



PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

„Risikoreduzierte“ Tabakprodukte Zukunftsoption des Rauchens?

Das wissenschaftliche Entwicklungsprogramm von PMI Science

Bern, 15.11.2018

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Before we start

- This scientific overview is for the purpose of sharing scientific information with the Swiss scientific community and not for advertising or marketing purposes regarding tobacco or nicotine containing products.
- The content of this overview is not and should not be regarded as an offer to sell, or a solicitation of an offer to buy or recommend any product of PMI or its affiliates



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



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INTERVIEW

Philip-Morris-Chef: «Ich will die Leute von den Zigaretten wegbringen»

Der Zigarettenabsatz der Tabakindustrie schrumpft. Der Philip-Morris-CEO äussert sich im Interview über die neue Strategie des Tabakkonzerns und erklärt, warum er nicht auf ein Comeback der Zigarette hofft und wieso seine Firma keine nikotinfreien Produkte führt.

NZZ;18.10.2018



PHILIP MORRIS GEGEN ZIGARETTEN

„Das Ende der Zigarette ist nah“

VON BETTINA WEIGUNY - AKTUALISIERT AM 05.11.2018 - 14:48



FAZ;05.11.2018

What Is the Objective of Tobacco Harm Reduction?

Schweizerische Gesundheitsbefragung 2017

„Raucherzahlen seit 10 Jahren gleichbleibend, verändertes Konsumverhalten beim Alkohol“*

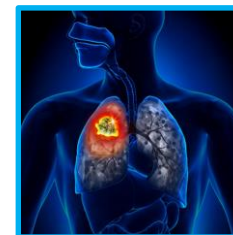
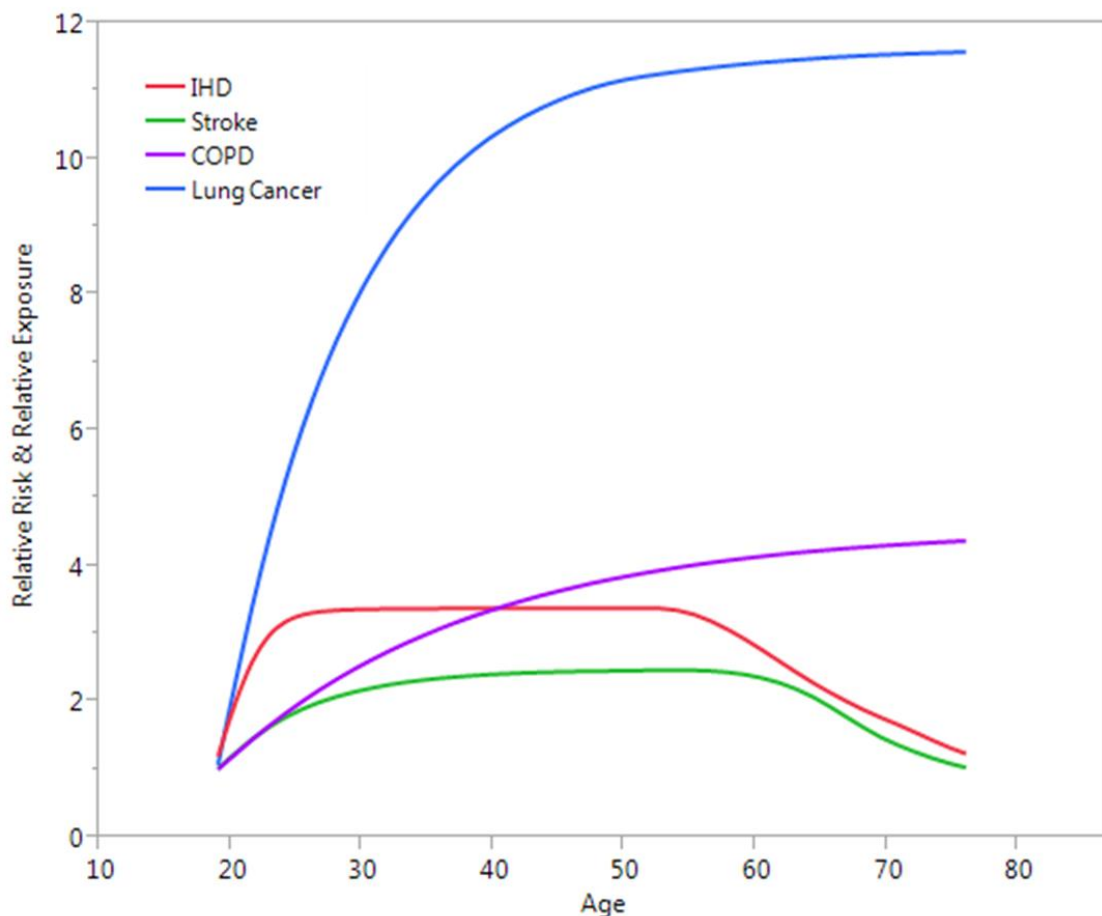
Raucheranteil bleibt gleich hoch

Nachdem der Anteil der Raucherinnen und Raucher von 1997 bis 2007 zurückgegangen ist, blieb er in den letzten 10 Jahren bei rund 27%. Der Anteil der Rauchenden ist bei den 15- bis 44-jährigen Männern mit 35% am höchsten. Stark reduziert hat sich jedoch die Menge des konsumierten Tabaks. So hat sich im Zeitraum von 1992 bis 2017 der Anteil der Rauchenden, die 20 oder mehr Zigaretten pro Tag rauchen, halbiert (1992: 41%; 2017: 21%).

For smokers who would otherwise continue to smoke an addition to existing tobacco control strategies is needed

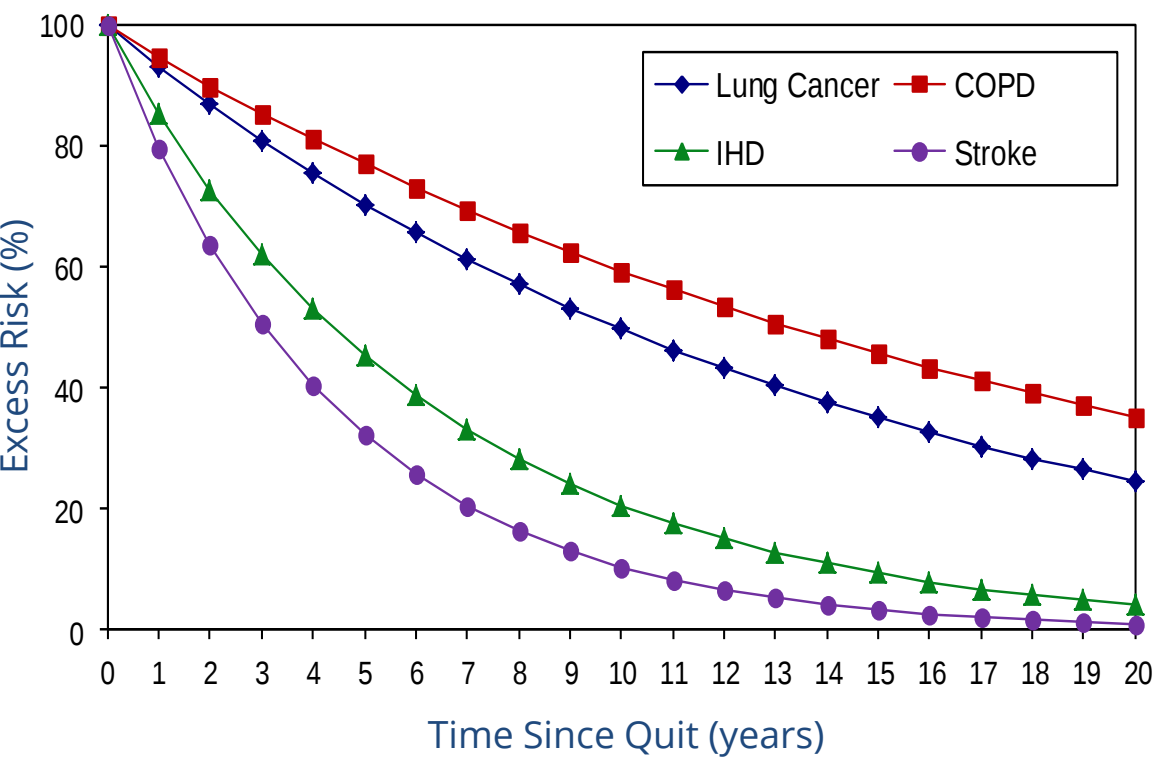
Excess Risk of Smoking-Related Disease

Disease-Specific Relative Risk (by age) *Relative risk of IHD, Stroke, COPD, and LC for an adult cigarette smoker*



