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RESPIRATORY EFFECTS OBSERVED WHEN USING THE TOBACCO HEATING SYSTEM (THS) COMPARED WITH CONTINUED SMOKING

Presentation at the Meeting of Pulmonary Specialists Organized by the InSpiro Foundation

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Patrick Picavet is an employee of Philip Morris International.

The research described in this presentation was sponsored by Philip Morris International.

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The Scientists

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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. PMI has a range of RRPs **in various stages of development, scientific assessment, and commercialization**. Because PMI’s 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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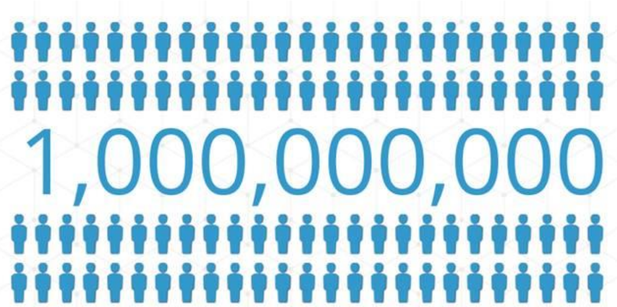
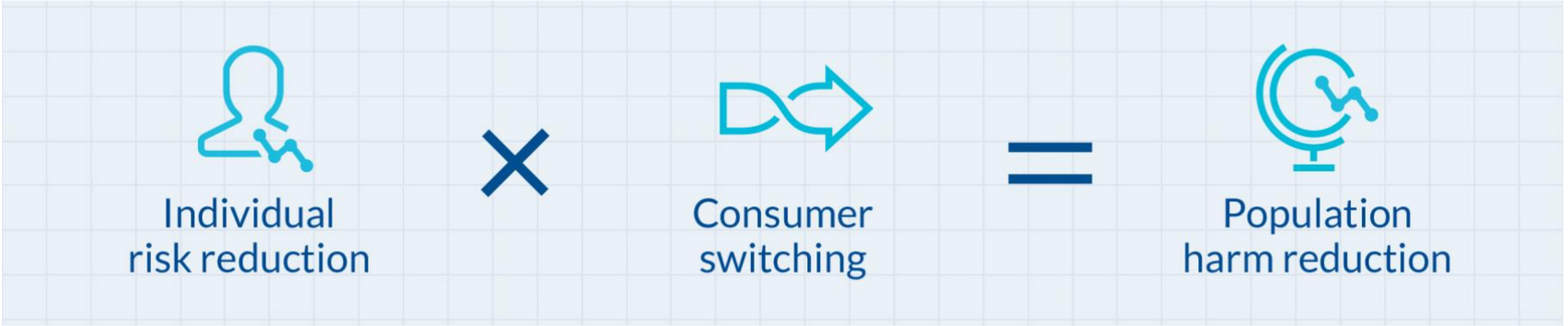
Tobacco Harm Reduction

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 switch to, should they decide not to quit.

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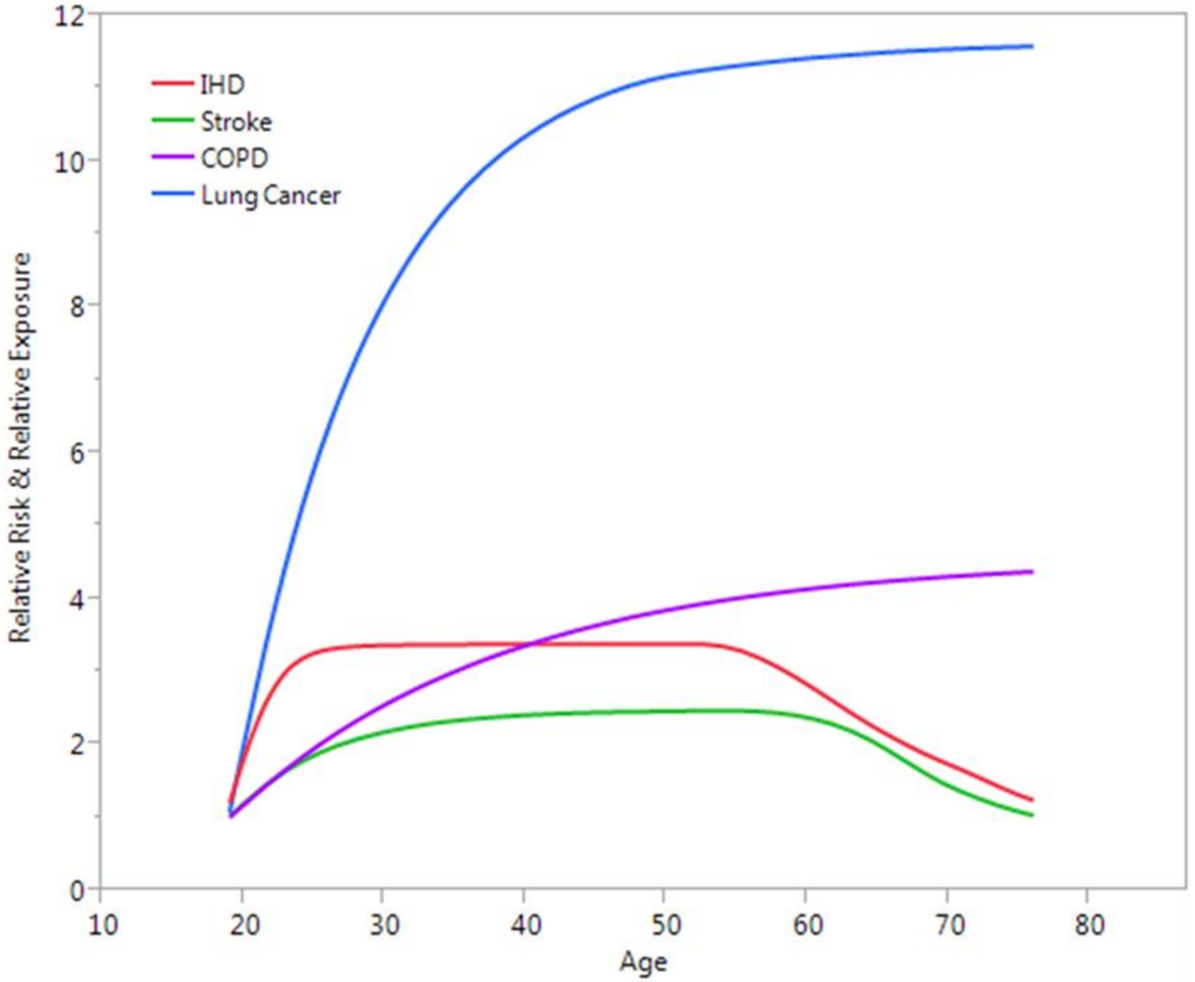
Source: http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html; Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present,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

