This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

TOX/2017/25

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature (Reserved Business)

Introduction

1. The COT, with support from COM and COC, has been requested to assess the toxicological risks from novel heat-not-burn tobacco products, and compare these risks to those from conventional cigarettes. This will provide the Department of Health (DH) and Public Health England (PHE) with a general opinion on the toxicological risks of such products, and is not to fulfil any regulatory function of PHE.

2. The Committees have considered scoping papers on the topic at the COT meetings in December 2016 and February 2017 (papers TOX/2016/42 and TOX/2017/09), the COM meeting in February 2017 (MUT/2017/01) and the COC meeting in March 2017 (COC/2017/07). During these discussions, it was agreed that the two manufacturers of heat-not-burn products notified to DH would be invited to present their data to address a list of data requirements compiled based on the comments provided by each Committee. The list is attached at Annex A.

3. The manufacturers have provided their presentations, attached at Annexes B and C, along with further data to the Secretariat. These have been briefly checked against the Committees' list of data requirements and the check is summarised in this paper. At the meeting each manufacturer will separately deliver their presentation which will be followed by a question session where further information and clarification can be sought from the manufacturer.

4. A basic literature search has been conducted to identify any peer-reviewed studies published on heat-not-burn tobacco products, and whether these contain any information in addition to that submitted by the manufacturers. A short summary is provided in this paper and further detail is available in Annex D.

5. The Committees are reminded that certain data contained in the remainder of this summary and presentations have been provided in confidence, and therefore the data presented should be treated as commercially sensitive.

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Questions for the Committees

6. Following the presentations and subsequent question sessions:

(i) Are Members satisfied that the Committees' data requirements have been adequately addressed?

(ii) Are the Committees in a position to be able to provide comment to DH and PHE on the toxicological risks of heat-not-burn tobacco products, and the relative risks compared to conventional cigarettes?

(iii) If not, is there any further information required from the manufacturers to facilitate the assessment?

Secretariat
May 2017

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature

RESERVED BUSINESS

Data provided by heat-not-burn manufacturers

7. Table 1, overleaf, details whether the Committees' list of requirements have been addressed by the manufacturers based on information provided in the presentations or supporting documents that were sent to PHE. Data in these materials have been briefly scanned to obtain a general overview of those areas that may require further attention during the discussion, and these are summarised below the table.

Table 1 and Paragraphs 8 to 11 have been redacted as they include commercially sensitive information

Literature search

12. A basic literature search of PubMed was conducted in April 2017, which is outlined in more detail in Annex D. The abstracts were then assessed for relevance. Due to time constraints, a full paper screen to confirm the relevance of the selected studies has not been conducted but is expected to be performed at a later date.

13. Based on the abstracts, 86 papers were considered potentially relevant. Most of these papers (n=69) were published by PMI on IQOS and potentially on related or earlier products (see Table D1). Of the six papers published by BAT, only one paper appears to have evaluated iFuse, while the remaining five did not specify the BAT product being evaluated in their abstract (see Table D2). Three papers were published by other organisations that evaluated PMI's IQOS product, or earlier versions (Table D3). No papers were identified, published by other organisations, that evaluated BAT's iFuse product. Eight reviews articles were selected from the search as being potentially relevant (Table D4). A total of 20 papers irrespective of the organisation did not specify in their abstract the nature of the modified risk tobacco product being evaluated.

Other papers

14. Seven additional relevant studies cited in the presentations and/or supporting information that were not captured in the literature search, are listed in Table D5,

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Annex D (PMI: n=1, BAT: n=6). These were pre-publication references that either have been just submitted to or just accepted by journals.

15. Finally, as previously reported in the scoping documents TOX/2016/42 and COC/2017/07, PMI's IQOS THS product has also been independently tested by The Netherlands National Institute for Public Health and the Environment (RIVM) and the China National Tobacco Quality Supervision and Test Centre (CNTQSTC). These organisations can be contacted for copies of their evaluations.

Questions for the Committees

16. Following the presentations and subsequent question sessions:

(i) Are Members satisfied that the Committees' data requirements have been adequately addressed?

(ii) Are the Committees in a position to be able to provide comment to DH and PHE on the toxicological risks of heat-not-burn tobacco products, and the relative risks compared to conventional cigarettes?

(iii) If not, is there any further information required from the manufacturers to facilitate the assessment?

PHE-Supported Imperial College Toxicology Unit
May 2017

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

References

COC/2017/07. Toxicological evaluation of novel heat-not-burn commercial products: Overview summary of genotoxicity data submitted (reserved business).

MUT/2017/01. Toxicological evaluation of novel heat-not-burn commercial products: Overview summary of genotoxicity data submitted (reserved business).

TOX/2016/42. Toxicological evaluation of novel heat-not-burn commercial products: Overview summary of data submitted (reserved business).

TOX/2017/09. Toxicological evaluation of novel tobacco products: Overview summary of data submitted – follow up. Following discussion of this topic at the December 2016 meeting, a data matrix has now been prepared to facilitate the Committee's evaluation (reserved business).

