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CARDIOVASCULAR EFFECTS OF THE TOBACCO HEATING SYSTEM (THS) 2.2 COMPARED WITH CONTINUED SMOKING

Athens, Greece

Dr. Patrick Picavet, M.D., on behalf of:
Baker, Gizelle; Haziza, Christelle; Hoeng, Julia; Ivanov, Nikolai; Luedicke, Frank; Maeder, Serge; Peitsch, Manuel; Phillips, Blaine; Poussin, Carine; Vanscheeuwijck, Patrick

Philip Morris International
9 June 2018

The Scientists

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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.

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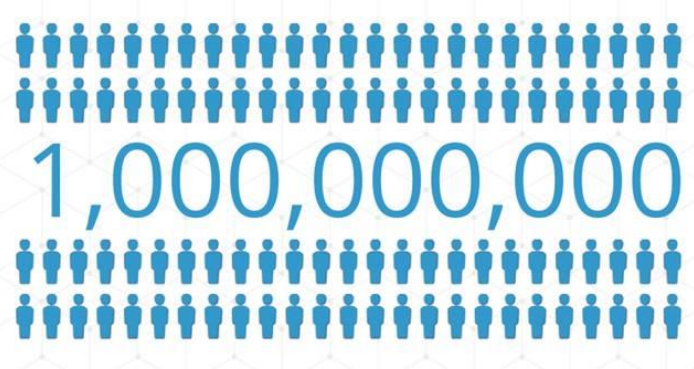
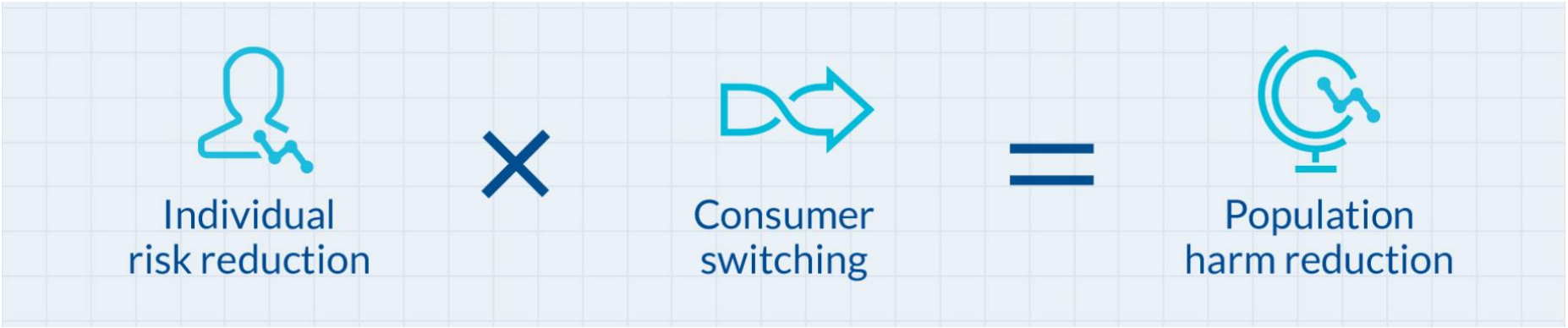
Tobacco Harm Reduction

What Is the Objective of 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 they can fully switched to, 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 switched to these products versus continued smoking.

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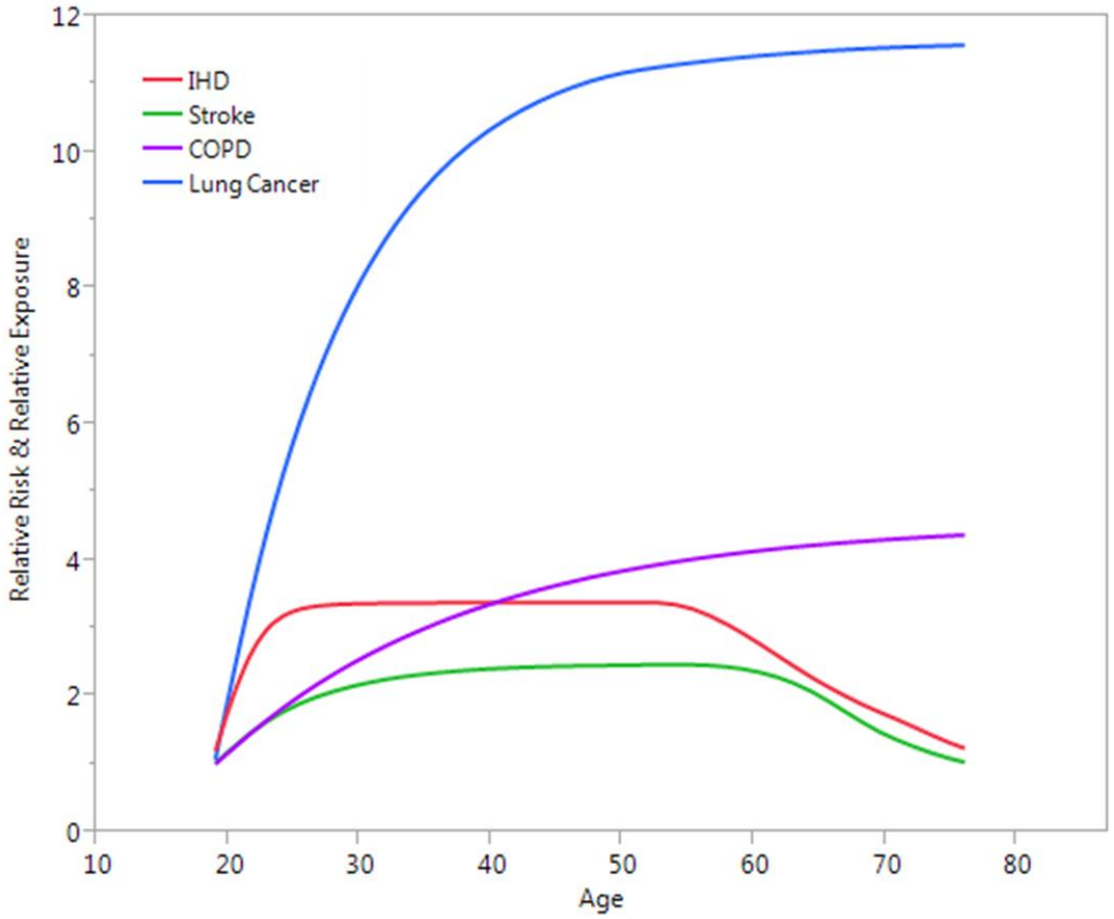
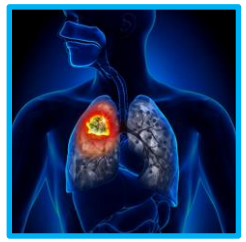
Excess Risk of Smoking-Related Disease

Disease-Specific Relative Risk [1] (by age) *Relative risk of IHD, Stroke, COPD, and LC for an adult cigarette smoker*





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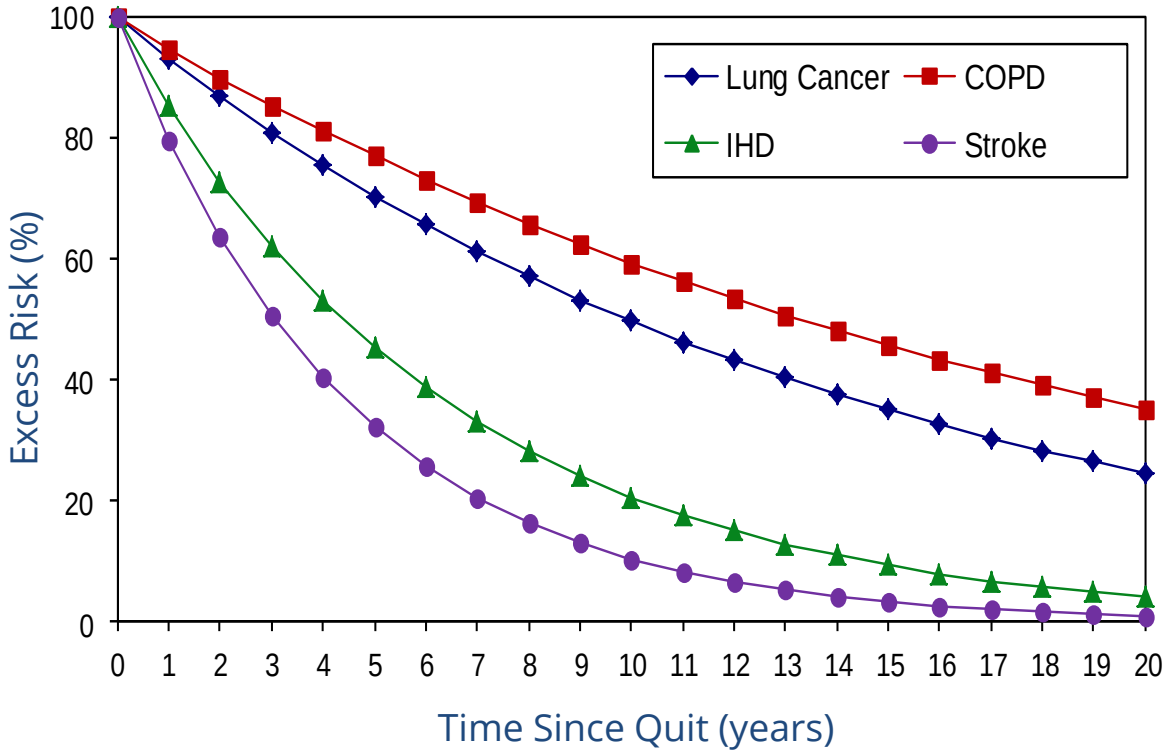
Excess Risk of Smoking-Related Disease

Reduction in Excess Risk Over Time



	Disease Risk Half-Life [2] (The time at which half of the Excess risk associated with cigarette smoking has disappeared)			
Age (*a*)	Lung Cancer	IHD	Stroke	COPD
Any age	-	-	4.78	13.32
to 49	6.98	1.47	-	-
50 to 59	10.39	5.22	-	-
60 to 69	10.60	7.48	-	-
70 to 79	12.99	13.77	-	-

[1] Sources for relative risk: Lung Cancer (Lee 2012), COPD (Forey 2011), IHD and Stroke (Lee 2016)
[2] Sources for half-life of risk: Lung Cancer (Fry 2013), COPD (Lee 2014), IHD (Lee 2012), Stroke (Lee 2014)

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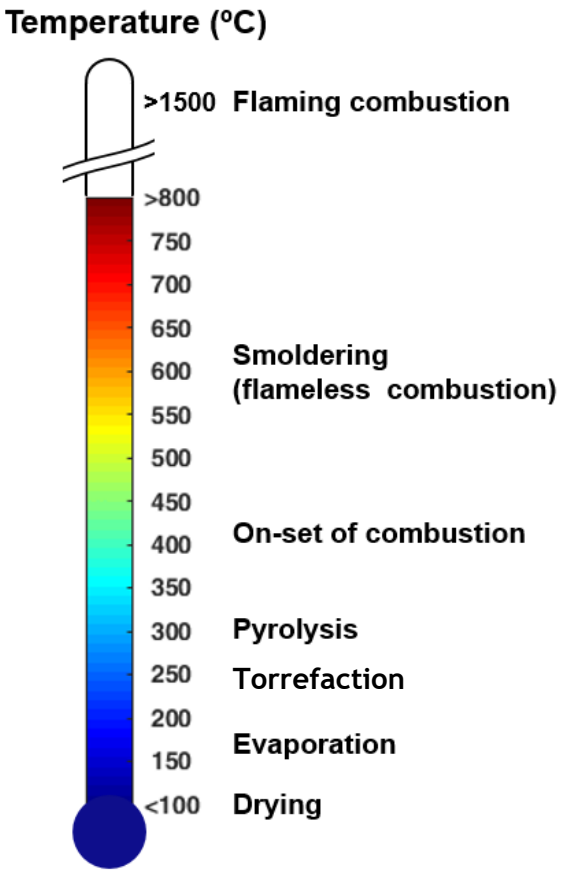
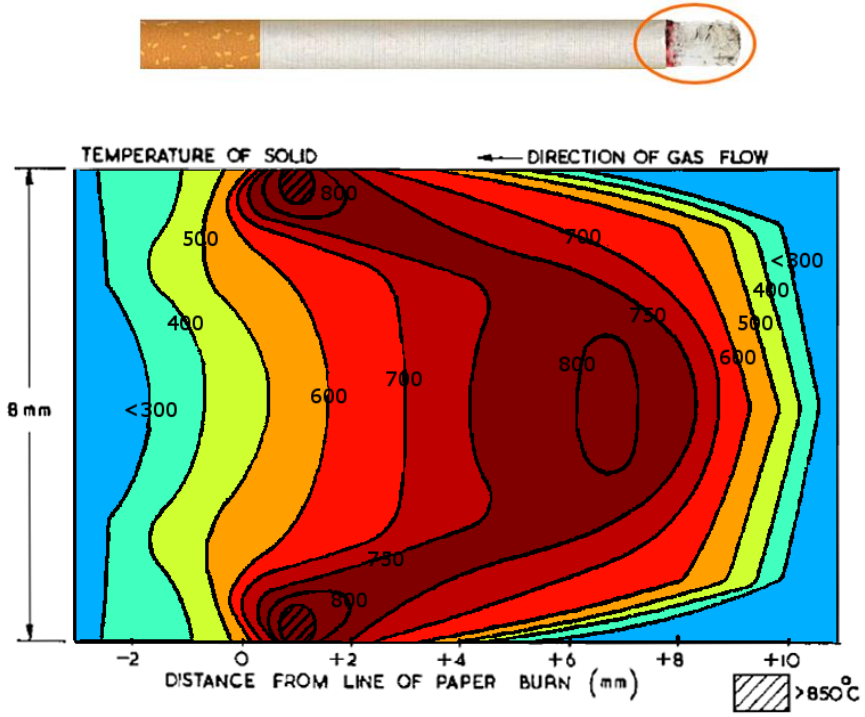
Combustion

