Assessing the Impact of Switching to the Tobacco Heating System on Cardiovascular Disease: Translating Basic Science into Clinical Benefit

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on behalf of PMI R&D

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The 7th International Conference on Prehypertension, Hypertension, Metabolic Disorders, and Cardiovascular Disease

The burden of non-communicable diseases (NCD)

Global burden of NCDs

NCDs such as cardiovascular disease (CVD), respiratory disease, and cancer caused:

- >42 million deaths globally in 2019
- ~18 million CVD deaths in 2019

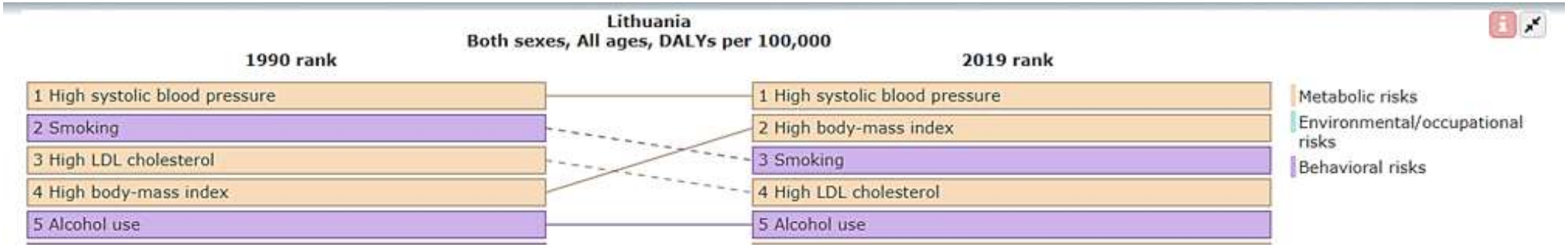
NCD burden in Lithuania

NCDs such as CVD, respiratory disease, and cancer caused:

- >35,000 deaths in Lithuania in 2019
- >21,000 CVD deaths in Lithuania in 2019

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2020. Available from http:// vizhub.healthdata.org/gbd-compare. (Accessed November 16th 2020)

Top 5 leading CVD risk factors in Lithuania



Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2020. Available from http:// vizhub.healthdata.org/gbd-compare. (Accessed November 16th 2020)

CVD burden due to smoking

- Smoking is a well-established risk factor for CVD incidence (morbidity) and mortality.[1]
- Smoking causes ischemic heart disease, cerebrovascular disease, peripheral artery disease, and aortic aneurysm.[2]
- 40% of cases of heart diseases are attributable to smoking (population-attributable risk), in contrast to an approximately 24% of cases for cholesterol and 31% for diastolic blood pressure.[3]
- Tobacco smoking is the single most important preventable cause of premature mortality, and quitting smoking is the most cost-effective strategy for preventing CVD.[4]
- Physicians perceive that diabetes is the most important risk factor for coronary heart disease, followed by hypertension and increased low-density lipoprotein cholesterol levels.[5]
- The clinical benefits of smoking cessation can be observed as early as one year after an acute coronary syndrome (ACS) event. [6]

1. Burns 2003 (Prog Cardiovasc Dis Jul-Aug 2003;46(1):11-29. DOI: 10.1016/s0033-0620(03)00079-3)
2. Ambrose 2004 (J Am Coll Cardiol. 2004 May 19;43(10):1731-7. doi: 10.1016/j.jacc.2003.12.047)
3. Isles 1992 (Lancet 1992 Mar 21;339(8795):702-6. doi: 10.1016/0140-6736(92)90599-x)
4. GBD 2015 (Lancet 2017 May 13;389(10082):1885-1906. doi: 10.1016/S0140-6736(17)30819-X)
5. Hobbs 2002 (Fam Pract 2002 Dec;19(6):596-604. doi: 10.1093/fampra/19.6.596)
6. Twardella 2004 (Eur Heart J 2004 Dec;25(23):2101-8. doi: 10.1016/j.ehj.2004.08.017)

Smoking cessation in CVD patients

Coronary artery disease (CAD): 48.6% of those smoking at the time of an event (CABG, PCI, or ACS) were persistent smokers 6 months later [1]

Stroke: At three months, 57% of the baseline smokers are still smoking [2]

Peripheral artery disease (PAD): 72% of all smokers with new or worsening claudication still continued to smoke after 12 months [3]

1. Kotseva 2016 (Eur J Prev Cardiol 2016 Apr;23(6):636-48 doi: 10.1177/2047487315569401)
2. Sauerbeck 2005 (J Neurosci Nurs 2005 Dec;37(6):316-9, 325)
3. Patel 2018 (J Am Heart Assoc 2018 Oct 16;7(20):e010076. doi: 10.1161/JAHA.118.010076)

TOBACCO HARM REDUCTION

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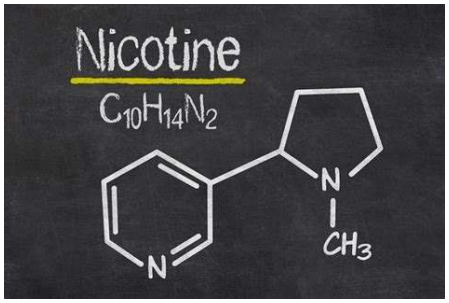
What is the risk associated with nicotine?