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature

Reserved Business

List of COT, COC and COM data requirements sent to manufacturers

Secretariat
May 2017

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Data requirements for COT, COM and COC evaluation of heat not burn tobacco products

Cigarette smoking has been associated with many health problems; for example addiction, cancer, and cardiovascular effects. In evaluating heat not burn products we wish to consider both hazard identification of aspects that may be new to heat not burn products (for example nanoparticles and device related issues) as well as comparing risk for known chemicals, and considering the risks associated with combined use of burn and heat not burn products.

Aspects relating to the Tobacco containing product:

- Constituents and Chemical composition
- Additives
- Temperature of heating, and chemical processes occurring at that temperature
    - How these differ from heating and burning processes occurring in conventional cigarettes – i.e. what is new chemistry

Aspects relating to the delivery device

- Releases (e.g. metals – nickel in particular was mentioned)
- What is the overlap with devices such as e-cigarettes, and any devices assessed by MHRA

Exposure

- Chemicals in the mainstream 'smoke'
- Nicotine levels
- Chemicals released to the environment

- What the user is inhaling
- What is in the air surrounding the user including what is exhaled by the user, resulting in passive/bystander exposure
- What is in the general environment as a result of use of the product

- How is air quality assessed
    - What particulate matter is in the aerosol
    - What nanoparticles arise from use
    - Other chemicals released during and after use

- Likely age groups for anticipated use – attractiveness of use to younger age groups
- Appropriate use levels
- Accidental exposure, and routes of exposure – especially to children
- Potential for deliberate mis-use or overdose – e.g. reports of use of e-cigarette fluids as eye drops

- Cumulative exposures, including to nicotine, arising from use in conjunction with conventional or electronic cigarettes
- Consider potential for formation of cancer-causing chemicals as a result of combination e.g. with dietary chemicals even if no longer present in 'smoke'

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Health effects

For each set of data it is important to know how the evaluation or tests were carried out, e.g. according to standard methods or otherwise. COT, COM and COC would require documentation of the methods and statistical analyses undertaken, as well as dose response data on the biological effects observed.

- Acute effects
    - Mutagenicity endpoints e.g.
        - DNA Strand breaks
        - Clastogenicity
        - Aneuploidy
        - Gene mutation (Point mutation, Deletion, Rearrangement or Recombination)
        - Genotoxicity test types (Bacterial, Mammalian in vitro or in vivo, Site of contact – oral and respiratory, Target organ, Germ cell)

- Chronic effects
    - Cancer effects
    - Respiratory toxicity
        - Lung lipid metabolism
    - Systemic toxicity
        - Hepatotoxicity
        - Cardiovascular toxicity

- Sensitisation potential

- Systems biology data

- Epidemiological data
- Volunteer studies or Clinical assessment
    - Pharmacokinetics and Pharmacodynamics
    - Biomarkers assessed – including relevant early markers
        - Cancer
        - Cardiovascular
- Post Market Assessment

- Specific toxicity effects of nicotine at the exposure levels resulting from use of these products

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature

Reserved Business

Presentation from Phillip Morris International

Secretariat
May 2017

PMI's Heat-Not-Burn Tobacco Product – The Tobacco Heating System (THS)

Presentation to the UK Scientific Advisory Committees on Toxicity (COT), Carcinogenicity (COC) and Mutagenicity (COM)

Manuel Peitsch, Chief Scientific Officer

16 May, 2017

The Objective is Harm Reduction

Offering adult smokers satisfying products that present less risk of harm versus continued smoking

- Smoking is addictive and causes serious diseases
- Worldwide it is estimated that more than one 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 consumers' acceptance can be maximized
- Intended audience are cigarette smokers. The impact on non-users needs to be assessed
- Our ambition is to lead a full-scale effort to ensure that non-combustible products ultimately replace cigarettes to the benefit of adult smokers, the society, our stakeholders and our company

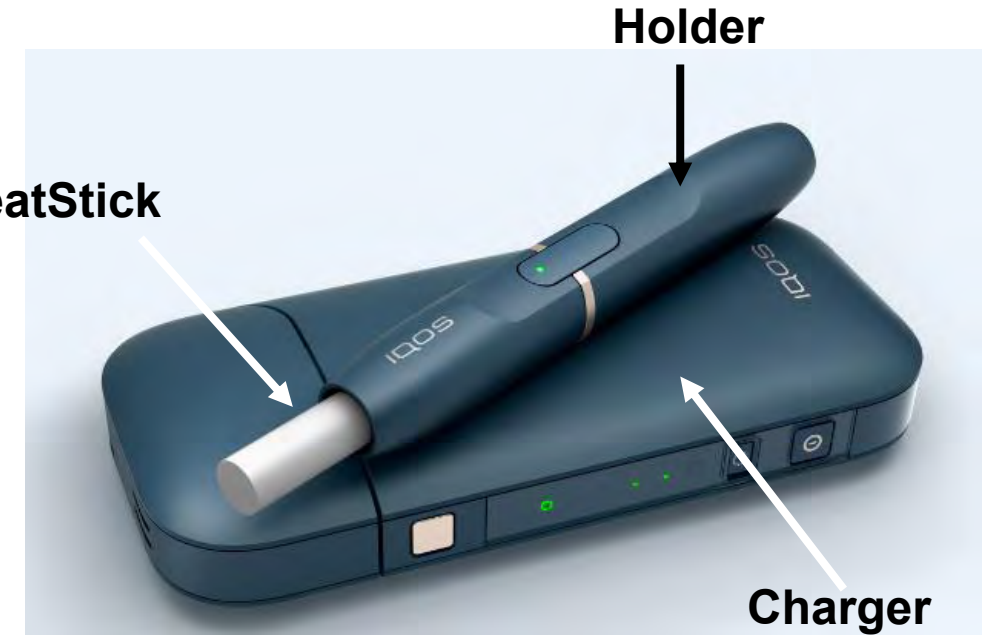
* Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