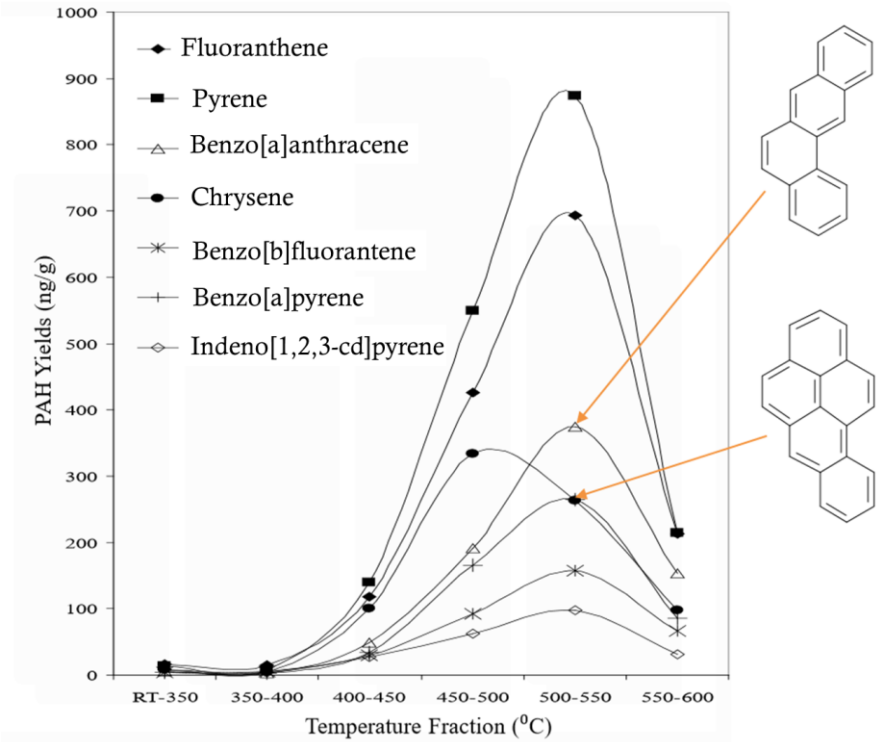
Elimination of Combustion Is Key

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





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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The Tobacco Heating System 2.2

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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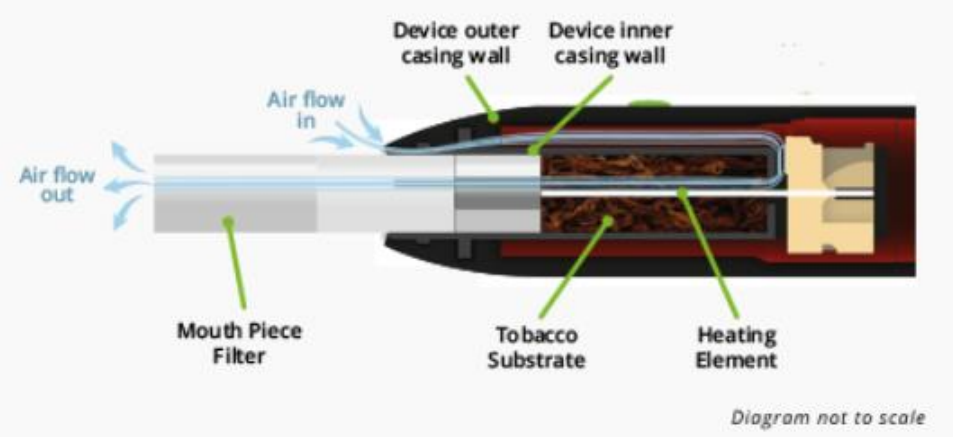
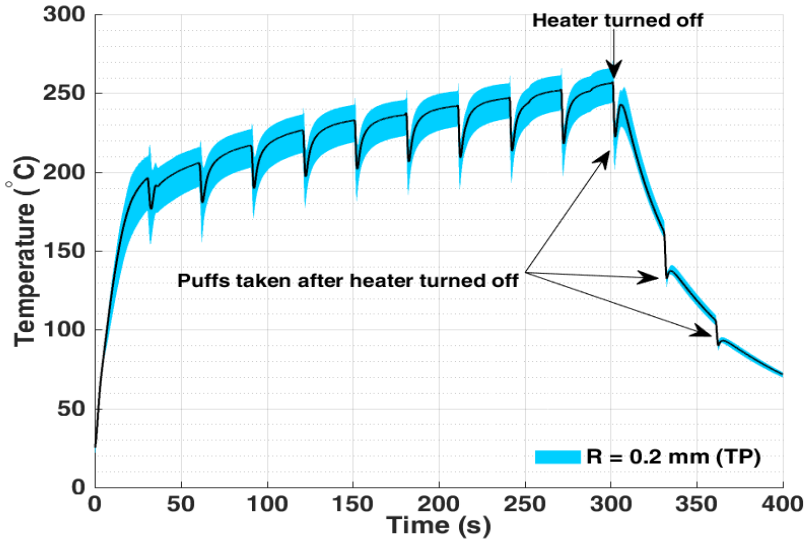
Why Heat Tobacco Rather than Burn It?

The Tobacco Heating System (THS) (currently commercialized as *IQOS* in > 38 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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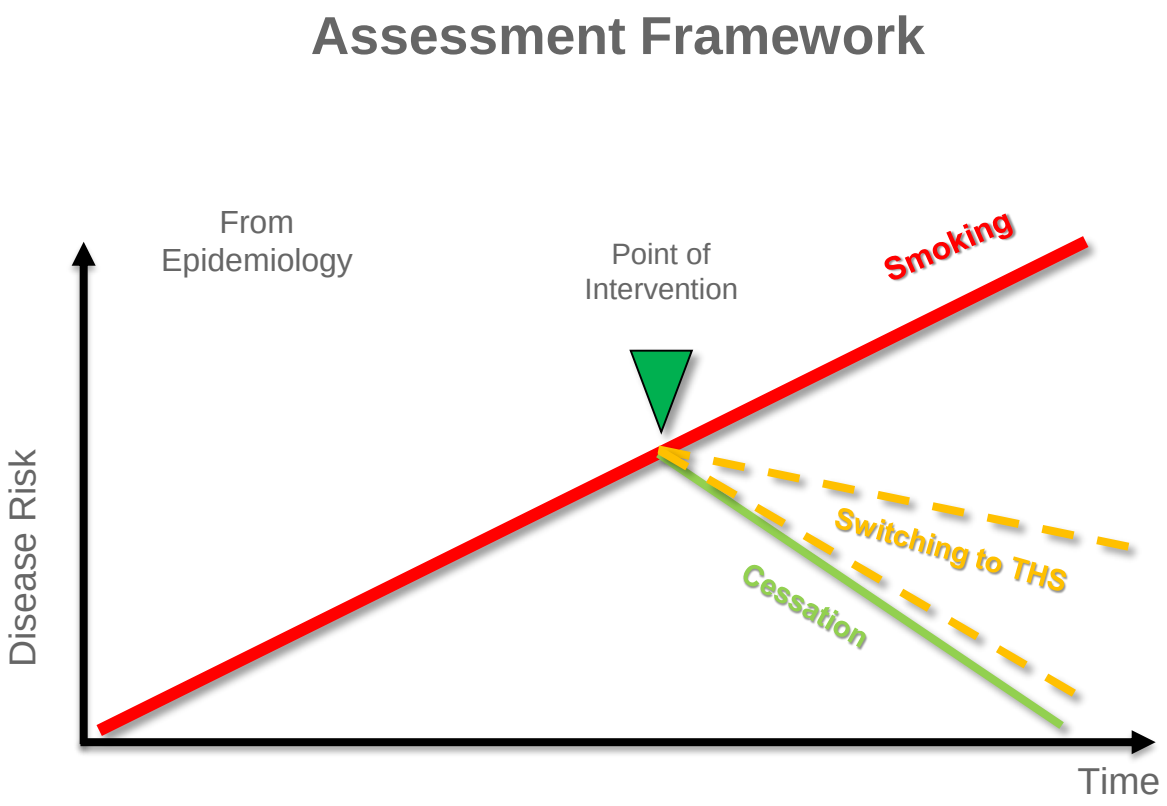
Scientific Assessment Approach

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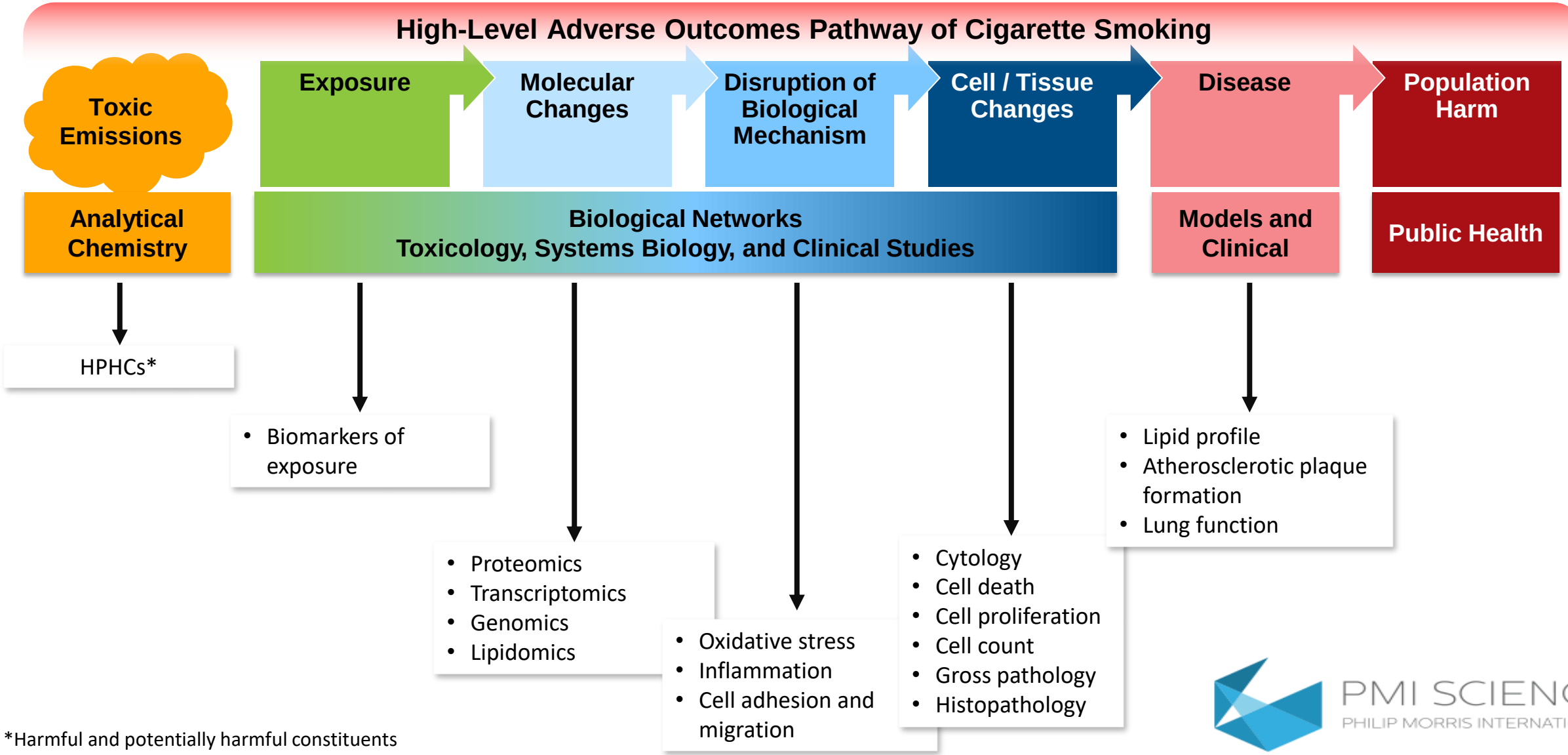
Source: Smith, M.R., et al., Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). http://dx.doi.org/10.1016/j.yrtph.2016.07.006

Assessment Framework: Informed by Epidemiology



*Harmful and potentially harmful constituents

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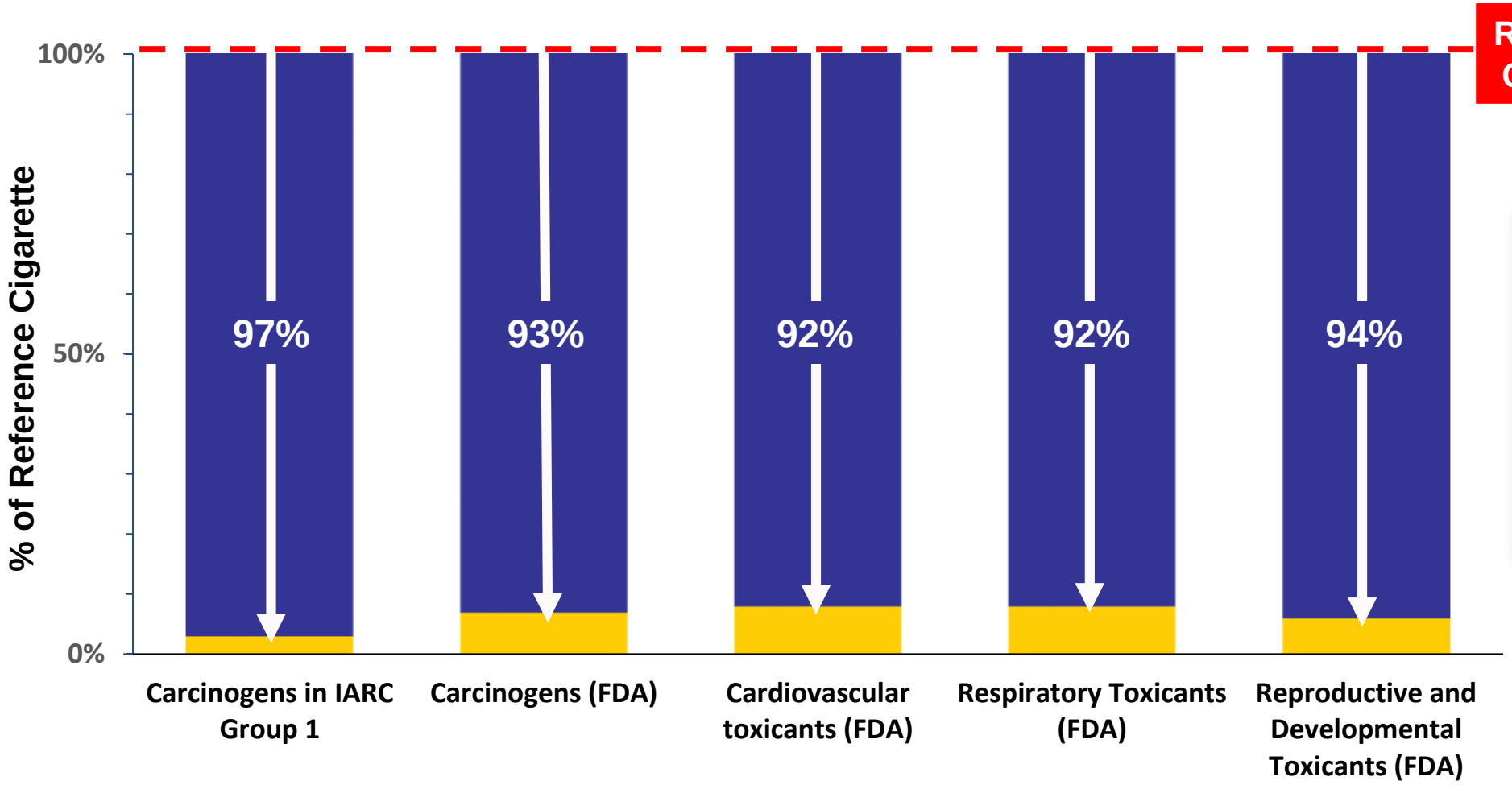
Exposure Reduction and Carbon-Based Nanoparticles