"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

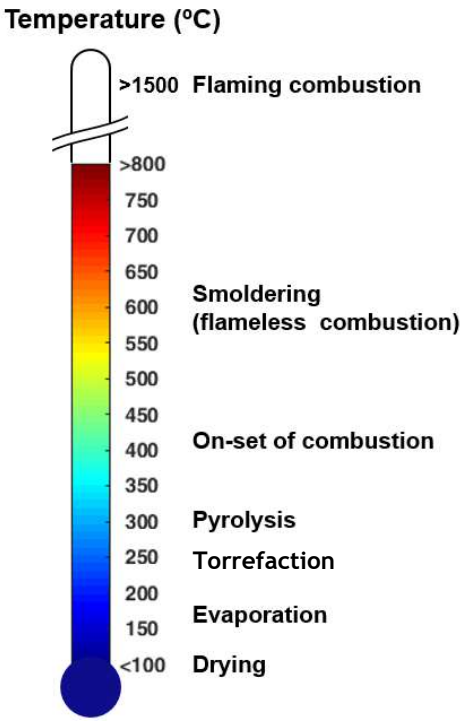
FDA

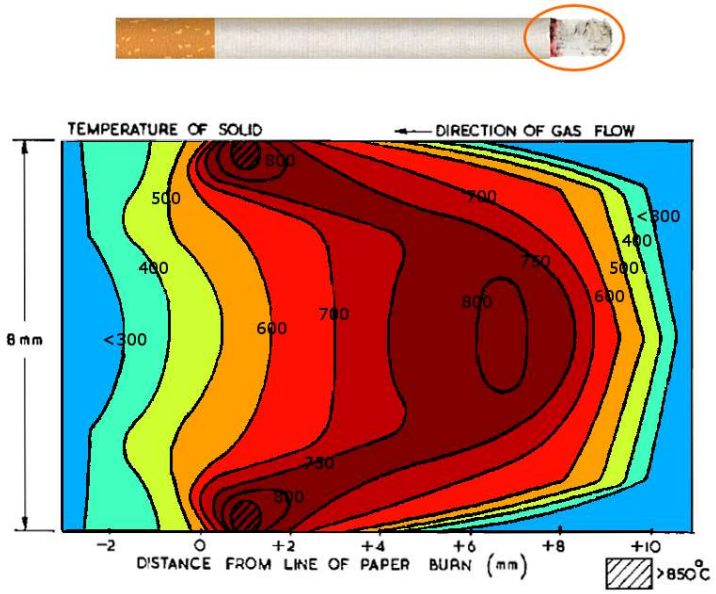
Royal College of Physicians

NICE National Institute for Health and Care Excellence

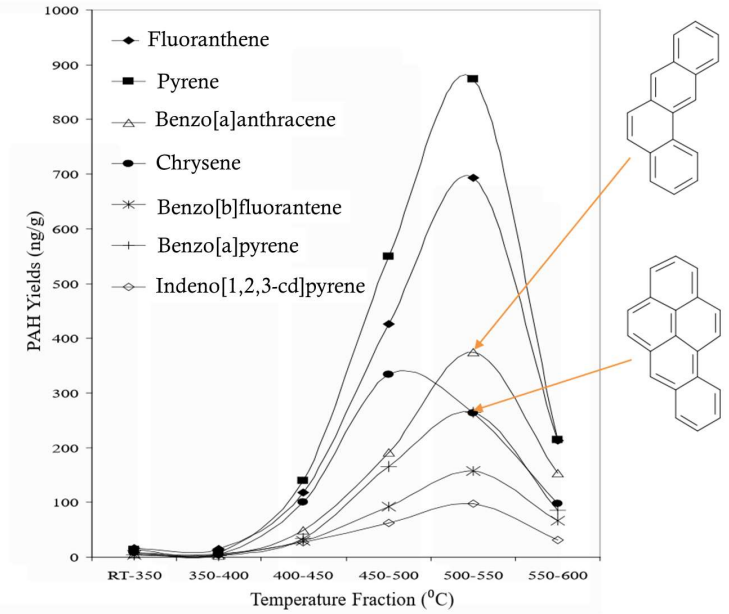
Elimination of combustion is key

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

TOBACCO HEATING SYSTEM (THS)

