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# Tabakerhitzer (*Heat-not-Burn*)

## Das Potenzial für Harm Reduction

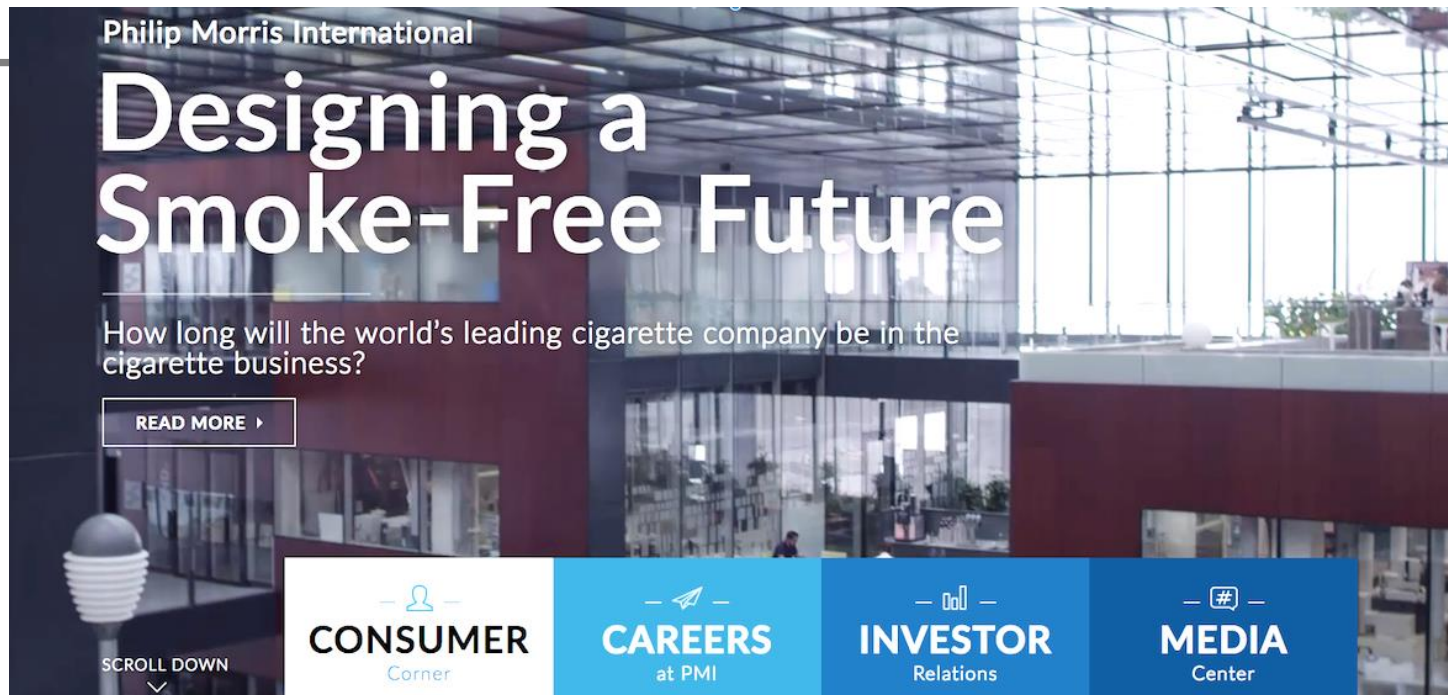
### Studienergebnisse von PMI Science

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*4th German Pharm-Tox Summit (85. Jahrestagung der DGPT)  
Symposium 14 – Rauchen 2.0: Neue Tabak- und Tabakersatzprodukte  
Stuttgart, 28. FEB 2019*

*Dr. Alexander (Sascha) K. Nussbaum  
Head of Scientific & Medical Affairs  
Philip Morris Germany*

# PMI Transformation towards a Smoke-Free Future



**“Our stated ambition is to convince all current adult smokers that intend to continue smoking to switch to smoke-free products as soon as possible.”**

André Calantzopoulos, CEO Philip Morris International

BBC, Nov 2016

# 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 RRP s in various stages of development, scientific assessment, and commercialization.*

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

# 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)



PLATFORM

3

NICOTINE DELIVERY SYSTEM



PLATFORM

4

E-VAPOR PRODUCTS



Note: The RRP's 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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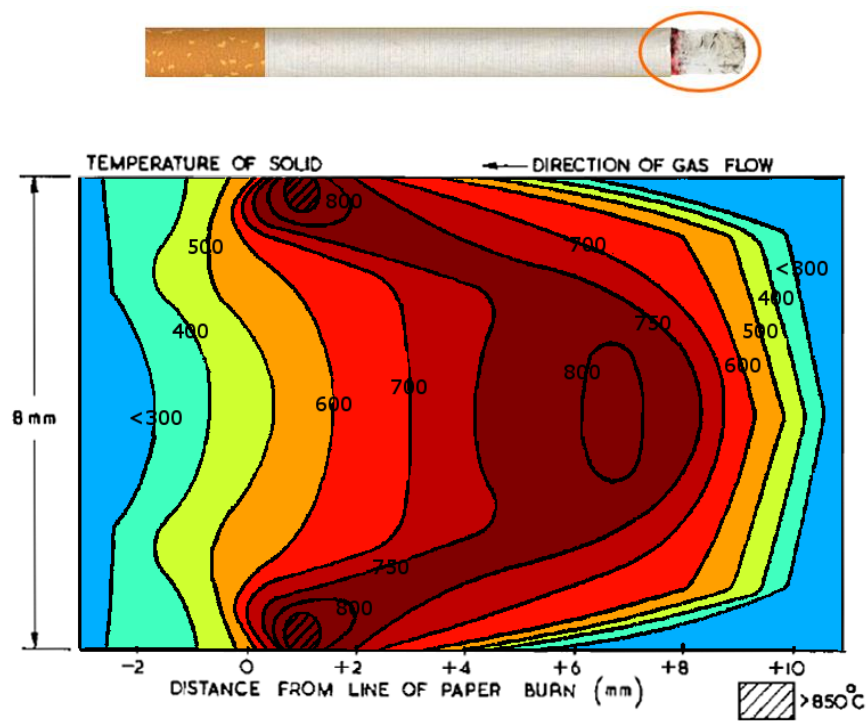
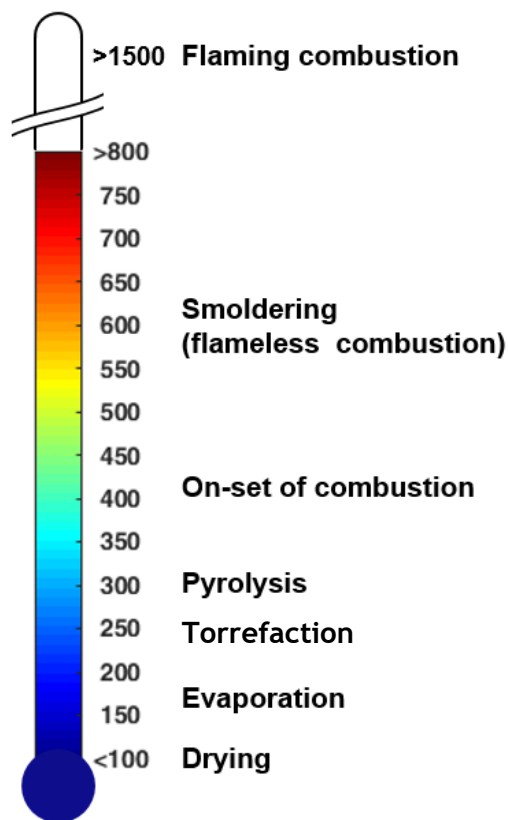
# Combustion



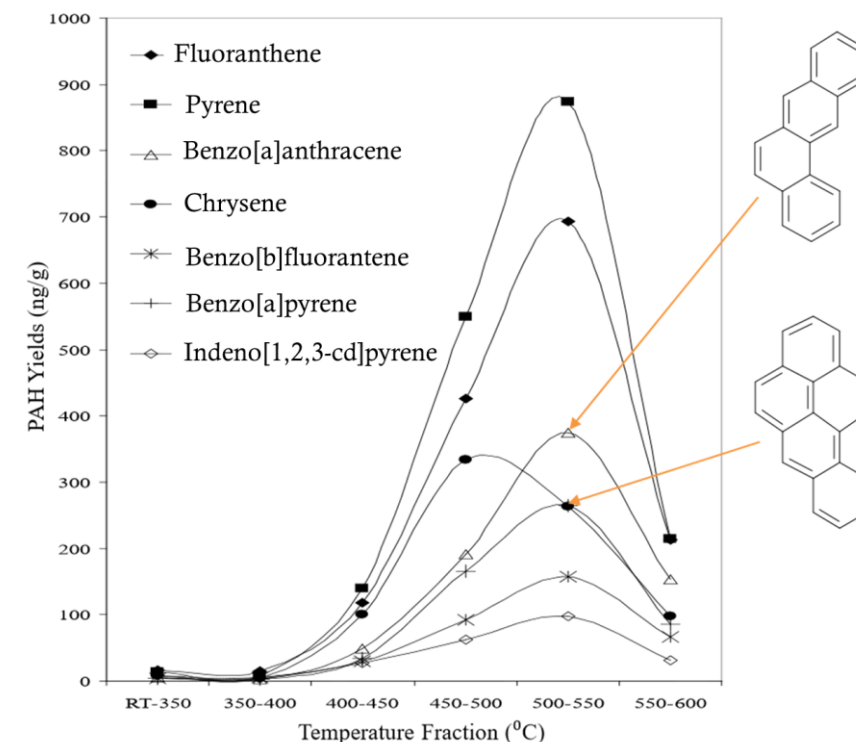
# Elimination of Combustion Is Key

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

Temperature (°C)



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.

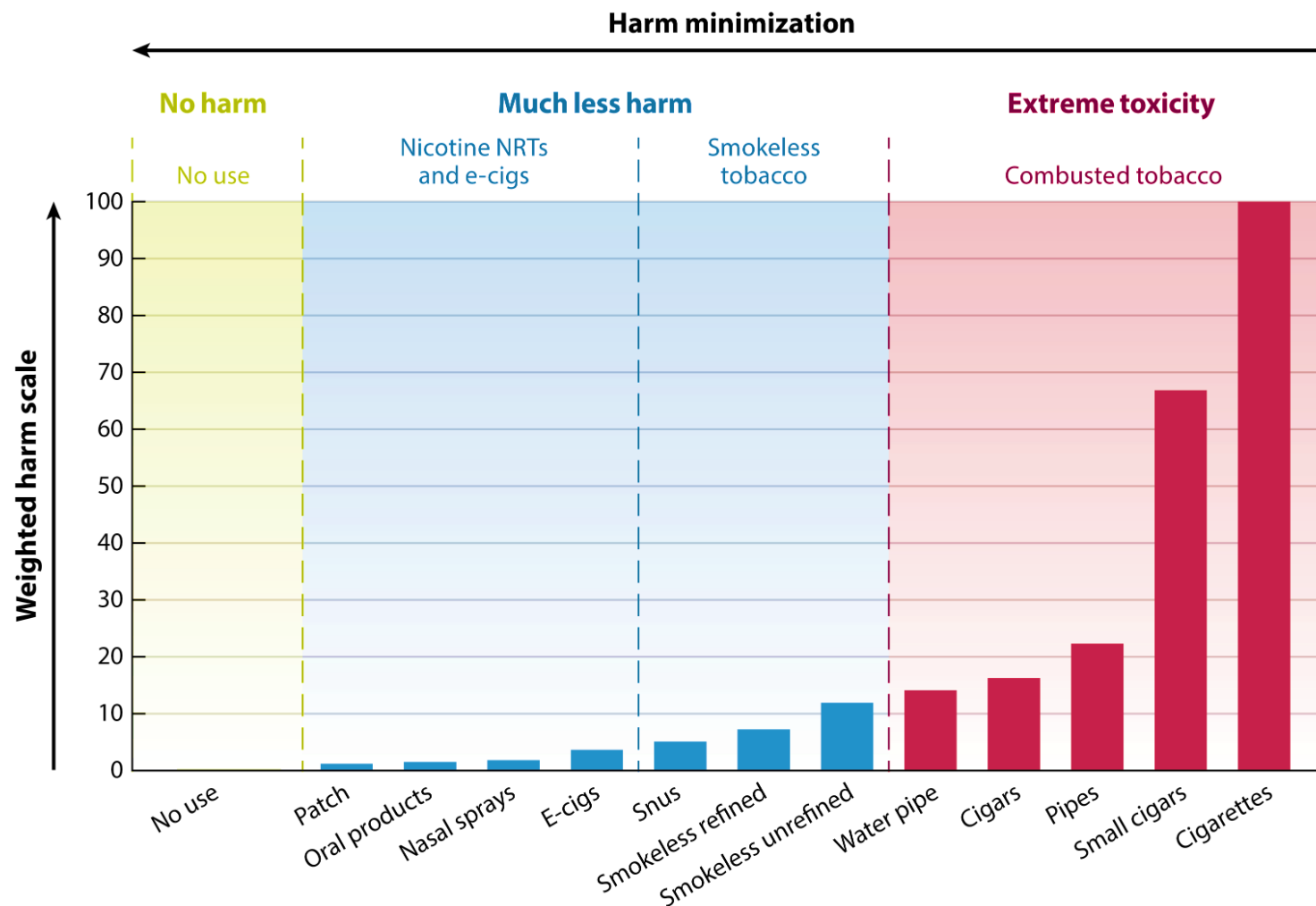


Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

# The Harm Minimization Continuum

## Open questions

- Where to place new product categories (e.g., **heat-not-burn**)?
- Scientific assessment **standards** to place (new) products?



# Drogen- und Suchtbericht 2018:

## Zigarette / Tabakerhitzer / E-Zigarette

	Tabakzigaretten	Tabakerhitzer	E-Zigaretten
Schadstoffgehalte im Rauch bzw. in den Emissionen	<b>Sehr hoch</b> Counts et al., 2005	<b>Deutlich reduziert</b> Schaller et al., 2016 Mallock et al., 2018	<b>Stark reduziert</b> Goniewicz et al., 2014
Gesundheitliche Risiken	<b>hoch</b>	<b>vorhanden</b> Für eine zuverlässige Bewertung inwieweit sich geringere Schad- stoffgehalte auf gesundheitliche Risiken auswirken, fehlen noch geeignete Modelle.	<b>vorhanden</b> Gesundheitsrisiken können wegehend minimiert werden und hängen vom Gerät, den Inhalts- stoffen der Liquids und den Betriebsbedingungen ab. Zu den Risiken einer langfristigen Nutzung besteht Klärungsbedarf.