Excess Risk of Smoking-Related Disease

Reduction in Excess Risk Over Time

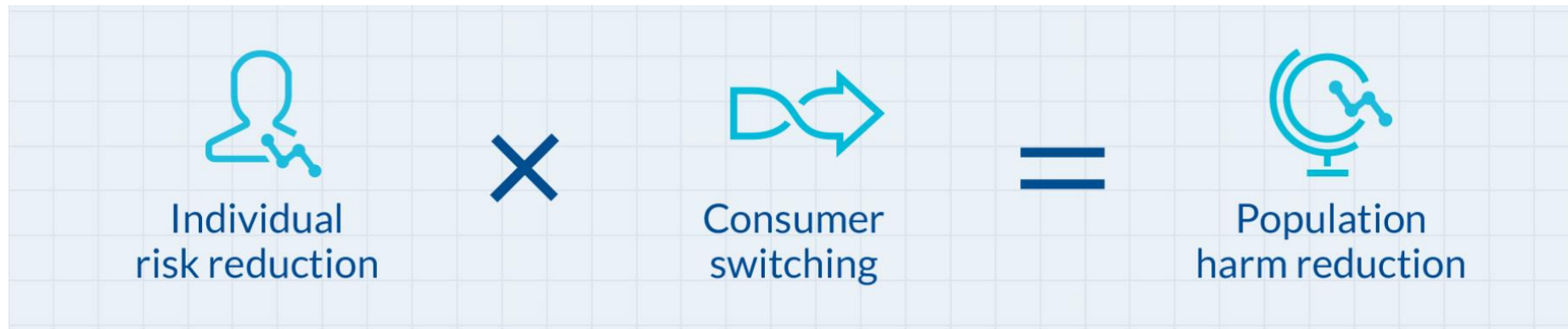


Disease Risk Half-Life ^[2]				
(The time at which half of the Excess risk associated with cigarette smoking has disappeared)				
Age (a)	Lung Cancer	IHD	Stroke	COPD
Any age	-	-	4.78	13.32
to 49	6.98	1.47	-	-
50 to 59	10.39	5.22	-	-
60 to 69	10.60	7.48	-	-
70 to 79	12.99	13.77	-	-

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

What Is the Objective of Tobacco Harm Reduction?

- Smoking is addictive and causes a number of serious diseases
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies



Successful harm reduction requires that current adult smokers be offered a range of reduced risk products they can fully switched to, should they decide not to quit.

Our mission



Aerosol Science
Chemical Engineering
Chemistry
Electrical Engineering
Physics

Mechanical Engineering
Organic Chemistry
Materials Engineering
Materials Science
Modelling

Genetics
Food Technology
Flavor Science
Mathematics
Plant Biology

Analytical Chemistry
Biochemistry
Toxicology
Biomedicine
Biotechnology

Pharmacology
Cell Biology
Molecular Biology
Pharmacy
Pharmaceutical Chemistry

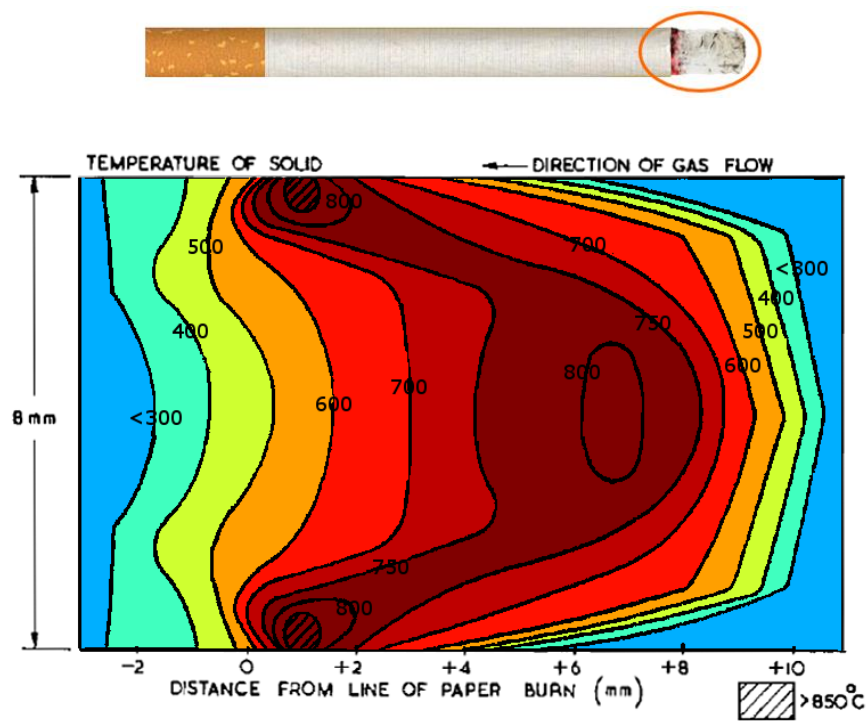
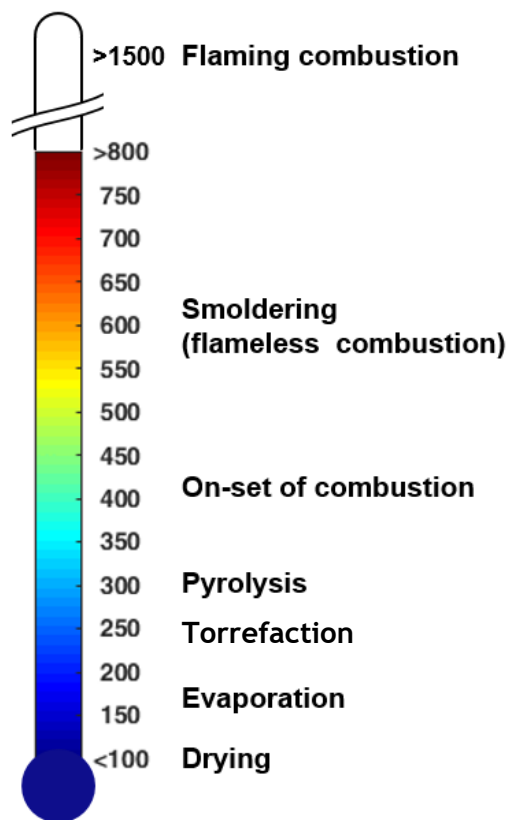
Computer Science
Clinical Science
Biostatistics
Epidemiology
Medicine

430 R&D Experts - One Goal: To develop and scientifically assess products, that when switched to completely, have the potential to reduce the risk of smoking related diseases compared to continued smoking.

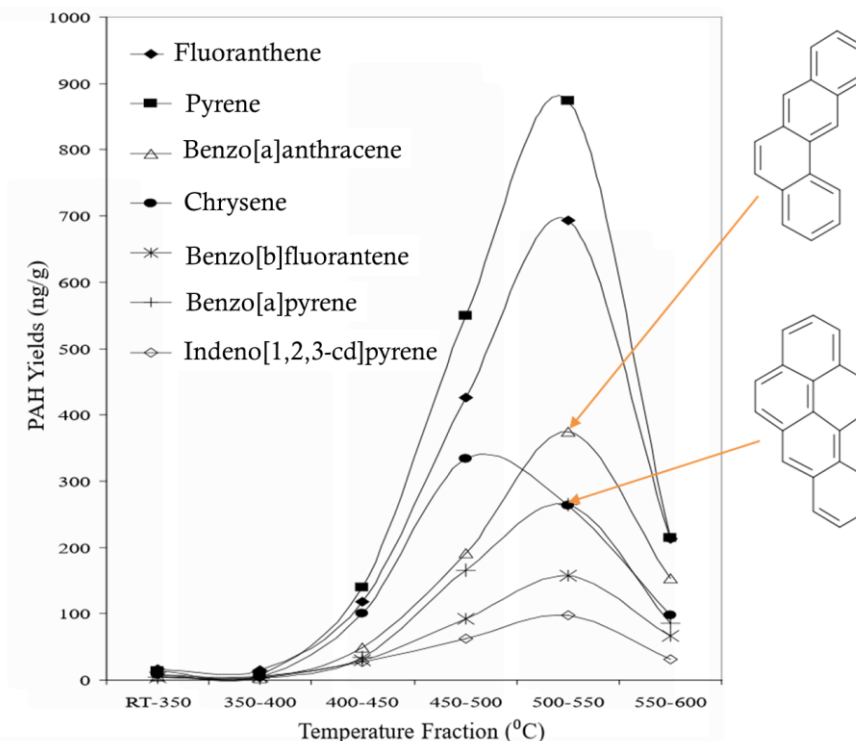
Elimination of Combustion Is Key

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

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

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)