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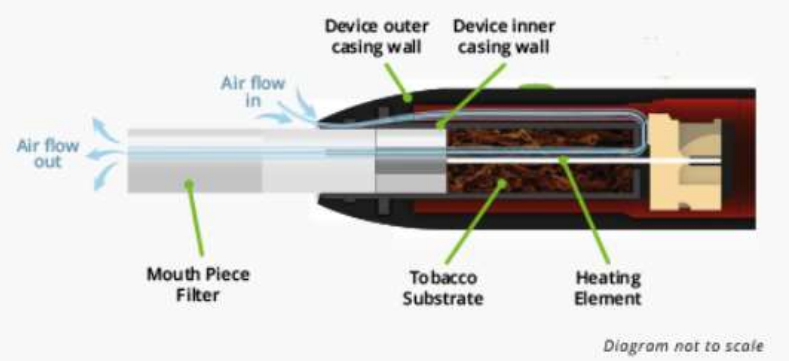
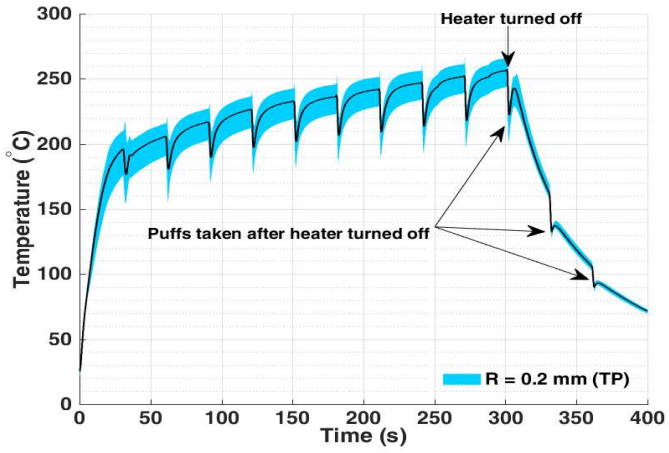
Why heat tobacco rather than burn it?

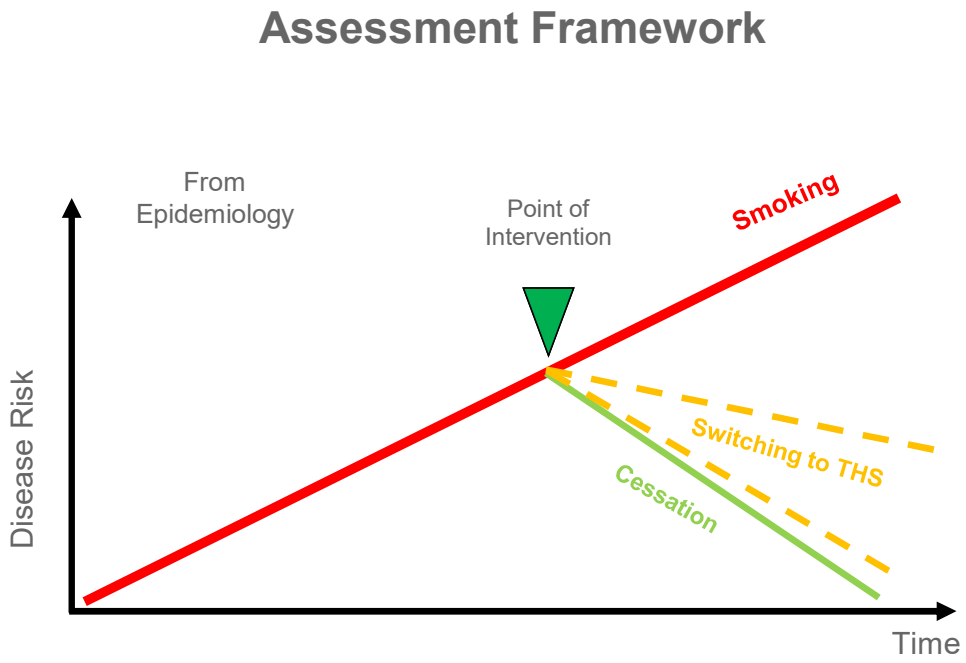
Tobacco Heating System (THS) is designed and has been demonstrated to:

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





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

Smith 2016 (Regul Toxicol Pharmacol 2016 Nov 30;81 Suppl 2:S17-S26. doi: 10.1016/j.yrtph.2016.07.006)

