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How innovation will deliver a smoke-free future

Innovation and Good Practices in the Health Sector

Rui Minhos
Head of Regional Scientific Engagement
Philip Morris International

6th November 2018

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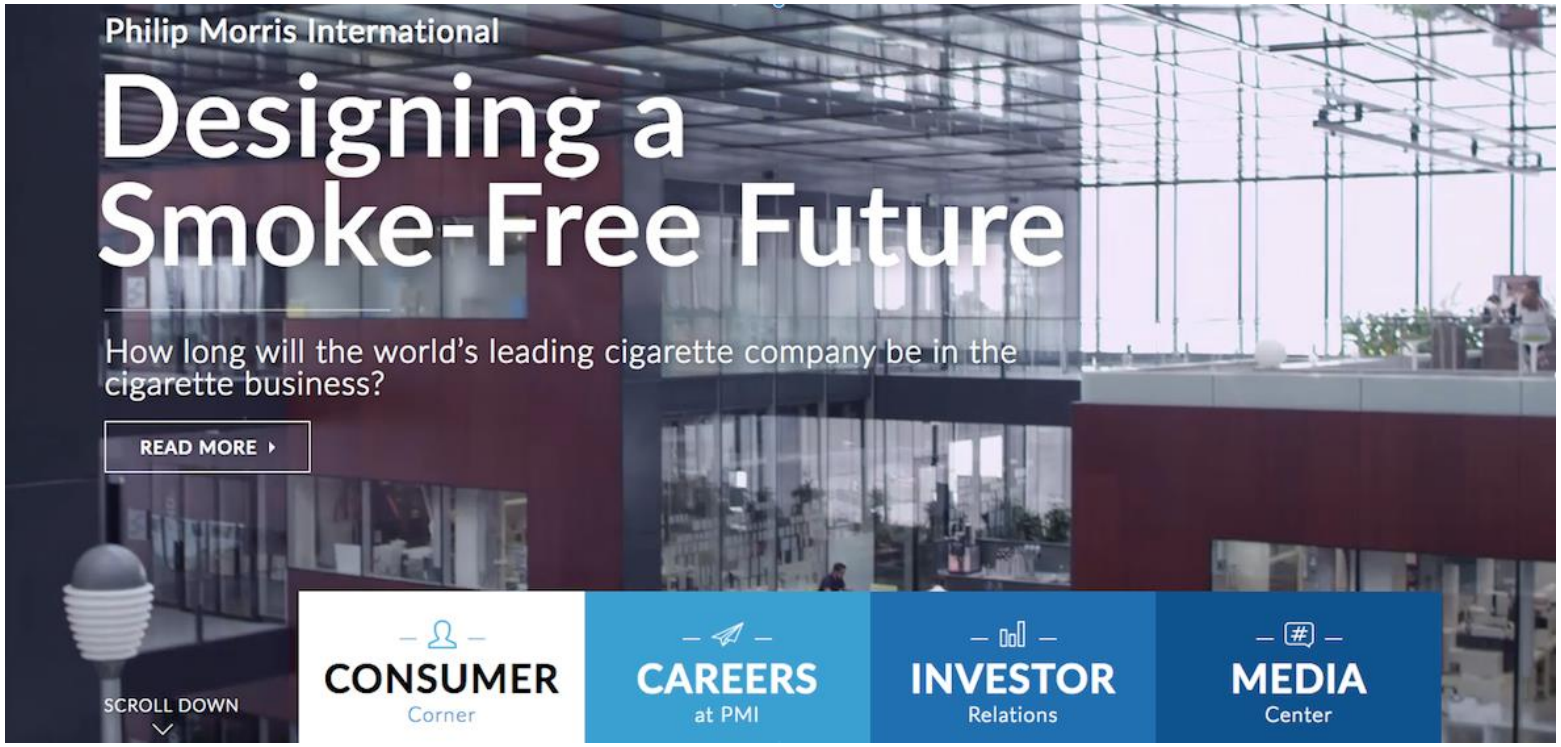
Our Business Is Changing…

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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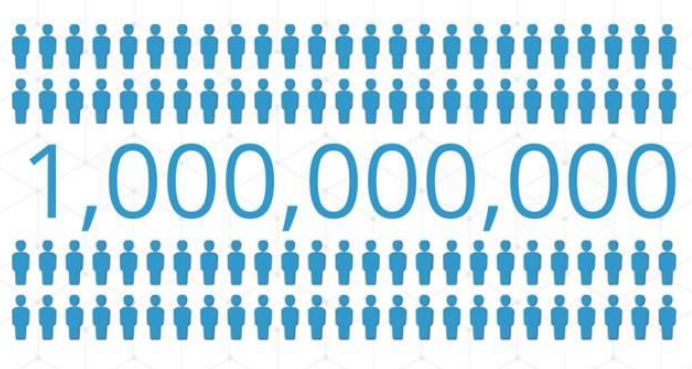
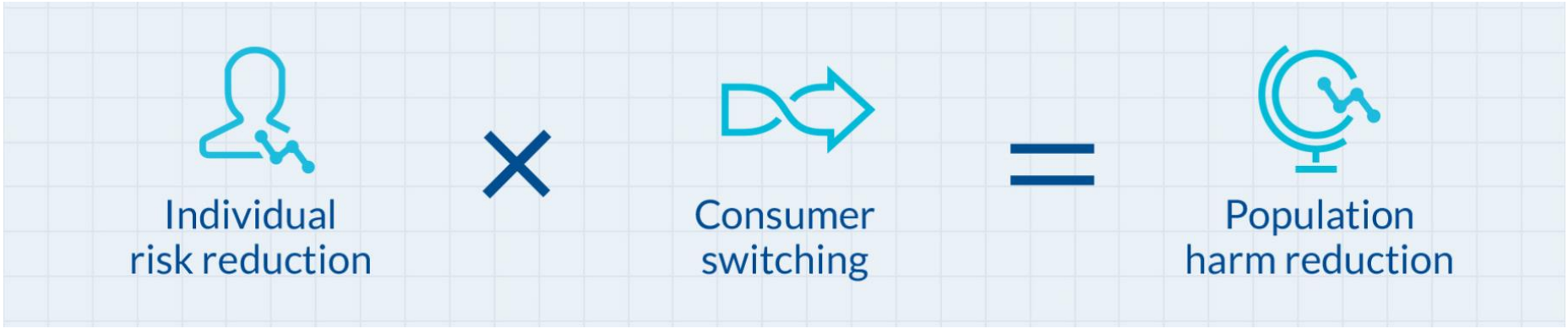
The Objective Is Harm Reduction

- Smoking is addictive and causes a number of serious diseases.
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*.
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies.





Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products so that consumer acceptance can be best fulfilled

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

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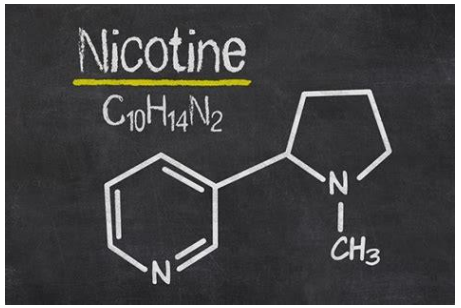
The Role of Nicotine

"It is primarily the toxins and carcinogens in tobacco smoke – not the nicotine – that cause illness and death."

-NICE Public Health Guidance: Tobacco: Harm Reduction Approaches to Smoking (2013)



Nicotine, though addictive and not risk-free, is not the primary cause of smoking-related diseases

"Nicotine is the core of the problem but also the centerpiece of the solution."

Mitch Zeller, director of US FDA's Center for Tobacco Products; Presentation at Food and Drug law Institute Conference (Washington 26 October 2017)

"Nicotine is the very same compound FDA has approved for over 30 years as a safe and effective medication. People are dying from the tobacco-related diseases from the smoke particles, not the nicotine… Can we start to take a different look at this?"

Mitch Zeller, Director of US FDA's Center for Tobacco Products; Presentation at Legacy Foundation

Public Health England

FDA

Royal College of Physicians

NICE National Institute for Health and Care Excellence

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Emerging Smoke-Free Regulatory Trends

FDA

*"…**new product innovations** could make a lot of sense and **help people transfer off cigarettes**"*

- Scott Gottlieb, Commissioner Food & Drug Administration

Public Health England

*"help people to quit smoking by **permitting innovative technologies that minimise the risk of harm**" / "maximise the availability of safer alternatives to smoking"*

MINISTRY OF HEALTH

MANATŪ HAUORA

*"**heat-not-burn**, snus, moist snuff, dissolvable and inhaled nicotine **may be significantly safer than cigarettes**."*

- Nicky Wagner, Associate Health Minister

A growing number of countries are recognizing the benefit of novel smoke-free products

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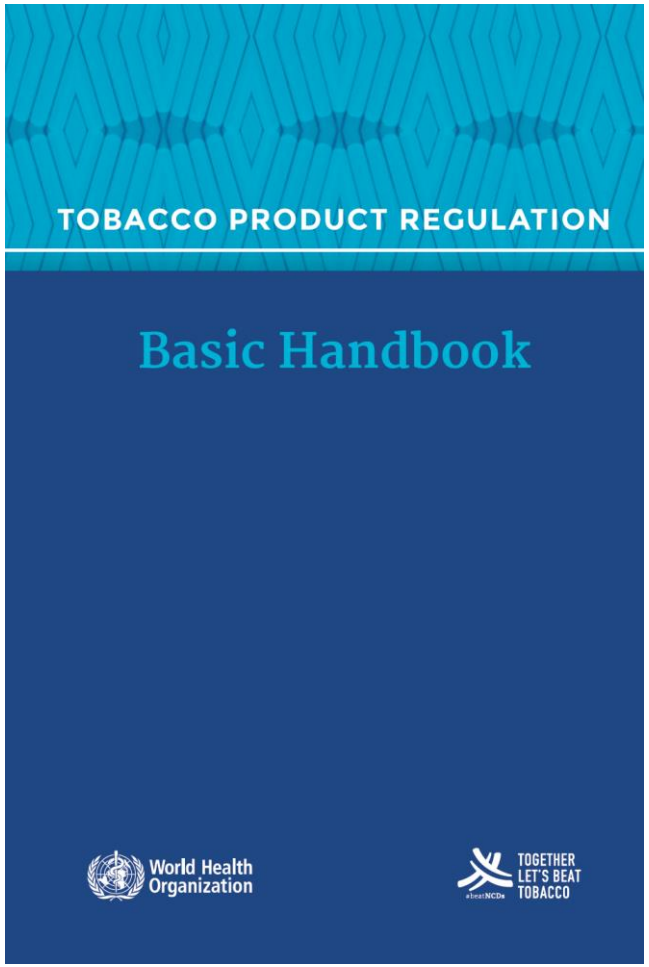

- "**If overall exposure to tobacco product toxicants is reliably lowered, population harm may be reduced** even if large numbers continue to use these products." (WHO Tobacco Handbook, p.7)
- "For the **purposes of developing a regulatory approach, it may prove useful initially to distinguish new products according to their relative degree of difference from traditional combusted or non-combusted tobacco products**." (WHO Tobacco Handbook, p.49)
- "In the case of novel, new or modified TRPs, it may be **necessary or desirable to consider the need for additional regulations** addressing the specific challenges posed by these products. For novel TRP (category 1) and novel technology (category 2) products, **this may include consideration of the kinds of health claims permissible** (if any), or differences relative to other existing tobacco products in how these products may be marketed or sold." (WHO Tobacco Handbook, p.50)
- "For countries where novel TRPs are permitted**, health authorities should at a minimum: (…) "provide adequate risk communication messages to the public,** while avoiding the trap of increasing public knowledge of the products on behalf of the tobacco manufacturers." (WHO Tobacco Handbook, p.55)

http://www.who.int/tobacco/publications/prod_regulation/basic-handbook/en/

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What Have We Created?

Creating a new category: Reduced-Risk Products

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Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

We have a range of RRPs in various stages of development, scientific assessment, and commercialization.