Overview of the THS*

Tobacco Heating System (THS)

IQOS ® (commercial name)

- **Tobacco Heating Device (THD)**
  - Holder (Heats the HeatStick)
  - Charger (Recharges the Holder)

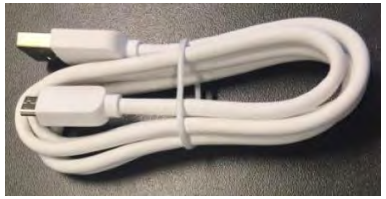


Electrically Heated Tobacco Product (EHTP) - HeatStick

HEETS ® (commercial name)

Accessories:

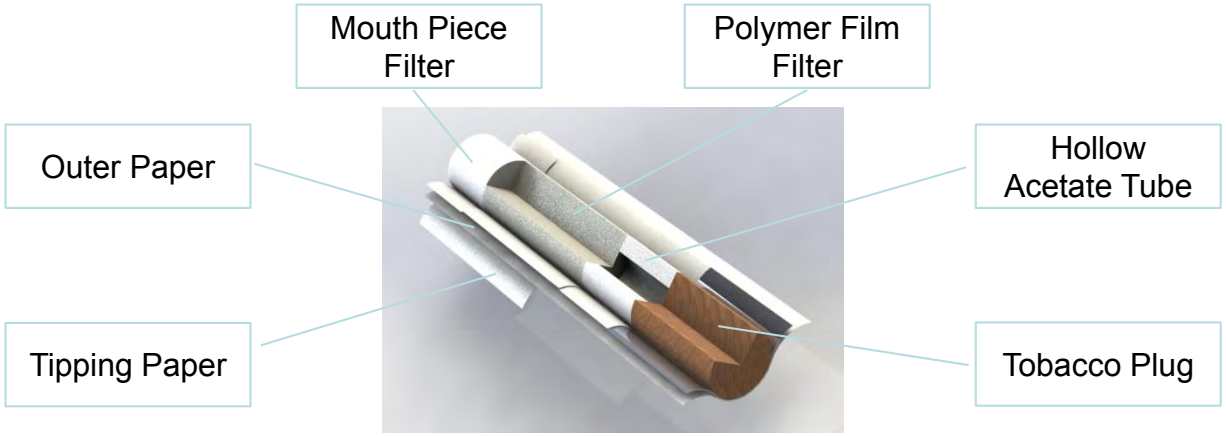
AC adaptor, cleaning brush, USB cable



CE declaration of conformity towards applicable EC standards

* THS is commercialized in many markets under the IQOS ® trademark.

HeatStick Structure and Bill of Materials



Brand: Heets Amber

Brand Variant HEETS

Pack Style: Flip Top Box - 20 *HeatSticks*

	%	mg/cig
tobacco	24.7	201.5
glycerol	6.4	52.3
water	4.4	36.1
guar gum	1.0	7.85
cellulose	0.642	5.23
propylene glycol	0.319	2.6
natural & artificial flavourings	0.017	0.141
wrapper and adhesive (tobacco plug)	2.4	19.8
polymer-film filter	36.4	296.5
hollow acetate tube	9.5	77.4
mouth piece filter	8.0	65.3
tipping paper and tipping paper inks	2.5	20.0
outer paper	2.9	23.8
adhesives	0.7	5.68
	100%	814.2

Brand: Heets Yellow

Brand Variant HEETS

Pack Style: Flip Top Box - 20 *HeatSticks*

	%	mg/cig
tobacco	24.8	201.5
glycerol	6.4	52.3
water	4.4	36.1
guar gum	1.0	7.85
cellulose	0.644	5.23
propylene glycol	0.037	0.3
natural & artificial flavourings	0.051	0.414
wrapper and adhesive (tobacco plug)	2.4	19.8
polymer-film filter	36.5	296.5
hollow acetate tube	9.5	77.4
mouth piece filter	8.0	65.3
tipping paper and tipping paper inks	2.5	20.0
outer paper	2.9	23.8
adhesives	0.7	5.68
	100%	812.2

