# Summary of Results on the Tobacco Heating System

**3rd July 2017 – Workshop at NAAMA's 30th International Medical Convention**

*Gizelle Baker and Patrick Picavet*

**Philip Morris International R&D**

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.

## 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*

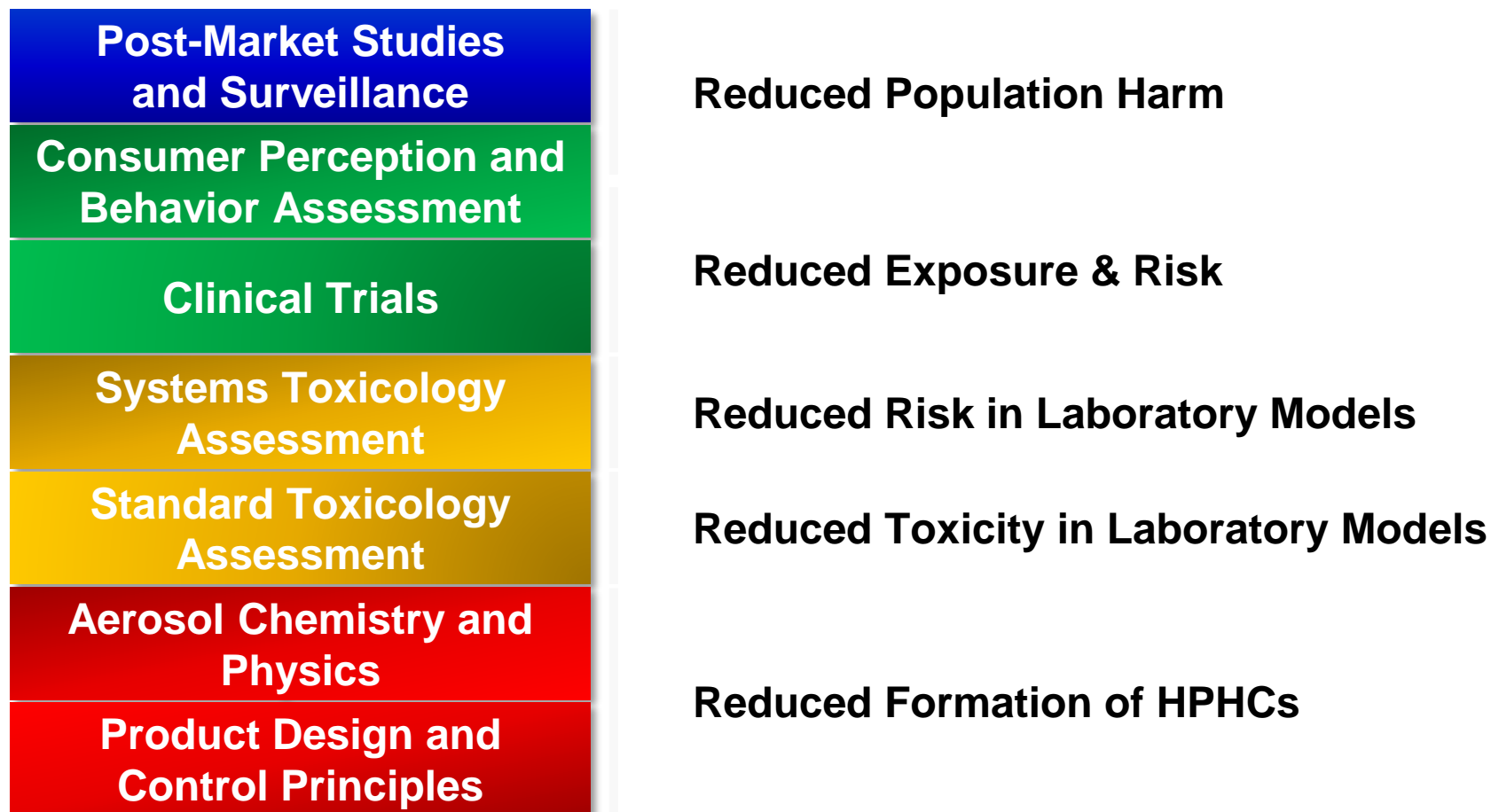$$\text{HARM REDUCTION} = \text{REDUCED-RISK PRODUCT} \times \text{PRODUCT ACCEPTANCE AND USAGE}$$

- 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)
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.

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**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**

**Product Design and Control Principles** → **Reduced Formation of HPHCs**

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

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



RRP HEALTH IMPACT MODELING

Consumer Perception and Behavior Assessment

Clinical Trials

Systems Toxicology Assessment

Smoking

Point of intervention

Switching to RRP

Cessation

[Disease Risk]

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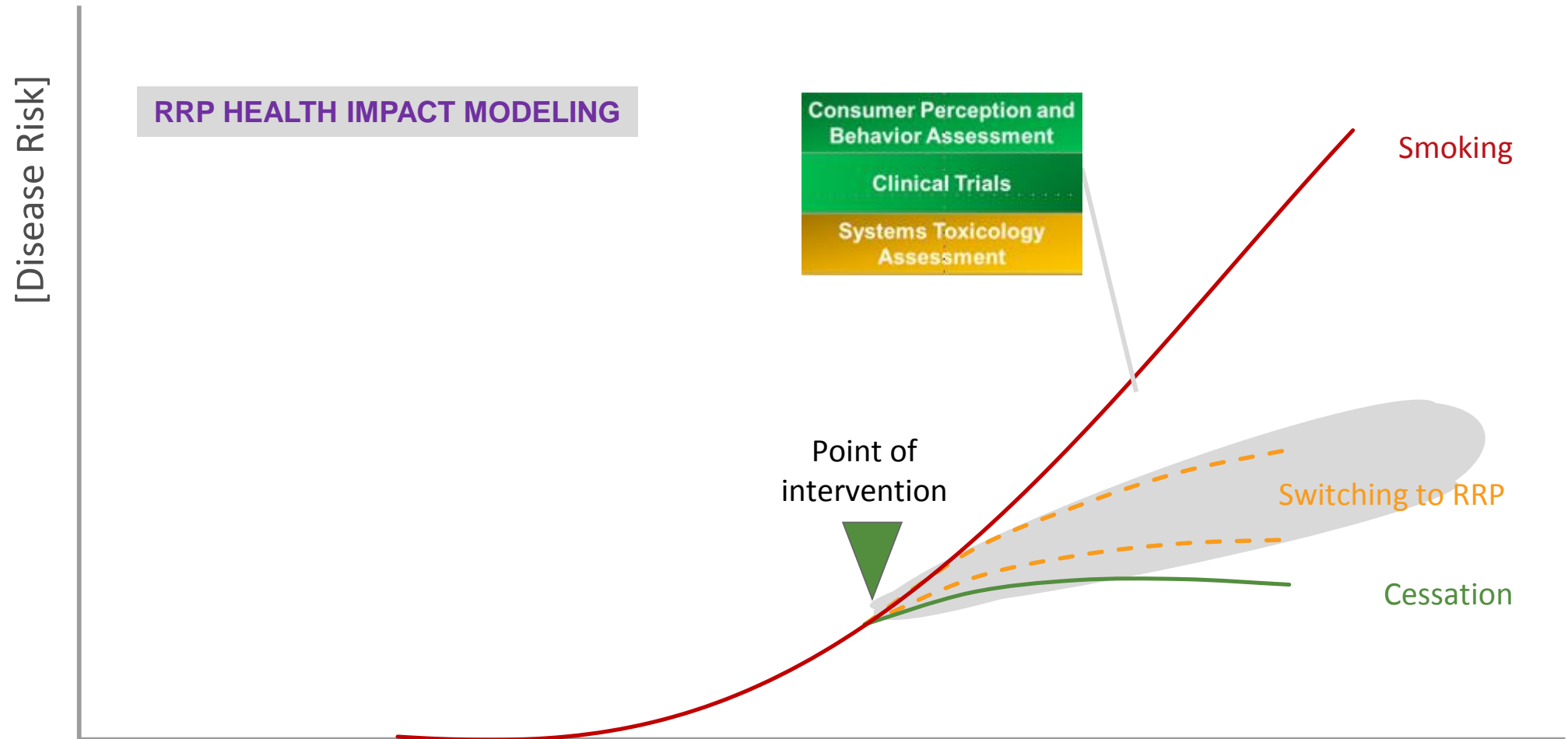
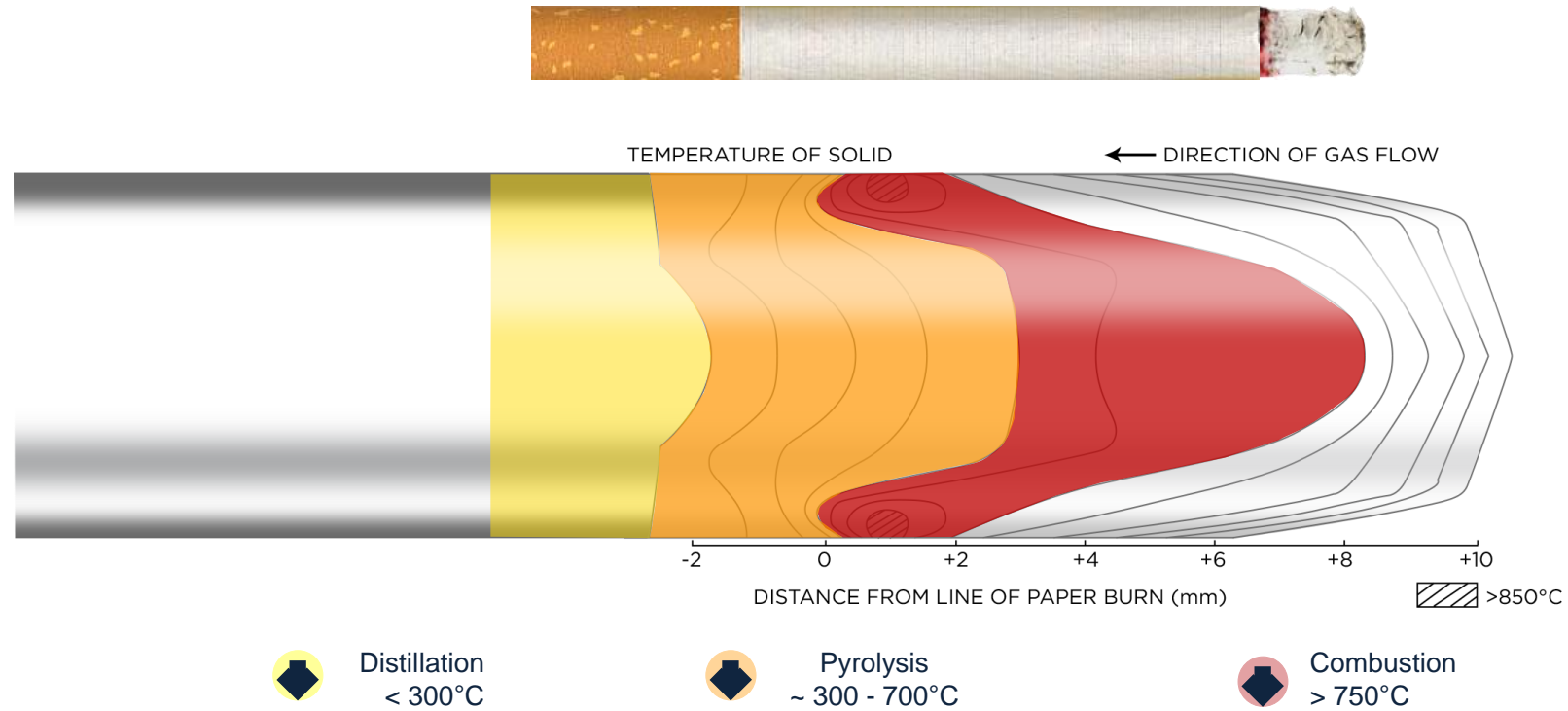[+]Source: IOM (Institute of Medicine), 2012, Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press.