AEROSOL CHEMISTRY IN VITRO AND IN VIVO MODELS OF DISEASE

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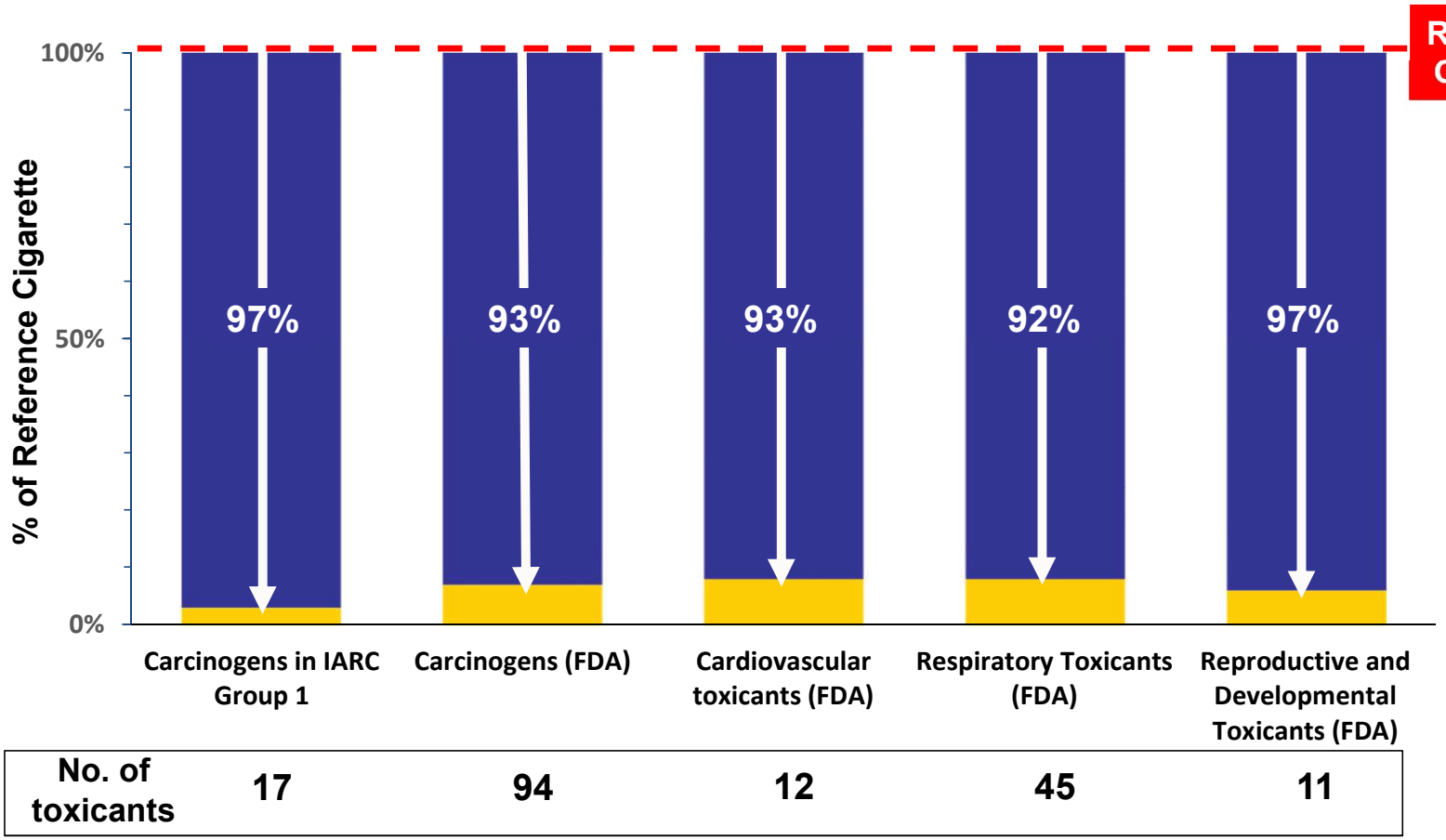
Reduced formation of HPHCs by disease category



THS 2.2 produces an aerosol that contains, **on average, 90–95% lower levels of harmful and potentially harmful constituents (HPHC) than a reference cigarette**[1]

CV toxicants: acrolein, arsenic, benz[*a*]anthracene, benzo[*b*]fluoranthrene, benzo[*k*]fluoranthrene, benzene, butyraldehyde, chrysene, cobalt, hydrogen cyanide, lead, phenol, propionaldehyde

Schaller 2016 (Regul Toxicol Pharmacol 2016 Nov 30;81 Suppl 2:S27-S47. doi: 10.1016/j.yrtph.2016.10.001) Note: Intense Health Canada's Smoking Regimen; Comparison on a per-stick basis; Excludes nicotine

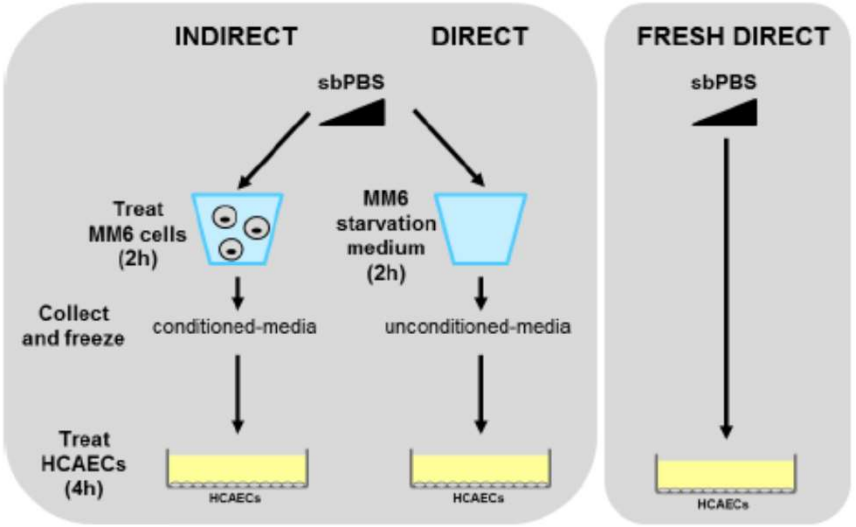
From risk assessment framework to *in vitro* study design