Brand: Heets Turquoise

Brand Variant HEETS

Pack Style: Flip Top Box - 20 *HeatSticks*

	%	mg/cig
tobacco	23.5	201.5
glycerol	6.1	52.3
water	4.2	36.1
guar gum	0.914	7.85
cellulose	0.609	5.23
propylene glycol	0.180	1.55
natural & artificial flavourings	0.006	0.053
wrapper and adhesive (tobacco plug)	2.31	19.8
polymer-film filter	37.7	323.5
hollow acetate tube	9.0	77.4
mouth piece filter	7.6	65.3
tipping paper and tipping paper inks	2.3	20.0
outer paper	5.0	42.8
adhesives	0.7	5.68
	100%	859.0

Note:
- weight of the filter segment contains the filtration material, the wrapper and the adhesive
- the adhesive line considers only the ones applied on outer paper and tipping paper
- menthol is part of the PLA

Overview of the THS

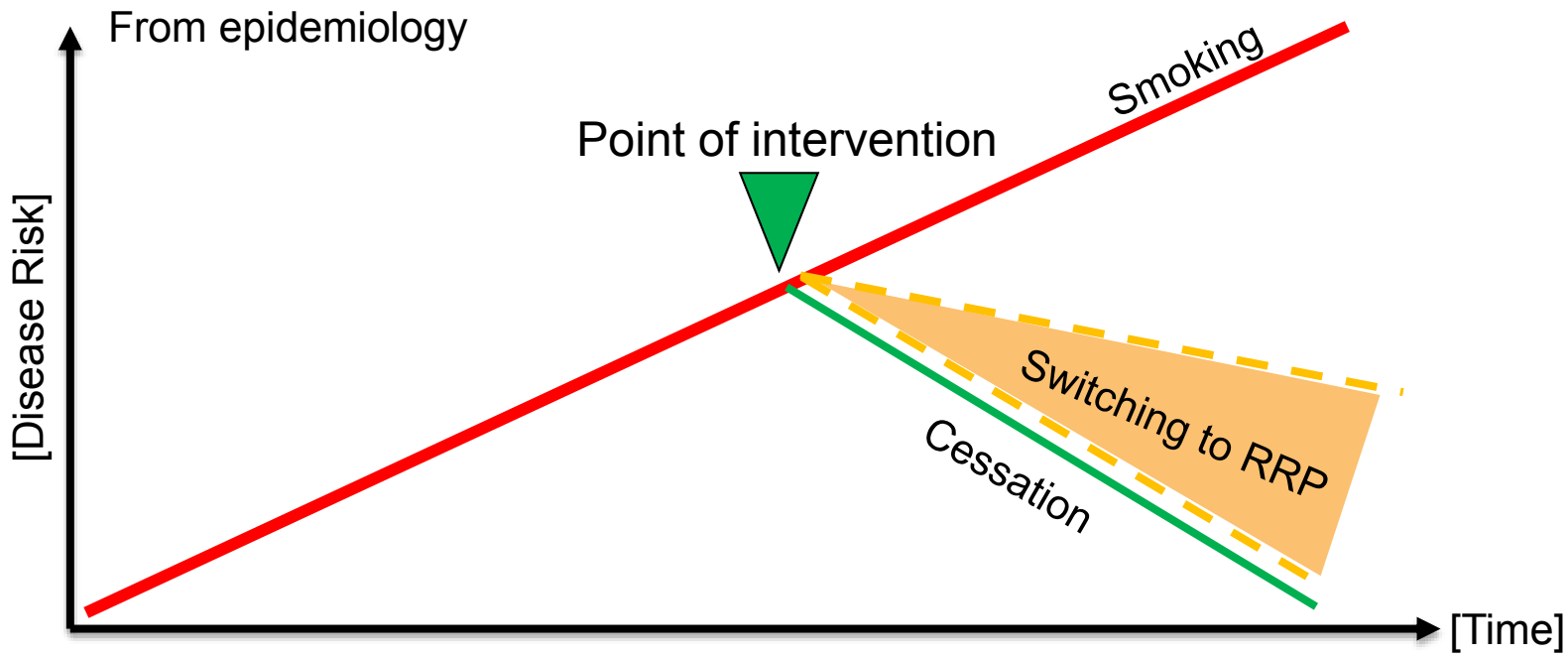
- THS is designed as an alternative to cigarettes for current, adult smokers who would otherwise continue to smoke

- The HeatStick is designed for the comparable duration (6 minutes, or up to 14 puffs) and nicotine deliveries as conventional cigarettes (CC)

- The main differences between the HeatStick and CC are:

HeatStick	CC
Cast-leaf made from homogenized tobacco powder	Cut leaf tobacco
Less tobacco (~ 300 mg)	More tobacco (~ 550-700 mg)
Controlled heating (< 350 °C), not burned	Lit with a flame, burned
Nicotine-containing aerosol is generated	Smoke is generated