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# Heat-not-Burn

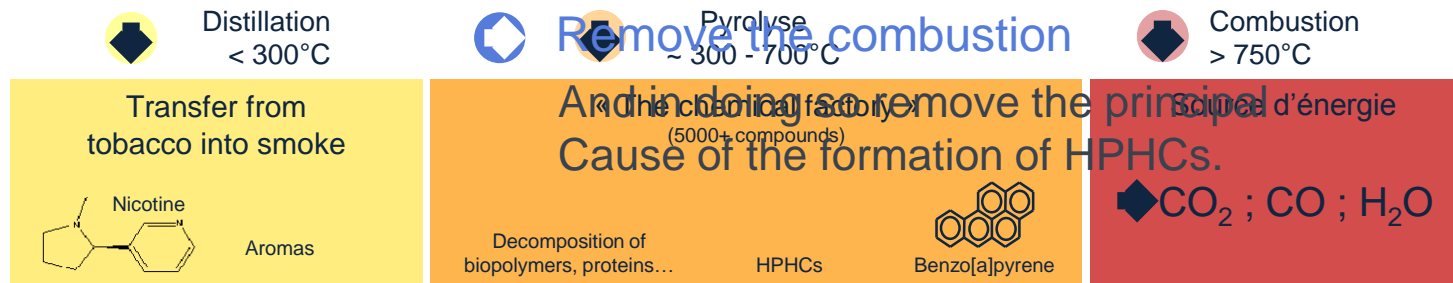*Product-Specific THS Science and Results to Date*

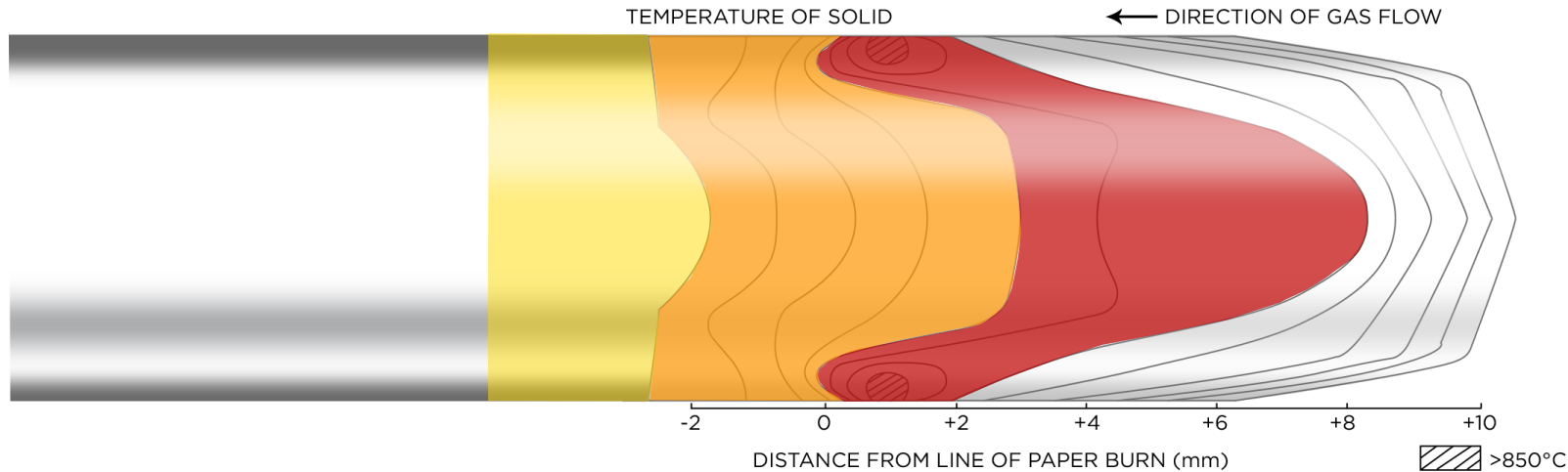TEMPERATURE OF SOLID          ← DIRECTION OF GAS FLOW

-2     0     +2     +4     +6     +8     +10

DISTANCE FROM LINE OF PAPER BURN (mm)          ▨ >850°C

Distillation
< 300°C

Pyrolysis
~ 300 - 700°C

Combustion
> 750°C

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# Impact of the temperature on the formation of toxicants



TEMPERATURE OF SOLID    ← DIRECTION OF GAS FLOW

-2    0    +2    +4    +6    +8    +10

DISTANCE FROM LINE OF PAPER BURN (mm)    >850°C

**Distillation**
< 300°C

**Transfer from tobacco into smoke**

Nicotine

Aromas

**Pyrolysis**
~ 300 - 700°C

**« The chemical factory »**
(5000+ compounds)

Decomposition of biopolymers, proteins...    HPHCs

Benzo[a]pyrene

**Combustion**
> 750°C

Energy source

$CO_2$ ; $CO$ ; $H_2O$

TEMPERATURE OF SOLID ← DIRECTION OF GAS FLOW

DISTANCE FROM LINE OF PAPER BURN (mm)

>850°C

**Distillation**
< 300°C

**Pyrolyse**
~ 300 - 700°C

**Combustion**
> 750°C

Remove the combustion

**Transfer from tobacco into smoke**

« Une chemical factory »
(5000+ compounds)

And in doing so remove the principal
Cause of the formation of HPHCs.

Source d'énergie

Nicotine

Aromas

Decomposition of
biopolymers, proteins…   HPHCs   Benzo[a]pyrene

$CO_2$ ; $CO$ ; $H_2O$

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# Aerosol Chemistry

3R4F        Health Canada smoking regime        THS



Pie chart (3R4F):
- Nicotine [mg/stick]; 2.07
- "Tar" ≈ 23 mg
- Water [mg/stick]; 20.51



Pie chart (THS):
- Others [mg/stick]; 5.25
- Glycerin [mg/stick]; 4.85
- Nicotine [mg/stick]; 1.43
- Water [mg/stick]; 44.65

 ≠
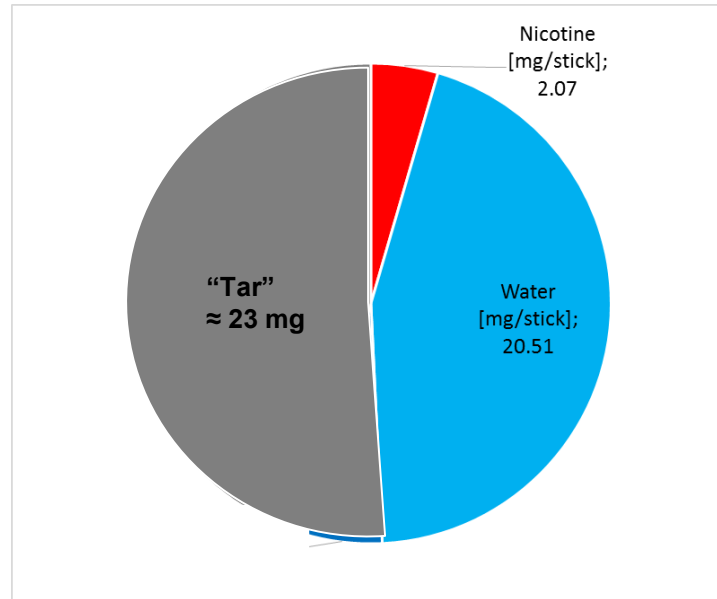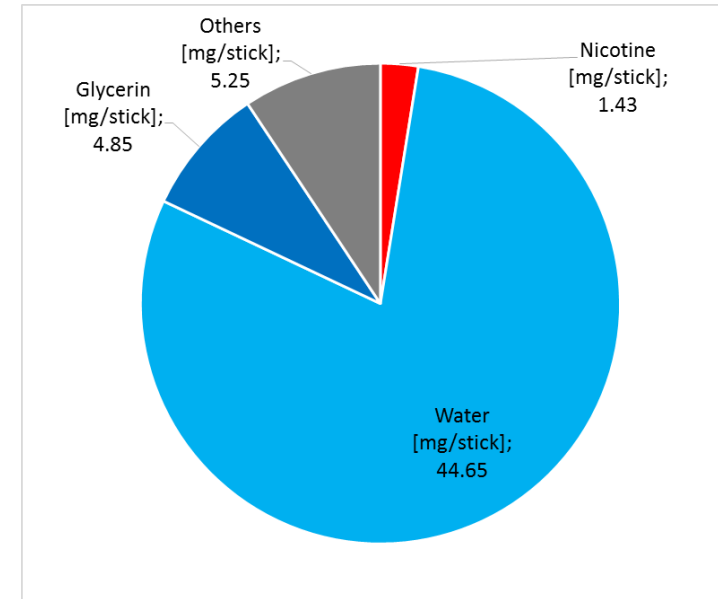
| | |
|---|---|
| Basic Parameters (5) | CO; nicotine; water; TPM; tar; menthol; glycerin |
| Acid Derivatives (3) | acrylonitrile, acrylamide; acetamide |
| Aliphatic Dienes (2) | 1,3-butadiene*; isoprene |
| Aromatic Amines (6) | 1-naphthylamine; 2-naphthylamine*; 3-aminobiphenyl; 4-aminobiphenyl*, o-toluidine*, benzidine |
| Aromatic Hydrocarbons (3) | Benzene*; toluene; styrene |
| Carbonyls (8) | acetaldehyde; acrolein; formaldehyde*; propionaldehyde; acetone; crotonaldehyde; butyraldehyde; methyl ethyl ketone |
| Inorganics (4) | HCN; NOx (NO/NOx); ammonia |
| N-Heterocycles (2) | pyridine; quinoline |
| Phenols (6) | catechol; phenol; hydroquinone; resorcinol; o-,m-,p-cresol |
| PAHs (4) | benzo[a]pyrene*, benz[a]anthracene; dibenz[a,h]anthracene, pyrene |
| TSNAs (4) | NNN*; NNK*; NAT (N'-nitrosoanatabine); NAB (N'-nitrosoanabasine) |
| Metals/Arsenic (7) | Arsenic*; cadmium*; chromium*; lead; nickel*; mercury; selenium |
| Epoxides (2) | propylene oxide; ethylene oxide* |
| Halogen compounds (1) | vinyl chloride* |
| Nitro compounds (1) | nitrobenzene |

\* Classified as carcinogens by IARC

**ISO list (6)** ✔

**Health Canada (45)** ✔

**WHO Tob Reg (9)** ✔

**PMI (58)**

**FDA complete list (93)**

**FDA abbreviated list (18)** ✔

**WHO 39 (2015)** ✔

✔ Included in the PMI 58

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# Aerosol constituents reductions vs. reference cigarette

Chart showing aerosol constituents reductions comparing Reference Cigarette (blue) and THS (orange/Placebo):

| Category | Reduction |
|---|---|
| WHO (9 chemicals) | ≈ 95% reduction |
| FDA (18 chemicals) | > 90% reduction |
| Health Canada (44 chemicals) | ≈ 95% reduction |
| PMI (58 chemicals) | > 90% reduction |
| Carcinogens (15 chemicals) | > 95% reduction |

Legend:
- Reference Cigarette
- Placebo / THS
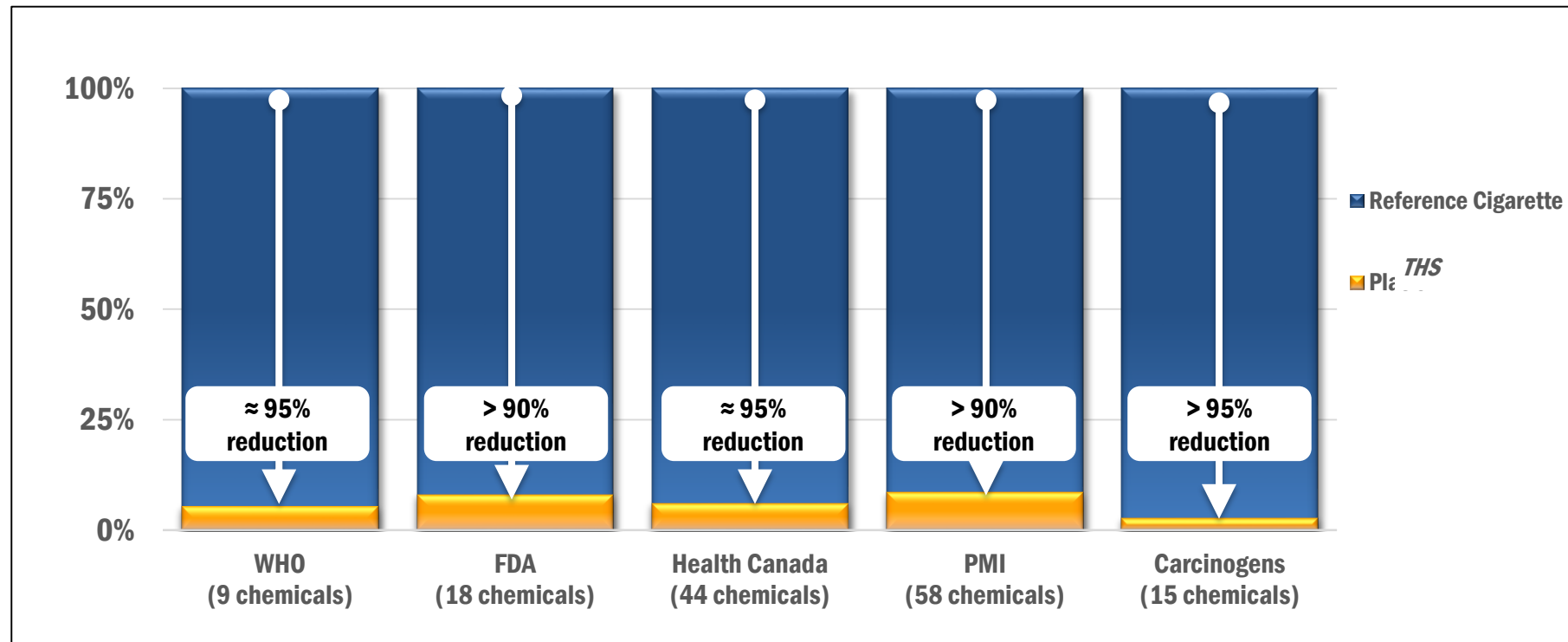
*Aerosol collection with Intense Health Canada's Smoking Regime (55 mL puff volume, 2 second puff duration, 30 second interval puff);
Comparison on a per-stick basis
Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter

**Reduced formation of HPHC's**

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# Toxicological assessment of cigarette smoke and aerosols from potentially Reduced Risk Products and nicotine

Philip Morris International

Overview of design/methods and results of the pre-clinical assessment of aerosol from the potentially Risk-Reduced Product (pRRP) THS, compared to smoke from the reference cigarette 3R4F :

*In vitro* assessment – cytotoxicity and mutagenicity

*In vivo* assessment – standard and systems toxicology

THS: Tobacco Heating System, commercialized as iQOS

Average reductions in <u>toxicity</u> compared to levels measured for the 3R4F reference cigarette.  Measured using Neutral Red Uptake, AMES and Mouse Lymphoma Assays



100% ⎯⎯⎯ **3R4F**

75%

■ Reference Cigarette

■ Plat **THS 2.2**

50%

*Under conditions of test, THS aerosol <u>not</u> mutagenic as opposed to smoke from reference cigarette*

