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# Uncovering Recent ENDS Scientific Research Data

*Next Generation Nicotine Delivery 2018*
*London, 14 NOV 2018*

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

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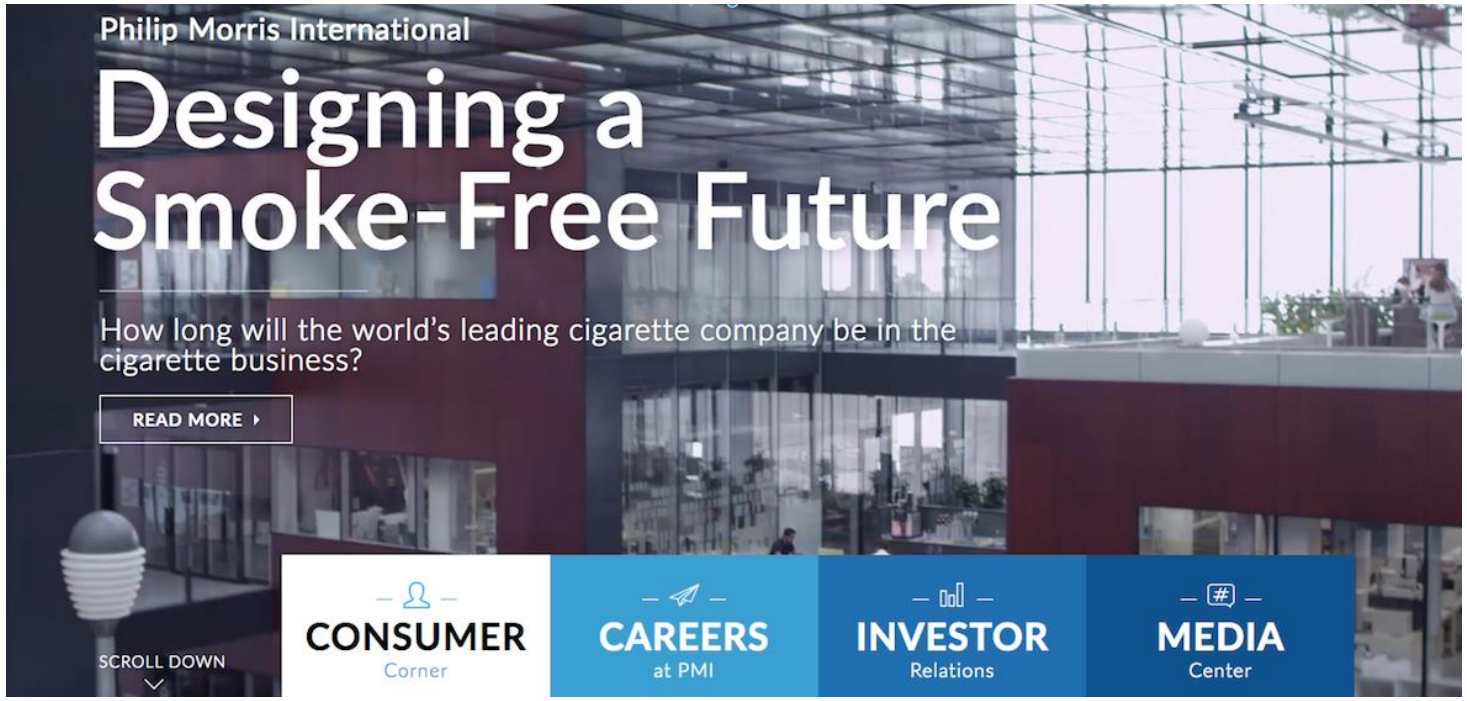
# Overview

- About smoking
- PMI Science
- HnB (THS): latest data
- E-cigarettes: selected data
- Relative harm reduction potential
- Debate on regulation
- Conclusions

# The Objective is Harm Reduction





**"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

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Reduced-Risk Products (“**RRPs**”) is the term we use to refer to products that present, are likely to present, or have the **potential to present less risk of harm to smokers** who switch to these products versus continued smoking. We have a range of RRPs **in various stages of development, scientific assessment, and commercialization**. Because our products do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

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

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# About Smoking

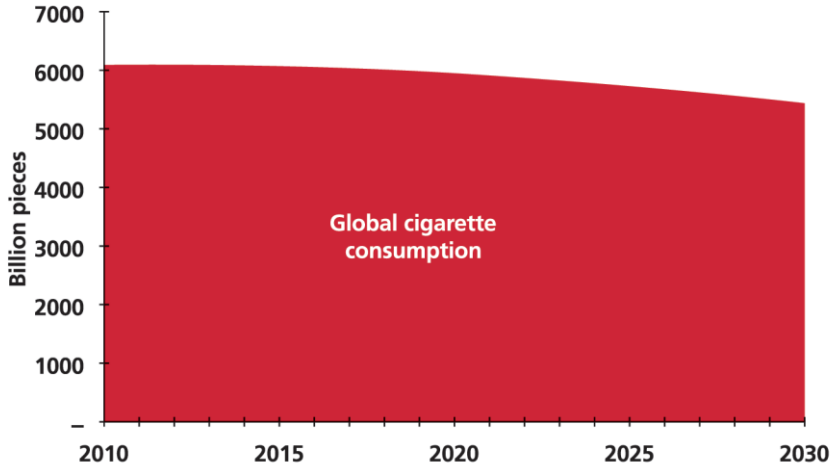
## Prevalence

## Cessation

## Tobacco Harm Reduction

# WHO[1]: >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.*

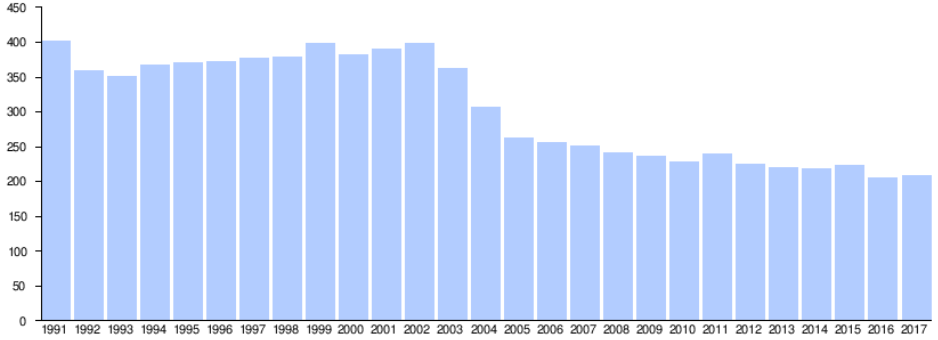
Germany[2]

**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

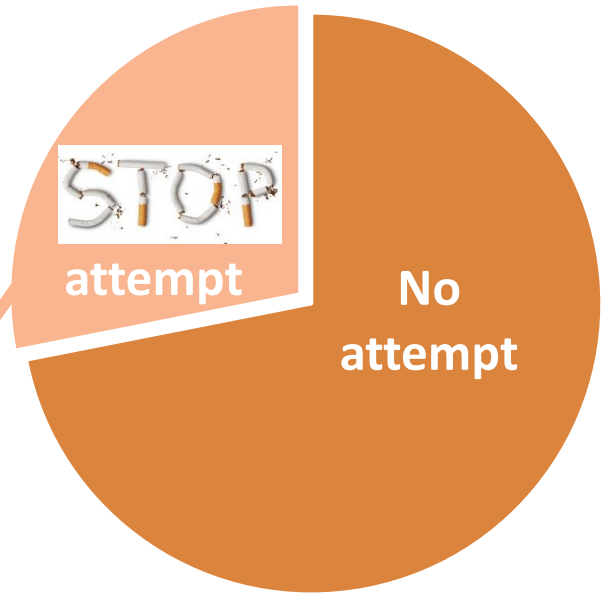
(2) Kotz et al., Nutzung von Tabak und E-Zigaretten sowie Methoden zur Tabakentwöhnung in Deutschland - Eine repräsentative Befragung in 6 Wellen über 12 Monate (die DEBRA-Studie); Dtsch Arztebl Int 2018; 115(14): 235-42; DOI: 10.3238/arztebl.2018.0235 https://www.aerzteblatt.de/archiv/197190/Nutzung-von-Tabak-und-E-Zigaretten-sowie-Methoden-zur-Tabakentwoehnung-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.

## Gold standard cessation

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

**Cessation attempt in the previous year**
**(DEBRA-Study, 2018[1])**




Most frequently used method*:
**E-cigarettes** (9.1%)[1]

(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

## Offering adult smokers satisfying products that reduce risk

- 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*


- Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products so that consumer acceptance can be best fulfilled
- Our ambition is to lead a full-scale effort to ensure that non-combustible products ultimately replace cigarettes to the benefit of adult smokers, society, our company, and our shareholders

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)

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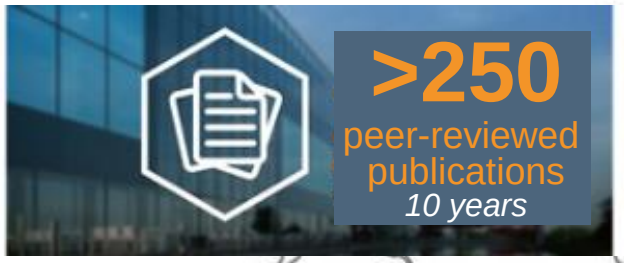
# Tobacco Harm Reduction
## The Contribution of PMI Science

# Introduction to PMI R&D




Europäisches Patentamt
European Patent Office
Office européen des brevets

2016 TOP 100 in the European Patent Office Ranking


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 RRPs worldwide
- **4,600 patent** applications **pending**

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https://www.pmiscience.com/discover/news/pmi-s-latest-clinical-results-findings-add-to-extensive-evidence-package-on-risk-reduction

# 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)**

## Products Without Tobacco

### 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 RRPs depicted are subject to ongoing development; therefore, the descriptions are illustrative and do not necessarily represent the latest stages of product development.

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### PLATFORM 4

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

**E-VAPOR PRODUCTS**

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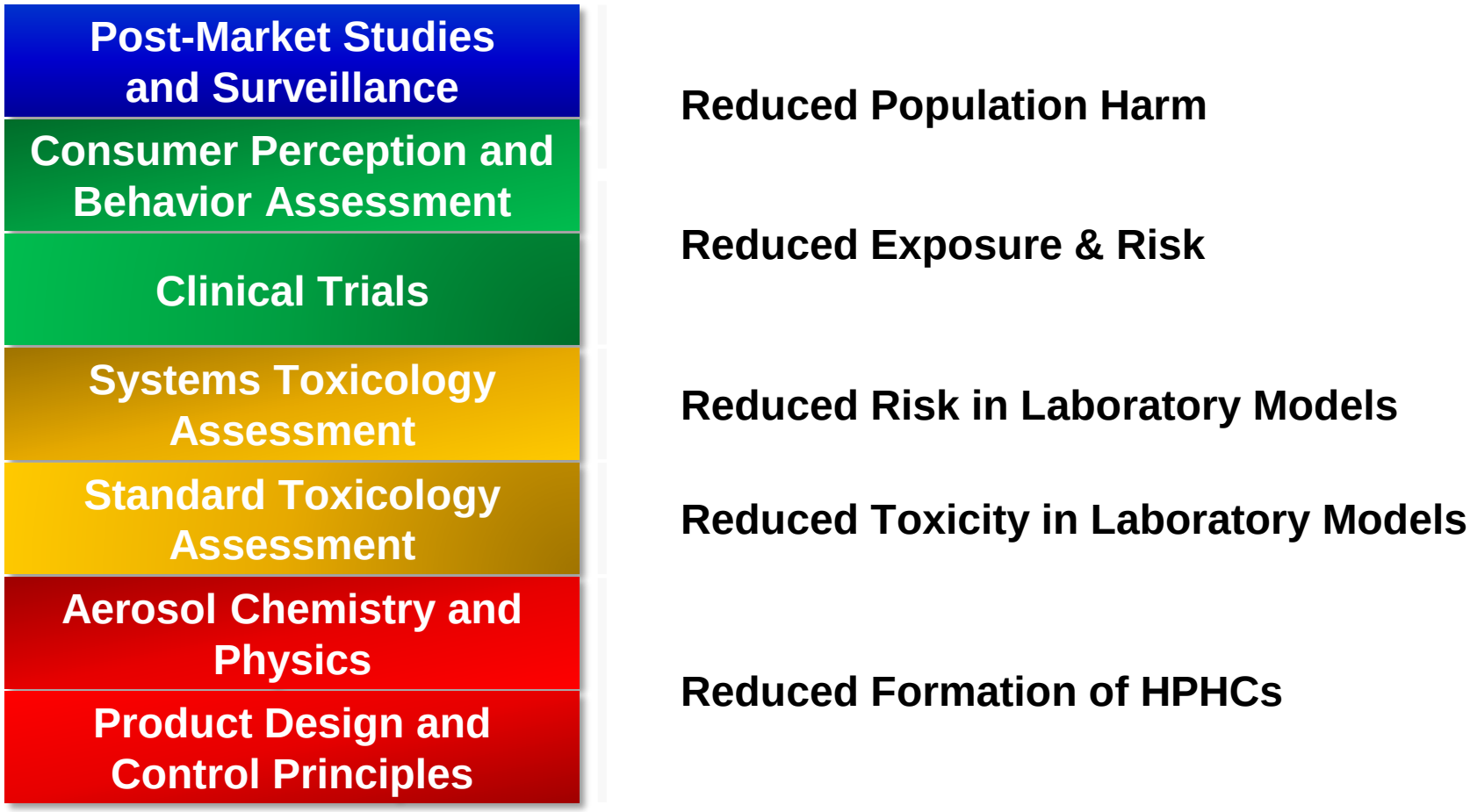
# Substantiating Reduced Risk: Totality of Scientific Evidence