Risk Assessment Framework



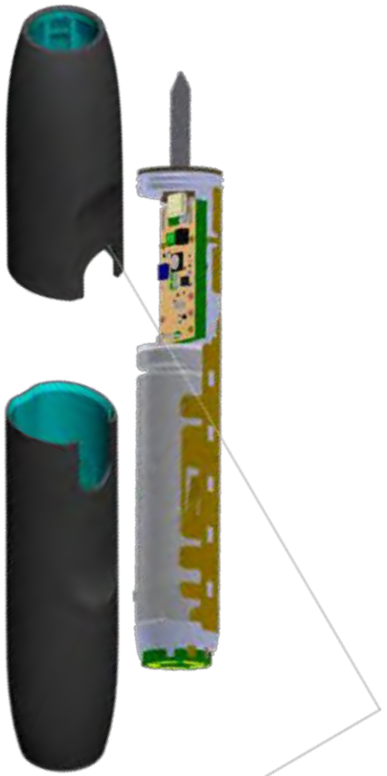
- Cessation is the ‘gold standard’ for risk reduction (IOM Report, 2012). "This provides an aspirational goal for risk and exposure for MRTPs — in principle, the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be in the chances for net public health benefit."
- The health risks of smoking and the reversal of risks after quitting smoking are well established and supported by epidemiological evidence (IARC 2004, 2007)

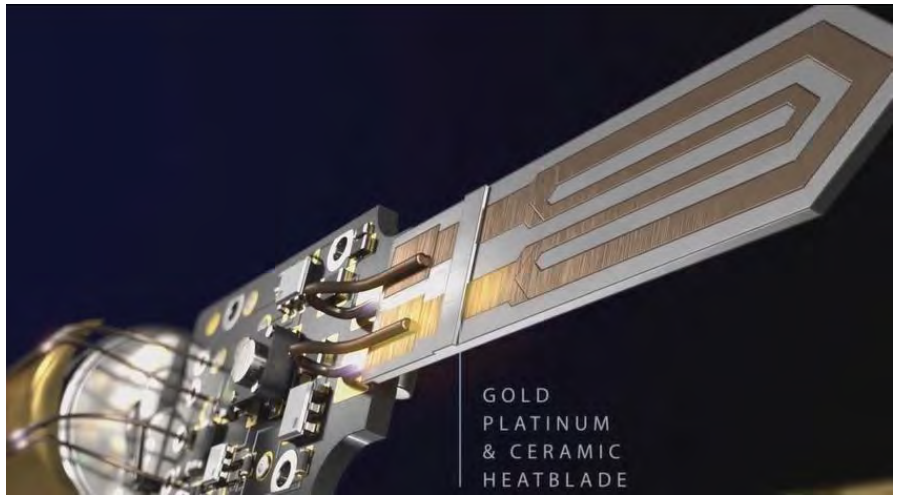
Note: The descriptions in the chart are for illustrative purposes only.

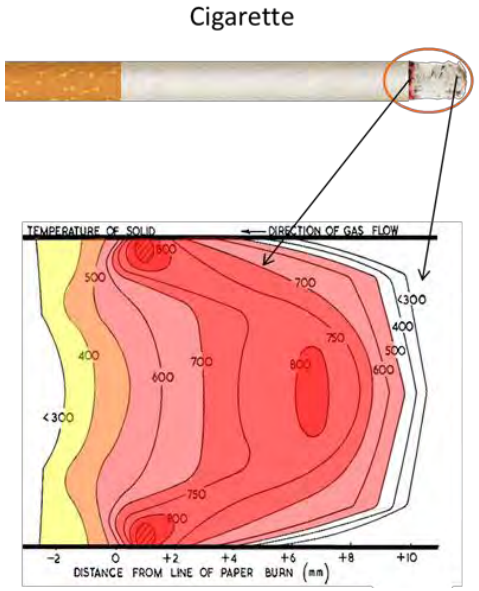
THS Assessment Overview

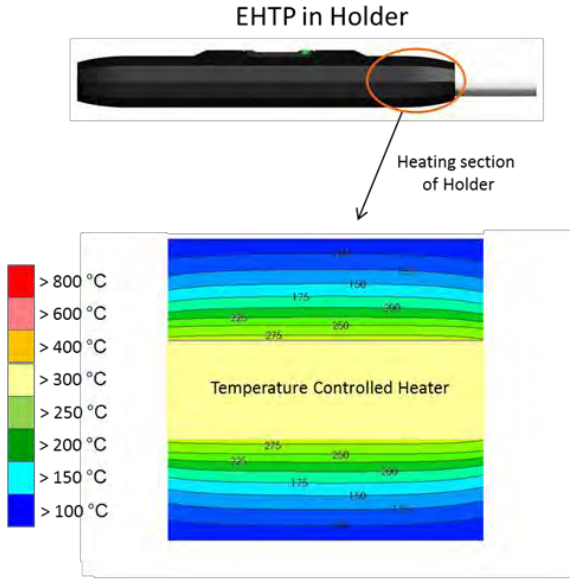
Assessment Strategy		Evidence
Assessment Layers	**Evidence Levels**	**Studies**
Post-Market Studies & Surveillance	Confirm Population Benefit	• Safety monitoring & Assessment
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations	7 Studies conducted in the US: • 1 Scale development (Risk Perception / Intent to Use) • 3 Message and Communication Material development • 2 Risk Perception, Product Understanding, Usability • 1 Actual Use in near to real-world conditions
Clinical Studies	PK/PD Studies, Reduced Exposure and Reduced Risk in Humans	• 4 PK/PD studies • 2 Reduced Exposure studies (5 days) • 2 Ambulatory Reduced Exposure studies (90 days)
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems	• *In vitro*: 6 mechanistic studies • *In vivo*: 4 mechanistic studies
Pre-Clinical Toxicology Assessment	Reduced Toxicity	• *In vitro*: 3 toxicity studies • *In vivo*: 3 toxicity studies
Aerosol Chemistry and Physics	Reduced Formation	• 58 HPHCs quantification & characterization
Product Design and Controls	Absence of Combustion	• Device characterization and controls • Analysis of aerosol chemistry & physics • Performance in oxygen-free environment

