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Heat-not-Burn Products: Scientific Assessment of Risk Reduction

Global Tobacco and Nicotine Forum 2015 Annual Meeting

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Philip Morris International R&D
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Developing Scientific Evidence: An Overview of PMI's Approach

Aerosol Chemistry	**Reduced Formation** of Harmful and Potentially Harmful constituents
Non-Clinical Studies	**Reduced Toxicity and Risk** in Laboratory Models
Clinical Studies	**Reduced Exposure** in Adult Smokers **Reduced Risk** in Adult Smokers
Population Impact Assessment	**Perception and Behavior Assessment** in Adult Smokers and Non-Smokers **Population Impact Modeling**
Post-Market Surveillance	**Prevalence** **Safety Surveillance**

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Heat-not-Burn

Product-Specific iQOS Science

Absence of Combustion

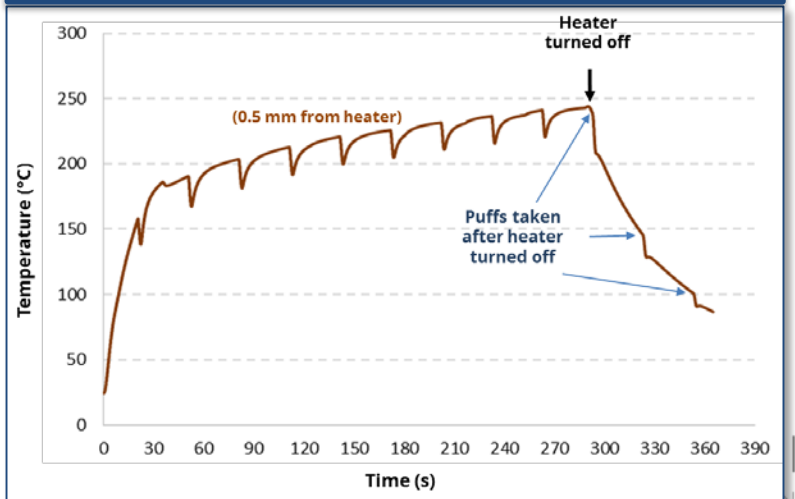
Combustion Basics

Fuel + Oxidizer (O_2) = Ashes and Gases + Energy/ Heat

Multiple different experimental observations show operation of *iQOS* does not result in the combustion of tobacco. This has been verified by multiple international combustion experts

- Operating iQOS and *Heatsticks* in an atmosphere of nitrogen – *where one of the essential elements for combustion (oxygen) is excluded* – yields equivalent aerosol composition compared to experiments run in air
- Measuring tobacco temperature (0.5mm from the heater) shows that it reaches a maximum of 250°C – well below the temperature of combustion