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

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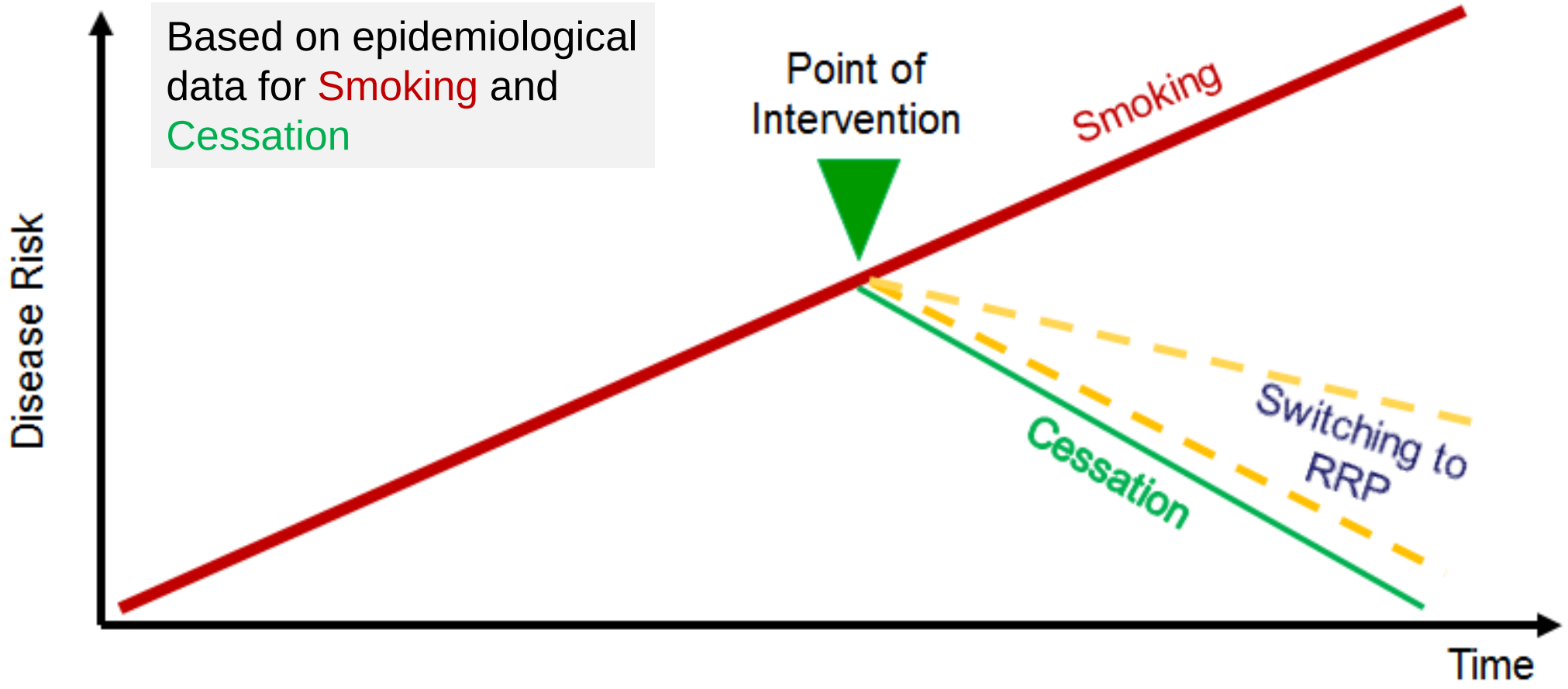
# Smoking Cessation: The "Gold Standard"

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




Source: IOM (Institute of Medicine), 2012, Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press.

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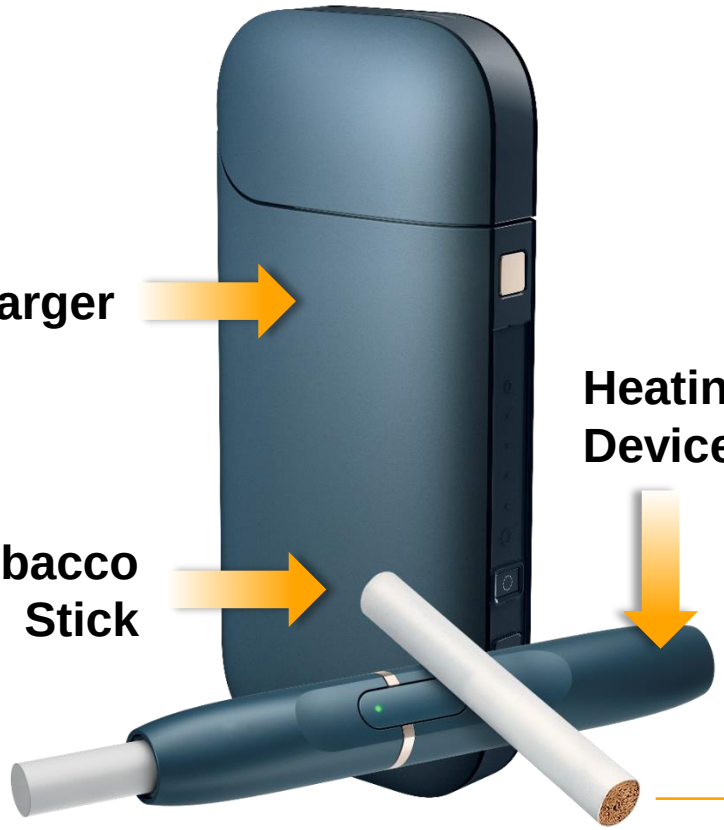
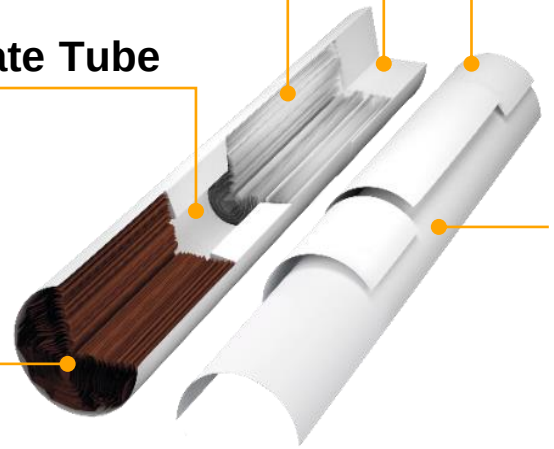
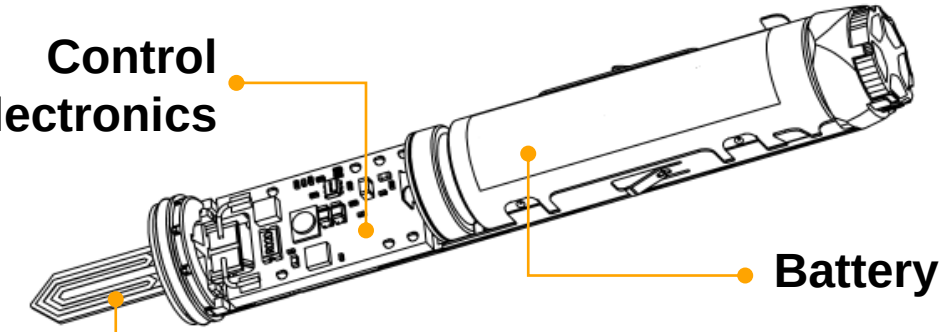
# Scientific Results for Tobacco Heating System

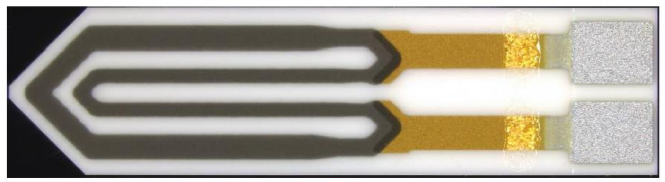
## (THS, brand name *IQOS*)

# Product Design: Tobacco Heating System (THS)

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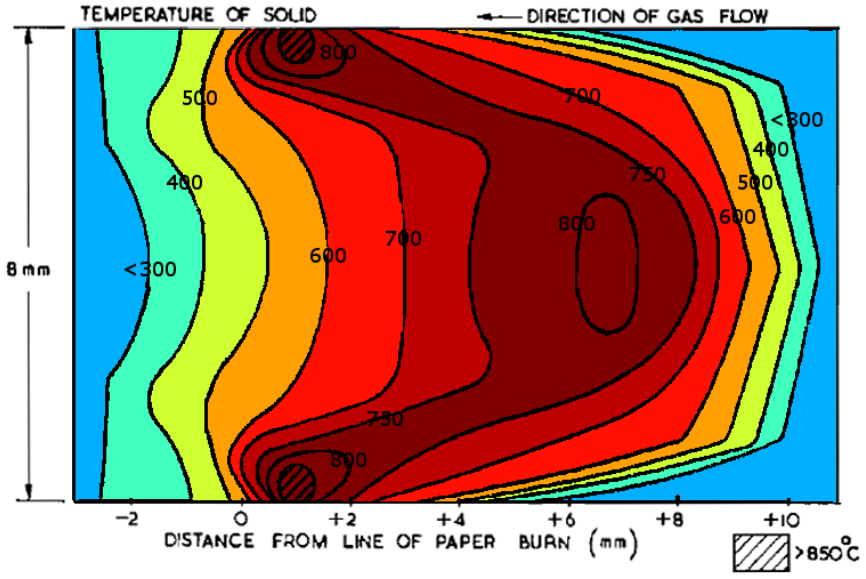
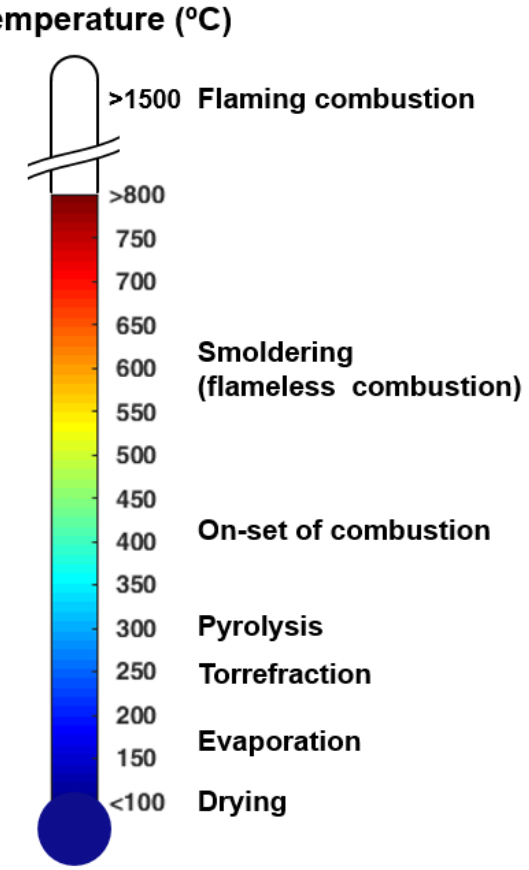
# Product Development: Absence of Combustion