Heating versus Burning









PMI List of Chemical Markers used for Assessment

Basic Parameters (7)	CO; nicotine; water; TPM; NFDPM; 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; quinolone
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

ISO list (5) ✓

Health Canada (44) ✓

WHO Tob Reg (9) ✓

FDA abbreviated list (18) ✓

WHO 39 (2015) ✓

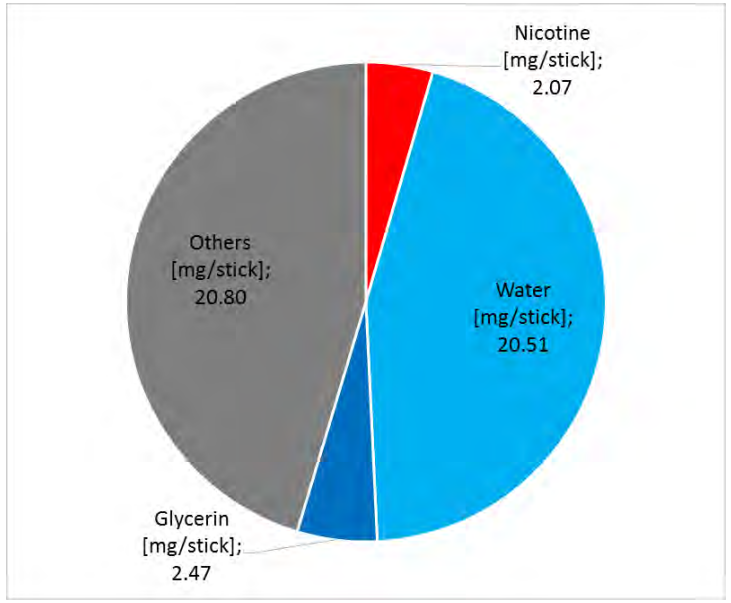
✓ Included in the PMI 58

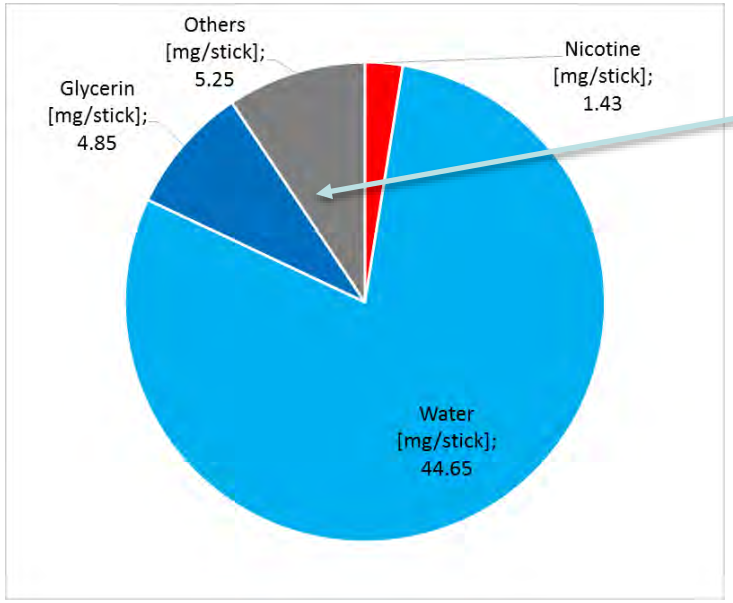