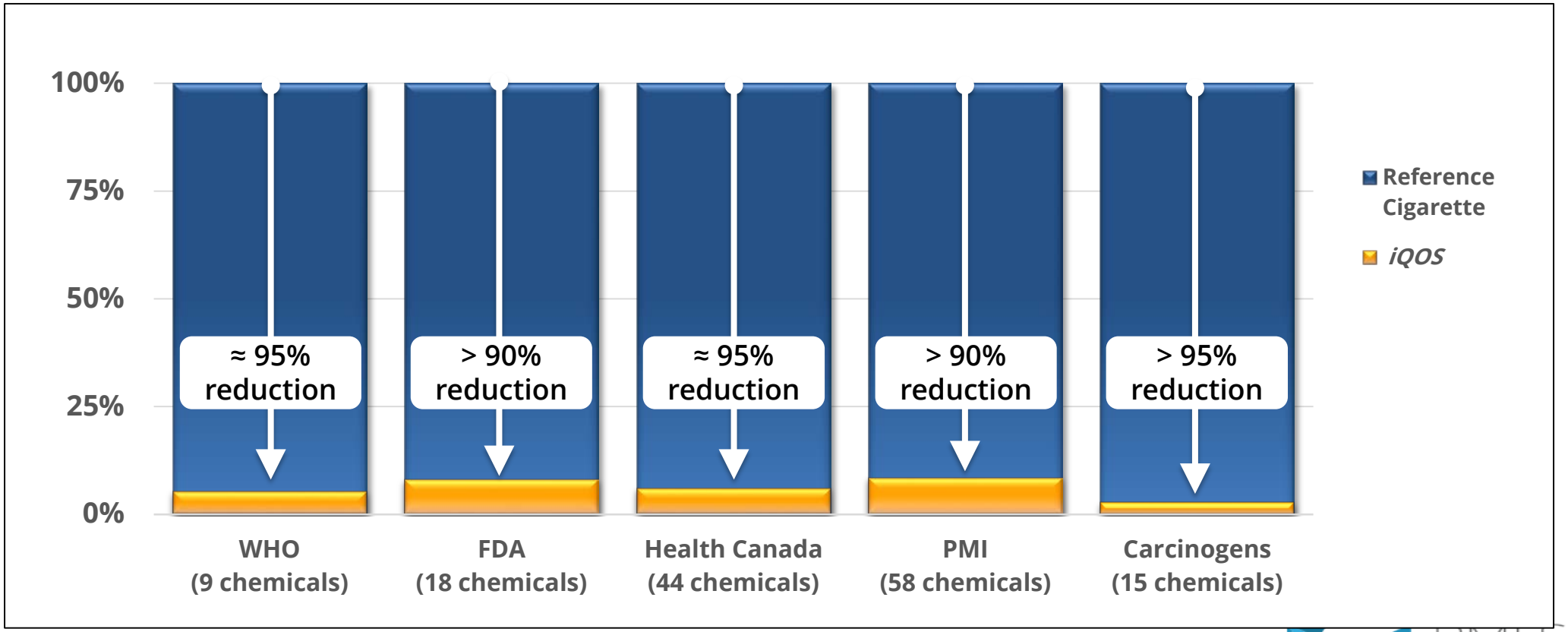
Tobacco Temperature Measurements



Reduced Formation

Aerosol Chemistry

Average reductions in formation of harmful or potentially harmful constituents for *iQOS* compared to levels measured in smoke from the 3R4F reference cigarette*



*Aerosol collection with Intense Health Canada's 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

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Indoor Air Quality

Aerosol Chemistry

Study conducted with analytical methods and facilities that are accredited under ISO17025 simulating real life situations in a controlled environment

Category
ISO Environmental Tobacco Smoke Markers 6 substances
Carbonyls 4 substances
Volatile Organic Compounds 5 substances
Inorganics 3 substances

Total of 18 substances measured

We have demonstrated that the operation of *iQOS* indoors does not have a negative impact on air quality

- ***iQOS* is not a source of Environmental Tobacco Smoke**
- **Levels of 16 substances are the same as background measurements**
- **Nicotine is detectable (1.8 µg/m³) → but at levels 275 fold lower than EU occupational exposure limits[1]**
- **Acetaldehyde is detectable (5 µg/m³) → but at levels 40 fold lower than EU indoor exposure limits[2]**