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

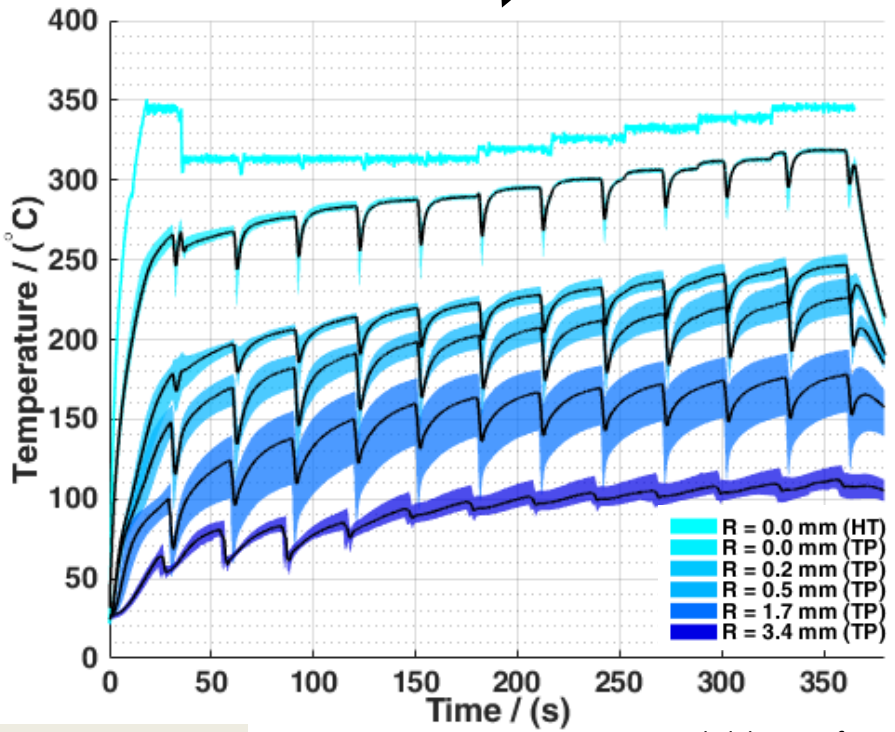
Cigarette




Tobacco stick in Holder

Heating section of Holder




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

- 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

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

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

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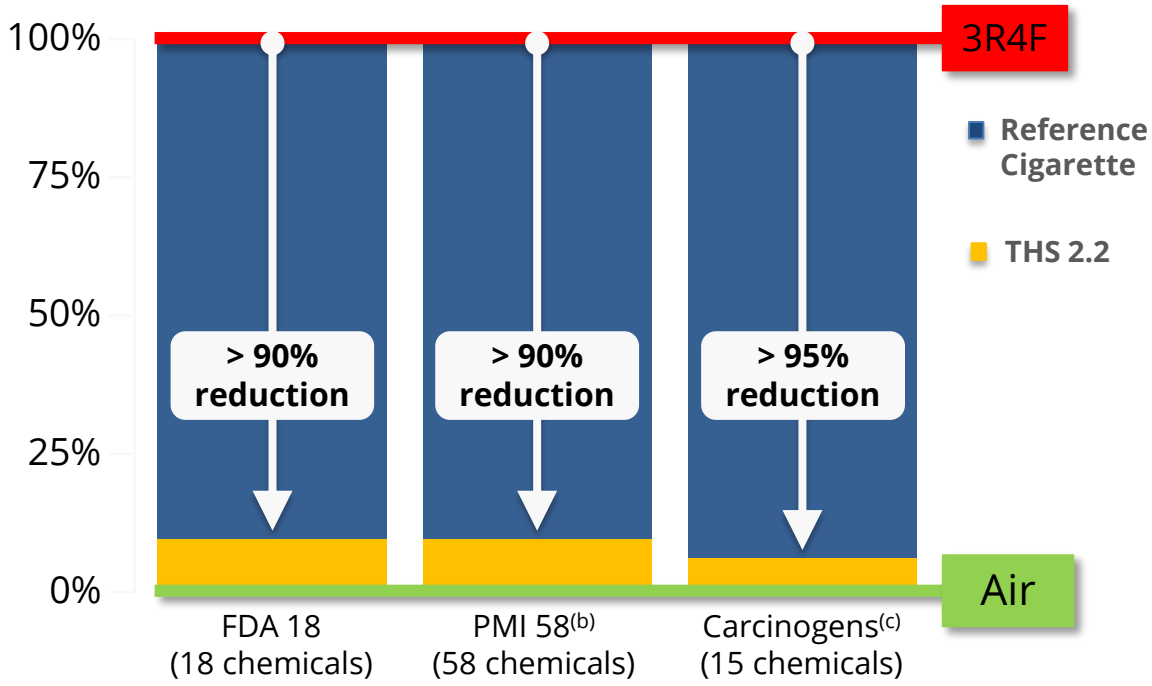
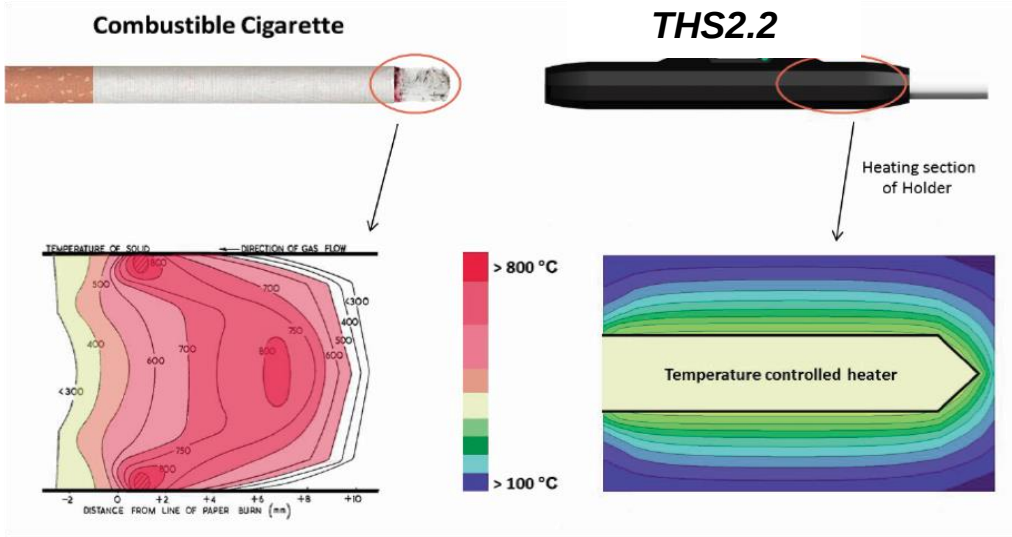
# Aerosol Chemistry: Reduced Formation

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

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

## Independent institutions confirm toxicant reduction in THS aerosol

BfR Bundesinstitut für Risikobewertung

- BfR (Federal Institut for Risk Assessment), Dec. 2017[1]

FDA U.S. FOOD & DRUG ADMINISTRATION

- FDA (U.S. Food and Drug Administration), Jan. 2018[2]

**"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."**

BfR Bundesinstitut für Risikobewertung

Pieper et al., Bundesgesundheitsblatt, OCT 2018 [3]

(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

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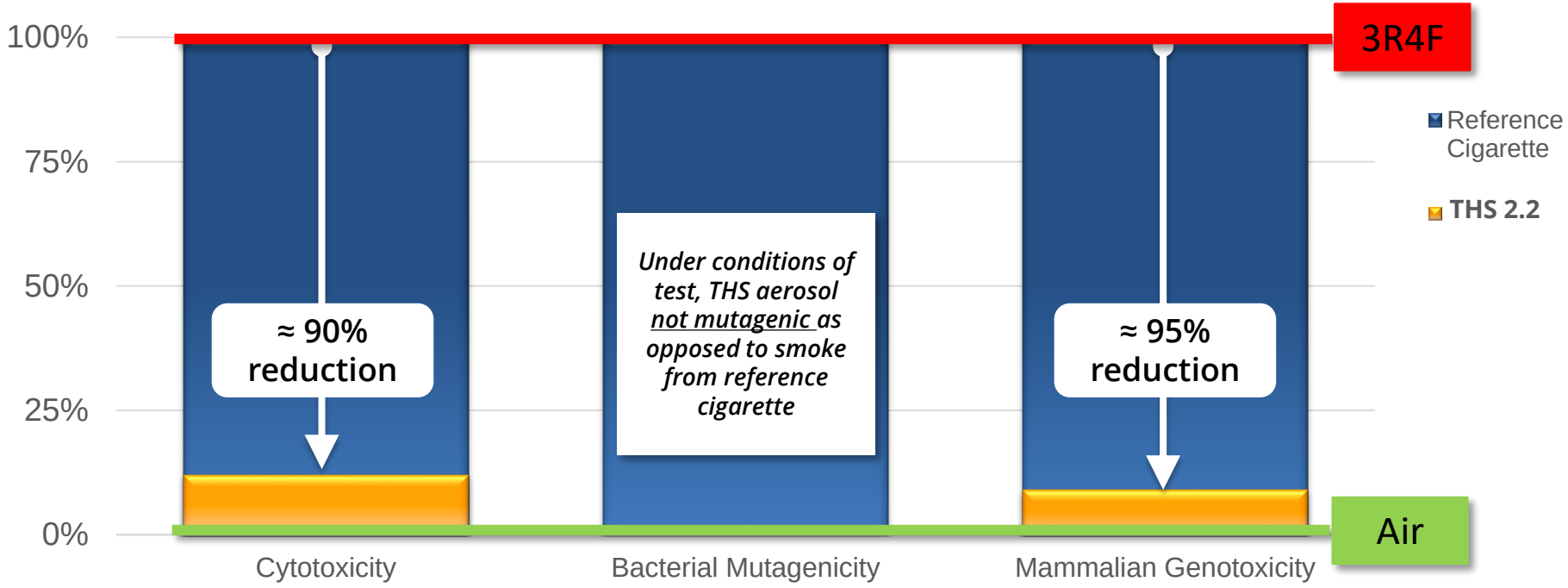
# Toxicological Assessment: Reduced Toxicity

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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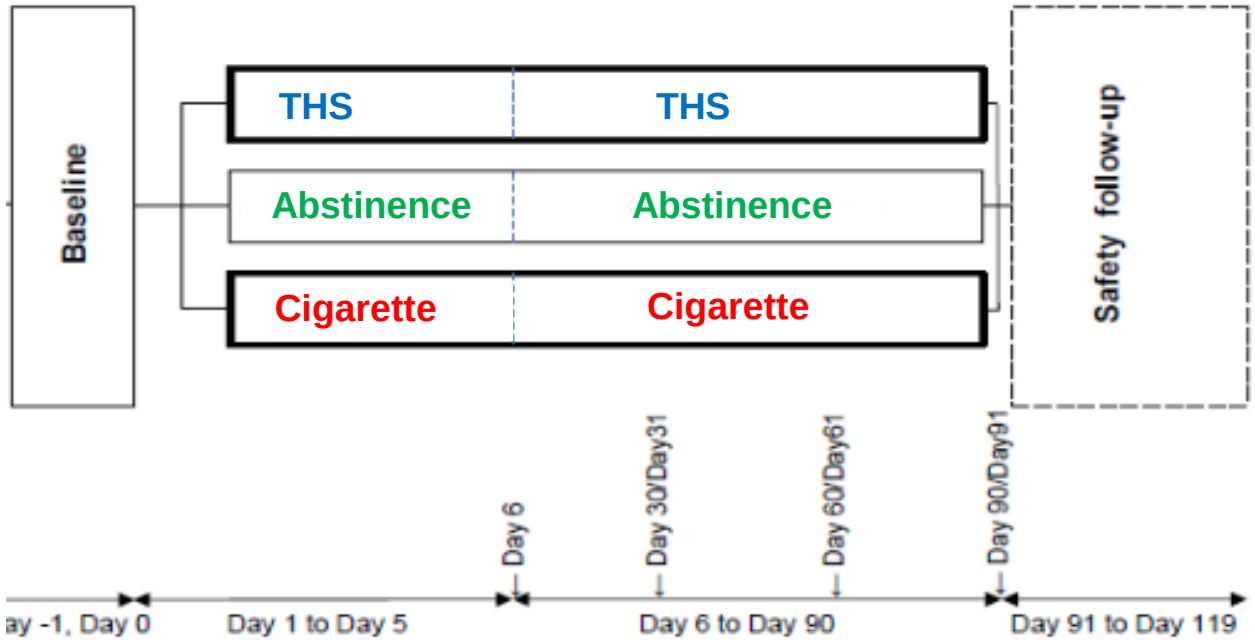
# Clinical Trials

## Reduced Exposure, Improved Biomarkers

## Study design:

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




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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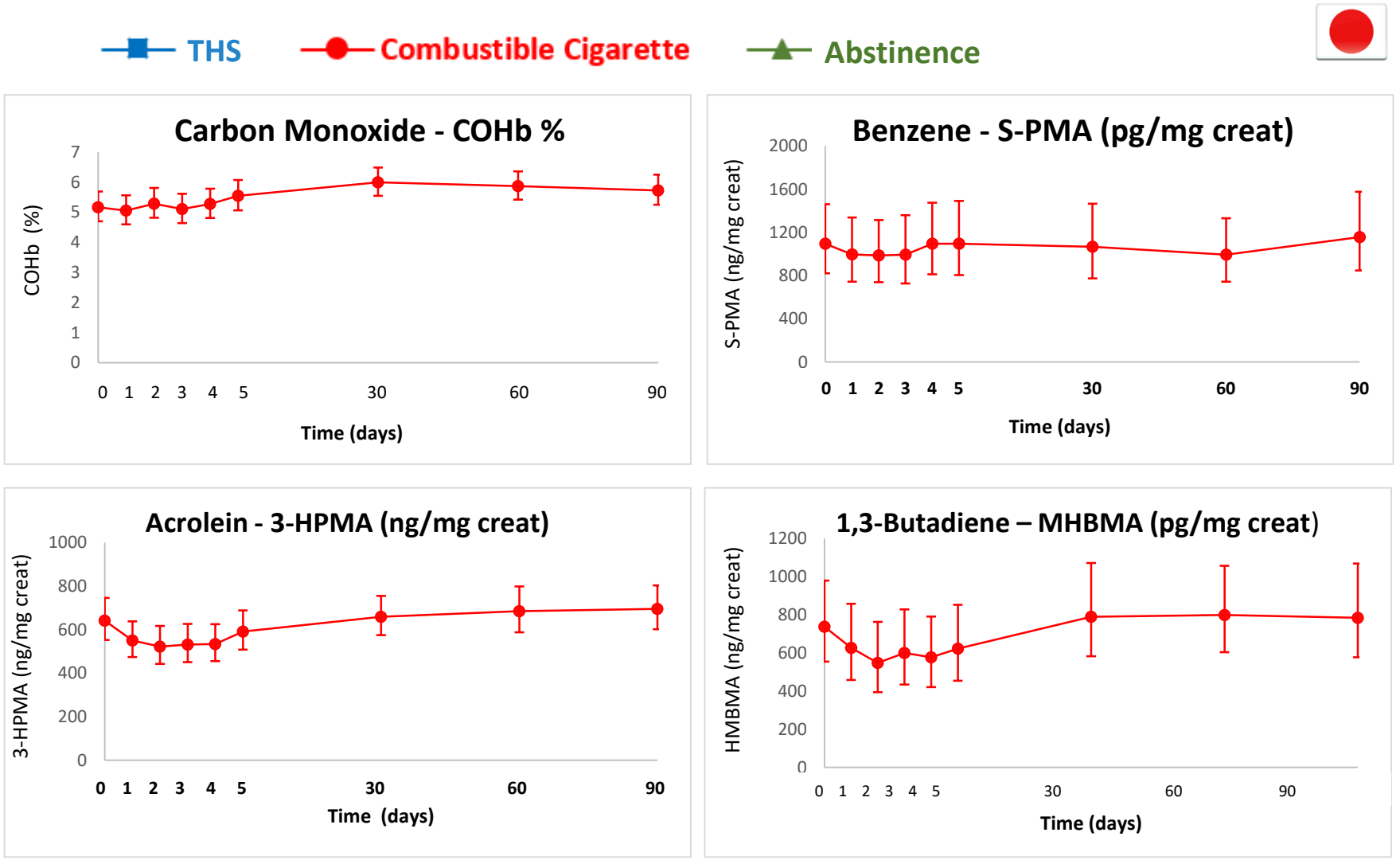
# Clinical Assessment: Reduced Exposure to Toxicants

