

# Methods for Tobacco Harm Reduction

## Introducing the Scientific Assessment Program of PMI Science

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*Clinical Operations in Oncology Trials – Europe 2018*  
*Munich, 15 NOV 2018*

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

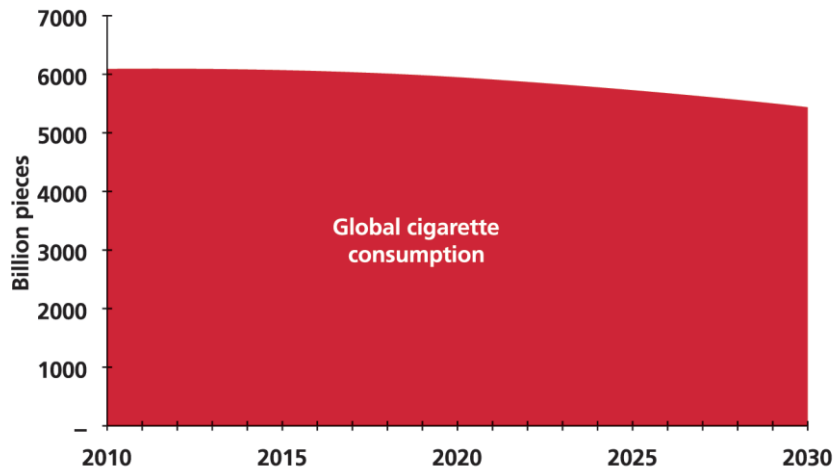
# Overview

- Smoking Prevalence
- Harmfulness of Smoking
- Harm Reduction (HR)
- E-cigarettes: Function and Assessment
- PMI Science: Assessment Program
- Study Results: Tobacco Heating System
- HR and Disease Prevention
- Conclusions

# About Smoking Prevalence Health Risks Cessation

## WHO<sup>1</sup>: >1 billion smokers globally through 2025

Cigarette global consumption trend projection to 2030



Consumption 2010–2030 on parabolic trend projection from 1908–2012 data from Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA 2014; 311: 183–92.

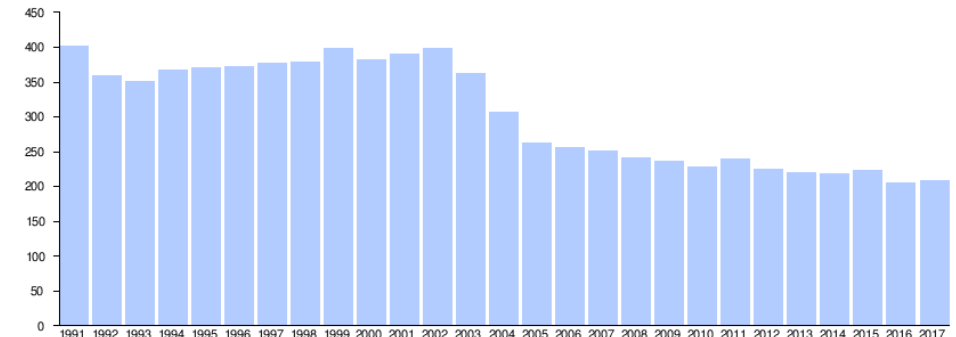


Germany<sup>2</sup>

28%

17 Mio

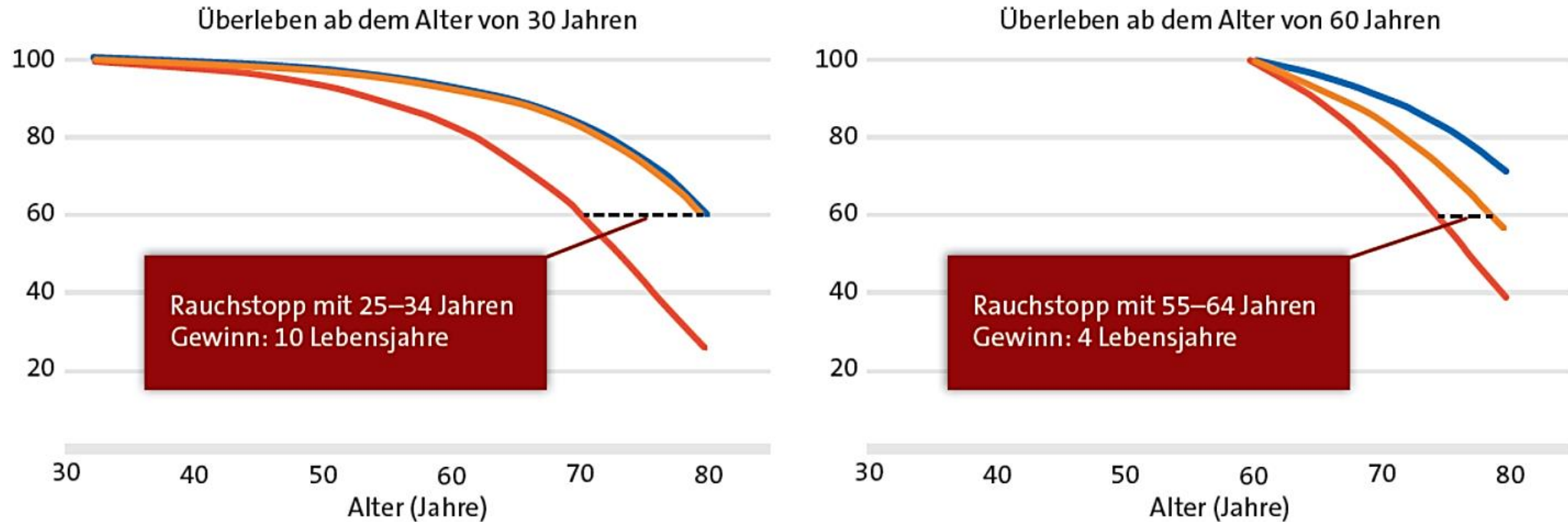
Annual cigarette consumption (GER)  
1991-2017 [Mio]



- (1) WHO global report on trends in tobacco smoking 2000-2025  
<http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html>
- (2) Kotz et al., Nutzung von Tabak und E-Zigaretten sowie Methoden zur Tabakentwöhnung in Deutschland - Eine repräsentative Befragung in 6 Wellen über 12 Monate (die DEBRA-Studie); Dtsch Arztebl Int 2018; 115(14): 235-42; DOI: 10.3238/arztebl.2018.0235 <https://www.aerzteblatt.de/archiv/197190/Nutzung-von-Tabak-und-E-Zigaretten-sowie-Methoden-zur-Tabakentwoehnung-in-Deutschland>

<https://de.wikipedia.org/wiki/Tabakrauchen> (accessed Oct 2018), Quellen: Statistisches Bundesamt, 1991–2015 und 2017\*, 2016\*\*  
\*Anzahl der im Schnitt täglich in Deutschland gerauchten Zigaretten von 1991 bis 2015, abgerufen zu verschiedenen Zeitpunkten (mit jeweils unterschiedlich einsehbaren Daten): 17. Oktober 2012, 12. Mai 2014, 31. Januar 2016, 3. März 2018  
\*\*Finanzen und Steuern Absatz von Tabakwaren, Fachserie 14 Reihe 9.1.1, Statistisches Bundesamt, erschienen am 13. Januar 2017, abgerufen am 18. März 2018.

## Cessation is beneficial at any age



Überlebensraten von ■ Rauchern, ■ Ex-Rauchern und ■ Nie-Rauchern  
Überleben ab dem Alter von 30 und 60 Jahren in Prozent

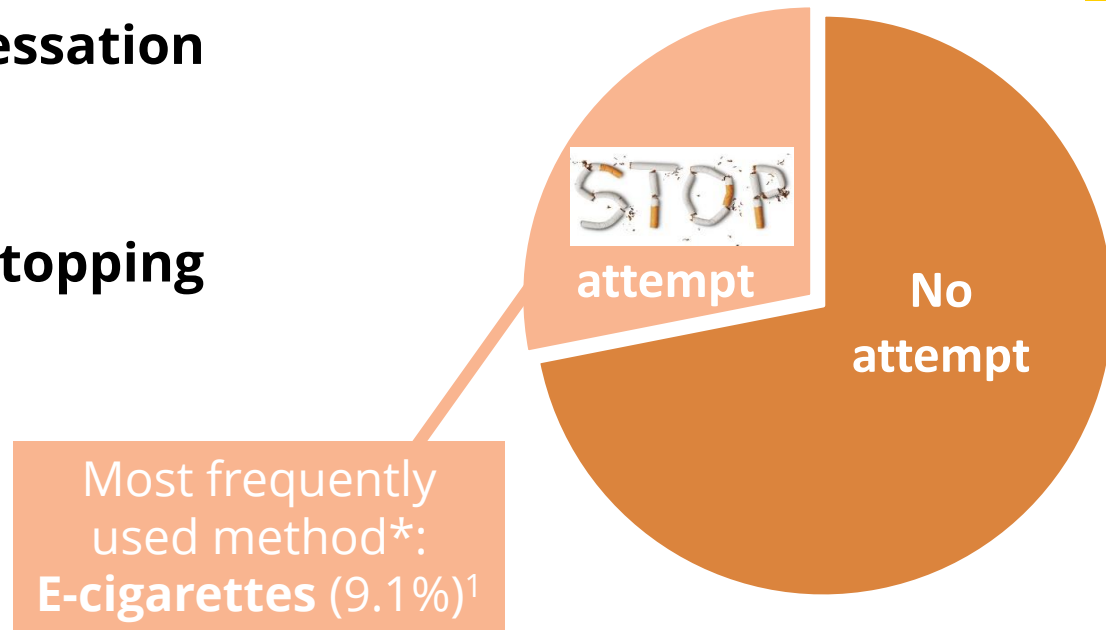
# Gold standard cessation: Option for only a minority of smokers?

## Gold standard cessation

- **> 70%** of German smokers **without cessation attempt** in the previous year<sup>1</sup>
- **> 90%** of smokers **not interested in stopping** in the near future<sup>2</sup>



Cessation attempt in the previous year  
(DEBRA-Study, 2018<sup>1</sup>)



(1) Kotz et al., Nutzung von Tabak und E-Zigaretten sowie Methoden zur Tabakentwöhnung in Deutschland - Eine repräsentative Befragung in 6 Wellen über 12 Monate (die DEBRA-Studie), Dtsch Arztebl Int 2018; 115(14): 235-42; DOI: 10.3238/arztebl.2018.0235;

<https://www.aerzteblatt.de/archiv/197190/Nutzung-von-Tabak-und-E-Zigaretten-sowie-Methoden-zur-Tabakentwoehnung-in-Deutschland>

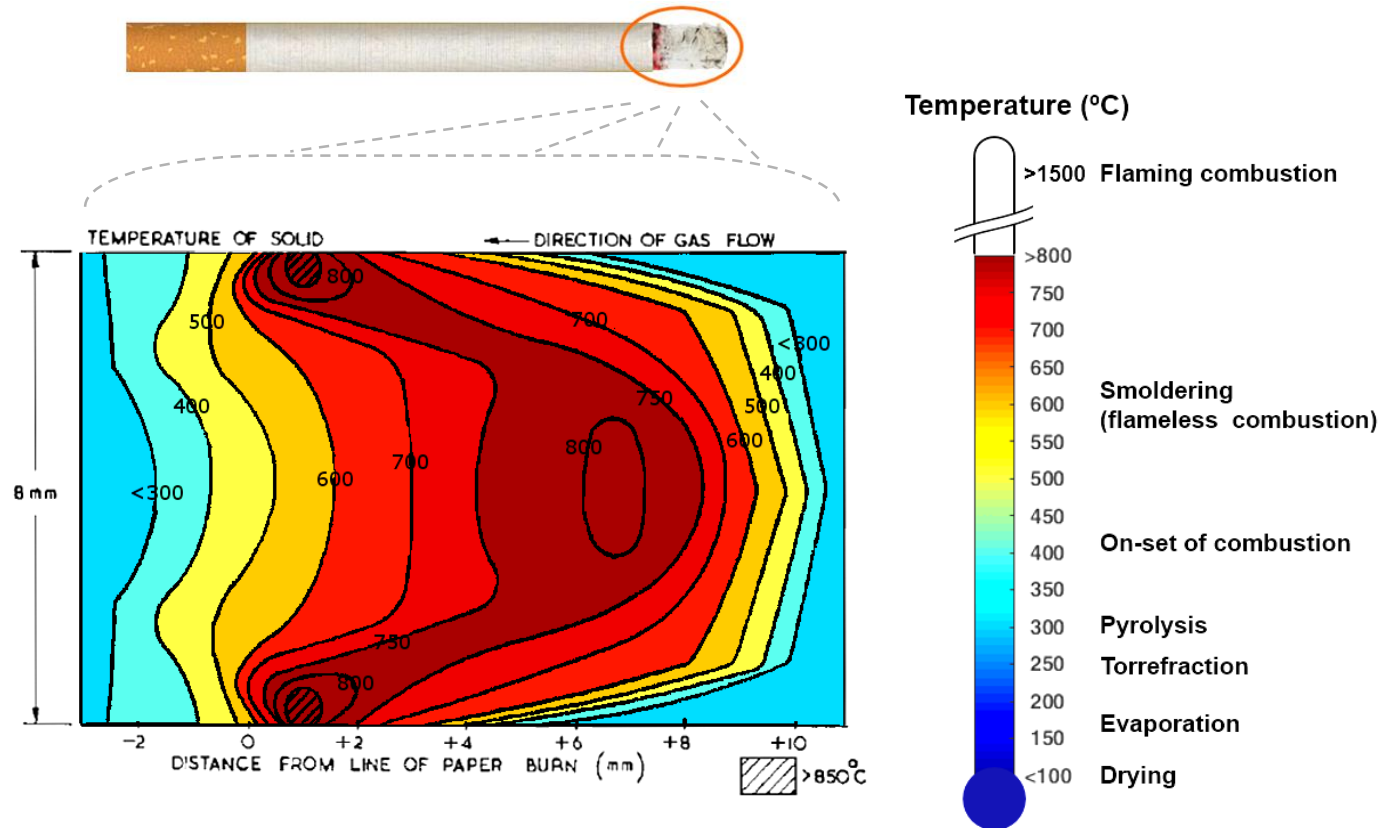
\*Includes e-cigarettes with (4.6%) and without (5.4%) nicotine; except will power (59%) and social groups (family/friends/colleagues) (19%)

(2) Wewers et al.(2003), Distribution of daily smokers by stage of change: Current Population Survey results. Prev Med 36:710–720

# Harmfulness of Smoking: Tobacco Combustion vs. Nicotine



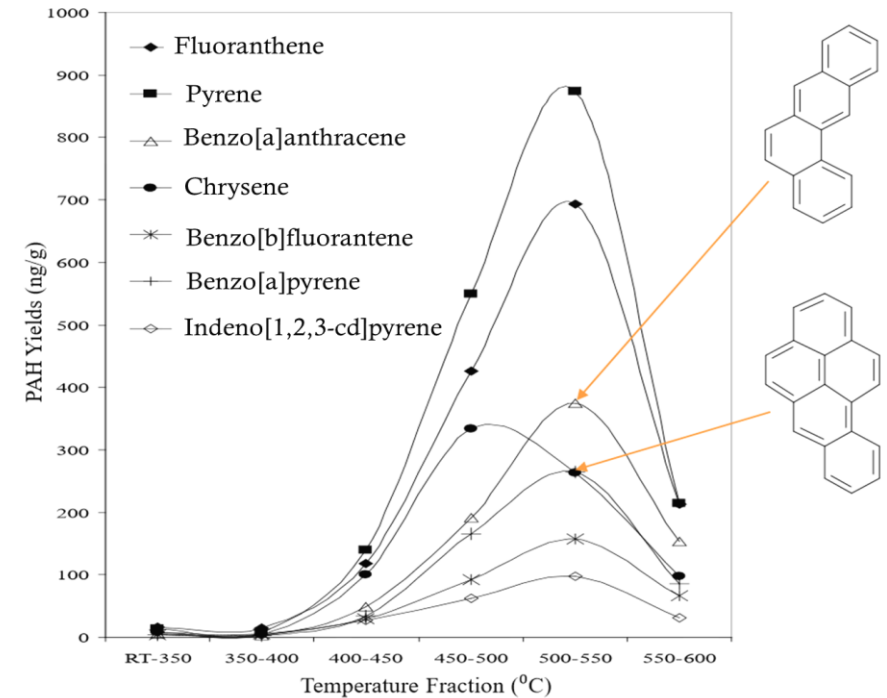
# Eliminating Combustion Is Key...