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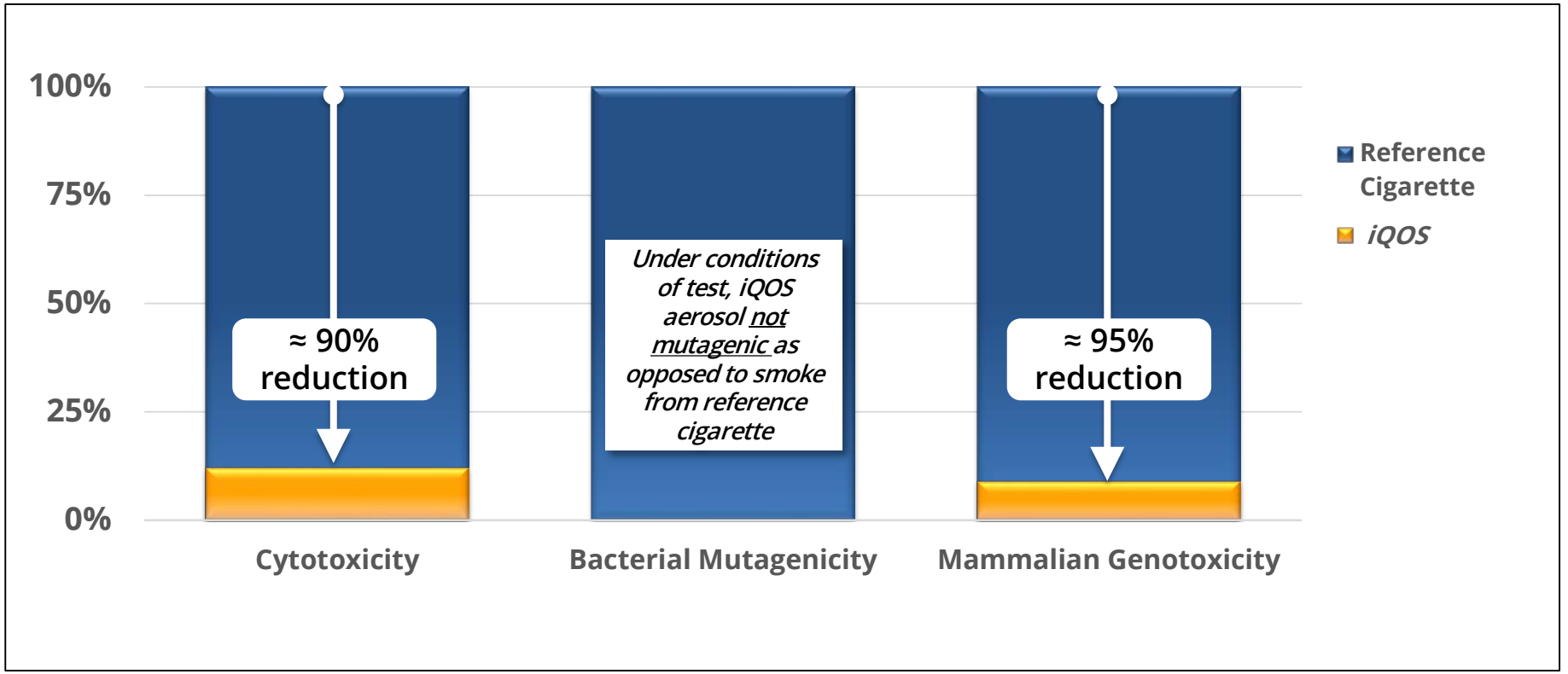
[1] European Agency for Safety and Health at Work: Directive 2006/15/EC
[2] The Index Project, Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU, EC, Joint Research Center, Institute for Health and Consumer Protection, January 2005

Reduced Toxicity

Non-Clinical Studies

Average reductions in toxicity compared to 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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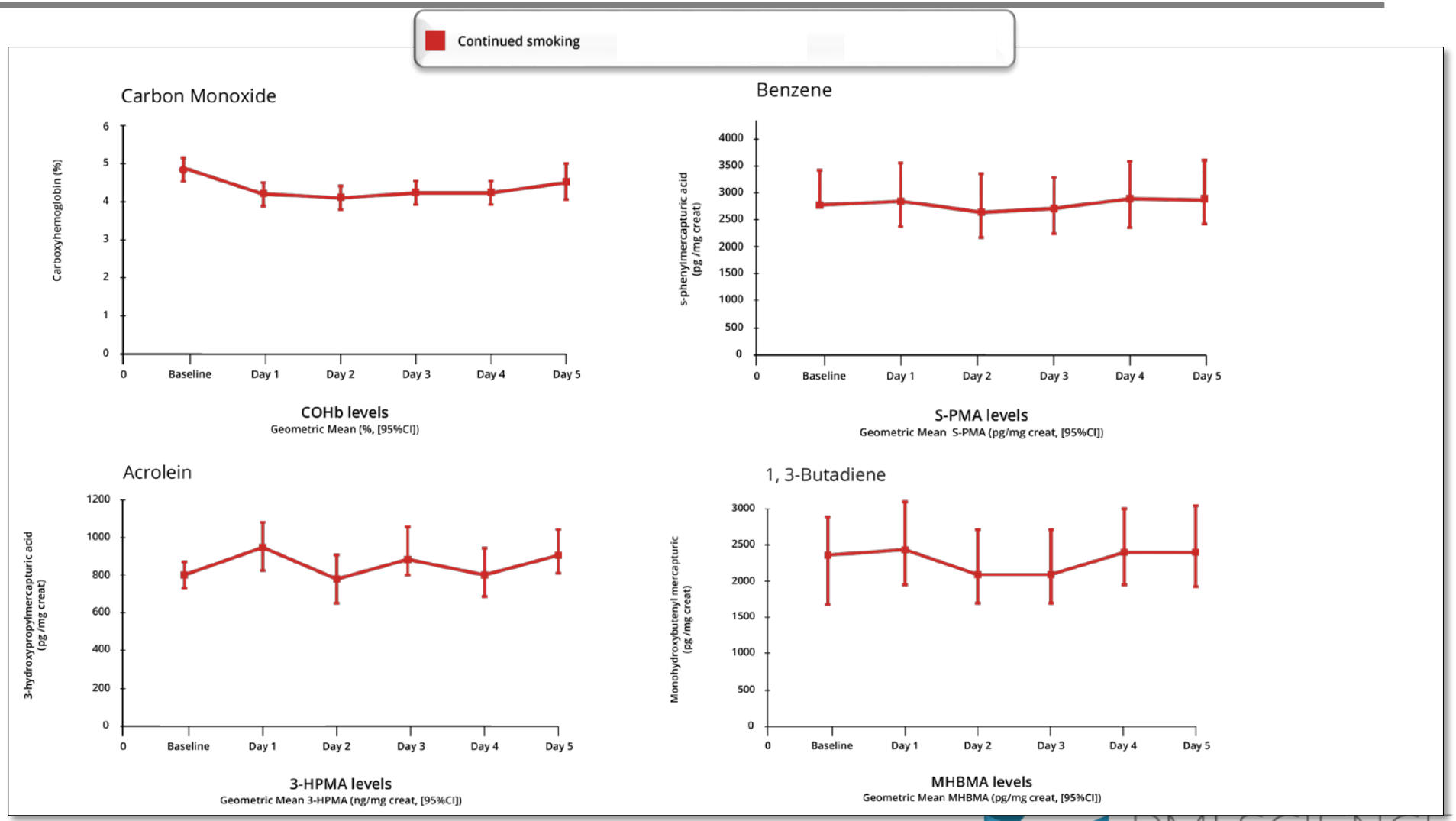
Reduced Exposure