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

Best-in-Class R&D Capability in the Industry

Since the spin-off from Altria (2008), PMI has significantly enhanced its R&D capabilities

1. Invested more than USD 4.5 billion
2. Hired more than **430 R&D experts** – more than one-third of our scientists have a life sciences background
3. Portfolio of more than **4,300**(a) **granted patents** worldwide
4. Pipeline of around **6,000**(a) **pending patent applications**
5. **58th largest patent filer** in EU(b), only tobacco company in top 100

(a) Status at December 31, 2017 - Source: PMI Research & Development
(b) European Patent Office (EPO) Statistics (link) - Top 100 applicants 2017

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PMI's Reduced-Risk Product Portfolio

Our objective is to offer adult smokers who would otherwise continue to smoke Reduced-Risk Products to which they could completely switch

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

E-VAPOR PRODUCTS

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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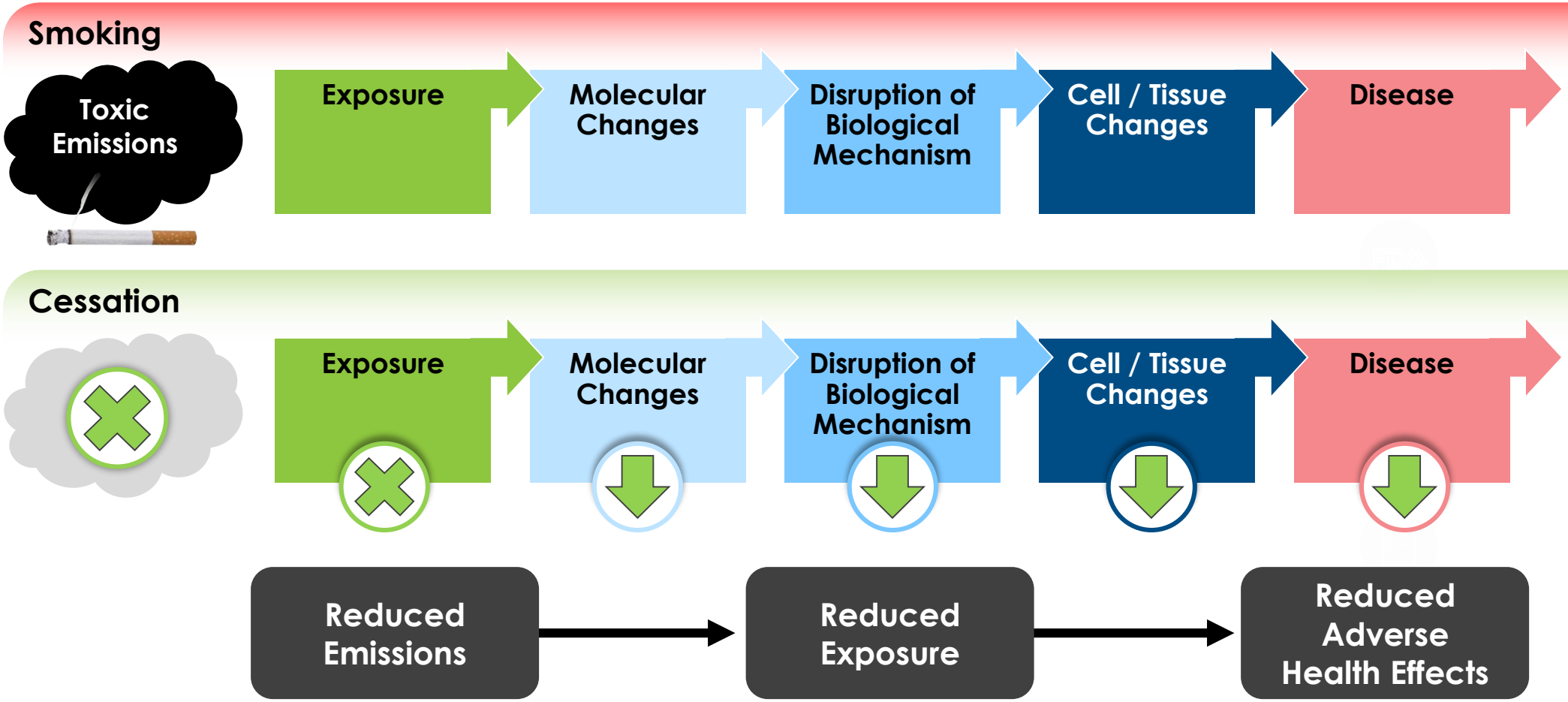
How Did We Create It?

Substantiating Reduced Risk: Assessment Framework



The health risks of **smoking** and **the reversal** of risks **after quitting smoking** are well established (IARC 2004, 2007)

The U.S. Institute of Medicine's "gold standard" for assessing risk reduction: benchmark against cessation

