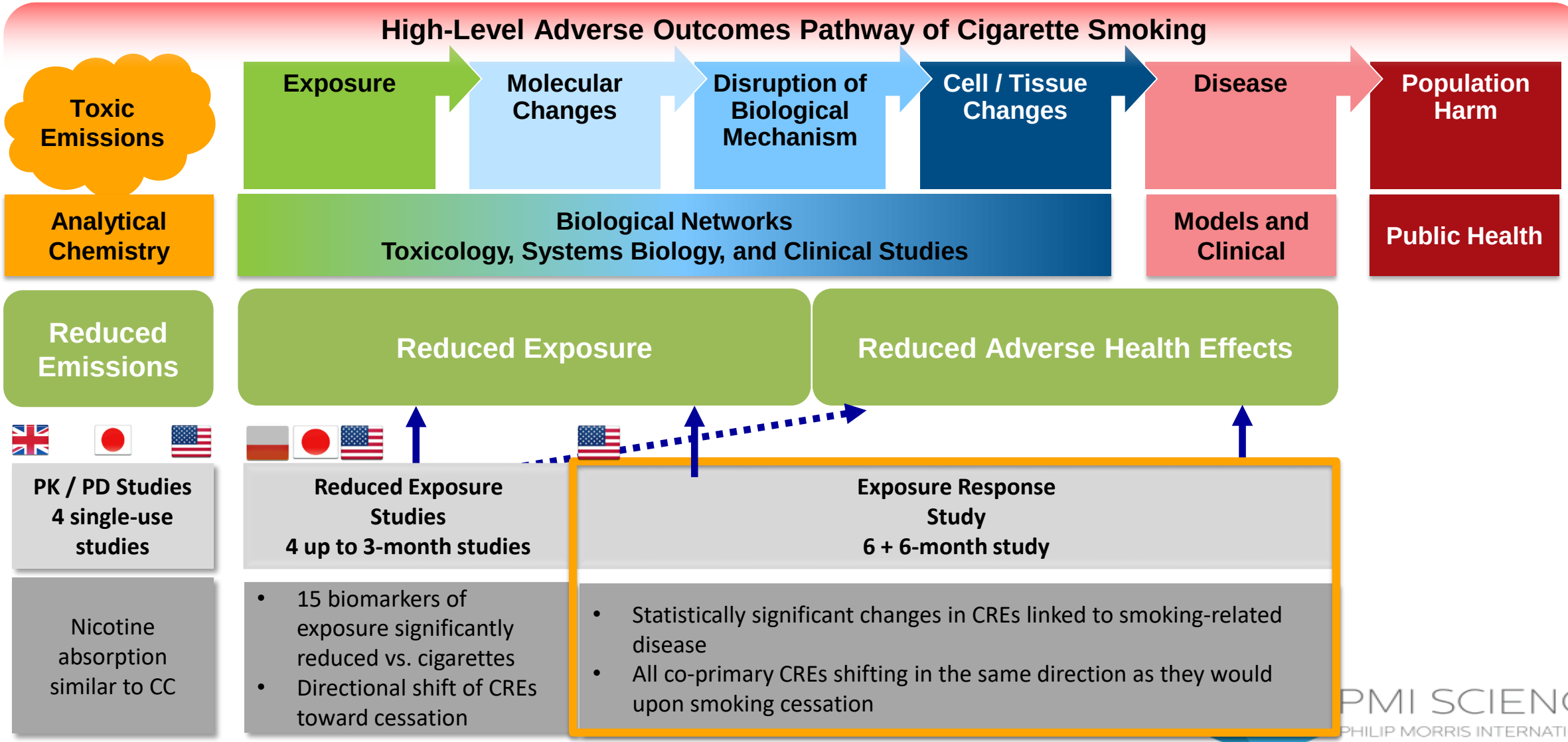
* On equivalent nicotine basis

Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects



Clinical Assessment – Results to Date



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Primary Objective and Co-Primary Endpoints

Smoking Cessation

Epidemiologic link to smoking-related disease?