Clinical Studies

Smokers used the products *ad libitum*

Smokers randomized to cigarettes or iQOS were free to use the product as often as they wished



Note: These data alone do not represent a claim of reduced risk.
Source: PMI Research and Development
Registered on clinicaltrials.gov: NCT 01959932

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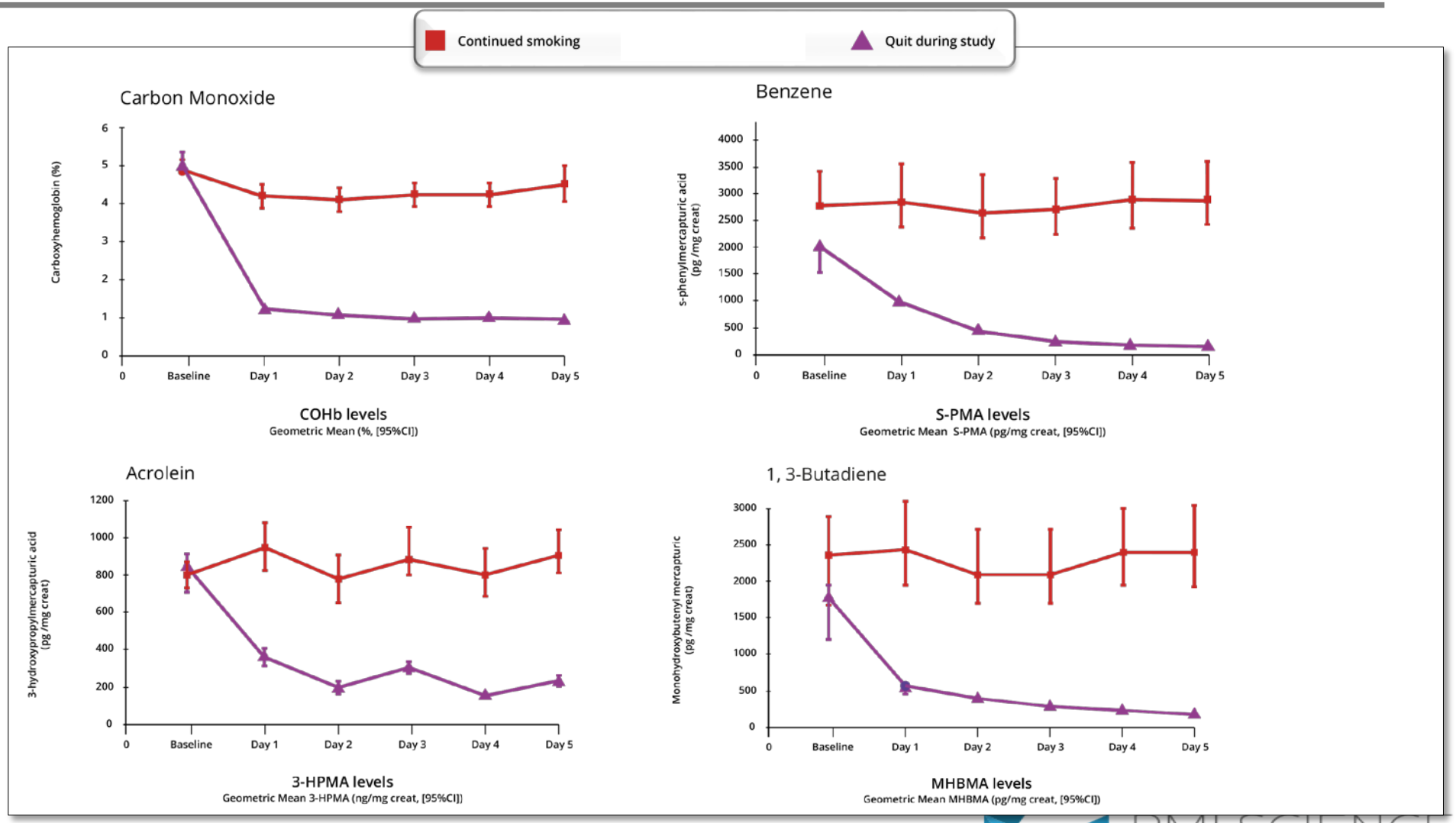