Excess Risk of Smoking-Related Disease



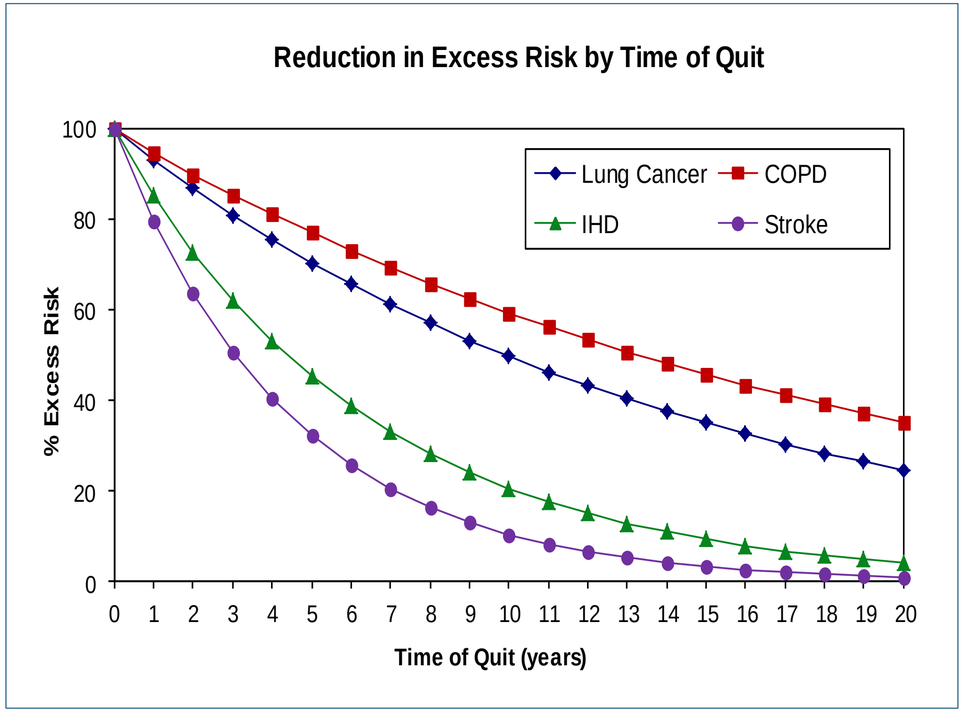
Disease-Specific Relative Risk [1] (By Age)

Relative risk of ischemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), and lung cancer for an adult cigarette smoker

Source: Relative risk: Lung Cancer (Lee 2012), COPD (Forey 2011), IHD and Stroke (Lee 2016)

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)

Source: Half-life of risk: Lung Cancer (Fry 2013), COPD (Lee 2014), IHD (Lee 2012), Stroke (Lee 2014)

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Eliminating Combustion and Reducing Toxicant Exposure

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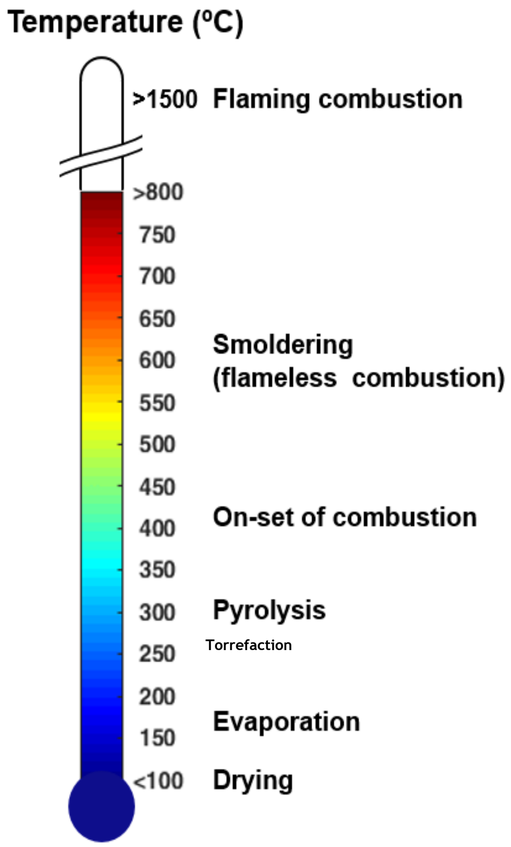
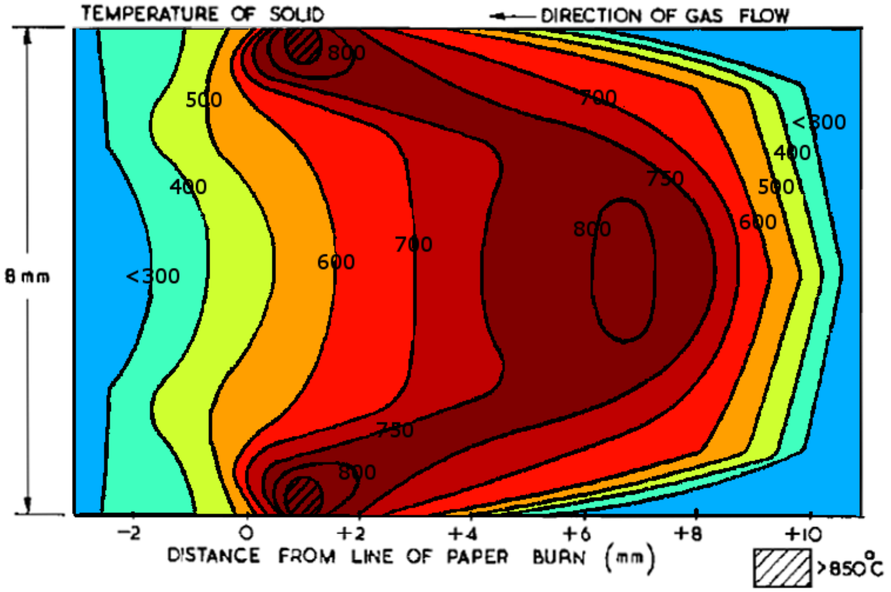
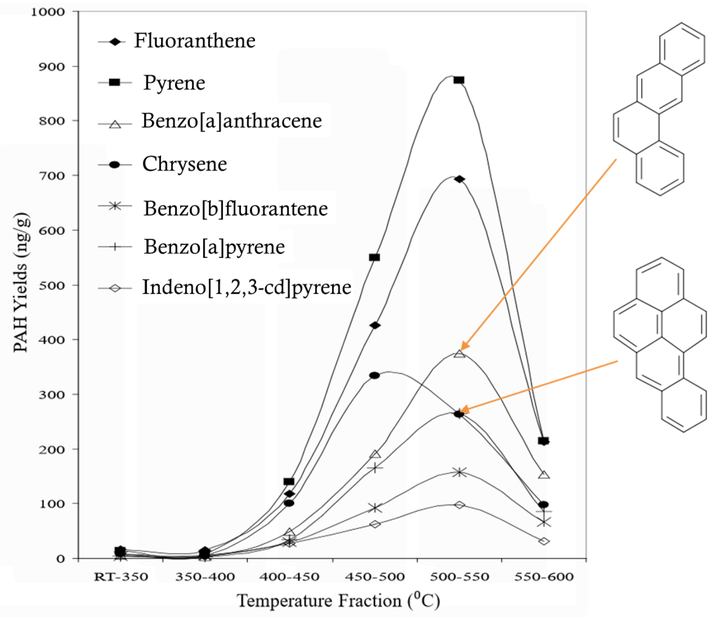
Elimination of Combustion Is Key

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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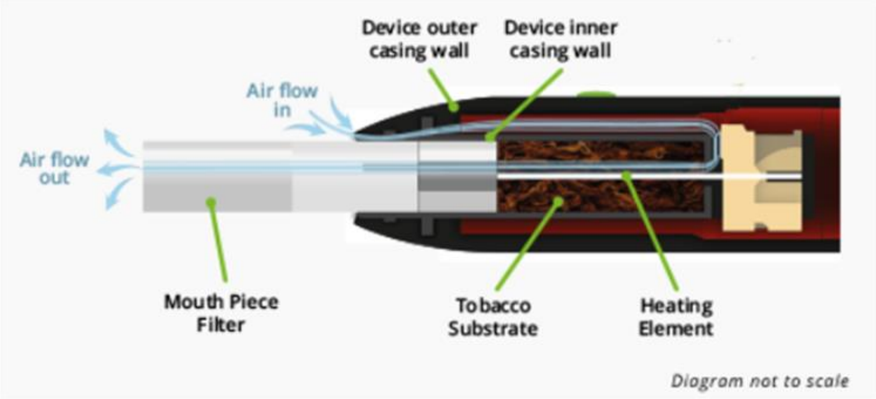
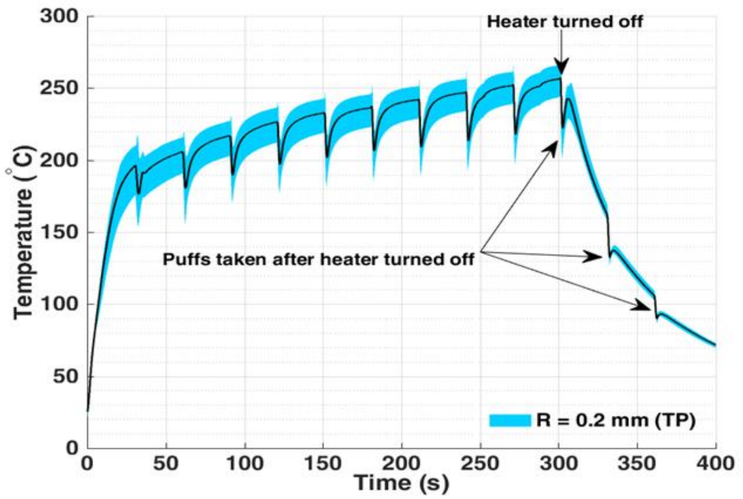
Why Heat Tobacco Rather than Burn It?