Affected by smoking status

Reversible upon smoking cessation

Co-Primary Endpoints Representative of Pathomechanisms	
Lipid Metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial Function	sICAM-1
CO Acute Effect	COHb
Inflammation	WBC
Oxidative Stress	8-epi-$PGF_{2\alpha}$
Lung Function	FEV_1
Genotoxicity	Total NNAL

Assess the changes across a set of the "8 co-primary clinical risk endpoints" in smokers who switch from smoking cigarettes to using THS as compared to those continuing to smoke cigarettes for 6 months

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Study Population – Main Eligibility Criteria

Healthy subjects, minimum 30 years of age

10 years of smoking history with at least 10 cigarettes/day for the last year

Subjects did not intend to quit smoking

Clinically relevant disorders that would jeopardize the participants' safety

Female, pregnant or breastfeeding

Subjects using medication with an impact on co-primary endpoints

Green Frame: Inclusion Criteria

Red Frame: Exclusion Criteria

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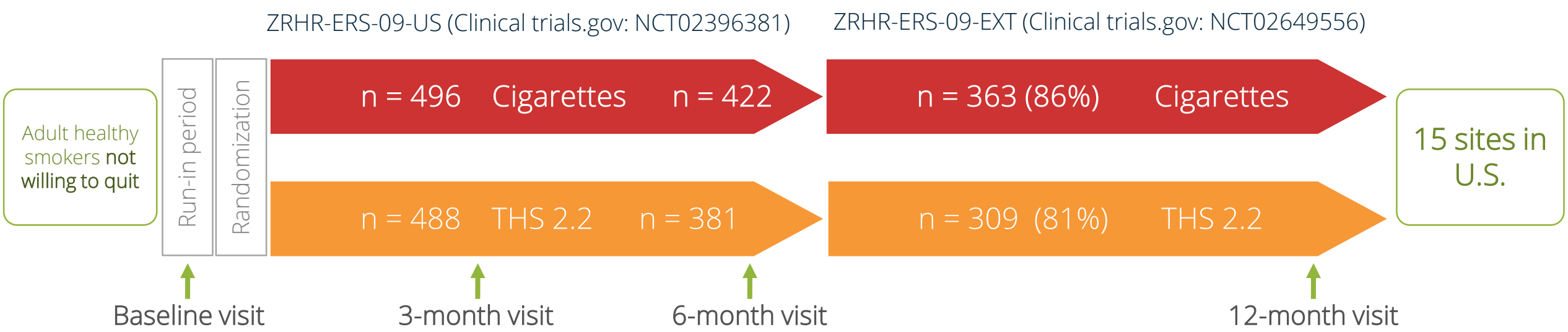
Study Design and Disposition - Exposure Response Study



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Changes in Clinical Risk Endpoints

Endpoint	Change From CC-use	Observed Change LS Mean Difference / Relative Reduction	Halparin Ruger Adjusted CI	1-sided p-value (0.0156)	THS directional change vs SA (literature)
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	<0.001*	✓ significant
WBC Count	Difference	-0.420 GI/L	-0.717, -0.123	0.001*	✓ significant
sICAM-1	% Reduction	2.86 %	-0.426, 6.04	0.030	✓
11-DTX-B2	% Reduction	4.74 %	-7.50, 15.6	0.193	✓
8-epi-$PGF_{2\alpha}$	% Reduction	6.80 %	-0.216, 13.3	0.018	✓
COHb	% Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV_1 %pred	Difference	1.28 % pred	0.145, 2.42	0.008*	✓ significant
Total NNAL	% Reduction	43.5 %	33.7, 51.9	<0.001*	✓ significant

* denotes significant *p*-value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

- All CREs shifted in the same direction as the smoking cessation effect observed in the literature
- 5 out of 8 clinical risk endpoints were statistically significant compared with continued smoking

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Conclusion of the Exposure Response Study

- All clinical risk endpoints shifted in the same direction as the smoking cessation effect described in the literature
- 5 out of 8 endpoints showed statistically significant and favorable changes after switching to THS…
- …despite the fact that up to 30% cigarette use was allowed in the primary analysis population
- Full switching is the best option for current adult smokers continuing to use tobacco products

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Independent Verification of PMI's Science – Govt. Bodies

Federal Institute for Risk Assessment (BfR) (Germany, 2018) – in line with our results:

"The herein confirmed reductions of relevant toxicants by about 80-99% are substantial"

Food and Drug Administration Briefing Document (U.S. FDA, 2018) – in line with our results:

"*The independent testing performed by STL* [FDA's Southeast Tobacco Laboratory] *confirmed the lower levels of selected [*harmful and potentially harmful compounds*] HPHCs in the aerosol from the HeatSticks compared to mainstream cigarette smoke*."