**≈ 90% reduction**

**≈ 95% reduction**

25%

0% ⎯⎯⎯ **Air**

Cytotoxicity | Bacterial Mutagenicity | Mammalian Genotoxicity
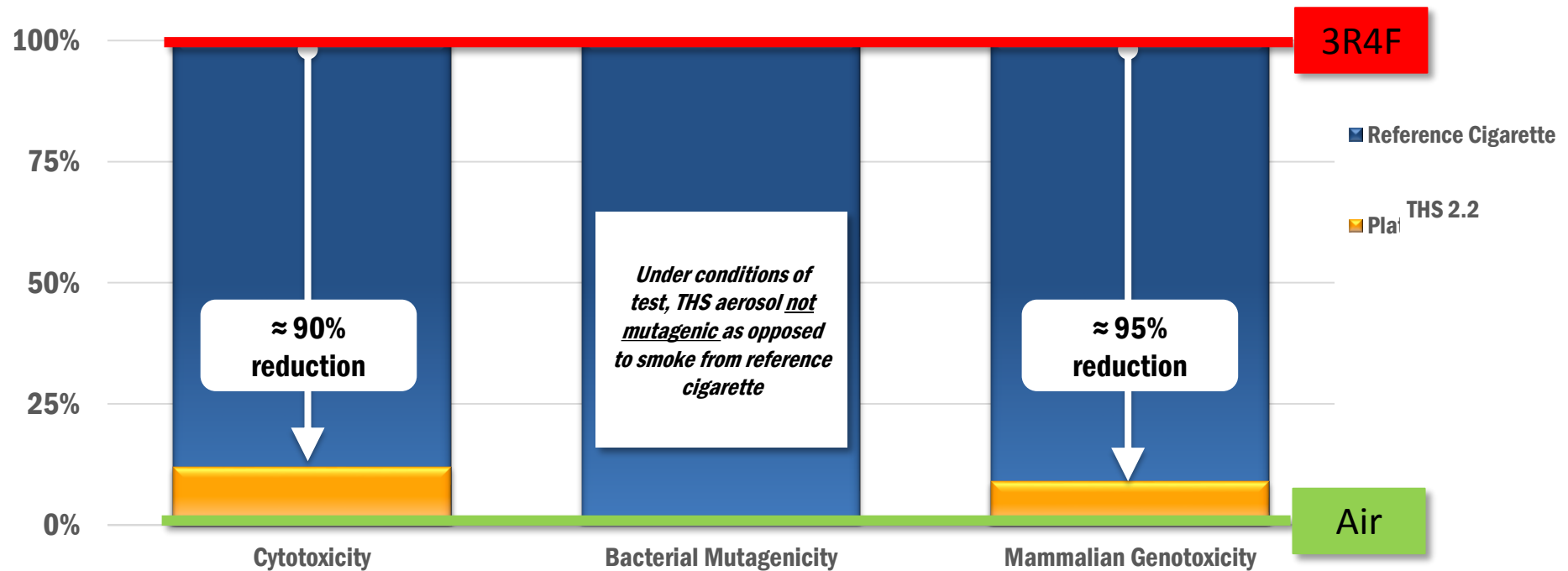
Comparison on a per-nicotine basis
Note: These data alone do not represent a claim of reduced exposure or reduced risk.
Source: PMI Research and Development

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# System Toxicology Research: Identify and Represent Disease Mechanisms

## Understanding of disease onset and progression

Chronic Cigarette Smoke Exposure → Molecular changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Physiological changes → Disease (CVD, COPD, Lung cancer)

Analytical Chemistry | Biological Networks – Systems Biology/Toxicology | Medicine

Literature-derived knowledge

TXT

Data-derived knowledge

Identify & Build Biological Network models

Xenobiotic metabolism network model



*Hoeng et al.*, Case Study: The Role of Mechanistic Network Models in Systems Toxicology. **Drug Discovery Today**, 2013, 19:183-192. (PMID: 23933191)

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**Exposure**

Test items

Test system

**Multi-Omics Data**

**Systems Response Profile**

**Biological Network models**

**Network Perturbation Amplitudes**

**Biological impact factor (BIF)**

3R4F

Sham

pRRP

-log10(fdr): how reproducible is the change across replicates

Downregulated in treatment vs. control

Upregulated in treatment vs. control

Significance threshold

Fold change threshold

Log2 FC: how much difference is there on average between treatment and control?

*1 per condition vs. control*

Inflammation (IPN)

Cell Proliferation (CPR)

Cell Stress (CST)

Cell Fate (CFA)

Tissue repair and angiogenesis (TRA)

*1 per condition vs. control*

*comparing conditions*

∑

Hoeng J *et al.* A network-based approach to quantifying the impact of biologically active substances. **Drug Discovery Today,** 2012, 17:413-418 (PMID: 22155224)

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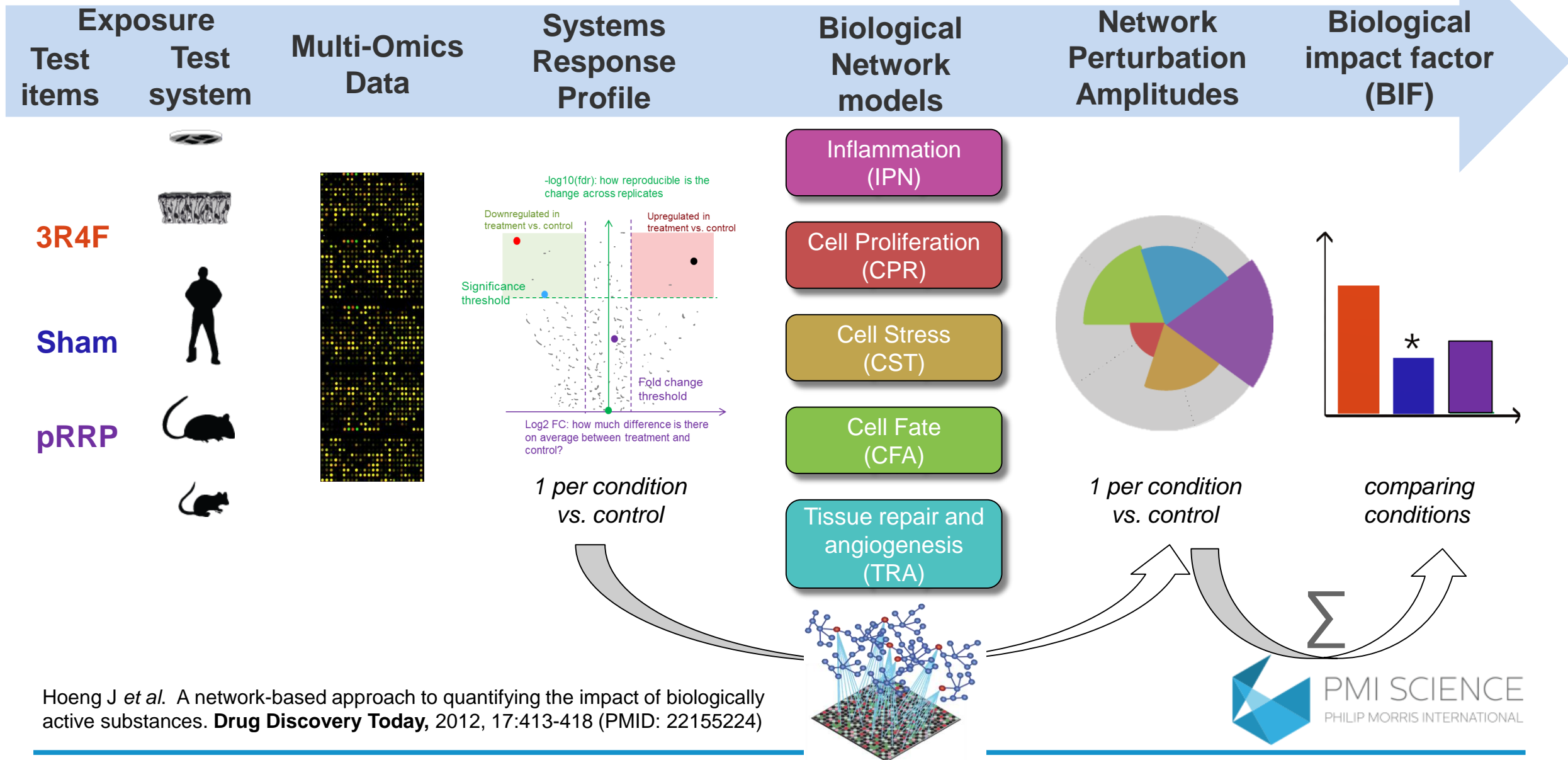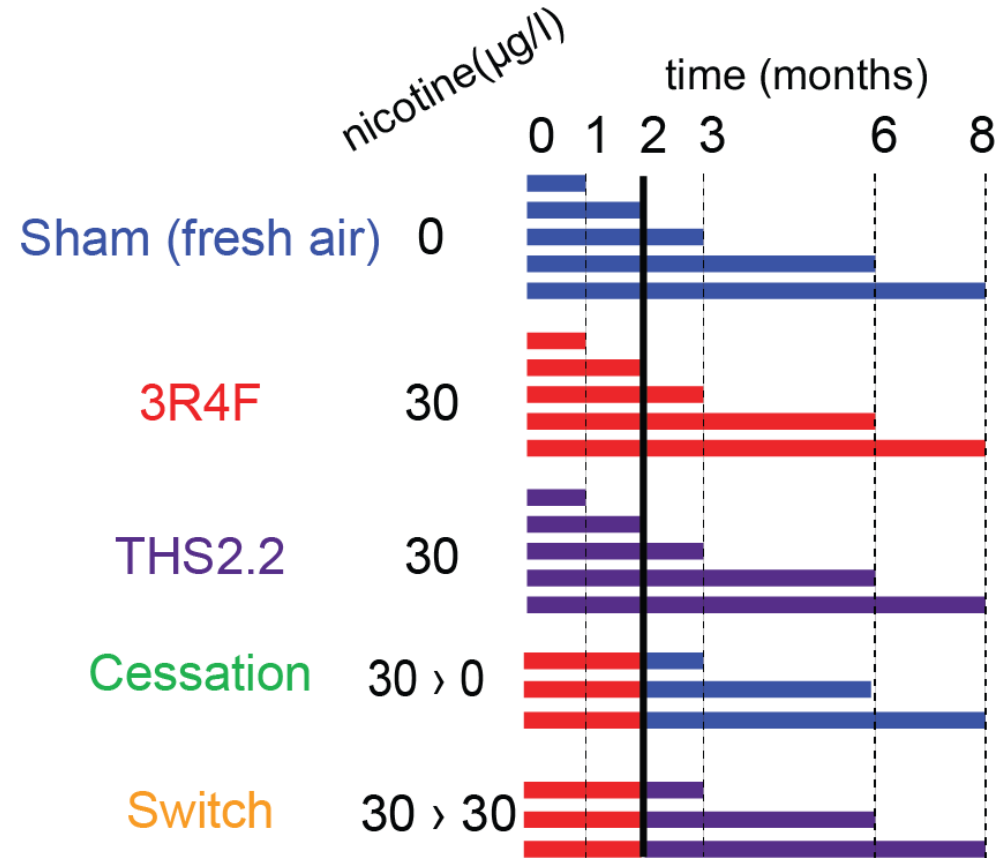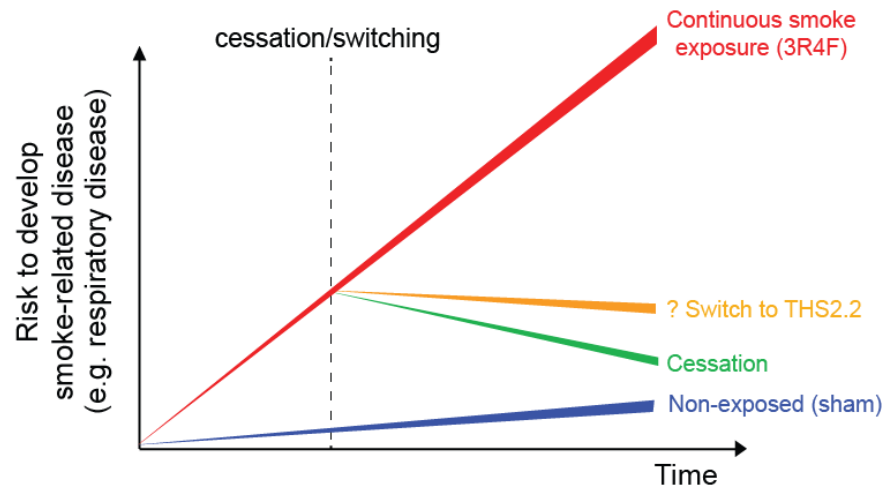
Cardiovascular, respiratory, and liver -related measurements covering apical and systems toxicology endpoints