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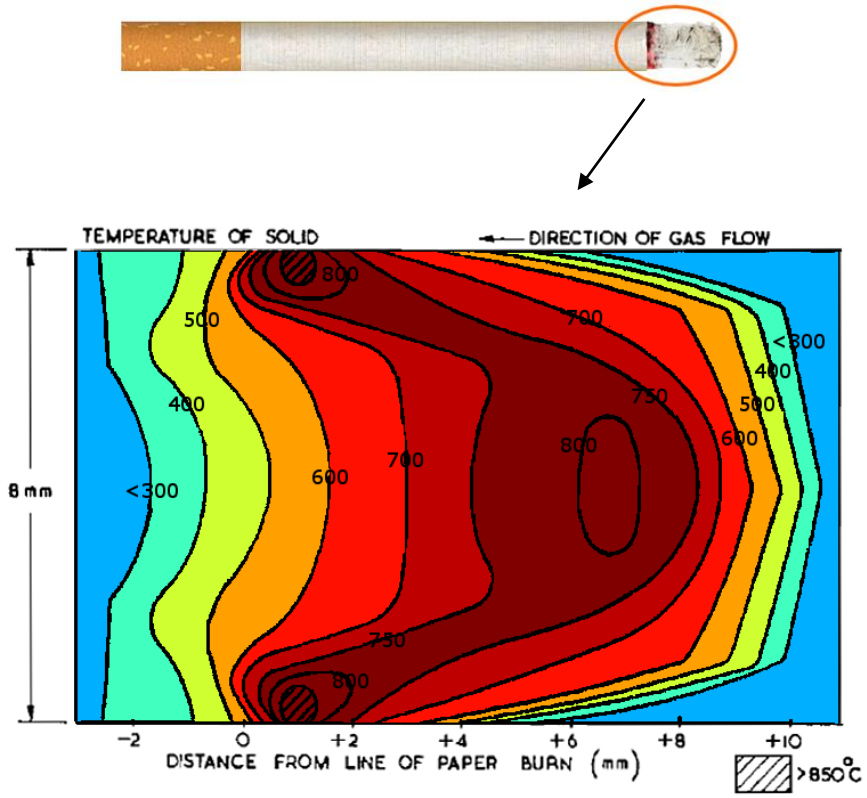
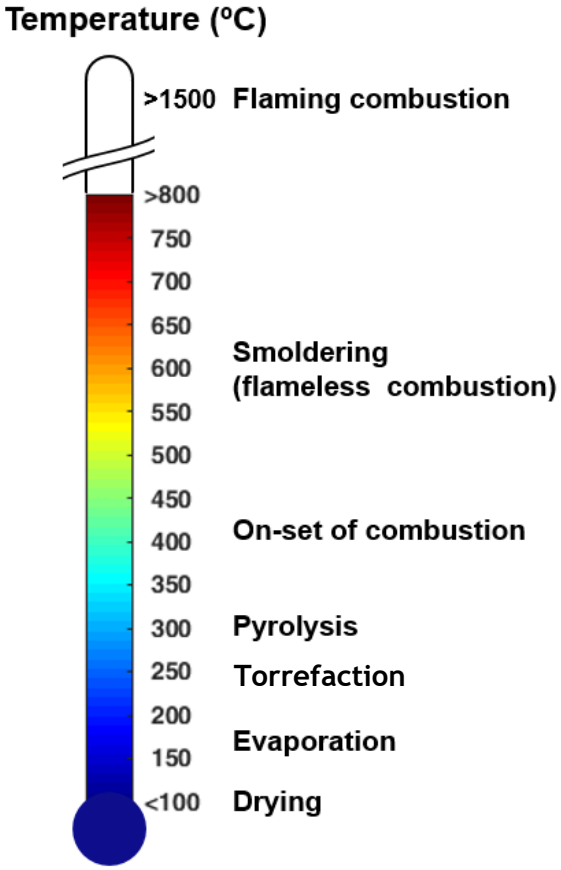
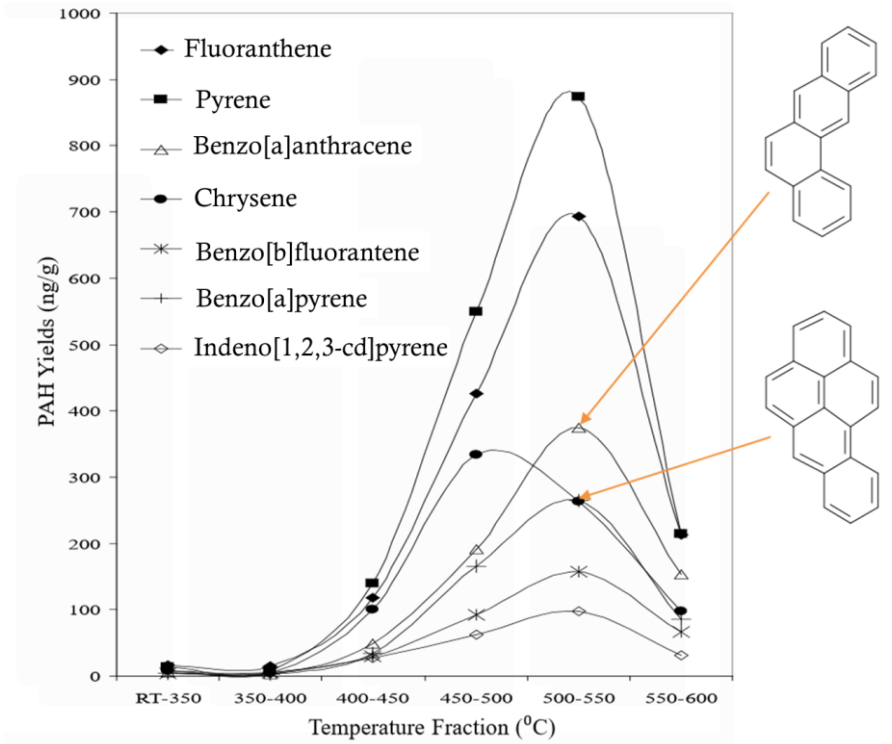
Eliminating Combustion Is Key…



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.



- 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

- More than **6,000** constituents have been identified in cigarette smoke
- About **100** of these constituents are categorized as **harmful or potentially harmful constituents (HPHC)**