PRODUCTS WITHOUT TOBACCO

PLATFORM
3

NICOTINE DELIVERY SYSTEM



PLATFORM
4

E-VAPOR PRODUCTS



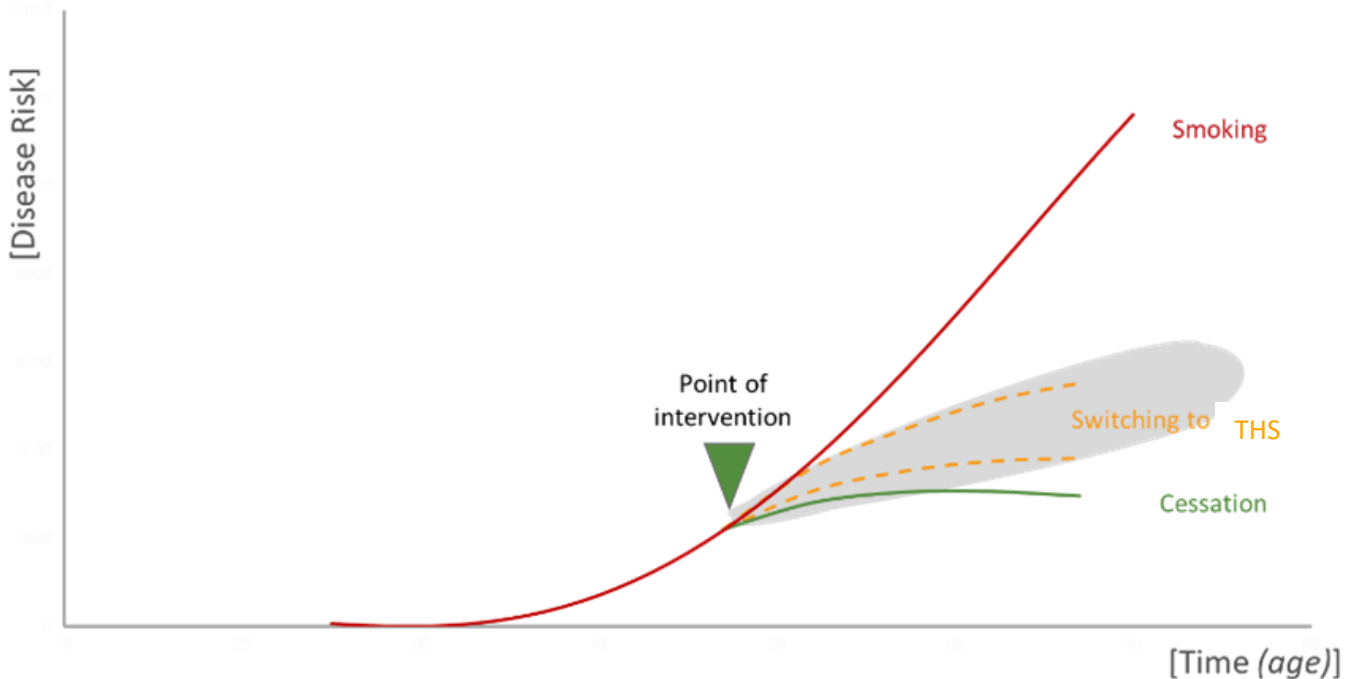
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking. The RRP's depicted are subject to ongoing development and therefore the descriptions are illustrative and do not necessarily represent the latest stages of product development.

PMI's Scientific Assessment Approach

RRP HEALTH IMPACT MODELING ²

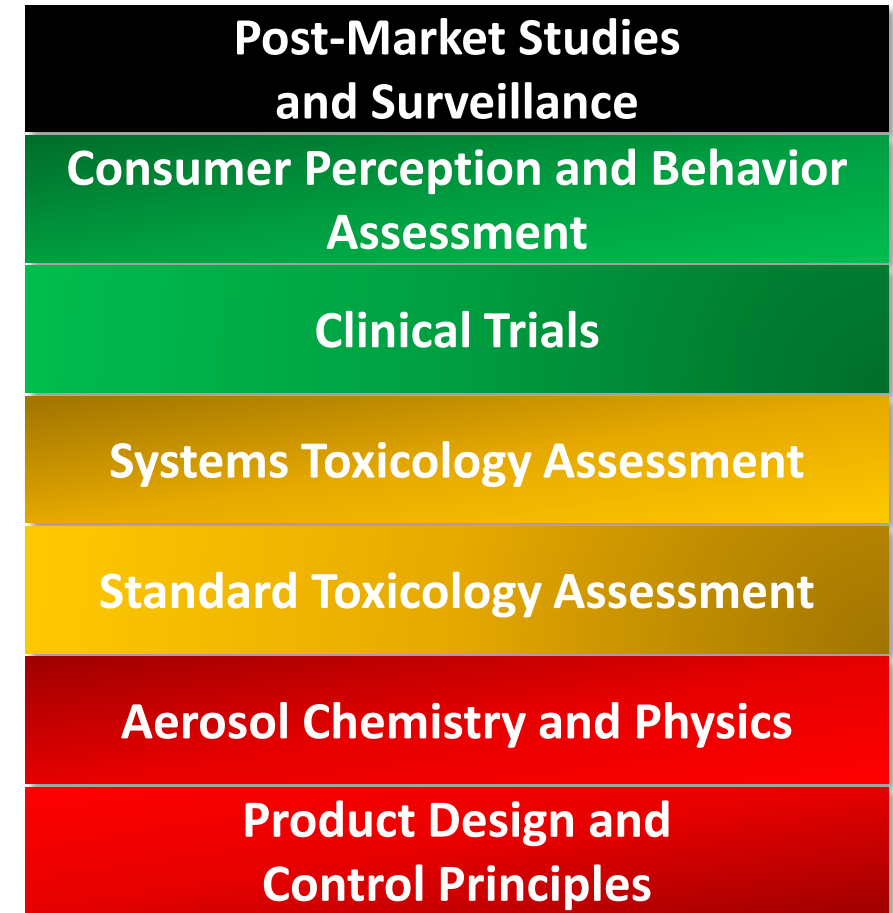
Curves are disease-specific

Shown here: Lung cancer



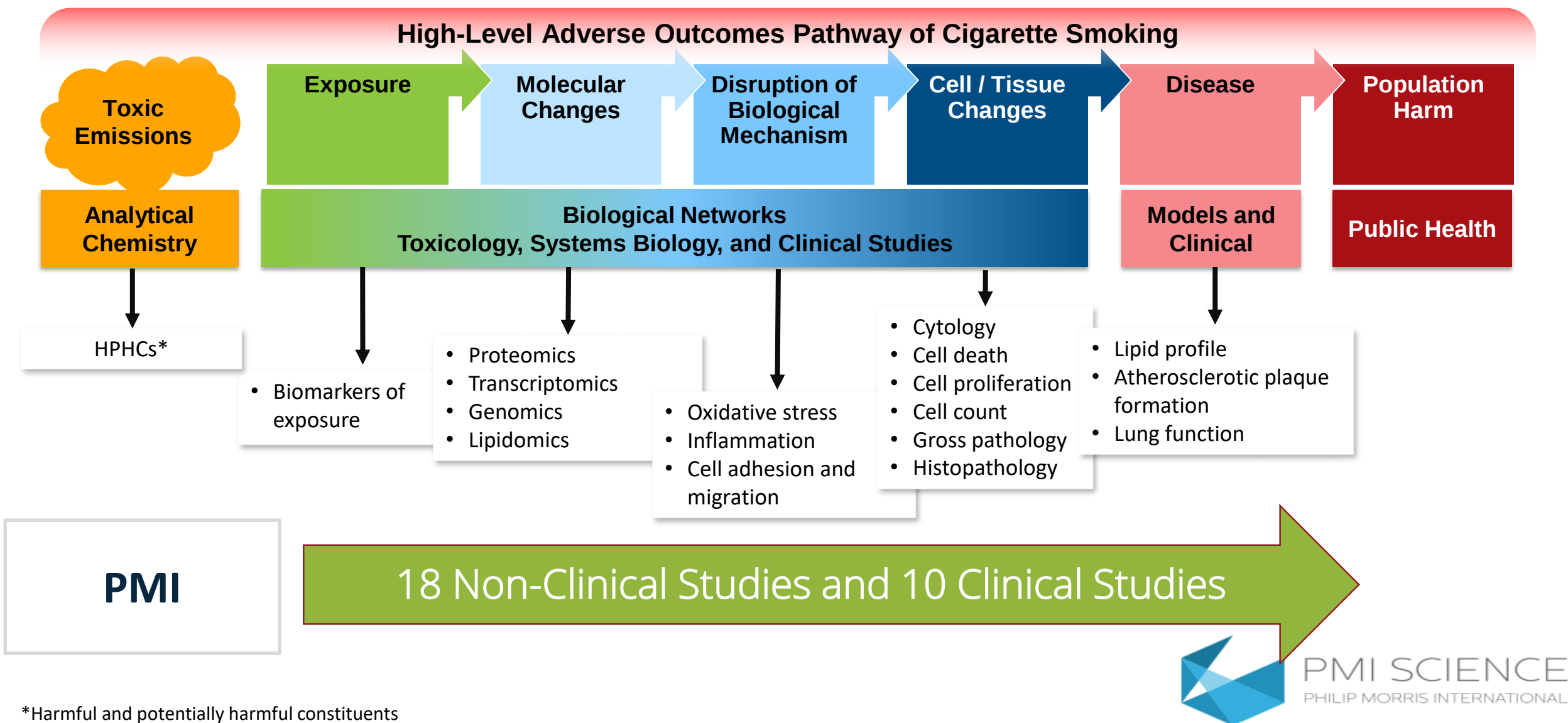
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking. Descriptions in the chart are for illustrative purposes only.