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.

- More than **6,000** constituents identified in cigarette smoke
- About **100** of these constituents are categorized as harmful or potentially harmful constituents ("**HPHCs**")
- Most of the HPHCs are formed when the tobacco burns

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



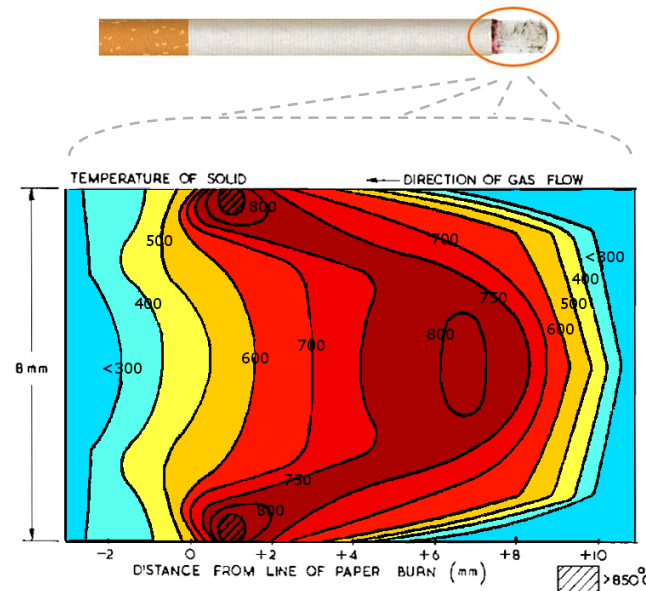
Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45, 6, 1039-1050



# Tobacco Combustion, Nicotine, and Harm Reduction

“Newer and more novel forms of delivering nicotine...could be incredibly helpful (...) if [smokers] completely switched.”

“At the end of the day, it’s not nicotine that causes disease and death.”



“E-cigarette use could be far less dangerous than smoking (...)”

“That’s mainly due to the many toxicants originating from the combustion of tobacco.”



Mitch Zeller, Director of the Center for Tobacco Products, FDA for Wall Street Journal, JUL 2017 <sup>1</sup>



Frank Henkler-Stephani, BfR for Stuttgarter Zeitung, OCT 2017 <sup>2</sup>

- (1) Zitat Mitch Zeller, FDA: Artikel „Big Tobacco Finds Surprise Allies in Smokeless Push“, WSJ, 21. Juli 2017 [https://www.wsj.com/articles/big-tobacco-finds-surprise-allies-in-smokeless-push-1500629402?mod=pls\\_whats\\_news\\_us\\_business\\_f](https://www.wsj.com/articles/big-tobacco-finds-surprise-allies-in-smokeless-push-1500629402?mod=pls_whats_news_us_business_f)
- (2) Zitat Frank Henkler-Stephani, BfR, Stuttgarter Zeitung, 20. OKT 2017; <http://www.stuttgarter-zeitung.de/inhalt.gesundheit-e-zigaretten-gefaehrden-passivraucher.612cc003-7ab6-4c67-9971-d0bf14c0fc44.html>

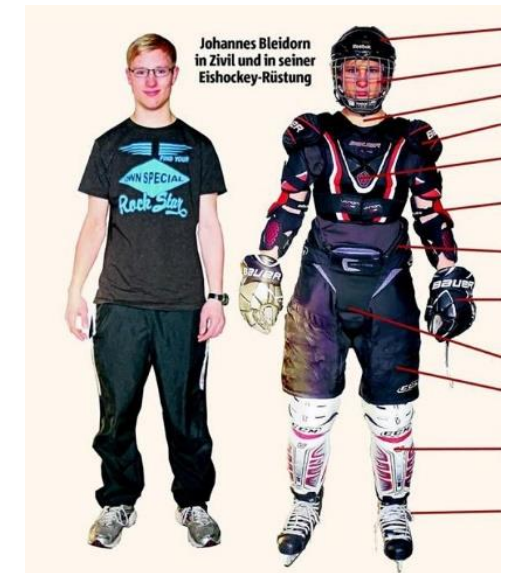
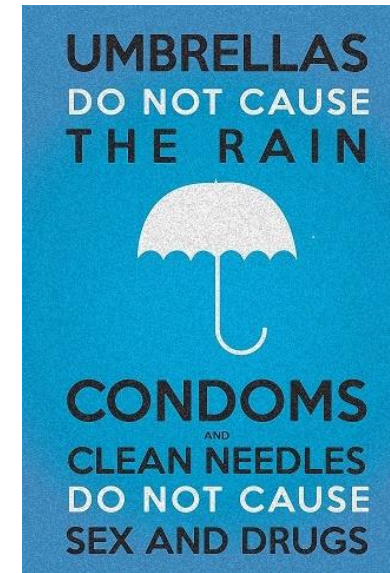


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# Tobacco Harm Reduction

## What is harm reduction?

- Harm reduction\* is a **strategy in medicine and social policy for the minimization of harm** to individuals and/or a population **by harmful behaviors that cannot be avoided or prevented completely**.
  - Examples\*\*:
    - Condoms to protect against STDs
    - Clean needles for drug addicts
    - Laws against drunk driving
    - Protective clothing for sports
    - Seatbelts



\* Harm Reduction: <https://www.hri.global/what-is-harm-reduction>

\*\* Examples shown here are for illustration purposes only. No direct comparison to smoking is intended.

## Tobacco harm reduction\* = Minimization of smoking-related health risks

### Goal:

- **Complements**, and does not replace, **existing strategies of tobacco control** (e.g., prevention, education, and smoking cessation)<sup>1,2</sup>
- Focusses on **smokers who would otherwise continue to smoke**
- These smokers **should be encouraged to use less harmful forms of consumption** of nicotine/tobacco to reduce smoking-related health risks<sup>3</sup>

\* Tobacco Harm Reduction: [https://en.wikipedia.org/wiki/Tobacco\\_harm\\_reduction](https://en.wikipedia.org/wiki/Tobacco_harm_reduction),  
Royal College of Physicians, London. 2016. <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>

<sup>1</sup> FDA (Food and Drug Administration). Guidance for industry 2012. <http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM297751.pdf>;

<sup>2</sup> Institute of Medicine of the National Academies (IOM). 2012 [updated 2012; cited 2016 Jun 23]; [328 p.].

[https://www.erowid.org/plants/tobacco/tobacco\\_health4\\_iom\\_scientific\\_standards\\_mrtp.pdf](https://www.erowid.org/plants/tobacco/tobacco_health4_iom_scientific_standards_mrtp.pdf);

<sup>3</sup> Kiviniemi MT, Kozlowski LT. Harm Reduction J 2015; 512-521

## Offering adult smokers satisfying products that reduce risk



\*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.

Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)

<https://www.pmisience.com/smoke-free/understanding-how-to-achieve-risk-reduction-for-smokers>

# The Objective Is Harm Reduction



*"For all the potential risks involved, **harm reduction** has **huge potential to prevent death and disability from tobacco use**, and to hasten our progress to a tobacco-free society. With careful management and proportionate regulation, **harm reduction** provides an **opportunity to improve the lives of millions of people.**"<sup>1</sup>*

*• "**Harm reduction** can both protect youth and speedily **save millions of smokers lives.**"  
• "**Products that do not burn tobacco are substantially less harmful** than deadly smoke.." <sup>2</sup>*



Preventive Medicine

Available online 23 June 2018

In Press, Corrected Proof ⓘ



## Managing nicotine without smoke to save lives now: Evidence for harm minimization

David B. Abrams <sup>a</sup> ✉, Allison M. Glasser <sup>a</sup>, Andrea C. Villanti <sup>b</sup>, Jennifer L. Pearson <sup>c</sup>, Shyanika Rose <sup>d</sup>, Raymond S. Niaura <sup>a</sup>

(1) Nicotine without smoke - Tobacco harm reduction. A report by the Tobacco Advisory Group of the Royal College of Physicians, April 2016, <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>

(2) Abrams et al., Managing nicotine without smoke to save lives now: Evidence for harm reduction, *Preventive Medicine* 2018; <https://doi.org/10.1016/j.ypmed.2018.06.010>

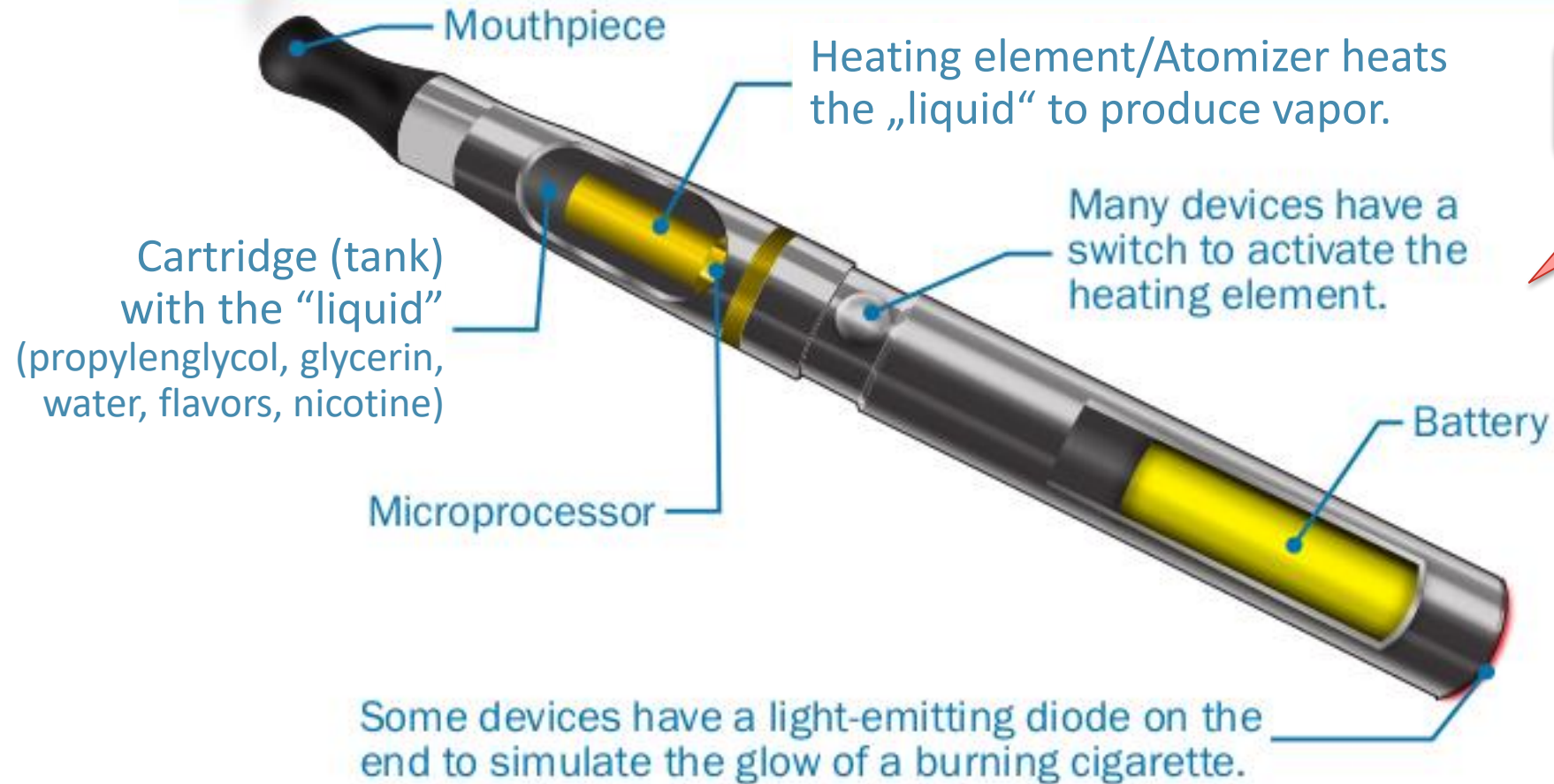


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# E-cigarettes Function and Assessment



## Parts of an Electronic Cigarette





# E-cigarettes: Assessment by British Health Authorities

 **E-cigarettes**  
Current evidence



**Are E-cigs safe?**  
E-cigarettes are significantly less harmful (95%) to health than smoking tobacco

**Are they a route into smoking cigarettes?**  
There is no evidence so far that e-cigarettes are acting as a route into smoking for children or non-smokers

**Do they harm others?**  
There is no evidence so far of harm to bystanders from second-hand vapour from e-cigarettes

**Can they help people quit?**  
The best thing a smoker can do is to stop smoking completely and forever. The evidence shows that e-cigarettes can be effective in helping people to quit and greatly reduce harm to health

**Should stop smoking services welcome them?**  
We're calling on all stop smoking services to welcome and support e-cigarette users who want to quit smoking

E-cigarettes: an evidence update, 2015

 **E-cigarettes**  
Current evidence

**Are E-cigs safe?**  
E-cigarettes are significantly less harmful (95%) to health than smoking tobacco

 **E-cigarettes**  
Current evidence

**At least 95% less harmful**



**E-cigarettes are not risk free but are far less harmful than cigarettes**

**REASONS WHY VAPING IS NOT AS BAD FOR YOU AS SMOKING TOBACCO**

-  **The evidence** so far shows that e-cigarettes are far safer than smoking
-  E-cigarettes contain nicotine but **not cancer causing tobacco**
-  Nicotine is addictive, but does **not cause cancer**
-  There is **no evidence** that e-cigarettes harm bystanders
-  **Tobacco** is the biggest cause of preventable death in the UK  
Over **100,000 deaths** per year  
 = 10,000

**LET'S BEAT CANCER SOONER**  
cruk.org



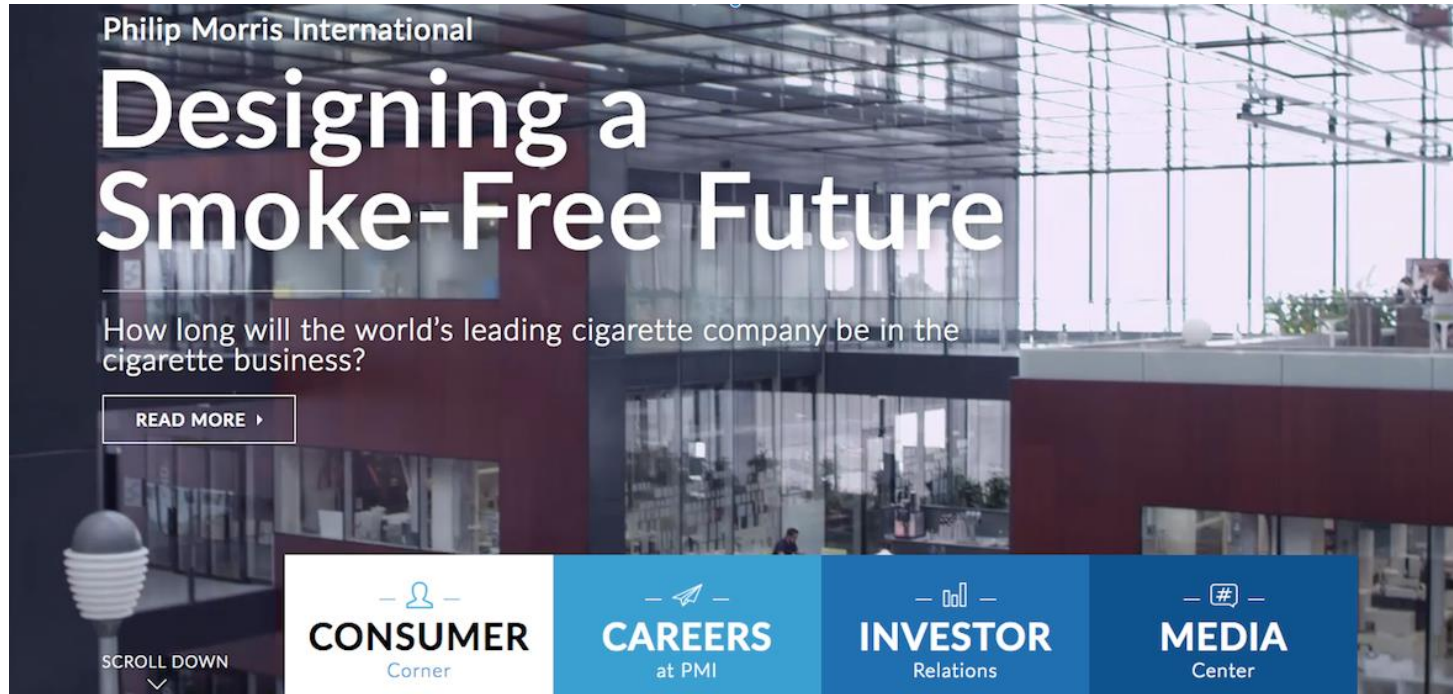
**STOP SMOKING WITH AN E-CIGARETTE THIS STOPTOBER**



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# **Tobacco Harm Reduction The Contribution of PMI Science**





**“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

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

Our RRP**s are not risk-free.** The best choice is to quit tobacco use altogether or never start in the first place.