The 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





R = Radial distance from heater

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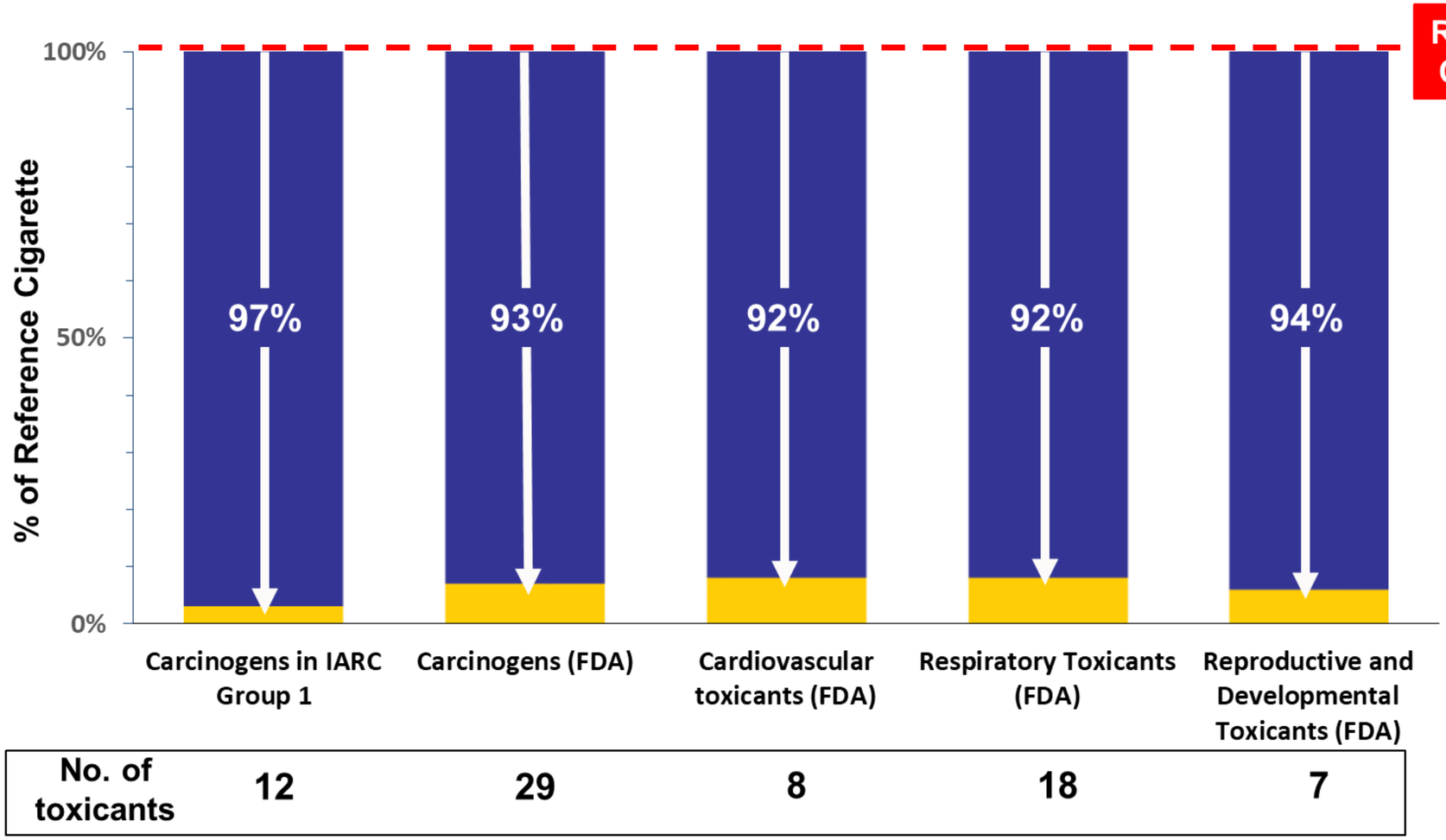
Source: PMI Research and Development

Reduced Formation of HPHCs by Disease Categories

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



No. of toxicants	12	29	8	18	7

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

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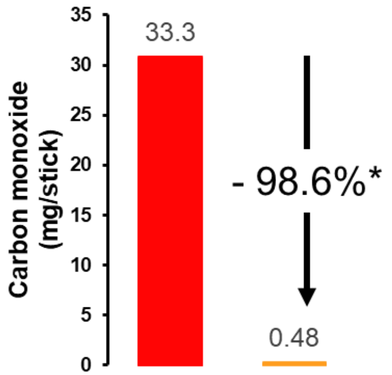
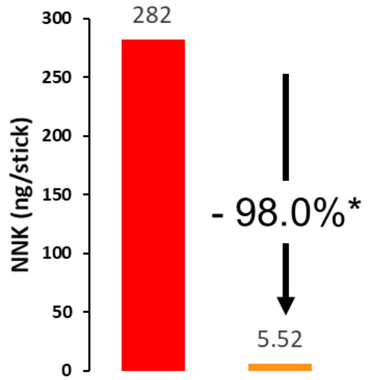
Notes: These data alone do not represent a claim of reduced exposure or reduced risk.
Source: PMI Research and Development;