Public Health England (U.K., 2018) – in line with our results:

"*Compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds. The extent of the reduction found varies between studies*."

National Institute for Public Health and the Environment (RIVM) (Netherlands, 2018) – in line with our results:

"The use of heatsticks with the IQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes."

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Overall Conclusion

- **Tobacco Harm Reduction** is about offering smoke-free alternatives to adult smokers who would otherwise continue smoking. It is a sensible, complementary addition to existing tobacco control strategies (prevention and cessation).

- Heated tobacco products, THS 2.2 in particular, are addictive and not risk-free. However, the totality of the scientific evidence demonstrates that switching completely to THS 2.2 **presents less risk of harm** than continuing to smoke.

- To date, a growing number of number of **independent studies** corroborate PMI findings.

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We Are Open & Transparent About Our Science

You are welcome to visit our R&D center in Neuchâtel (Switzerland) to meet and discuss our study results with our scientists.

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Thank you for your attention

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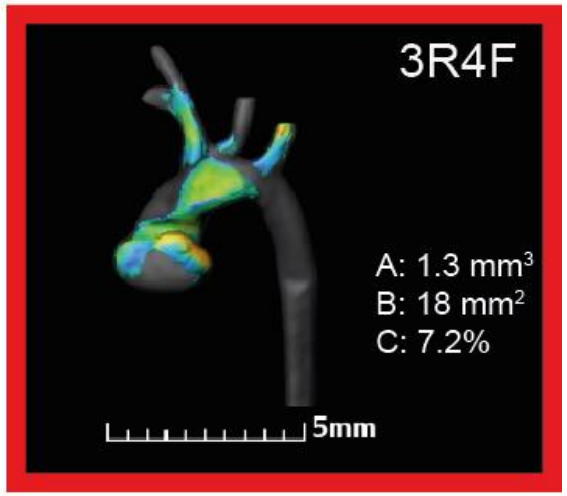
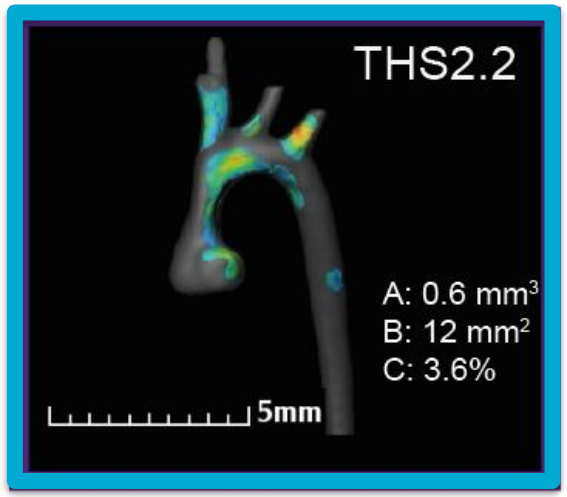
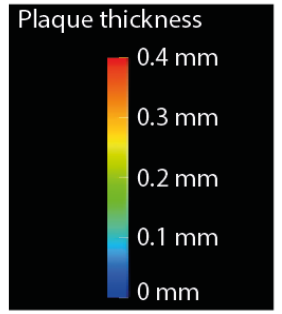
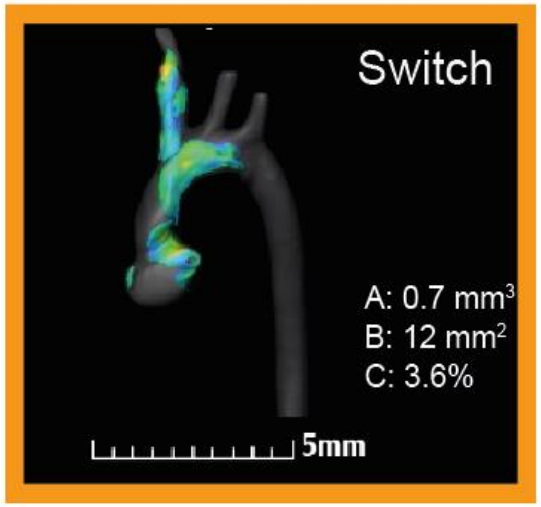
Back-up slides