Technology and Scientific Network (2016)  
2 R&D Centers  
Major partners and service providers



- More than **430 scientists and tech experts**
- More than **30 fields of expertise**, including toxicology, medicine and systems biology
- More than **\$4.5 billion invested** in the RRP program since 2008

- **2,900 patents granted** in RRP's worldwide
- **4,600 patent applications pending**



Our objective is to offer **adult smokers who would otherwise continue to smoke** products that reduce risk\* and maximize full switching

## 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: 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. 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.



# PMI's Reduced-Risk Product Portfolio

Our objective is to offer **adult smokers who would otherwise continue to smoke** products that reduce risk\* and maximize full switching

## 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

**IQOS MESH launched  
in UK in July 2018**

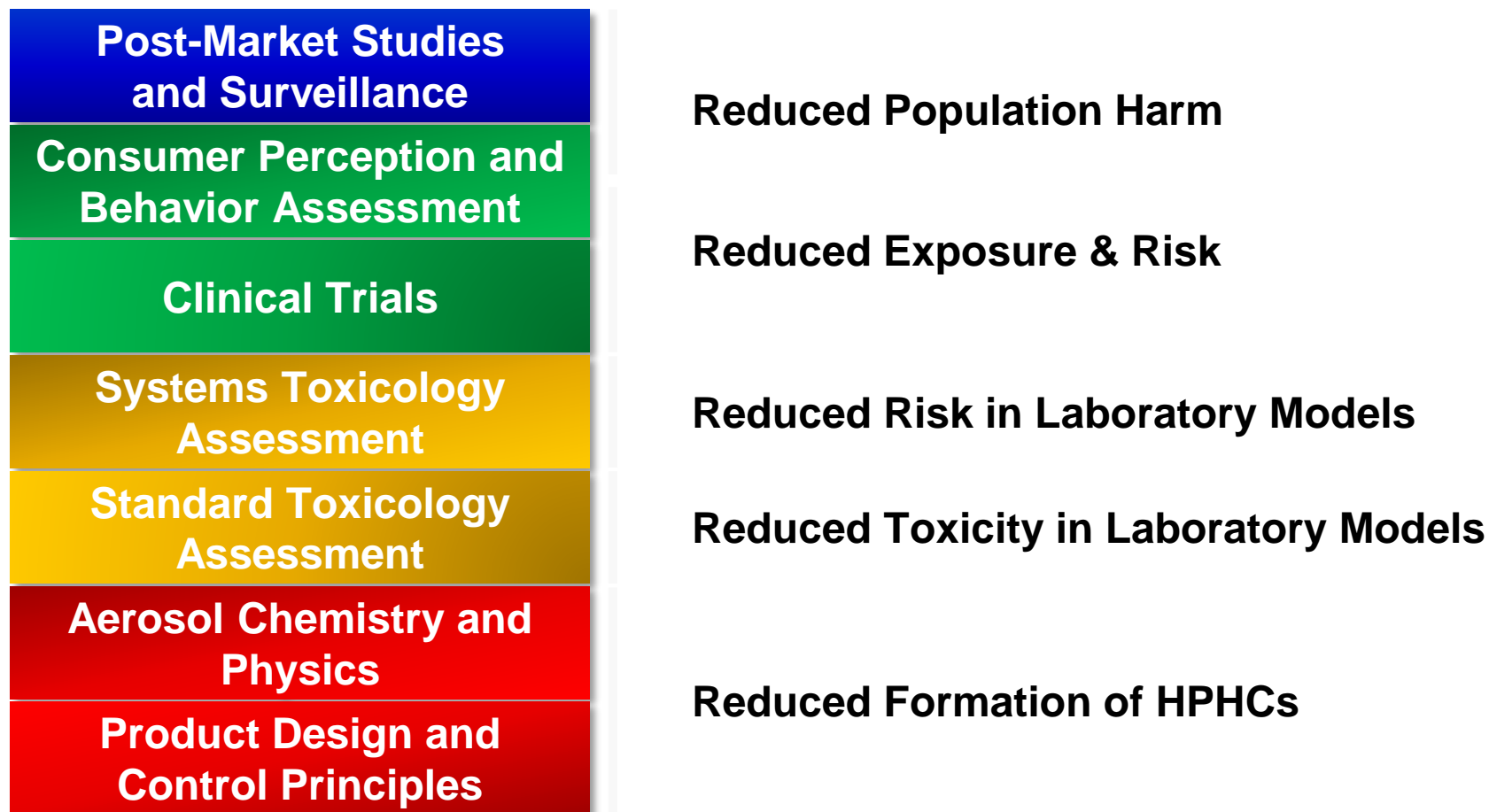
E-VAPOR PRODUCTS

4



\*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.  
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.

# Substantiating Reduced Risk: Totality of Scientific Evidence

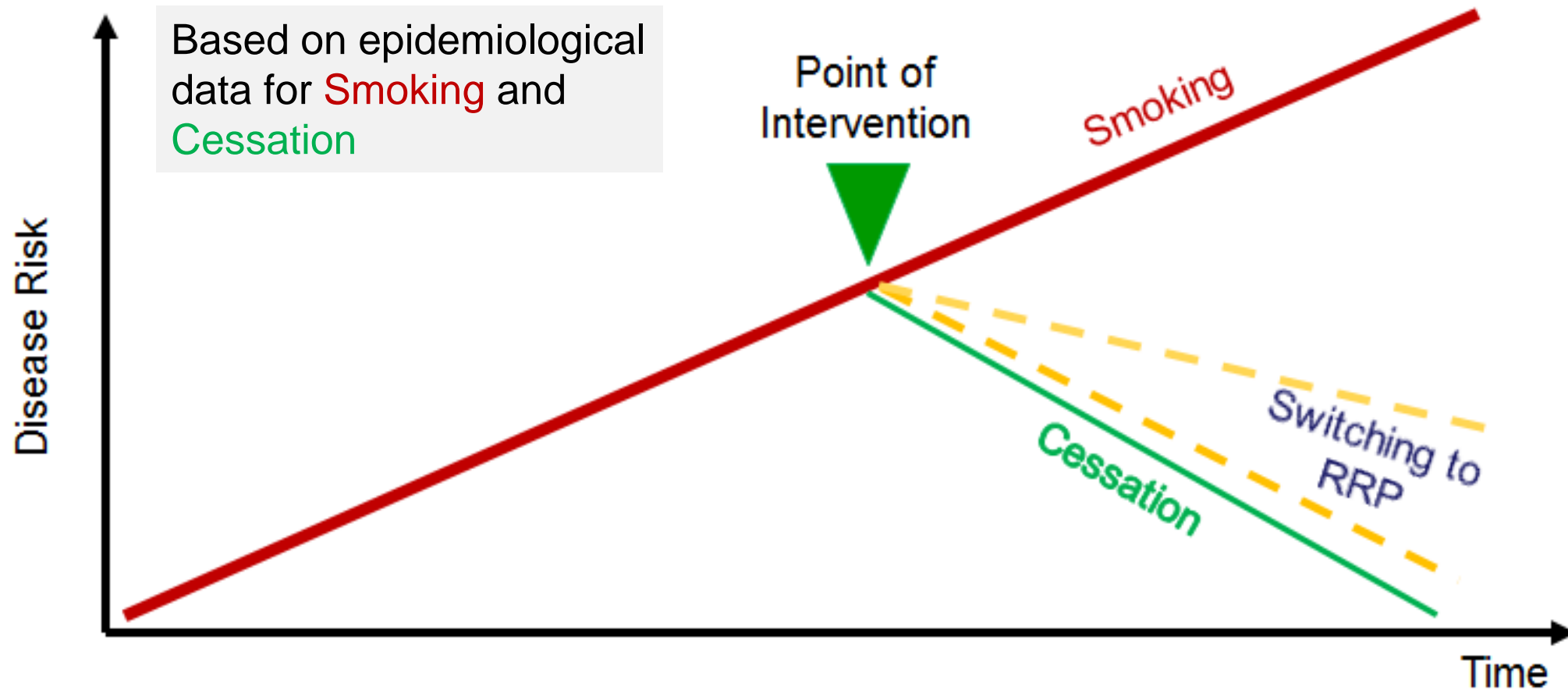


Note: Reduced-Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. HPHCs stands for harmful or potentially harmful constituents.

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>

# Smoking Cessation: The “Gold Standard”

- We apply the U.S. Institute of Medicine’s “gold standard” for assessing risk reduction: benchmark against cessation



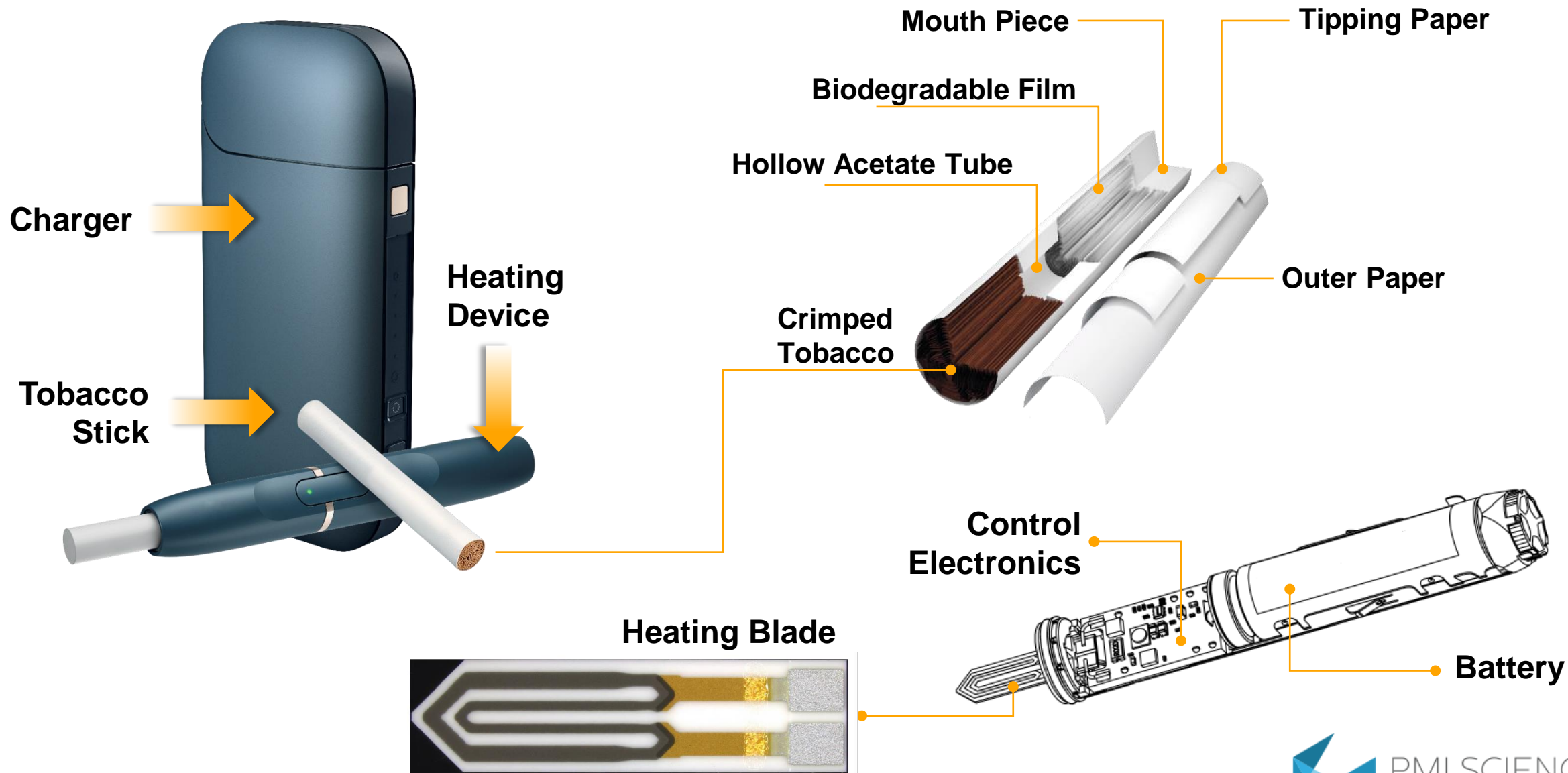


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# Scientific Results for Tobacco Heating System (THS, brand name *IQOS*)

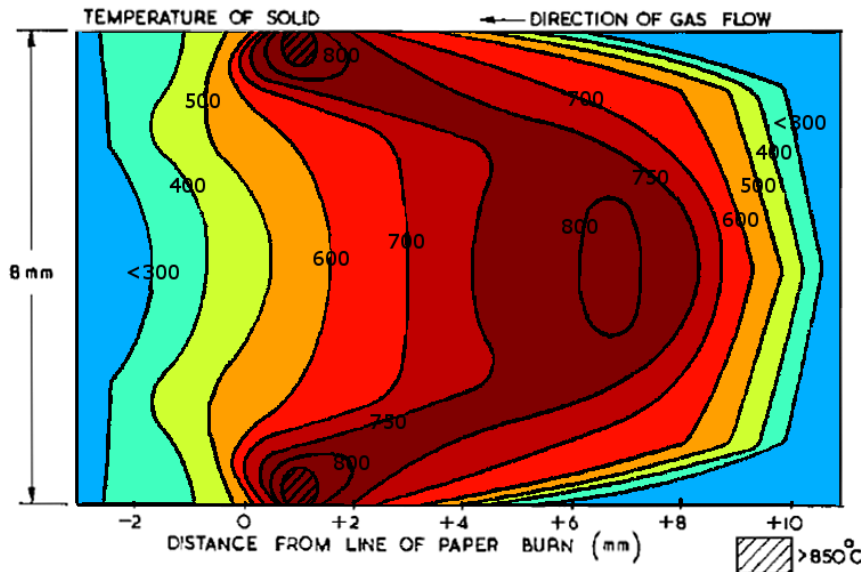


# Product Design: Tobacco Heating System (THS)



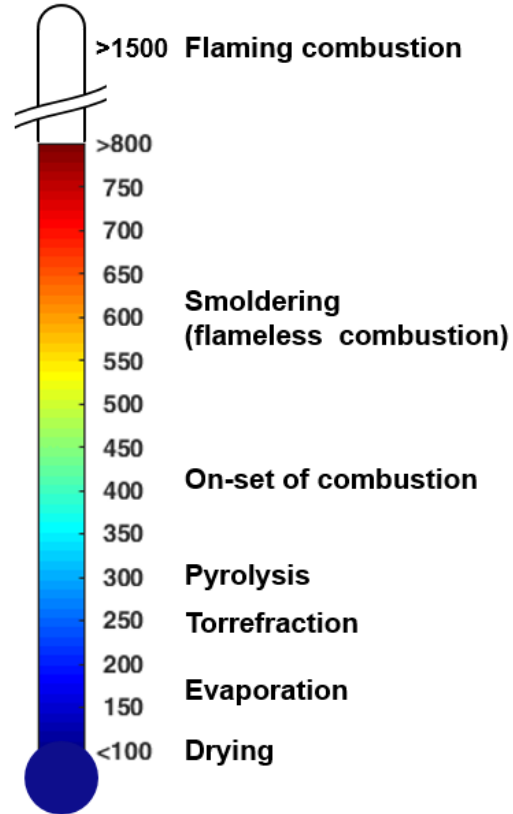
## Temperature of the tobacco material in THS 2.2 compared to cigarettes

Cigarette



Source: Baker R. R., 1975, High Temp. Sci., 7, 236-247.