Reduced Exposure in Healthy Human Subjects

Levels of HPHCs are Drastically Reduced in THS Aerosol



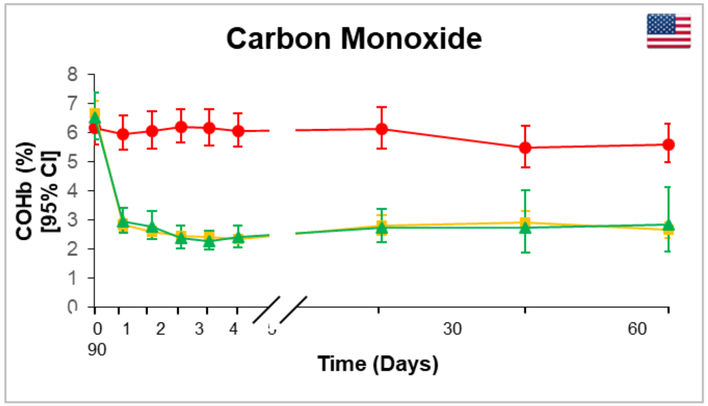


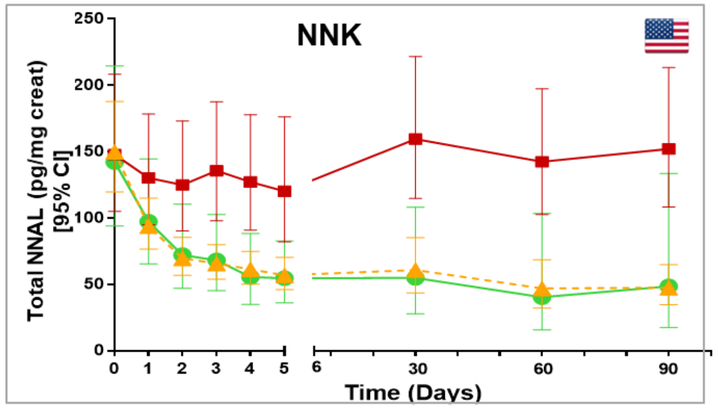
Leads to

Cigarette
THS
Smoking Abstinence

Leads to

Exposure is Significantly Reduced After Switching to THS





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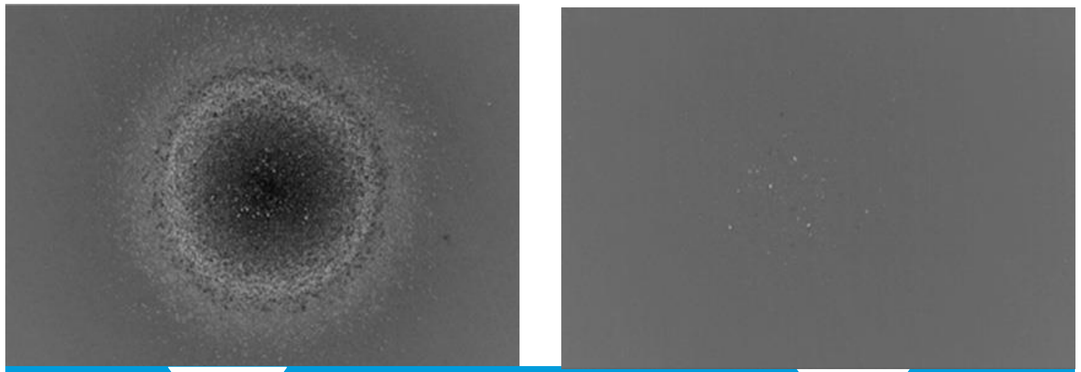
Notes: These data alone do not represent a claim of reduced exposure or reduced risk.
* On equivalent nicotine basis . THS stands for Tobacco Heating System version 2.2
Source: PMI Research and Development; Registered on clinicaltrials.gov: NCT01989156

Solid Ultrafine Particle Deposition in the Lung

Cigarette smoke

Carbon-based nanoparticles
$6x10^{11}$ particles ~= 0.7 mg*

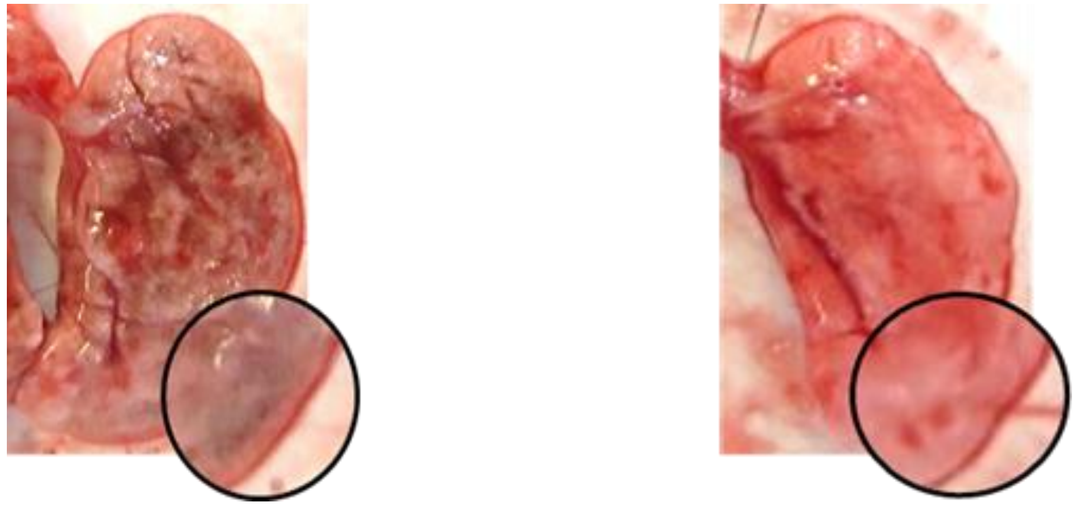


THS aerosol

Carbon-based nanoparticles

Lung Deposition after 6 months

Cigarette smoke*



IQOS aerosol*

* Corresponding nicotine concentrations

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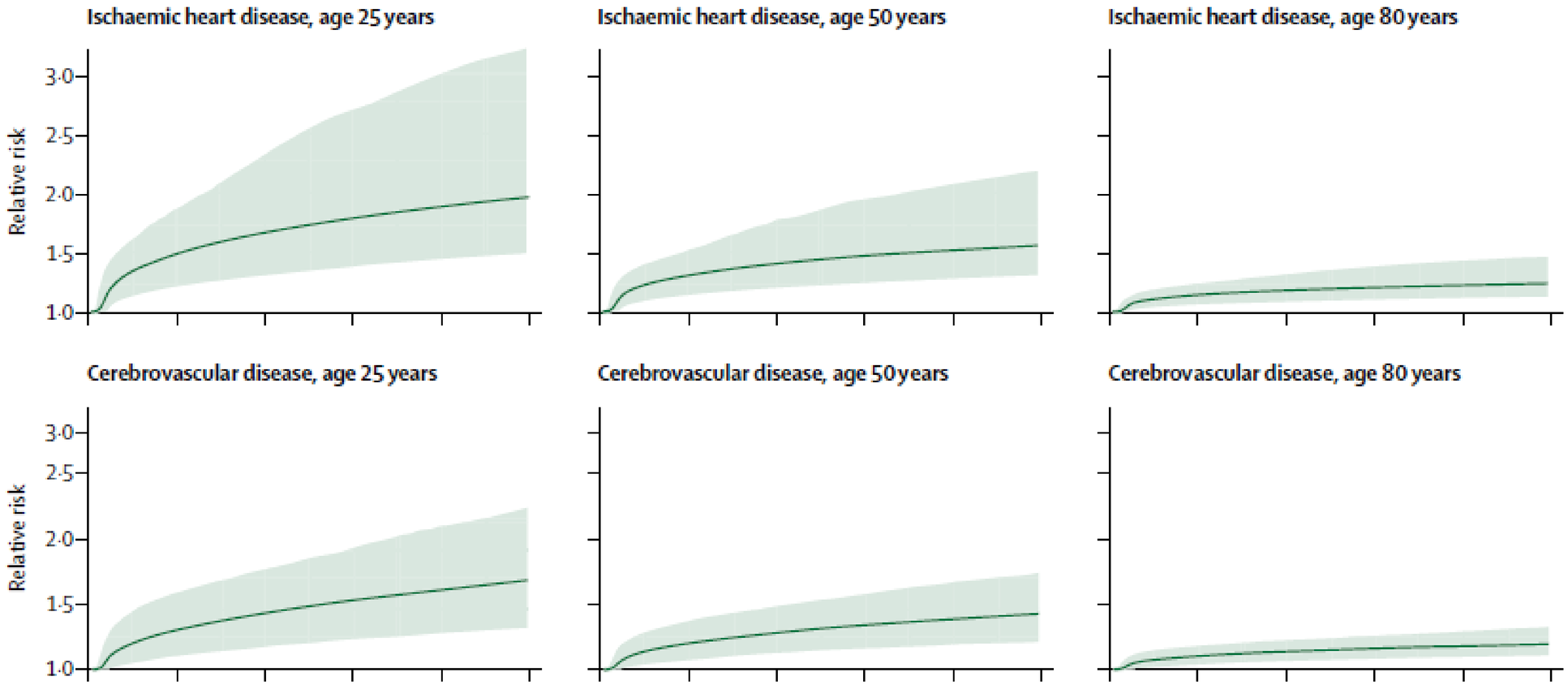
Note: These data alone do not represent a claim of reduced exposure or reduced risk.
ApoE-/- mice exposed for 6 months, 3 hours/day, 5 days/week.
Source: You et al. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623

Global Disease Risk Associated with PM 2.5



Source: 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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Respiratory Effects