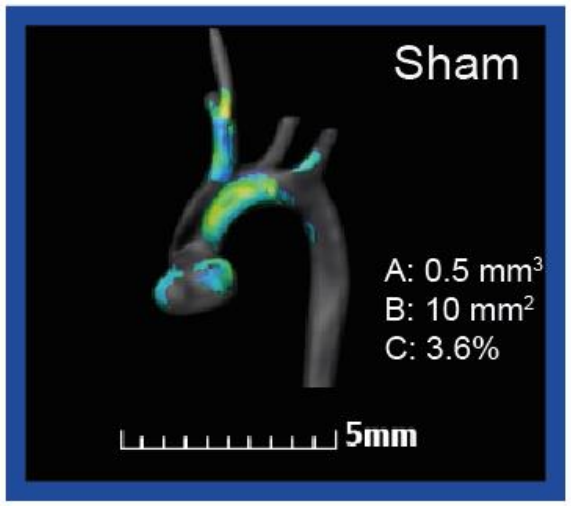
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at month 7

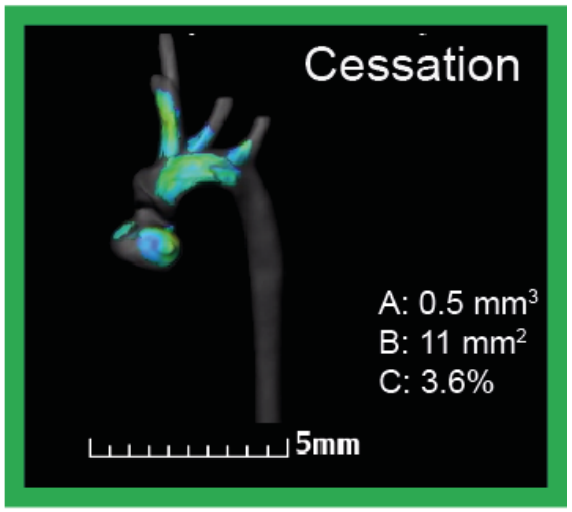












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