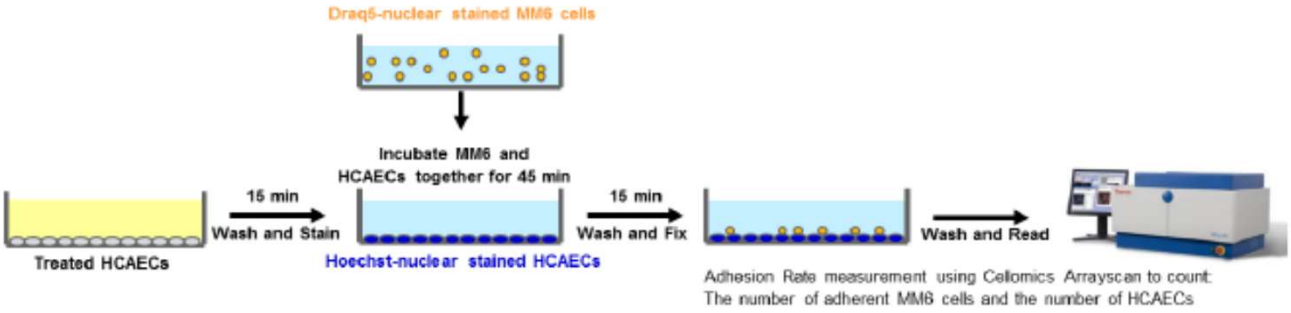
In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells (HCAEC)

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

2. **Treatment of HCAECs**

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





Poussin 2016 (Toxicology 2016 Jan 2;339:73-86. doi: 10.1016/j.tox.2015.11.007)

From risk assessment framework to *in vitro* study design

In vitro model: Adhesion of monocytic cells to HCAECs

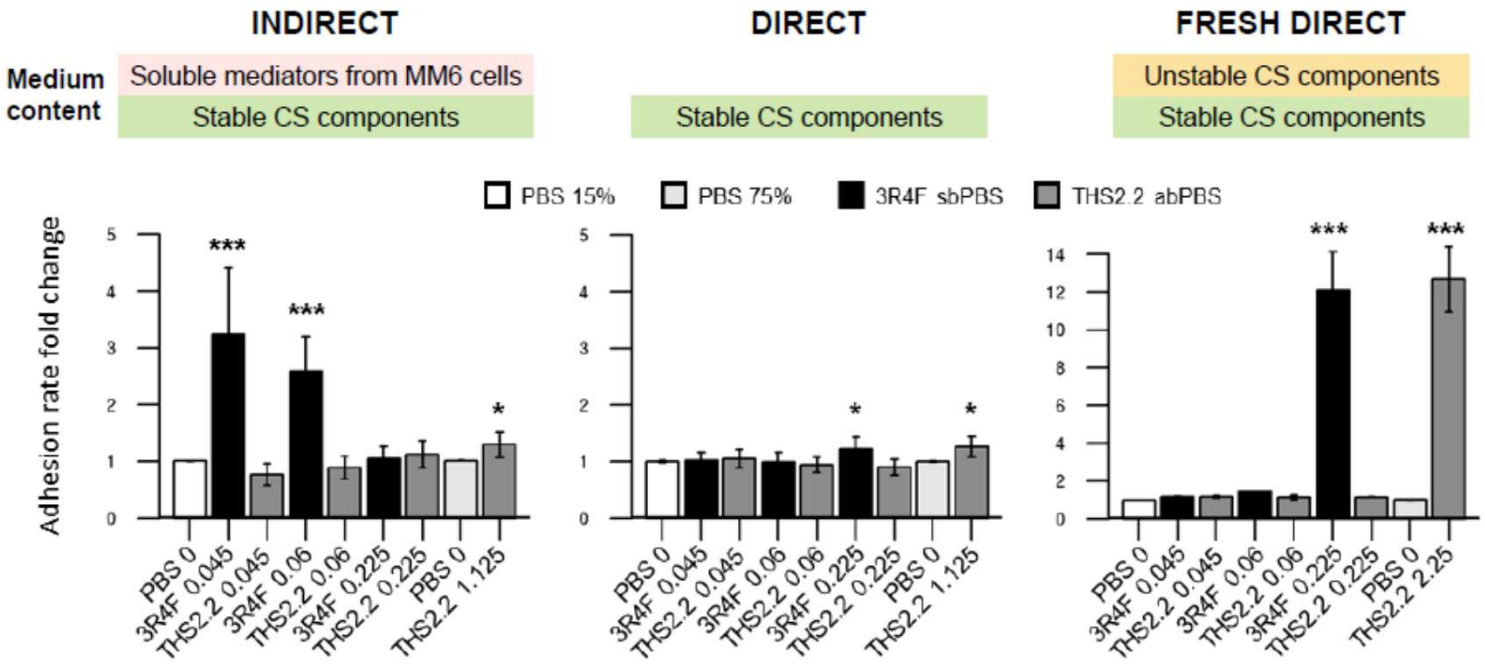


*Figure 1: Effects of THS2.2 abPBS and 3R4F sbPBS on the adhesion of MM6 cells to HCAECs following indirect, direct, and fresh direct treatments of HCAECs. Bar charts represent fold changes of the adhesion rate relative to respective vehicle controls. The adhesion rate reflects the number of adherent 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%).*