Quelle: BfR 2018

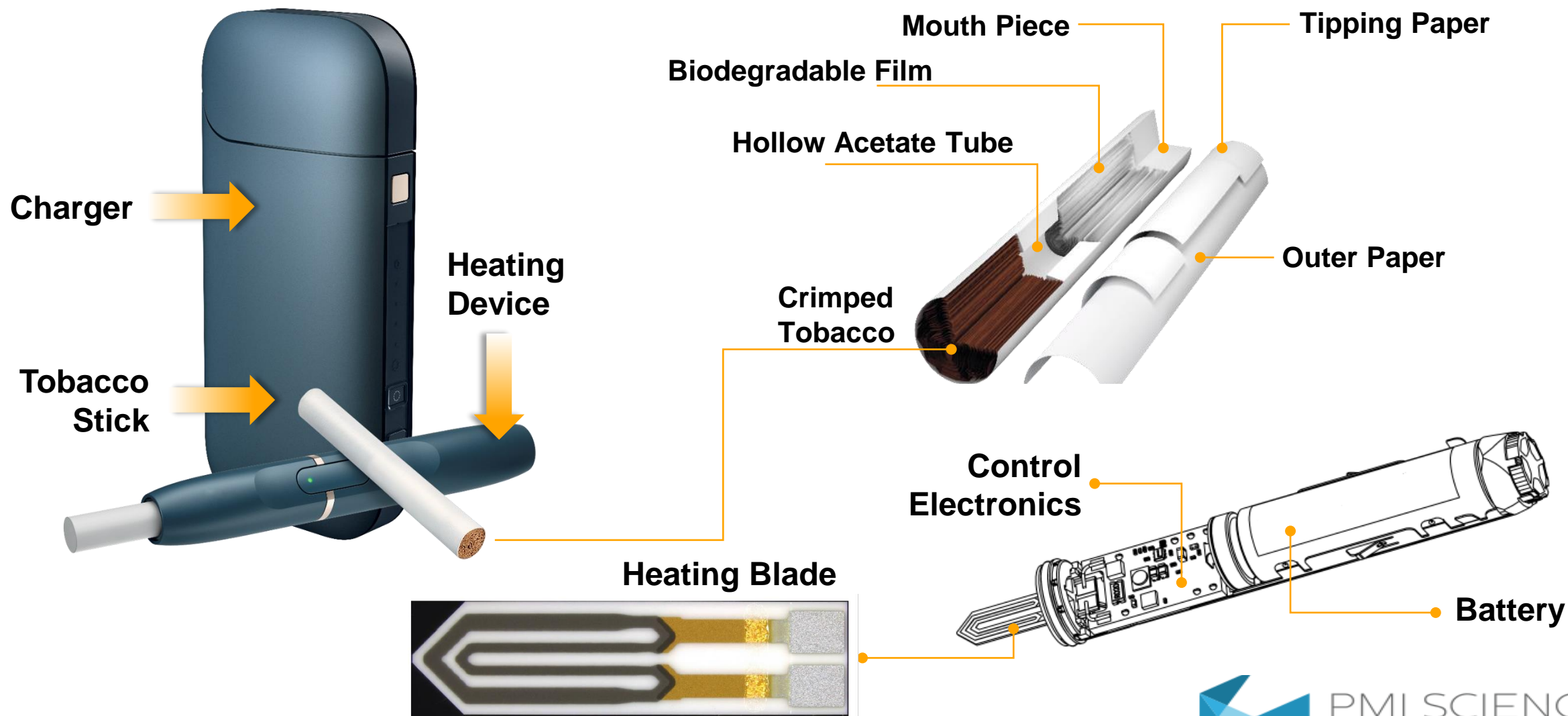




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# The Tobacco Heating System 2.2 (THS)

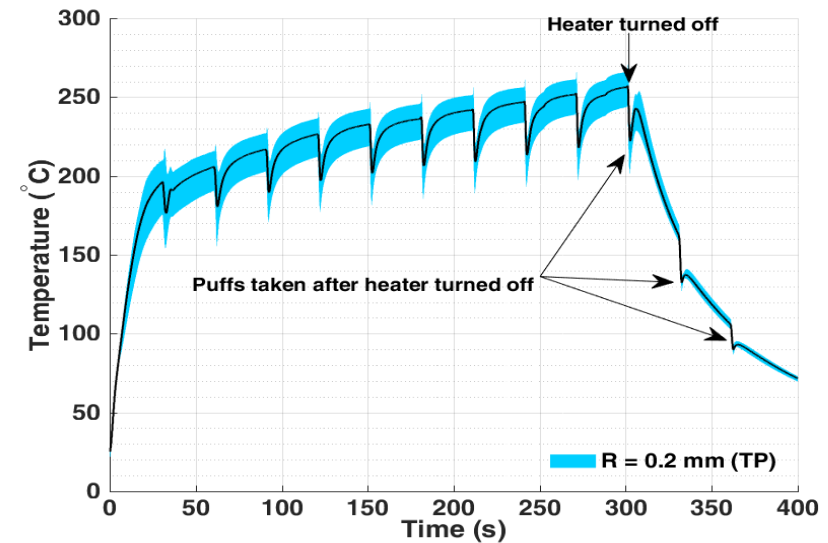
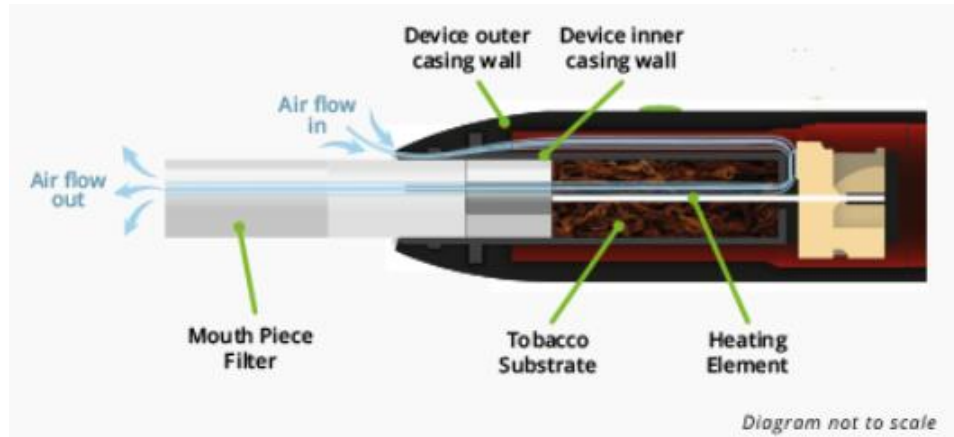
# Product Design: Tobacco Heating System (THS)



# Why Heating Tobacco Rather than Burning It?

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

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



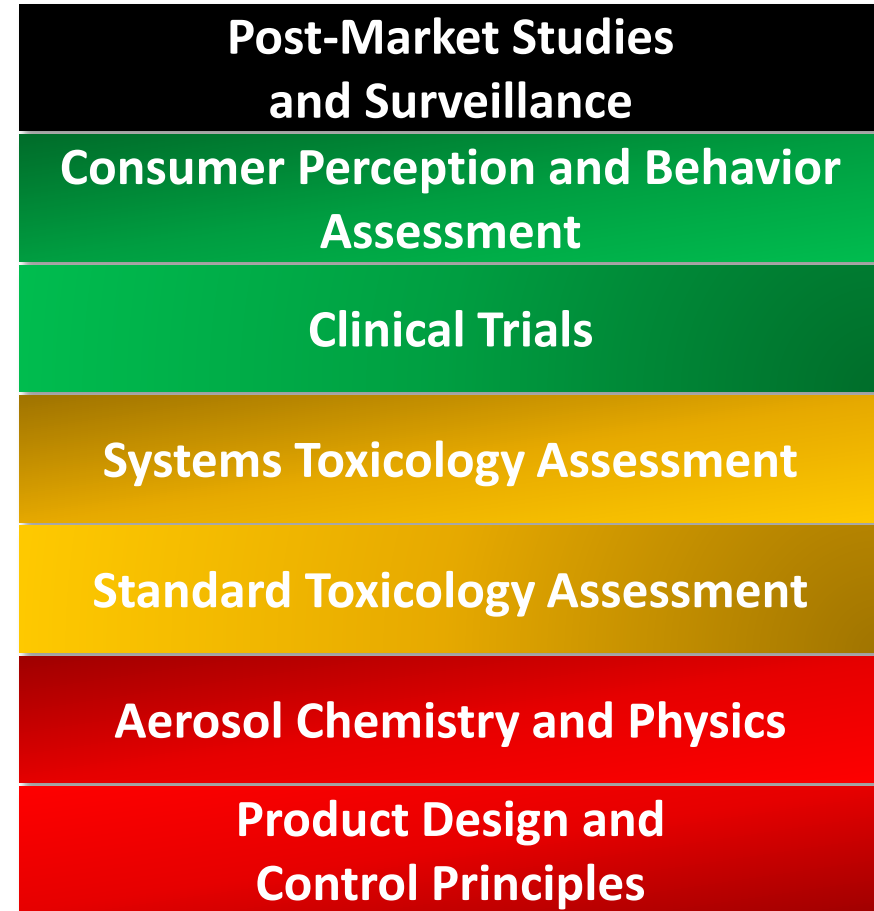
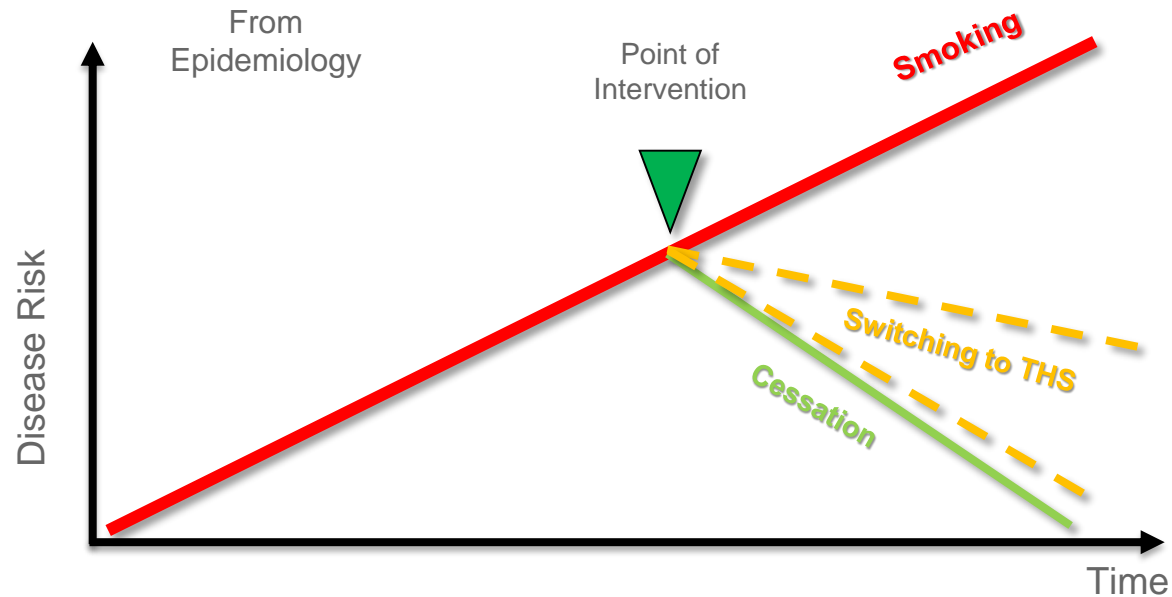


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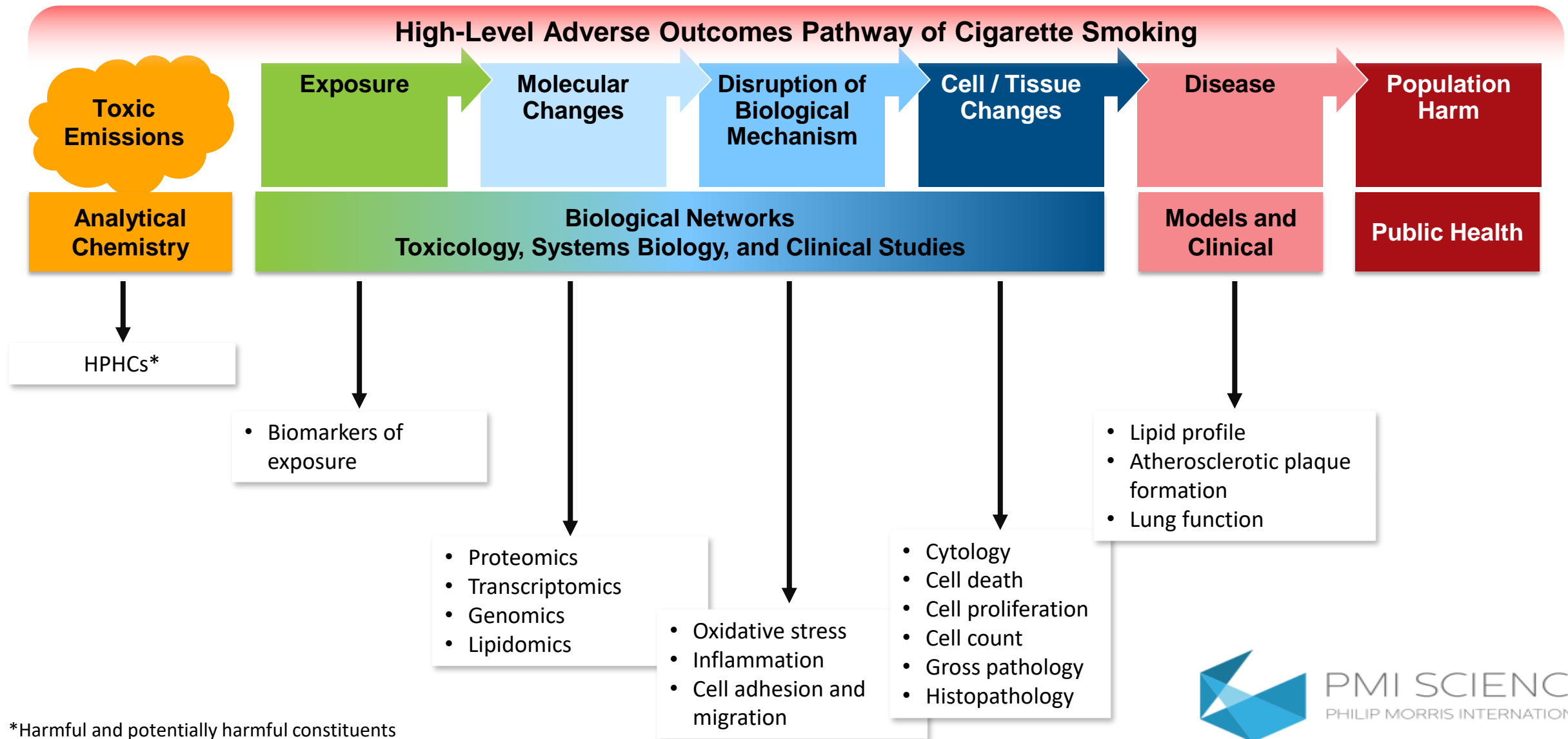
# Scientific Assessment Approach

# PMI's Scientific Assessment Approach

## Assessment Framework



# Assessment Framework: Informed by Epidemiology





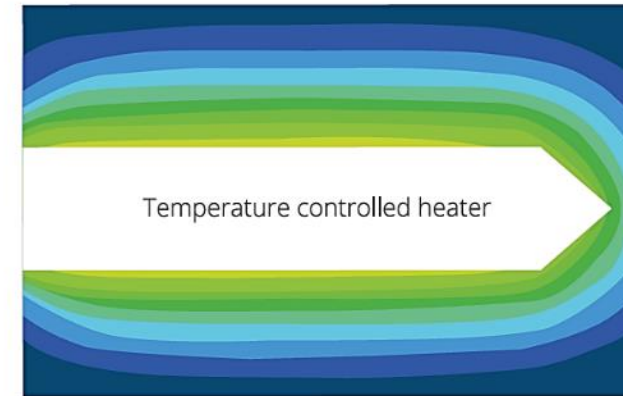
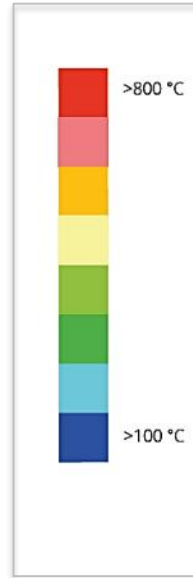
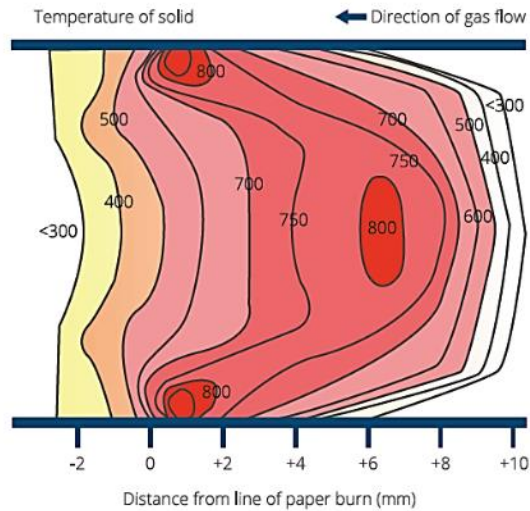


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# HPHC\* Reduction and Carbon-Based Nanoparticles