# Lung function – PV loops



## Lung volume



**Legend:**
- Sham (blue, dotted)
- 3R4F (red, solid)
- THS2.2 (purple, dash-dot)
- Cessation (green, dash-dot)
- Switch (orange, dashed)
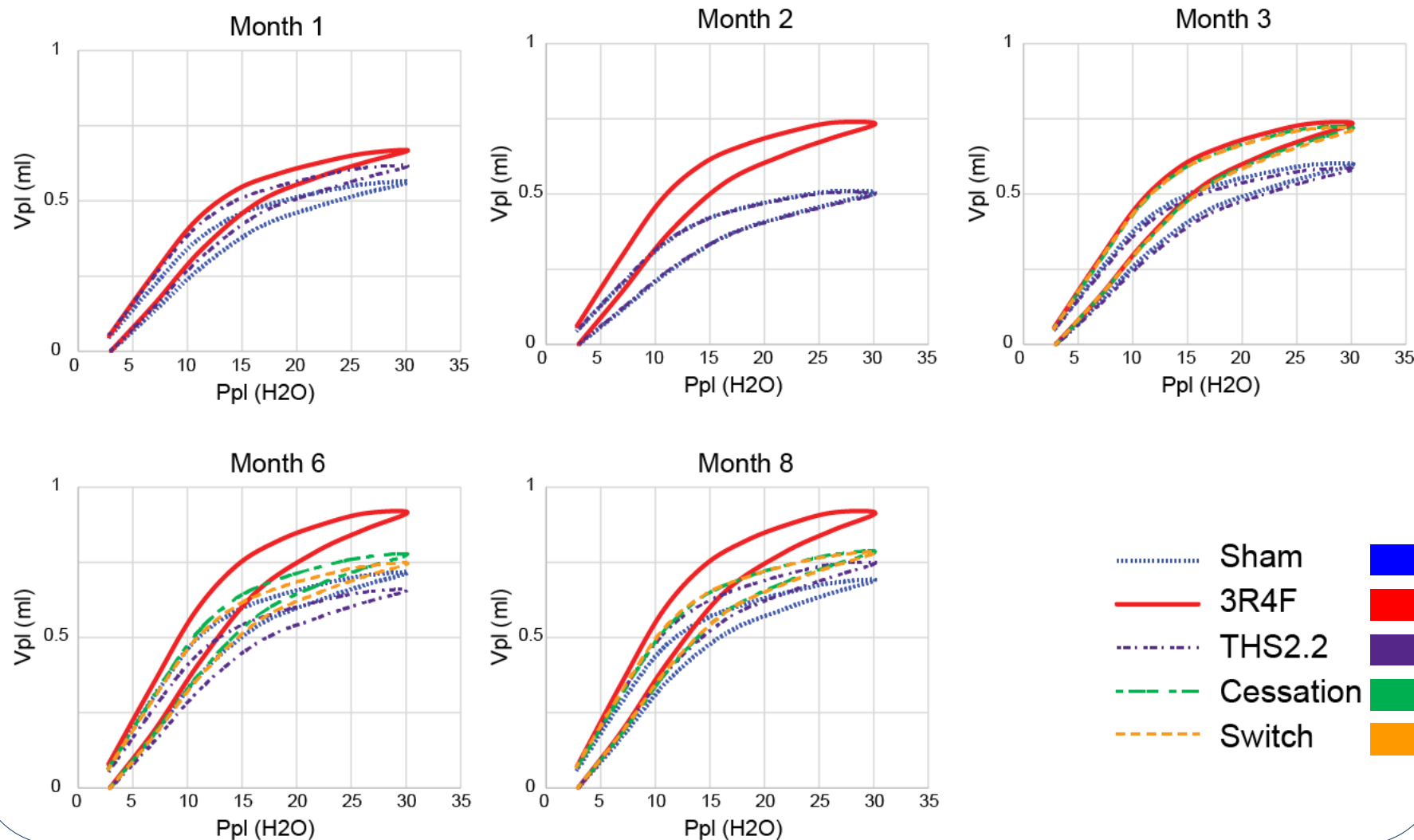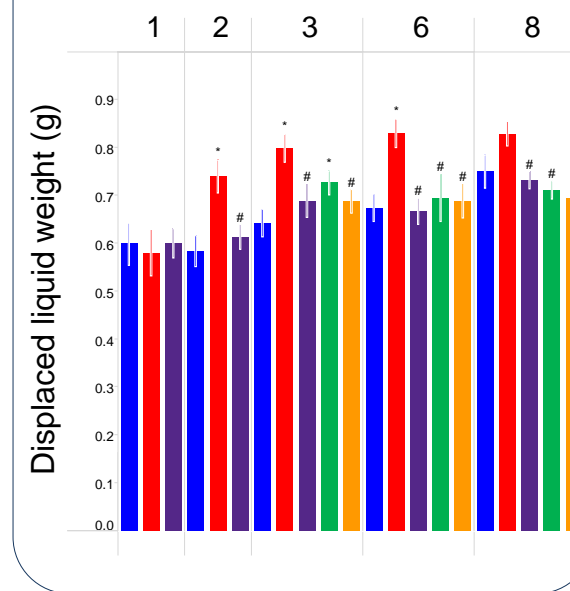
# Switching Study in an Animal Model of Disease Result Summary: Differential Gene Expression - Lung
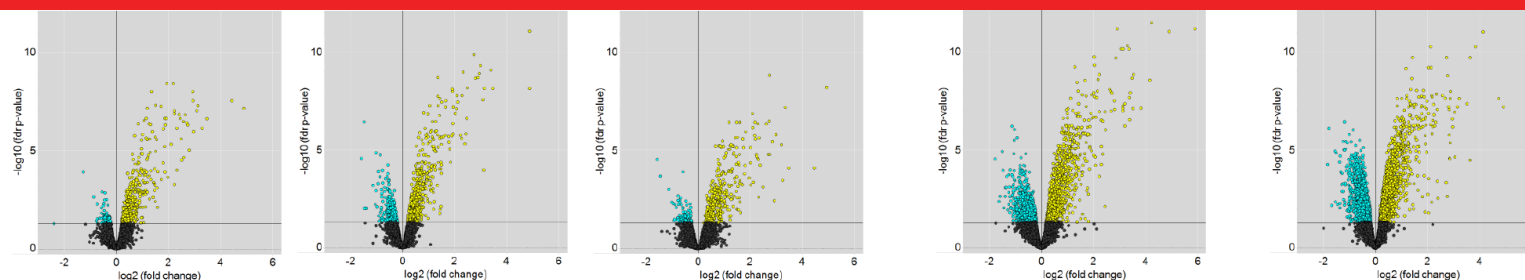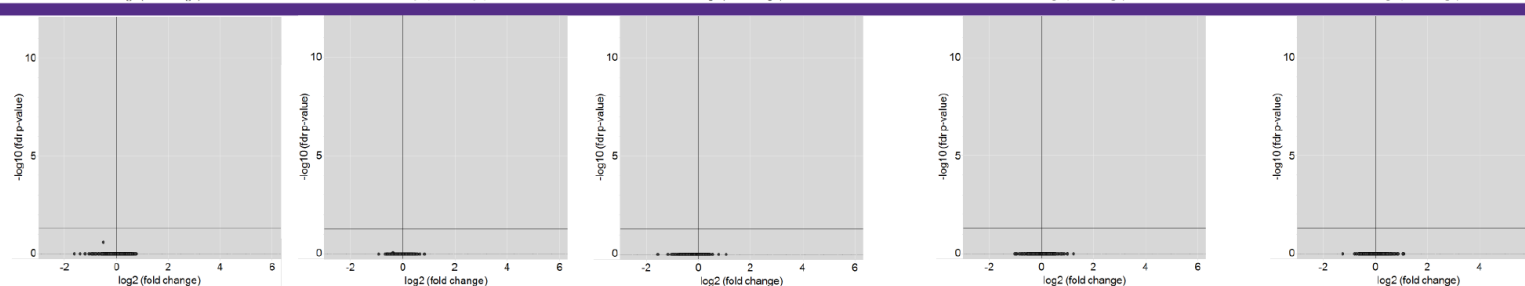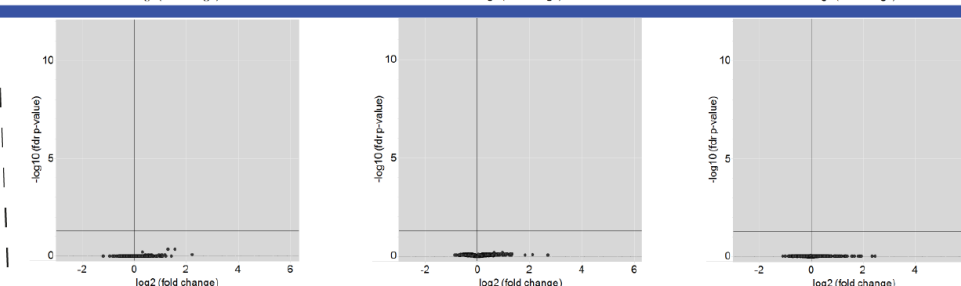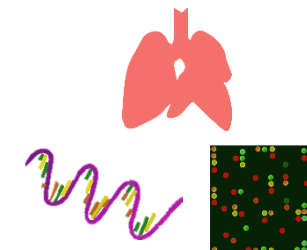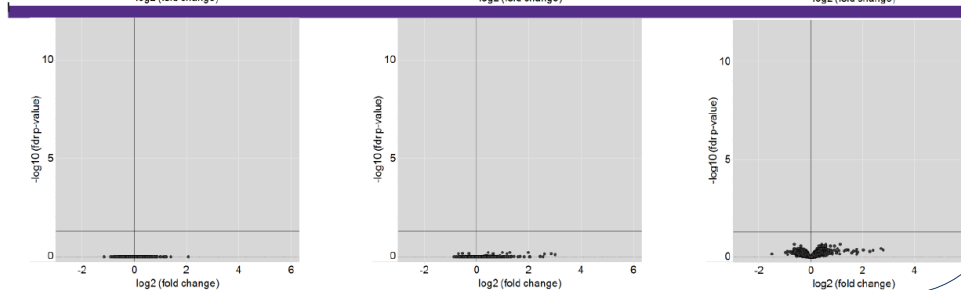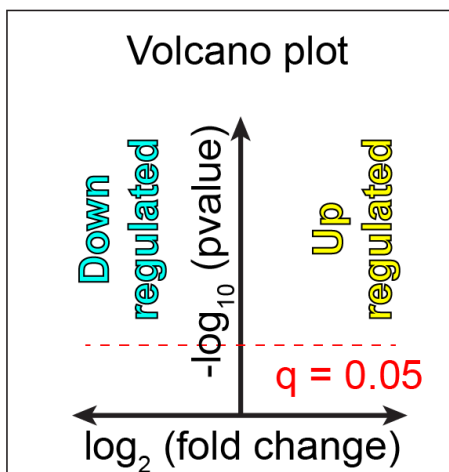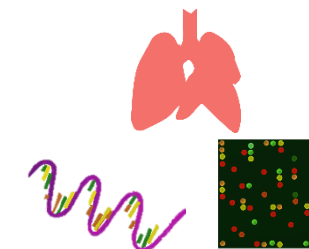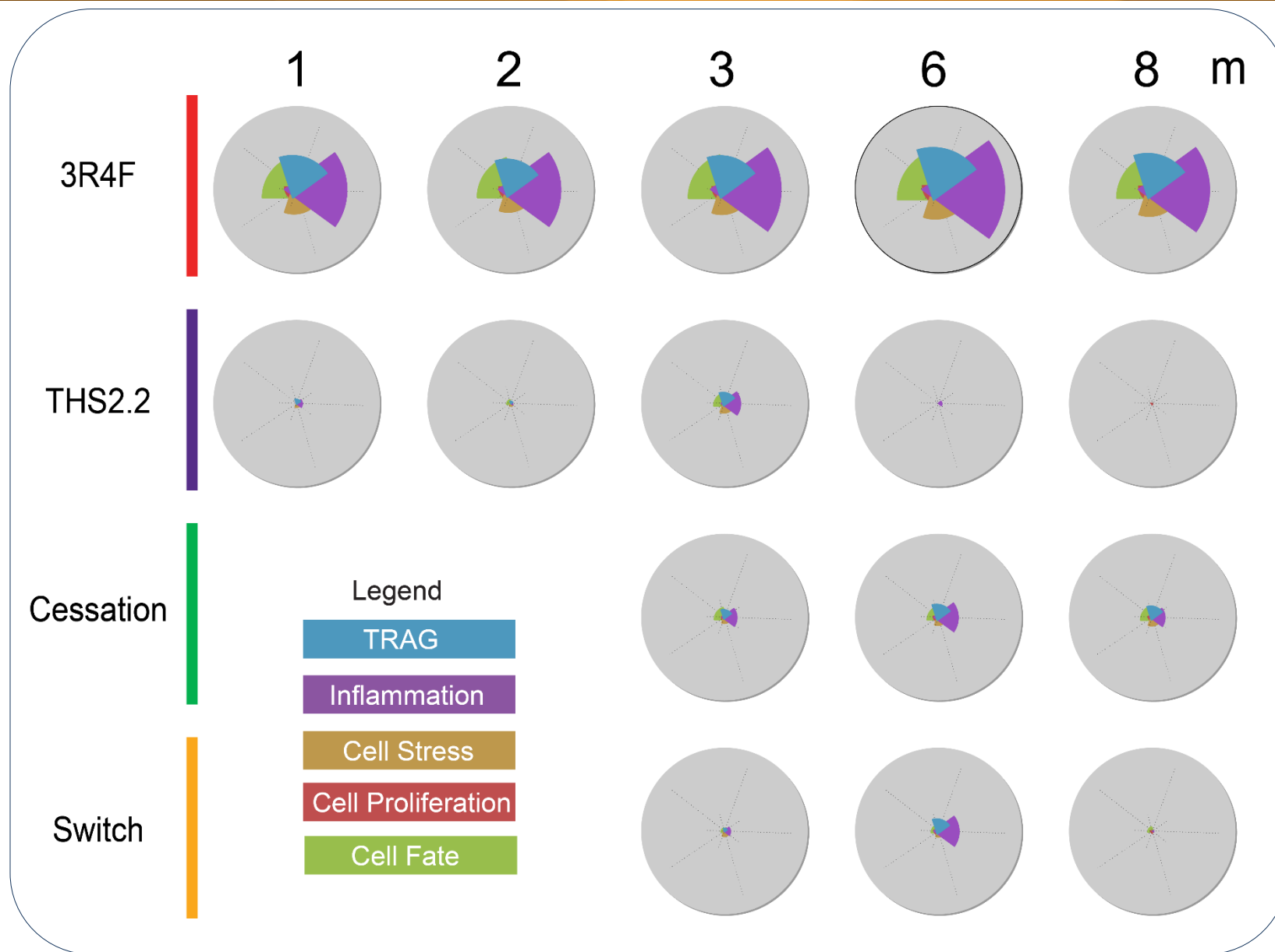
Legend
- TRAG
- Inflammation
- Cell Stress
- Cell Proliferation
- Cell Fate