**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)*




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
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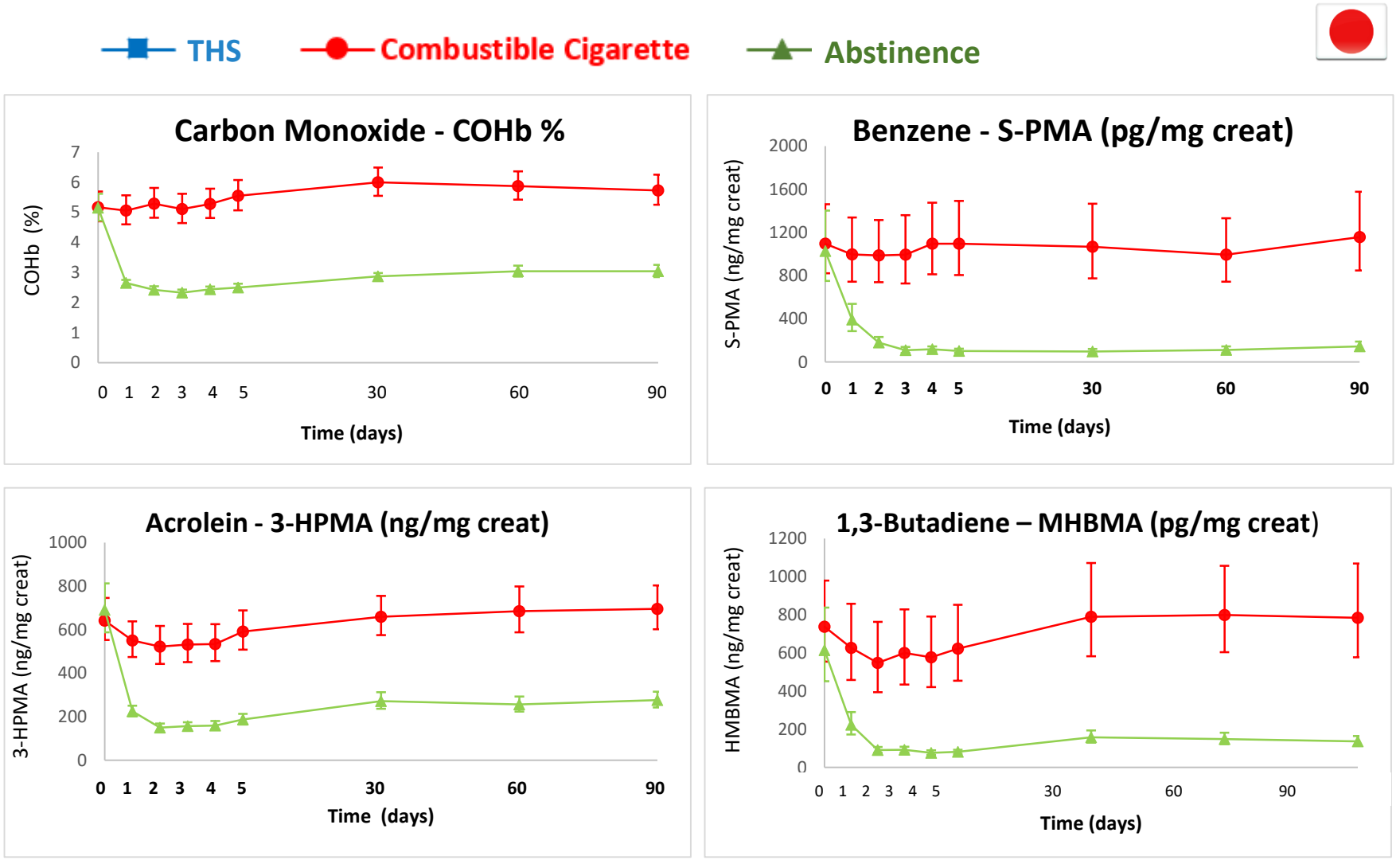


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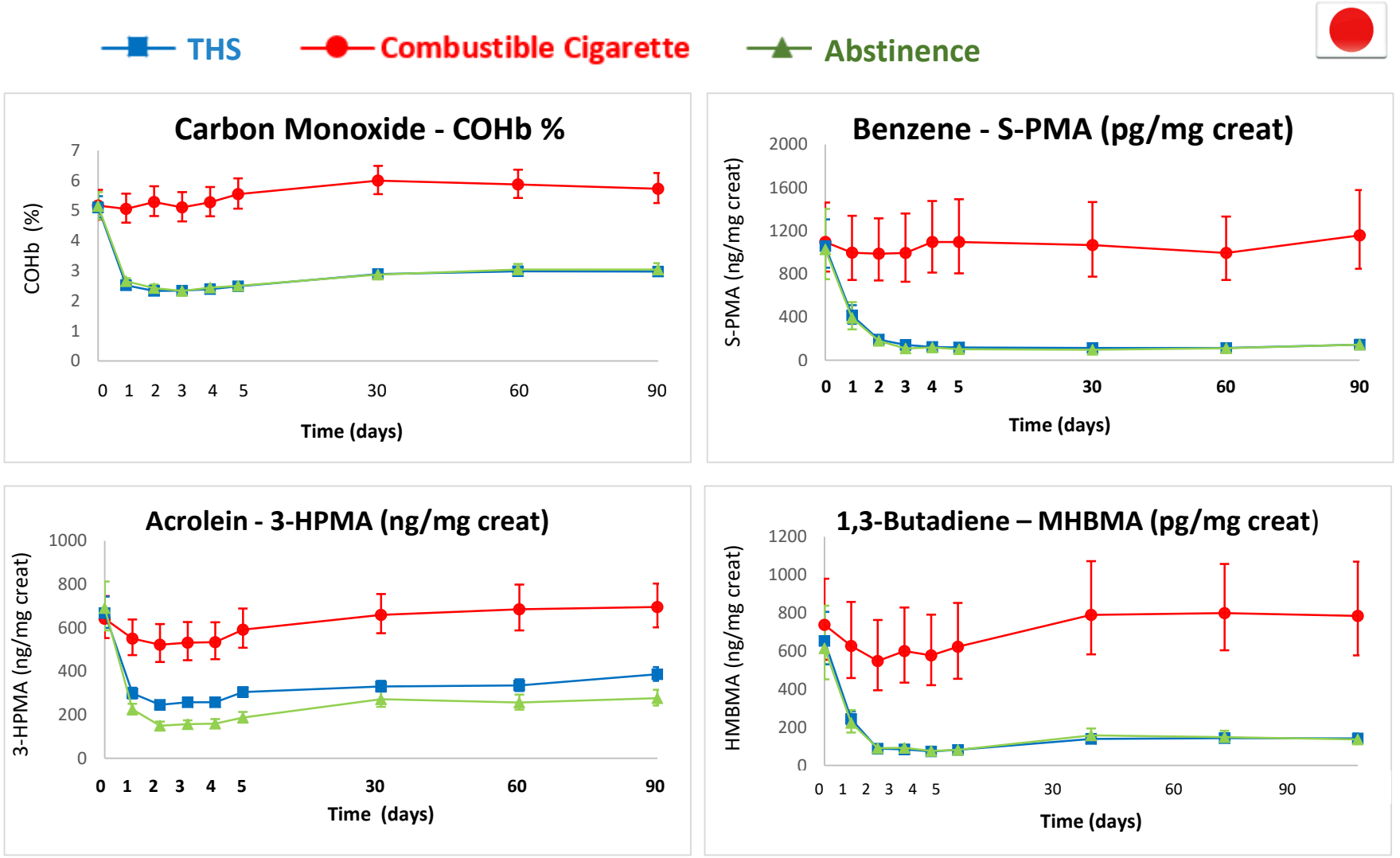


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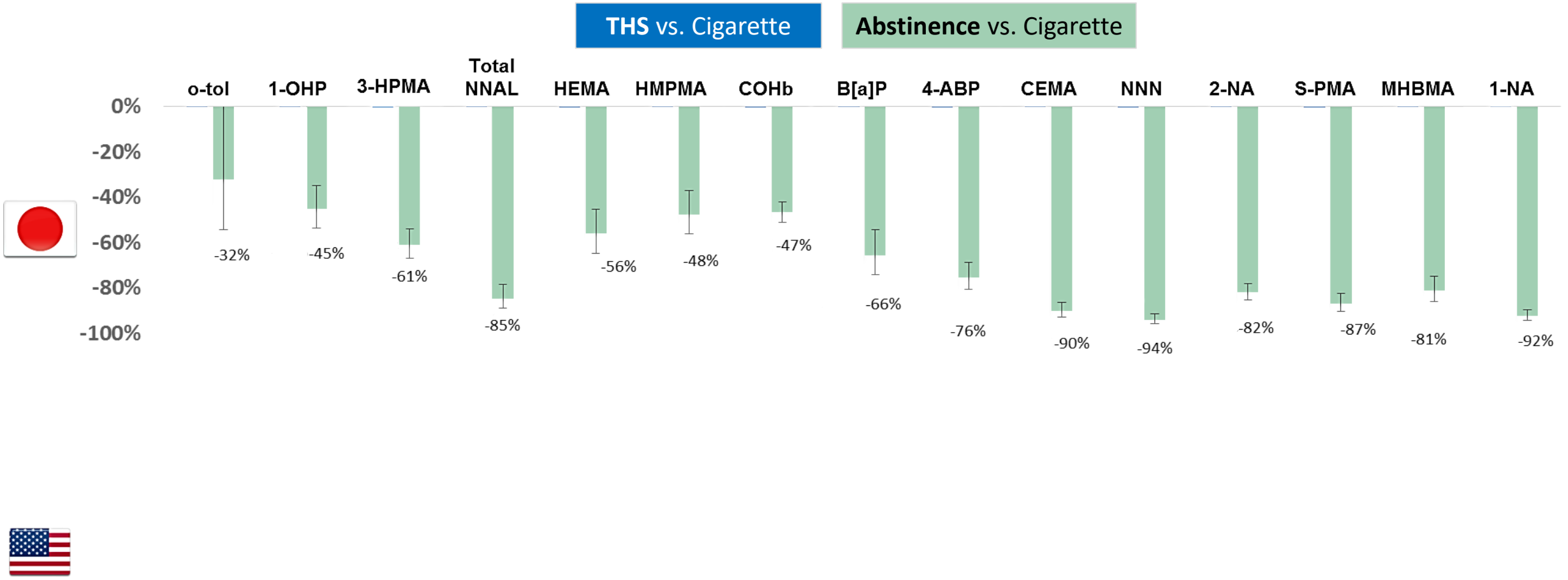
# Clinical Evidence for Toxicant Exposure Reduction (Japan and U.S.)