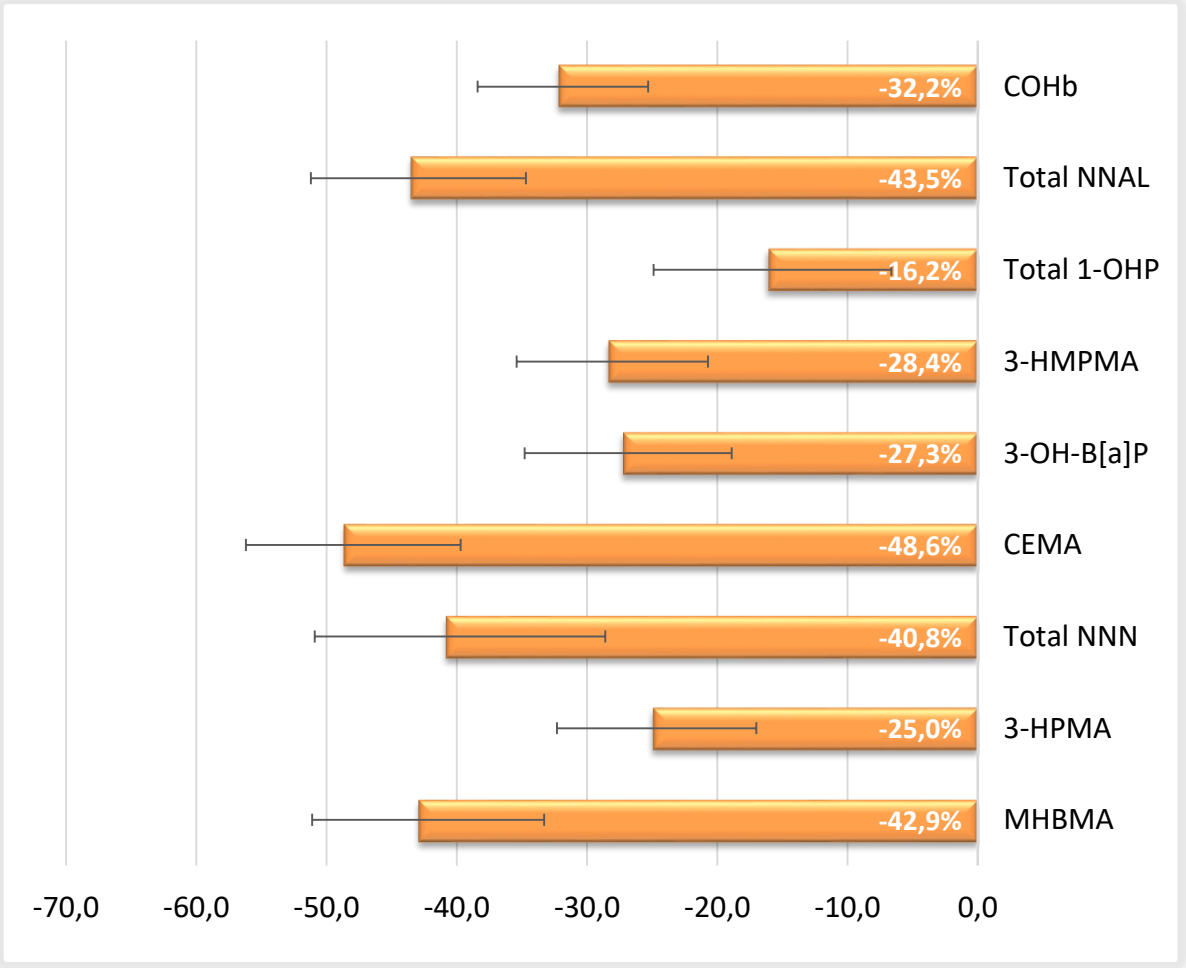
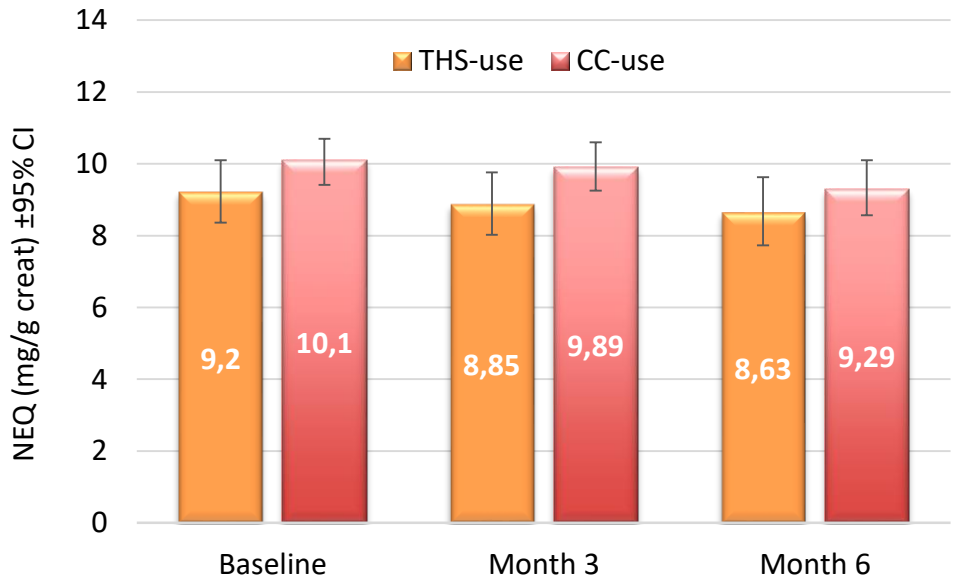
Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences **149(2): 411-432.**