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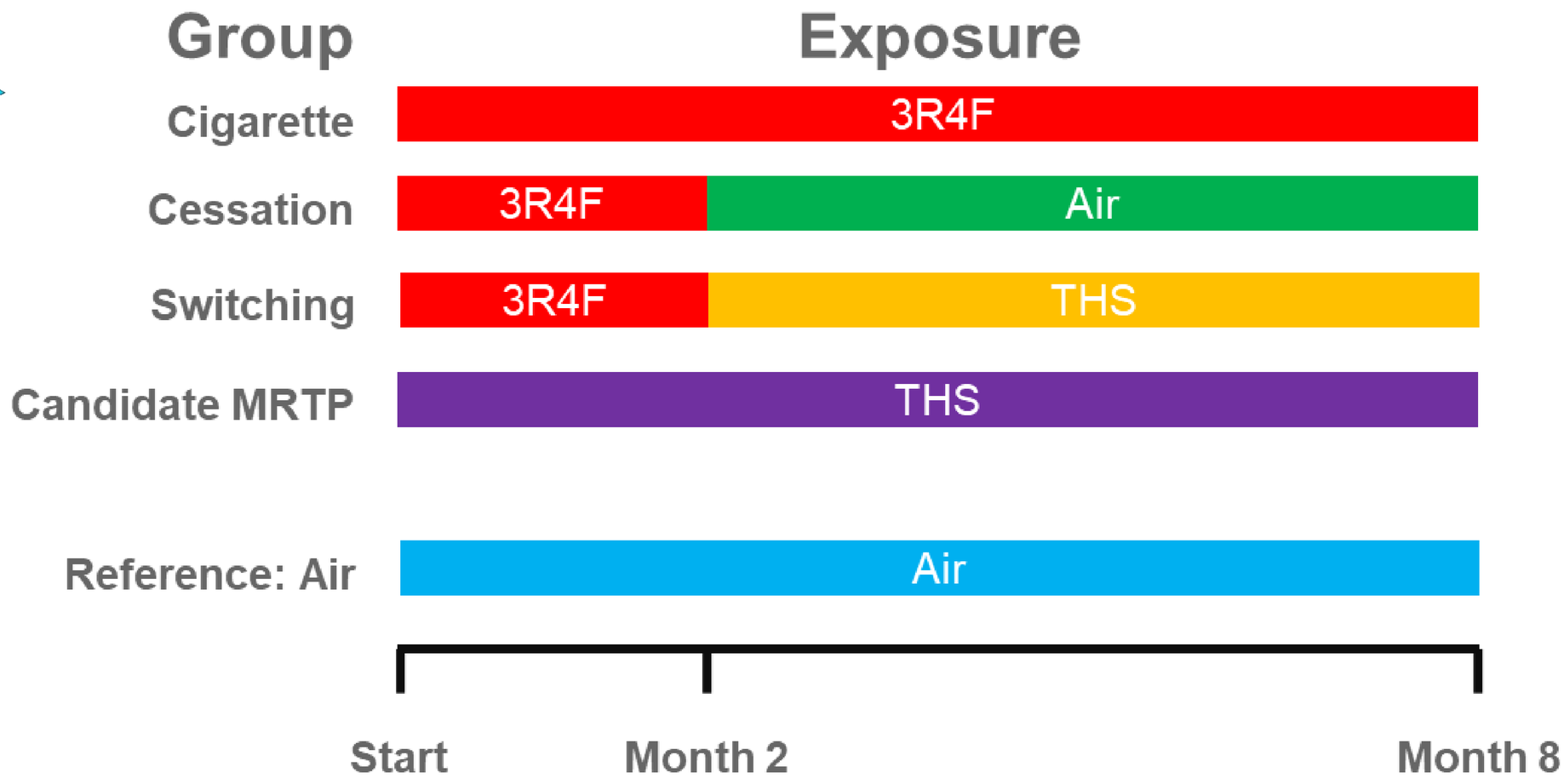
Animal Model of CVD and COPD in ApoE$^{-/-}$ Mice



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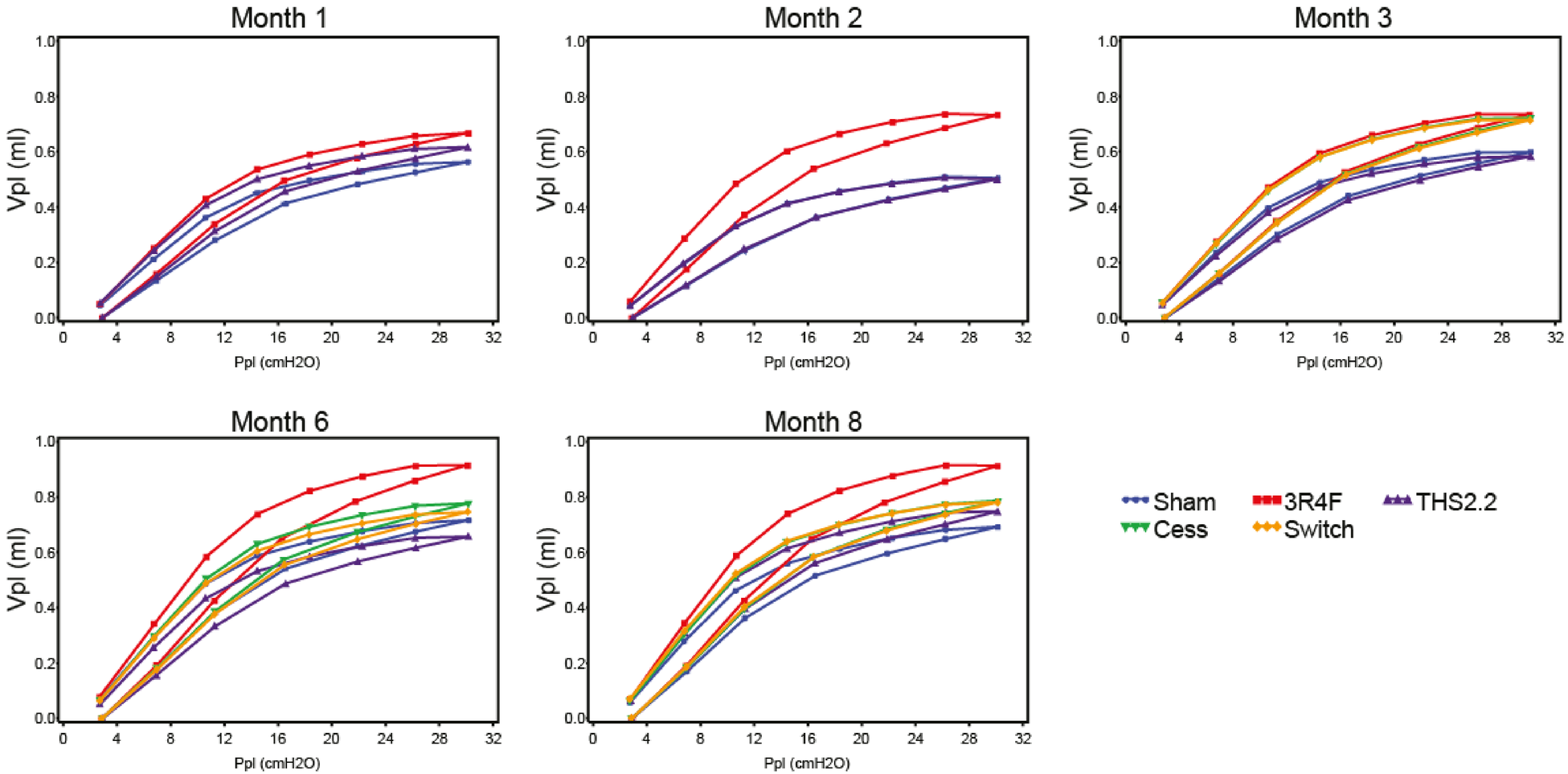
Note: Use of animal model reviewed in: Lo Sasso et al. The Apoe−/− mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. J. Transl. Med., 2016; 14:146.