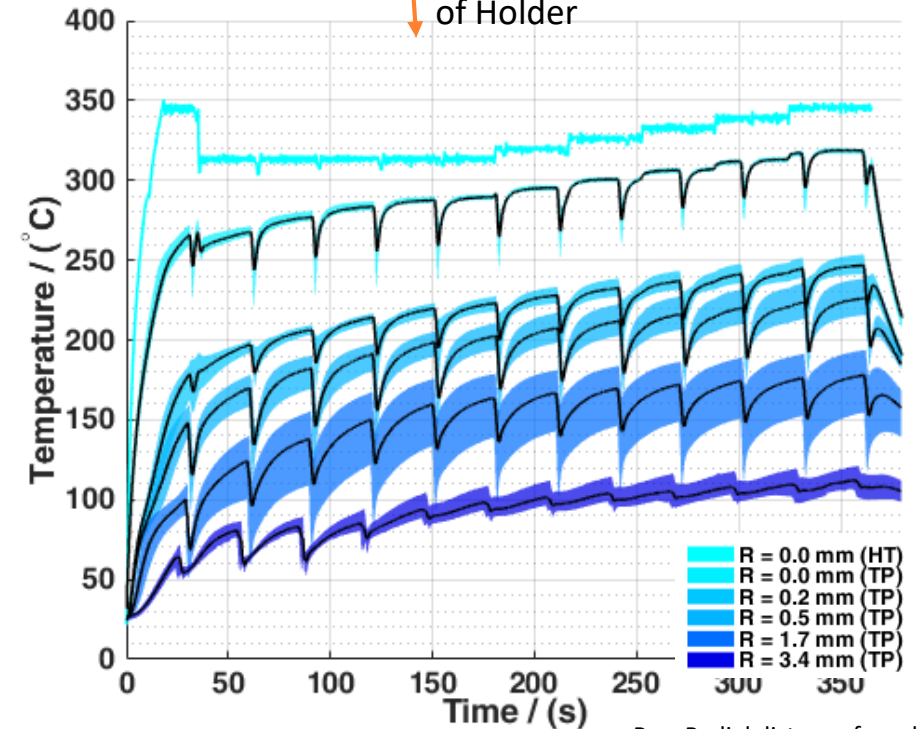
Temperature (°C)



Tobacco stick in Holder



Heating section of Holder

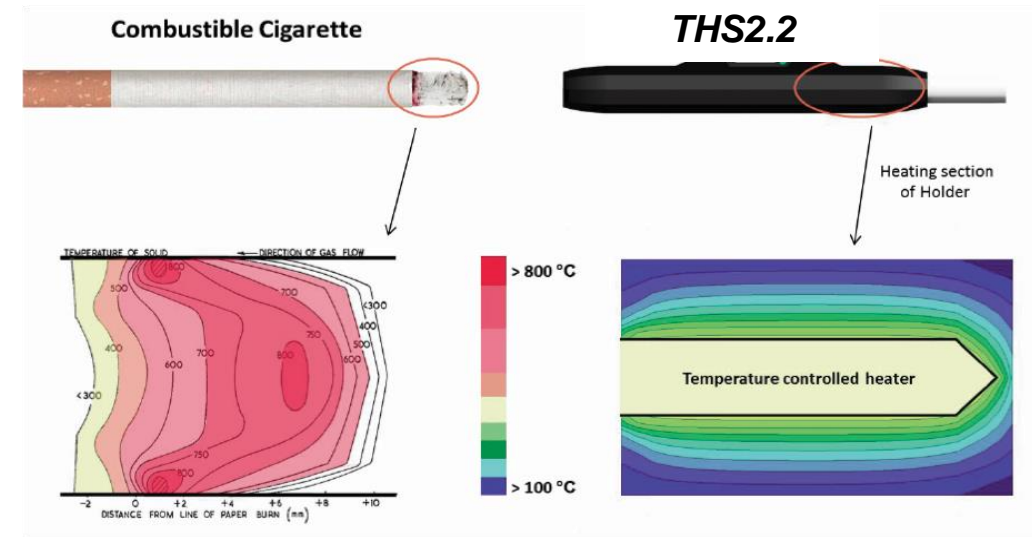
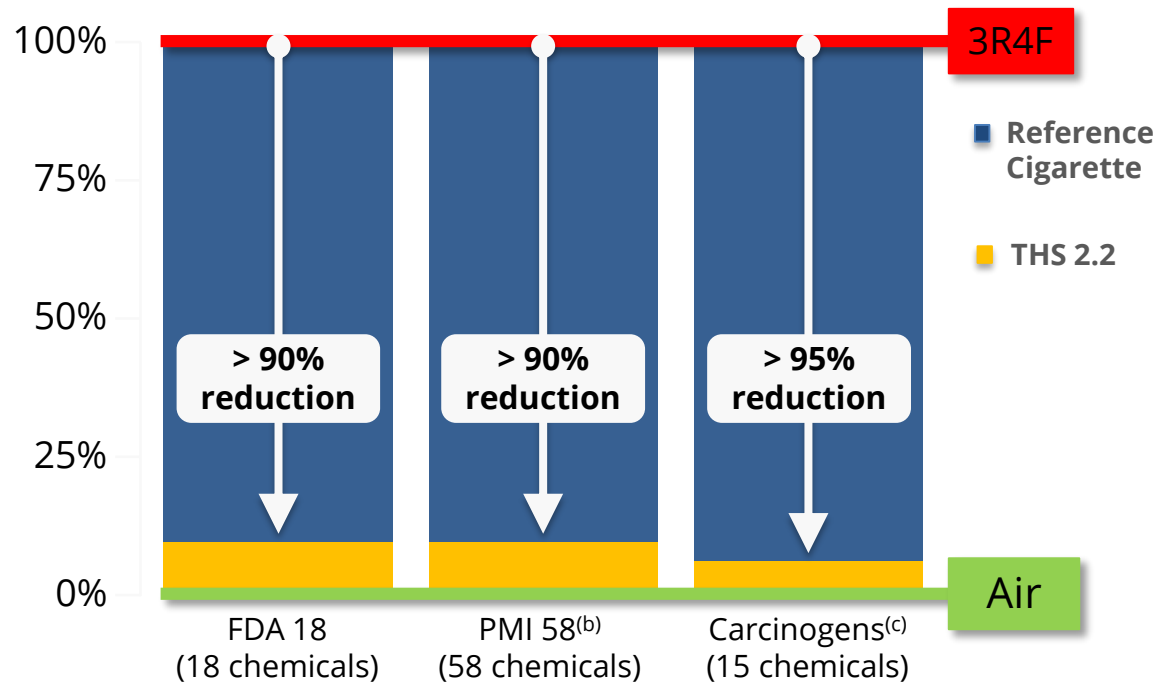


R = Radial distance from heater  
TP = Tobacco Plug  
HT = Heater

- More than **6,000** constituents identified in cigarette smoke
- About **100** of these constituents are categorized as harmful or potentially harmful constituents ("HPHCs")
- Most of the HPHCs are formed when the tobacco burns



Average reductions in **formation** of HPHCs for THS compared with levels measured in smoke from the 3R4F reference cigarette



Photographs of the Cambridge filter pads after the collection of:



Cigarette smoke



THS 2.2 aerosol

THS 2.2 stands for Tobacco Heating System version 2.2 and refers to a commercialized version of IQOS.

(a) Aerosol collection with Health Canada Intense Smoking Regime (55 mL puff volume, 2-second puff duration, 30-second interval puff); comparison on a per-stick basis. Reduction calculations exclude nicotine, glycerin, and total particulate matter.

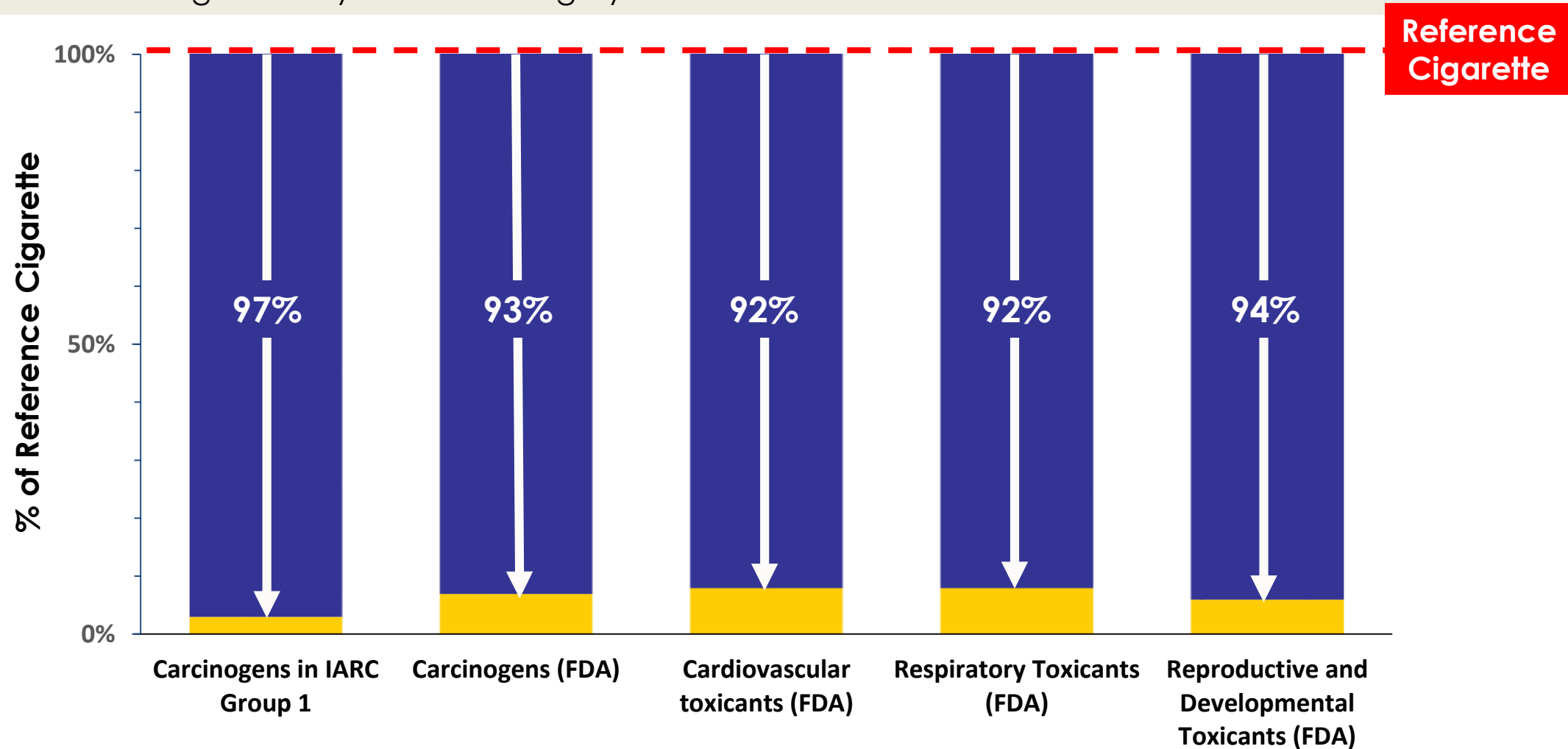
(b) The PMI 58 list includes the FDA 18 and (c) the 15 carcinogens of IARC Group 1

Source: PMI Research and Development



# Aerosol Chemistry: Reduced Formation

Average reductions in **formation** of HPHCs for THS compared with levels measured in smoke from the 3R4F reference cigarette by disease category



Number of toxicants

12

29

8

18

7

Note:

- THS 2.2 stands for Tobacco Heating System version 2.2 and refers to a commercialized version of IQOS.

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



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# Institutions Starting to Confirm PMI's Aerosol Measurements on THS

## Independent institutions confirm toxicant reduction in THS aerosol



- BfR (Federal Institut for Risk Assessment), Dec. 2017<sup>1</sup>



- FDA (U.S. Food and Drug Administration), Jan. 2018<sup>2</sup>

“In light of the significantly reduced release of toxins, **lower health risks are to be expected** provided no further consumption of other tobacco products takes place.”