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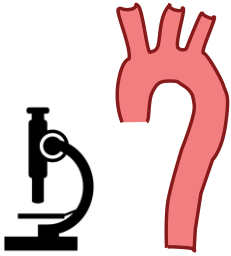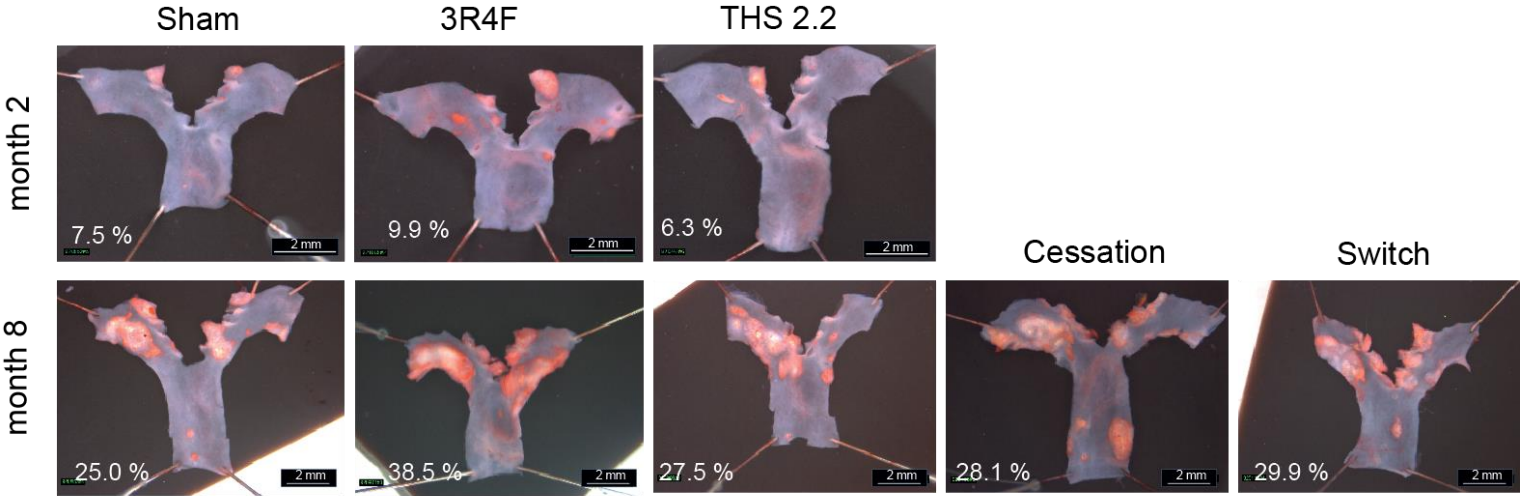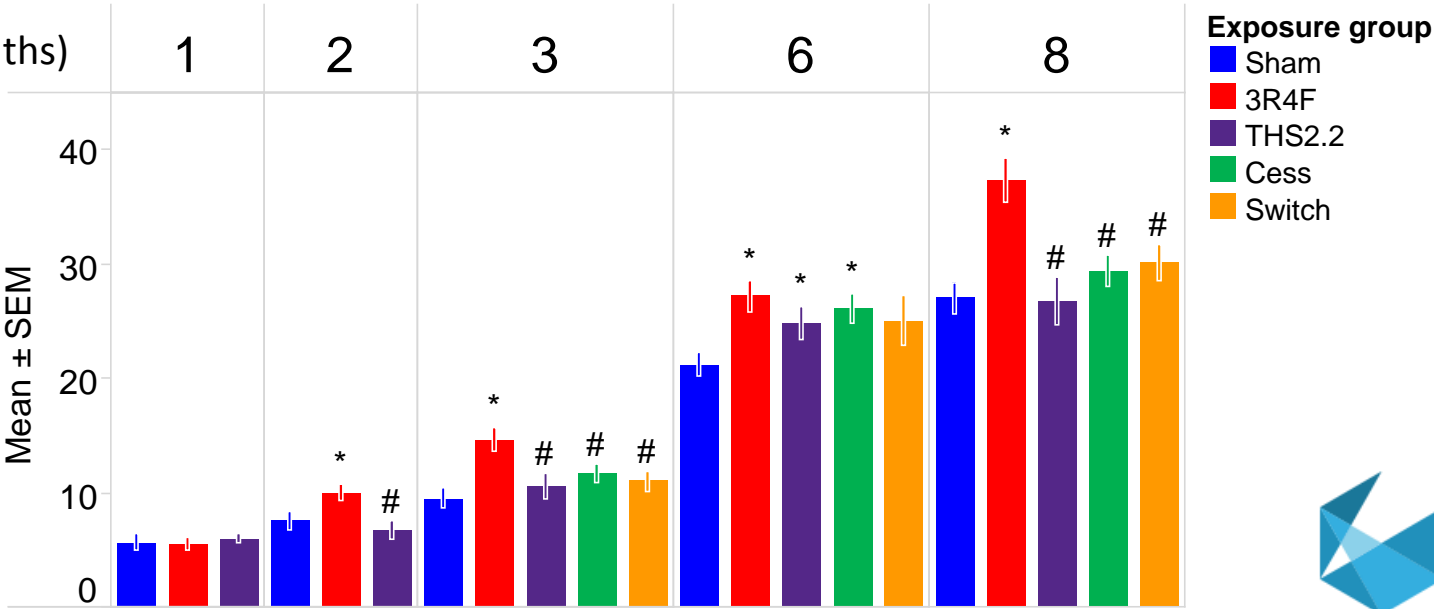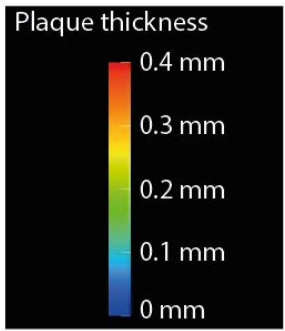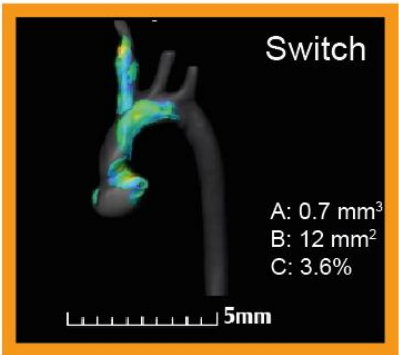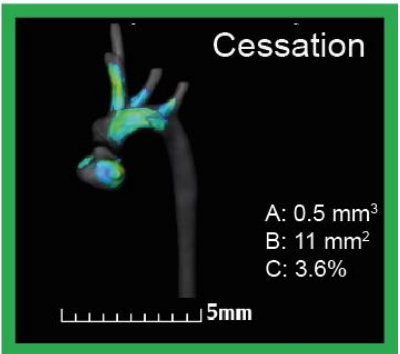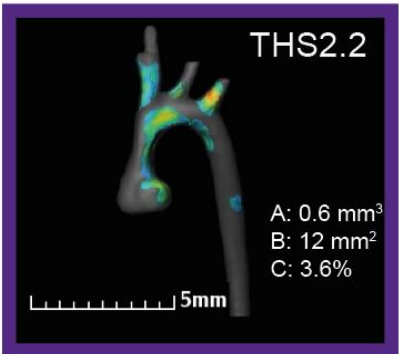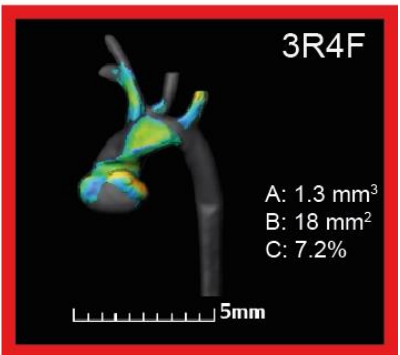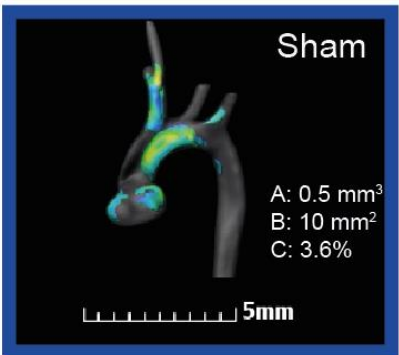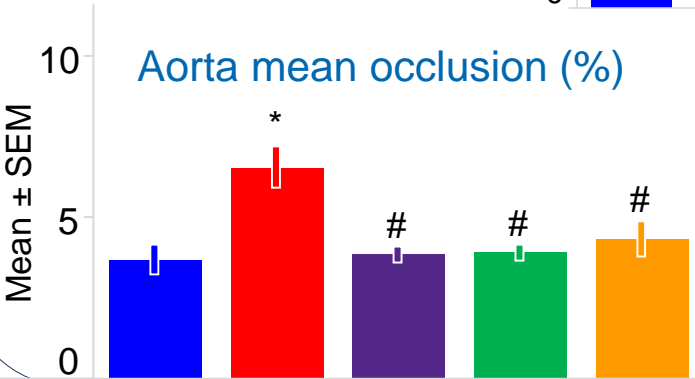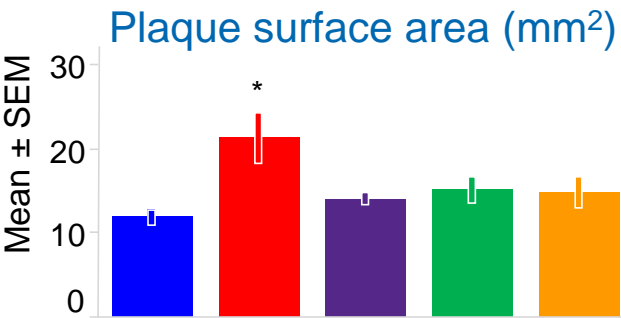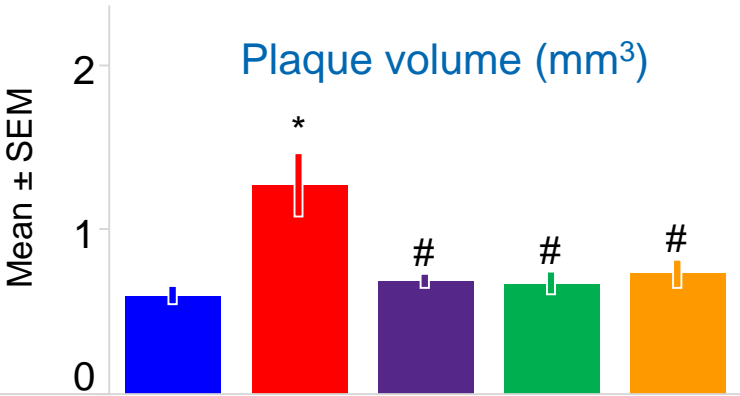
# Tobacco Heating System: Clinical Assessment

**Post-Market Studies and Surveillance**

**Consumer Perception and Behavior Assessment**

**Clinical Trials**

**Systems Toxicology Assessment**

**Standard Toxicology Assessment**

**Aerosol Chemistry and Physics**

**Product Design and Control Principles**

**1** Pharmacokinetics/ Pharmacodynamics

**4 Studies completed 2015**

Determine nicotine absorption profile

**2** Reduced Exposure 5 day exposure confinement

**2 Studies completed 2015**

**3** Reduced Exposure 5 day confinement followed by 85 day ambulatory

**2 Studies completed 2015**

Demonstrate reduced exposure to harmful and potentially harmful constituents

**4** Exposure Response 6 months

**1 Study initiated 2016. Results in Q3 2017**

Demonstrate favorable biological and functional changes

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# PK Nicotine Profiles – Tobacco Heating System and CC