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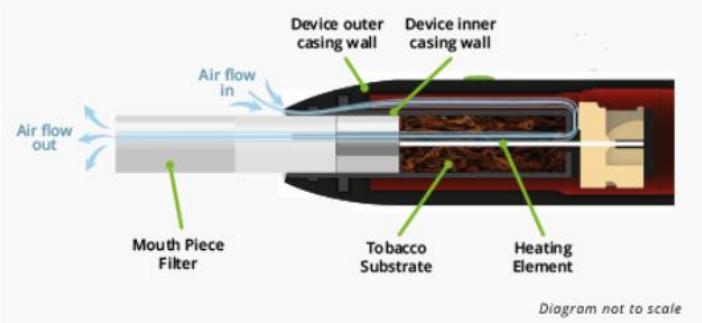
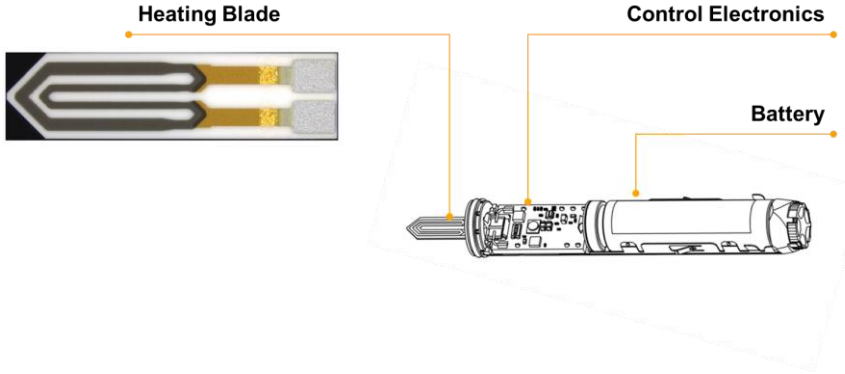
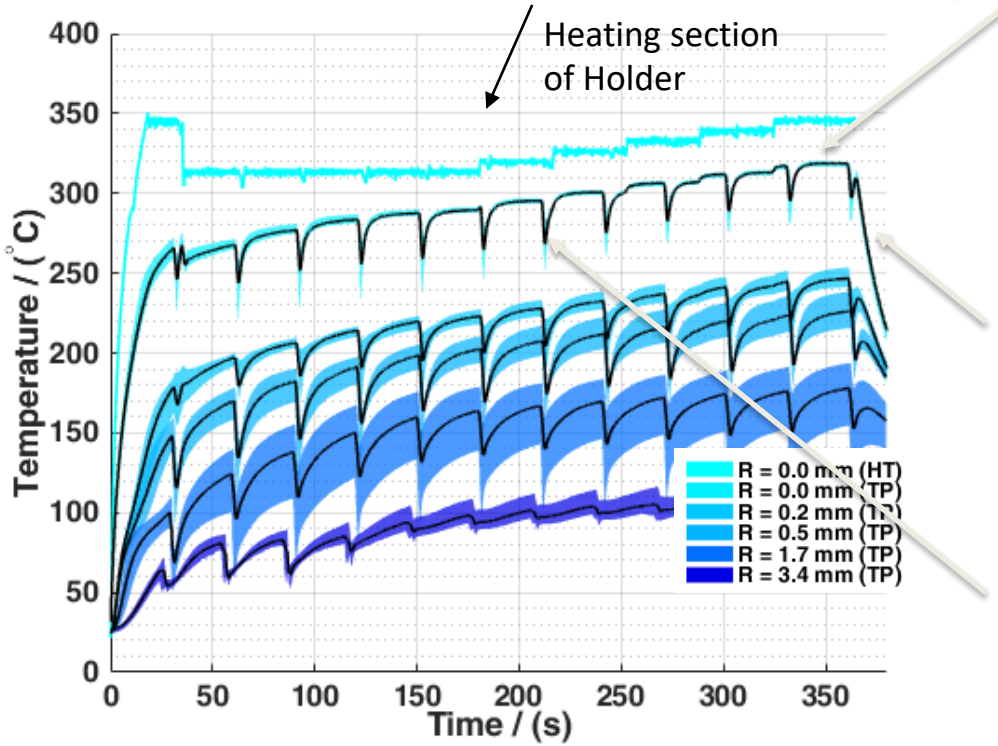
Product Development: Absence of Combustion







The tobacco touching the heater surface reaches a maximum temperature of 320°C, well below the temperatures required for combustion of the tobacco to occur.

Temperature drop when the heater is stopped while puffing. This indicates that no self-sustaining combustion occurs.

Temperature drop each time a puff is taken. The system needs to compensate by bringing heat.

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

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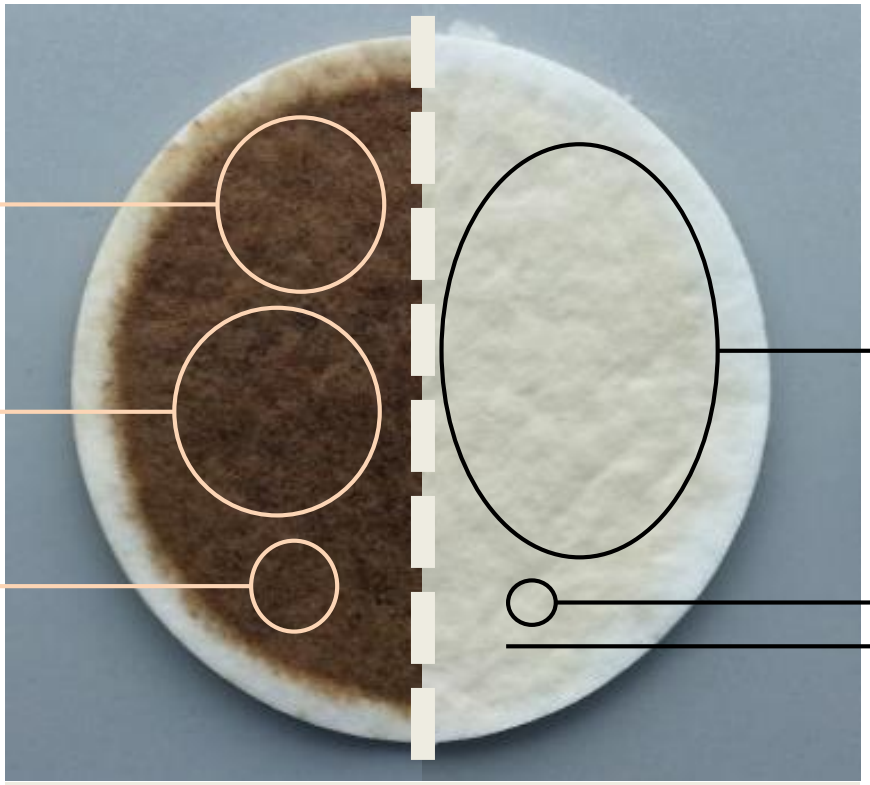
Why Heat Tobacco Rather than Burn It?

Water and glycerin form 50% of smoke mass

Toxicants

Contains carbon-based solid particles



Water and glycerin form 90% of aerosol mass

Toxicants reduced by >90%

No carbon-based solid particles

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

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Note: THS stands for Tobacco Heating System version 2.2