Lung Function - Pressure Volume Loops



Note: These data alone do not represent a claim of reduced exposure or reduced risk.
Source: 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.

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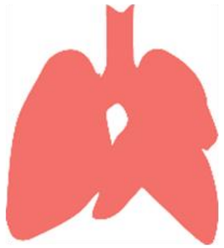
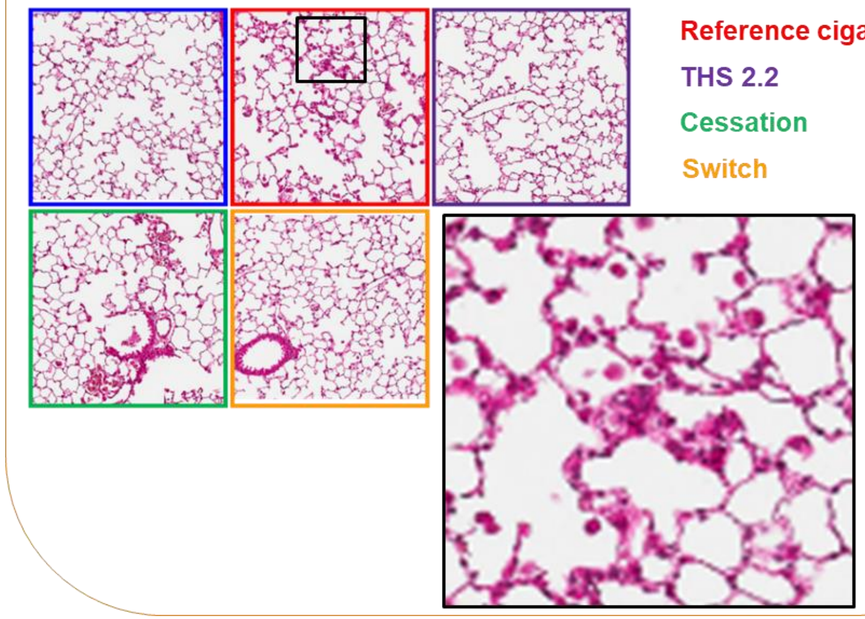
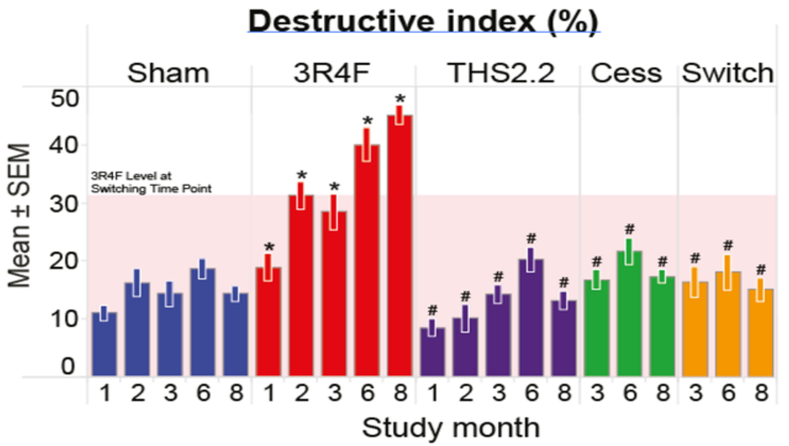
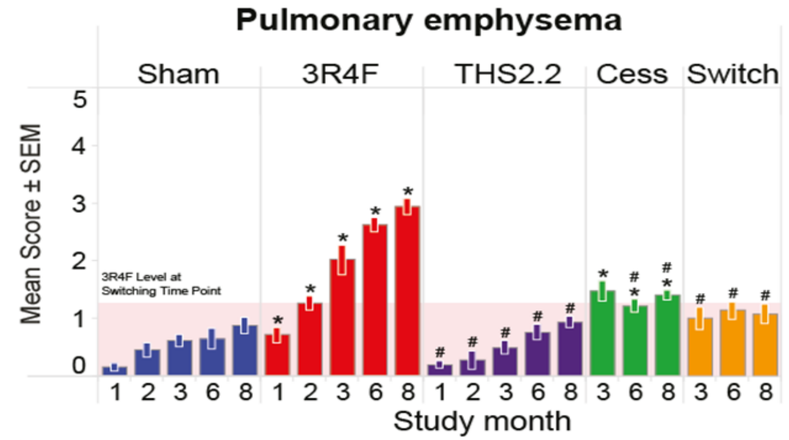
Respiratory Tract Histology









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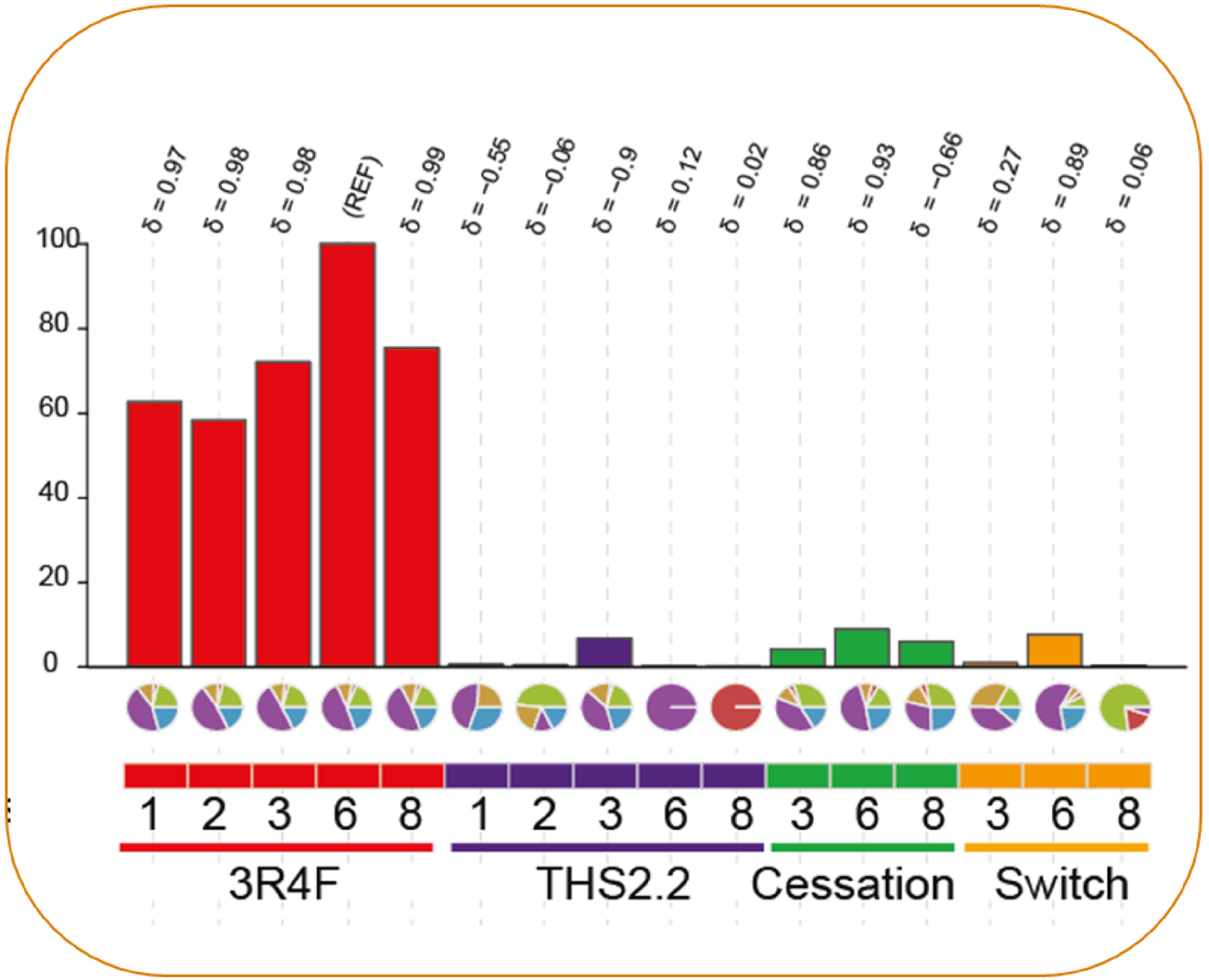
Source: Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences 149(2): 411-432.