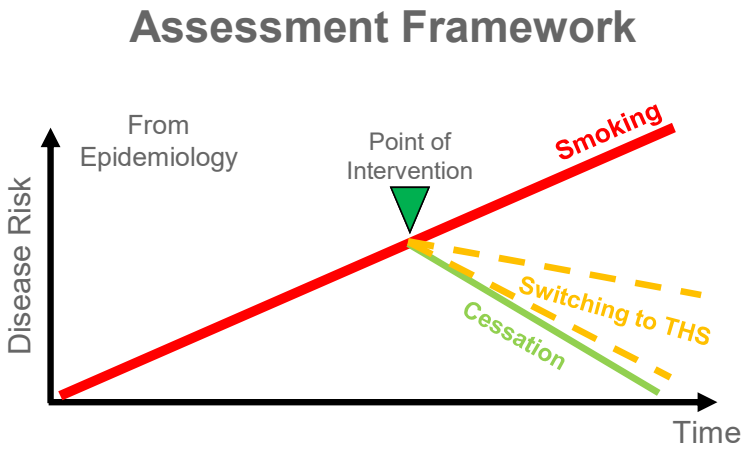
- 3R4F cigarette smoke aqueous extract promoted adhesion of MM6 cells to HCAECs in indirect and fresh direct exposure conditions
- At the same concentrations, no significant adhesion of MM6 cells to HCAECs was promoted by THS 2.2
- The concentrations of THS 2.2 required to be increased by ~10 and 20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

Poussin 2016 (Toxicology 2016 Jan 2;339:73-86. doi: 10.1016/j.tox.2015.11.007)

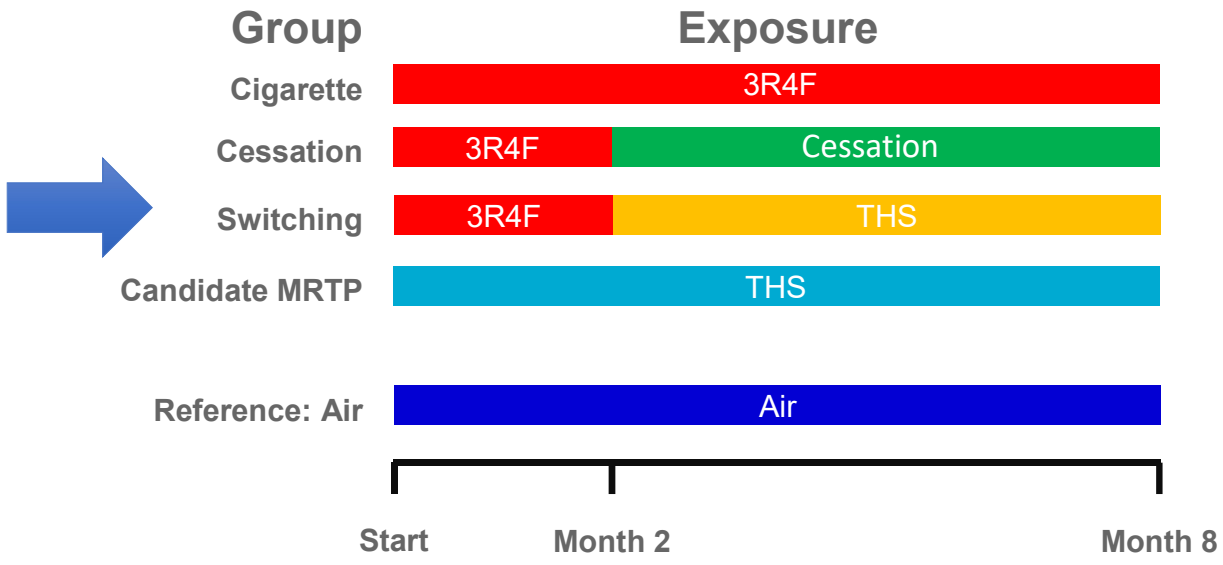
From risk assessment framework to *in vivo* study design

Apoe$^{-/-}$ mouse model: *In vivo* study to investigate atherosclerotic plaque in the aortic arch

- Eight-month duration (approximately 40% of lifetime)
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison



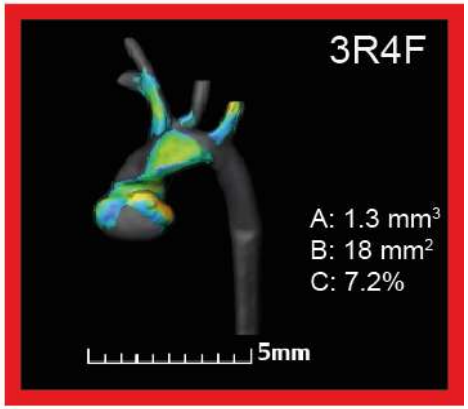
Note: The descriptions in the chart are for illustrative purposes only