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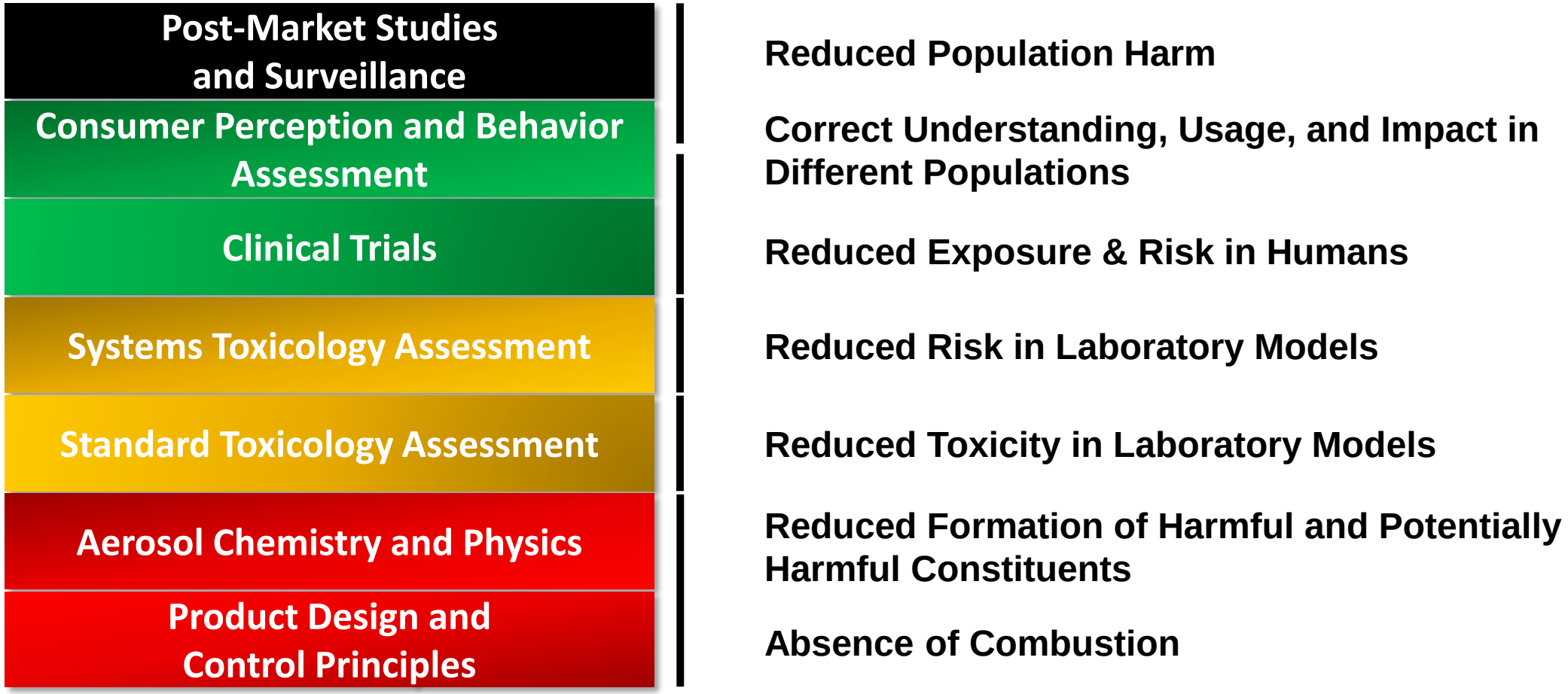
How Did We Assess It?

PMI's Scientific Assessment Approach



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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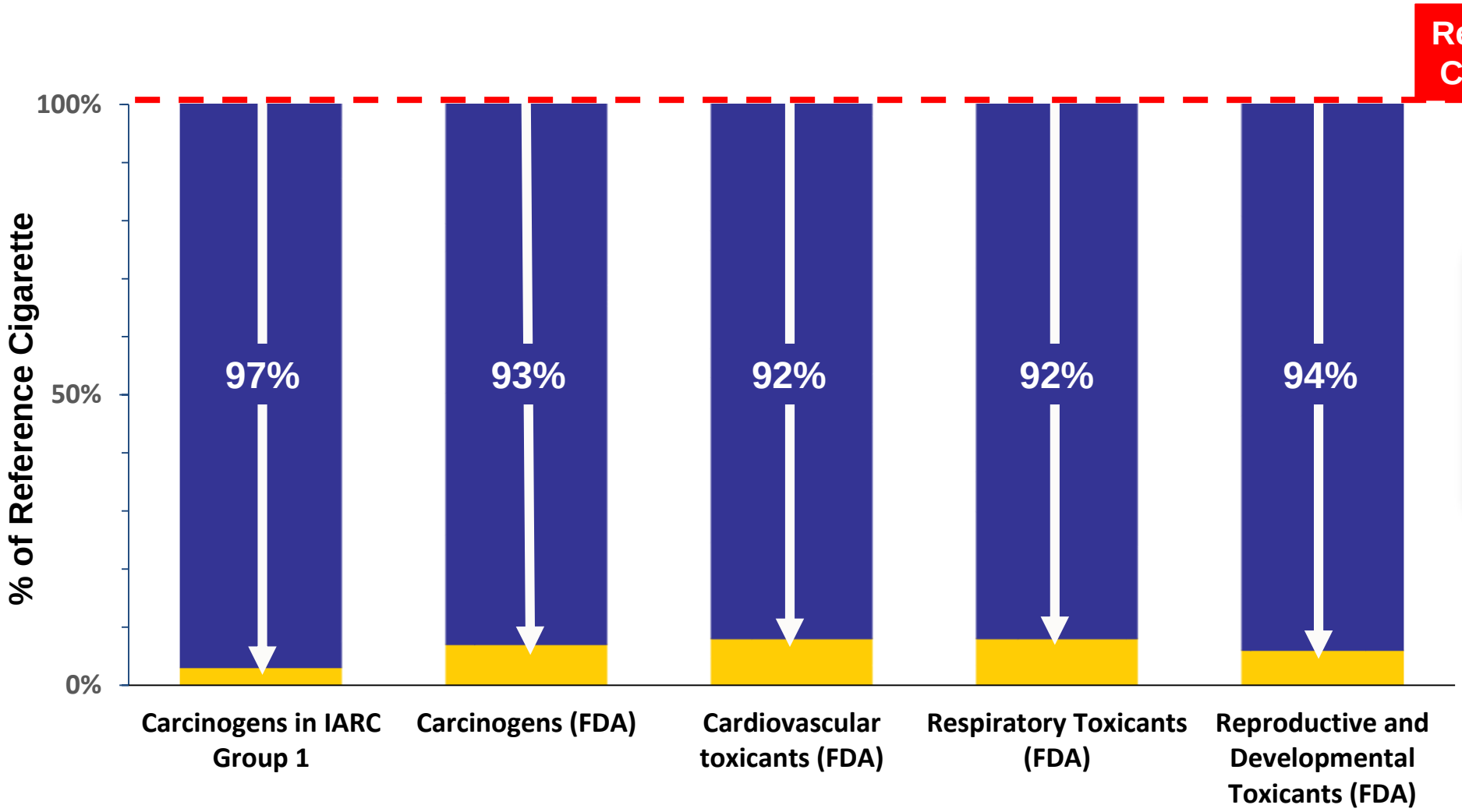
Results So Far

Reduced Formation of HPHCs by Disease Categories



No. of toxicants	**12**	**29**	**8**	**18**	**7**

THS 2.2 produces an aerosol that contains **on average 90-95% lower levels of HPHCs than a reference cigarette**.