## % 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

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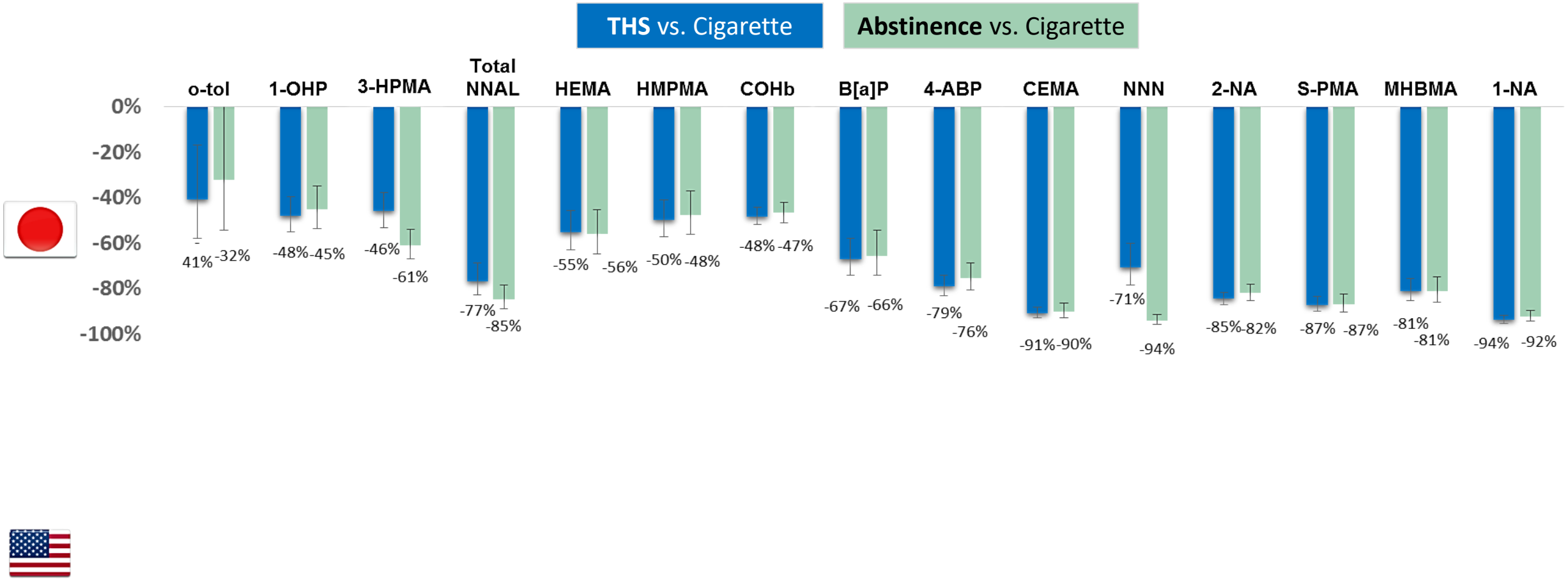


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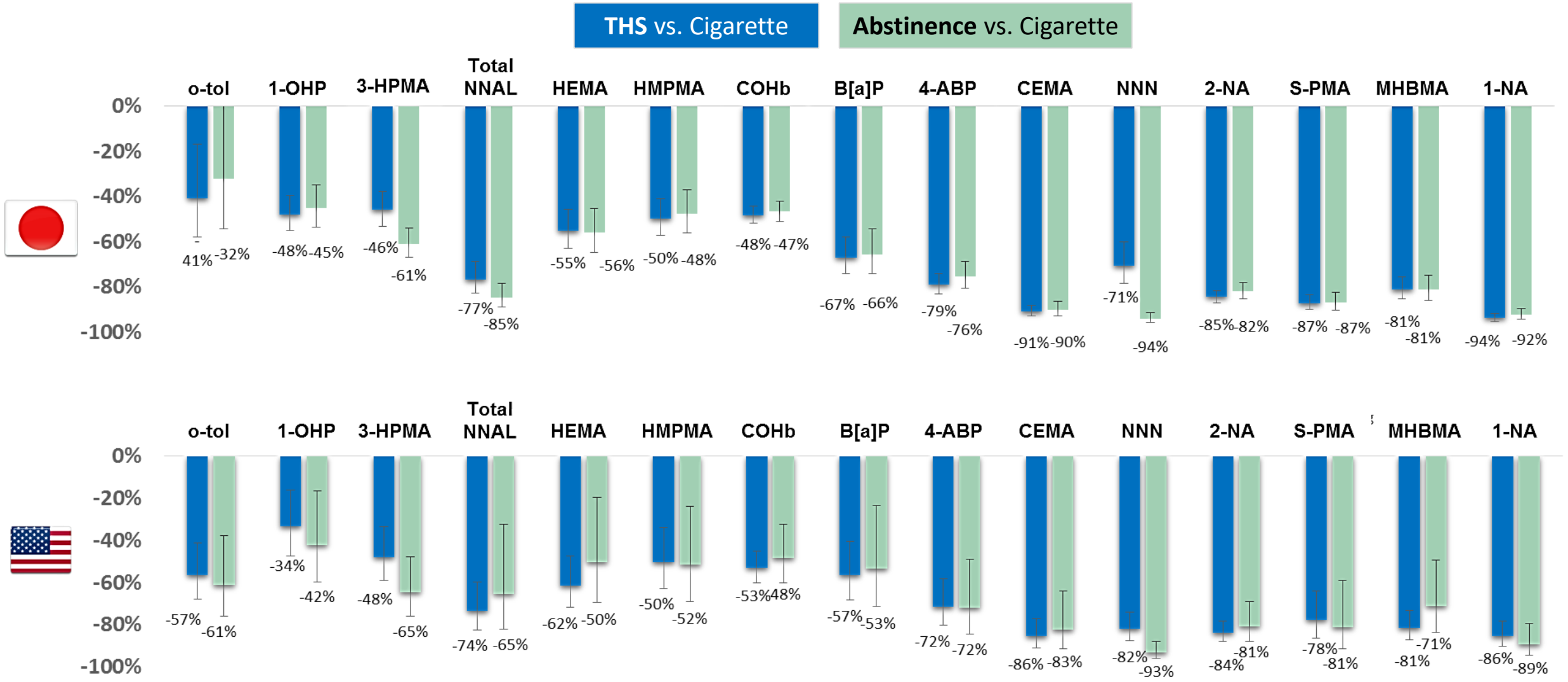


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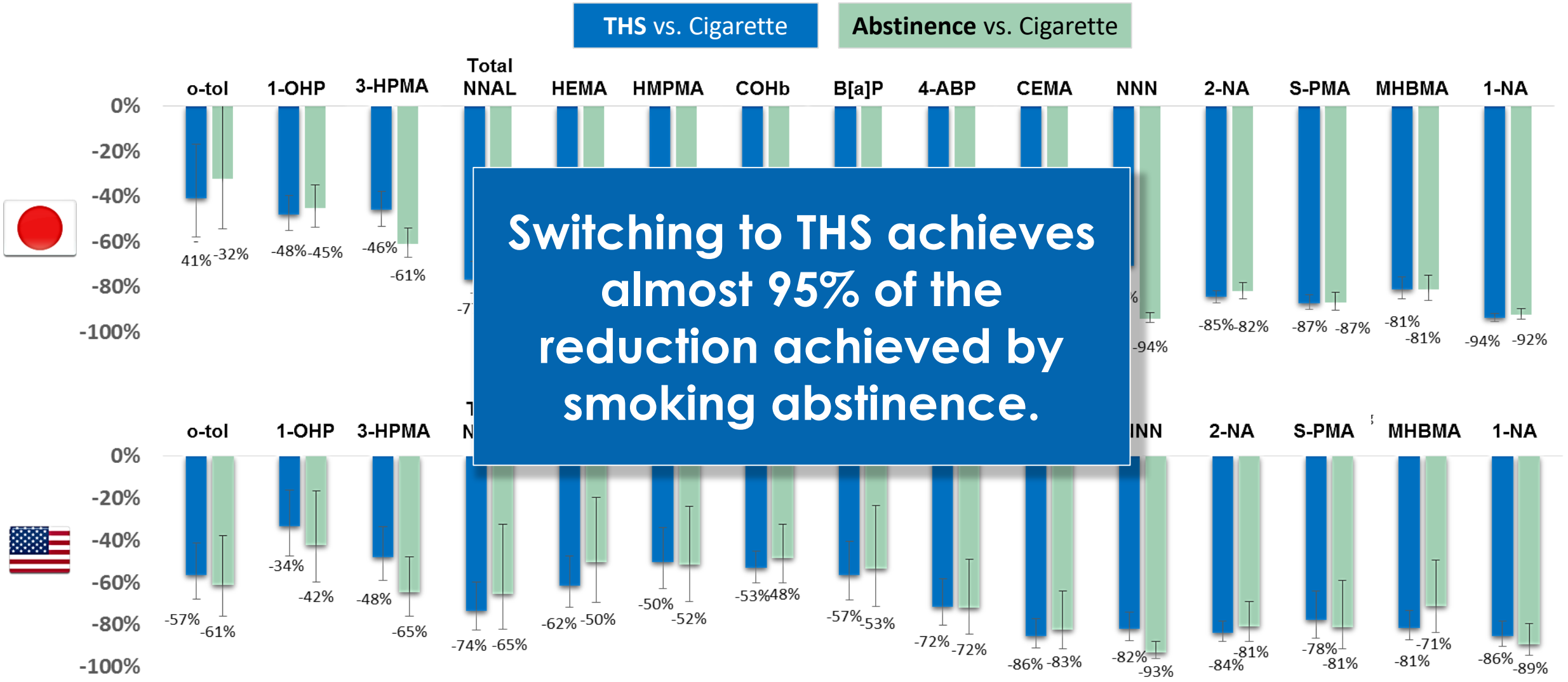
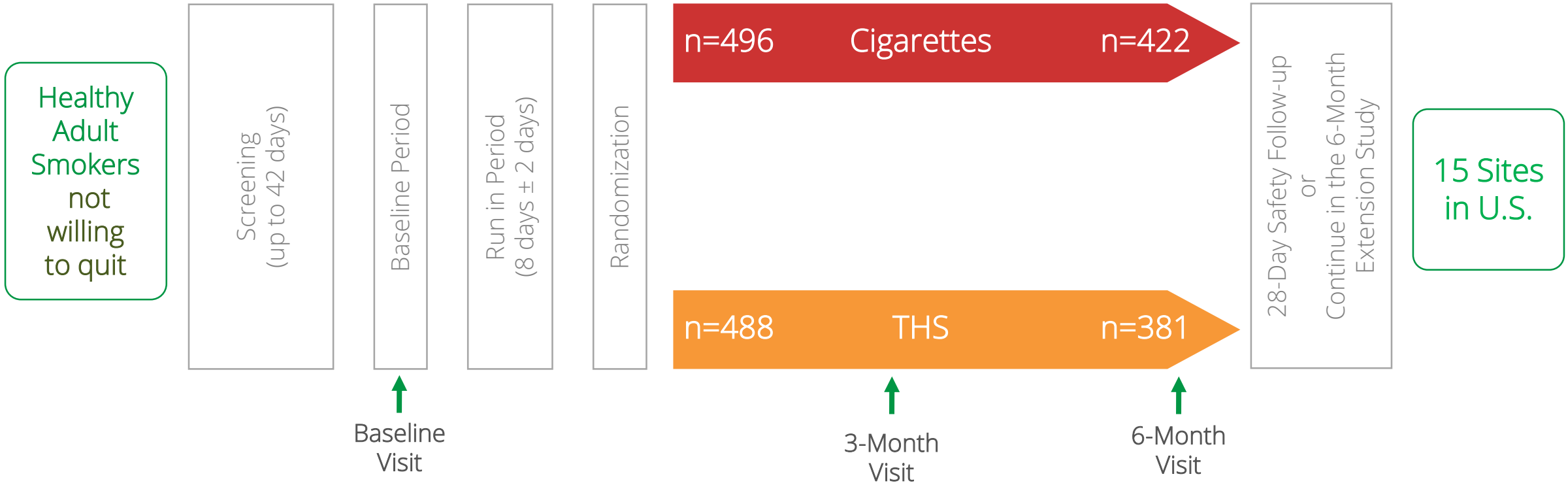



**Switching to THS achieves almost 95% of the reduction achieved by smoking abstinence.**

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

# 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)

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

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# 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 | $FEV_1$ %Pred ✓✓ |
| | Genotoxicity | Total NNAL ✓✓ |

✓✓ Statistically significantly different to continued smoking

✓ In the same direction of change as smoking cessation

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PMI Investor Day, 27 SEP 2018, Presentation by Mirek Zielinski, President, Science and Innovation
https://sites.media-server.com/mmc-custom-portals/Philip_Morris_Intl/2018-09-27_Investor_Day_2018/Downloads/Mirek_Zielinski_v1.pdf

# Summary – Reduced Risk Products (RRPs)

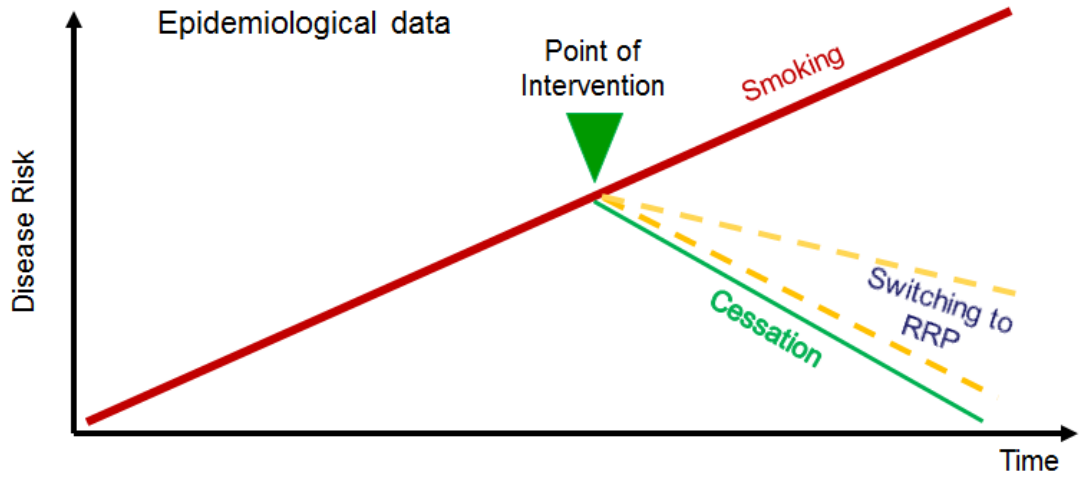
1

HARM REDUCTION = REDUCED-RISK PRODUCT X PRODUCT ACCEPTANCE AND USAGE

2

| Heated Tobacco Products | | Products Without Tobacco | |
|---|---|---|---|
| PLATFORM 1 | PLATFORM 2 | PLATFORM 3 | PLATFORM 4 |
| ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP) OR TOBACCO HEATING SYSTEM (THS) | CARBON-HEATED TOBACCO PRODUCT (CHTP) | NICOTINE DELIVERY SYSTEM | E-VAPOR PRODUCTS |