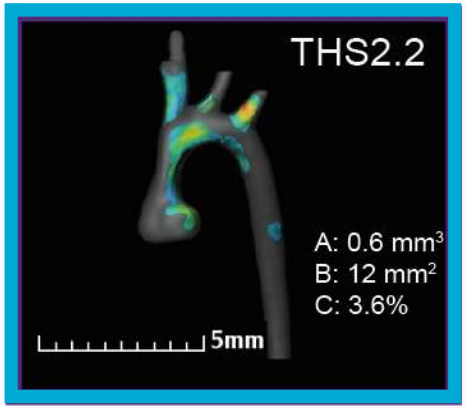


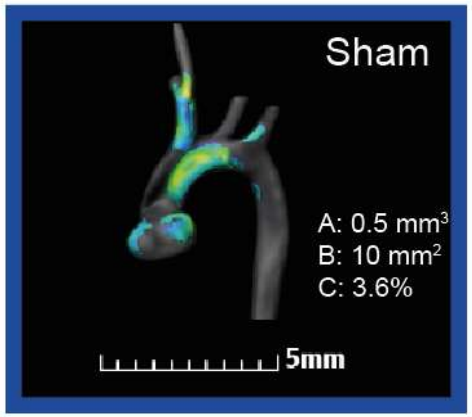
Poussin 2016 (Toxicology 2016 Jan 2;339:73-86. doi: 10.1016/j.tox.2015.11.007)

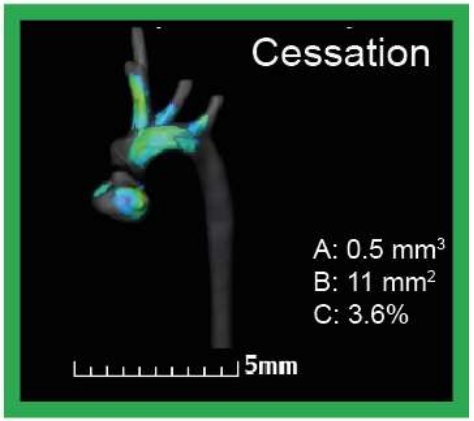
Atherosclerotic plaque in the aortic arch

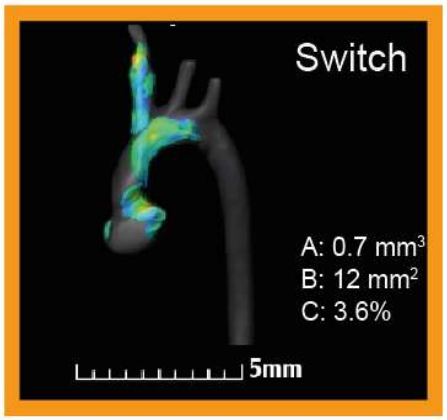
Data from µCT at month 7

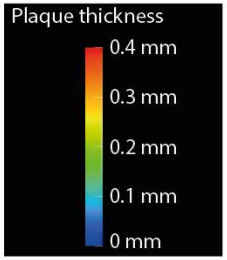












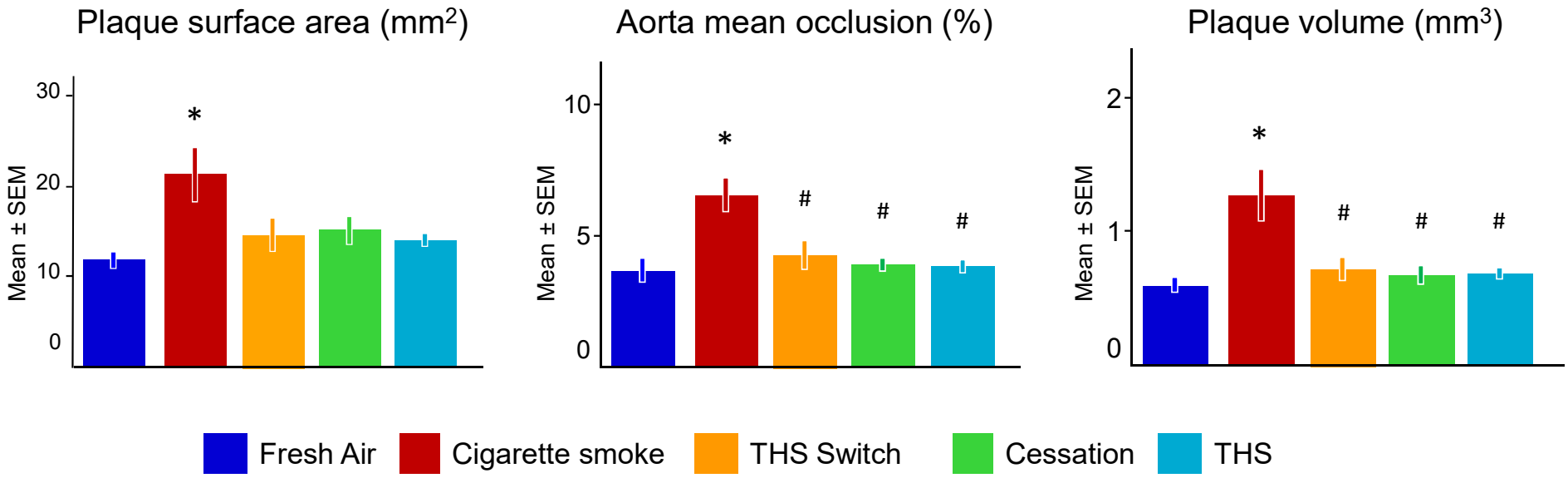
Phillips 2015 (Toxicol Sci 2016 Feb;149(2):411-32. doi: 10.1093/toxsci/kfv243)