- (1) 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>
- (2) Baker et al., Modeling the impact of changes in tobacco use on individual disease risks; poster, SRNT 2017; https://www.pmiscience.com/system/files/publications/baker_srnt_2017_0.pdf



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Assessment Framework: Informed by Epidemiology

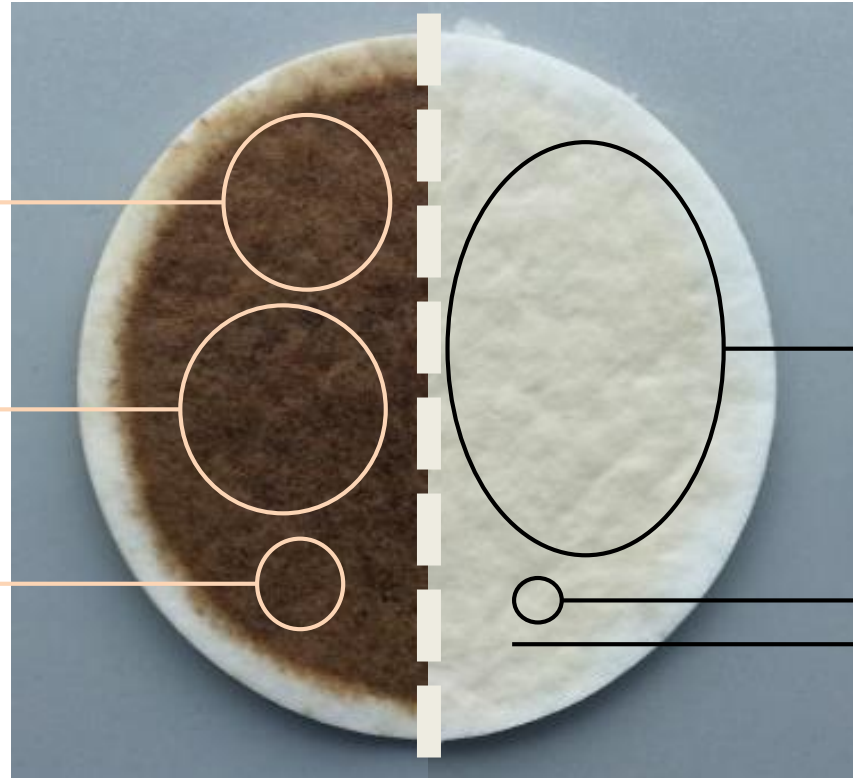




Water and glycerin
form 50% of
aerosol mass

Toxicants

Contains
Carbon-based solid
particles

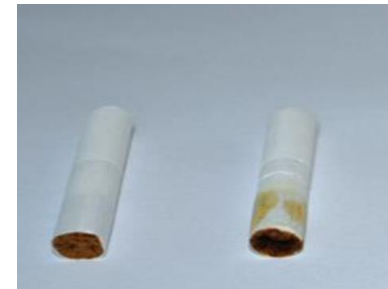


Smoke and aerosol were collected on a
Cambridge filter pad using Health
Canada Intense smoking regime

Water and glycerin
form 90% of
aerosol mass

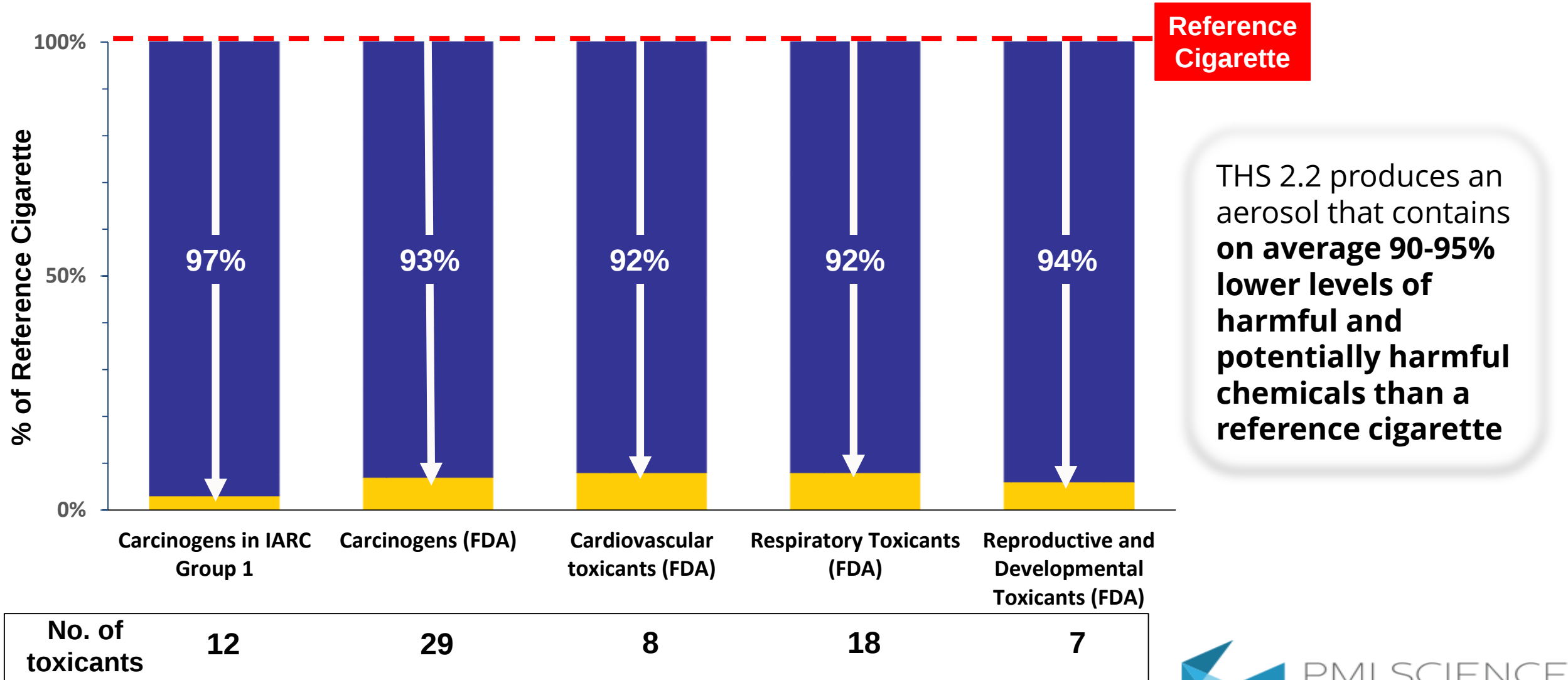
Toxicants reduced
by >90%

No Carbon-based
solid particles



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Reduced Formation of HPHCs by Disease Categories



Notes:
THS stands for Tobacco Heating System version 2.2
Health Canada Intense Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

Independent Studies Results

Aerosol Chemistry



Committee on Toxicology (COT)



British American Tobacco



National Tobacco Quality
Supervision and Test Center



Federal Institute for Risk Assessment (BfR)