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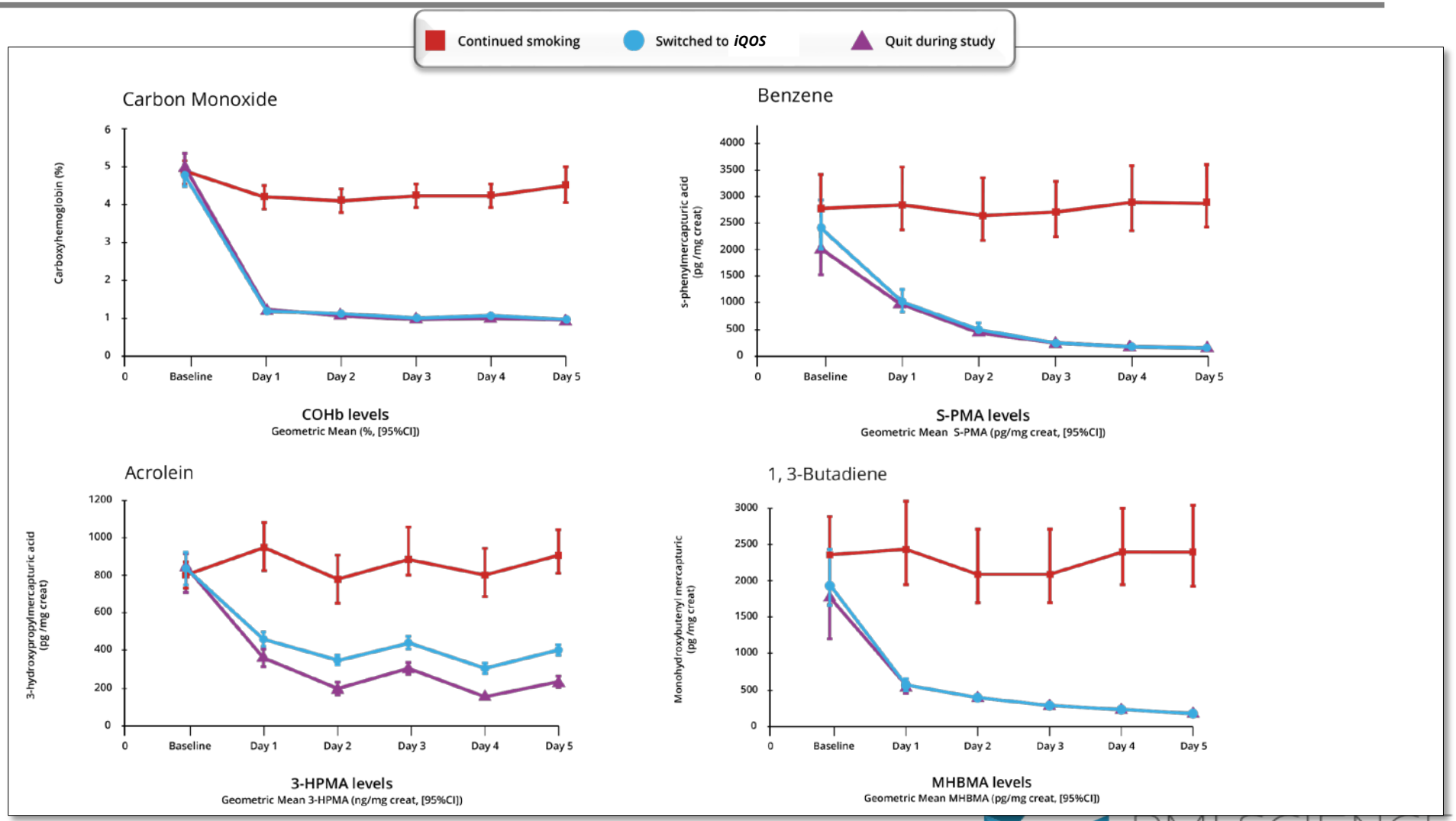