Atherosclerotic plaque in the aortic arch
Data from µCT at month 7

Disease endpoints for CVD

Atherosclerotic plaque in the aortic arch

Data from µCT at month 7



*: different from sham (p<0.05), #: different from cigarette smoke (p<0.05)

Phillips 2015 (Toxicol Sci 2016 Feb;149(2):411-32. doi: 10.1093/toxsci/kfv243

CLINICAL EXPOSURE RESPONSE STUDY

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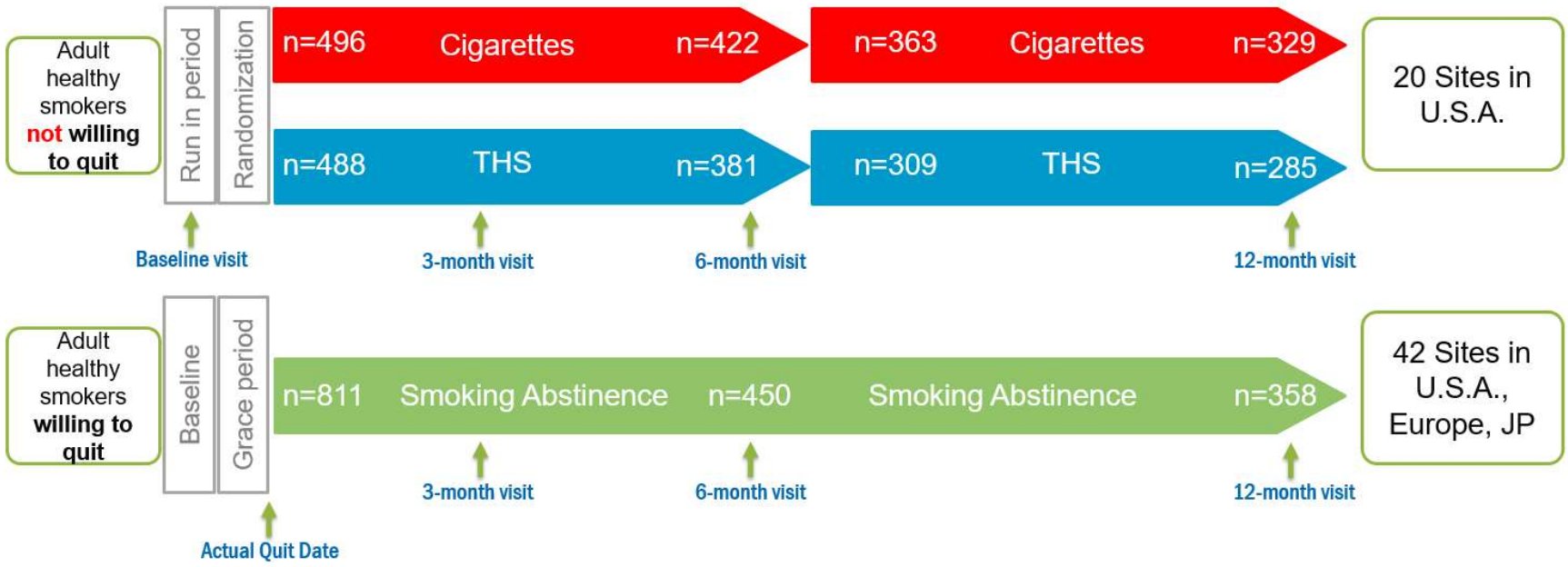
Study design – Exposure Response Study



ZRHR-ERS-09-US (Clinical trials.gov: NCT02396381) ZRHR-ERS-09-EXT (Clinical trials.gov: NCT02649556)

Primary objective and co-primary endpoints

Smoking cessation

- Epidemiologic link to smoking-related diseases?
- Affected by smoking status
- Reversible upon smoking cessation

Co-primary endpoints representative of pathomechanims	
Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	sICAM-1
CO acute effect	COHb
Inflammation	WBC
Oxidative stress	$PGF_{2\alpha}$
Lung function	FEV_1
Genotoxicity	Total NNAL

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

Changes in endpoints

Endpoint	Change from CC use	Observed change LS mean difference / relative reduction	Hailperin–Rüger-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	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	✓
$PGF_{2\alpha}$	%Reduction	6.80 %	–0.216, 13.3	0.018	✓
COHb	%Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV_1	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 by using the Hailperin–Rüger approach

- **All CREs shifted in the same direction as the smoking cessation effect observed in the literature**
- **Five out of eight CREs showed statistically significant changes relative to continued smoking**

Lüdicke 2019 (Cancer Epidemiol Biomarkers Prev 2019 Nov;28(11):1934-1943. doi: 10.1158/1055-9965.EPI-18-0915)

Summary — Potentially reduced-risk products

- The CVD risk attributable to smoking is high, and guideline-recommended smoking cessation therapies and interventions have significant limitations.

- PMI has completed 18 non-clinical and 10 clinical studies. The evidence available to date indicates that switching to THS presents less risk of harm than continuing smoking and has the potential to reduce the risk of smoking-related diseases, such as CVD.

- **As a next step, PMI plans cardiovascular outcome studies intended to demonstrate the clinical benefits of switching to THS in the cardiovascular area over continuing smoking as part of the THS assessment program .**

THANK YOU FOR YOUR ATTENTION

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