University of Bern



National Institute of Public Health



Food & Drug Administration



Onassis Cardiac Surgery Center



National Institute for Public Health and the
Environment (RIVM)



Ministry of Food and Drug Safety

Indoor Air quality



Fondazione IRCCS Istituto Tumori



Sapienza University



Medved Research Center of Preventing
Toxicology, Food and Chemical Safety

Pre-Clinical



British American Tobacco



UCSF



Roswell Park Comprehensive Cancer Center

Clinical



Kazan Federal University



National Scientific Centre "M.D.
Strazhesco Institute of Cardiology"



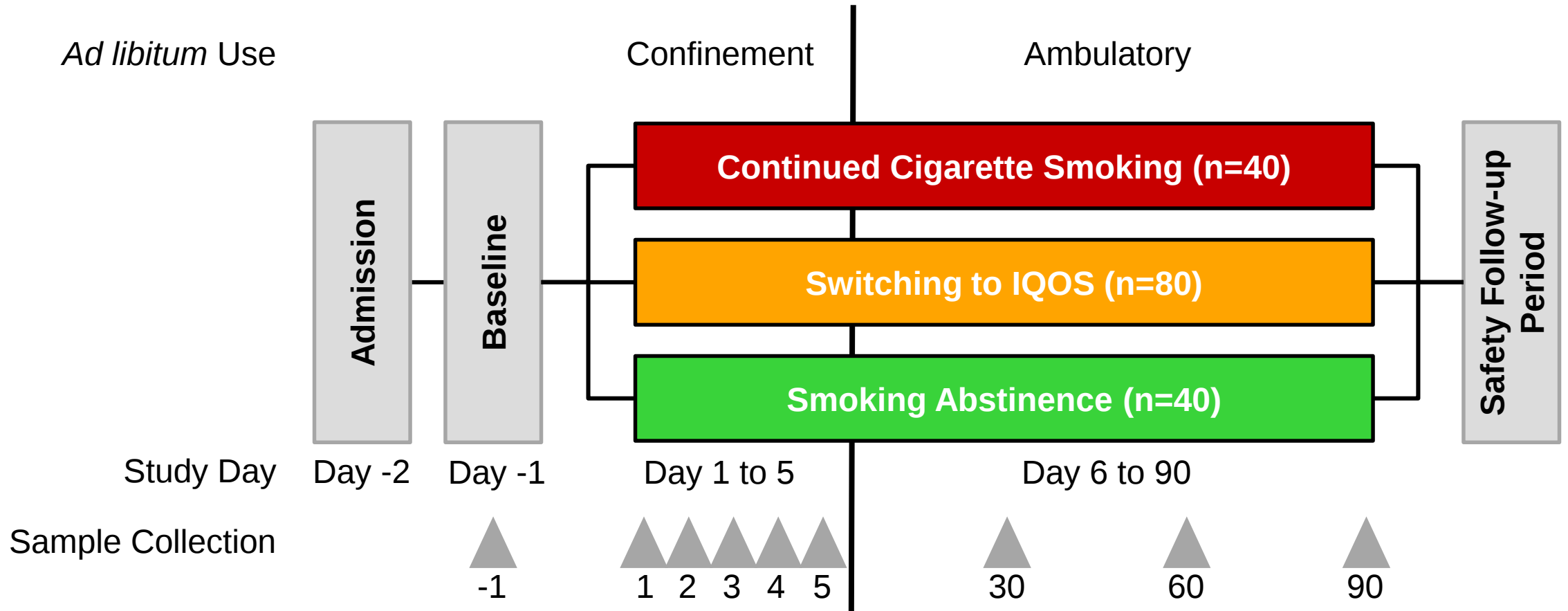
British American Tobacco



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Study Design

Reduced Exposure in Healthy Human Subjects



Measurements: Biomarkers of Exposure; Nicotine and its metabolites



ClinicalTrials.gov ID: NCT01970995



ClinicalTrials.gov ID: NCT01989156

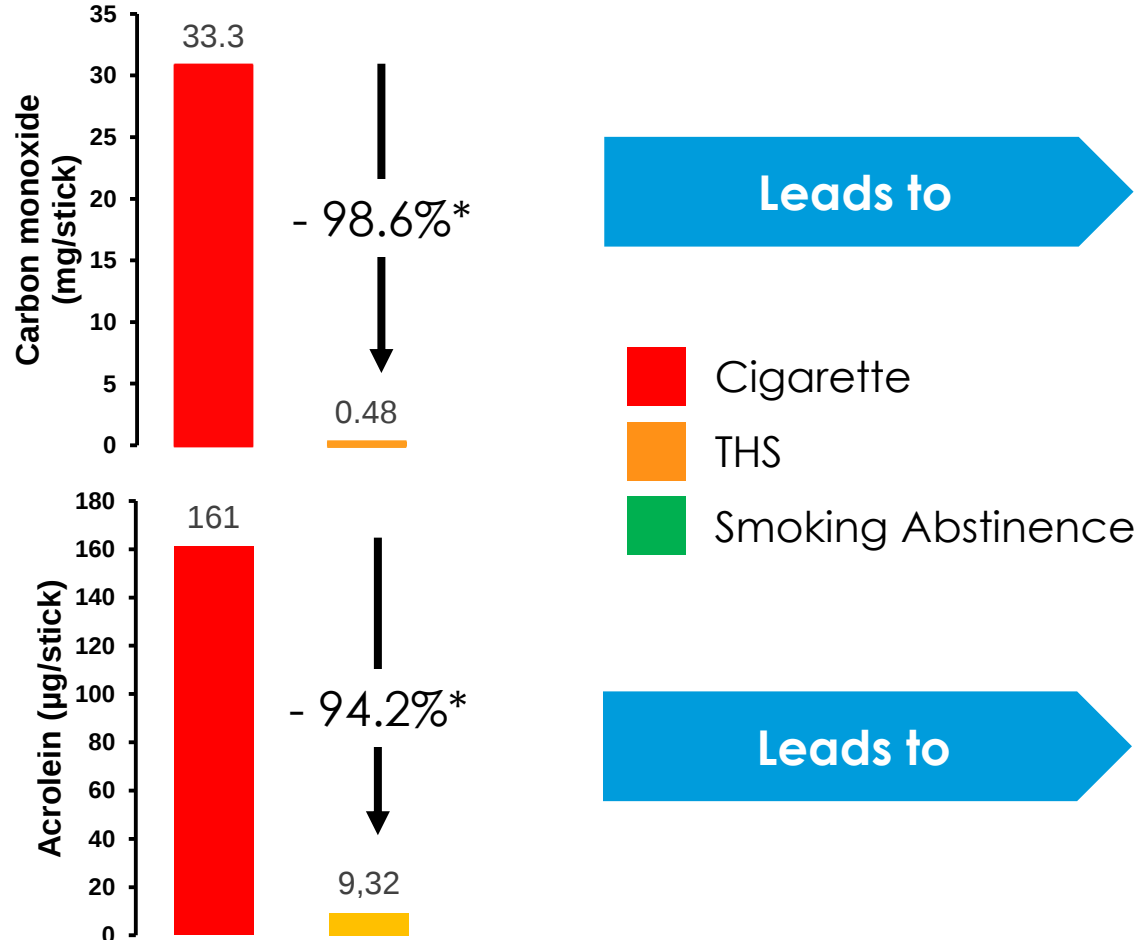