Biological Impact Factor (BIF)



Note: These data alone do not represent a claim of reduced exposure or reduced risk.

Source: 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.

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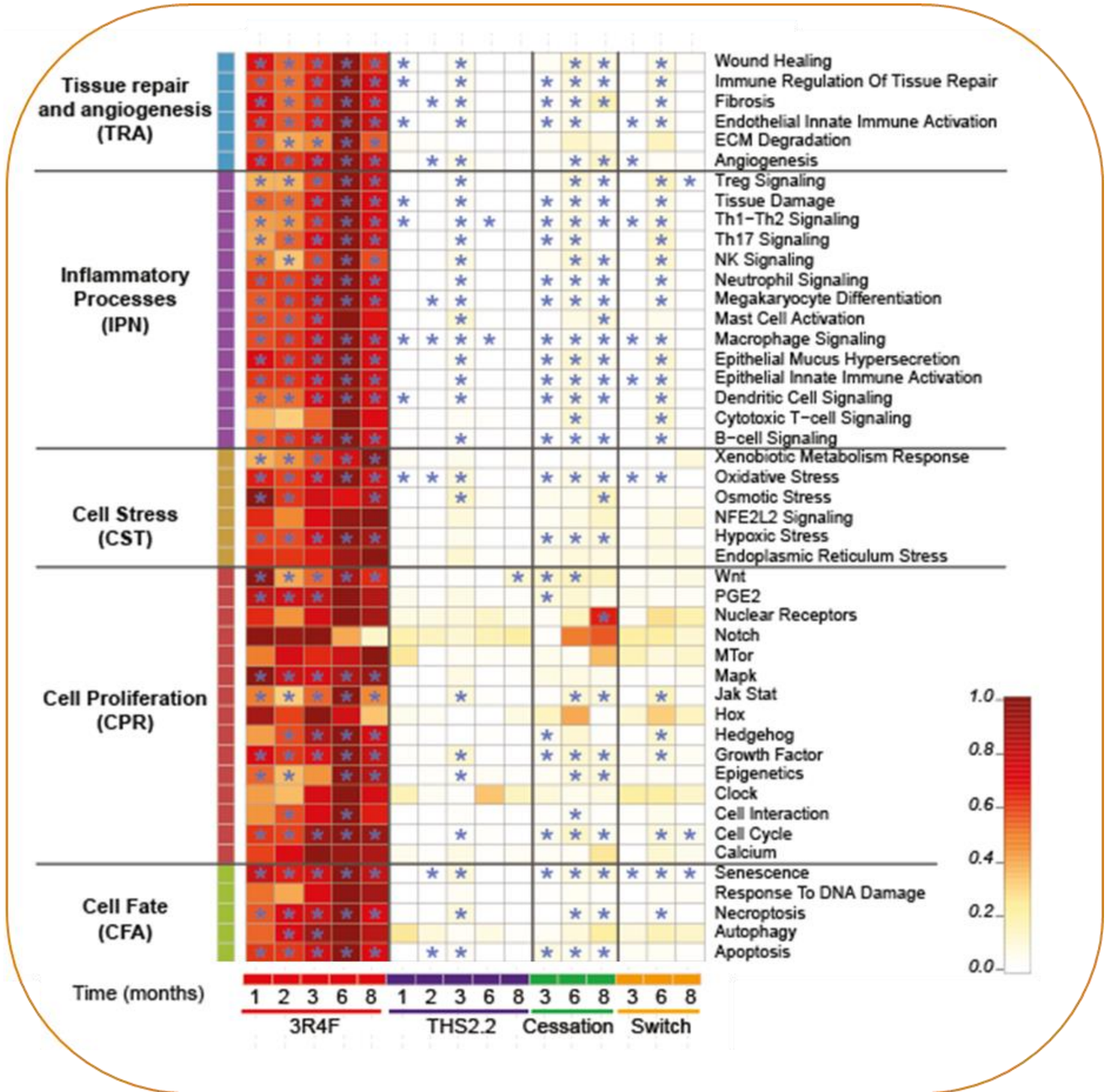
Network Perturbation Amplitude (NPA) - Lung



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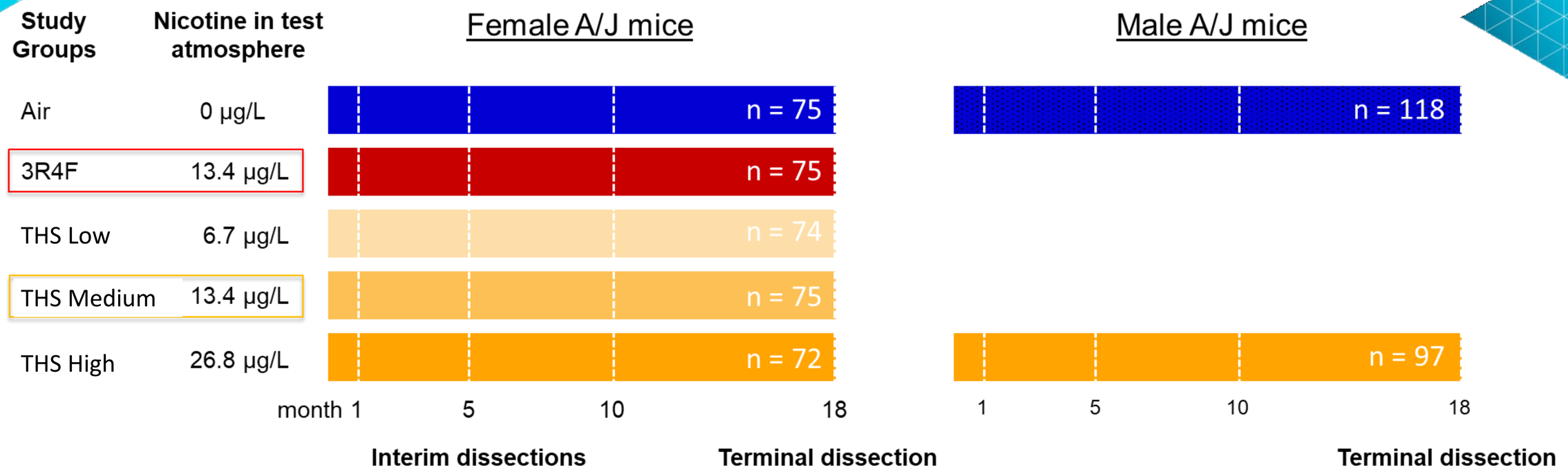
Animal Model of Lung Cancer in A/J Mice

26.8 µg/L nicotine concentration in THS aerosol represents 56 Sticks/day*



n = Number of animals at months 18 assessable for carcinoma incidence.