\***HPHCs**: Harmful and Potentially Harmful Constituents

# THS: Controlled Heating → No Combustion → No Ash



# THS Aerosol Different from Cigarette Smoke

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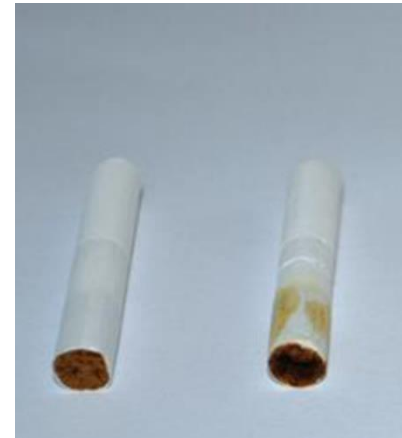


Cigarette smoke

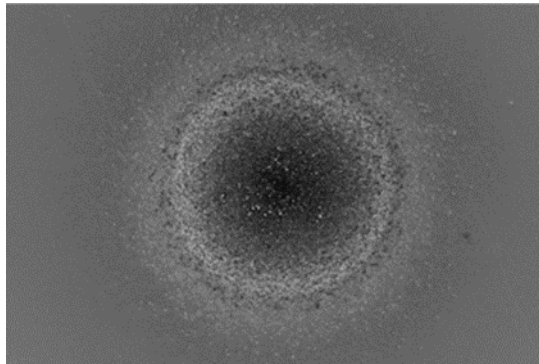
Cigarette smoke  
(particulate matter) (left)  
and THS aerosol (right)  
collected on Cambridge  
glass-fiber filter pads



THS 2.2 aerosol



# THS: No More Carbon-Based Solid Nanoparticles

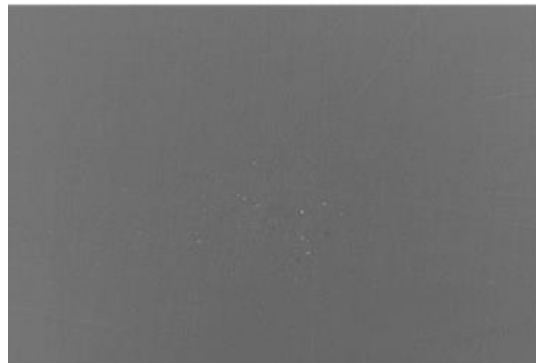


**Cigarette smoke**

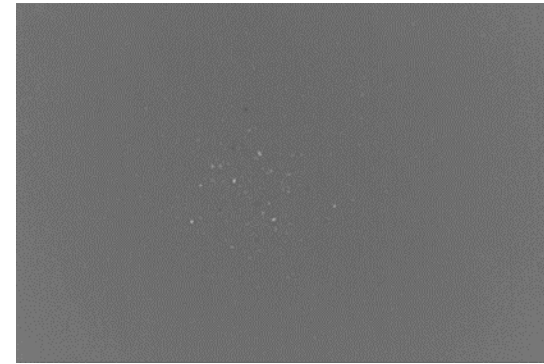
Carbon-based nanoparticles

Median diameter = 75 nm

Amount:  $6 \times 10^{11}$  particles  $\approx$  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 300°C to remove the volatile portion/collected material characterized by electron diffusive X-ray.**

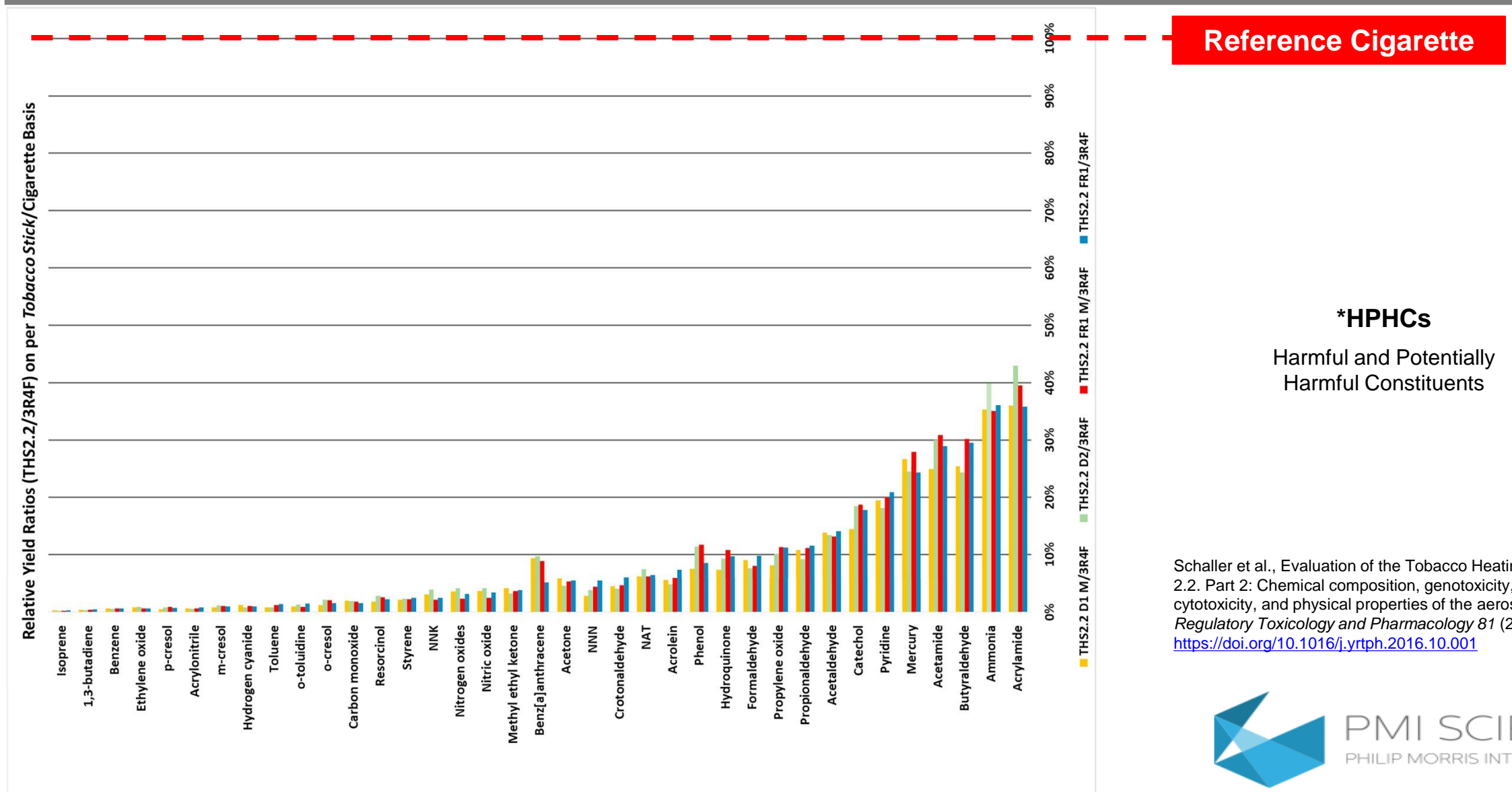
\* Under the Health Canada Intense Smoking Regime.

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. <https://doi.org/10.1177/0960327116681653>



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# Reduced Formation of HPHCs\* by Compound

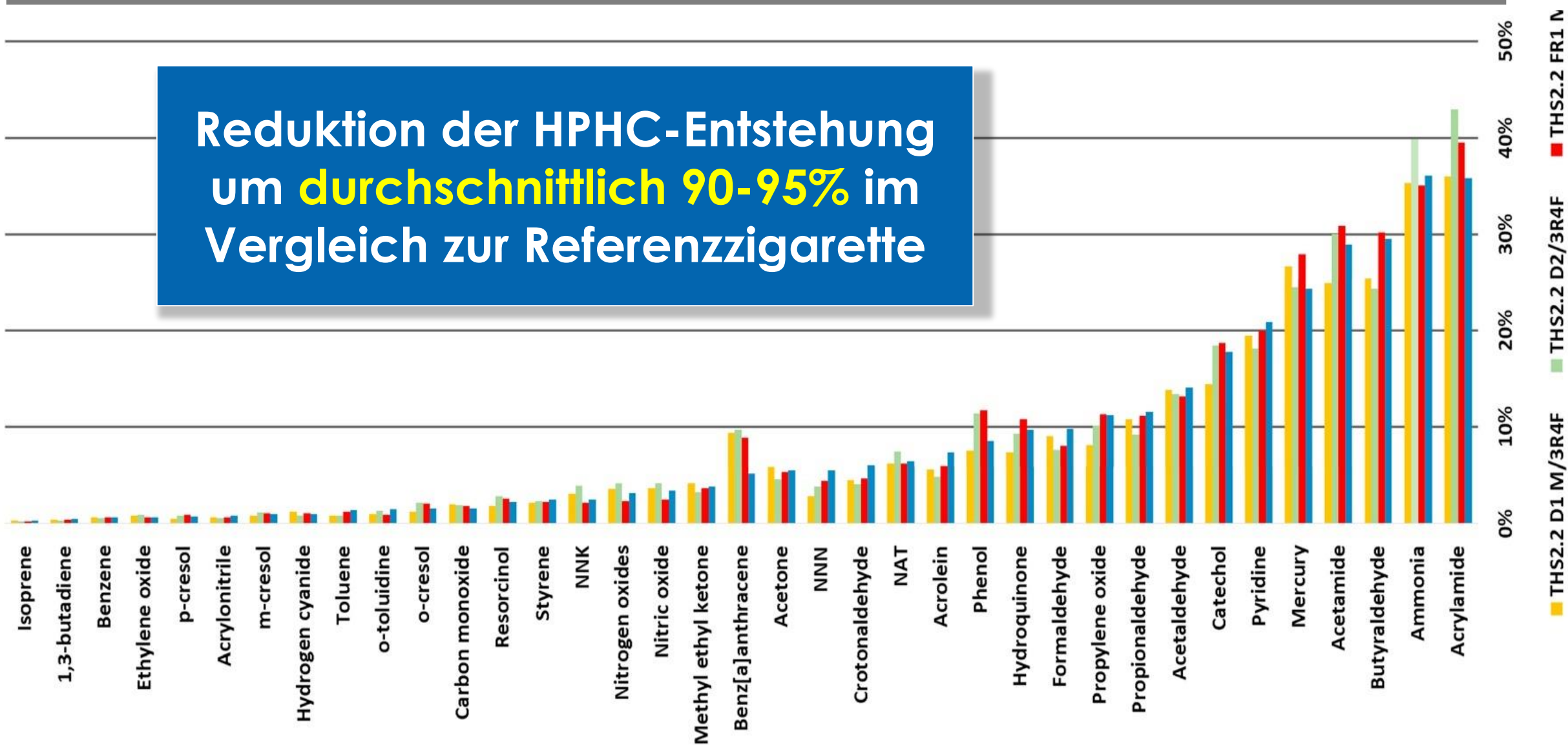




# Reduced Formation of HPHCs by Compound

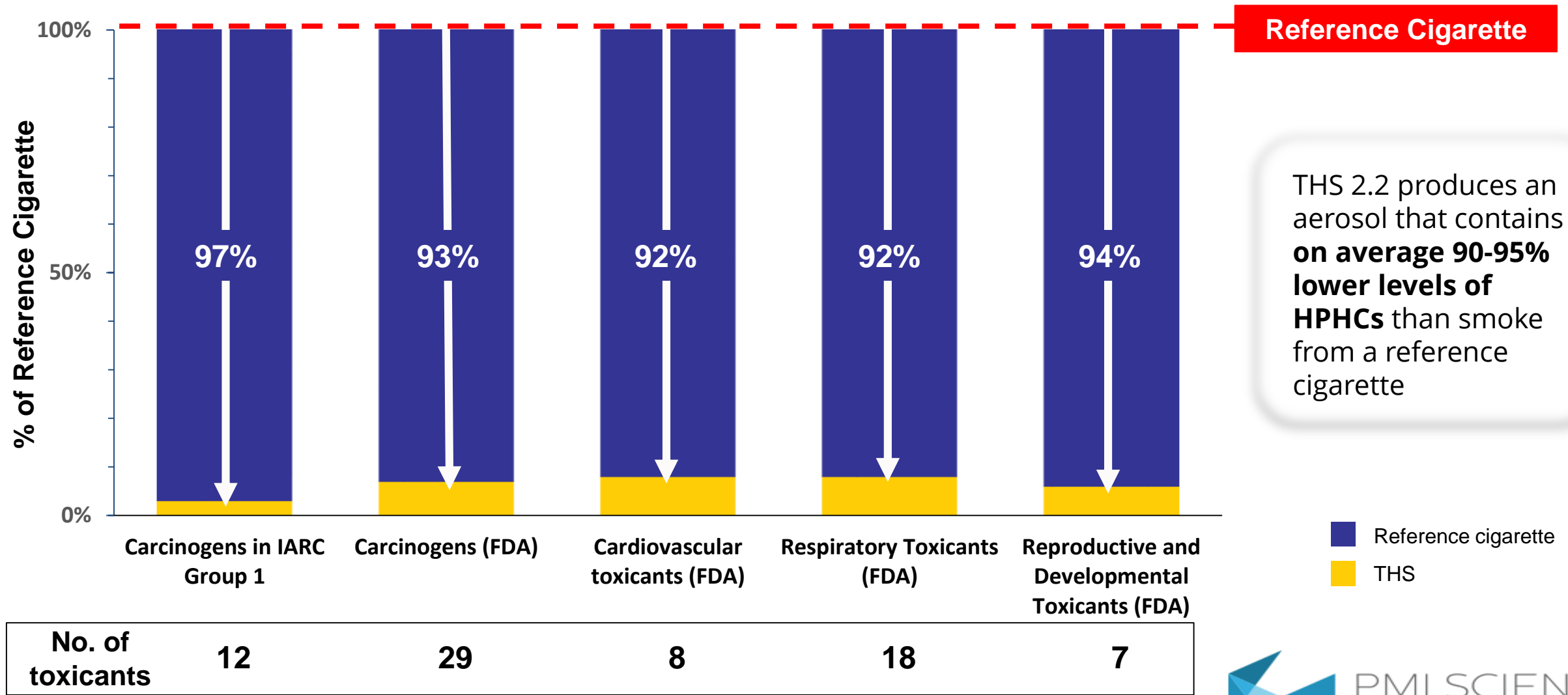
Reduktion der HPHC-Entstehung  
um **durchschnittlich 90-95%** im  
Vergleich zur Referenzzigarette

Relative Yield Ratios (THS2.2/3R4F) on per T<sub>c</sub>





# Reduced Formation of HPHCs by Disease Categories



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

# Independent Confirmation of THS Aerosol Chemistry



BfR (Bundesinstitut für Risikobewertung)  
Dez. 2017<sup>1</sup>

„Im Vergleich zur Zigarette fallen **80-90%** *weniger krebserregende Aldehyde* und sogar **97-99%** *weniger krebserregende flüchtige organische Verbindungen an.*“<sup>4</sup>



FDA (US Food and Drug Administration)  
Jan 2018<sup>2</sup>

- „ **>90%** *reduction* (...) *for acrolein and benzo[a]pyrene*“
- „ **>80%** *reduction* (...) *for formaldehyde*“
- “*levels of ammonia, NNN, and NNK (...) similar to the levels reported by the applicant.*”<sup>2</sup>

(1) Mallock et al., Levels of selected analytes in the emissions of “heat not burn” tobacco products that are relevant to assess human health risks, Arch Toxicol (2018).