THS  CC

### PK-02-JP
### Non-Menthol

$T_{max}$ = 6 min
$T_{max}$ = 6 min

### PK-01-EU
### Non-Menthol

$T_{max} \cong$ 6 min
$T_{max} \cong$ 6 min

### PK-05-JP
### Menthol

$T_{max}$ = 6 min
$T_{max}$ = 6 min

### PK-06-US
### Menthol

$T_{max} \cong$ 7 min
$T_{max} \cong$ 10 min

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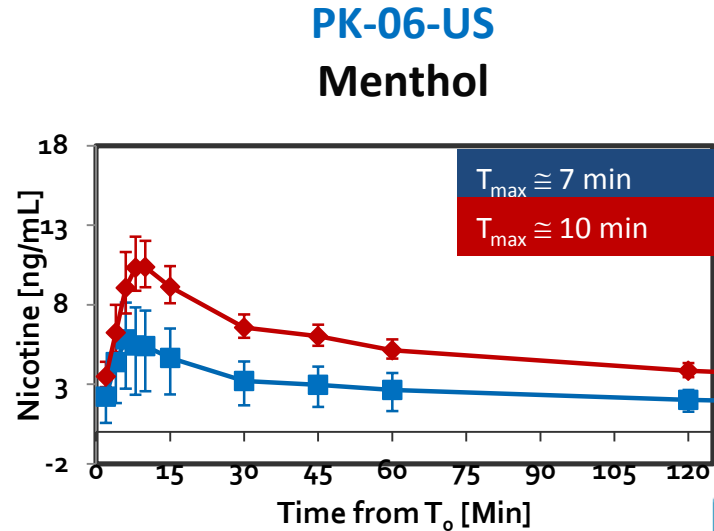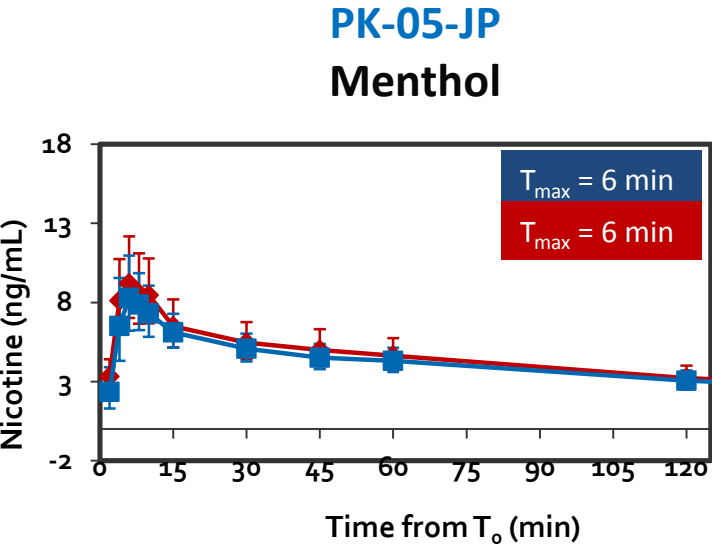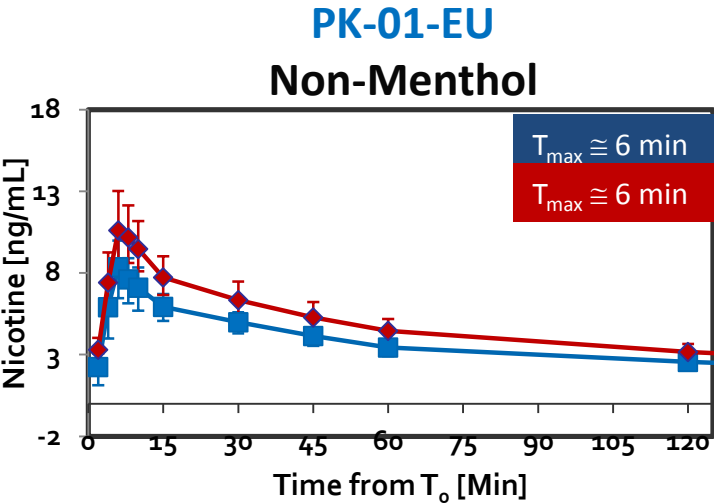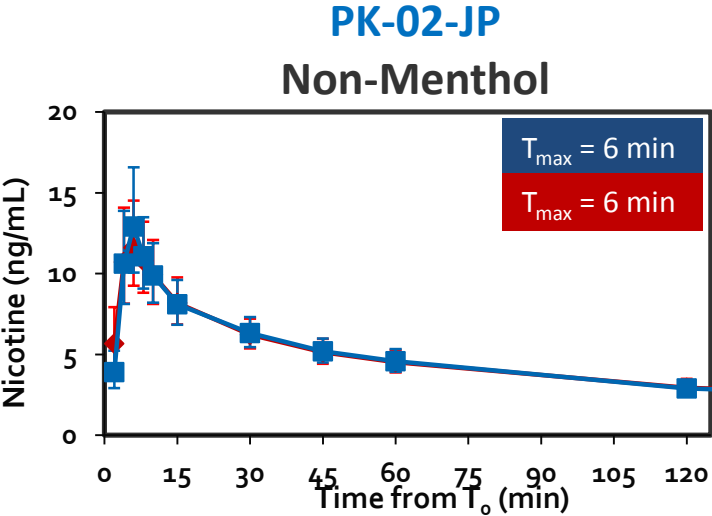
# Harmful and Potentially Harmful Constituents - Characteristics and Related Biomarkers of Exposure

| HPHC | PMI BoExp | HPHC lists WHO 2009 | HPHC lists FDA 2012 | Organ Class Toxicity (FDA) | Temperature Range of Formation (°C) | Reported BoExp Elimination Half-Life |
|---|---|:---:|:---:|---|---|---|
| Acrolein | 3-HPMA | • | • | CT, RT | 200-400 | 9 h |
| Benzene | S-PMA | • | • | CA, CT, RDT | >400 | 9 h |
| 1,3-Butadiene | MHBMA | • | • | CA, CT | >400 | 5-9 h |
| Carbon monoxide | COHb | • | • | RDT | >250 | 1-4 h |
| Acrylonitrile | CEMA | | • | CA, RT | 500-800 | 7-9 h |
| 4-Aminobiphenyl | 4-ABP | | • | CA | 25-500 | 31 h (in rats) |
| 1-Aminonaphthalene | 1-NA | | • | CA | 300-500 | Not reported |
| 2-Aminonaphthalene | 2-NA | | • | CA | 25-500 | Not reported |
| NNK | Total NNAL | • | • | CA | Direct transfer | Up to 45 days |
| NNN | Total NNN | • | • | CA | Direct transfer | < 24 h |
| o-Toluidine | o-Toluidine | | | CA | ND | 4 h (plasma) |
| Pyrene | Total 1-OHP | | | - | 700–800 | < 10 h |
| Benzo[a]Pyrene | 3-OH-B[a]P | • | • | CA | 500-800 | 2.5-4.3 h |
| Toluene | S-BMA | | • | RT, RDT | 500-800 | < 10 h |
| Ethylene oxide | HEMA | | | - | >600 | < 5 h |
| Crotonaldehyde | 3-HMPMA | | • | CA | 25-500 | 5-9 h |

# 90-Day Exposure Study in Japan and US
## Study Design

ClinicalTrials.gov ID: NCT01970995    REXA-07-JP

ClinicalTrials.gov ID: NCT01970995    REXA-08-US

Screening* | Admission | Baseline

THS 2.2 Menthol | THS 2.2 Menthol

Smoking Abstinence | Smoking Abstinence

mCC | mCC

Safety follow-up

*Screening within 1-4 weeks prior to admission

Day -2 | Day -1, Day 0 | Day 1 to Day 5 | Day 6 | Day 6 to Day 90 | Day 91 to Day 119

Day 6 | Day 30/Day31 | Day 60/Day61 | Day 90/Day91

mCC ad libitum

THS 2.2 Menthol and mCC ad libitum | THS 2.2 Menthol and mCC ad libitum

9 days in confinement | 85 days ambulatory | 28 days follow-up

Abbreviations: mCC = Menthol conventional cigarette(s); THS = Tobacco Heating System; Figure not to scale.

REXA studies completed 2014:
- 160 healthy adult smokers
- 5 day exposure in confined setting followed by 85 day exposure ambulatory
- 3 arm randomized parallel design
- Ad libitum Product use (THS, cigarette, smoking abstinence)

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| | **REXA-07-JP and REXA-08-US** |
|---|---|
| Primary objective<br><br><u>Confirmatory</u><br><u>with statistical power</u> | **Demonstration of reduced exposure if the levels of:**<br><br>• COHB, S-PMA, MHBMA, and 3-HPMA after 5 day of product use in confinement AND<br>• Total NNAL after 90 days of product use in ambulatory condition<br><br>are at least 50 % decreased from baseline |
| Sample size consideration | Statistical power: at least 90 %<br>one-sided test with 2.5% type I error probability |
| Other<br>Objectives<br><br>Descriptive with no<br>statistical power | To describe the changes in<br>• Other HPHCs<br>• Clinical risk endpoints (e.g. hsCRP, homocysteine, HDL, fibrinogen, HbA1c, 11-DTXB2, 8-epi-PGF2a, sICAM-1, FEV1)<br>• Product use, human topography, related subjective effects....<br>• To monitor safety |

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# 90-Day Exposure in Japan and US
## Timecourse Exposure to CO and Nitrosamine
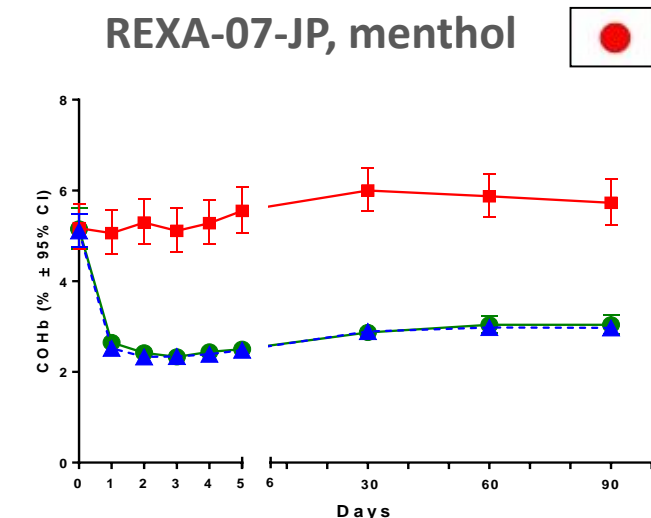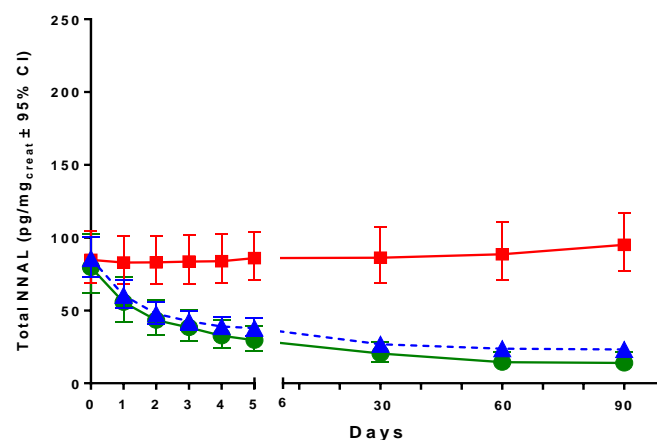
REXA-07-JP, menthol    REXA-08-US, menthol
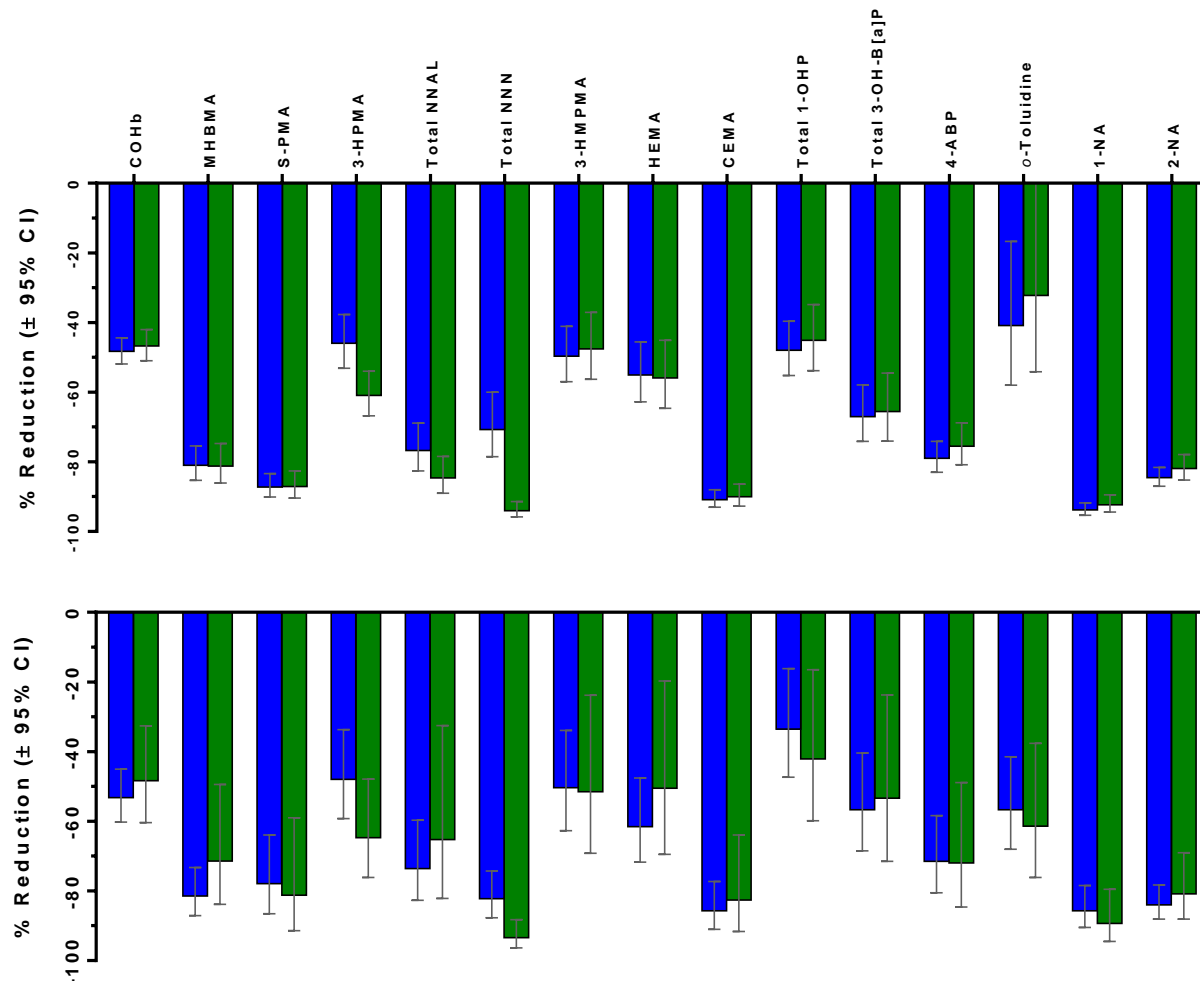
THS    CC    SA