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: Intense Health Canada's Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

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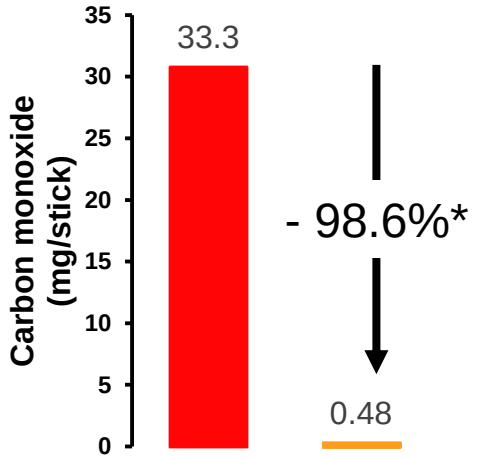
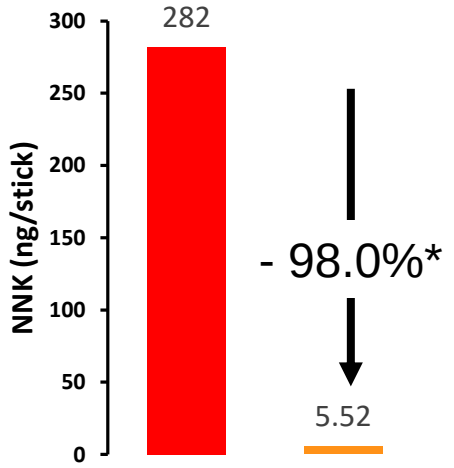
Changes in Exposure to HPHCs

Reduced Exposure in Healthy Human Subjects

Levels of HPHCs are Drastically Reduced in THS Aerosol





Leads to

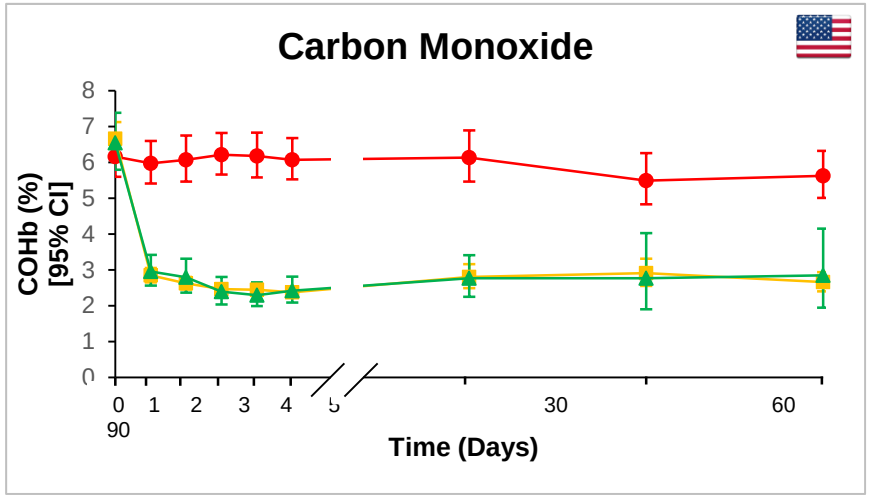
Cigarette

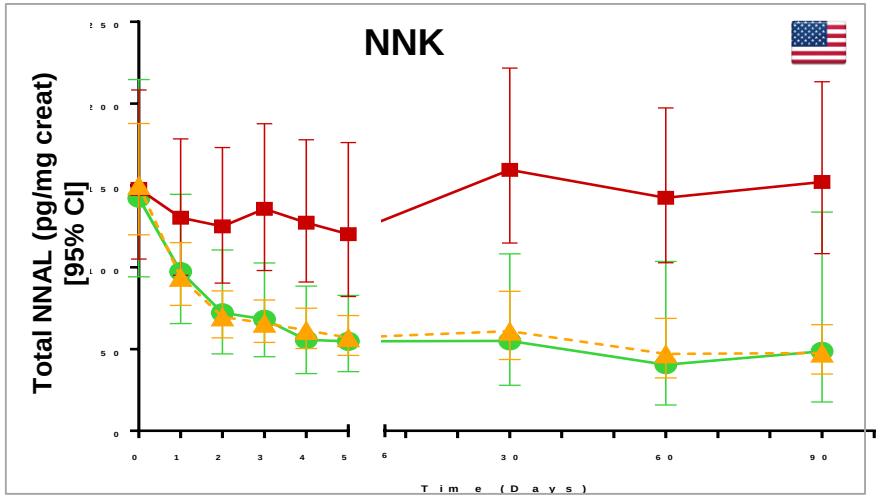
THS

Smoking Abstinence

Leads to

Exposure is Significantly Reduced After Switching to THS

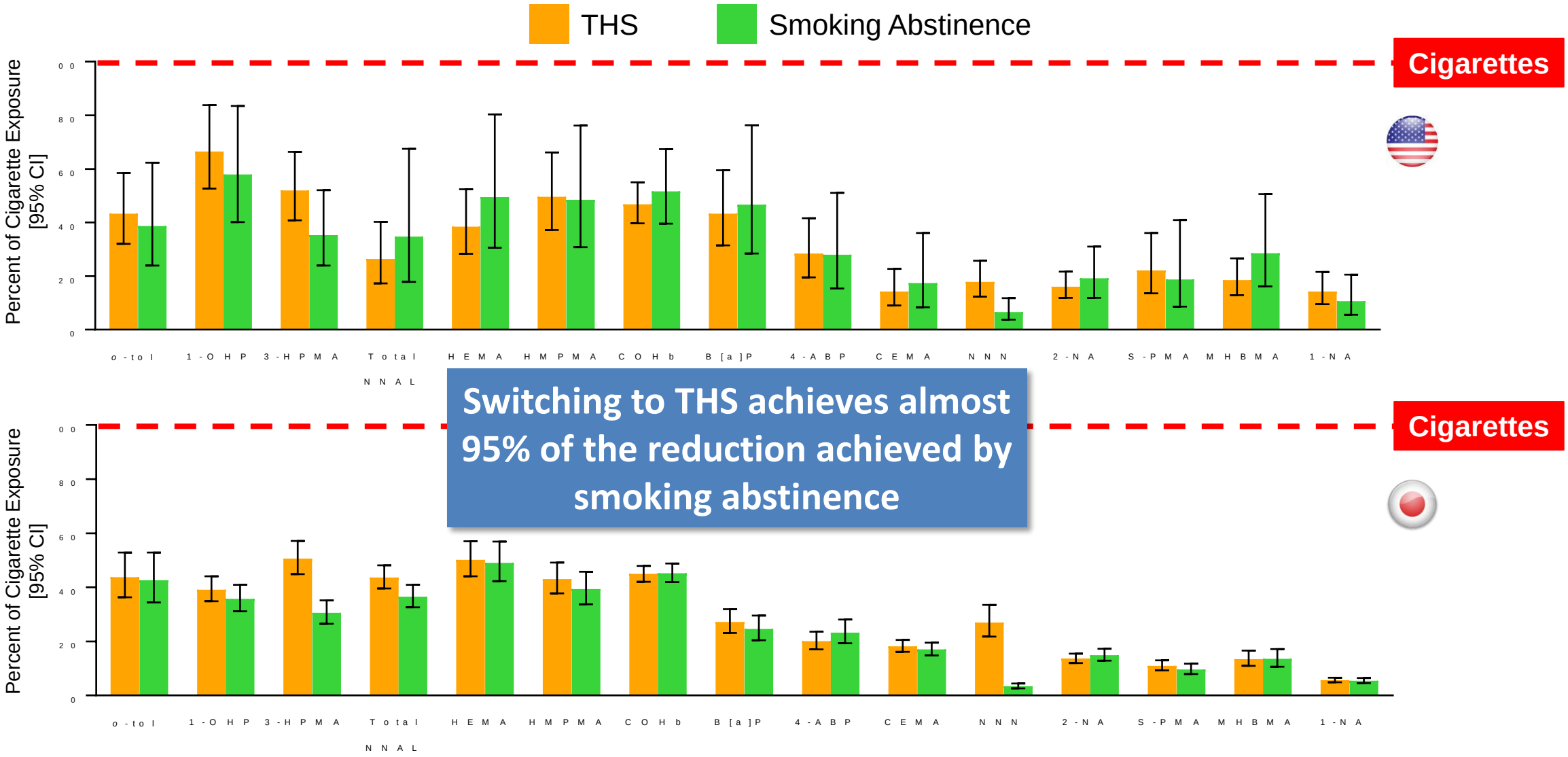




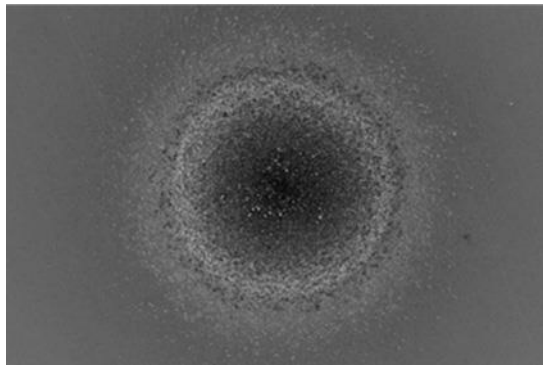
* On equivalent nicotine basis

Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects

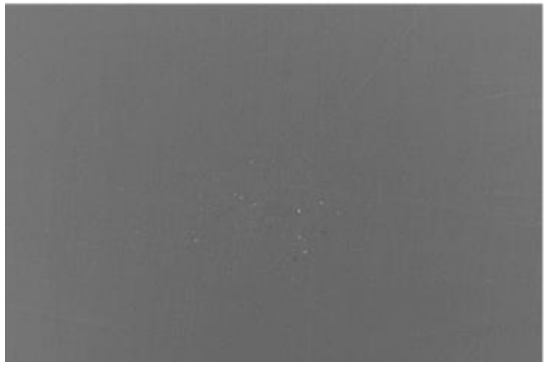


Reduced Formation of HPHCs by Disease Categories

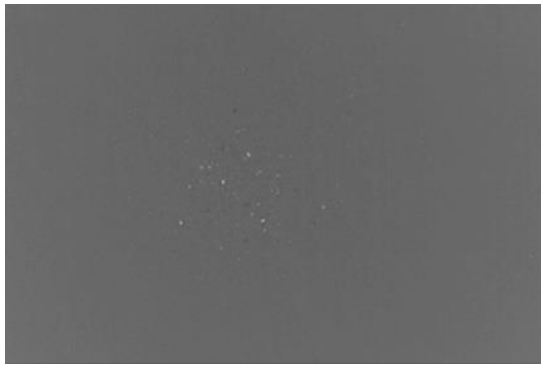


Cigarette smoke

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



Blank (Air)



THS aerosol

No solid particles

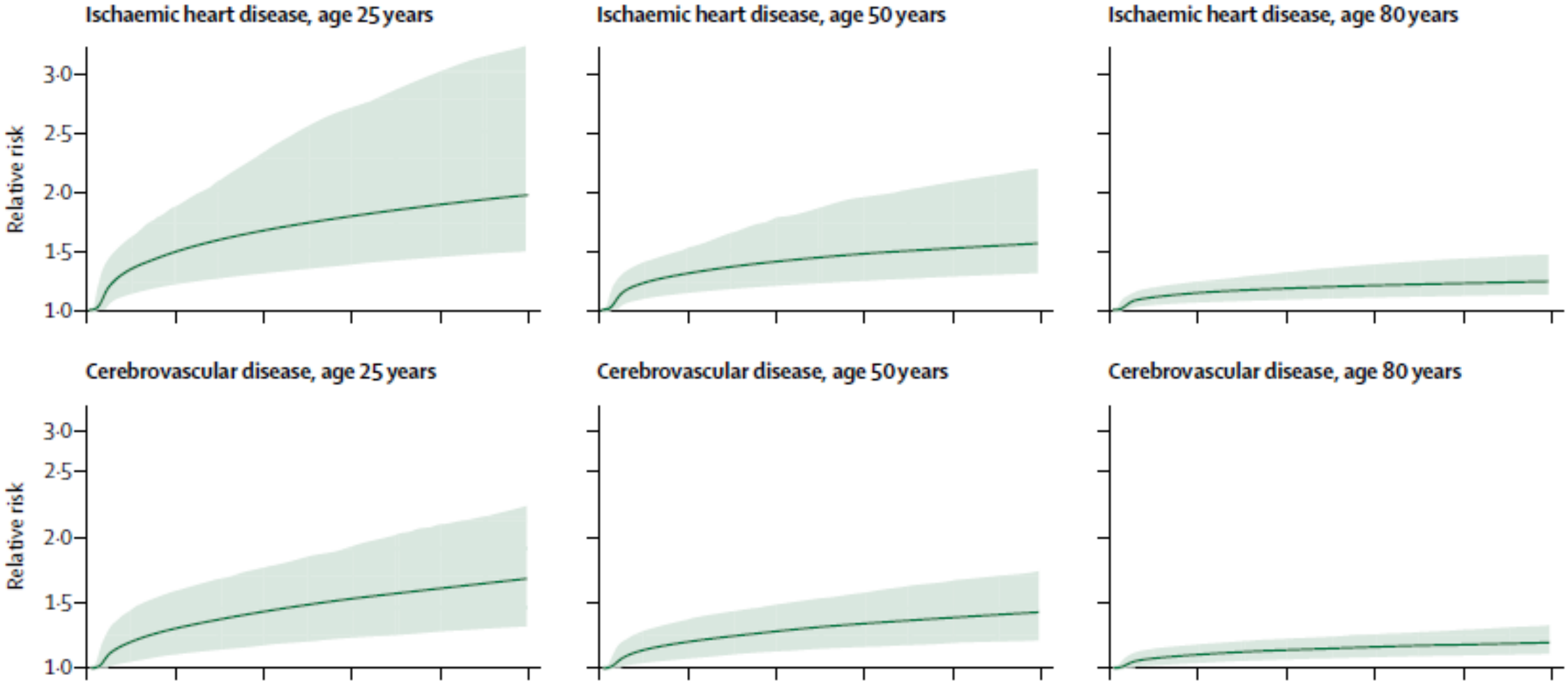
Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300º C to remove the volatile portion / collected material characterized by Electron Diffusive X-ray.