Reduction in Exposure and Exposure to Nicotine





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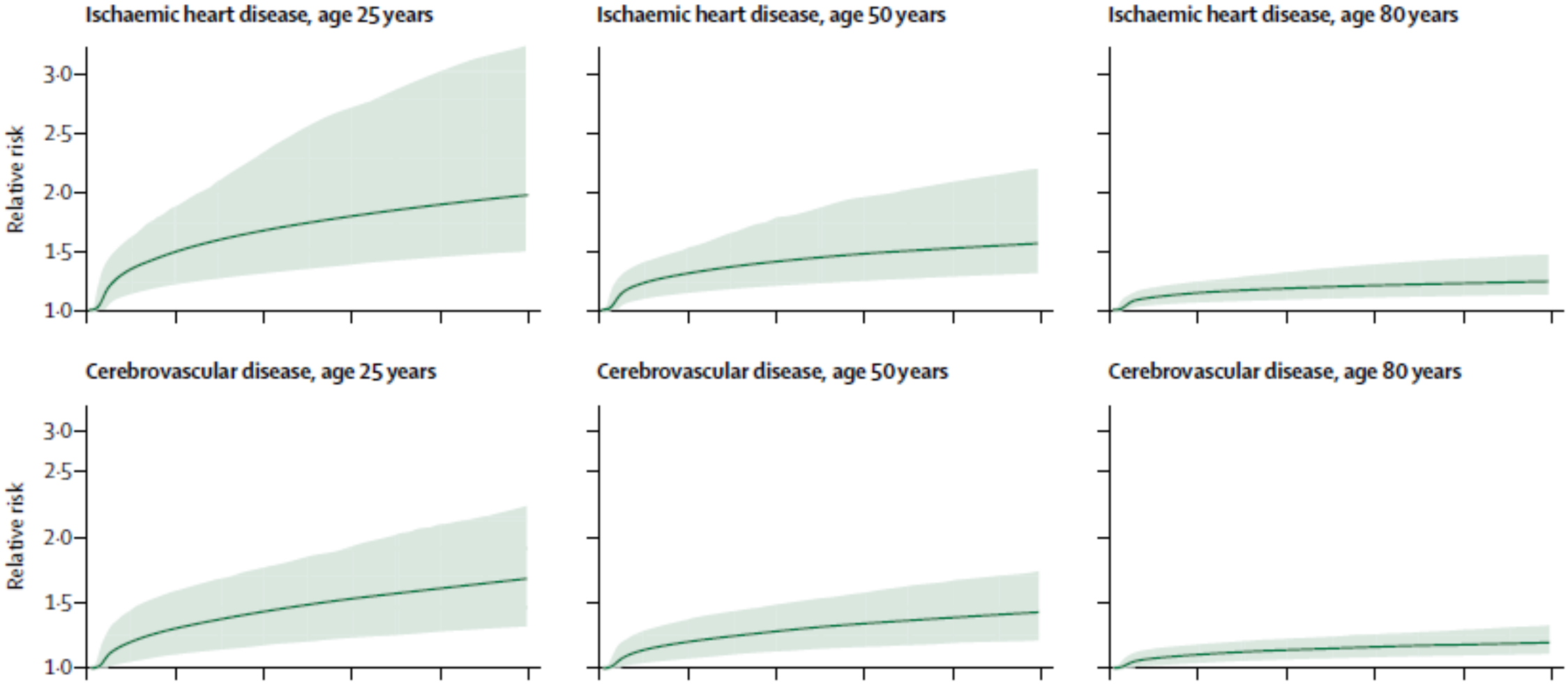
Global Disease Risk Associated with PM 2.5



Cohen et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; 1907-1918.

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SD-654

Statistical Analysis

Success criteria:

To establish that the risk profile of THS is modified compared to cigarettes

1. All co-primary endpoints shift in the direction of cessation
2. ≥ 5 out of 8 clinical risk endpoints are statistically significant (Hailperin-Rüger Approach)
3. Majority of the smoking cessation effect is preserved

Primary analysis: predominant users of THS > 70%

Establish modification of risk

Smokers' Health Profile
Study-wise α=0.05
Test-wise α=0.031

If modification of risk is established

≥ 5/8 significant clinical risk endpoints*

Results of the study can be verified with the effects measured for smoking cessation

*By using a 1-sided test with the Hailperin-Rüger adjusted α level for multiple testing (1.5625%).