COHb
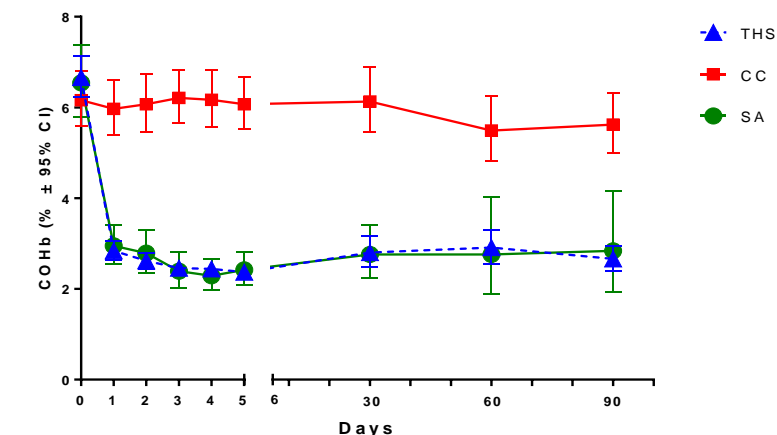
Total NNAL
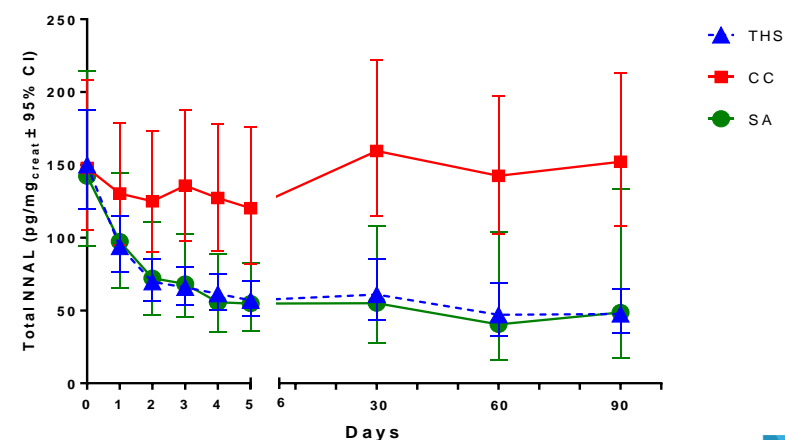
90-Day Exposure in Japan and US
Exposure Reduction to Selected HPHCs

Reduction of THS vs. cigarette and Smoking Abstinence vs cigarette after 90 Days

THS vs CC

SA vs CC

REXA-07-JP, menthol

REXA-08-US, non menthol

Reduction of 15 biomarkers of exposure in both studies
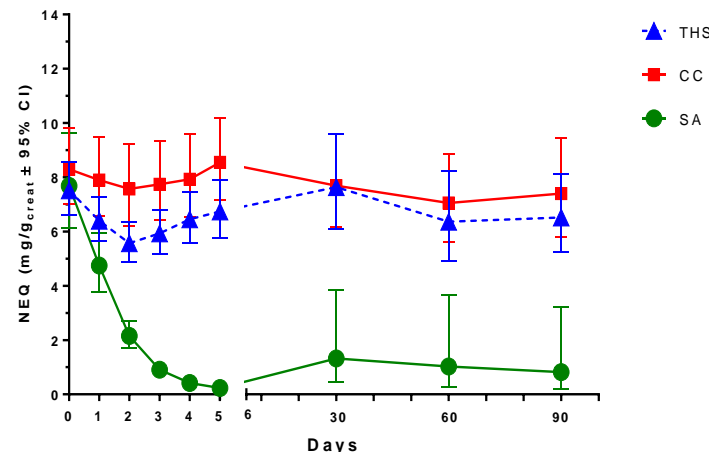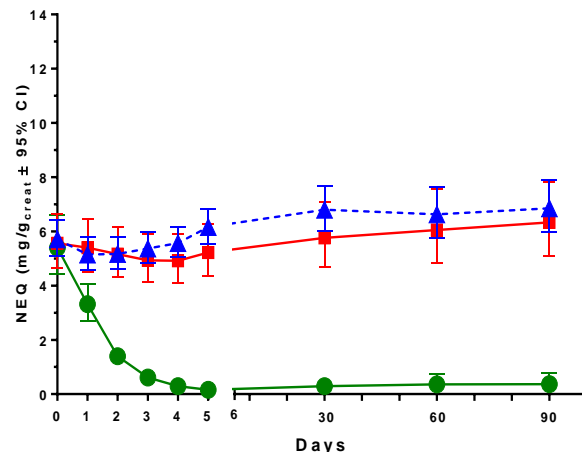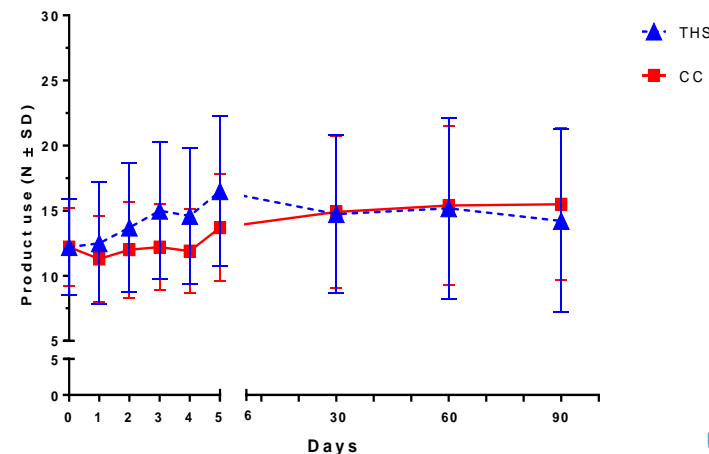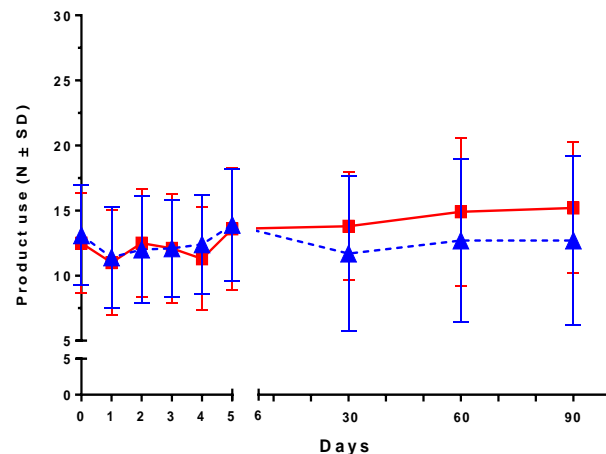
# 90-Day Exposure in Japan and US
## Clinical Risk Endpoints

| Disease Mechanisms | Marker | Expected Direction of Change | Japan THS versus CC | U.S. THS versus CC | Direction of Change |
|---|---|---|---|---|---|
| Lipid Metabolism | HDL-C | ↑ | 4.53 mg/dL ↑ | 1.40 mg/dL↑ | ✓ ✓ |
| Inflammation | WBC | ↓ | -0.57 GI/L ↓ | 0.17 GI/L → | ✓ |
| Airway Impairment | $FEV_1$ | ↑ | 1.9 % pred ↑ | 0.5 % pred ↑ | ✓ ✓ |
| Endothelial Dysfunction | sICAM-1 | ↓ | 8.7%↓ | 10.6%↓ | ✓ ✓ |
| Oxidative Stress | $8\text{-epi-PGF}_{2\alpha}$ | ↓ | 12.7%↓ | 13.5%↓ | ✓ ✓ |
| Clotting | $11\text{-DTX-B}_2$ | ↓ | 5.4%↓ | 3. 6%↓ | ✓ ✓ |

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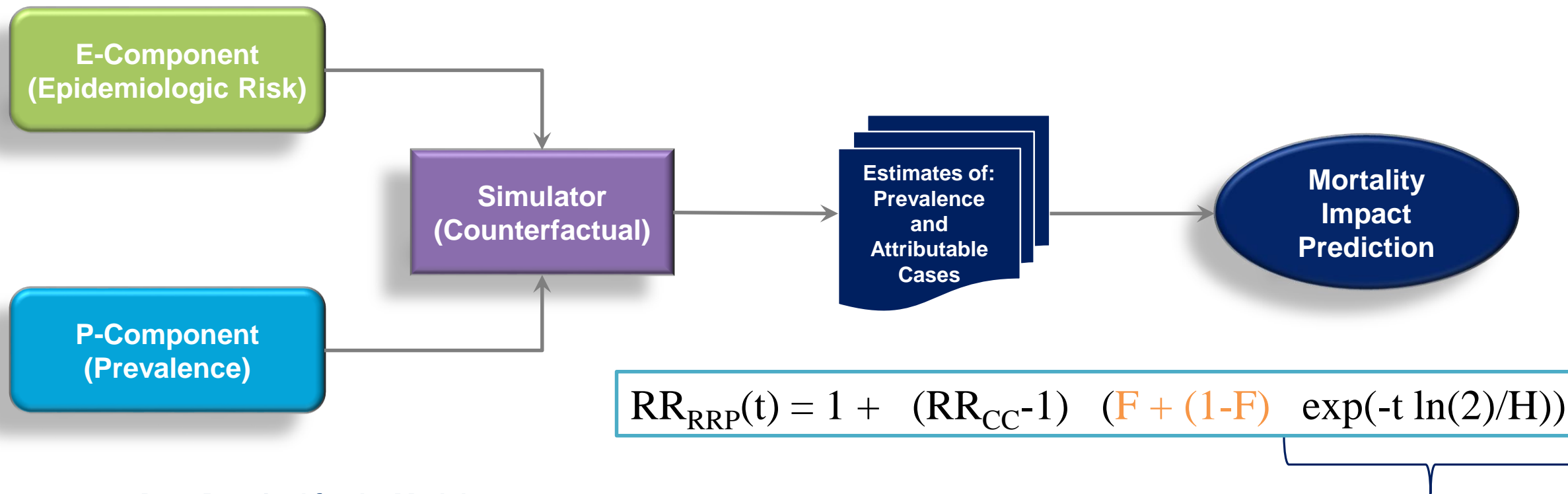
# Population Health Impact Modeling (PHIM)

- Philip Morris International has developed a Population Health Impact Model (PHIM) to estimate the effects that marketing of Reduced Risk Products (RRPs)* has on population health.

- It was designed to assess the impact of an RRP on population harm as a function of the risk or toxicity of the product to the individual user, and the prevalence of use in the population.

**The modeling exercise presented here aims at:**

- Understanding the impact of harm reduction to smokers who quit or switch to RRP products versus continued smoking or never smoking

- Across different age groups (20+, 30+, 40+ and 50+ years old)

- Evaluated as changes in relative and absolute risk over time for the four main smoking-related diseases:

  ➢ lung cancer (LC)

  ➢ ischemic heart disease (IHD)

  ➢ stroke and

  ➢ chronic obstructive pulmonary disease (COPD).

# Population Health Impact Modeling Methods



**Data Required for the Model**

- Disease mortality risks → RR of CC smoking
- Disease mortality risks reductions over time → cessation
- Tobacco use prevalences (age and sex – specific)

$$RR_{RRP}(t) = 1 + (RR_{CC}-1) \; (F + (1-F) \; \exp(-t \ln(2)/H))$$

Reduction of Risk Over Time – since Cessation

# Population Health Impact Modeling Methods

- Relative Risk Estimates – sex, age and smoking history specific

- Model uses the known reduction in excess relative risk over time from epidemiological data on smoking cessation