<https://doi.org/10.1007/s00204-018-2215-y>

(2) FDA Briefing Document, Seiten 12-13 (Januar 2018)

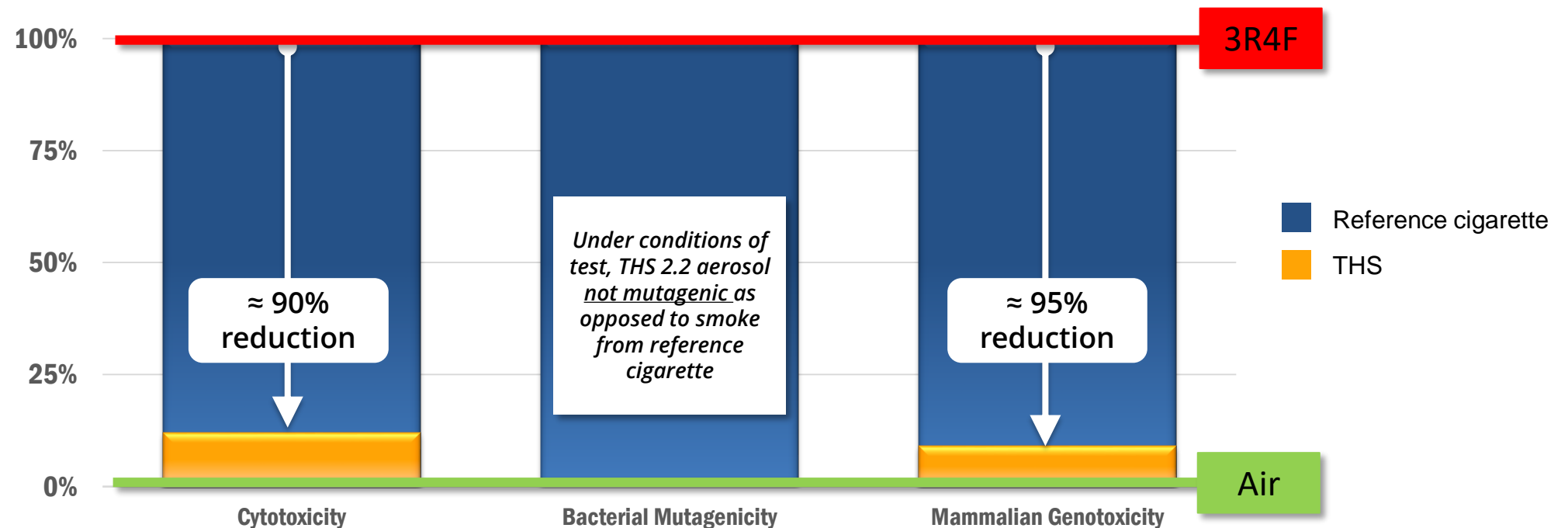
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf>

(3) Pieper et al., Tabakerhitze als neues Produkt der Tabakindustrie: Gesundheitliche Risiken; Bundesgesundheitsblatt, 04 OKT 2018, <https://doi.org/10.1007/s00103-018-2823-y>

(4) 20 Minuten CH, „*So riskant sind E-Zigs, Snus und Tabakerhitze*“ (30.01.2019)

# Toxicological Assessment: Reduced Toxicity

Average reductions in **toxicity** 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



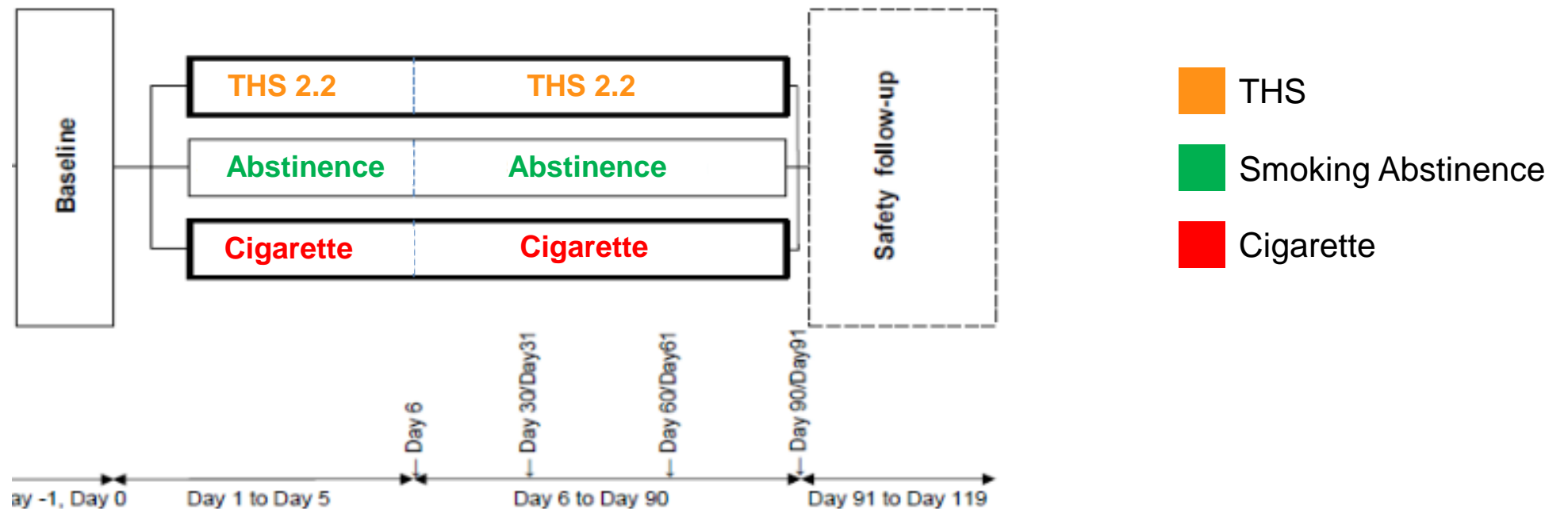
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# Clinical Study: Reduced Exposure

Reduced HPHC Exposure  
in Healthy Human Subjects

# Clinical Assessment: Reduced Exposure to Toxicants

Study design: 3-month clinical study on reduced exposure to smoking-related toxicants

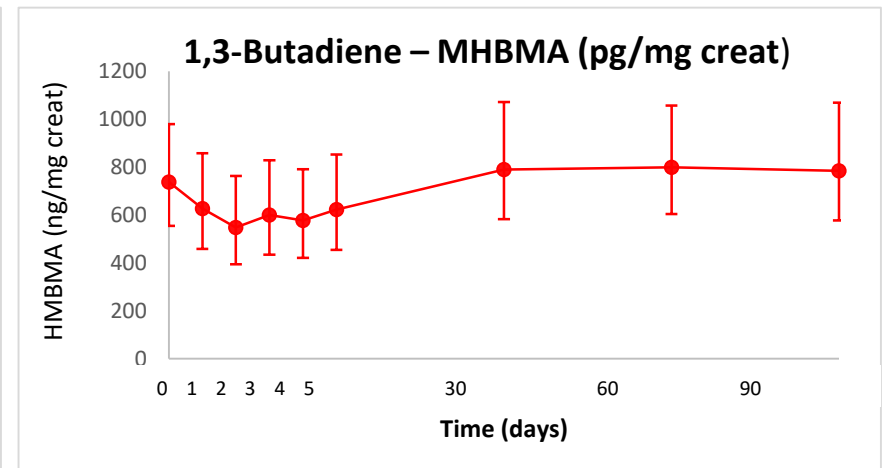
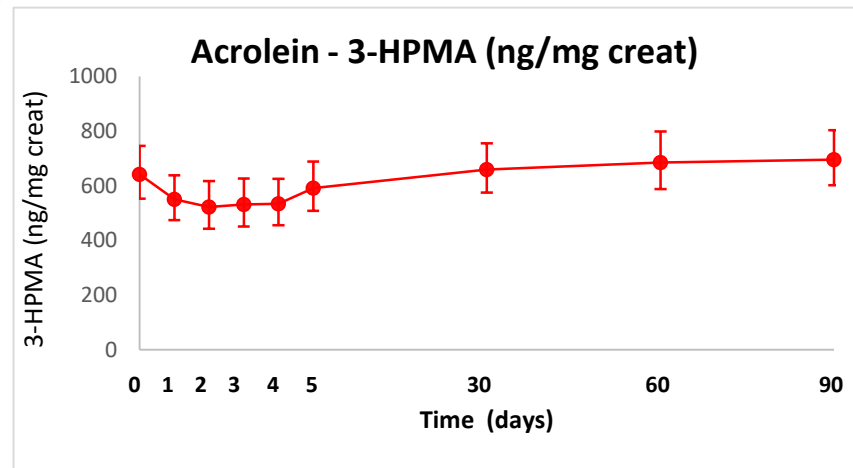
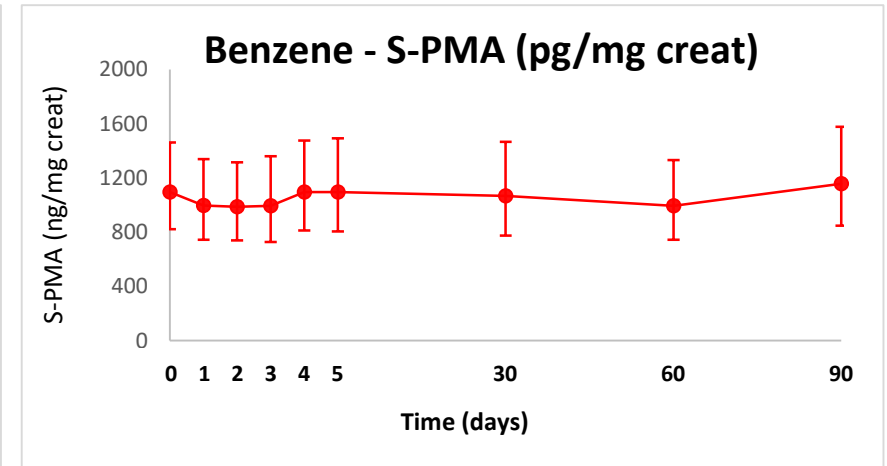
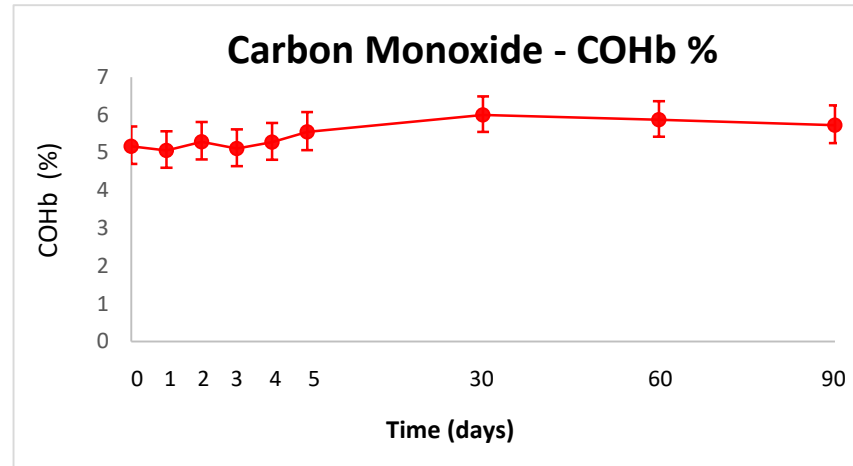


# Clinical Assessment: Reduced Exposure to Toxicants

—■— THS    —●— Combustible Cigarette    —▲— Abstinence

**Adult smokers  
used the products  
*ad libitum***

*Adult smokers  
randomized to  
cigarettes or THS 2.2  
were free to use the  
product as often as  
they wished, in  
confinement  
(5 days) and then  
ambulatory  
(85 days)*



Note: These data alone do not represent a claim of reduced risk.  
Source: PMI Research and Development  
Registered on clinicaltrials.gov: NCT01970995

Haziza et al., poster at SRNT, Chicago, USA, 2016

<https://www.pmiscience.com/library/reduced-exposure-harmful-and-potentially-harmful-constituents-after-90-days-use-tobacco-1>

Lüdicke et al. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). Nicotine Tob. Res. (2017)

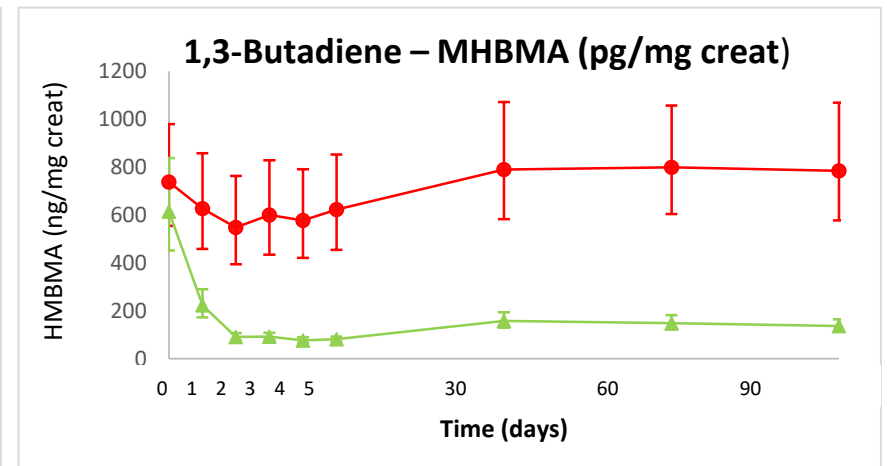
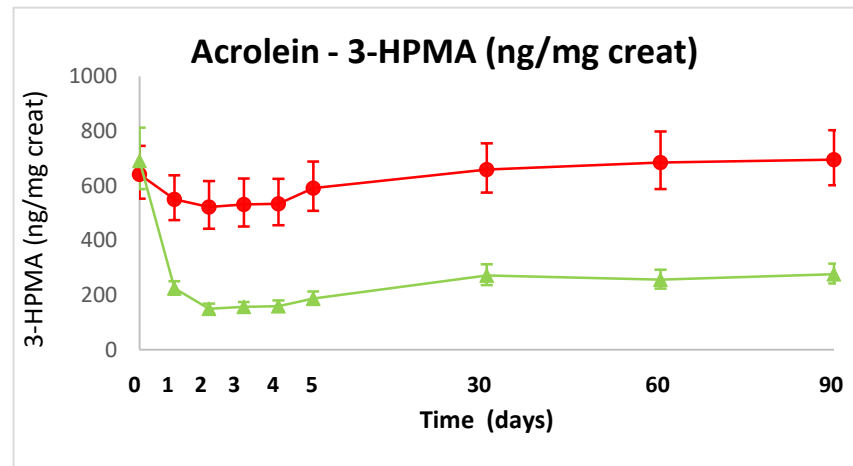
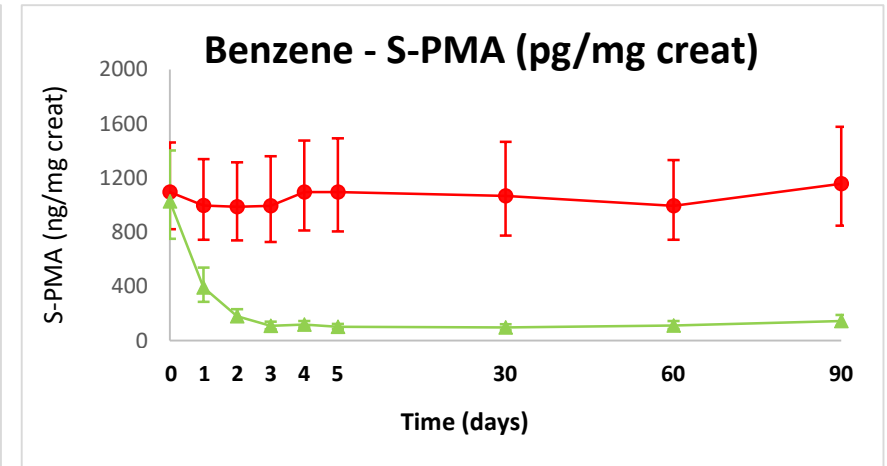
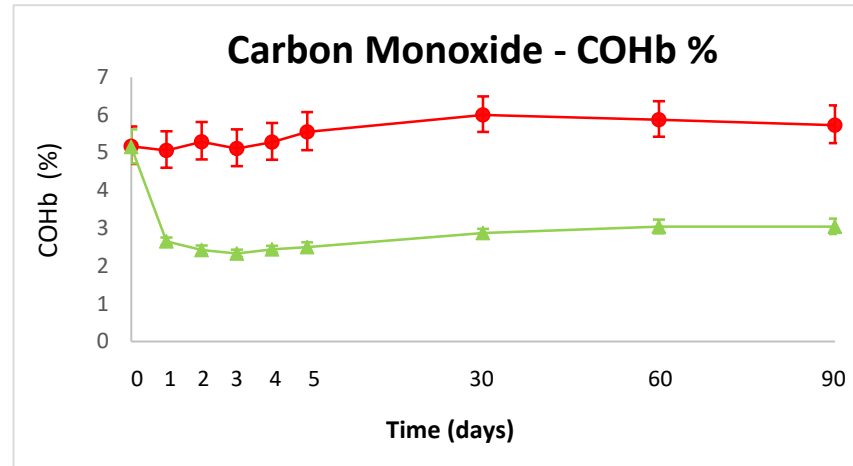