* Under the Health Canada's 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.

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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In Vitro Models of Disease

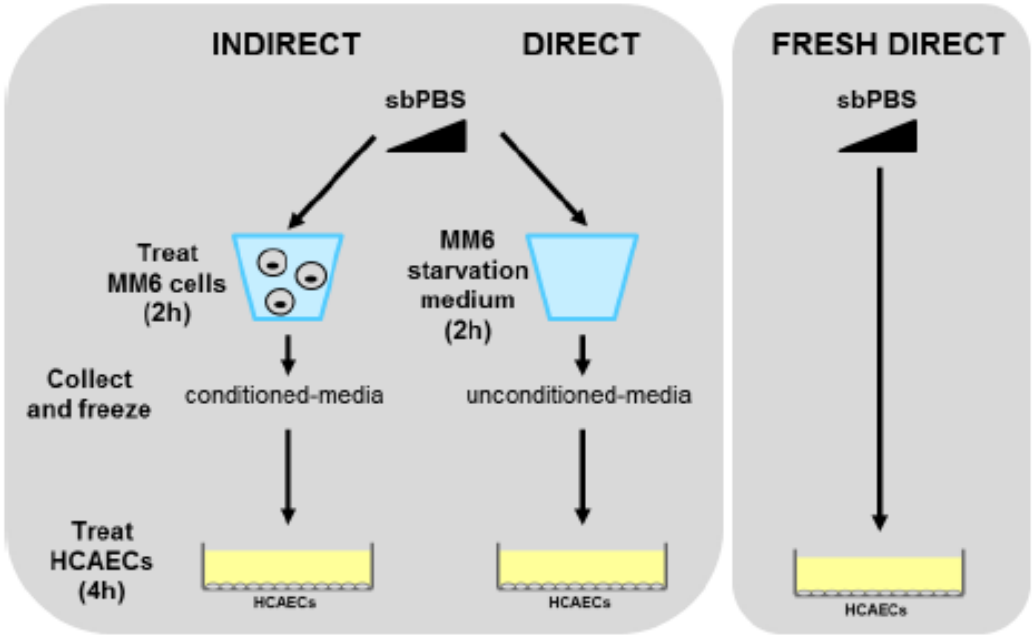
From Risk Assessment Framework to *In Vitro* Study Design

In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells

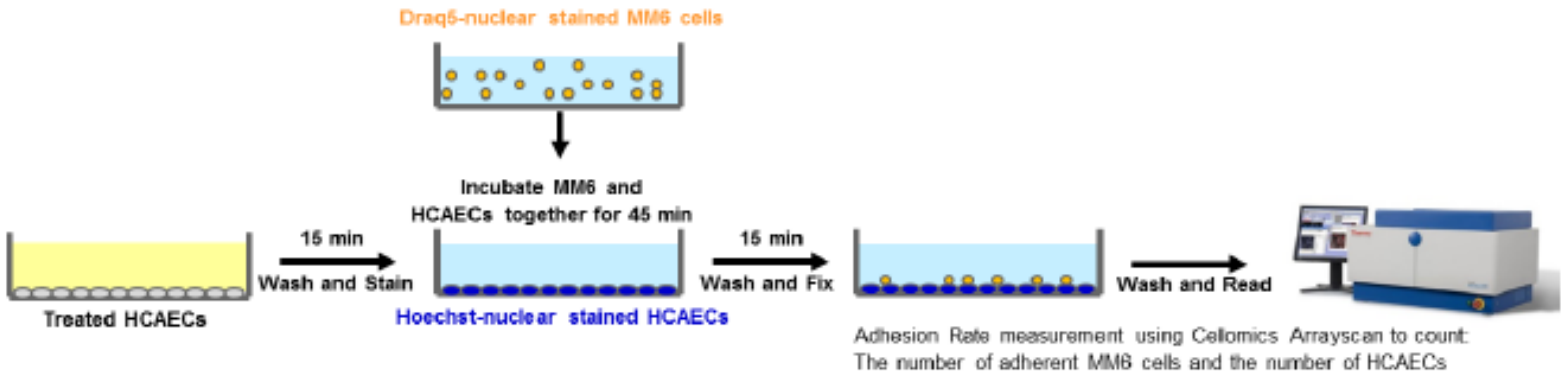
1. **Cell exposure to 3R4F or THS 2.2 (aqueous smoke / aerosol extract)**

2. **Treatment of human coronary arterial endothelial cells (HCAEC)**

3. **Adhesion Assay**
   - Untreated MM6 cells and 4h-treated HCAECs were nuclear-stained for 15 min. and then incubated together for 45 min
   - After cell fixing and washing, remaining adherent MM6 cells and HCAECs were counted
   - The adhesion rate was calculated



- **Adhesion assay (functional endpoint)**
- **Transcriptomics (molecular endpoints)**



Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. *Toxicology 2016*; 73–86.

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From Risk Assessment Framework to *In Vitro* Study Design

In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells

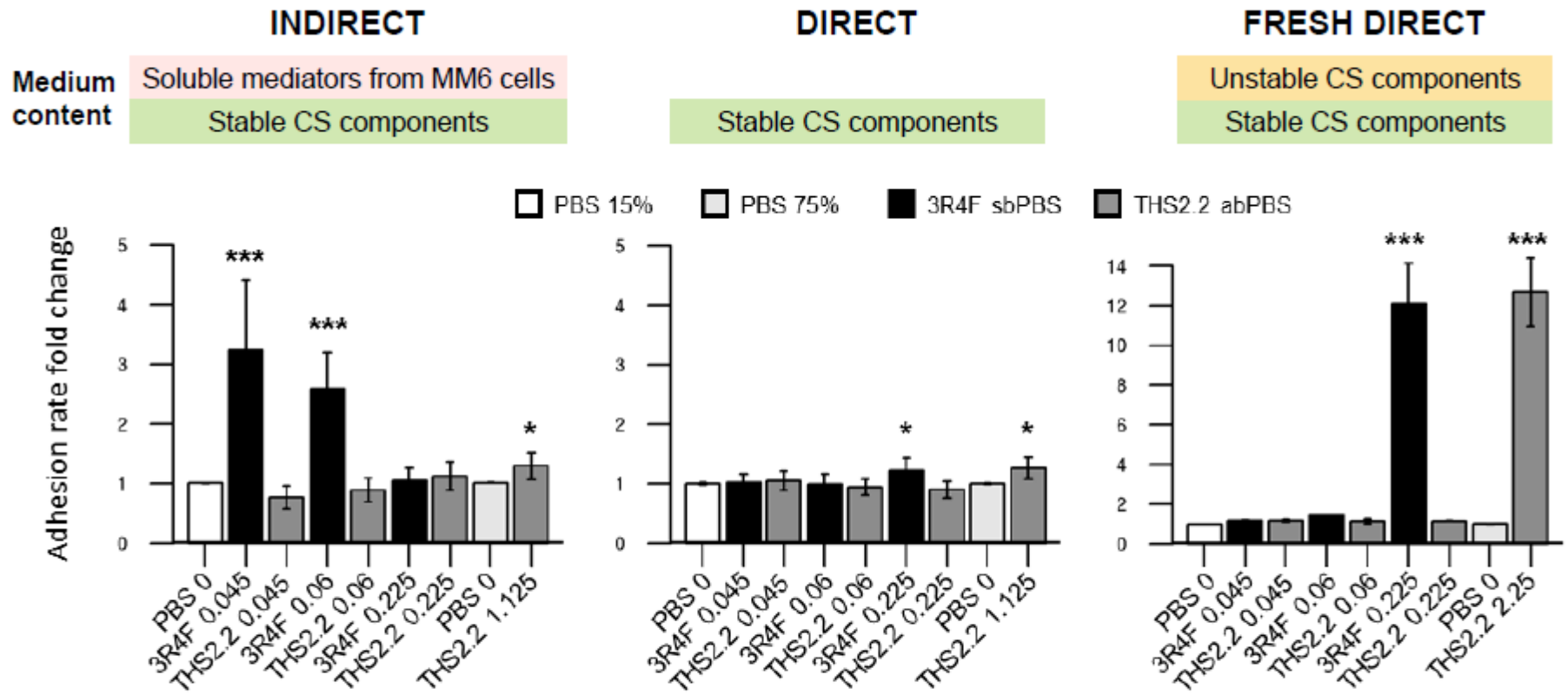

*Figure 1: Effects of THS2.2 abPBS and 3R4F sbPBS on the adhesion of MM6 cells to HCAECs following indirect, direct, and fresh direct treatments of HCAECs. Bar charts represent fold changes of the adhesion rate relative to respective vehicle controls. The adhesion rate reflects the number of adherent MM6 cells relative to the total number of HCAECs counted in the same well multiplied by 100. Data are presented as the mean ± SEM; N=2–3 independent experiments (n=3–6 replicates). *p≤0.05, ***p≤0.001 vs. 0 puffs/ml (PBS 15% or 75%).*

Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. *Toxicology 2016*; 73–86.

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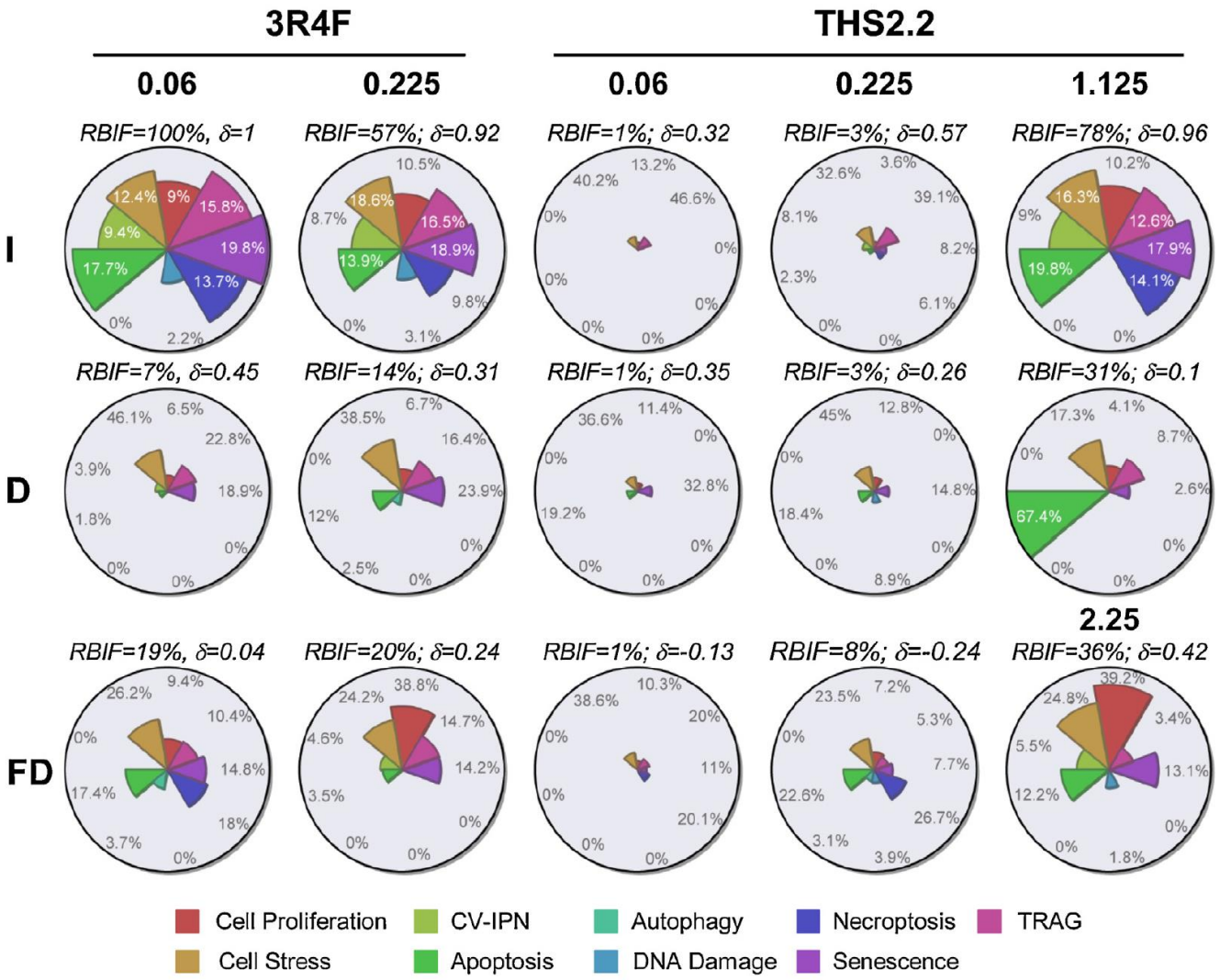
From Risk Assessment Framework to *In Vitro* Study Design

In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells



Conclusions:

- 3R4F aqueous cigarette smoke extract promoted adhesion of MM6 cells to HCAEC in indirect and fresh direct exposure conditions
- At the same concentrations, no significant adhesion of MM6 cells to HCAECs
- The concentrations of THS 2.2 required to be increased by ~10 and 20 times to observe similar effects at functional and molecular levels to the ones observed with 3R4F

Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. *Toxicology 2016*; 73–86.