Pieper et al.,  
Bundesgesundheitsblatt,  
OCT 2018 <sup>3</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 (January 2018)

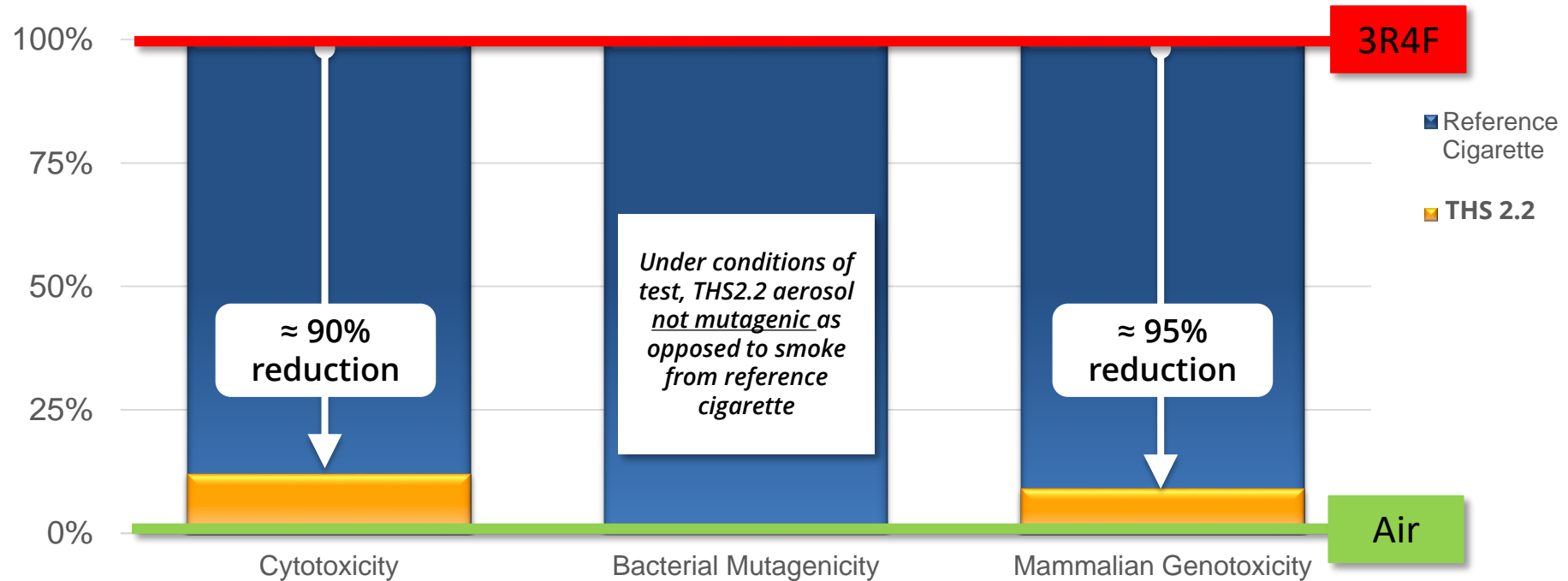
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf>

(3) Pieper et al., Tabakerhitzer als neues Produkt der Tabakindustrie: Gesundheitliche Risiken; Bundesgesundheitsblatt, 04 OCT 2018,

<https://doi.org/10.1007/s00103-018-2823-y>

# Toxicological Assessment: Reduced Toxicity

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



Comparison on a per-nicotine basis

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

Source: PMI Research and Development



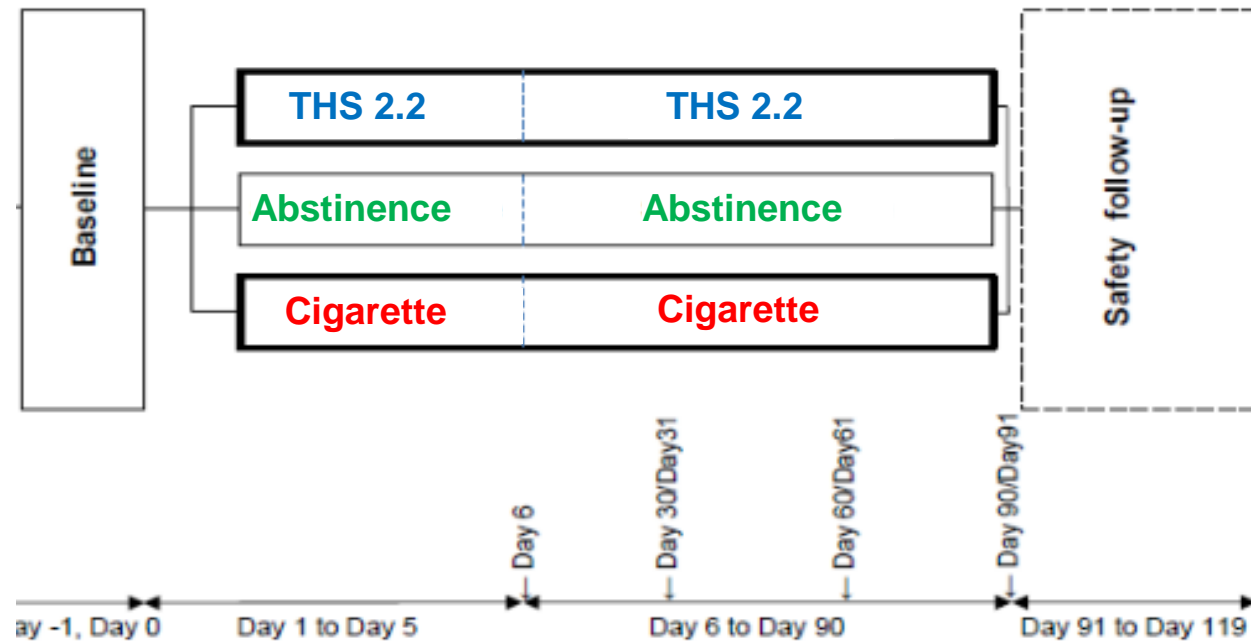
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# Clinical Trials

**Reduced Exposure, Improved Biomarkers**

## Study design:

### 3-month clinical study on reduced exposure to smoking-related toxicants

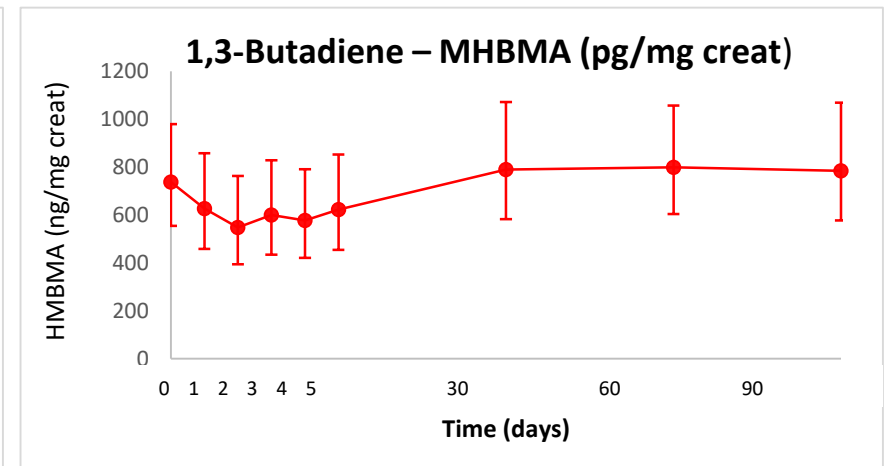
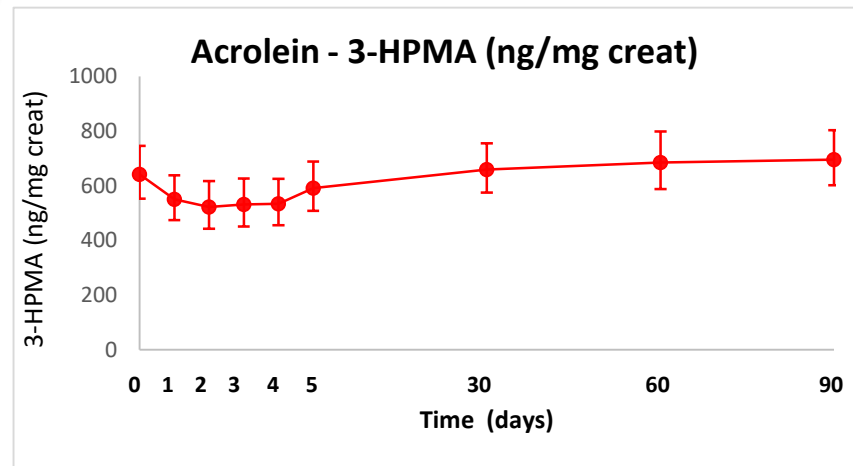
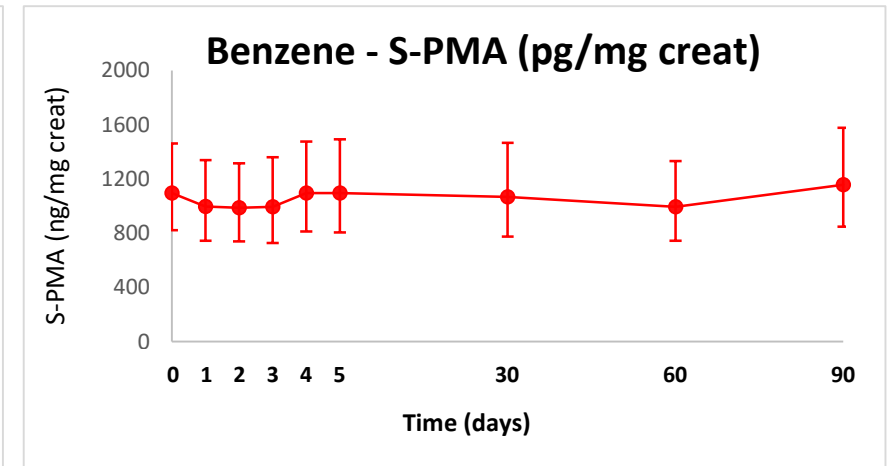
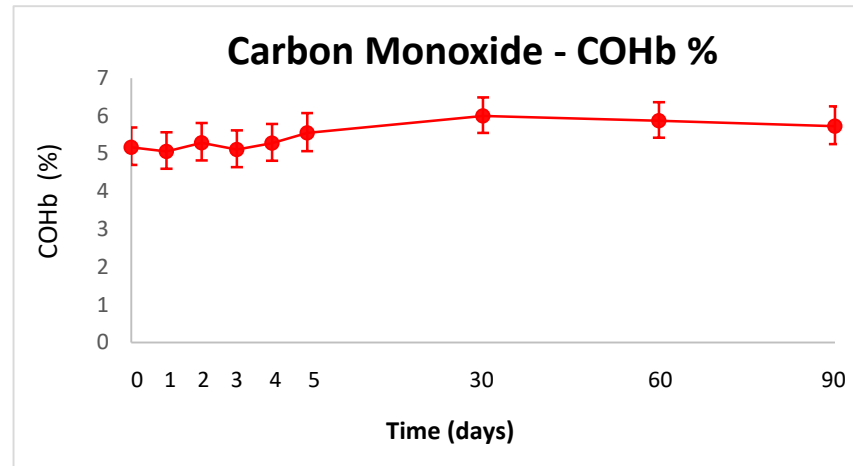


# Clinical Assessment: Reduced Exposure to Toxicants

**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)*

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



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>

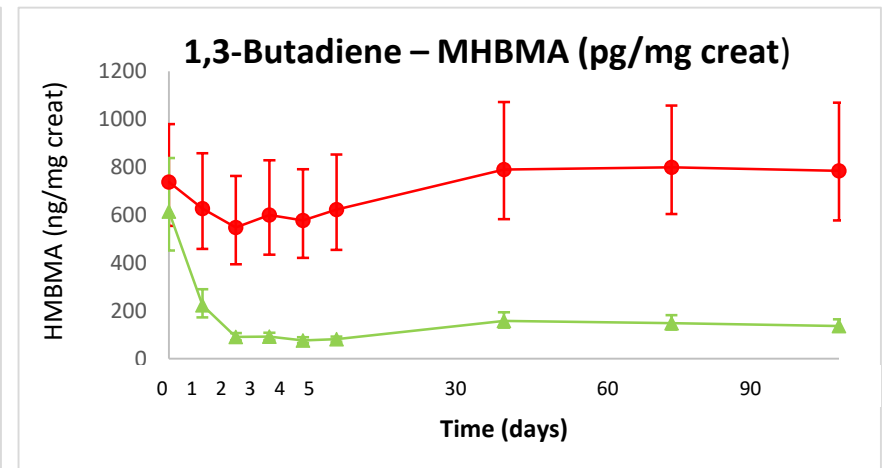
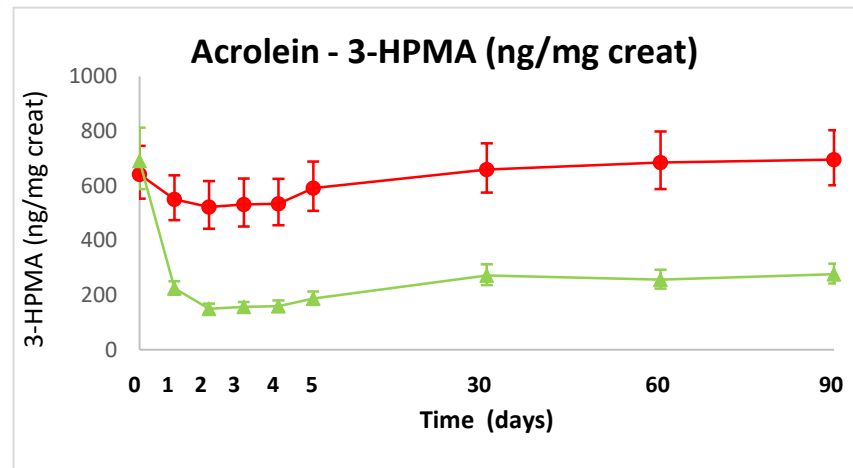
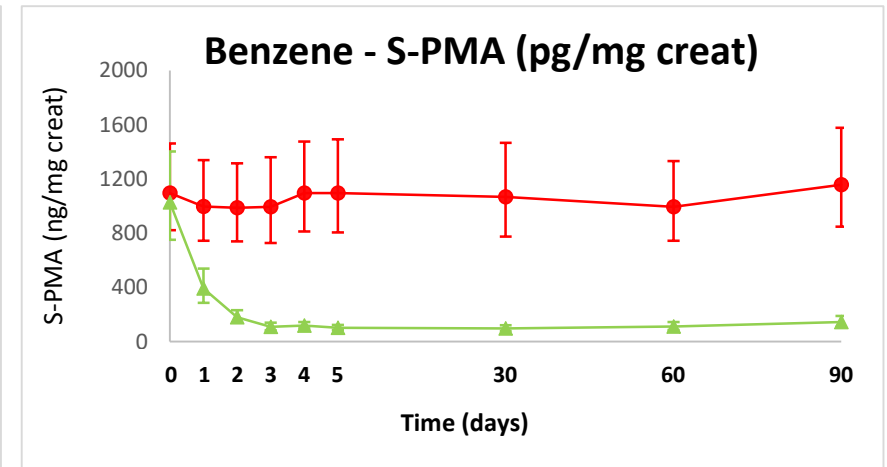
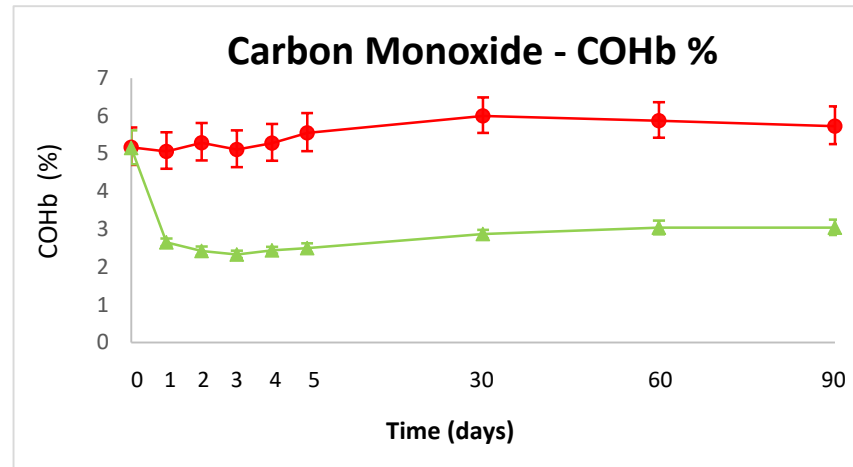
Lüdicke et al. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). Nicotine Tob. Res. (2017)

# Clinical Assessment: Reduced Exposure to Toxicants

**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)

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



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)