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

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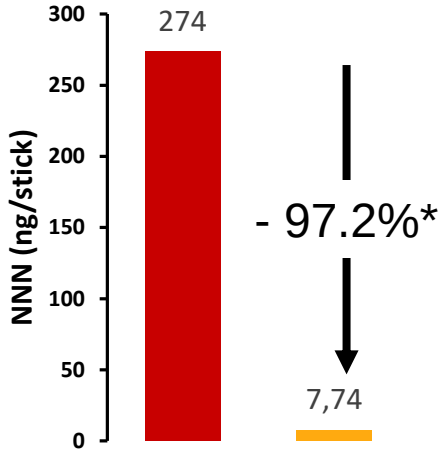
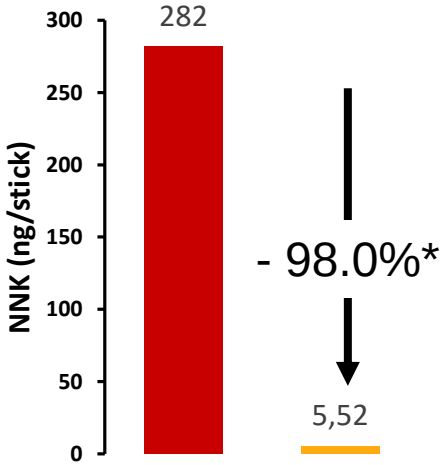
Changes in Exposure to HPHCs: Reduced Exposure in Healthy Human Subjects