$$RR_{RRP}(t) = 1 + (RR_{CC}-1) \ (F + (1-F) \ \exp(-t \ \ln(2)/H))$$

Reduction of Risk Over Time Since Quit
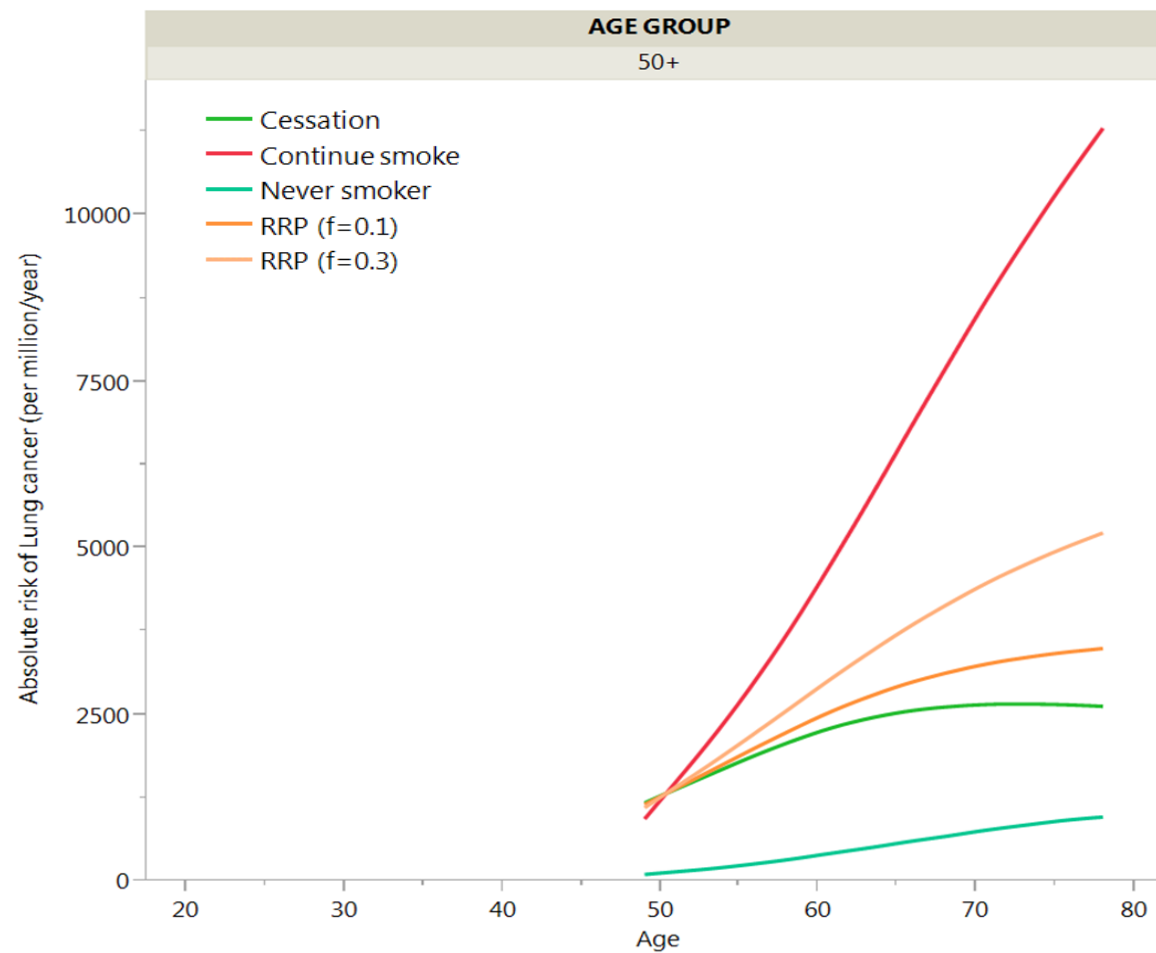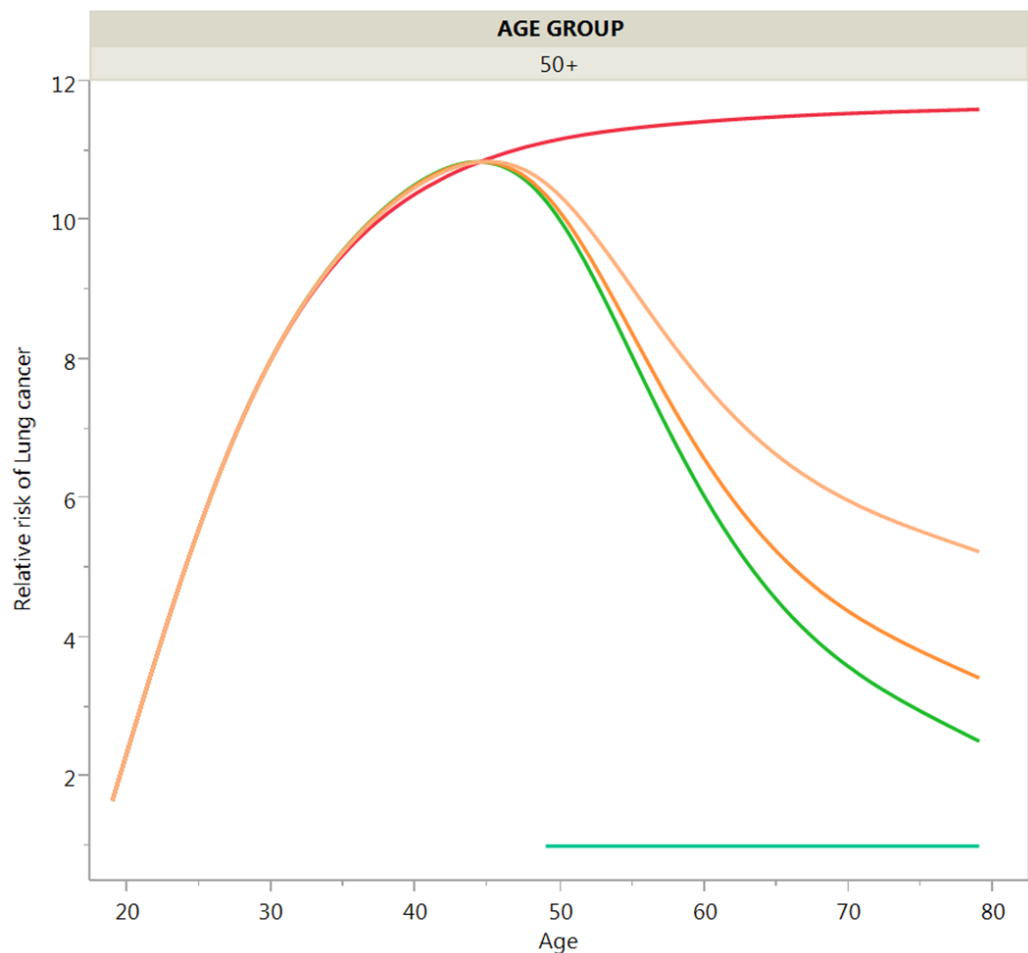
### Reduction in Excess Risk Over Time



Legend: Lung Cancer, COPD, IHD, Stroke

X-axis: Time Since Quit (years)
Y-axis: Excess Risk (%)
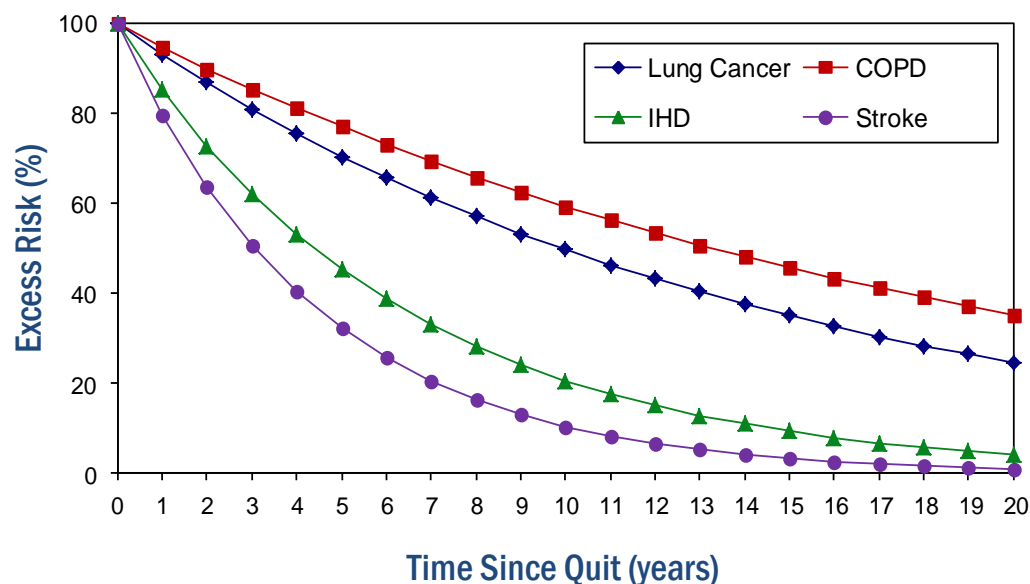
| Disease | RR half-life (95% CI) | # of Studies | Blocks* of Data |
|---|---|---|---|
| IHD | **4.40** years (3.26, 5.95) | 23 | 41 |
| Lung Cancer | **9.93** years (9.31, 10.60) | 85 | 106 |
| Stroke | **4.78** years (2.17, 10.50) | 9 | 11 |
| COPD | **13.32** years (11.86, 14.96) | 11 | 13 |

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# Population Health Impact Modeling

- Work described in here covers the series of modeling simulations (1-4) on different age groups (20+, 30+, 40+ and 50+ years old) to understand the:

  1) Impact of quitting tobacco smoking – **CESSATION**

  2) Impact of switching to an RRP with low and high effective dose – **RRP ($f=0.3$) and RRP ($f=0.1$)**

  3) Impact of continuing to smoke cigarettes – **CONTINUE SMOKING**

  4) Impact of never smoking – **NEVER SMOKING**

- All individuals initiated smoking at 20 years old.

- Cessation and switching to RRP take place 1 year after entering the simulation.

- The effective dose for RRP are estimates derived from non-clinical and clinical data in PMI.

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# Population Health Impact Modeling



- Simulated profiles for LC in a 50+ year old male shows the reduction in relative and absolute risk over time follow a negative exponential decay.
- Switching to an RRP brings a noticeable reduction in relative and absolute risk of LC versus continued smoking and therefore can be considered as an alternative to smoking.

# Population Health Impact Modeling
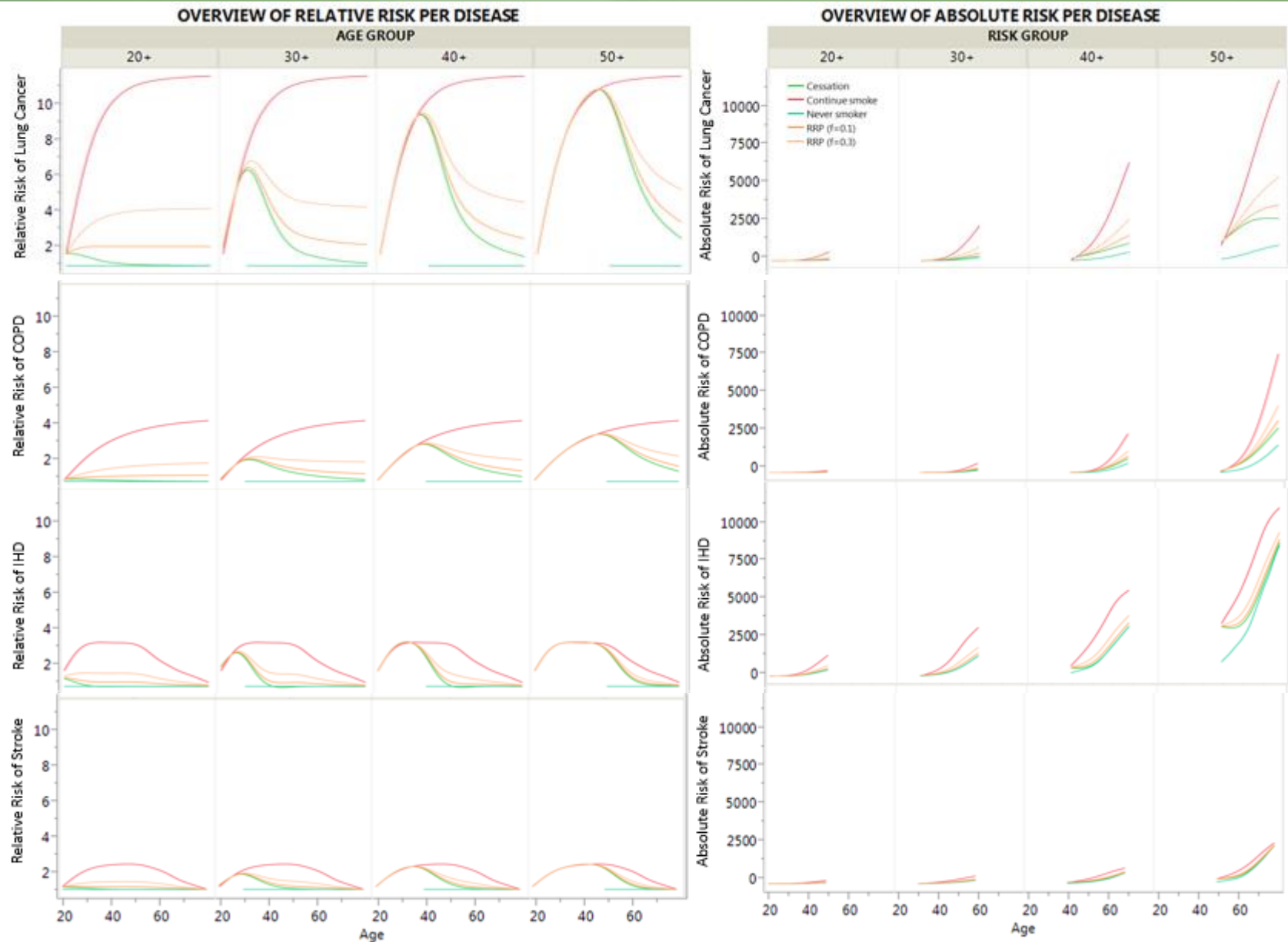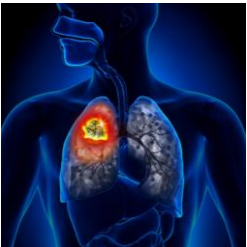
# Population Health Impact Modeling

Overview of all simulation results for four smoking diseases and age groups show a differentiation in relative and absolute risk in line with what is expected from the changes in effective dose (0 for never smoker; 1 for smoker; $f=0.1$ and $f=0.3$ for RRPs).

Cessation is overall the most effective in population harm reduction.

These simulations demonstrate the extent to which an RRP could contribute to population harm reduction across the different smoking-related diseases given a reasonable assumption that the reduced exposure from the RRP resulted in an effective dose of between 0.1 and 0.3.

Switching to RRPs for smokers in their 20s and 30s can be considered as mostly risk prevention; while for smokers in their 40s and 50s this can be more risk reduction.

Population Health modeling is an established and recognized field of science. The PHIM described here  can be a valuable tool to quantify both individual and population changes that can be expected from marketing RRPs, with the ability to test a variety of  different scenarios in both pre- and post- market settings.

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# THANK YOU!