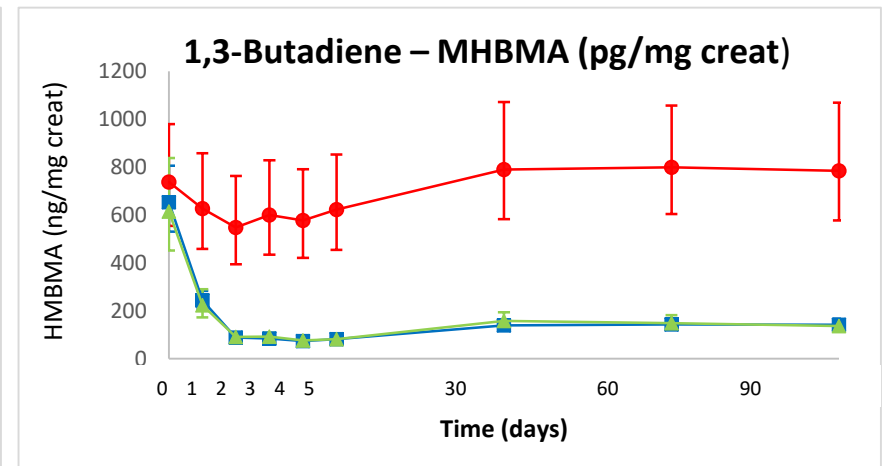
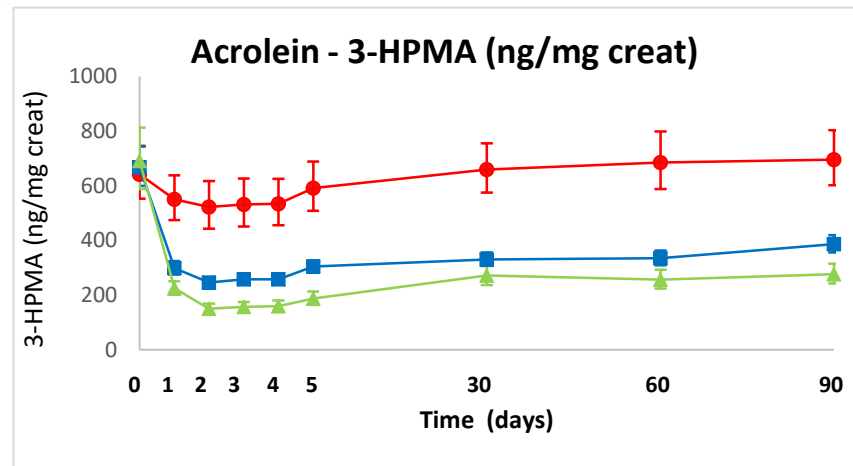
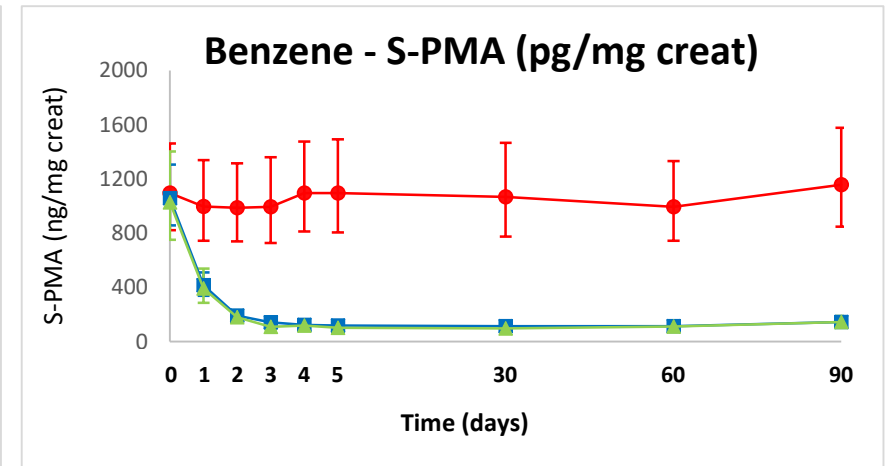
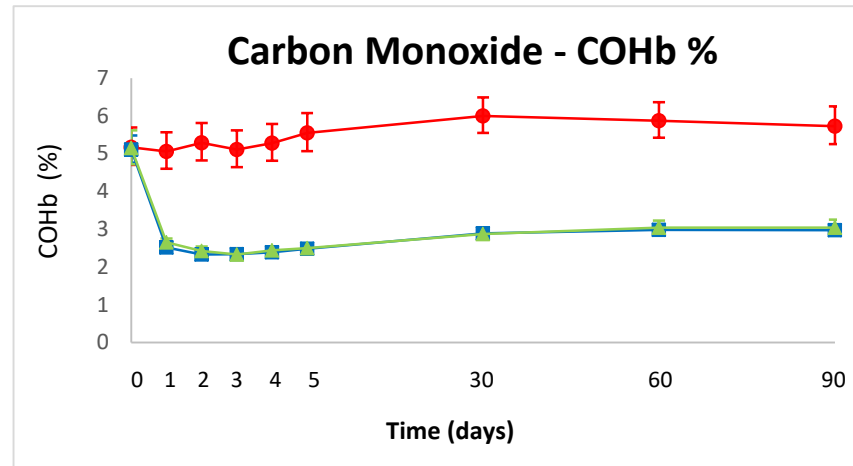


# Clinical Assessment: Reduced Exposure to Toxicants

**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)*

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



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

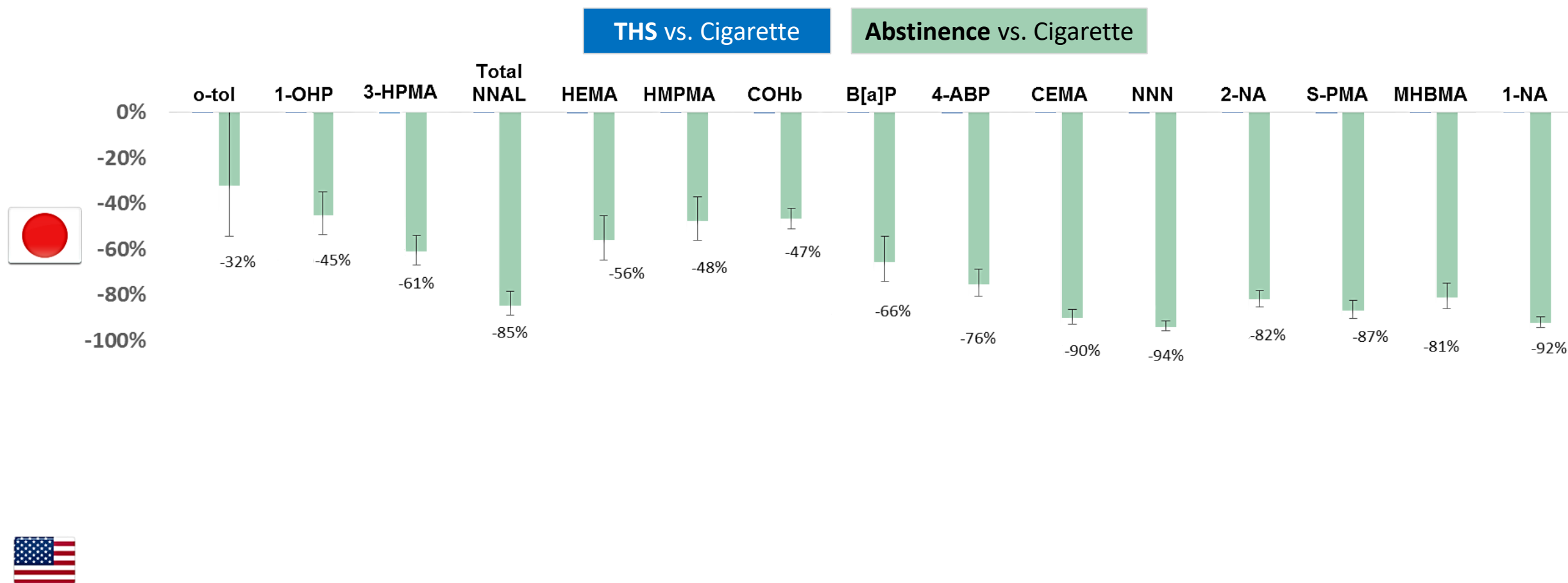
Haziza et al., poster at SRNT, Chicago, USA, 2016

<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)

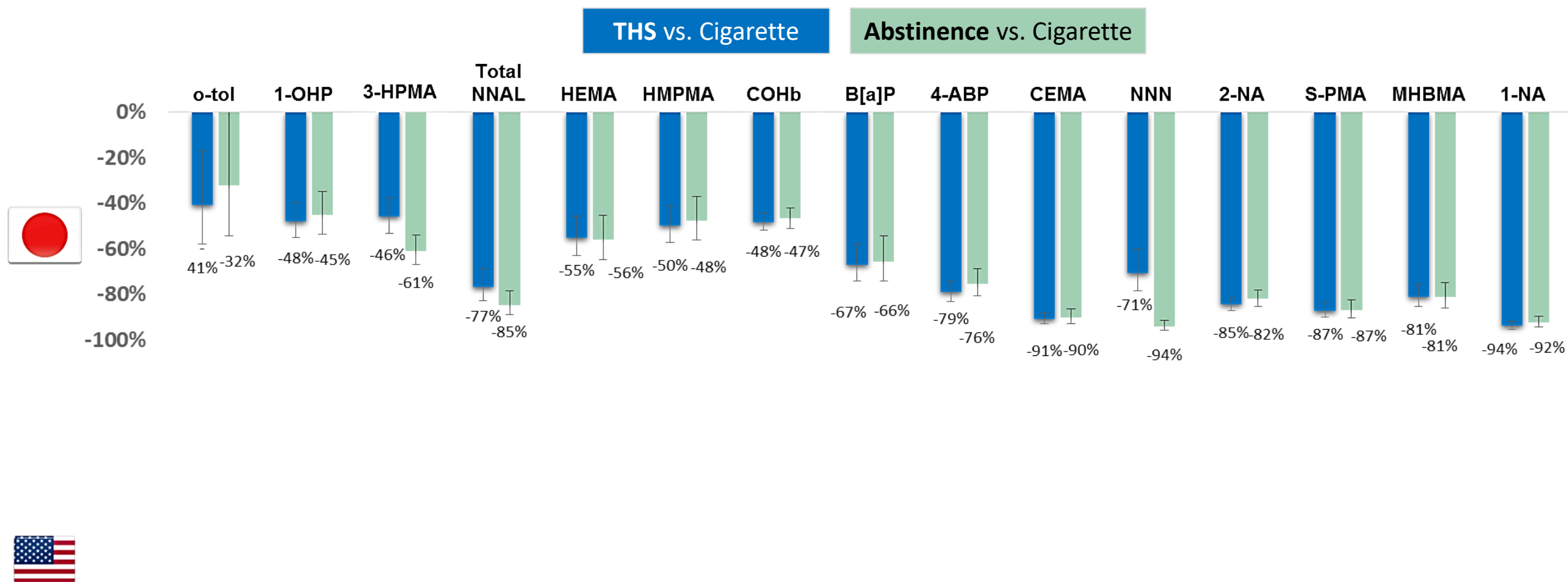
# Clinical Evidence for Toxicant Exposure Reduction (Japan and U.S.)

## % Reduction in Biomarkers of Exposure After Switching to THS for Three Months



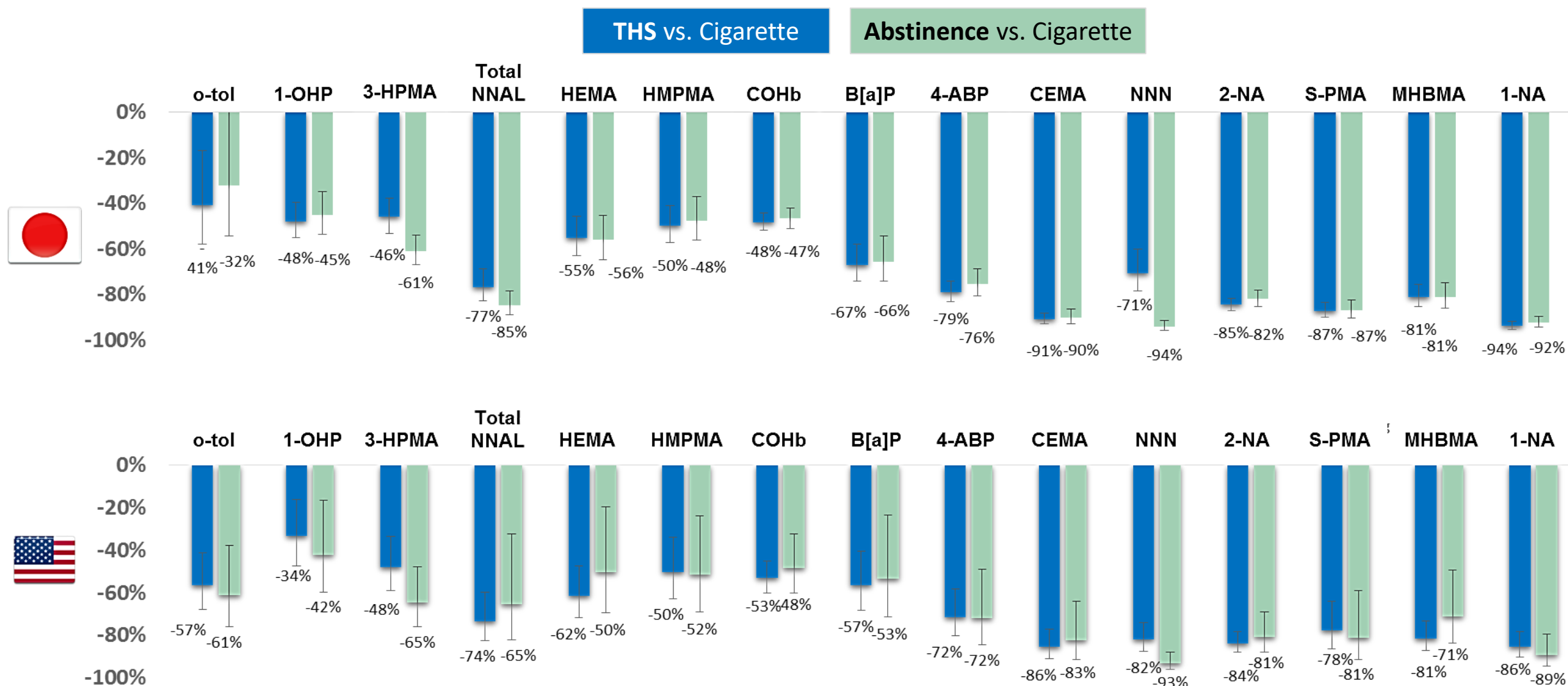
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# Clinical Evidence for Toxicant Exposure Reduction (Japan and U.S.)

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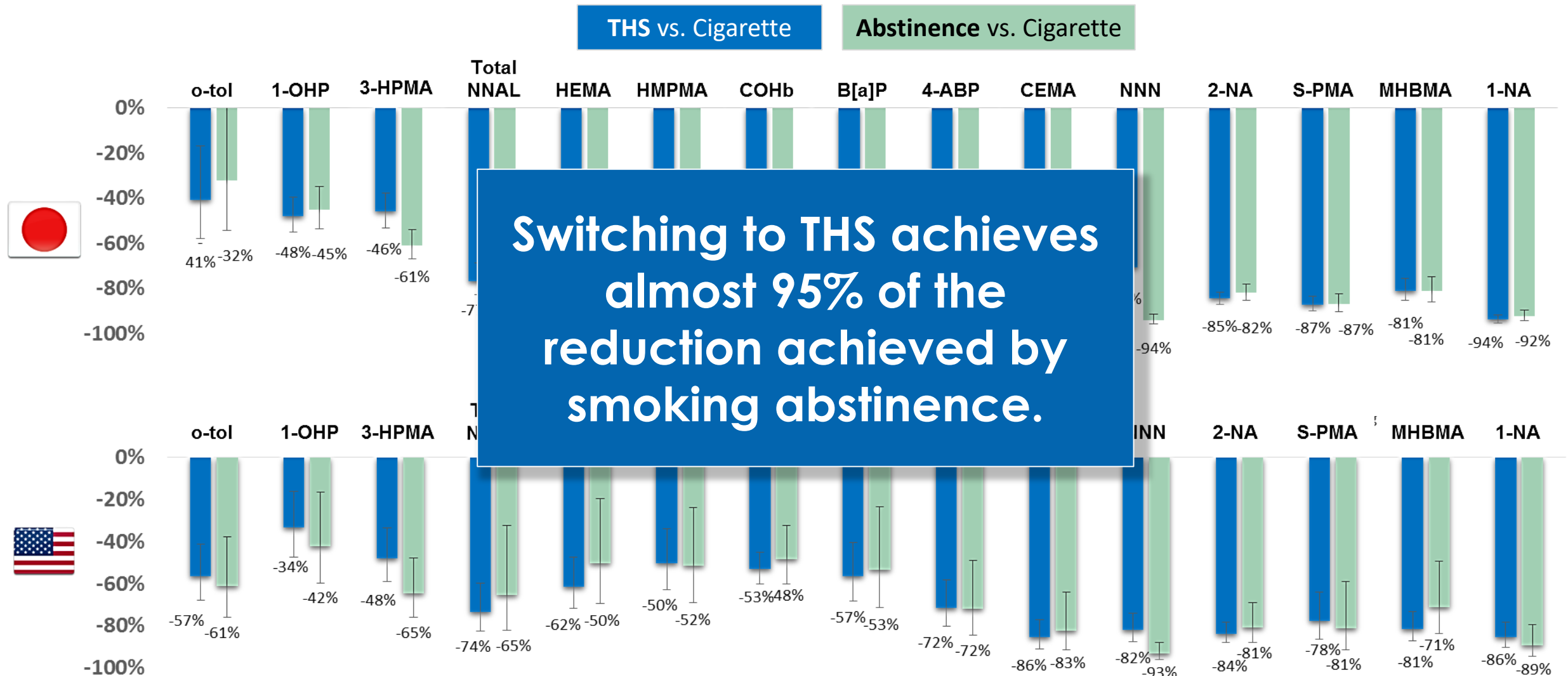


Japanese study: Lüdicke et al. Effects of switching to the menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers (...) (Part 2). Nicotine Tob. Res.