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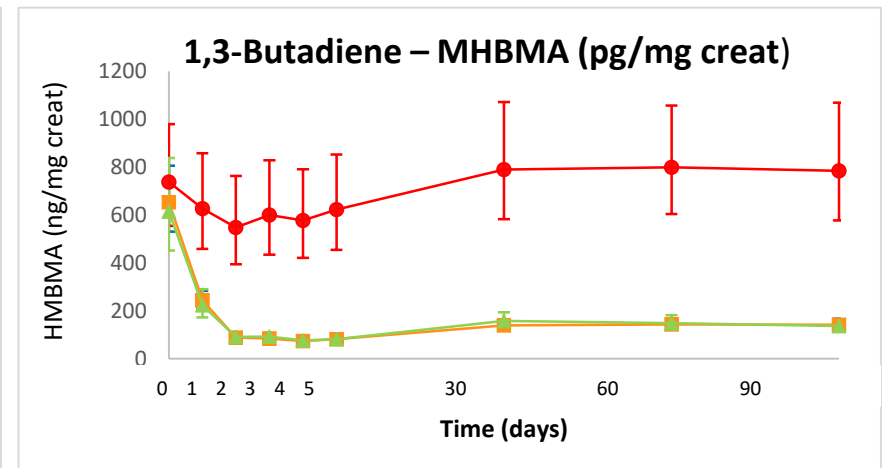
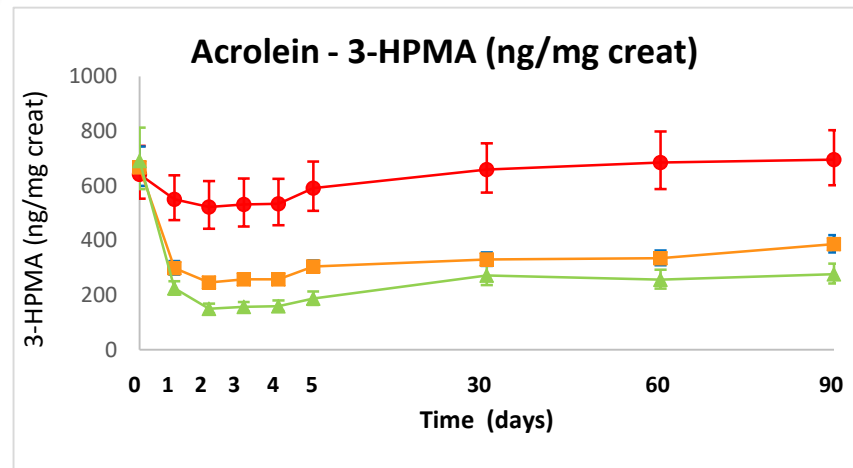
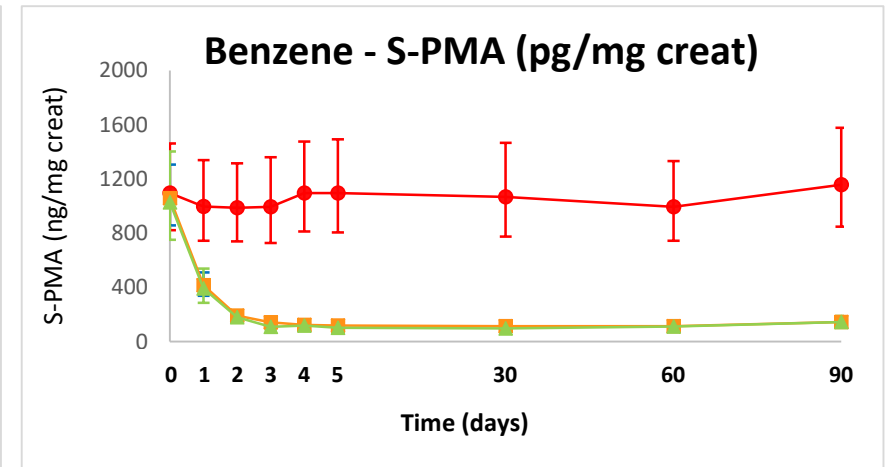
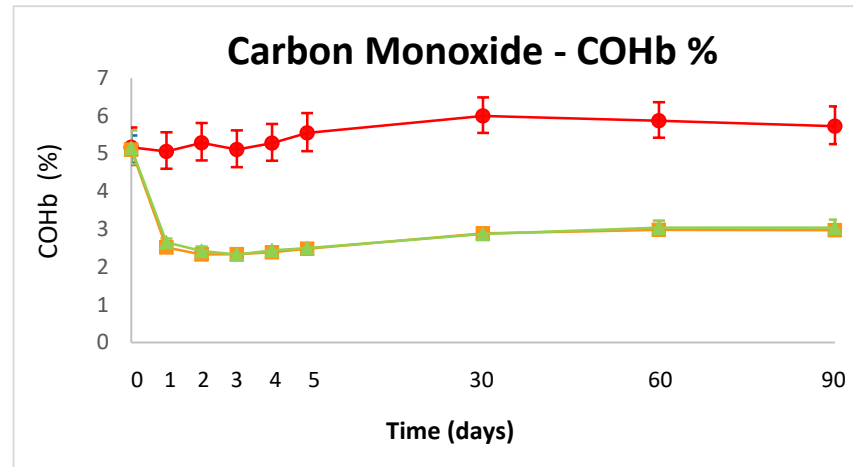
Lüdicke et al. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). Nicotine Tob. Res. (2017)

# Clinical Assessment: Reduced Exposure to Toxicants

■ THS
 ● Combustible Cigarette
 ▲ Abstinence

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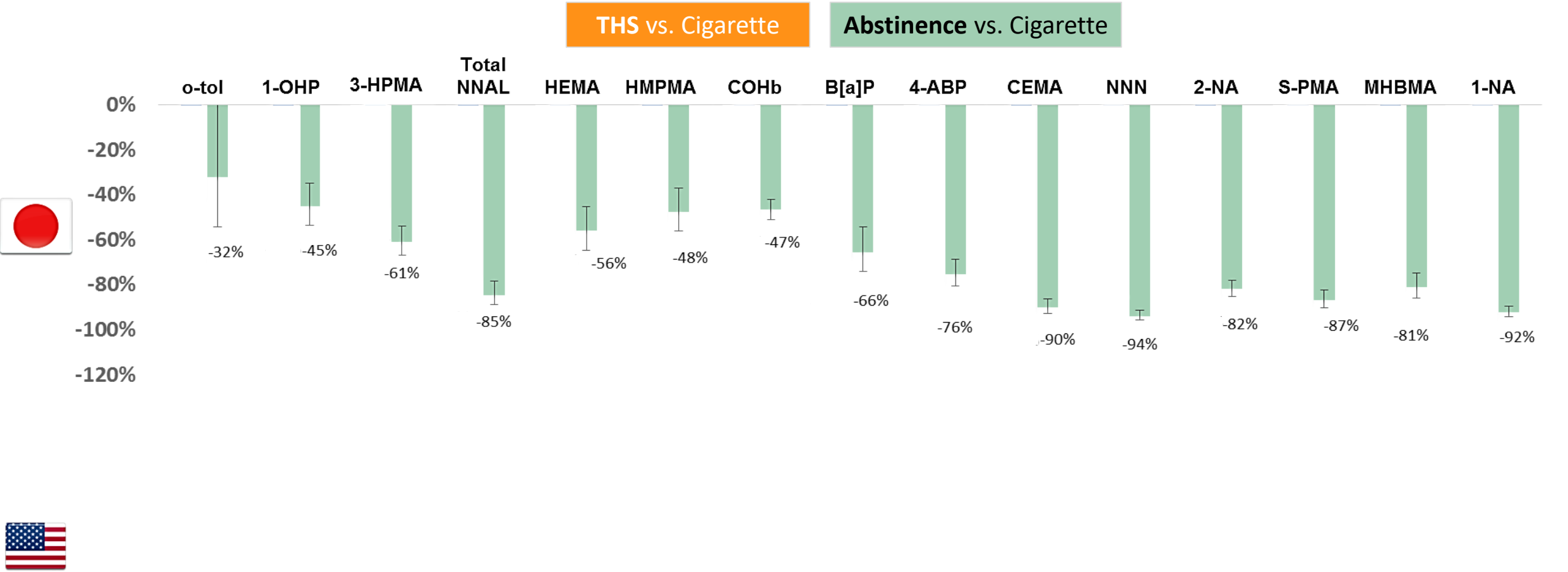
Haziza et al., poster at SRNT, Chicago, USA, 2016

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# Clinical Evidence for Toxicant Exposure Reduction

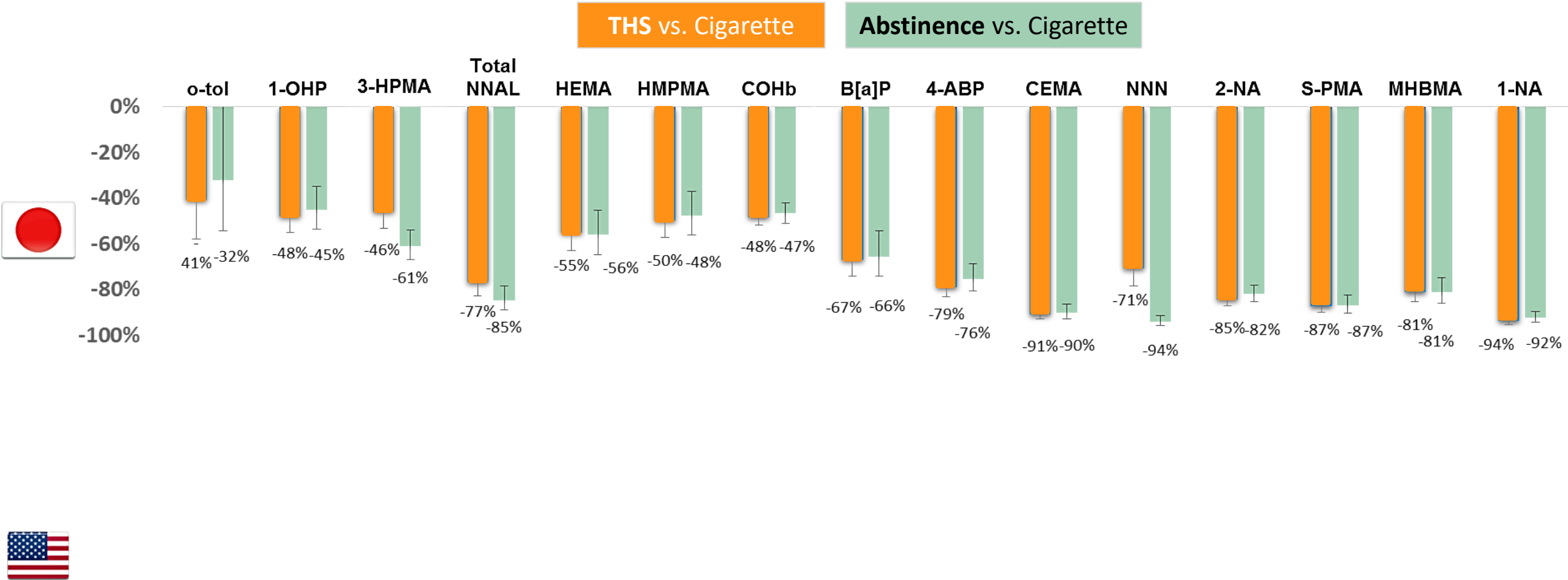
% Reduction in biomarkers of exposure after switching to THS for three months



Japanese study: Lüdicke et al. Effects of switching to the menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers (...) (Part 2). Nicotine Tob. Res.  
Graph based on: THS Executive Summary, PMI Science, 2017 - [https://www.pmiscience.com/library/pmi-science-ths-executive-summary?utm\\_source=Global](https://www.pmiscience.com/library/pmi-science-ths-executive-summary?utm_source=Global)