3




4

| | |
|---|---|
| Post-Market Studies and Surveillance | Reduced Population Harm |
| Consumer Perception and Behavior Assessment | |
| Clinical Trials | Reduced Exposure & Risk |
| Systems Toxicology Assessment | Reduced Risk in Laboratory Models |
| Standard Toxicology Assessment | Reduced Toxicity in Laboratory Models |
| Aerosol Chemistry and Physics | Reduced Formation of HPHCs |
| Product Design and Control Principles | |

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

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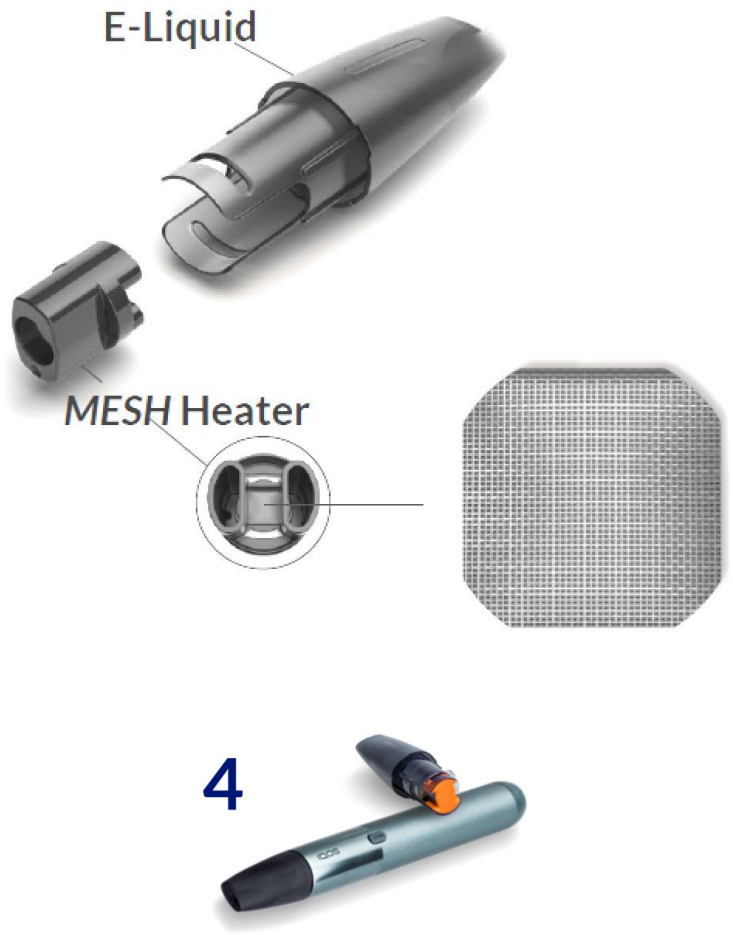
# E-cigarettes

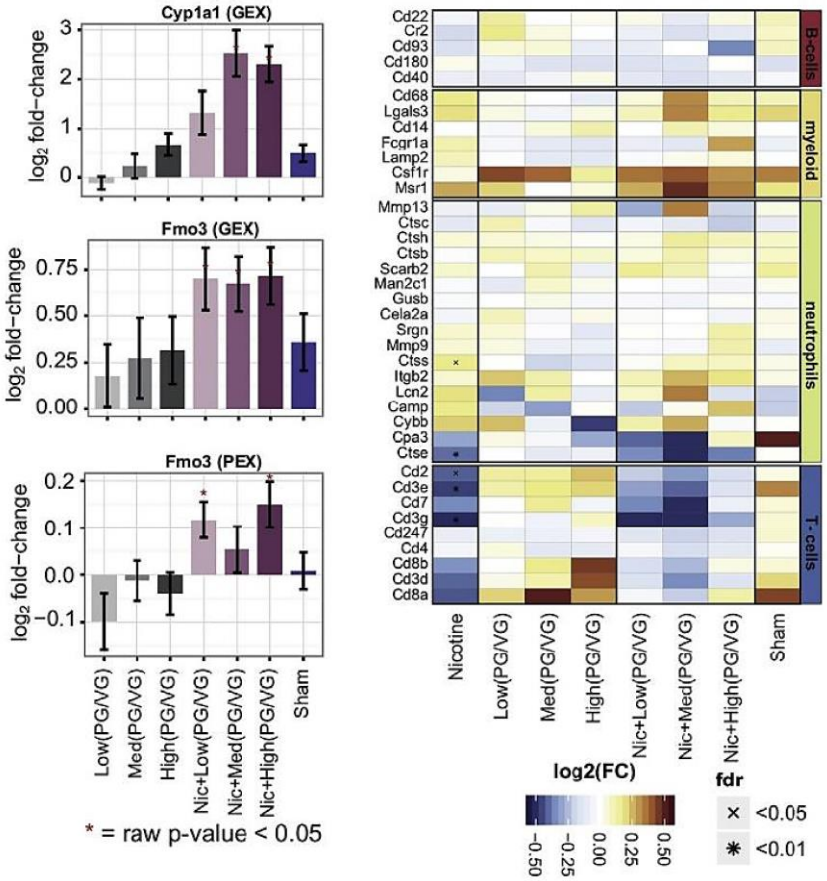
## Selected recent literature

# PMI's E-cigarette Platform: Role of nicotine vs. PG/VG

## Systems toxicology
### (*in vivo*)

- Expected biological effects of nicotine exposure
  - E.g. up-regulation in some xenobiotic metabolism enzymes (Cyp1a1 and Fmo3), down-regulation of T-cell-related transcripts[7] and a slight shift toward lipid oxidation, gluconeogenesis, ketone body formation and cholesterol biosynthesis due to the sympatomimetic effects of nicotine.
- PG/VG solutions had no different effect than exposure to air.
- Thus, in the absence of flavoring agents, the observable effects are mainly due to exposure to nicotine.
- The magnitude of these effects is in line with what is reported in the literature.




Phillips B et al. (2017). Toxicity of the main electronic cigarette components, propylene glycol, glycerin, and nicotine, in Sprague-Dawley rats in a 90 day OECD inhalation study complemented by molecular endpoints. *Food Chem Toxicol* 109: 315332. (PMID: 28882640)- doi:10.1016/j.fct.2017.09.001
Product pictures taken from PMI Investor Day, 27 SEP 2018, Presentation by Mirek Zielinski, President, Science and Innovation

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## Risk perception in Germany

- „Central result: **54 %** of respondents **perceive e-cigarettes as equally as harmful or even more harmful than tobacco cigarettes**. [1]
- In a survey in **2016** this percentage was at **56 %** and thus **almost unchanged**.“ [1]

MEDIZIN

aerzteblatt.de

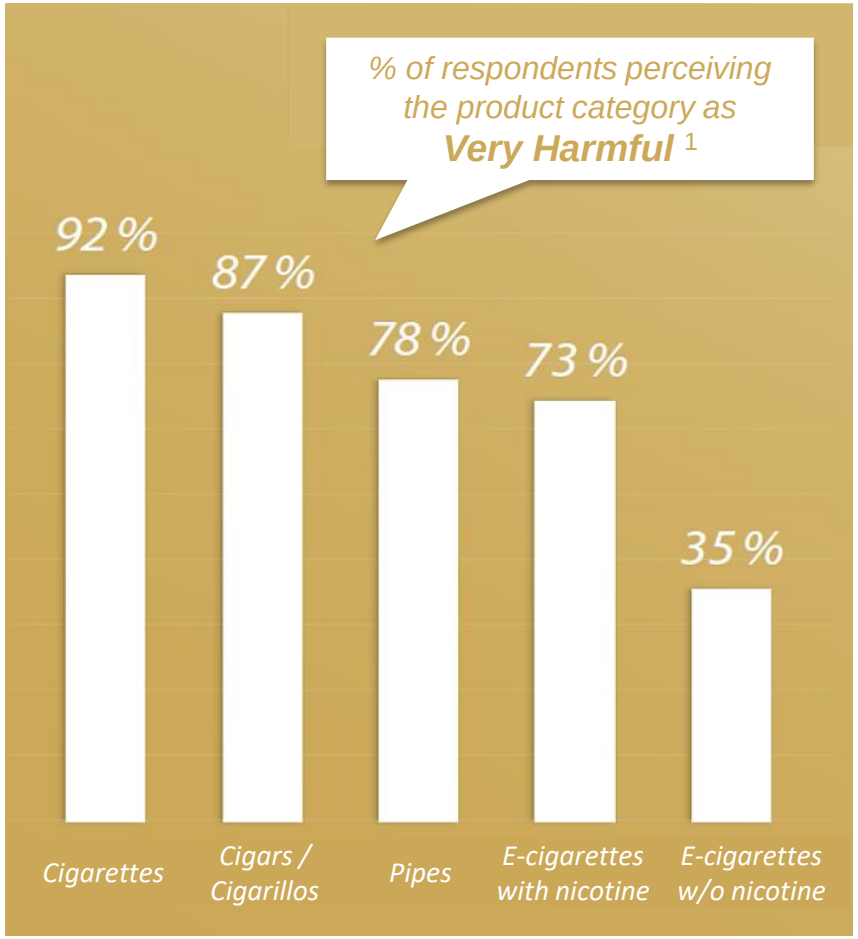
ORIGINALARBEIT

**Nutzung elektronischer Zigaretten**

Eine bevölkerungsrepräsentative Querschnittsbefragung unter 4 002 Personen aus dem Jahr 2016

Martin Eichler, Maria Blettner, Susanne Singer

„More than **60 %** of Germans perceive **e-cigarettes** as **equally harmful or more harmful** than **tobacco cigarettes**.“ [2]




(1) Vdeh: E-Zigaretten – die unterschätzte Chance. 31 JAN 2018 www.vd-eh.de/e-zigarettenumfrage2018/
http://www.vd-eh.de/wp-content/uploads/2018/02/vdeh_e-zigaretten_die_unterschaetzte_chance.pdf

(2) Eichler M, Blettner M, Singer S: The use of e-cigarettes—a population-based cross-sectional survey of 4002 individuals in 2016. Dtsch Arztebl Int 2016; 113: 847–54.
DOI: 10.3238/arztebl.2016.0847; https://www.aerzteblatt.de/pdf/113/50/m847.pdf?ts=08.12.2016+10%3A41%3A09

# Carbonyl Emissions from HnB vs. E-cigarette vs. Tobacco Cigarette

## Substantial reduction of carbonyls

- Conclusions:
  - *"The **IQOS** heated tobacco product emits **substantially lower levels of carbonyls than a commercial tobacco cigarette** (Marlboro Red) but **higher** levels **than** a Nautilus Mini **e-cigarette**."*
- Results for exposure reduction vs. smoking:
  - HnB: **85%–95%**, e-cigarette: **97%–>99%**

Based on comparison of 20 heated tobacco sticks vs. 20 tobacco cigarettes vs. 5 g e-cigarette liquid (HCI puffing regimen)

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.14365

**Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette**

**Konstantinos E. Farsalinos[1,2,3], Nikoletta Yannovits[4], Theoni Sarri[4], Vassilis Voudris[1], Konstantinos Poulas[2] & Scott J. Leischow[5]**

Department of Cardiology, Onassis Cardiac Surgery Center, Kallithea, Greece,[1] Department of Pharmacy, University of Patras, Rio-Patras, Greece,[2] National School of Public Health, Athens, Greece,[3] Skylab-Med Laboratories of Applied Industrial Research and Analysis SA, Marousi, Greece[4] and Arizona College of Health Solutions, Arizona State University, Phoenix, AZ, USA[5]

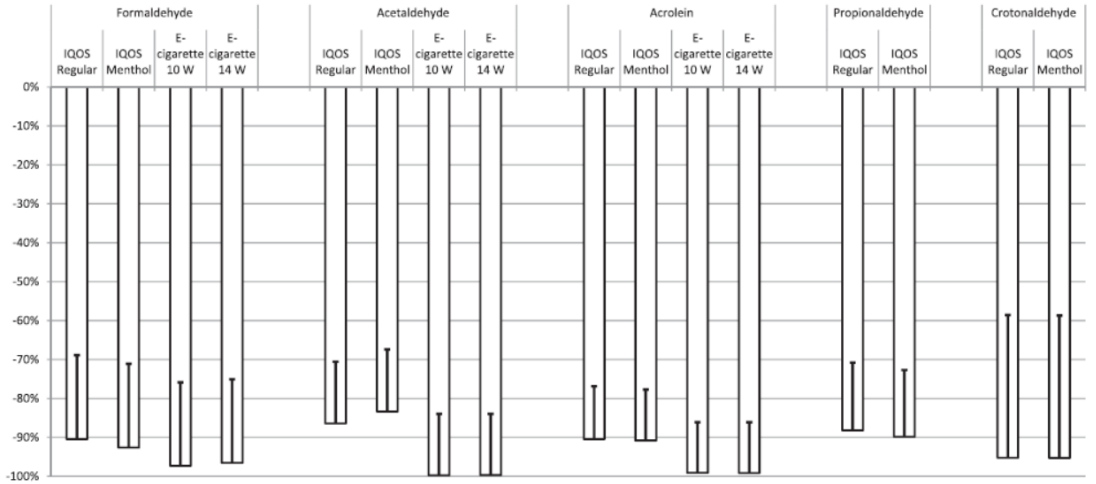



**Figure 1** Percentage reduction in exposure to carbonyls from using 20 IQOS (heated tobacco product); sticks and five g e-cigarette liquid compared to 20 tobacco cigarettes at Health Canada Intense puffing regime (PR1, 2-s puff duration, 50-ml puff volume, 30-s interpuff interval). Bars represent mean difference, lines represent lower 95% confidence interval of the difference