In red: HPHCs

* Classified as Group 1 carcinogens by IARC

Cigarette Smoke vs. Heat-Not-Burn Aerosol: Gross Composition

3R4F* Health Canada Intense smoking regime THS





≠

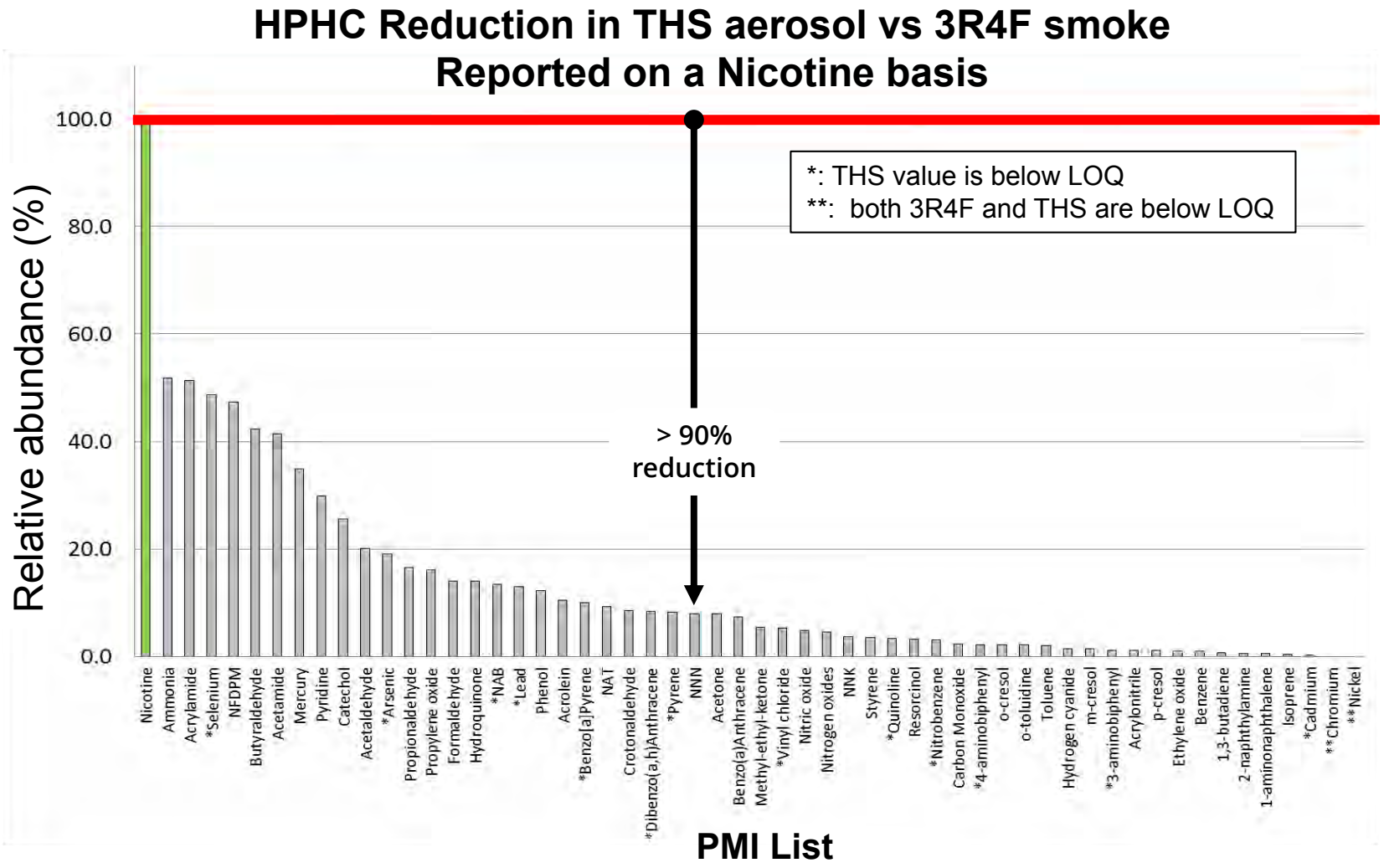
Non-targeted semi-quantitative analyses performed on Total Particulate Matter (TPM) enabled us to identify ~99% of the TPM:

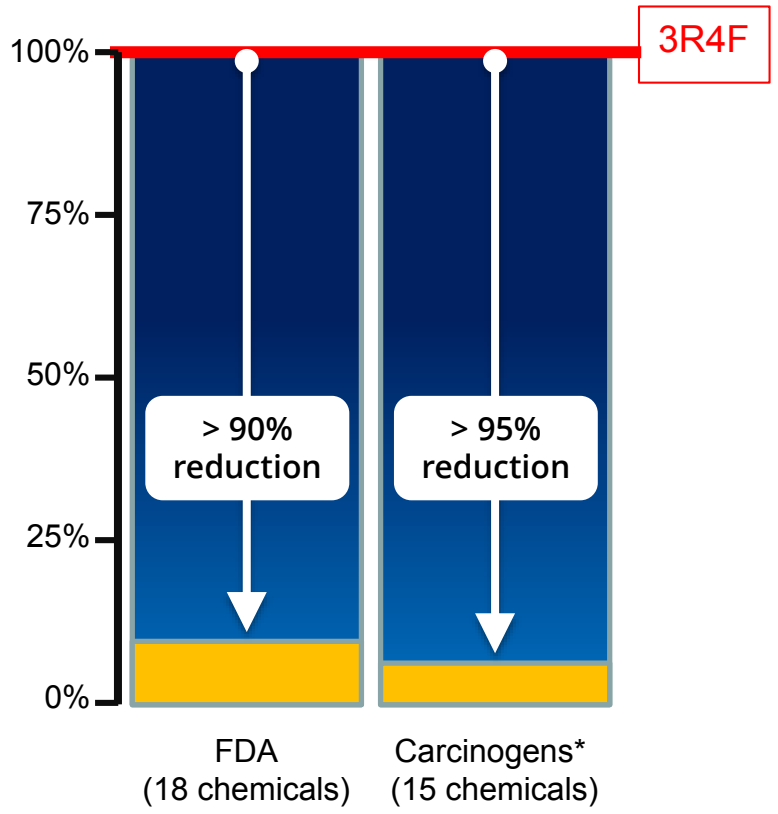
> 400 chemical constituents identified as being present in “others”.