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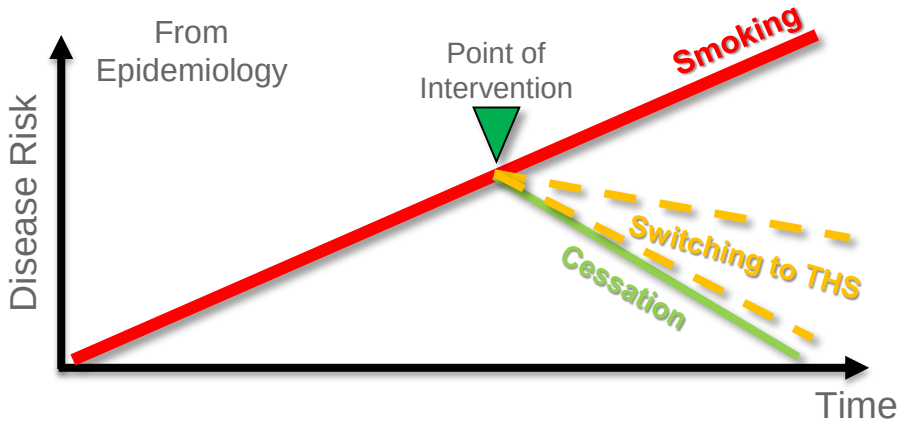
Animal Models of Disease

From Risk Assessment Framework to in vivo Study Design

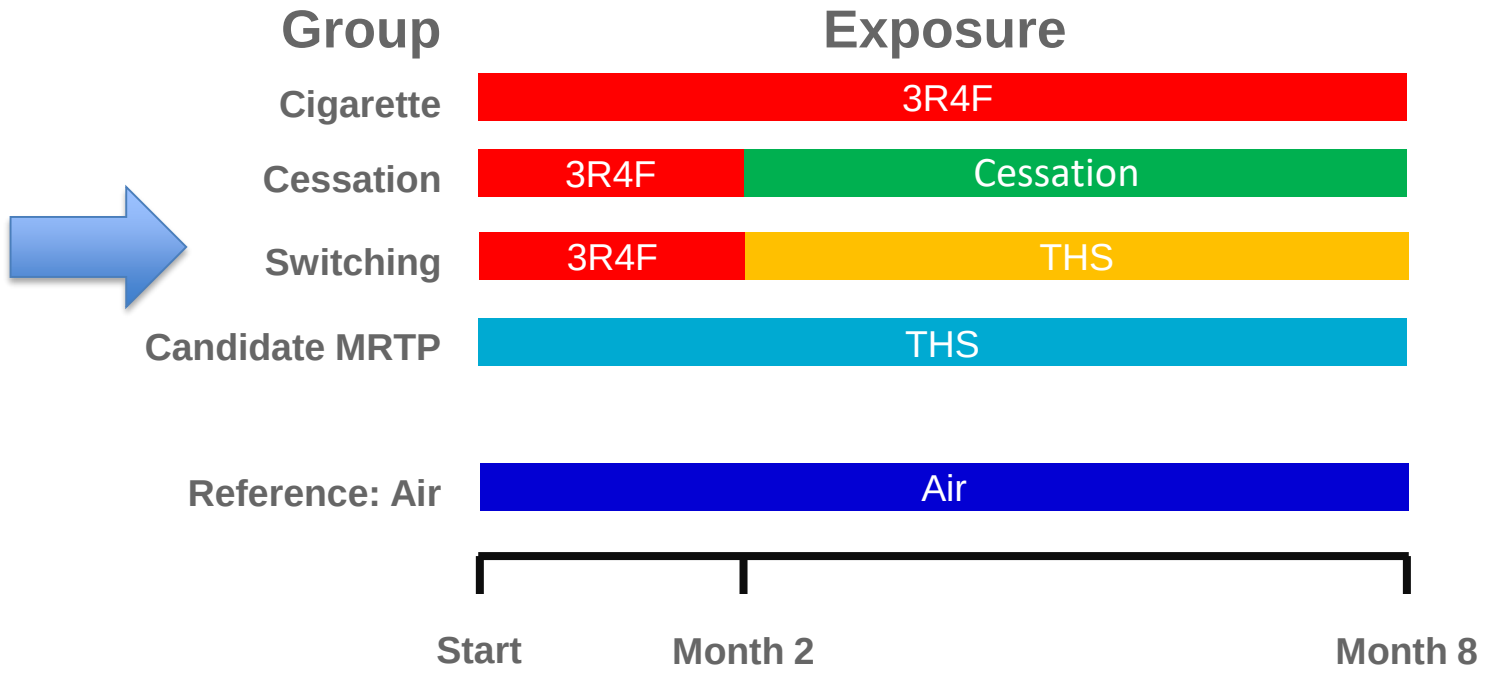
Animal Model: ApoE -/- mouse – Concomitant analysis of CVD and COPD endpoints

- 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



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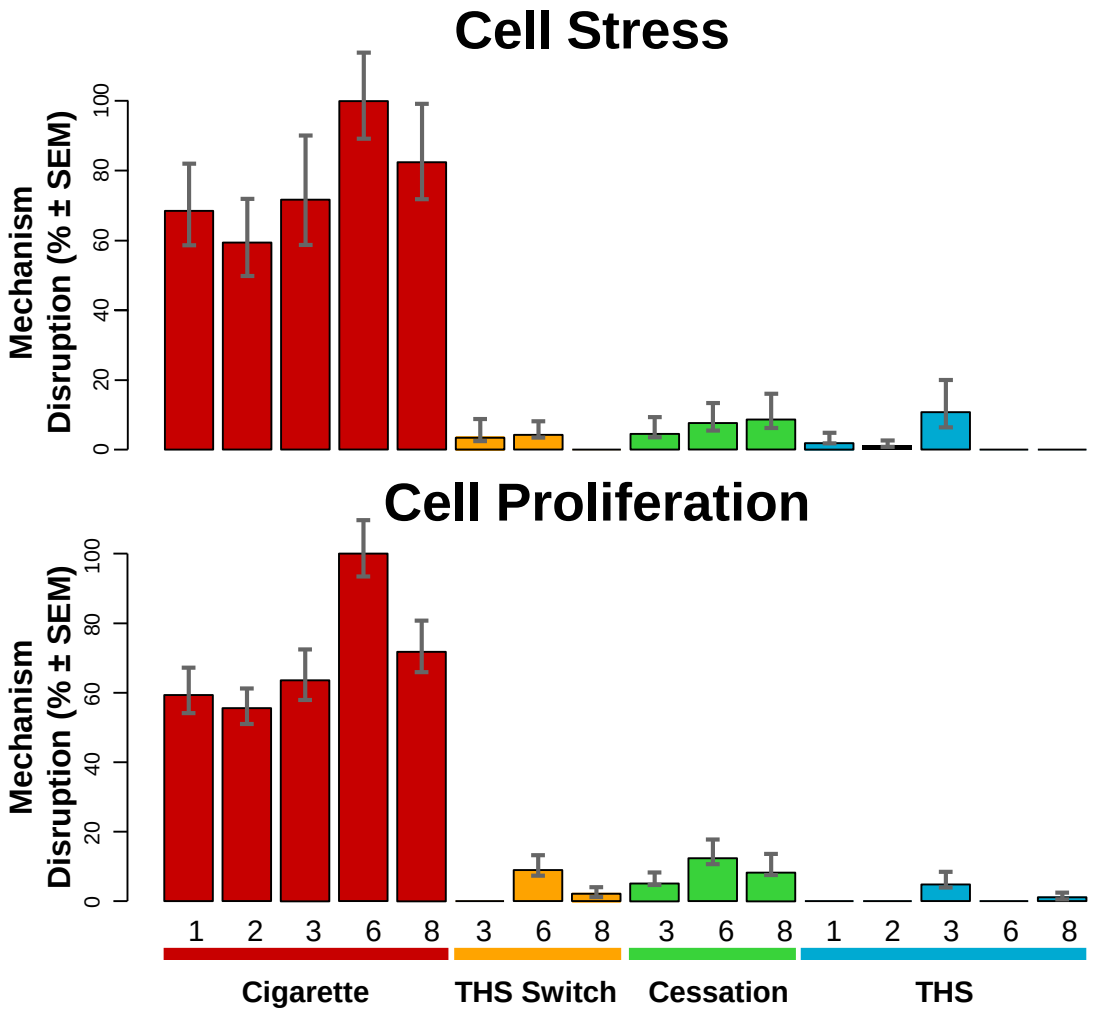
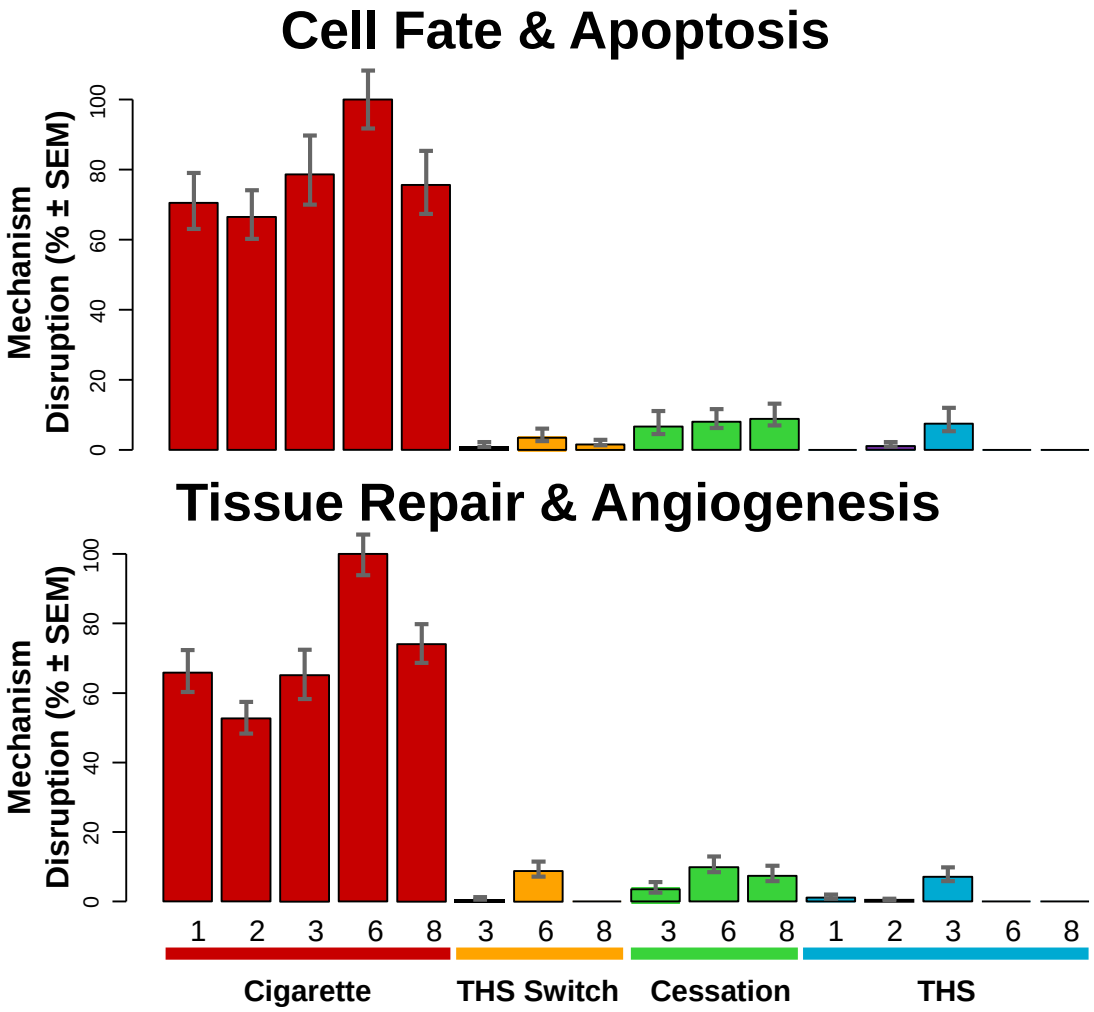
Phillips *et al.* (2015) An 8-Month Systems Toxicology Inhalation/Cessation Study in Apo e-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared with Conventional Cigarettes. Toxicological Sciences, in press

Reduced Effects on Disease Mechanisms





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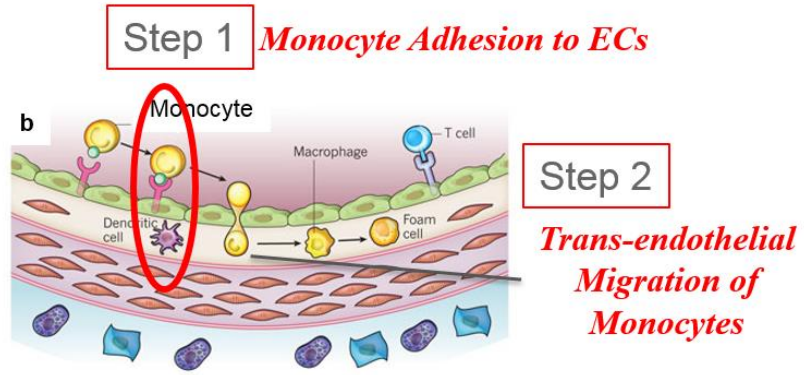
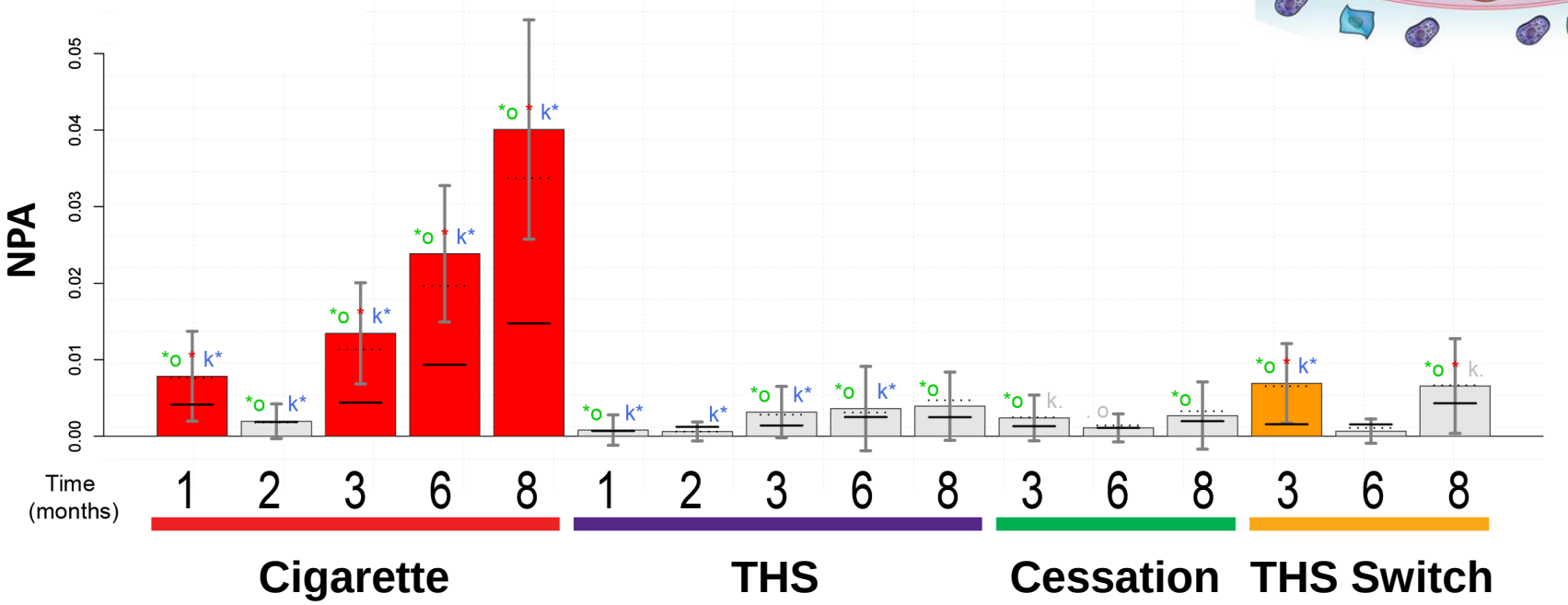
8-month Apoe-/- mouse switching study