Farsalinos KE et a., Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette, *Addiction* 19 June 2018.
https://doi.org/10.1111/add.14365

# COPD: Potential Positive Long-Term Effect from Switch to E-cigarettes

## E-cigarette use may ameliorate harm from smoking in COPD patients

- Conclusions:
  - *"**EC use may ameliorate objective and subjective COPD outcomes** and that the benefits gained may persist **long-term**."*
  - *"**EC use may reverse some of the harm** resulting from tobacco smoking in COPD patients."*

- Results (44 patients, vs. baseline):
  - EC users: marked decline in conventional cigarette use
  - No change in lung function
  - Significant improvements in COPD exacerbation rates, CAT* scores, and 6MWD** were observed consistently in the EC user group over the 3-year period (p□0.01).
  - Similar findings in COPD EC users who also smoked cigarettes ("dual users")

*CAT: COPD Assessment Tool, **6MWD: 6-minute walk distance

International Journal of COPD

Dovepress
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ORIGINAL RESEARCH

Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up

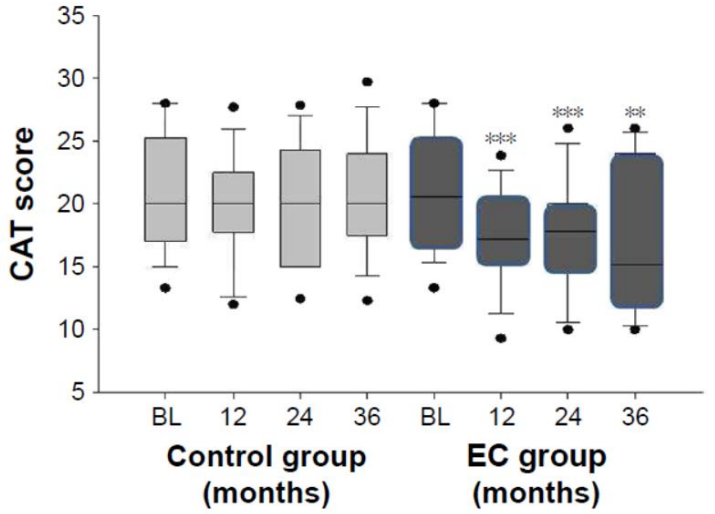


**Figure 4** Changes in the CAT scores from baseline, at follow-up visit 1 (12±1.5 months), visit 2 (24±2.5 months), and visit 3 (36±3 months) separately for COPD EC users (dark gray boxes) and COPD controls (light gray boxes). The boxes represent the 25th to 75th percentiles; the lines in the boxes indicate the median, and error bars are 5th and 95th percentiles. The ** and *** indicate the within-group *p*-value of <0.01 and <0.001, respectively, compared to baseline.
**Abbreviations:** COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; BL, baseline; CAT, COPD Assessment Tool.

Polosa R et al., Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *International Journal of COPD* 2018:13 2533–2542 (28. AUG 2018)
https://www.prnewswire.com/news-releases/electronic-cigarette-use-may-reverse-the-harm-resulting-from-tobacco-smoking-in-copd-patients-even-in-the-long-term-300702914.html

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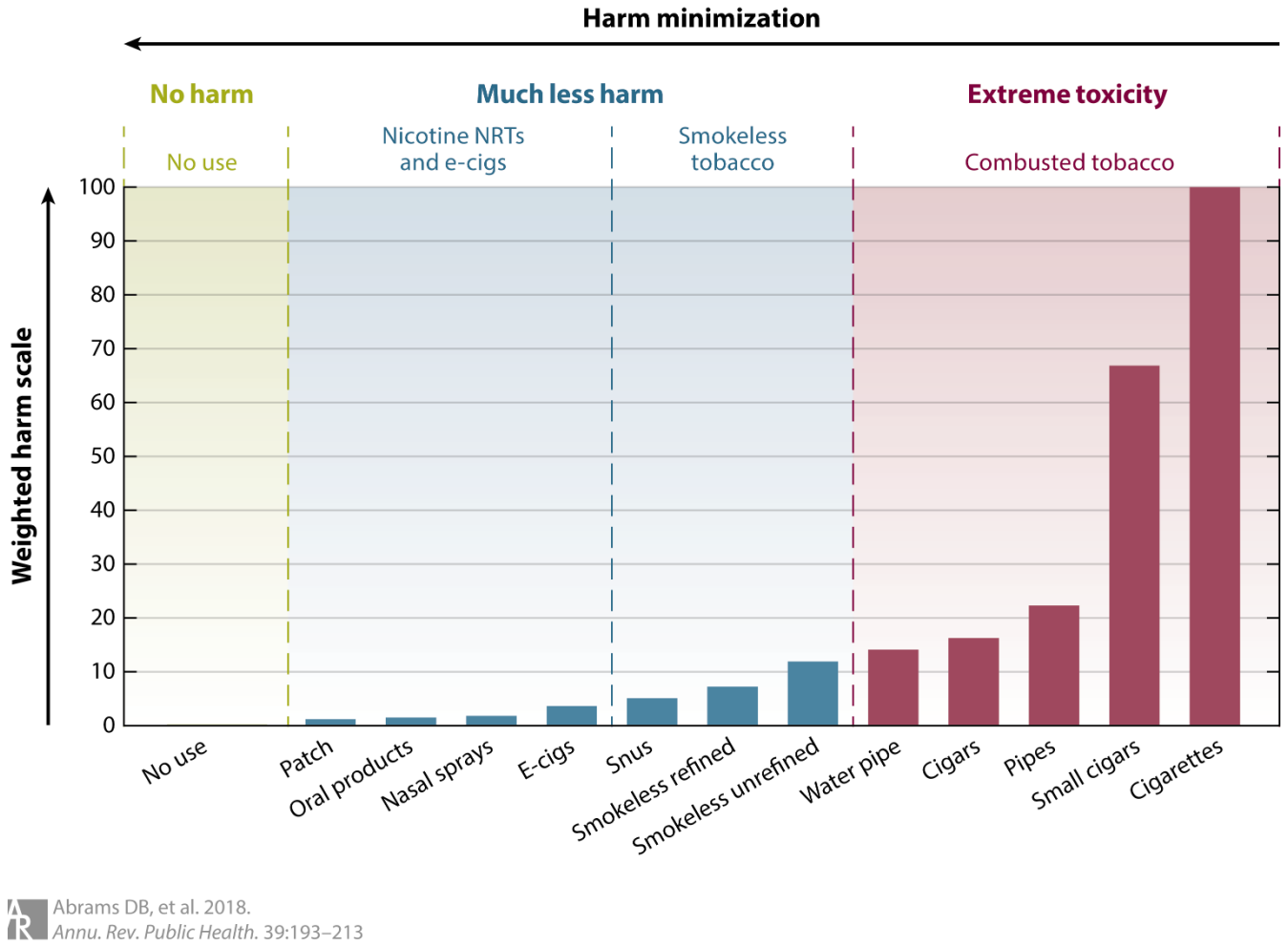
# Relative Harm (Reduction) Potential

## Guessing, Modeling, Measuring

## Relative risk potential – open questions

- Correct placement on the continuum?
- Where to place new product categories?
- Scientific assessment standards to place (new) products?

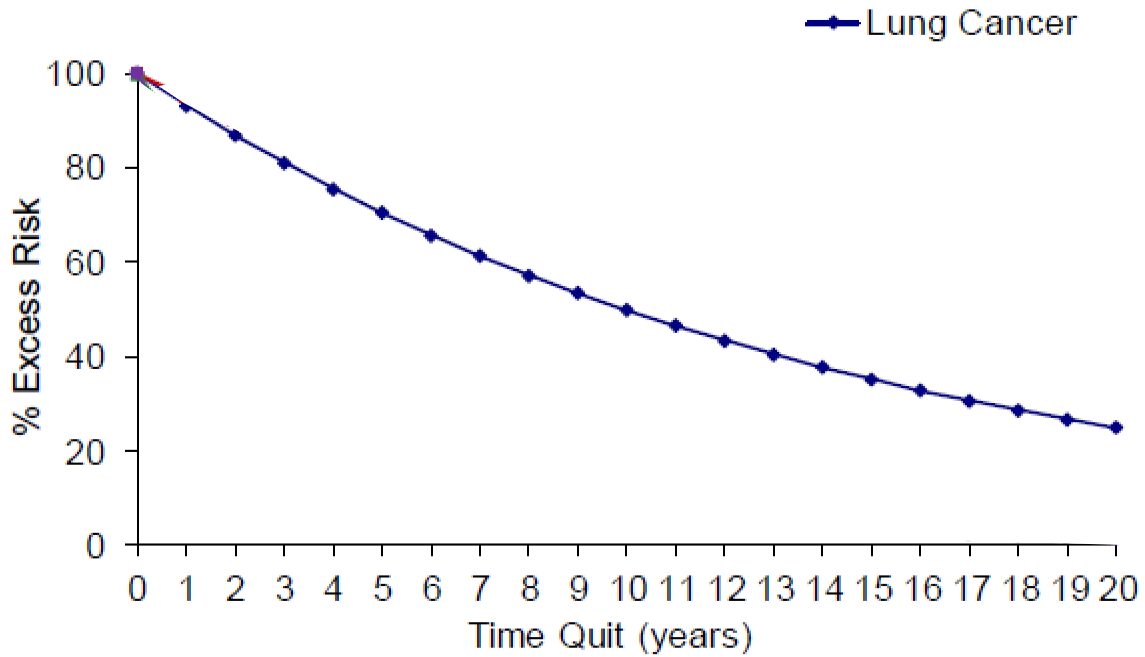



Graph from Abrams DB et al., Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives, ***Annual Review of Public Health,*** Vol. 39:193-213. First published as a Review in Advance on January 11, 2018 https://doi.org/10.1146/annurev-publhealth-040617-013849, https://www.annualreviews.org/doi/full/10.1146/annurev-publhealth-040617-013849

# 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.

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# 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.**

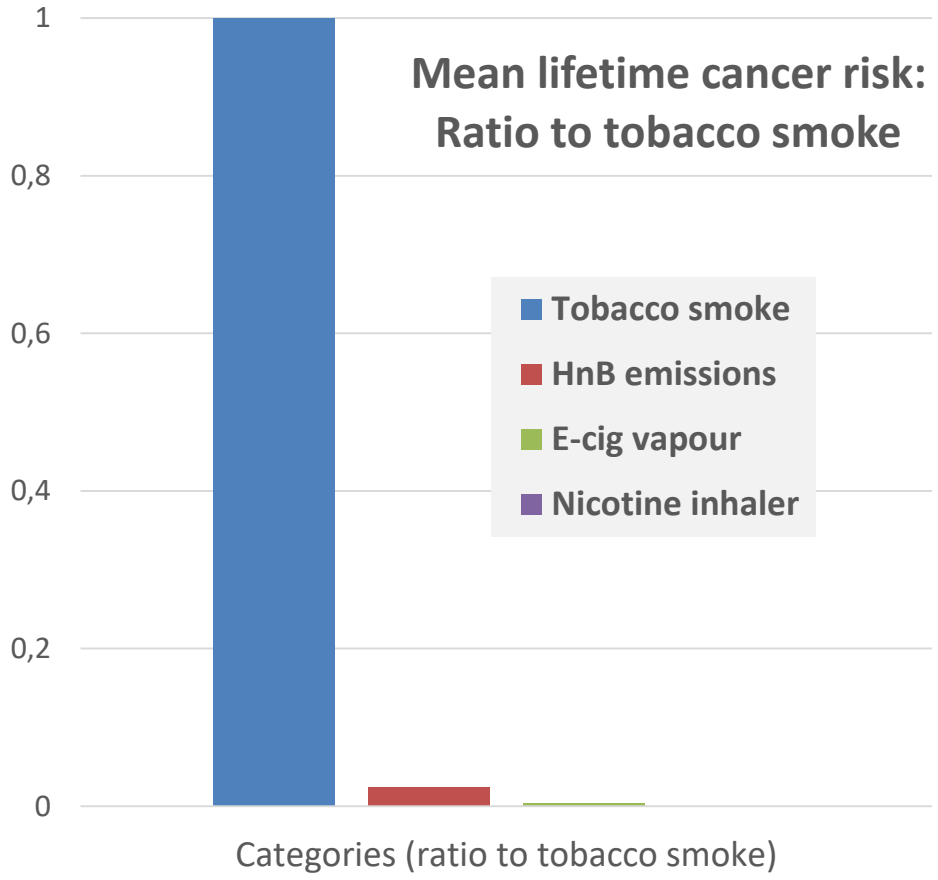
Stephens WE.