HPHCs Are Drastically Reduced in IQOS Aerosol





* On equivalent nicotine basis

Leads to

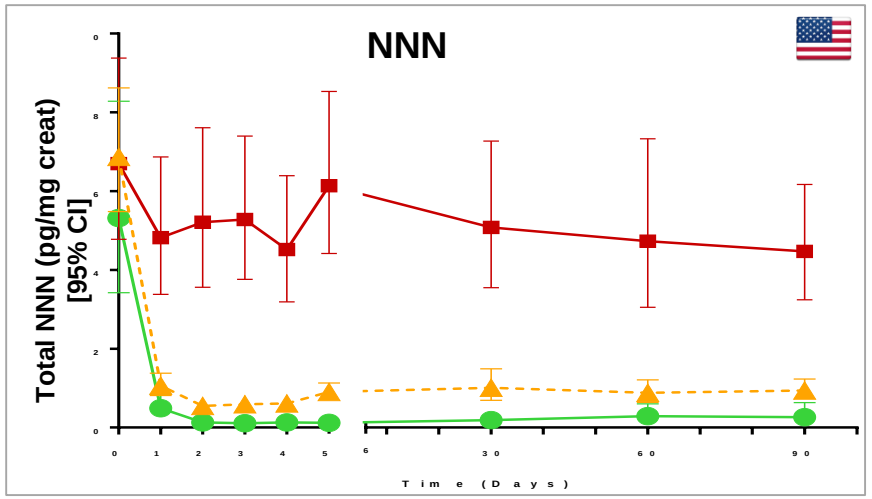
Cigarette

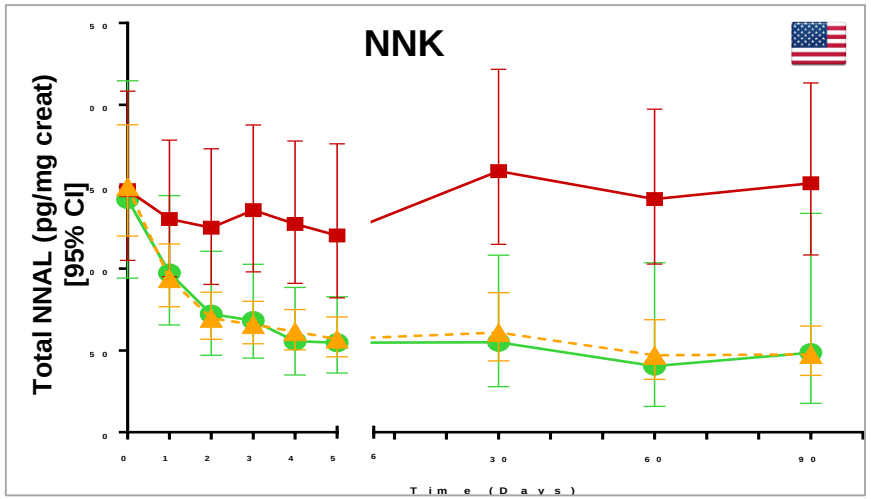
IQOS

Smoking Abstinence

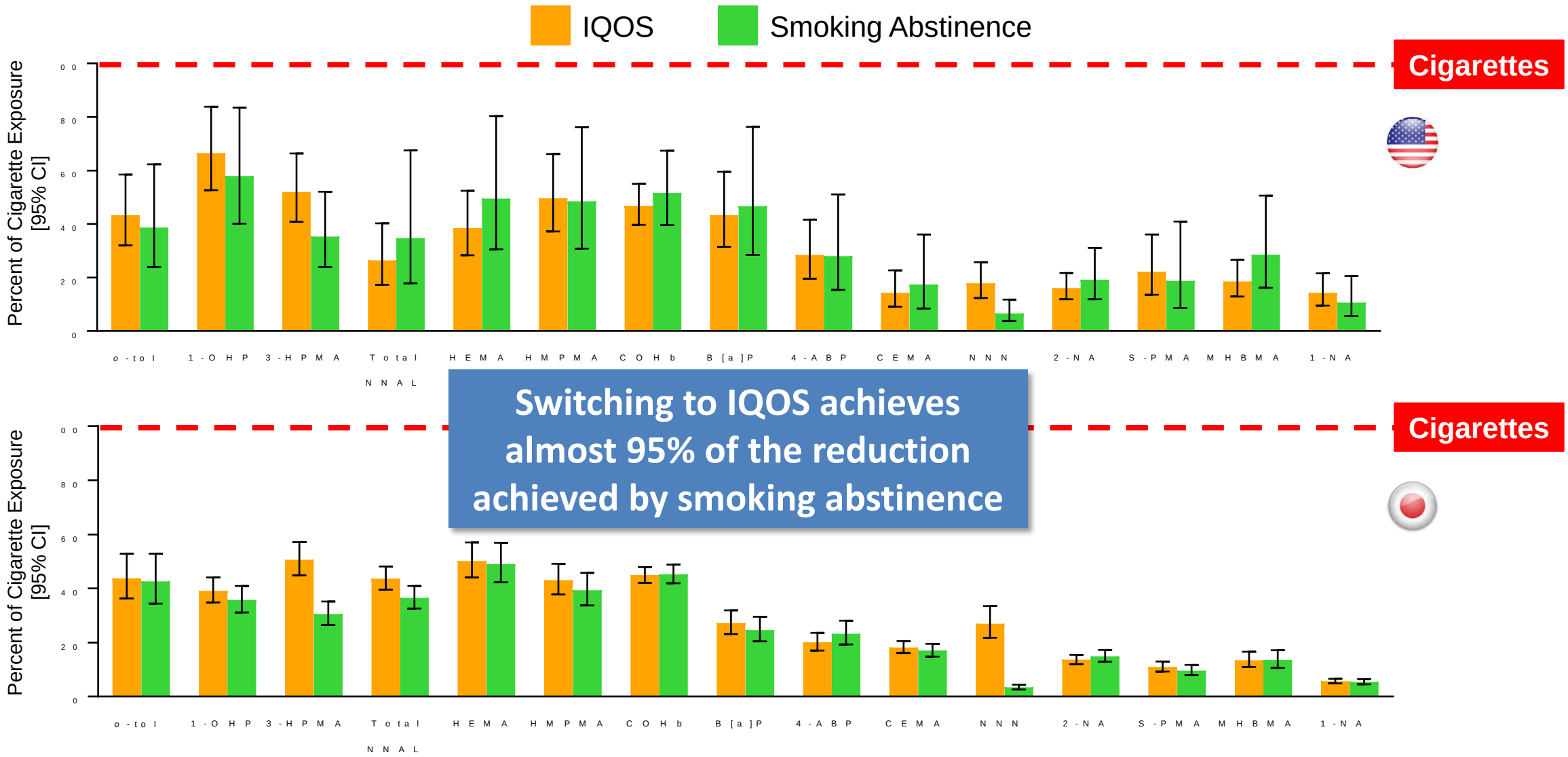
Leads to

Exposure Is Significantly Reduced After Switching to IQOS





Reduced Exposure Similar to Smoking Abstinence: Reduced Exposure in Healthy Human Subjects



Improvements in Clinical Risk Endpoints After Six Months

Pathomechanisms	Co-Primary Endpoints	Type of Change	Observed Change*	Halperin-Rüger Adjusted CI	1-Sided p-Value (0.0156)	THS Directional Change vs. SA (Literature)
Lipid Metabolism	**HDL-C**	Difference	3.09 mg/dL	1.10, 5.09	<0.001**	✓ Significant
Inflammation	**WBC Count**	Difference	–0.420 GI/L	–0.717, –0.123	0.001 **	✓ Significant
Endothelial Function	**sICAM-1**	% Reduction	2.86 %	–0.426, 6.04	0.030	✓
Clotting	**11-DTX-B2**	% Reduction	4.74 %	–7.50, 15.6	0.193	✓
Oxidative Stress	**8-epi-$PGF_{2\alpha}$**	% Reduction	6.80 %	–0.216, 13.3	0.018	✓
Acute Effects	**COHb**	% Reduction	32.2 %	24.5, 39.0	<0.001**	✓ Significant
Lung Function	**FEV_1 %pred**	Difference	1.28 %pred	0.145, 2.42	0.008 **	✓ Significant
Genotoxicity	**Total NNAL**	% Reduction	43.5 %	33.7, 51.9	<0.001 **	✓ Significant

- All CREs shifted in the same direction as the smoking cessation effect observed in the literature
- 5 out of 8 clinical risk endpoints were statistically significant compared to continued smoking

Notes:
* Observed change presented as LS Mean Difference / Relative Reduction
** Denotes significant p value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach
These data alone do not represent a claim of reduced risk.
THS stands for Tobacco Heating System version 2.2

Registered on clinicaltrials.gov: NCT02396381

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Adult Consumer Perception and Behavior: Approach and Results

Designed to Measure Risk Perception, Comprehension, and Intention to Use in a Pre-Market Setting:

Effect on Tobacco Use Behavior Among Adult Smokers

Effect on Tobacco Use Initiation Among Adult Non-Smokers

Effect on Consumer Understanding and Perceptions

- **Non-intended audiences express negligible intention to use**
- **Adult smokers correctly understand the tested reduced risk communication**
- **Adult smokers correctly understand that THS 2.2 is <u>not without risk</u> and is <u>not an alternative to quitting</u>**
- **Adult smokers react positively to the THS 2.2 proposition and express sizeable intention to use**

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Increasing Number of Third-Party Studies

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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Independent Verification of PMI's Science – Governmental Bodies

Federal Institute for Risk Assessment (BfR) (Germany, 2018) – in line with our results:

"The herein confirmed reductions of relevant toxicants by about 80-99% are substantial"

U.S. Food and Drug Administration (FDA) Briefing Document (U.S., 2018) – in line with our results:

"*The independent testing performed by STL* [FDA's Southeast Tobacco Laboratory] *confirmed the lower levels of selected [*harmful and potentially harmful compounds*] HPHCs in the aerosol from the HeatSticks compared to mainstream cigarette smoke*."

Public Health England (U.K., 2018) – in line with our results:

"*Compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds. The extent of the reduction found varies between studies*."

National Institute for Public Health and the Environment (RIVM) (Netherlands, 2018) – in line with our results:

"The use of heatsticks with the IQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes."

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Scientific Substantiation Results to Date

The totality of the scientific evidence on THS 2.2 demonstrates that it presents less risk of harm to individual adult smokers. MRTP and PMTA applications filed with the U.S. FDA.

Totality of Scientific Evidence Supporting Reduced Risk Potential

- No combustion
- Reduced toxicant formation
- Reduced toxicity
- Reduced exposure
- Reversal of clinical risk endpoints
- Pre-market perception & behavior assessment
- Validated Population Health Impact Model

Reduced Impact on Users and Those Around Them

- Less smell
- No ash
- No risk of burning
- No negative impact on indoor air quality

Improved Oral Hygiene

- Better breath
- Less unpleasant after taste
- Reduced tooth staining

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