Interaction between monocytes and endothelial cells

- **Network Perturbation Amplitude of:**
  - **Inflammation/Endothelial cell activation ↓**
  - **Inflammation/Neutrophil Signaling ↓**



Vascular Inflammation/
Endothelial cell – monocyte interaction



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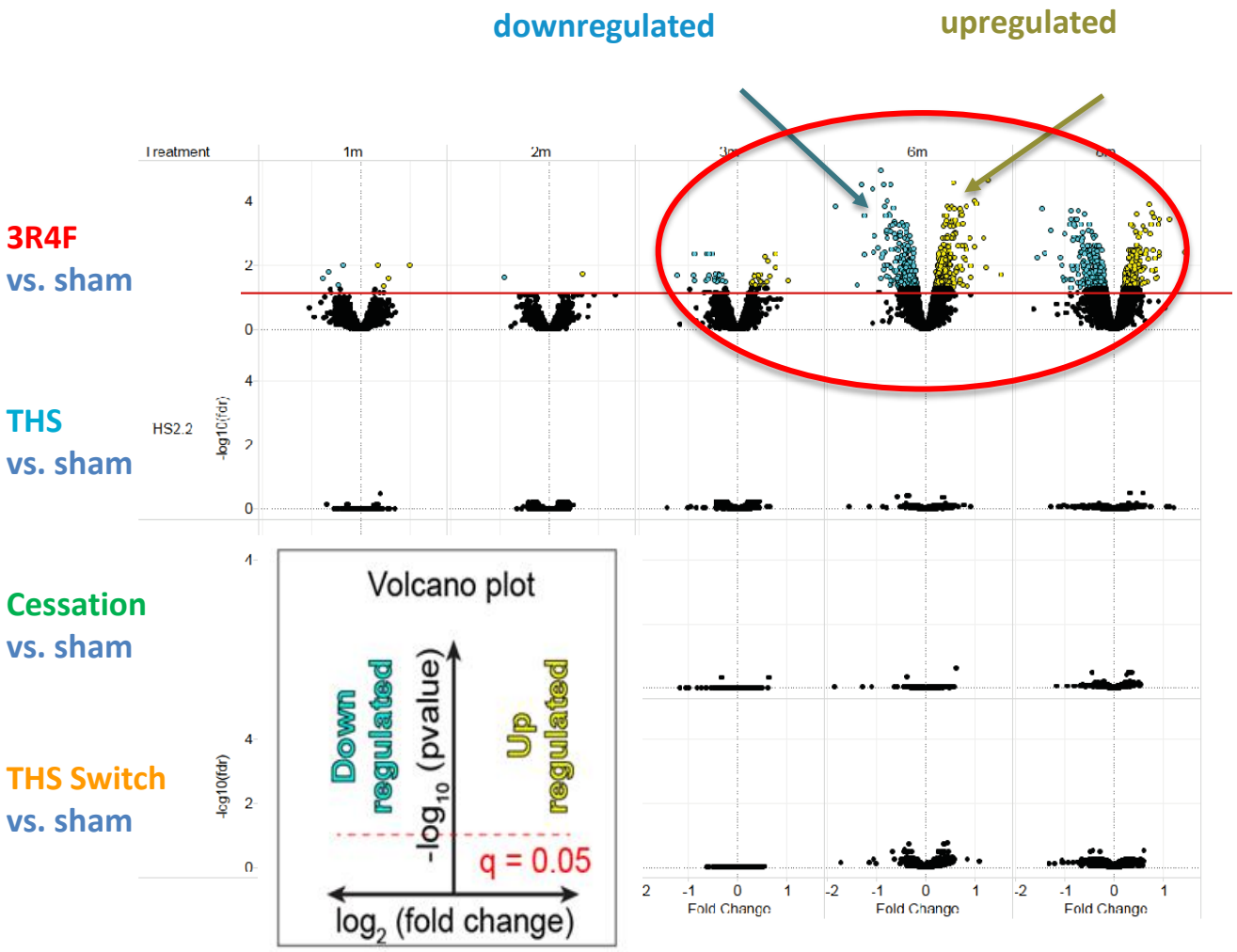
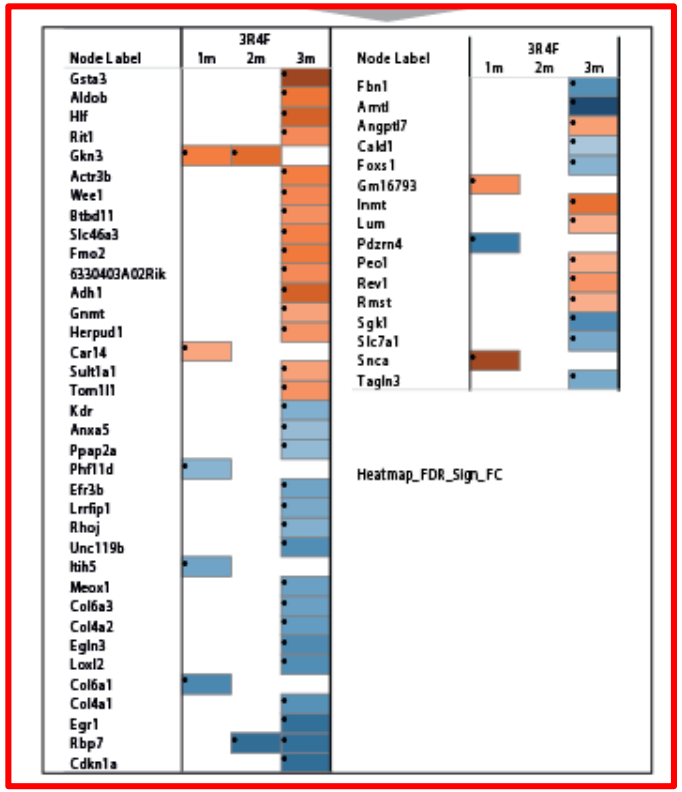
Heart (left ventricle) Transcriptomics





- Muscle structure and function
- Inflammatory response
- Cardiovascular disease

Szostak, J., et al. (2017). "Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke." Food and Chemical Toxicology 101: 157-167.

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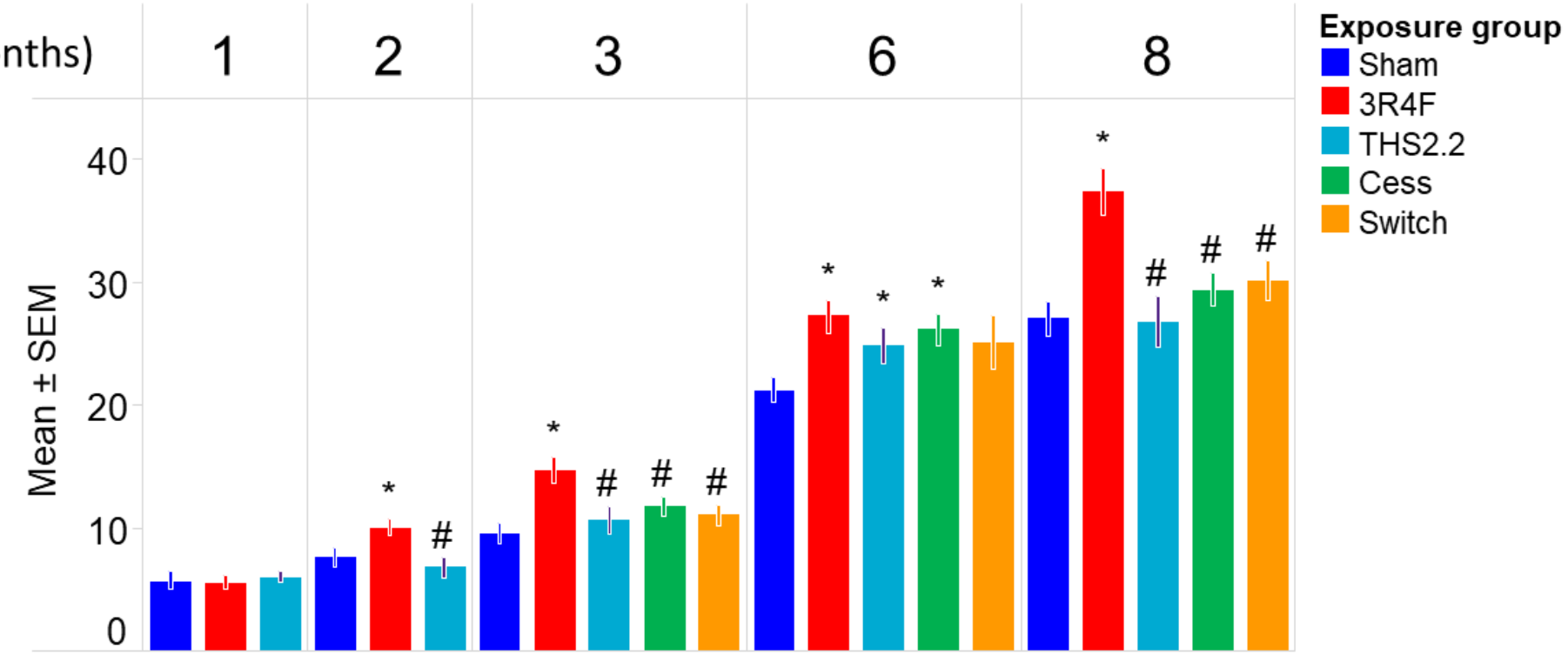
From Risk Assessment Framework to in vivo Study Design

Percentage of plaque based on mm^2



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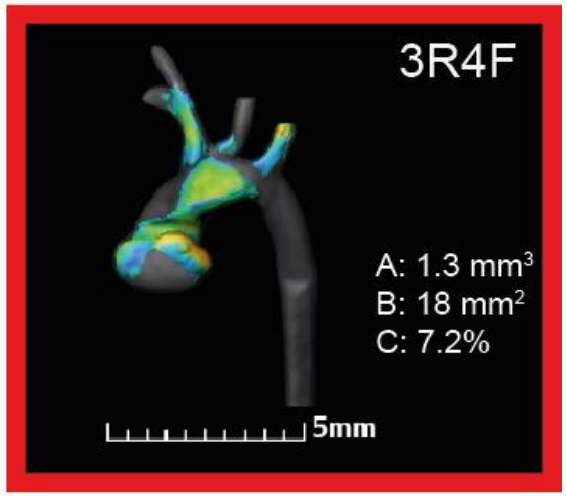
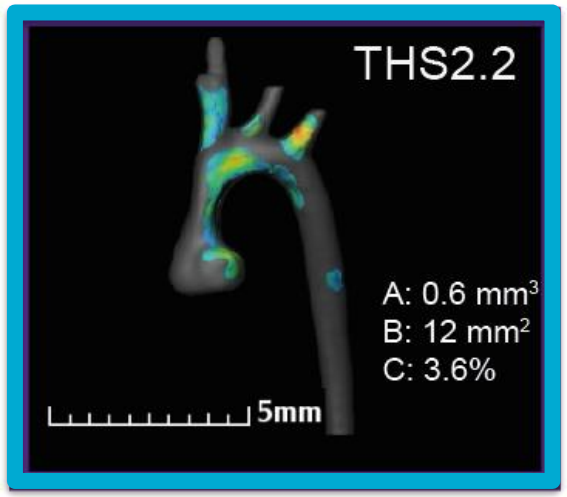
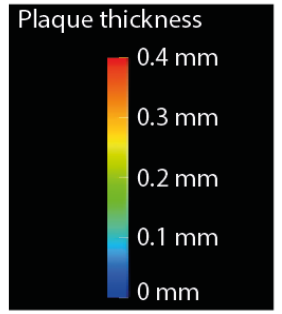
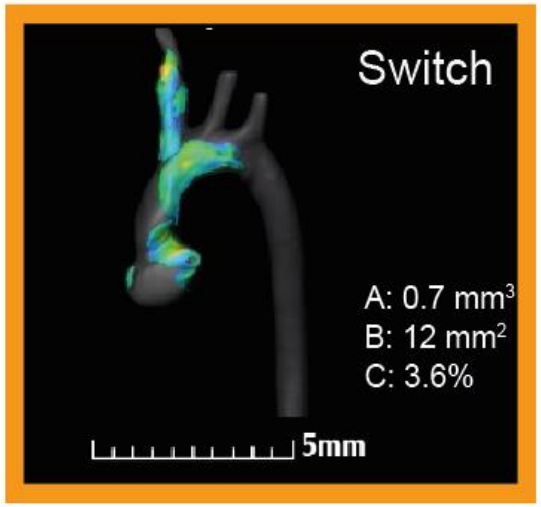
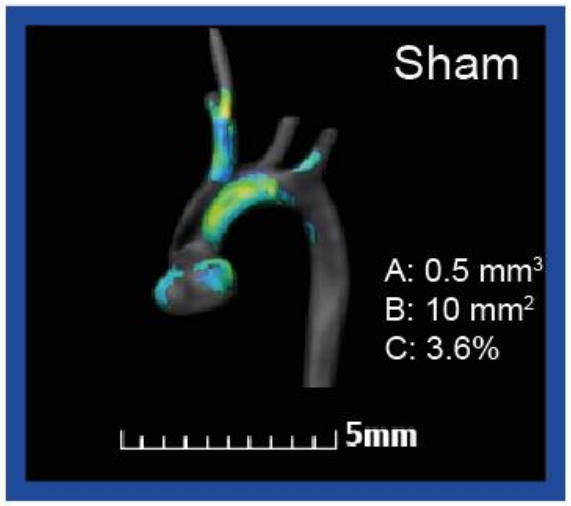
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at month 7