**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

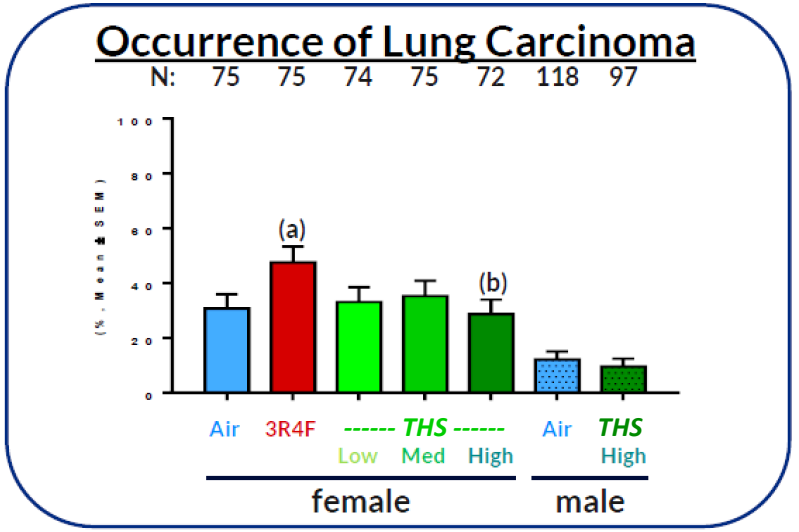


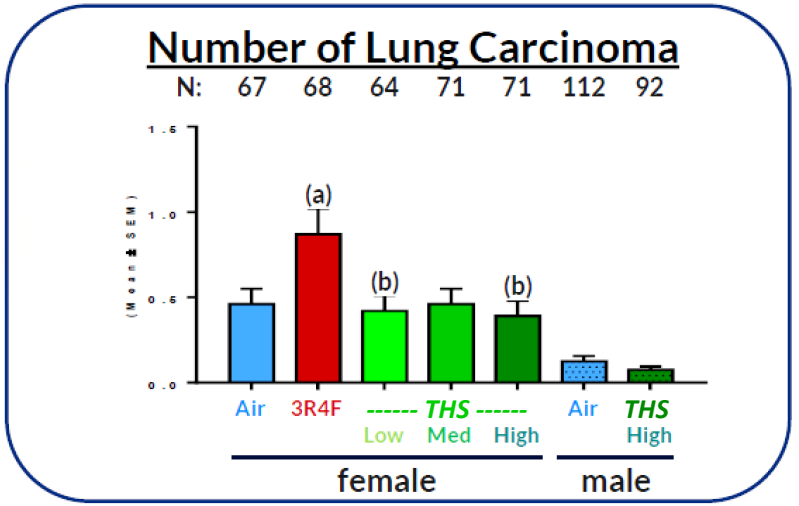

Stephens WE., Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke, Tobacco Control 2017;**0**:1–8. doi:10.1136/tobaccocontrol-2017-053808
http://tobaccocontrol.bmj.com/content/early/2017/08/04/tobaccocontrol-2017-053808

# 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)

PMI Investor Day, 27 SEP 2018, Presentation by Mirek Zielinski, President, Science and Innovation
https://sites.media-server.com/mmc-custom-portals/Philip_Morris_Intl/2018-09-27_Investor_Day_2018/Downloads/Mirek_Zielinski_v1.pdf

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# Debate on Regulation

## Walking the Talk

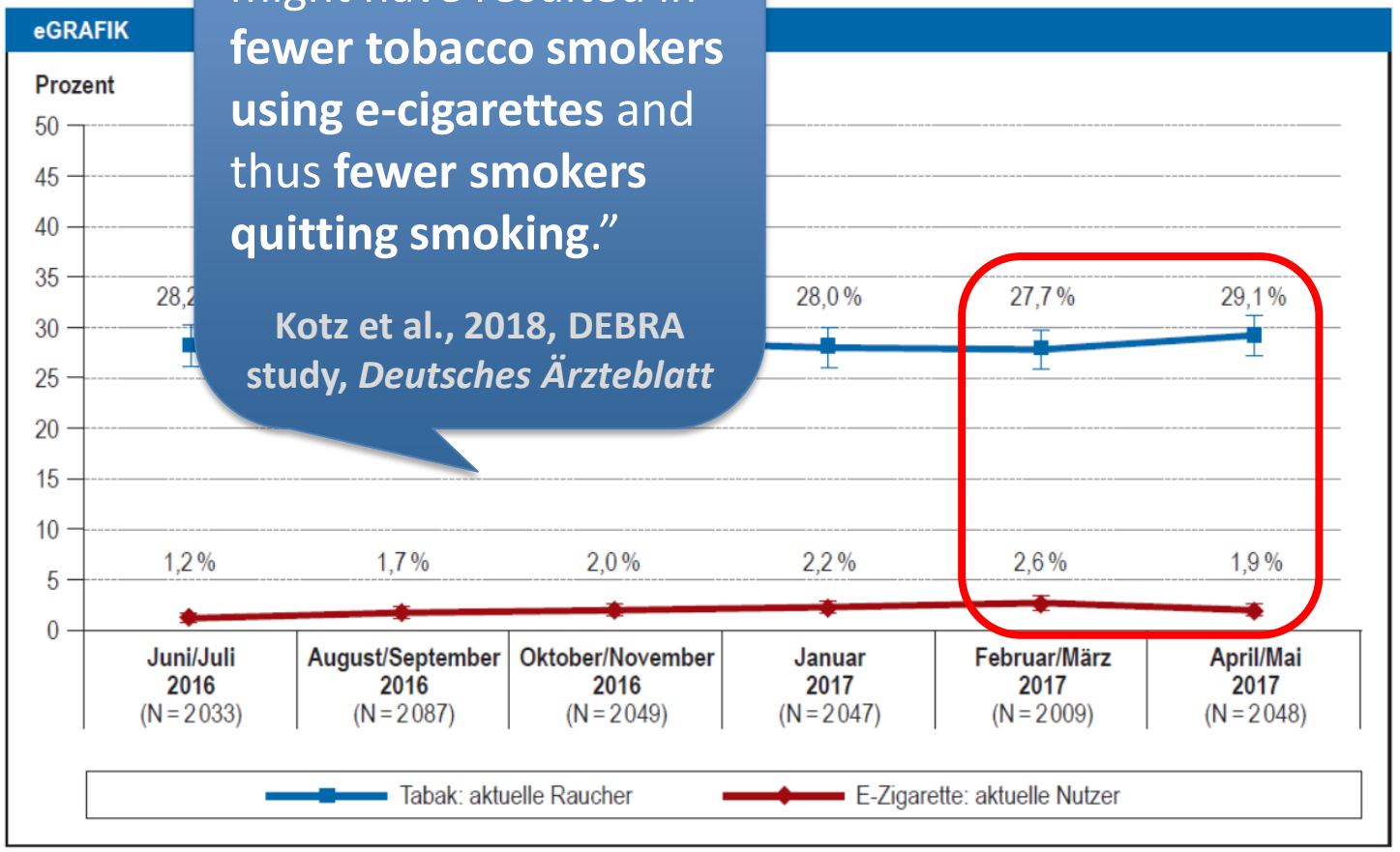
## Smoking prevalence, cessation, and e-cigarette use impacted by REGULATION?

- **Cigarettes**: relatively strong increase between FEB/MAR 2017 and APR/MAY 2017
- **E-cigarettes**: simultaneous strong decrease
- Possible correlation:
  - MAY 2017: new **EU tobacco product directive** comes into effect, including **stricter e-cigarette regulation**

DEBRA Deutsche Befragung zum Rauchverhalten

"The **new regulation** might have resulted in **fewer tobacco smokers using e-cigarettes** and thus **fewer smokers quitting smoking**."

**Kotz et al., 2018, DEBRA study, *Deutsches Ärzteblatt***




**Gewichtete Prävalenz aktueller Tabak- und E-Zigarettenkonsumenten je Erhebungswelle.** Gesamtstichprobengröße N = 12 273

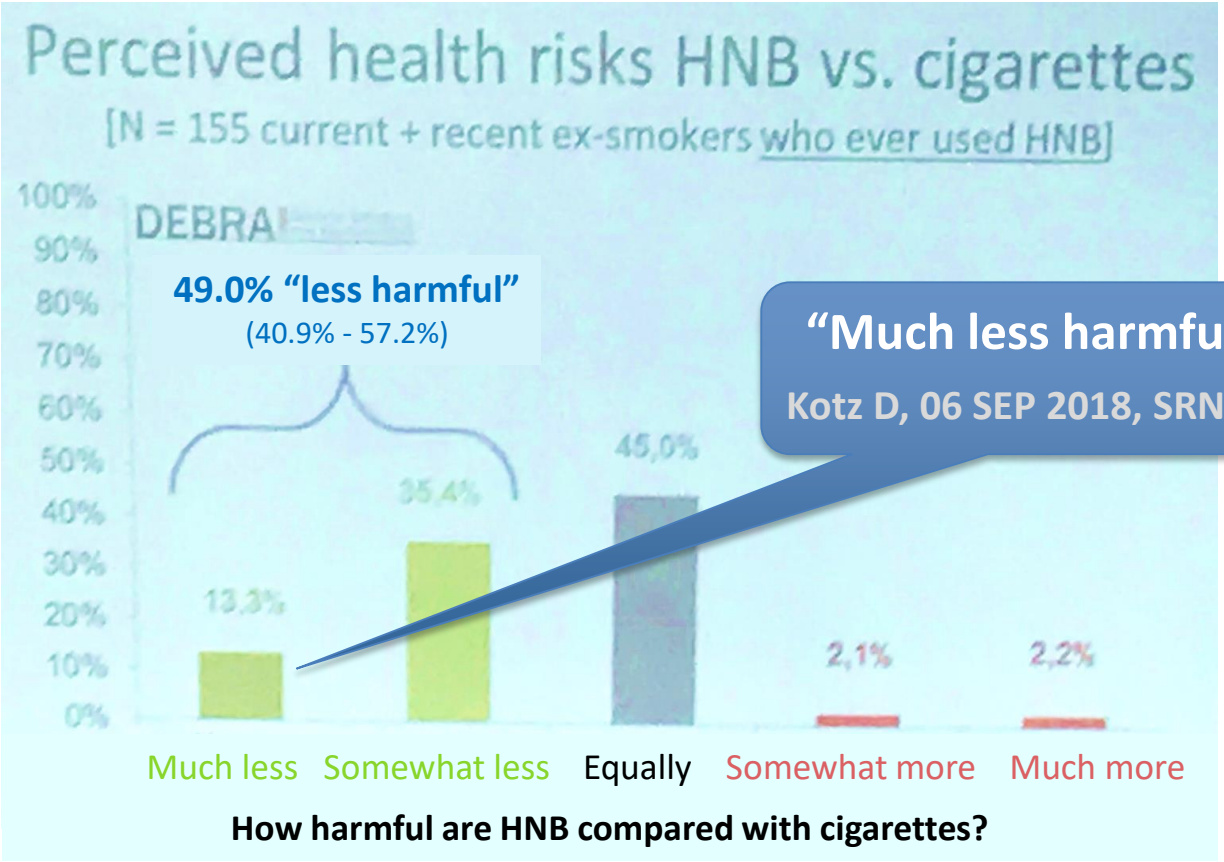
Kotz D et al., Nutzung von Tabak und E-Zigaretten sowie Methoden zur Tabakentwöhnung in Deutschland - Eine repräsentative Befragung in 6 Wellen über 12 Monate (die DEBRA-Studie), Dtsch Arztebl Int 2018; 115(14): 235-42; DOI: 10.3238/arztebl.2018.0235; https://www.aerzteblatt.de/archiv/197190/Nutzung-von-Tabak-und-E-Zigaretten-sowie-Methoden-zur-Tabakentwoehnung-in-Deutschland

# Risk Perception (Public vs. Expert) and the Success of Harm Reduction

## Switching to NGP/RRP impacted by PUBLIC PERCEPTION?

- "Approximately **half of ever users think HnB are less harmful** than conventional cigarettes"

- Study author's **expert opinion** ("HnB is much less harmful") is shared by **only 13.3%** of HnB ever-users




DEBRA Deutsche Befragung zum Rauchverhalten

Kotz D, HnB products: representative data on consumer behaviour and associated factors in the German population (the DEBRA study), oral presentation SRNT Europe 2018

# PMI Good Conversion Practices: Highest Standards of Responsibility

## PMI Good Conversion Practices for Smoke-Free Products

- Smoke-free products are **for adult smokers who want to continue enjoying tobacco or nicotine**.
- **We do not offer smoke-free products to people who have never smoked or who have quit smoking.**
- **Our goal is to switch every adult smoker who would otherwise keep smoking** combustible products to smoke-free products, such as IQOS. We are committed to supporting adult smokers in their switching journey through education and guidance.
- Smoke-free products are **not an alternative to quitting**. The best choice for consumers concerned about the health risks of smoking is to quit altogether.
- **To experience the benefit** of smoke-free products, **adult smokers should switch completely** and abandon smoking permanently.
- Smoke-free products **are not risk-free or** a **safe alternative** to cigarettes, but they are a much better choice than smoking.


PMI News, Youth and Nicotine: Tobacco Companies Must Do Their Part, 22 OCT 2018
https://www.pmi.com/media-center/news/youth-and-nicotine
Adapted from PMI Investor Day, 27 SEP 2018, Presentation by Mirek Zielinski, President, Science and Innovation
https://sites.media-server.com/mmc-custom-portals/Philip_Morris_Intl/2018-09-27_Investor_Day_2018/Downloads/Mirek_Zielinski_v1.pdf

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# 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).