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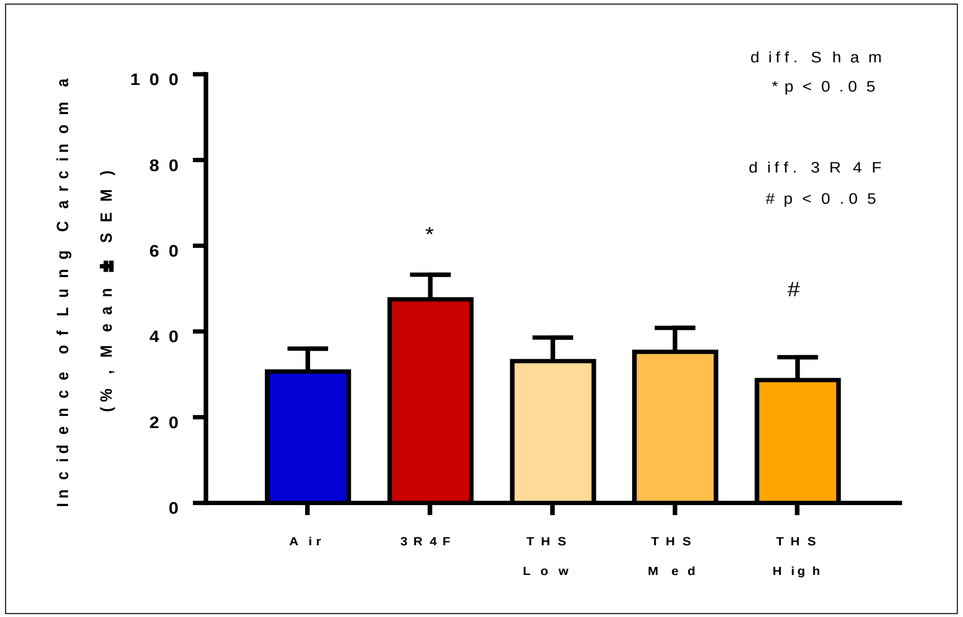
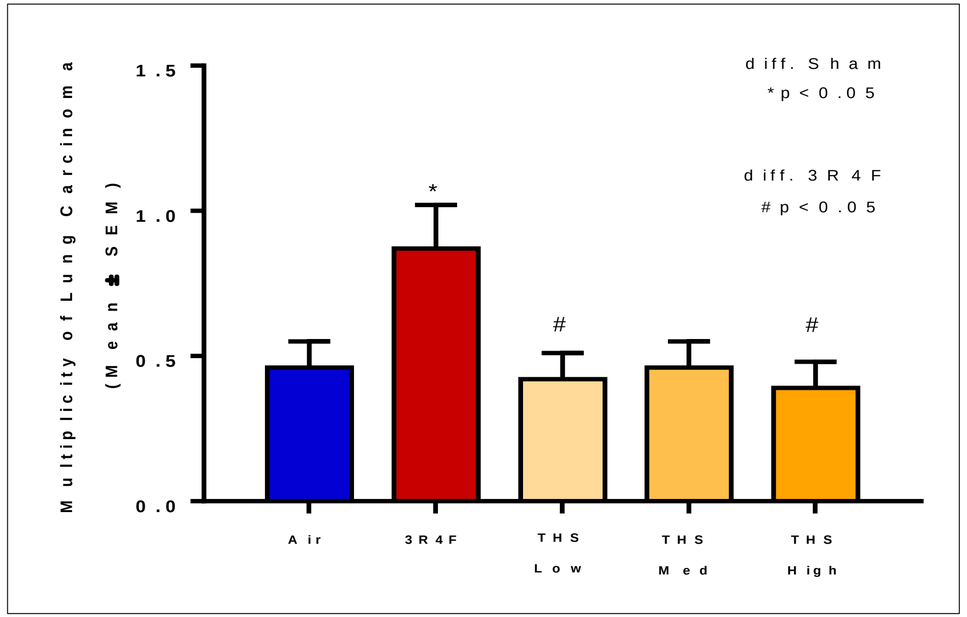
Sources: *FDA, 2005. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Food and Drug Administration, Washington, DC. http://www.fda.gov/cder/guidance.
Stinn et al., 2013, Toxicology. 2013, 305:49-64. doi: 10.1016/j.tox.2013.01.005

Incidence and Multiplicity of Lung Carcinoma in an AJ Mouse Cancer Study

Incidence Bronchiolo-Alveolar Carcinoma in AJ Mouse Lungs



Multiplicity Bronchiolo-Alveolar Carcinoma in AJ Mouse Lungs



Incidence and multiplicity of Lung Carcinomas in THS exposed mice was significantly lower compared to 3R4F smoke exposed mice and similar to air exposed mice.

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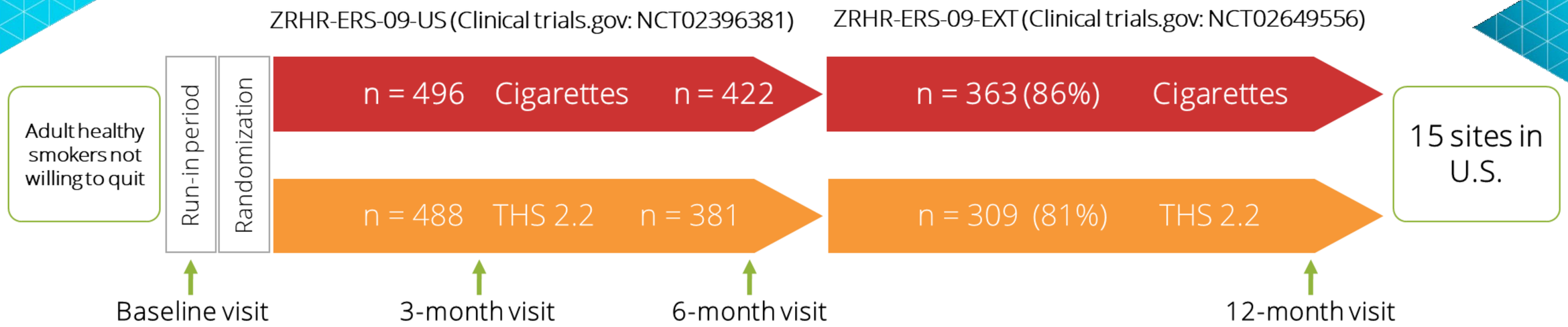
Note: These data alone do not represent a claim of reduced exposure or reduced risk.
Results submitted to the U.S. FDA on August, 2018, as an amendment to PMI's MRTP Application for THS
Source: PMI Research and Development; PMI Study Report of Study - Study number 15020

Exposure Response Study – 6 months



Note: Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS

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Statistical Analysis

Success criteria:

To establish that the risk profile of THS is 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

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Note: Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS

Note: THS stands for Tobacco Heating System version 2.2

Registered on clinicaltrials.gov: NCT026396381

Changes in Clinical Risk Endpoints

Patho-Mechanisms	Co-Primary Endpoints	Type of Change	Observed Change*	Halperin-Ruger Adjusted CI	1-sided p-value (0.0156)	Statistical Significance
Lipid Metabolism	**HDL-C**	Difference	3.09 mg/dL	1.10, 5.09	<0.001	
Inflammation	**WBC Count**	Difference	-0.420 GI/L	-0.717, -0.123	0.001	
Endothelial Function	**sICAM-1**	% Reduction	2.86 %	-0.426, 6.04	0.030	Borderline
Clotting	**11-DTX-B2**	% Reduction	4.74 %	-7.50, 15.6	0.193	
Oxidative Stress	**8-epi-PGF_{2a}**	% Reduction	6.80 %	-0.216, 13.3	0.018	Borderline
Acute Effects	**COHb**	% Reduction	32.2 %	24.5, 39.0	<0.001	
Lung Function	**FEV_1 %pred**	Difference	1.28 %pred	0.145, 2.42	0.008	
Genotoxicity	**Total NNAL**	% Reduction	43.5 %	33.7, 51.9	<0.001	

Primary objective met:
5 of 8 clinical risk endpoints were statistically significant compared to continued smoking

Notes:
*** Observed change presented as LS Mean Difference / Relative Reduction**
Borderline = 0.05>p-value>0.0156
These data alone do not represent a claim of reduced risk.
THS stands for Tobacco Heating System version 2.2

Registered on clinicaltrials.gov: NCT026396381

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Note: Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS

Summary

- **THS significantly reduces systemic and lung inflammation compared to continued smoking.**
- **Switching to THS slows the decline in lung function compared to continued smoking.**
- **THS reduces incidence and multiplicity of lung adenomas and lung carcinomas in a validated animal model of disease.**
- **THS contains nicotine and is addictive. It is not risk-free, and the best alternative for smokers is to quit.**

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Thank you for your attention.