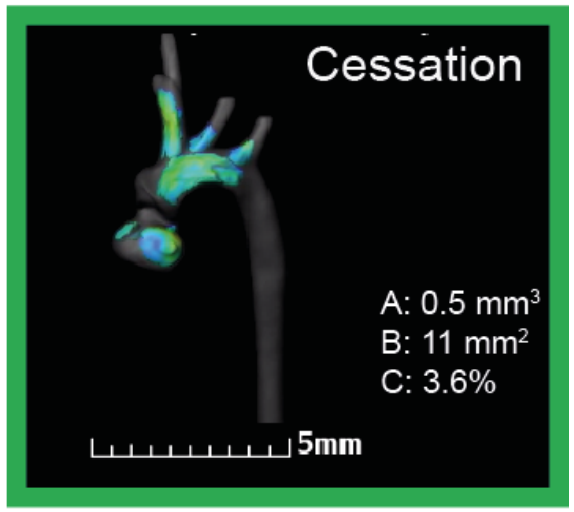












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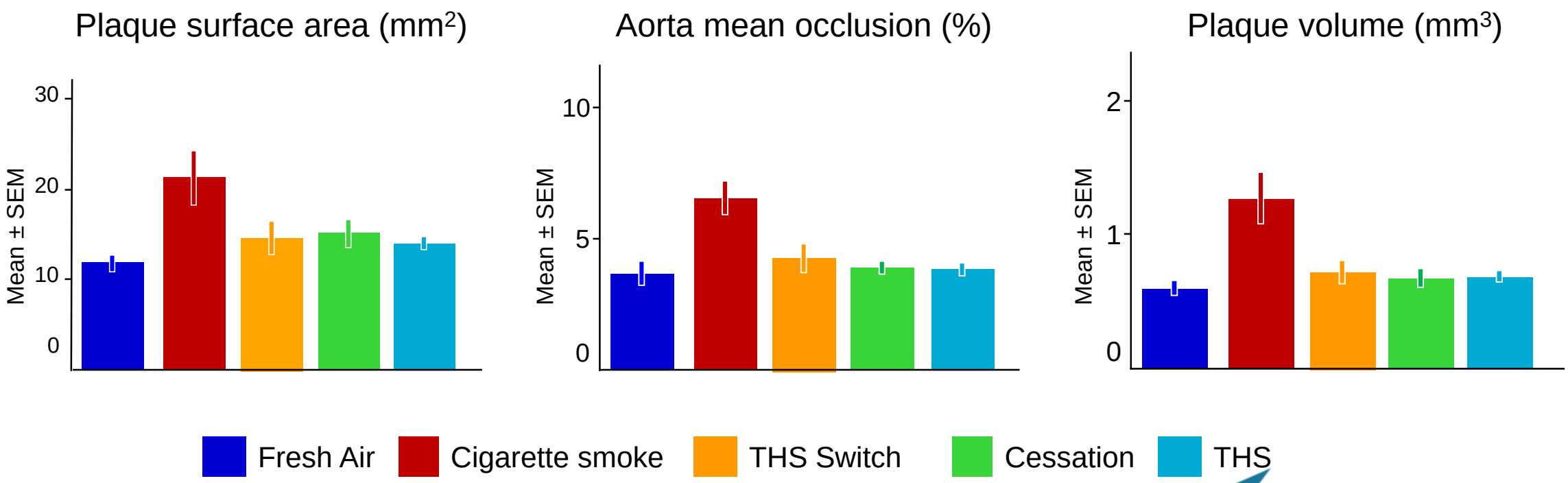
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at month 7

Disease Endpoint for CVD

Atherosclerotic Plaque in the Aortic Arch

Data from µCT at month 7



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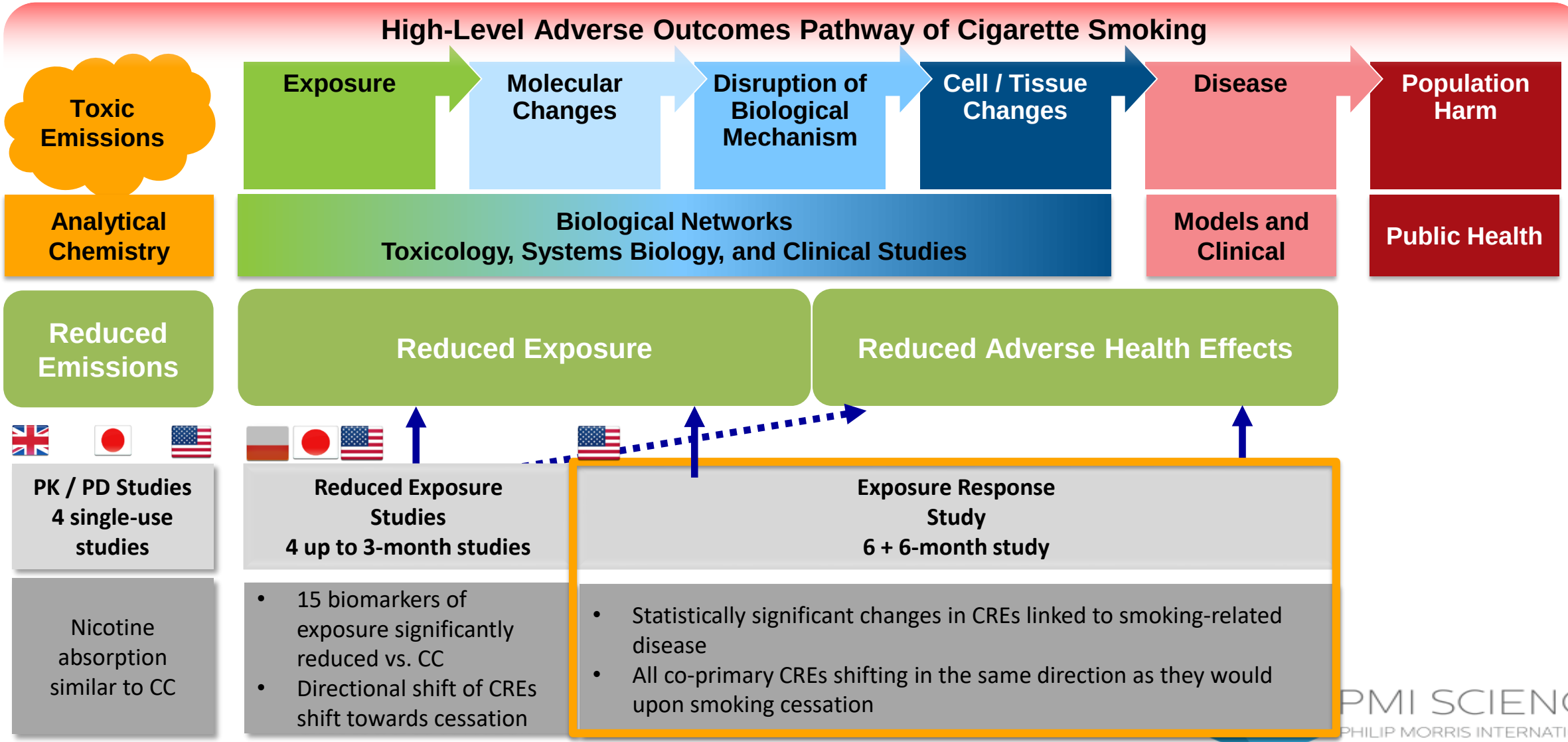
Exposure Response Study

Clinical Assessment – Results to Date



*Harmful and potentially harmful constituents

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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 Patho-Mechanims	
Lipid Metabolism	HDL - C
Clotting	11 – DTBX - 2
Endothelial function	S – ICAM - 1
CO acute effect	COHb
Inflammation	WBC
Oxidative stress	PGF2 - a
Lung Function	FEV1
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 year of age.

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

Subjects did not intent to quit smoking

Clinically relevant disorders that would jeopardize the participants safety

Female, not pregnant or breast feeding

Subjects did use medication with an impact on co-primary endpoints

Green Frame: Inclusion Criteria

Red Frame: Exclusion Criteria

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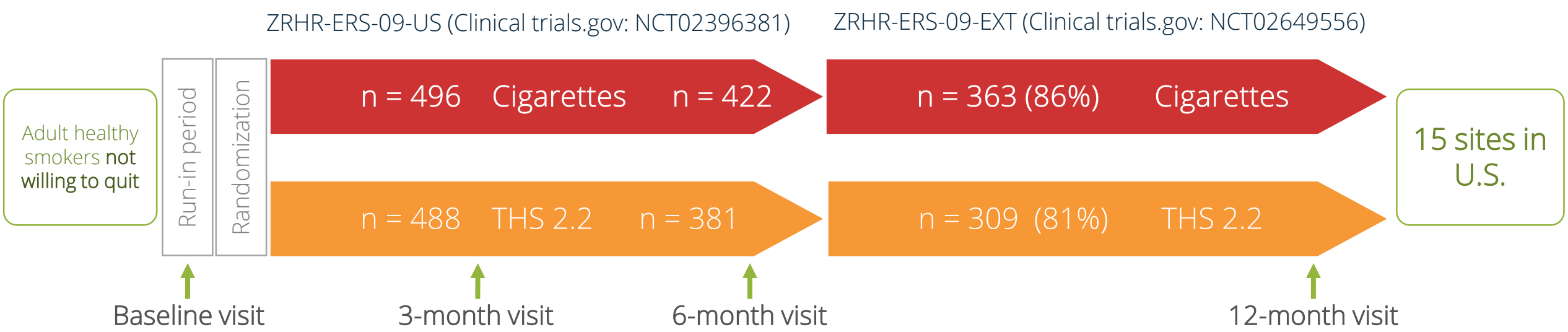
Study Design and Disposition - Exposure Response Study



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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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Analysis Populations
Reduced Exposure Studies vs Exposure Response Study

Primary Analysis Population	Primary Assessment Objective
3 months Reduced Exposure Study • Use of no more than 2 CC in a single day during the 30 days preceding the visit • Average product use within a 3-month period of not more than 0.5 CC/day	Analysis of the effect of THS **after full switching**
6 months Exposure Response Study • Analysis population: **THS 2.2 as it is actually used** • ≥70% THS use over the 6-month analysis period • ≥70% THS use on >50% of days in the 6-month analysis period	Analysis of the effect of THS **as actually used (up to 30% use of cigarettes)**

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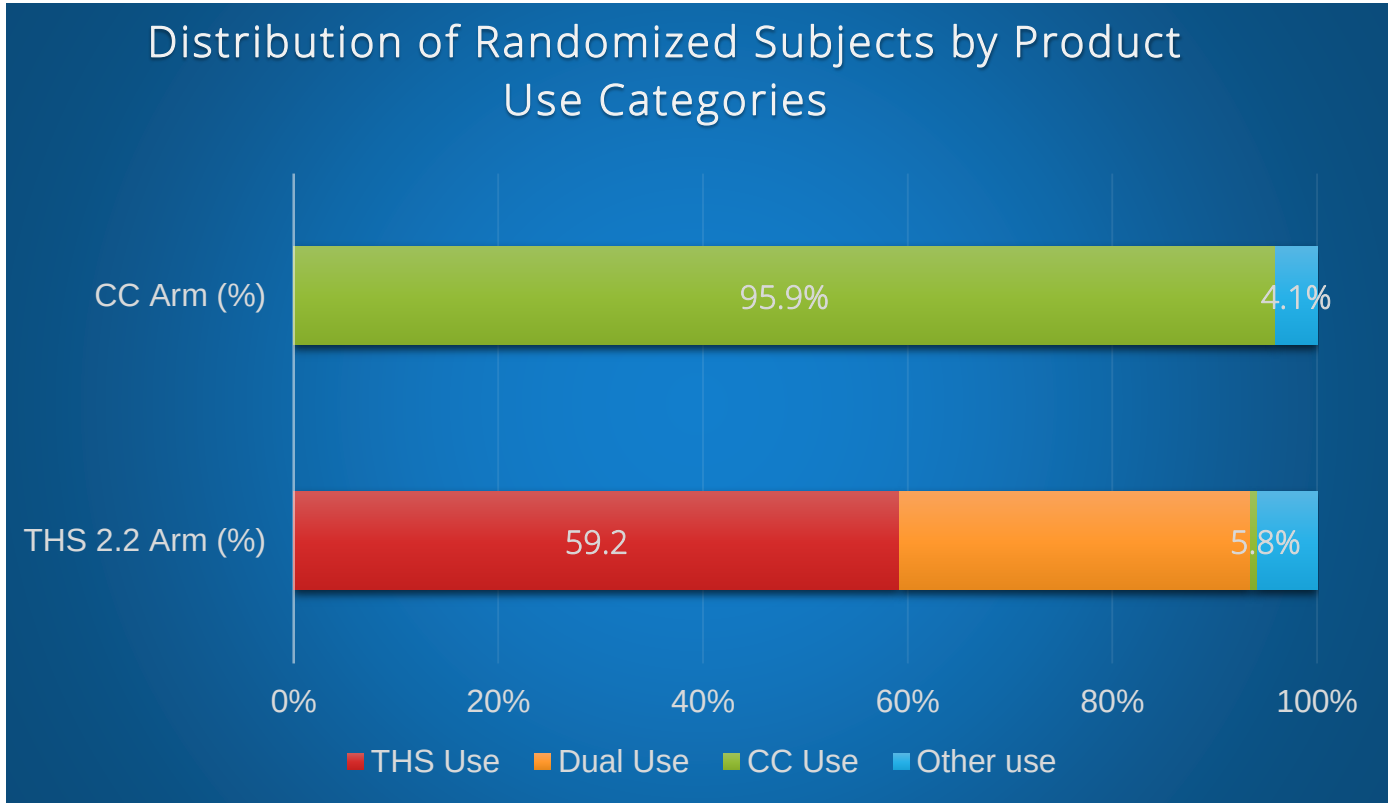
Main Analysis Population