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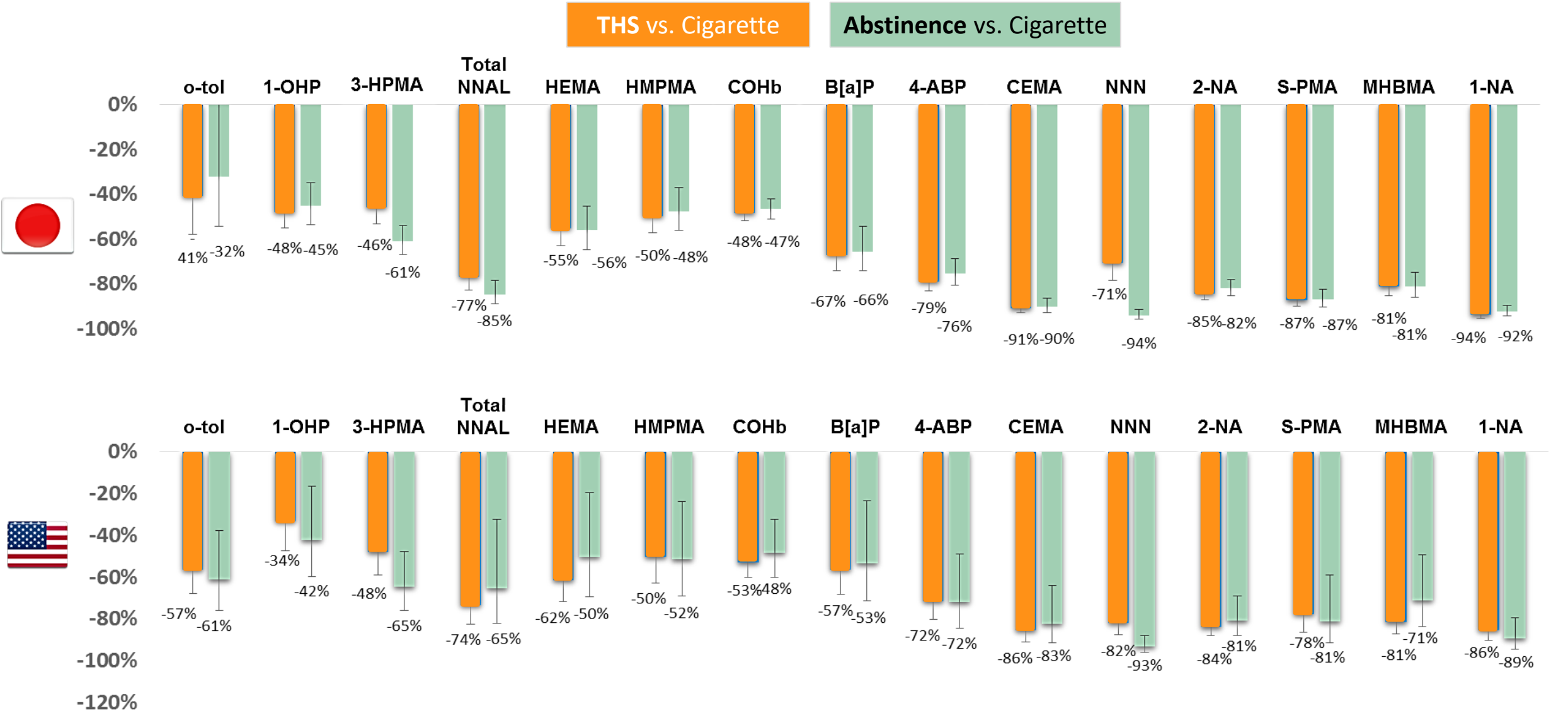
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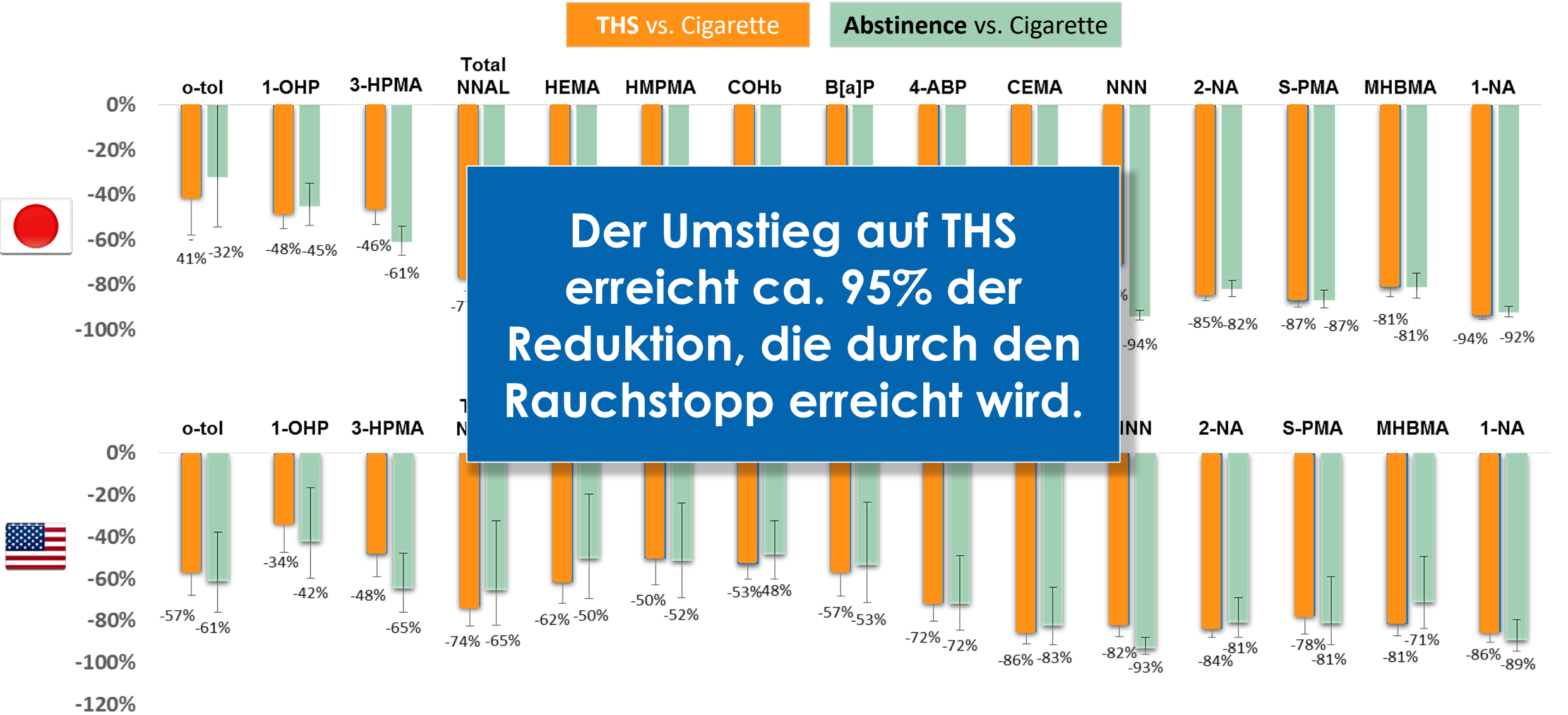
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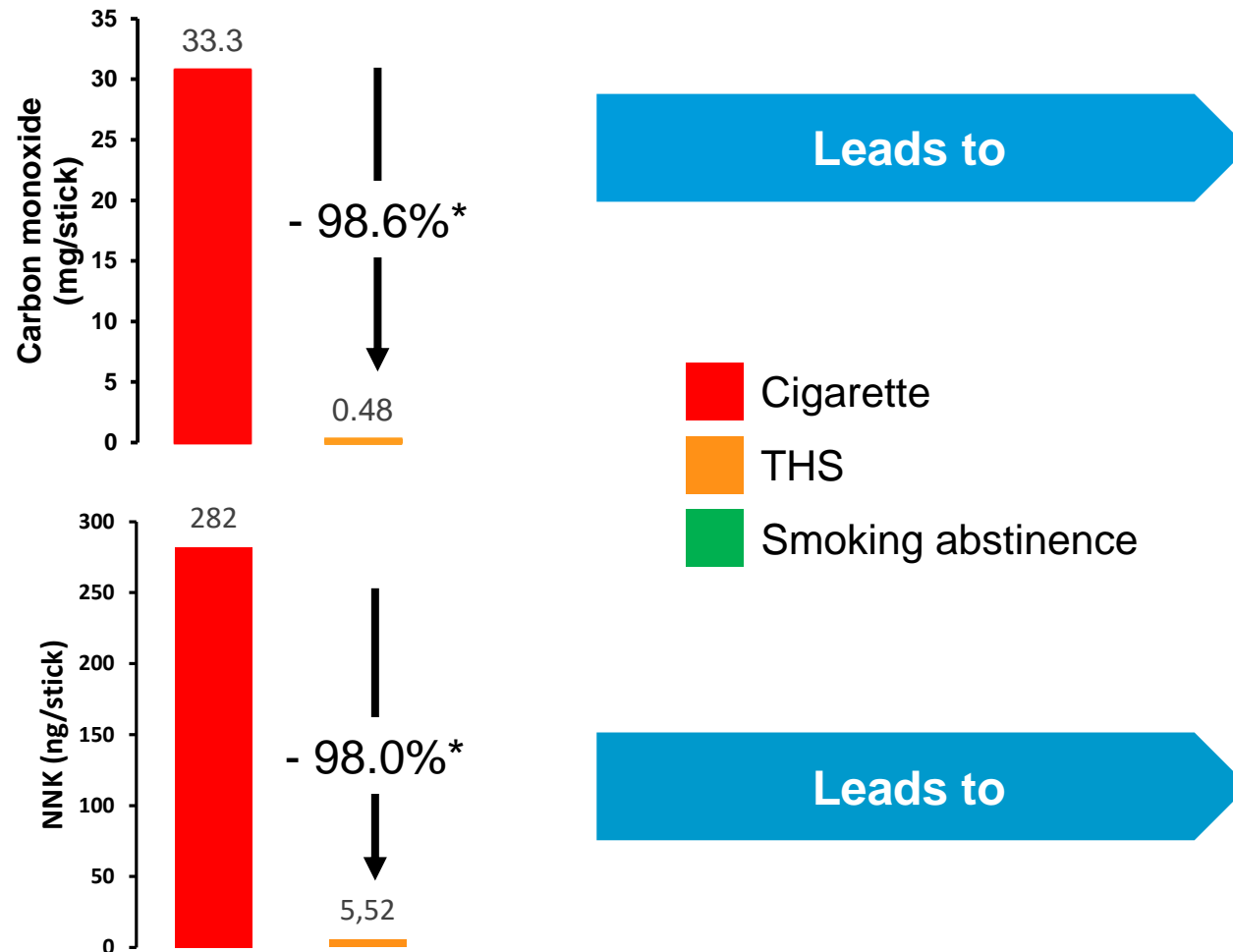
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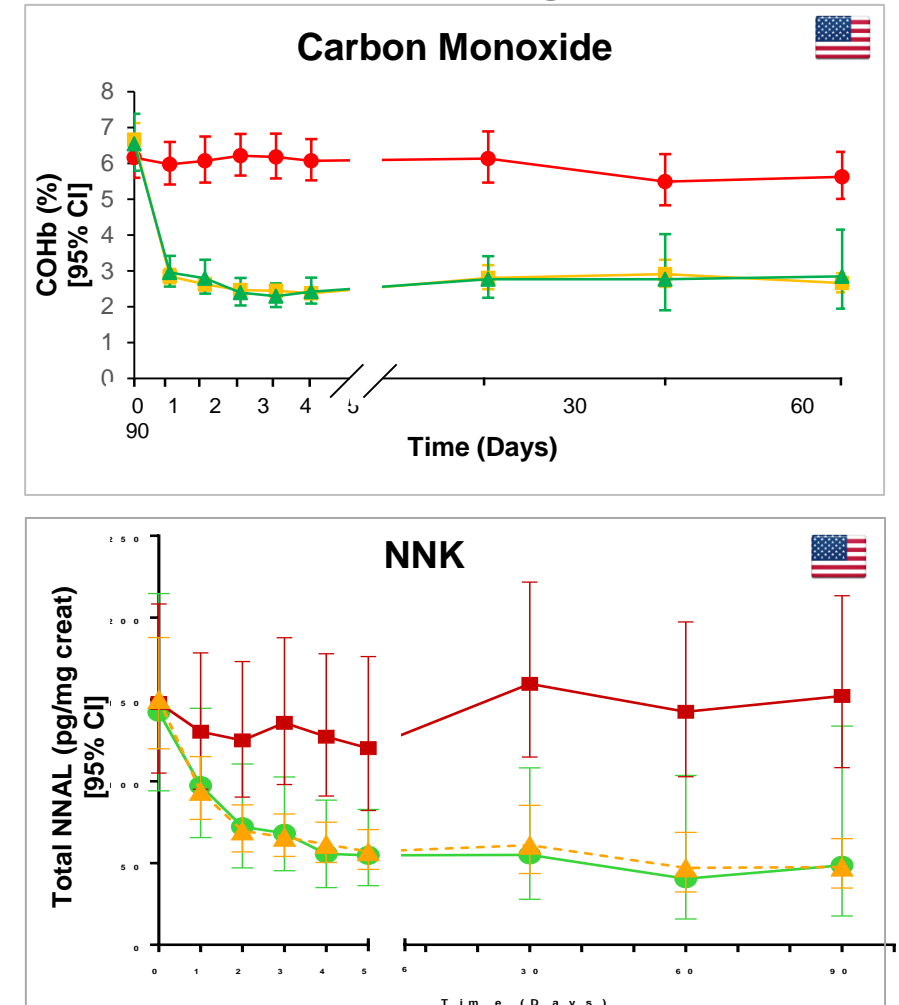
# Changes in Exposure to HPHCs

## Reduced Exposure in Healthy Human Subjects

Levels of HPHCs are drastically reduced in THS aerosol



Exposure is significantly reduced after switching to THS



\* On equivalent nicotine basis



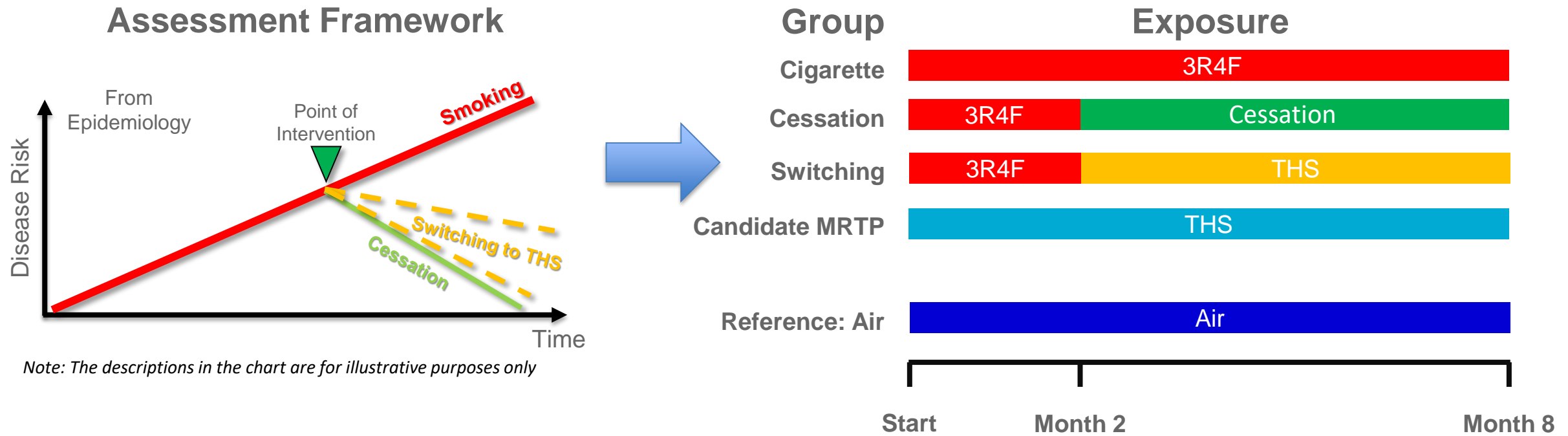
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# Animal Models of Disease

# From Risk Assessment Framework to *In Vivo* Study Design

## Animal Model: ApoE<sup>-/-</sup> Mouse – Concomitant Analysis of CVD and COPD Endpoints

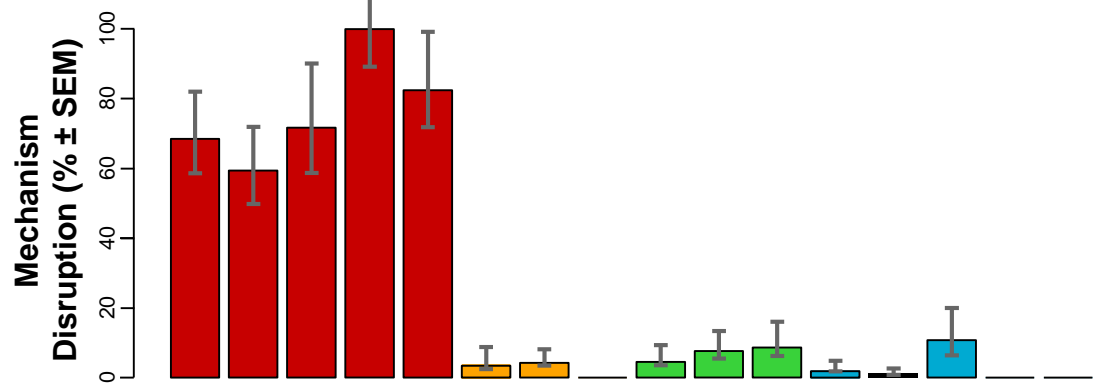
- Eight months duration (approximately 40% of lifetime)
- Concomitant analysis of CVD and COPD endpoints
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison



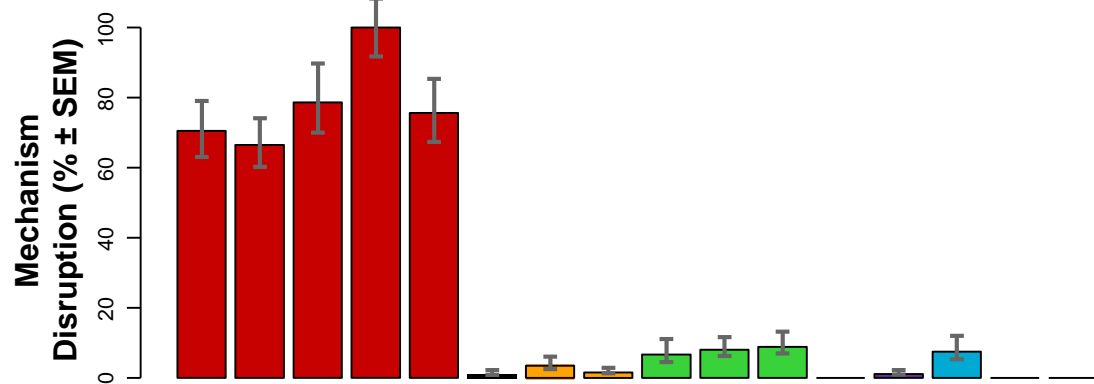
# Reduced Effects on Disease Mechanisms

Network-based biological impact factor (BIF) and network perturbation amplitude (NPA) analysis from the lung