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)

# Clinical Evidence for Toxicant Exposure Reduction (Japan and U.S.)

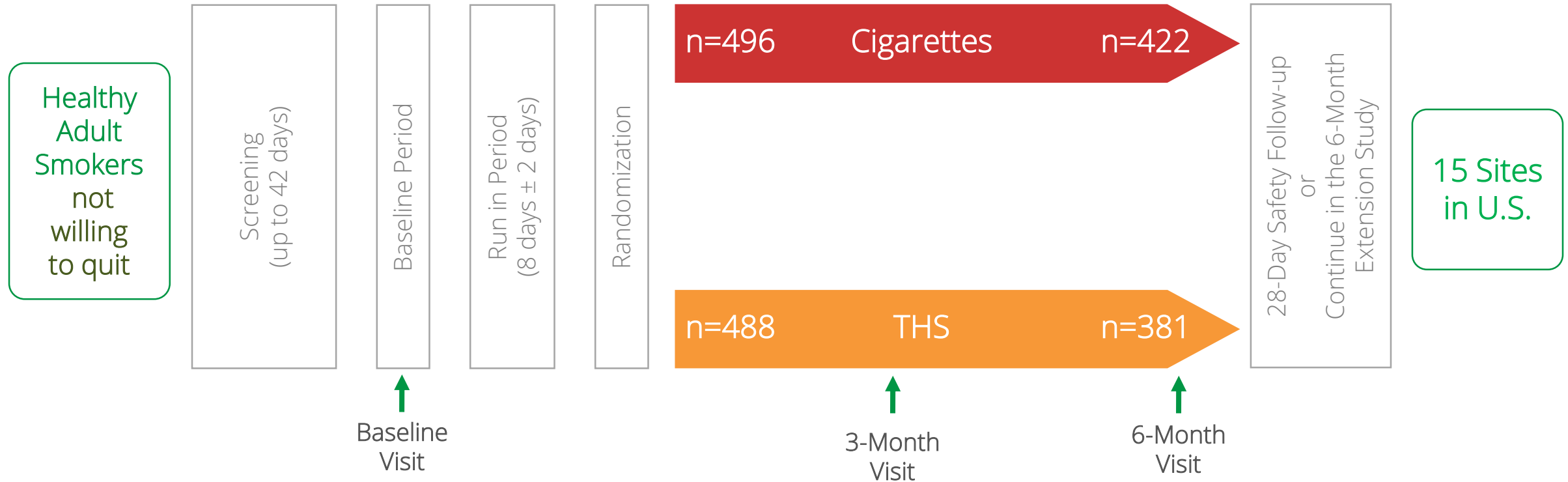
## % Reduction in Biomarkers of Exposure After Switching to THS for Three Months





# 6-Month Clinical Study Supports Risk Reduction Potential of THS

## Exposure Response Study (6 months) – Study Design



Exposure Response Study (ERS)  
ZRHR-ERS-09-US ([Clinicaltrials.gov: NCT02396381](https://clinicaltrials.gov/ct2/show/study/NCT02396381))

Haziza C. Global Forum on Nicotine, 2018, <https://gfn.net.co/downloads/2018/PRESENTATIONS/FRIDAY/Parallel2/ChristelleHaziza.pdf>  
[https://www.pmiscience.com/library/publication/changes-in-biological-and-functional-markers-after-six-months-in-three-populations-ths-2.2-\(iqos\)-users-continued-smokers-and-smoking-abstinence](https://www.pmiscience.com/library/publication/changes-in-biological-and-functional-markers-after-six-months-in-three-populations-ths-2.2-(iqos)-users-continued-smokers-and-smoking-abstinence)

# 6-Month Clinical Study Supports Risk Reduction Potential of THS

## Exposure Response Study (6 months)

- The clinical study met its primary objective:
  - All co-primary endpoints shift in the same direction as smoking cessation
  - Majority of co-primary endpoints statistically significantly different vs. continued smoking
- Results achieved even with 30% concomitant use of cigarettes
- Results correlate with the amount of concomitant cigarette use

Co-Primary Endpoints Linked to Smoking-Related Diseases			
Disease	Mechanism	Clinical Risk Endpoint	
Cardiovascular Disease	Lipid Metabolism	HDL-C	✓
	Clotting	11-DTX-B2	✓
	Endothelial Function	sICAM - 1	✓
	Acute Effect	COHb	✓
Respiratory Disease and Cancer	Inflammation	WBC	✓
	Oxidative Stress	8-epi-PGF2α	✓
	Lung Function	FEV <sub>1</sub> %Pred	✓
	Genotoxicity	Total NNAL	✓



Statistically significantly different to continued smoking

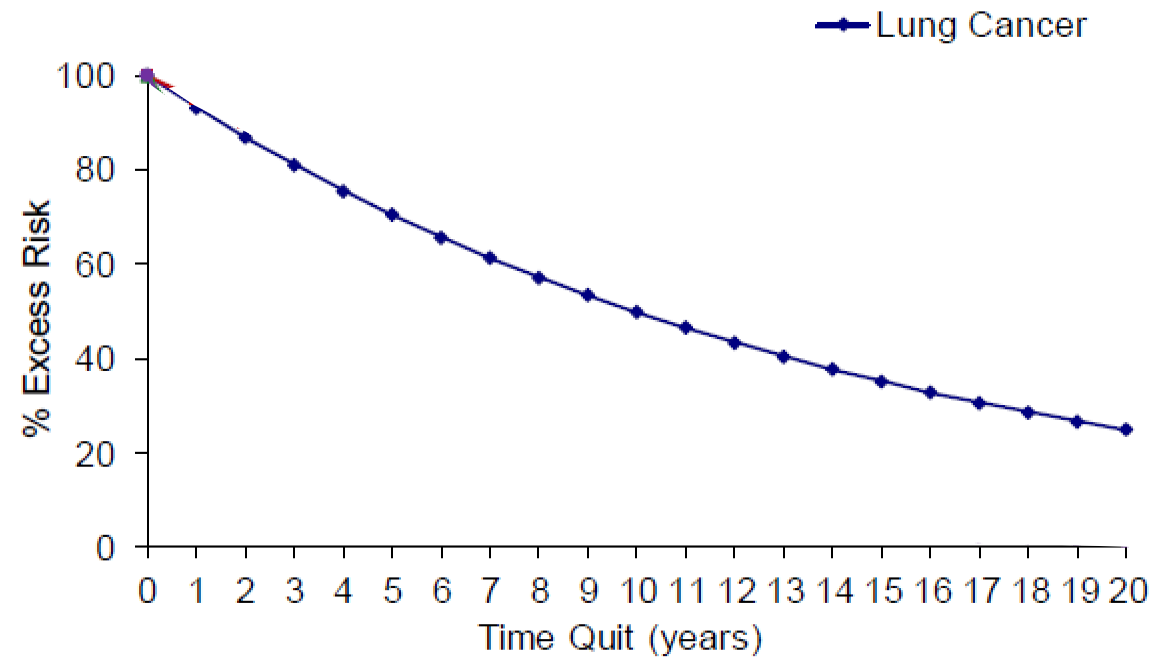


In the same direction of change as smoking cessation

# The Complexity of Showing Reduced Risk for Smoking-Related Disease

## The nature of disease vs. unequivocal scientific evidence

- Example lung cancer:
  - 50% reduction or relative risk only 10 years after quitting smoking\*



Reduction in Excess RR for four diseases as a function of time after quitting as described by the NEM.

\*Source for relative risk of Lung Cancer: Lee 2012.

Negative exponential model (NEM) is used to calculate the reduction in excess RR over time using the relationships between smoking cessation and reduced excess RR.

# Calculation of Carcinogenic Potential (Cigarettes / E-cigs / Heat-Not-Burn)

## Modeling of “cancer potencies” and “lifetime cancer risks”

- Possible limitation: Pure modeling based on published data

### Research paper

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

William E Stephens

*Tob. Control.* 2017 Aug 4. pii: tobaccocontrol-2017-053808. doi: 10.1136/tobaccocontrol-2017-053808. [Epub ahead of print]

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

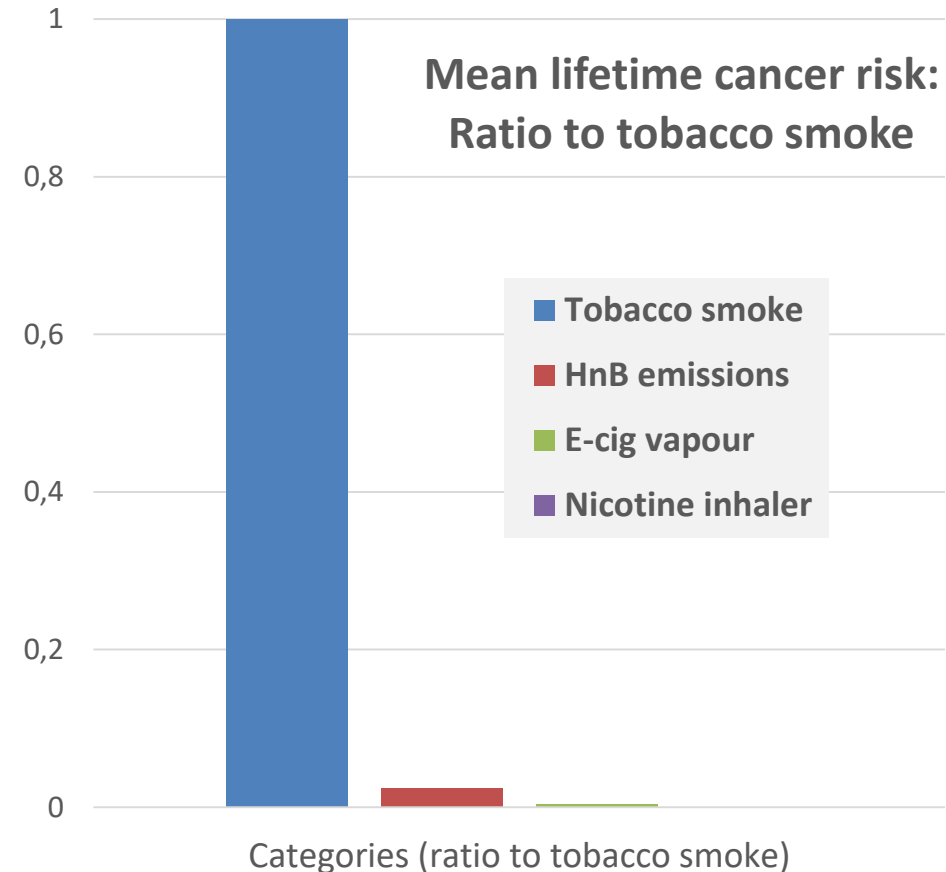
Stephens WE.

#### Abstract

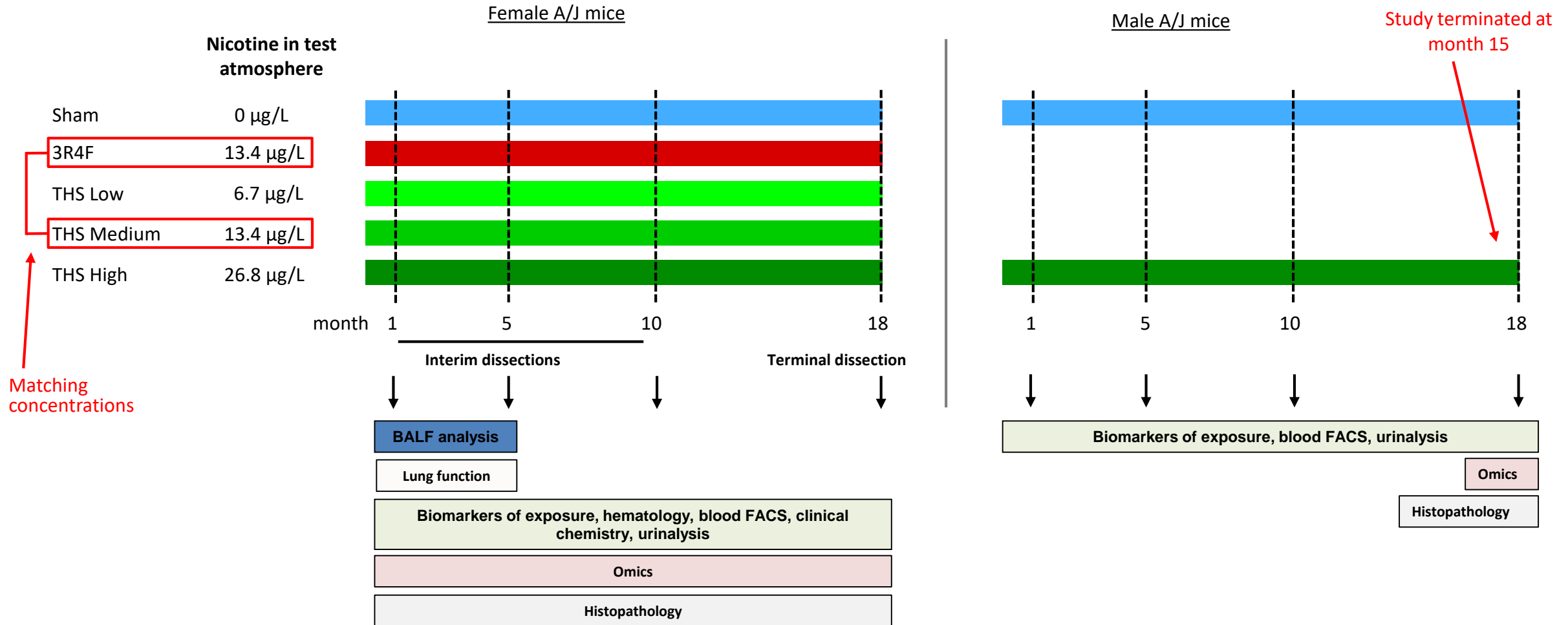
**BACKGROUND:** Quantifying relative harm caused by inhaling the aerosol emissions of vapourised nicotine products compared with smoking combustible tobacco is an important issue for public health.

**METHODS:** The cancer potencies of various nicotine-delivering aerosols are modelled using published chemical analyses of emissions and their associated inhalation unit risks. Potencies are compared using a conversion procedure for expressing smoke and e-cigarette vapours in common units. Lifetime cancer risks are calculated from potencies using daily consumption estimates.