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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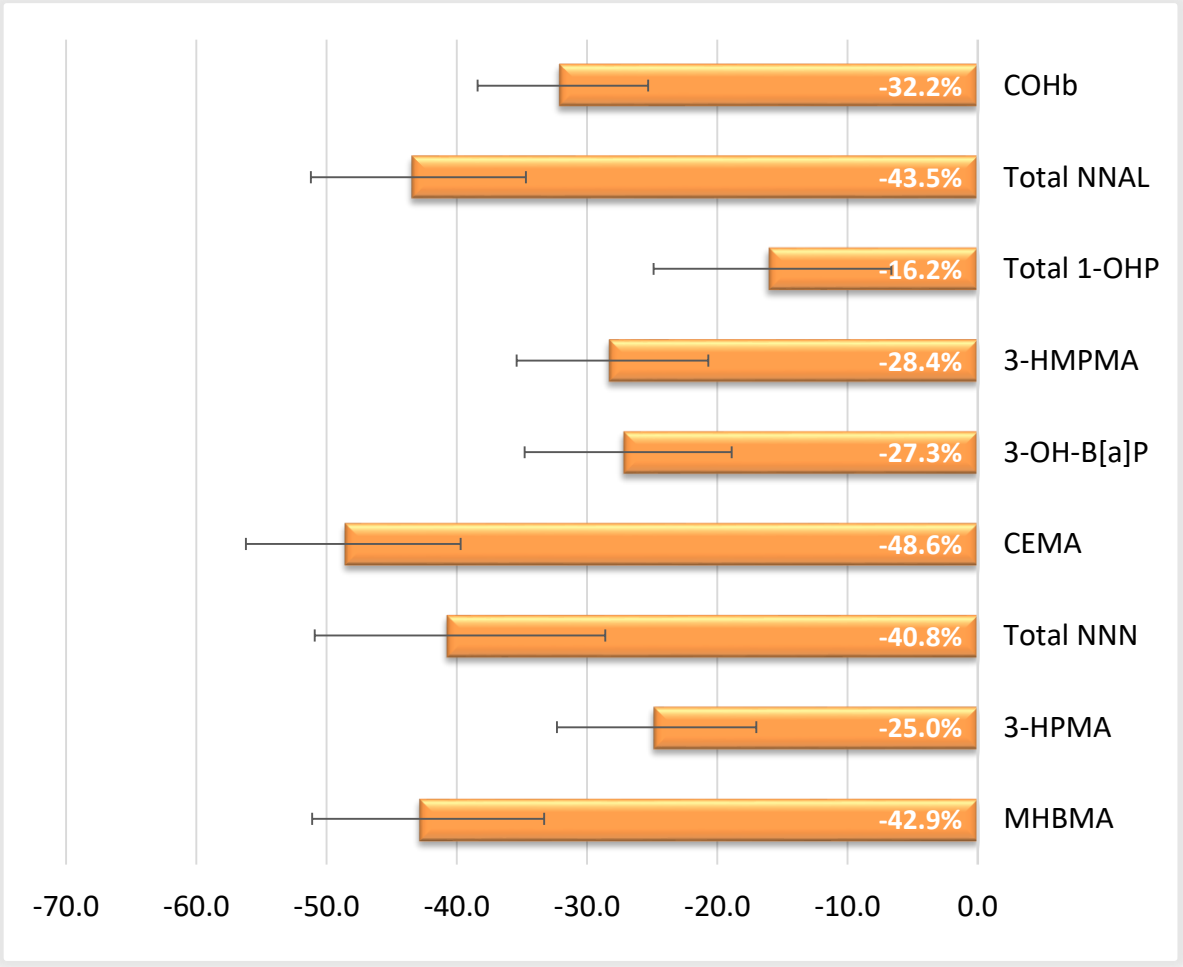
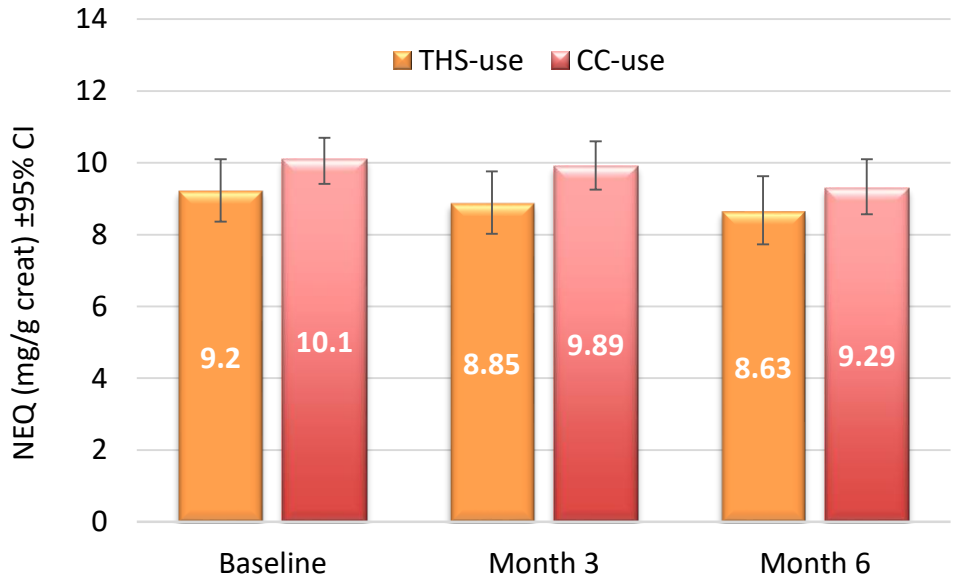
Product Use

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)

Reduction in Exposure and Exposure to Nicotine





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Clinical Changes After 90 Days
Reduced Exposure in Healthy Human Subjects

Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to THS Effect at 3m [95%CI]
Lipid Metabolism	HDL-C	0.0 mg/dL [-5.77; 5.84]	↑	1.4 mg/dL [-2.3;5.0]
Inflammation	WBC	-0.94 10^9/L [-2.00; 0.13]	–	0.17 10^9/L [-0.47; 0.81]
Airway Impairment	FEV1	2.0 % pred [-3.37; 7.36]	↑	0.53 % pred [-2.79; 3.85]
Endothelial Dysfunction	sICAM-1	-9.9 % [-19.7;1.1]	↓	-10.6 % [-16.7; -4.0]
Oxidative Stress	8-epi-PGF2α	-8.5 % [-25.13; 11.8]	↓	-13.5 % [-23.6;-1.95]
Clotting	11-DTX-B2	-7.2 % [-37.7; 38.3]	↓	-3.6 % [-24.6; 23.3]

Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to THS Effect at 3m [95% CI]
Lipid Metabolism	HDL-C	6.4 mg/dL [2.5; 10.3]	↑	4.5 mg/dL [1.17, 7.88]
Inflammation	WBC	-0.41 10^9/L [-0.95; 0.14]	↓	-0.57 10^9/L [-1.04, -0.10]
Airway Impairment	FEV_1	1.94 % pred [-0.44; 4.31]	↑	1.91 % pred [-0.14, 3.97]
Endothelial Dysfunction	sICAM-1	-10.9 % [-17.8; -3.4]	↓	-8.7 % [-14.94;-2.05]
Oxidative Stress	8-epi-$PGF_{2\alpha}$	-5.9 % [-17.1; 6.8]	↓	-12.7 % [-21.81;-2.55]
Clotting	11-DTX-B_2	-19.4 % [-30.1; -7.0]	↓	-8.98 % [-19.52, 2.94]

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 Gl/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-PGF2α	% Reduction	6.80 %	-0.216, 13.3	0.018	✓
COHb	% Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV1 %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 CRE shifted in the same direction as smoking cessation effect observed in the literature
- 5 out of 8 clinical risk endpoints were statistically significant compared to continued smoking

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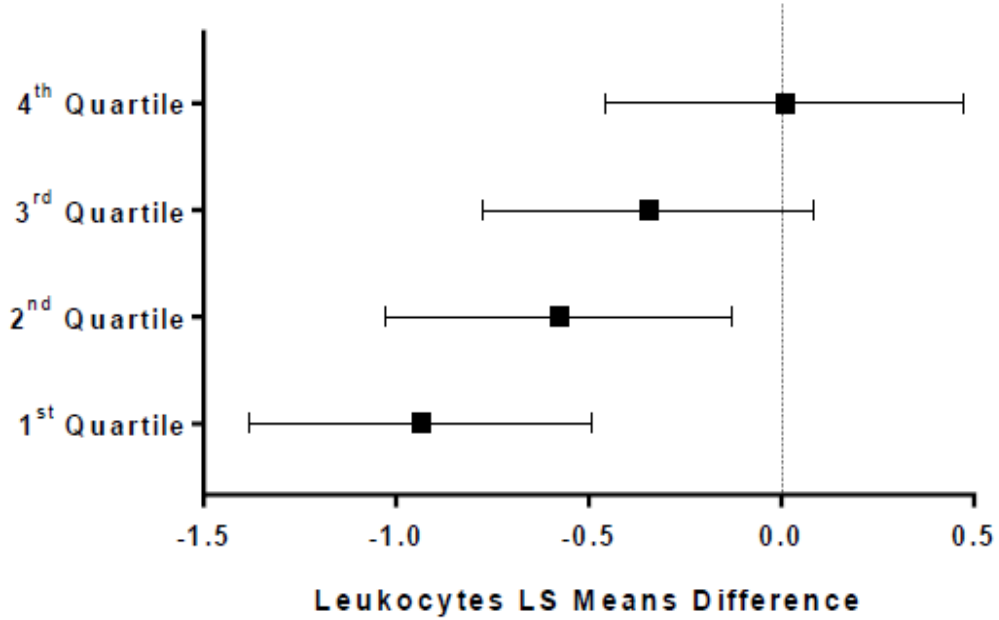
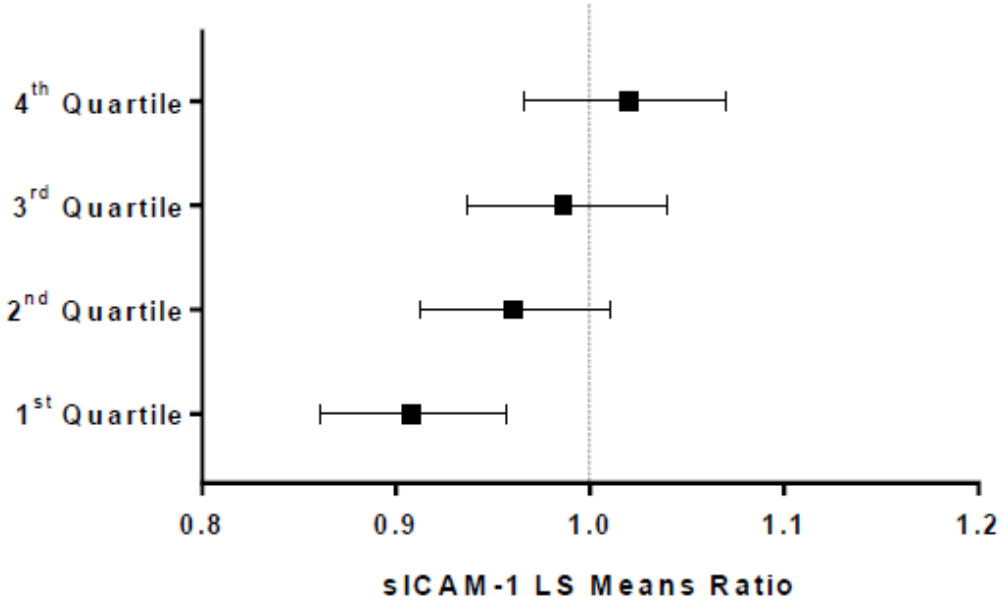
Changes in Clinical Risk Endpoints When Adjusted for CEMA Exposure Levels





Note: The predominant THS Use category group was stratified by CEMA quartiles 1 (bottom) to 4 (top).
Note: Higher CEMA levels are indicative of higher levels of cigarette smoking. The panel for sICAM-1 shows the THS vs. continued smoking LS means ratios. The panel for leukocytes (WBC) shows the THS minus cigarette smoking LS means differences.

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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% CC 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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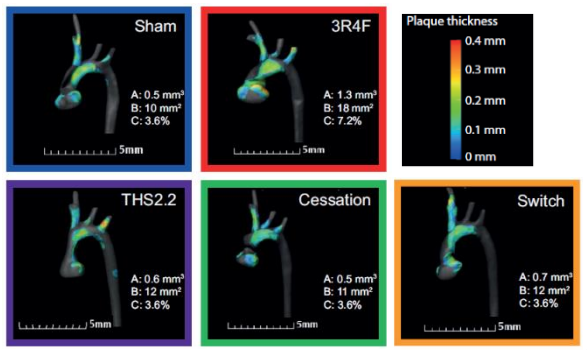
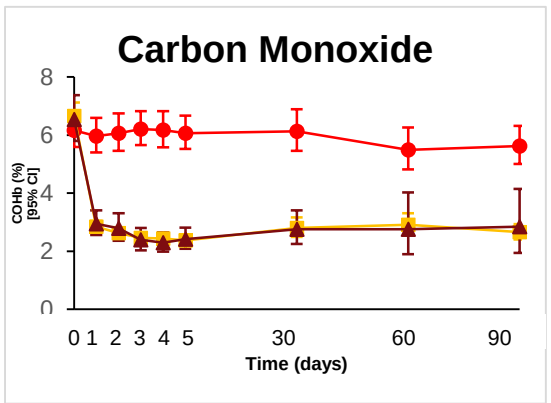
Summary

Cardiovascular

Micro CT



Exposure Reduction



In Vivo Endpoints		Summary of effect versus 3R4F		
		THS 2.2	Cessation	Switching to THS 2.2
Exposure markers	NNAL, 3-HPMA, SPMA, CEMA, COHb	↘	↘	↘
Cardio vascular disease	Rate of atherosclerotic plaque growth	↘	↘	↘
	Blood lipidomics (including 11-DTX-B2 and isoprostanes)	↘	↘	↘
	Aorta lipidomics	↘	↘	↘
Respiratory disease	Lung function measured using a FlexiVent system	↘	↘	↘
	Histopathological evaluation of the respiratory nasal epithelium	↘	↘	↘
	Histopathological evaluation of the lung tissue	↘	↘	↘
	Inflammatory mediators and cells in the bronchoalveolar lavage fluid (BALF)	↘	↘	↘
	Lung lipidomics	↘	↘	↘
	Whole transcriptome analysis of the Respiratory Nasal Epithelium: Perturbation of xenobiotic metabolism, inflammation, hypoxia, apoptosis, cell proliferation.	↘	↘	↘
	Whole transcriptome analysis of the lung tissue: Perturbation of xenobiotic metabolism, inflammation, hypoxia, apoptosis, cell proliferation.	↘	↘	↘

Clinical Risk Endpoints		THS 2.2
Cardiovascular Diseases	HDL-C	↑↑
	WBC count	↓↓
	sICAM-1	↓
	11-DTX-B2	↓
	8-epi-$PGF_{2\alpha}$	↓
	COHb	↓↓
Respiratory Disease	FEV_1 %pred	↑↑
Cancer	Total NNAL	↓↓

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Phillips B, Veljkovic E, Boue S, Schlage WK, Vuillaume G, Martin F, et al. 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 : an official journal of the Society of Toxicology. 2016 Feb;149(2):411-32.

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Thank you for your attention