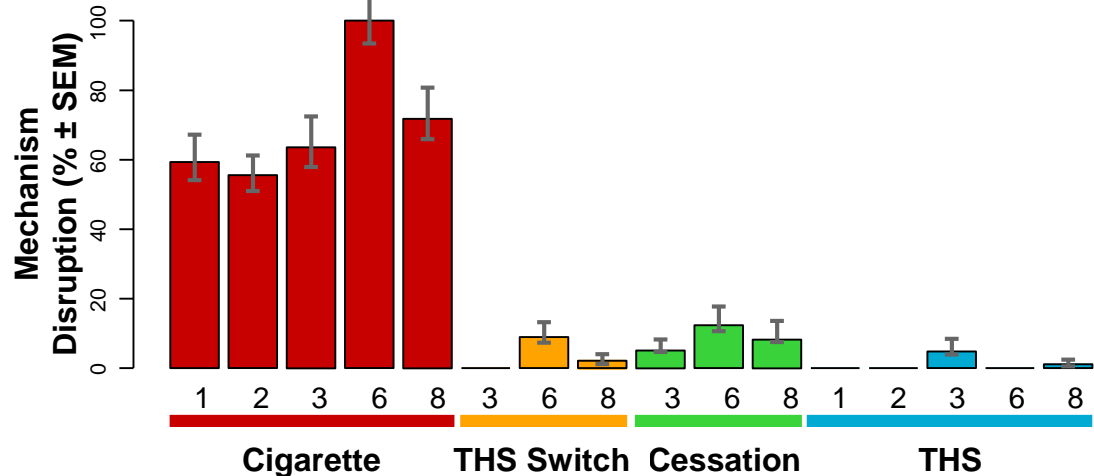
Cell Stress



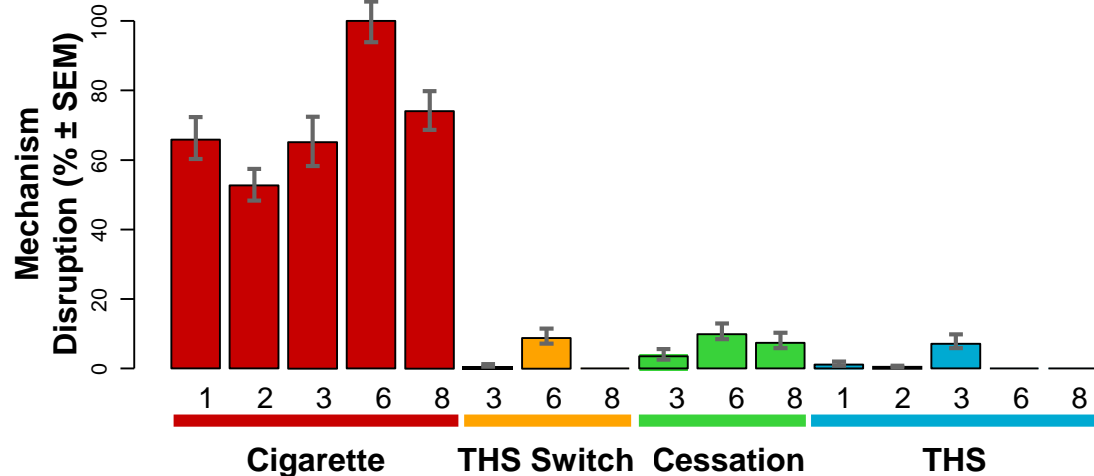
Cell Fate & Apoptosis



Cell Proliferation



Tissue Repair & Angiogenesis



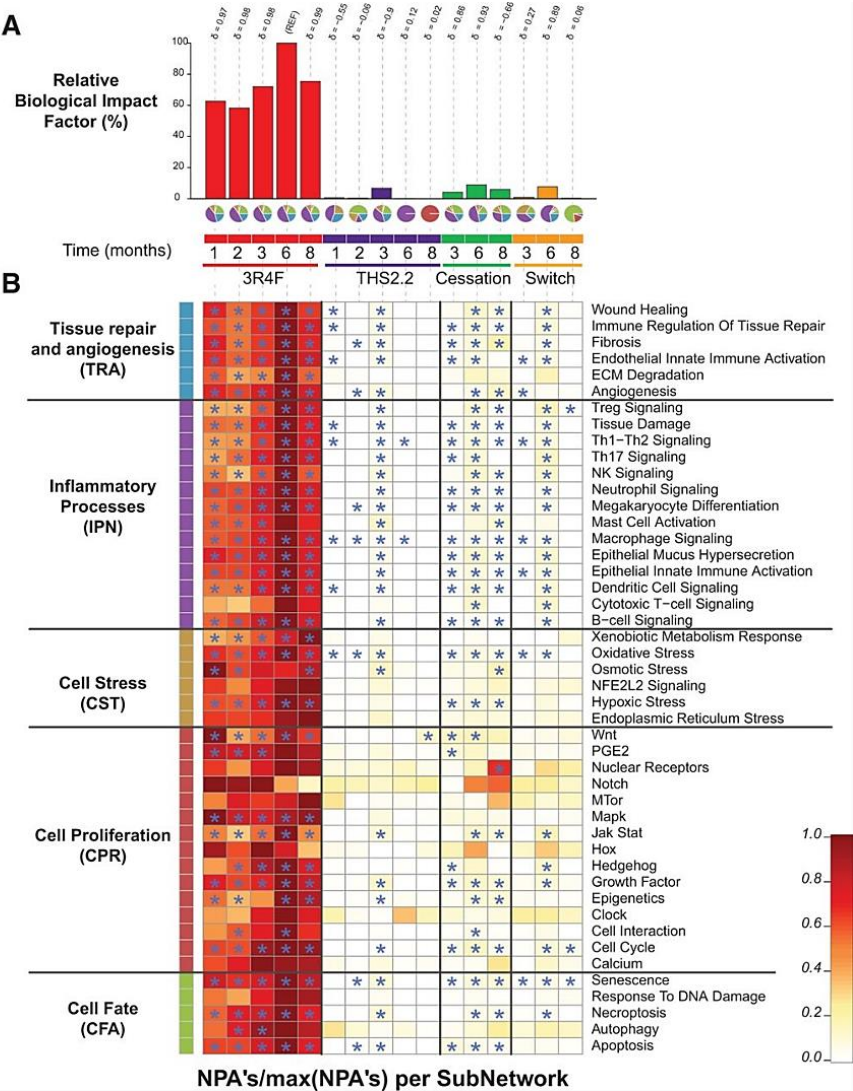
Phillips *et al.* (2015) An 8-Month Systems Toxicology Inhalation/Cessation Study in Apo e-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared with Conventional Cigarettes. *Toxicological Sciences*, <https://doi.org/10.1093/toxsci/kfv243>

# Reduced Effects on Mechanisms of Lung Disease

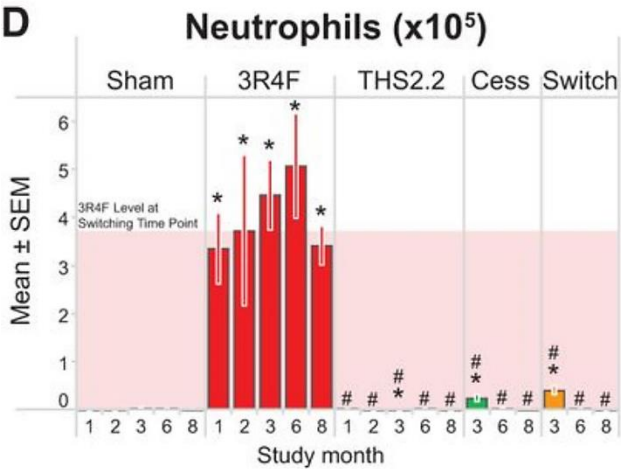
Reduced Gene Activation

→ Reduced Inflammation

→ Reduced Pathology



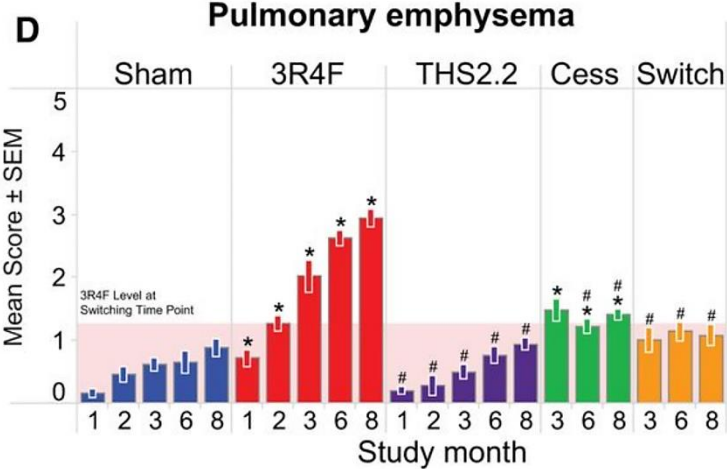
**FIG. 8.** Free lung cells in BALF. Light scatter and relative immunofluorescence were measured in BALF cells by flow cytometry. D, Neutrophil count.



★: different from sham (p<0.05), #: different from 3R4F (p<0.05)

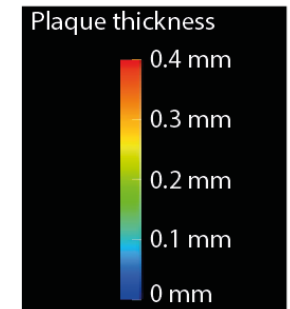
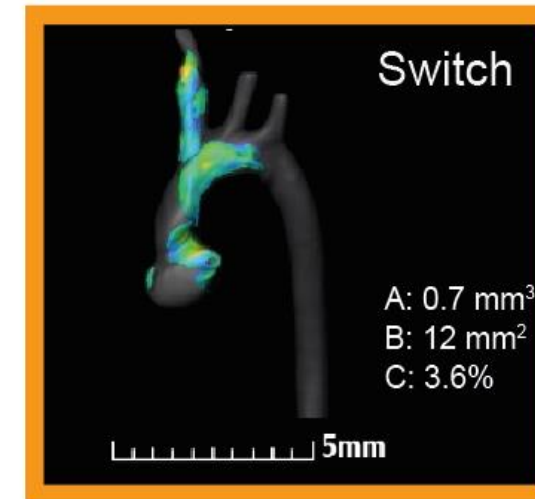
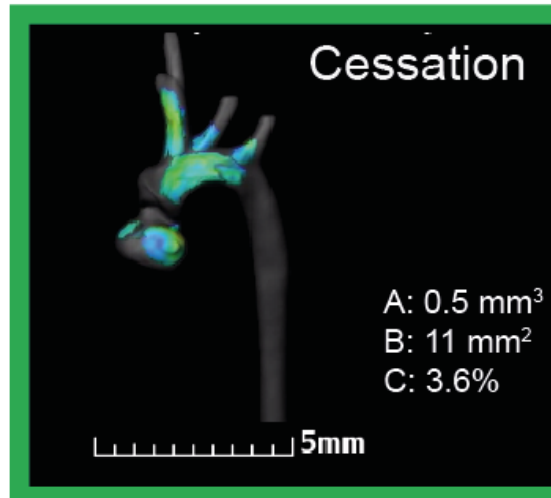
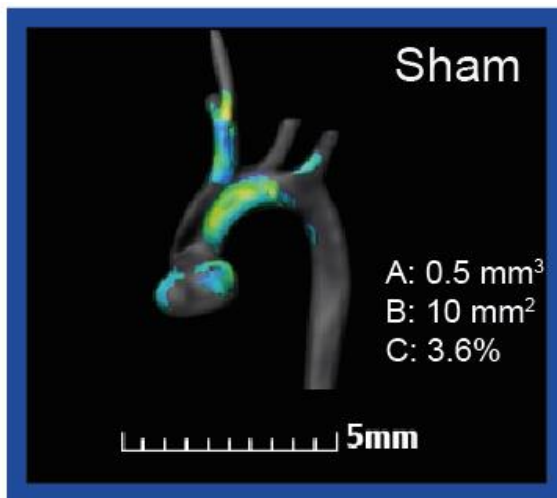
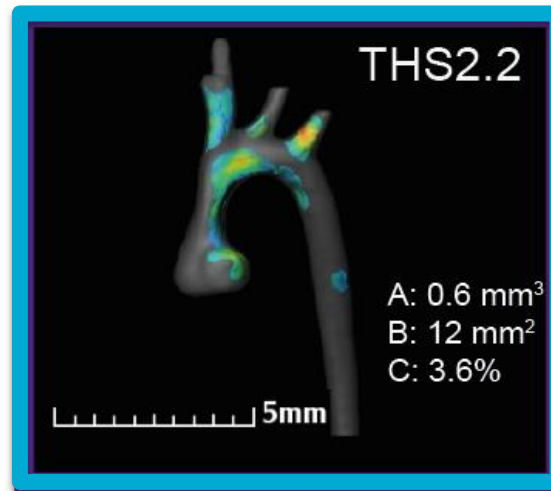
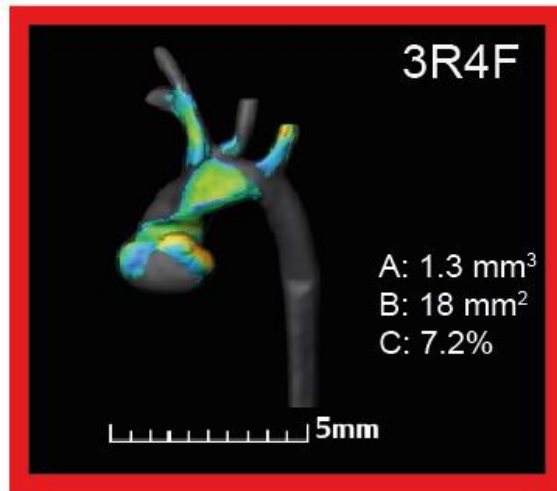
**FIG. 14.** Network-based biological impact factor (BIF) and network perturbation amplitude (NPA) analysis from the lung

**FIG. 12.** Emphysema assessment by morphometry and histopathological evaluation of lung sections. D, Semiquantitative histopathological scoring.