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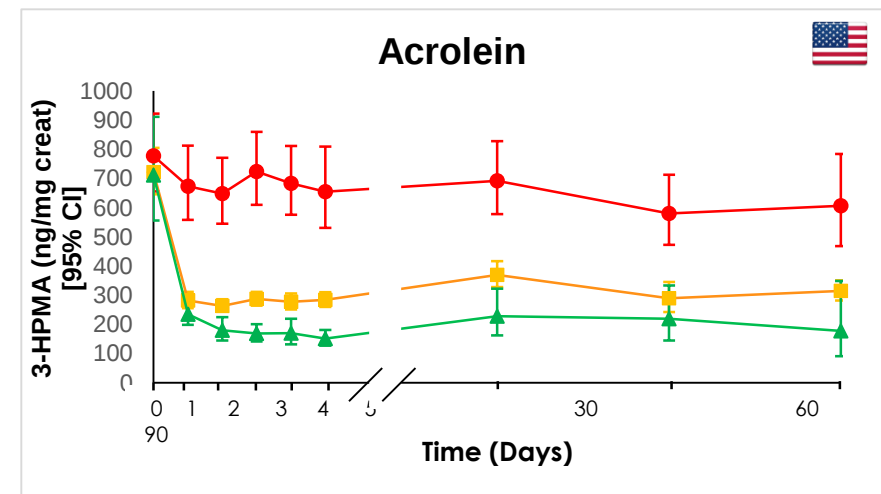
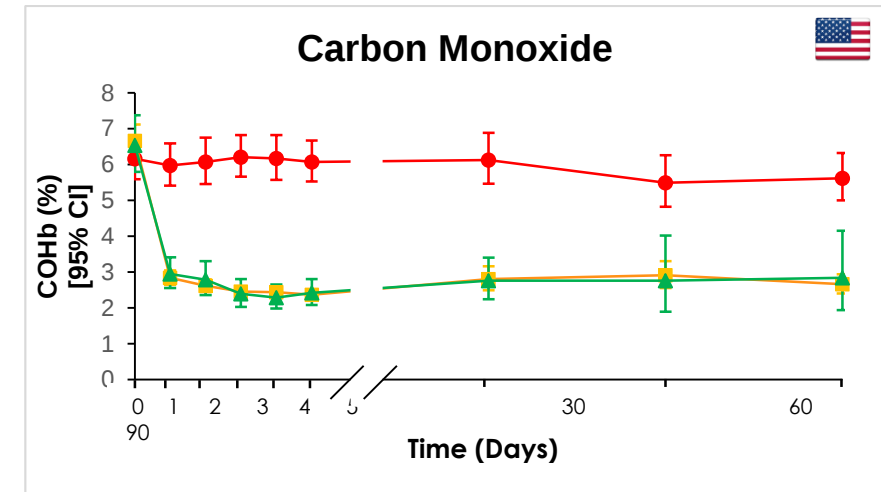
Changes in Exposure to HPHCs

Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in THS Aerosol



Exposure is Significantly Reduced After Switching to THS



Notes:

* On equivalent nicotine basis

THS stands for Tobacco Heating System version 2.2

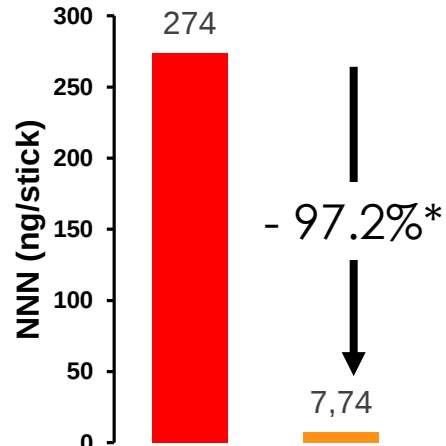
Source: PMI Research and Development

Registered on clinicaltrials.gov: NCT01989156

Changes in Exposure to HPHCs

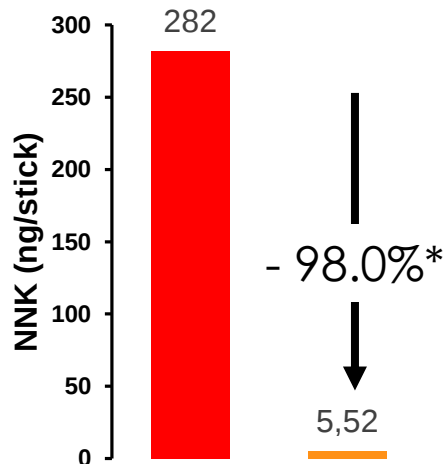
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically
Reduced in THS Aerosol



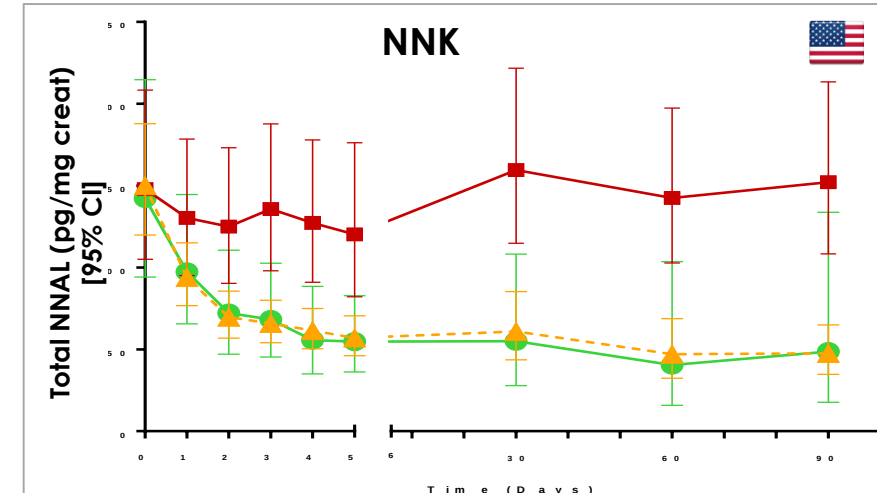
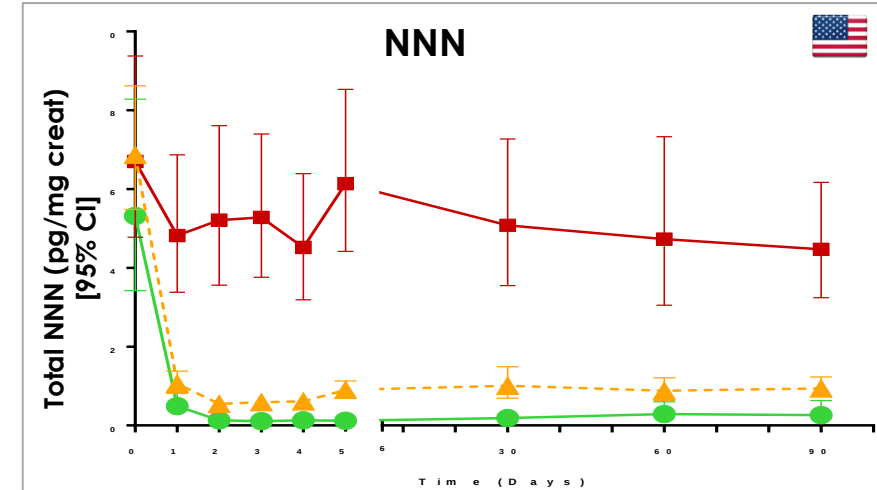
Leads to

- Cigarette
- THS
- Smoking Abstinence



Leads to

Exposure is Significantly Reduced
After Switching to THS



Registered on clinicaltrials.gov: NCT01989156

Notes:

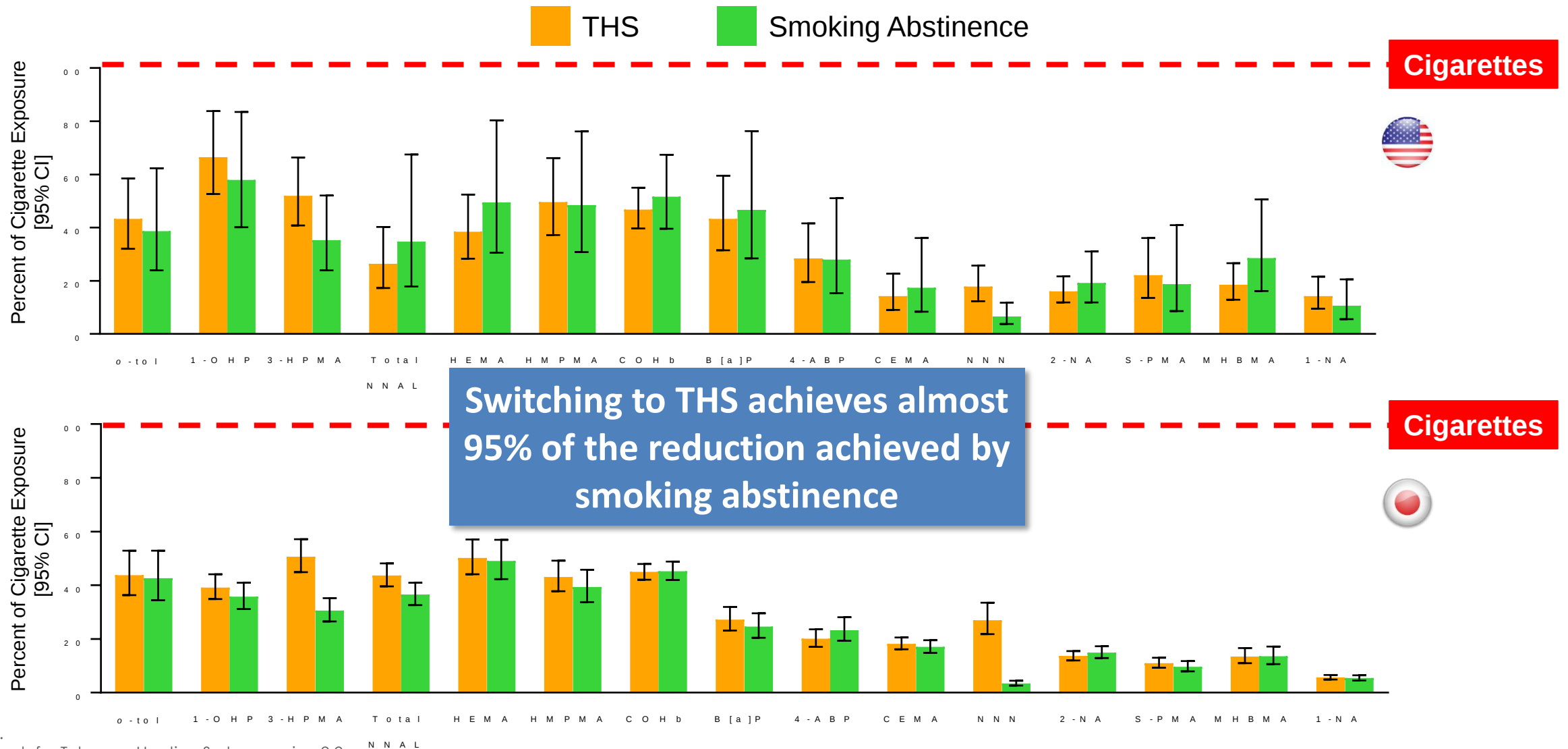
* On equivalent nicotine basis

THS stands for Tobacco Heating System version 2.2

Source: PMI Research and Development

Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects



Notes:

THS stands for Tobacco Heating System version 2.2

Source: PMI Research and Development

Registered on clinicaltrials.gov: NCT01989156 and NCT01970995



Epidemiologic link to smoking-related disease?

Reversible upon smoking cessation



Lipid Metabolism

HDL-C

Clotting

11-DTX-B2

Endothelial Function

sICAM - 1

Acute Effect

COHb

Inflammation

WBC

Oxidative Stress

8-epi-PGF2 α

Lung Function

FEV₁ %Pred

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 IQOS THS 2.2 as compared to those continuing to smoke cigarettes for 6 months

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

Summary of Scientific Results

We are committed to transparency and encourage independent verification

1



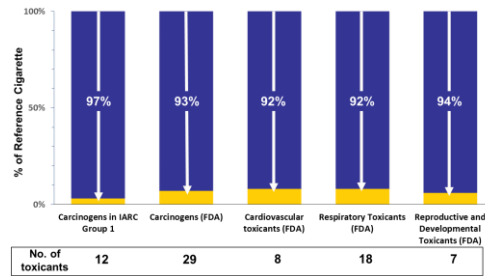
2

Heated Tobacco Products

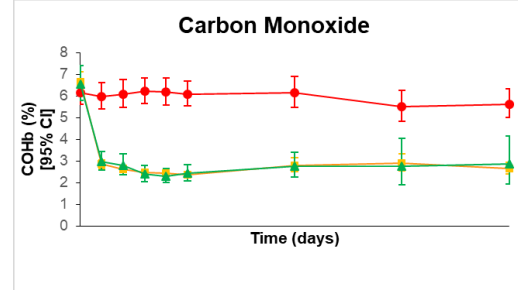
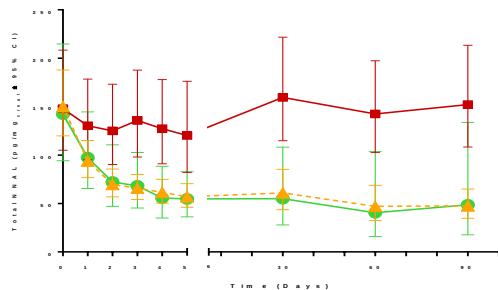
Products Without Tobacco



3



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
Respiratory Disease and Cancer	Acute Effect	COHb
	Inflammation	WBC
	Oxidative Stress	8-epi-PGF2α
	Lung Function	FEV ₁ %Pred
	Genotoxicity	Total NNAL



4

Aerosol Chemistry

- Committee on Toxicology (COT)
- British American Tobacco
- National Tobacco Quality Supervision and Test Center
- Federal Institute for Risk Assessment (BfR)
- University of Bern
- National Institute of Public Health
- Food & Drug Administration
- Onassis Cardiac Surgery Center
- National Institute for Public Health and the Environment (RIVM)
- Ministry of Food and Drug Safety

Indoor Air quality

- Fondazione IRCCS Istituto Tumori
- Sapienza University
- Medved Research Center of Preventing Toxicology, Food and Chemical Safety

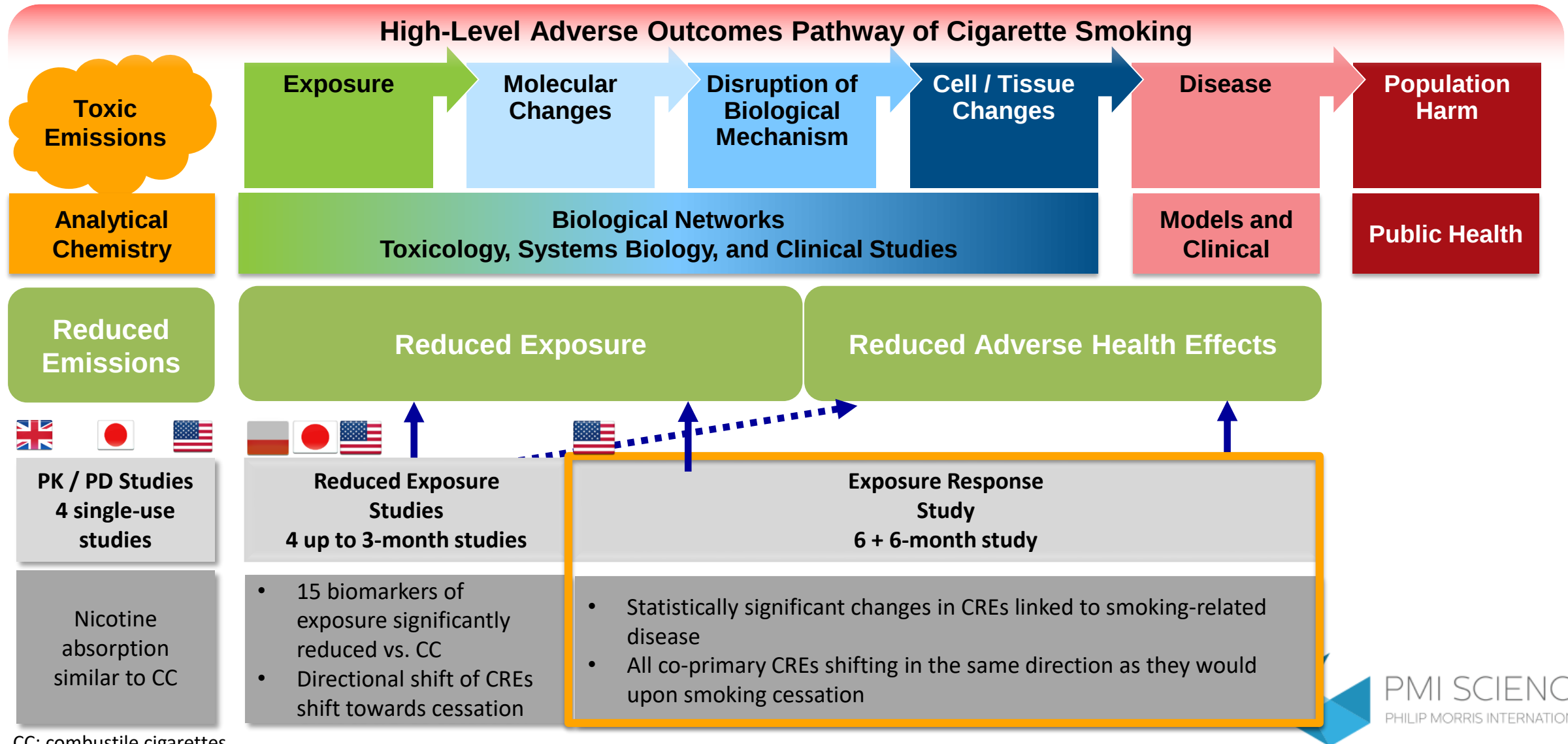
Pre-Clinical

- British American Tobacco
- UCSF
- Roswell Park Comprehensive Cancer Center

Clinical

- Kazan Federal University
- National Scientific Centre "M.D. Strazhesco Institute of Cardiology"
- British American Tobacco