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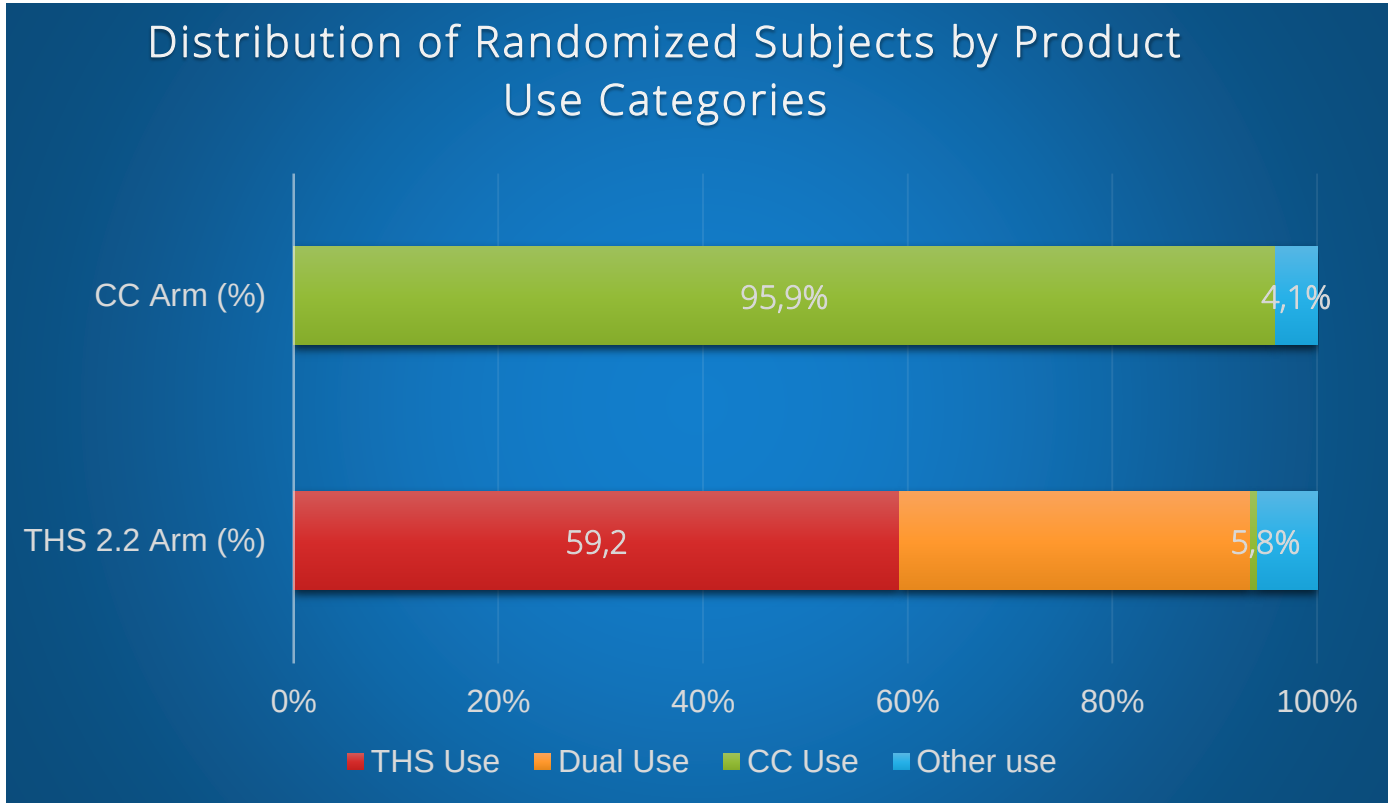
Main Analysis Population

THS-Use

- Randomized Product Use
- ≥ 70% THS use*

CC-Use

- Randomized Product Use
- ≤ 1% THS use*



* Calculated over the study and on at least 50% of the Study Days

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Product Use

Time Period	Product	THS Use Mean / Day (Min, Max)	CC Use Mean / Day (Min, Max)
Baseline	Cigarettes	18.5 (10.0, 65.0)	19.5 (10.0, 90.0)
Post-randomization	THS	16.5 (3.2, 63.0)	< 0.01 (0.0, 0.44)
	Cigarettes	1.95 (0.0, 14.0)	16.8 (3.0, 43.7)
	Overall tobacco	18.5 (3.2, 63.5)	16.9 (3.1, 43.7)