Graph based on data from Stephens, *Tobacco Control*, 2017



# Combined Chronic Toxicity and Carcinogenicity Study – A/J Mice: Study Design



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

\*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

# Toxicology: *In Vivo* Lung Cancer Study Supports Risk Reduction

## First-ever *in vivo* lung cancer study on smoke-free tobacco product alternative

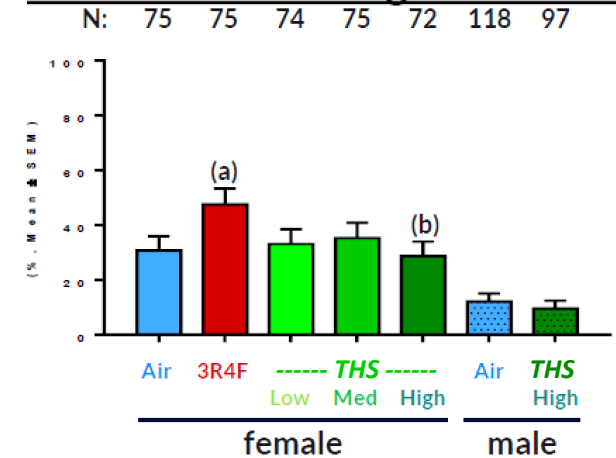
- **18-month *in vivo* A/J mouse** lung cancer study showed encouraging results:
  - **THS aerosol did not cause an increase in lung inflammation or emphysema** compared to air exposure in the A/J mouse model
  - **THS aerosol did not cause an increase in occurrence or number of lung tumors** compared to air exposure in the A/J mouse model

(a)  $p < 0.05$  vs. Air; (b)  $p < 0.05$  vs. 3R4F

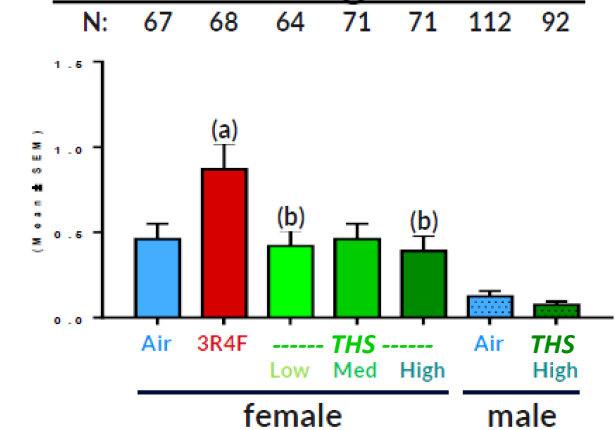
Note: "N" refers to the number of mice per group

Source: PMI Research & Development. Study Report (study number 15020)

Occurrence of Lung Carcinoma



Number of Lung Carcinoma





# Summary – Reduced Risk Products (RRPs)

1



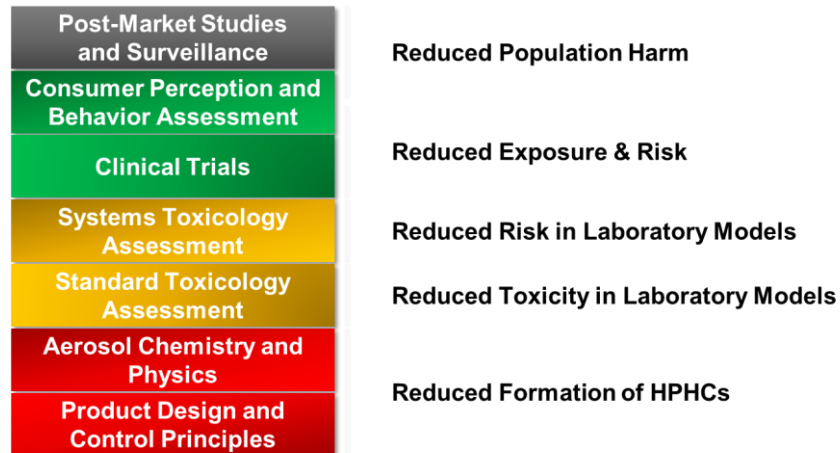
2

## Heated Tobacco Products

## Products Without Tobacco



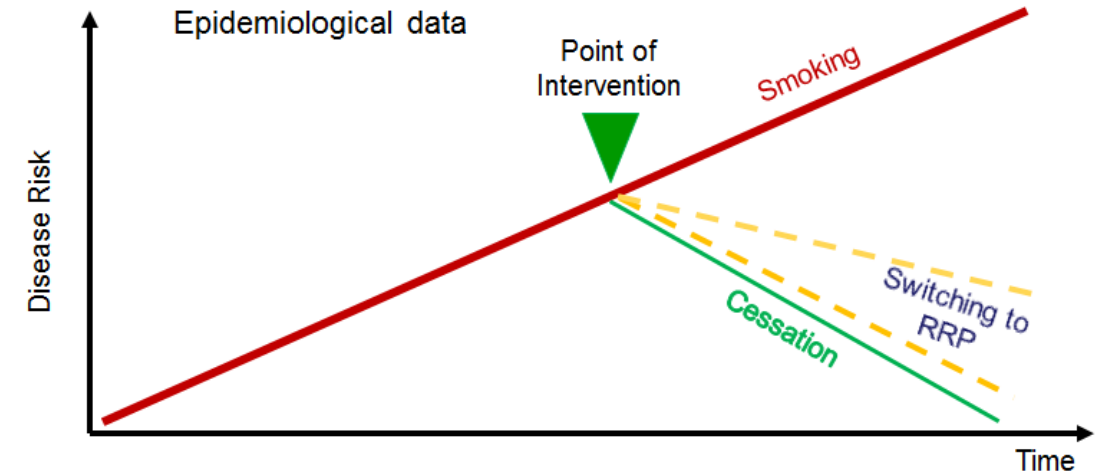
4



We are committed to **transparency** and encourage **independent verification** of our results.

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3



# Harm Reduction for the Prevention of Noncommunicable Diseases (NCD)?

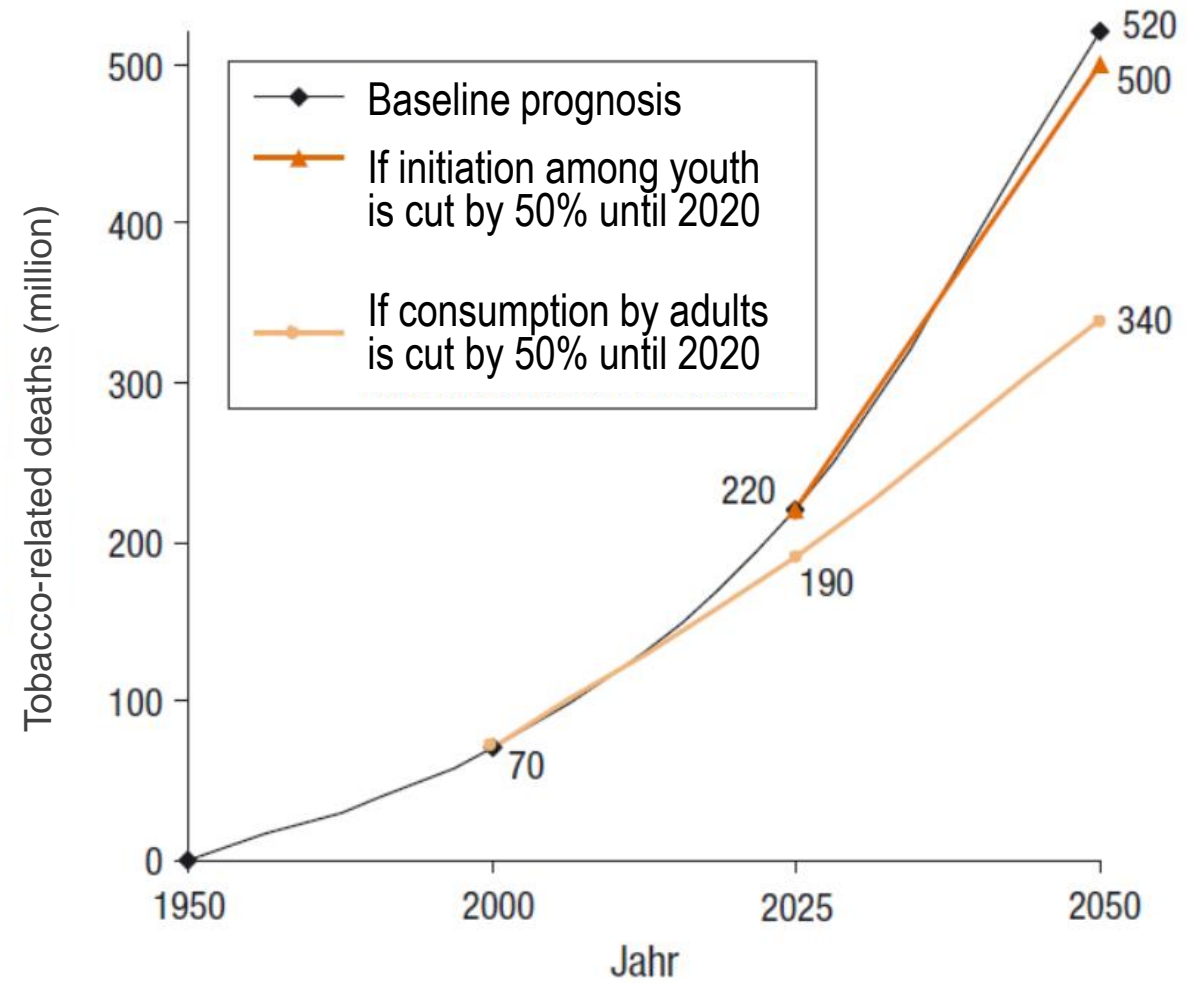
# Prevention of Initiation vs. Promotion of Cessation

## Effective prevention of NCDs by the promotion of smoking cessation

“If today’s smokers won’t give up smoking, the number of tobacco-related deaths will rise dramatically in the next 50 years.”

World Bank (1999) \*

*Estimated, cumulated number of smoking-related deaths 1950-2050 according to different intervention strategies \**



\*Der Tabakepidemie Einhalt gebieten: Regierungen und wirtschaftliche Aspekte der Tabakkontrolle; Weltbank (deutsche Version 2003)

Curbing the Epidemic: Governments and the Economics of Tobacco Control; Copyright © 1999 by The International Bank for Reconstruction and Development/THE WORLD BANK; <http://documents.worldbank.org/curated/en/914041468176678949/Curbing-the-epidemic-governments-and-the-economics-of-tobacco-control>

# Modeling: E-cigarettes Avert Premature Deaths from Smoking

## Modeling

- **E-cigarettes** could prevent **1.6–6.6 million premature deaths** from smoking in the U.S.<sup>1</sup>



## Potential deaths averted in USA by replacing cigarettes with e-cigarettes

David T Levy,<sup>1</sup> Ron Borland,<sup>2</sup> Eric N Lindblom,<sup>3</sup> Maciej L Goniewicz,<sup>4</sup> Rafael Meza,<sup>5</sup> Theodore R Holford,<sup>6</sup> Zhe Yuan,<sup>7</sup> Yuying Luo,<sup>7</sup> Richard J O'Connor,<sup>4</sup> Raymond Niaura,<sup>8</sup> David B Abrams<sup>1,8</sup>

Research paper

MEDIZINREPORT: Studien im Fokus

Rauchen: Nach Modellrechnung verhindert die E-Zigarette vorzeitige Todesfälle

Dtsch Arztebl 2017; 114(44): A-2043 / B-1724 / C-1688

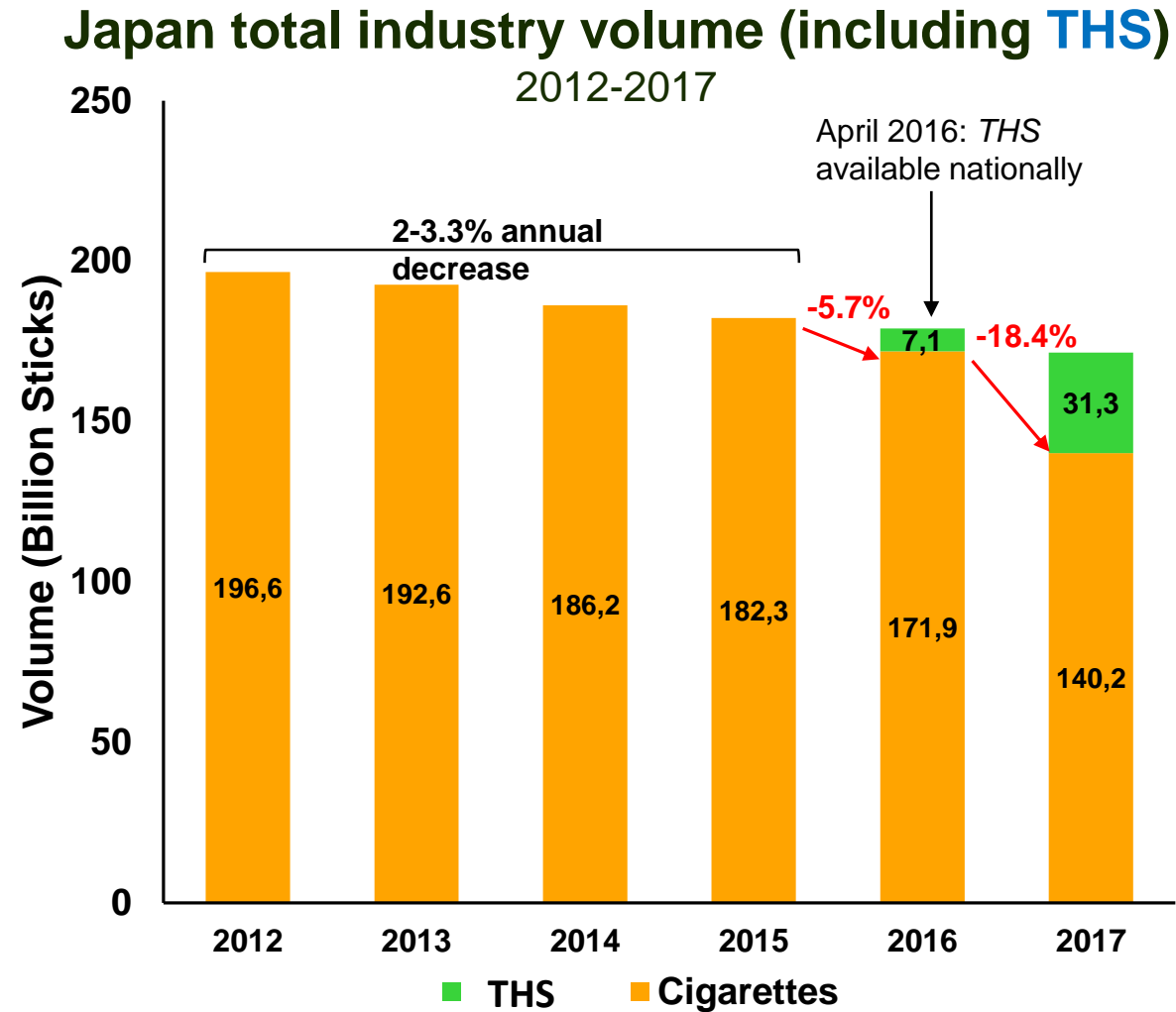
Gießelmann, Kathrin

aerzteblatt.de

(1) Levy DT, Borland R, Lindblom E; [Potential deaths averted in USA by replacing cigarettes with e-cigarettes](https://doi.org/10.1136/tobaccocontrol-2017-053759). Tobacco Control 2017; doi: 10.1136/tobaccocontrol-2017-053759.

(2) Rauchen: Nach Modellrechnung verhindert die E-Zigarette vorzeitige Todesfälle, Dtsch Arztebl 2017; 114(44): A-2043 / B-1724 / C-1688; <https://www.aerzteblatt.de/archiv/194270/Rauchen-Nach-Modellrechnung-verhindert>

# Post-Market Assessment: Unprecedented Decline in Cigarette Sales



# Conclusions



## Conclusions



- **Smoking** remains a **challenge** for the prevention of NCDs **and the best option for every smoker is to quit.**
- **Tobacco Harm Reduction**, i.e. offering smoke-free alternatives to adult smokers, 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).