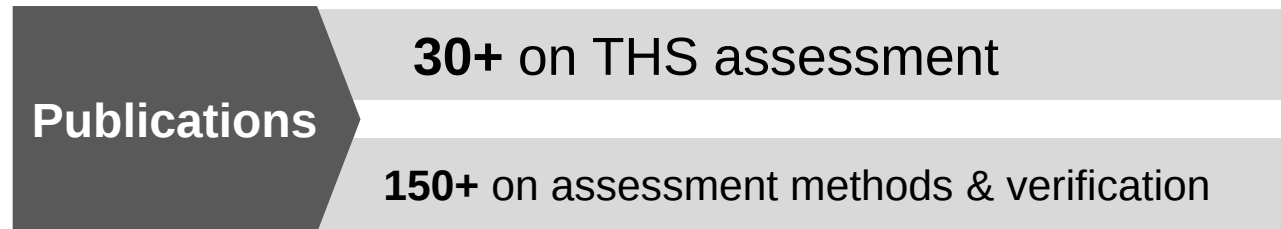
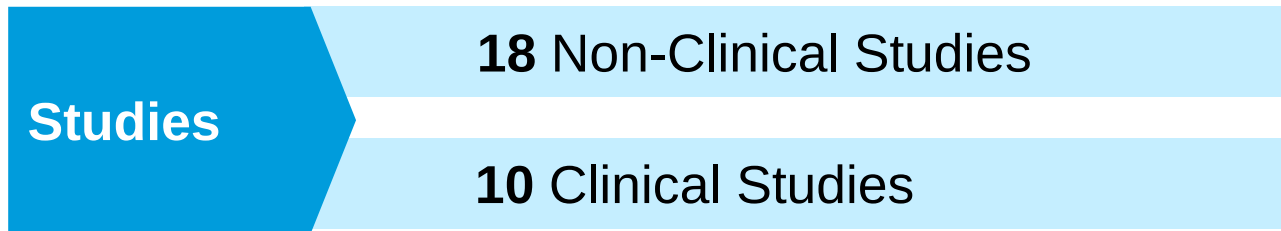
Clinical Assessment - Results to Date



Scientific Evidence to Date



PMI Studies



Five Government Reports & > 25 independent studies

Independent research generally confirms that THS emits significantly lower levels of harmful chemicals compared to cigarettes and significantly reduces exposure to these toxicants in adult smokers who switch completely.

THS is the most researched smoke-free product in the market

Summary



- THS is not risk free and the best choice is to quit smoking
- Smokers carry a time-dependent relative risk of disease based on their smoking history when they quit or switch to THS
- THS is a much better choice for smokers than to continue smoking cigarettes
- Switching exclusively to THS is less harmful than continuing to smoke cigarettes.





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Thank you for your attention

Independent Studies Results - Aerosol Chemistry

Compounds Classes	Forster ¹	Farsalinos ²	Bekki and al ³	Auer and al ⁴	Li and al ⁵	Mallock and al ⁶	RIVM ⁷	Compounds per Class
ISO parameter	✓	✓	✓	✗	✓	✓	✓	Nicotine, TPM, Water, CO, Glycerin
Carbonyls	✓	✓	NA	✗	✓	✓	✓*	Acetaldehyde, Acetone, Acrolein, Butyraldehyde, Crotonaldehyde, Formaldehyde, Methyl-ethyl-ketone (MEK), Propionaldehyde
Polyaromatic Hydrocarbons (PAH)	✓	NA	NA	✓	✓	NA	NA	Benz[a]anthracene, Benzo[a]pyrene, Dibenzo[a,h]anthracene, Pyrene
Tobacco Specific Nitrosamines (TSNA)	✓	NA	✓	NA	✓	NA	✓*	NNN, NAT, NAB, NNK
Aliphatic dienes	✓	NA	NA	NA	✓		✓*	1,3-butadine, Isoprene
Acid derivaties	✓	NA	NA	NA	✓	NA		Acetamide, Acrylamide, Acrylonitrile
Epoxides	✓	NA	NA	NA	NA	NA	✓*	Ethylene oxide, Propylene oxide
Nitro compounds	✓	NA	NA	NA	NA	NA	NA	Nitrobenzene
Aromatic amines	✓	NA	NA	NA	✓	NA	NA	1-Aminonaphthalene, 2-Aminonaphthalene, 3-Aminobiphenyl, 4-Aminobiphenyl, o-Toluidine
N-heterocyclic aromatics	✓	NA	NA	NA	NA	NA	NA	Pyridine, Quinoline
Halogen compounds	✓	NA	NA	NA	NA	NA	NA	Vinyl chloride
Inorganic compounds	✓	NA	NA	NA	✓	NA	✓*	Ammonia, Hydrogen cyanide, Nitric oxide, Nitrogen oxides
Monocyclic aromatic hydrocarbon	✓	NA	NA	NA	✓	✓	✓*	Benzene, Styrene, Toluene
Phenols	✓	NA	NA	NA	✓	NA	NA	Catechol, Hydroquinone, o,m,p-cresol, Phenol, Resorcinol
Metals/elements	✓	NA	NA	NA	NA	NA	✓*	Arsenic, Cadmium, Chromium, Lead, Mercury, Nickel, Selenium



Confirm PMI results



Contradictory to PMI results

1. Assessment of novel tobacco heating product heating product THP1.0 part 3: Comprehensive chemical characterization of harmful and potentially harmful aerosol emissions, Forster and al (BAT). Regulatory Toxicology and Pharmacology, 2017

2. Farsanilos presentation given at the Global Forum on Nicotine, Warsaw 2017

3. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes, Bekki and al., J UOEh, 2017

4. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name, Auer and al., JAMA Internal Medicine, 2017

5. Chemical Analysis and Simulated Pyrolysis of Thobacco Heating System 2.2 Compared to Conventional Cigarette, Xiangyu Li and al. Nicotine & Tobacco Research, January 2018

6. Levels of selected analytes in the emissions of «heat not burn» tobacco products that are relevant to assess hum health risks, Mallock and al., Archives of Toxicology, April 2018

7. National Institute for Public Health and the Environment (RIVM) Ministry of Health, Wellbeing and Sports, 2018 * Beside nicotine that were published, HPCs were not reported but mentioned to be in line with Philip Morris published data

HPHC Characteristics and Related Biomarkers of Exposure

PMI Biomarker	Smoke Constituents	FDA 2012 (FDA-18)	Toxicity (IARC)	Formation Temperature °C	Estimated Biomarker Elimination Half-life
3-HPMA	Acrolein	x	Respiratory, cardiovascular	300-500	10h
S-PMA	Benzene	x	Carcinogenic (1), cardiovascular, reproductive and developmental	> 400	9 to 15h
MHBMA	1,3-Butadiene	x	Carcinogenic (1), respiratory, reproductive and developmental	> 400	4 to 16h
COHb	Carbon monoxide	x	Cardiovascular, reproductive and developmental	> 300	1 to 6h
CEMA	Acrylonitrile	x	Possibly carcinogenic (2B), respiratory	400-550	1-2 days
4-ABP	4-Aminobiphenyl	x	Carcinogenic (1)	300-500	26h
1-NA	1-Naphtylamine	x	Not classifiable as carcinogenic to humans	300-500	
2-NA	2-Naphtylamine	x	Carcinogenic (1)	300-500	9h
Total NNAL	NNK	x	Carcinogenic (1)	direct transfer	10-18 days
Total NNN	NNN	x	Carcinogenic (1)	direct transfer	15h
o-Toluidine	ortho-Toluidine	-	Carcinogenic (1)	300-500	10 to 16h
1-OHP	Pyrene	-	Surrogate for Polycyclic Aromatic Hydrocarbons	400-600	20h
B[a]P	Benzo[a]pyrene	x	Carcinogenic (1)	450-600	3 to 4h
S-BMA	Toluene	x	Respiratory, reproductive and developmental	> 400	9h
HEMA	Ethylene Oxide	-	Carcinogenic (1) , respiratory, reproductive and developmental	< 400	5h
3-HMPMA	Crotonaldehyde	x	Not classifiable as carcinogenic to humans	300-500	2 days