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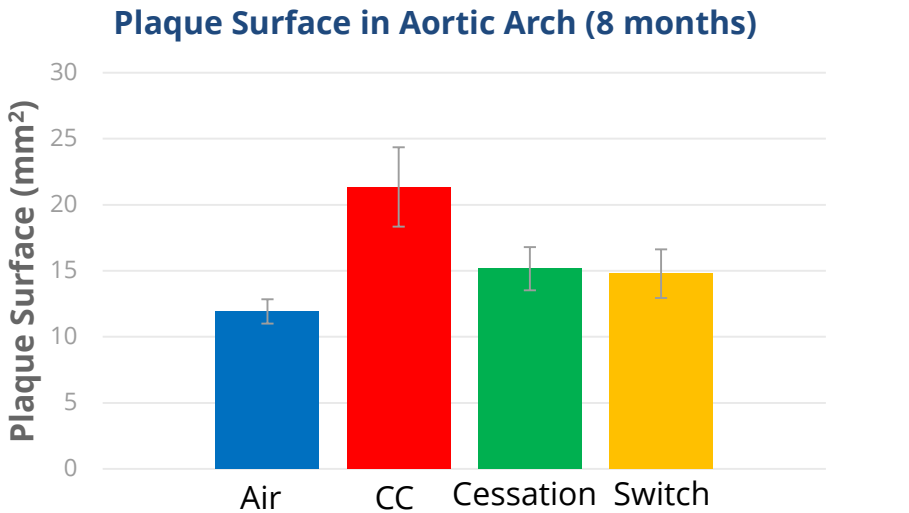
Reduced Risk

Non-Clinical Studies

Clinical Studies

Studies using animal models of disease show favorable changes in smoking-related disease endpoints*

Markers for Cardiovascular Disease and Chronic Obstructive Pulmonary Disease show changes similar to cessation



Human clinical studies verify results obtained in *in vitro* and *in vivo* models

Clinical studies provide pivotal data to show whether favorable changes in disease risk markers are achieved under realistic conditions of use

Clinical program is on-going

Markers known to be associated with smoking-related diseases (including Cardiovascular Disease, Chronic Obstructive Pulmonary Disease and others) are being measured over different timeframes up to 12 months in duration

ClinicalTrials.gov Identifiers:
NCT01970995, NCT01970995, NCT02396381

* Systems toxicology analysis of cardiovascular and respiratory endpoints from ApoE-/- mice showed similar effects after switching to a candidate modified risk tobacco product, THS 2.2, or to smoking cessation. F1000Posters 2015, 6: 206 (poster).

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Assessing a Product's Potential to Contribute to Tobacco Harm Reduction

Adult smokers should be informed on the different risk profiles of products, provided that these differences **are substantiated by robust, product-specific scientific evidence**

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Reduced-Risk Products ("RRPs") is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking combustible cigarettes. PMI's RRPs are **in various stages of development and commercialization**, and we are conducting **extensive and rigorous scientific studies** to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when **compared to smoking combustible cigarettes**.

Before making any such claims, we will need to **rigorously evaluate the full set of data** from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims **may also be subject to government review and approval**, as is the case in the US today.

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Source: Philip Morris International R&D

Data generated by:
Aerosol Chemistry Team
Toxicology Team
Clinical Team
Perception and Behavioral Assessment Team

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