# Atherosclerotic Plaque in the Aortic Arch

## Data from $\mu$ CT at Month 7

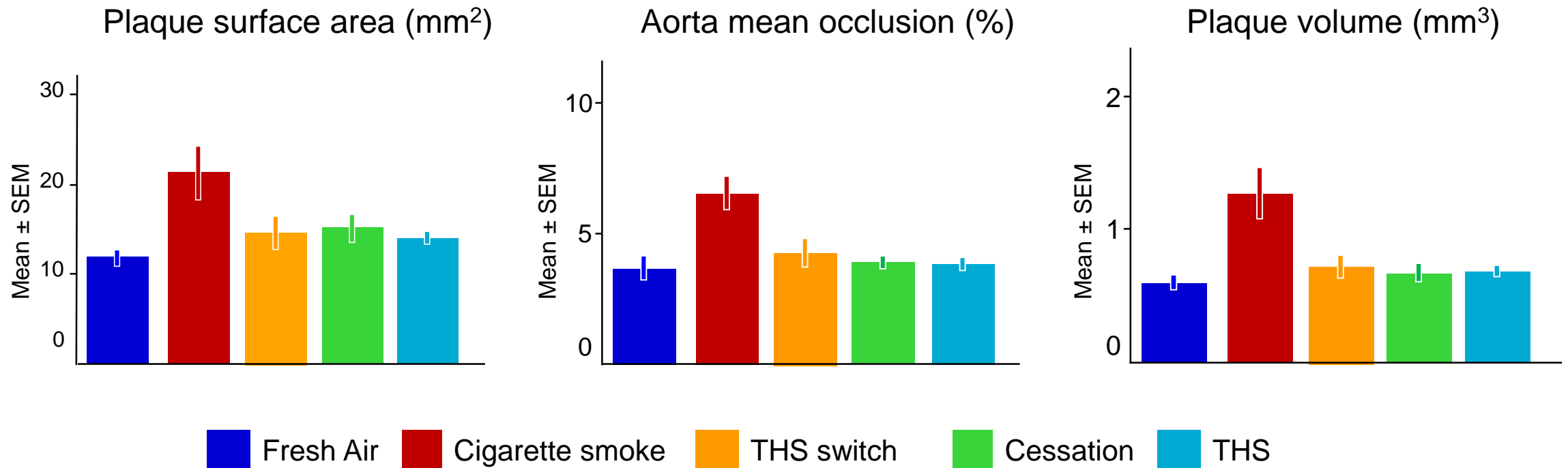




# Atherosclerotic Plaque in the Aortic Arch

## Disease Endpoint for CVD

Data from  $\mu$ CT at Month 7

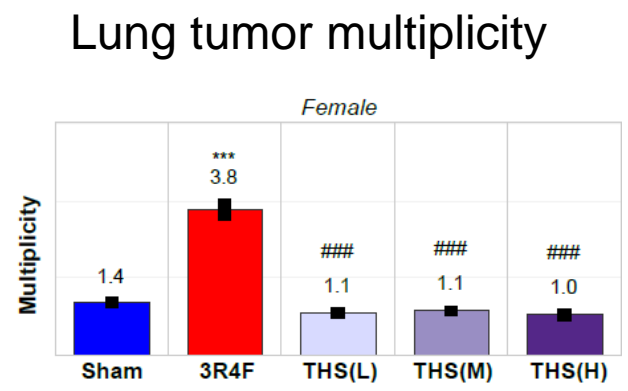
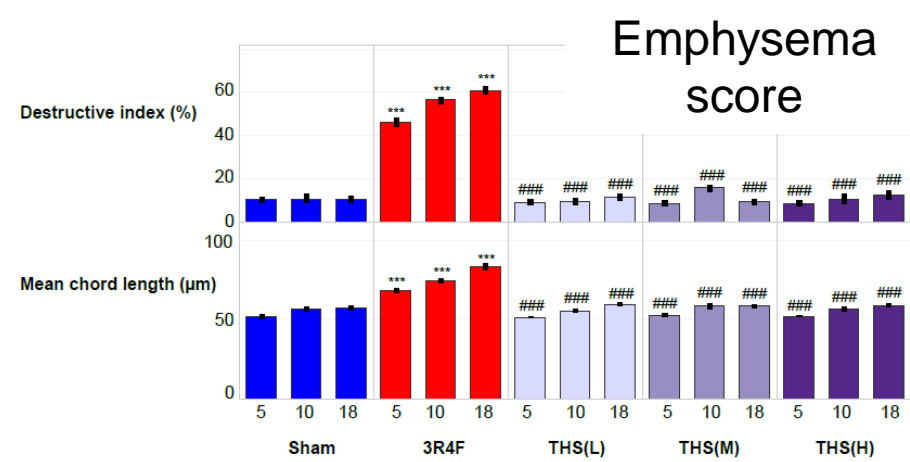
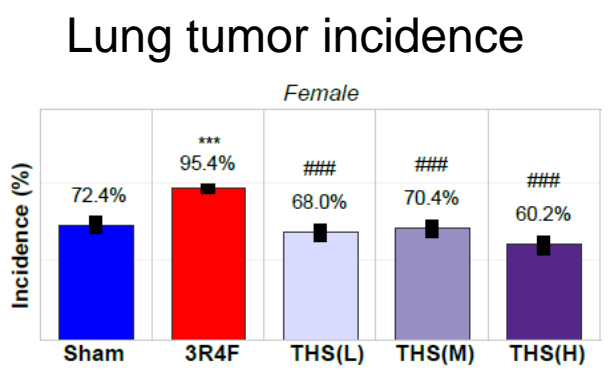
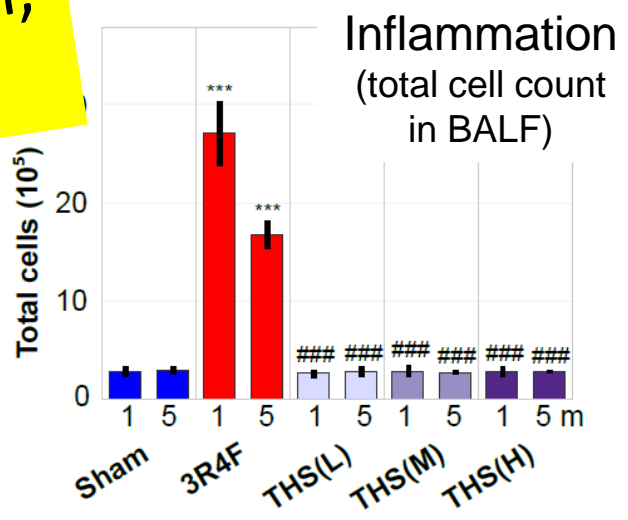


# Chronic Toxicity and Lung Tumorigenesis in A/J mice Following Lifetime Exposure (THS vs. 3R4F, 18 months)

Inflammatory mediators in BALF

	Month 1				Month 5			
vWF	4.75	0.83	0.79	0.80	5.33	1.20	1.12	1.17
VEGF-A	8.83	1.05	0.97	1.19	4.00	1.12	1.12	1.17
VCAM-1	11.1	1.31	1.45	1.02	13.4	1.15	1.15	1.17
TNF-alpha	7.37	1.38	1.00	1.00	7.97	1.14	1.32	1.00
TIMP-1 Mouse	10.7	1.12	1.14	1.09	6.74	1.13	1.22	1.05
Thrombopoietin	5.01	1.00	1.00	1.00	5.70	1.23	1.42	1.41
SCF	7.42	1.09	0.85	0.90	6.83	1.02	0.91	0.74
SAP	1.36	1.00	1.00	1.00	1.93	1.00	1.18	1.00
Resistin	1.30	0.94	0.97	1.17	1.04	0.85	0.89	0.83
PAI-1	5.00	1.03	0.99	1.01	4.37	1.01	1.05	1.07
Oncostatin-M	6.38	1.00	1.00	1.00	6.25	1.00	1.00	1.00
Myoglobin	0.84	1.61	1.12	1.38	4.32	2.40	2.79	7.64
MCP-5	70.6	1.00	1.00	1.00	29.2	1.00	1.00	1.00
MCP-3	350	1.00	1.51	1.00	200	1.07	1.19	0.79
MCP-1	1498	1.00	1.78	1.00	417	1.12	0.88	0.76
MMP-9	181	0.51	0.89	0.47	51.8	1.22	0.70	0.62
MIP-3 beta	4.72	0.91	0.88	0.87	4.62	1.24	1.10	1.13
MIP-2	6.43	0.94	1.03	1.13	3.55	1.12	1.04	0.94
MIP-1 gamma	17.5	1.05	1.07	0.93	12.4	0.83	0.97	1.03
MIP-1 beta	84.4	1.04	0.98	1.07	101	0.80	1.13	0.75
MIP-1 alpha	7.82	1.00	1.00	1.00	14.5	1.00	1.00	1.00
MDC	20.1	1.01	1.02	0.92	9.54	0.93	0.96	0.92
M-CSF-1	7.27	1.08	1.07	1.11	6.20	1.10	0.97	1.01
LIF	5.97	1.02	0.87	0.86	4.08	0.98	0.86	0.96
Leptin	0.92	0.76	0.87	0.89	0.70	0.63	0.89	0.73
IL-18	7.47	1.00	1.00	1.00	3.55	0.99	1.20	1.02
IL-11	2.32	1.00	1.00	1.00	2.24	1.00	1.00	1.00
IL-7	2.96	1.10	1.00	1.00	3.08	1.00	1.00	1.00
IL-6	8.97	1.27	1.22	1.00	6.32	1.00	1.14	1.00
IL-4	1.87	1.21	1.11	1.10	1.12	1.00	1.11	1.00
IL-1 beta	3.01	1.00	1.00	1.00	2.95	1.00	1.00	1.00
IL-1 alpha	13.7	1.00	1.00	1.00	18.6	1.00	1.00	1.00
IP-10	30.4	1.00	1.00	1.11	6.00	1.00	1.00	1.11
Insulin	1.08	1.27	0.78	1.17	0.68	0.71	0.96	0.87
IgA	24.8	0.81	5.35	0.66	146	1.01	1.08	0.93
Haptoglobin	1.00	0.97	0.97	0.98	1.02	1.00	1.00	1.00
KC/GRO	68.3	1.19	1.00	1.00	20.2	1.13	1.00	1.00
GM-CSF	6.28	1.00	1.00	1.00	2.59	1.00	1.00	1.00
GCP-2 Mouse	2.54	0.78	0.69	0.76	2.86	1.17	0.82	0.82
FGF-basic	1.40	1.00	1.00	1.00	1.87	0.90	1.44	1.00
Fibrinogen	5.23	0.86	0.90	0.85	4.32	1.11	2.02	1.31
EGF Mouse	4.40	1.00	1.00	1.00	9.52	0.63	0.89	0.95
Eotaxin	5.14	0.88	0.93	0.75	4.78	0.93	1.05	0.89
CRP Mouse	1.95	1.00	1.00	1.00	1.64	1.00	1.17	1.00
Apo A-I	1.56	0.81	0.51	0.59				

K. Luettich, P144



Significance and fold-change vs. respective Sham

Color	Symbol	Meaning
Blue	▼	p<0.001
Red	▲	p<0.001
Blue	▼	p<0.01
Red	▲	p<0.01
Blue	▼	p<0.05
Red	▲	p<0.05
Grey	-	n.s.

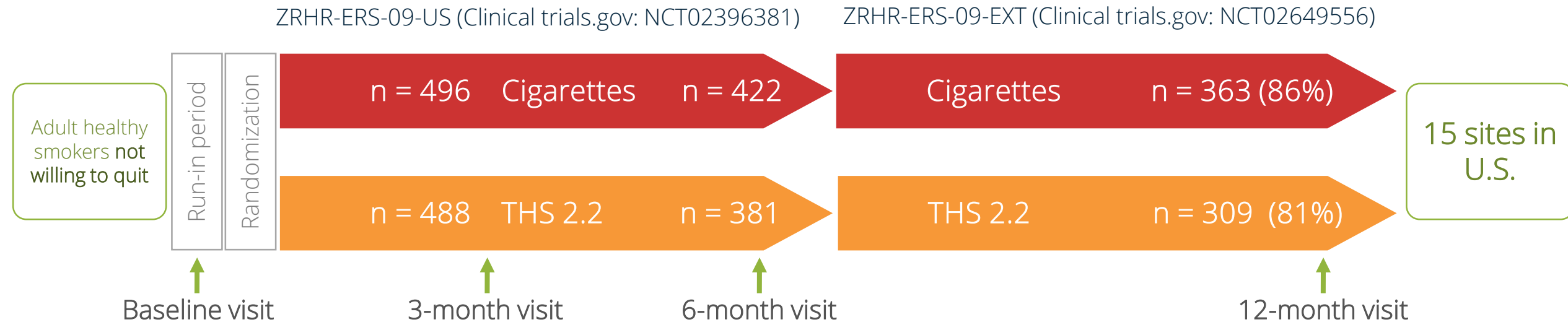


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# Clinical Study: Exposure Response

Reduced Adverse Health Effects  
in Healthy Human Subjects

# Study Design and Disposition - Exposure Response Study



## Cigarette-Use

- Randomized product use
- $\leq 1\%$  THS use\*

## THS-Use

- Randomized product use
- $\geq 70\%$  THS use\*

\* Calculated over the study and on at least 50% of the study days

# 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-mechanisms

**Lipid Metabolism**

**HDL-C**

**Clotting**

**11-DTX-B2**

**Endothelial function**

**sICAM-1**

**CO acute effect**

**COHb**

**Inflammation**

**WBC**

**Oxidative stress**

**8-epi-PGF<sub>2α</sub>**

**Lung function**

**FEV<sub>1</sub>**

**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

# Changes in Clinical Risk Endpoints

Endpoint	Change from CC use	Observed change LS mean difference / relative reduction	Hailperin-Rüger-adjusted CI	1-sided <i>p</i> -value (0.0156)	THS directional change vs. SA (literature)
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	<0.001*	✓ significant
WBC cCount	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 <sub>2α</sub>	% Reduction	6.80 %	-0.216, 13.3	0.018	✓
COHb	% Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV <sub>1</sub> %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 CREs were statistically significant compared to continued smoking



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# Modelling the Harm Reduction Potential



# Modeling of “Lifetime Cancer Risk” based on HPHC “Cancer Potencies”<sup>1</sup>

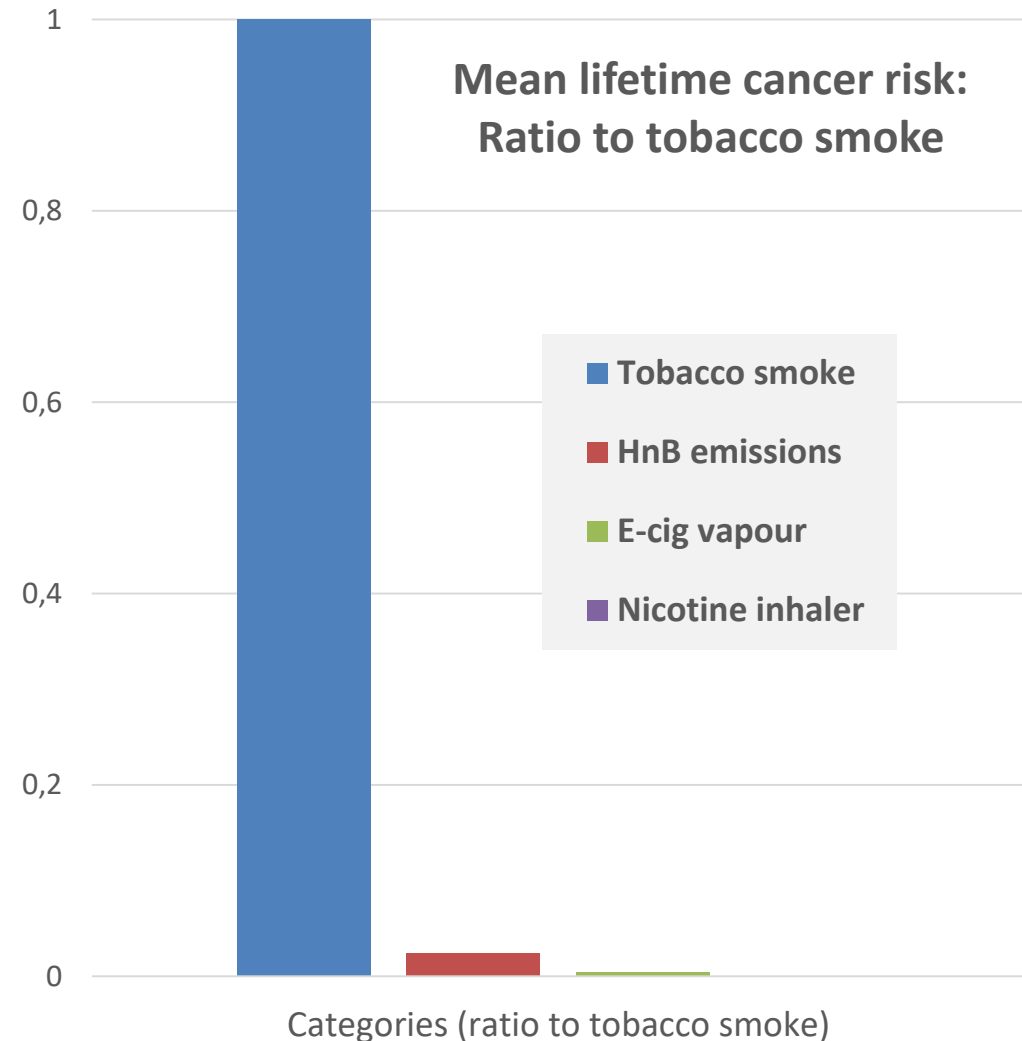
## Research paper

Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke

William E Stephens

Graph based on data from Stephens, *Tobacco Control*, 2017 <sup>1</sup>

■ HnB = Heat-not-Burn = heated tobacco product



(1) Stephens WE., Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke; *Tobacco Control* 2017;0:1–8. doi:10.1136/tobaccocontrol-2017-053808, <https://tobaccocontrol.bmj.com/content/27/1/10>



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# Conclusions

# Conclusions

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- **Smoking** remains a **challenge** for the prevention of NCDs, **and the best option for every smoker is to quit** tobacco and nicotine use altogether.
- **Tobacco Harm Reduction** (i.e., offering smoke-free alternatives to adult smokers who would otherwise continue smoking) is a sensible, **complementary addition** to existing tobacco control strategies\*.
- **Although addictive and not risk-free, scientific data on smoke-free products** provide clear evidence of their **potential for harm reduction**.
- The **totality of the scientific evidence on THS** demonstrates that **switching completely to THS** presents **less risk of harm than continuing to smoke**.
- **Long-term studies to quantify risk reduction** for specific smoking-related **diseases** are needed.
- **Marketing applications** for THS with the **U.S. FDA** are **pending**.

\*THS and appropriately developed and manufactured e-cigarettes have a role to play in Tobacco Harm Reduction strategies, complementary to the role of traditional pharmacotherapy and nicotine replacement therapy (NRT).



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# Thank you for your attention