Just 23 represent 80% of this mass (4.07 mg) representing only 5% of the total number of constituents.

* A standard reference cigarette supplied by University of Kentucky and referred to as 3R4F

Evidence of Reduced Formation

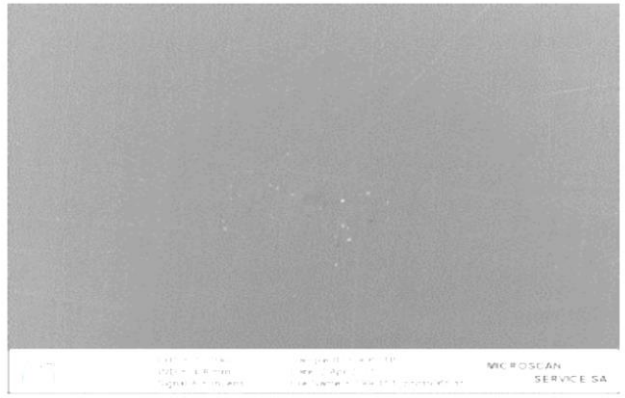




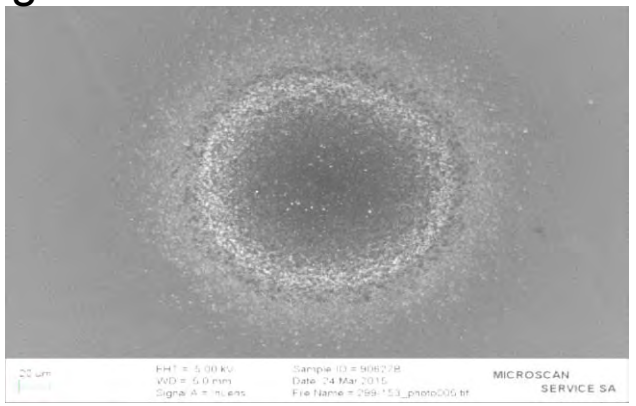
*Chemicals classified as Group 1 carcinogens by IARC

Heating Rather than Burning does not Generate Carbon Based Nanoparticles

Scanning electron microscopy image of collected smoke/aerosol



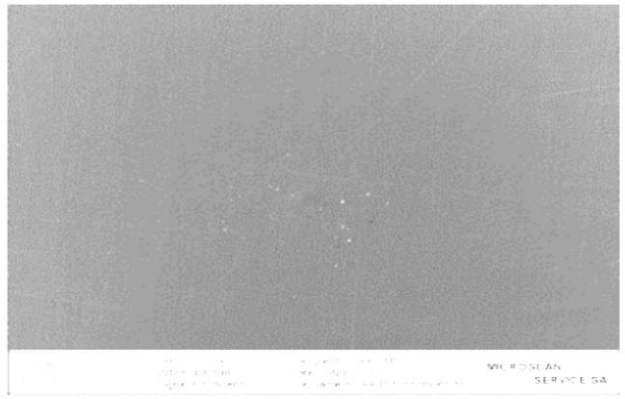
Blank impaction spot



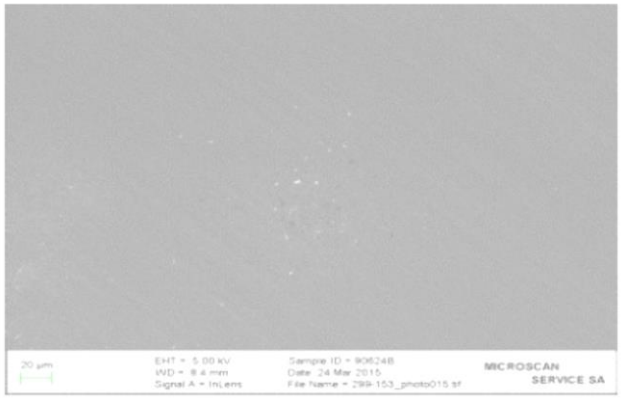
3R4F impaction spot

Cigarette smoke

Sub micron (median: 75 nm) solid particles are present in the smoke of 3R4F.
The X-ray analysis of these particles show that they are carbon based



Blank impaction spot



THS aerosol impaction spot

THS aerosol

No significant difference could be found between the blank and heated tobacco

→ Aerosol from THS does not contain solid particles resulting from combustion

Indoor Air Chemistry Room, Simulated Environments and Experimental Process

Sampling area

Environmental specifications according to CEN Standard (EN 15251:2007):

- "Hospitality": 7.68 air changes/h, 4.8 m^2/person;
- "Office": 2.16 air changes/h, 8 m^2/person;
- "Residential I": 1.68 air changes/h, 8 m^2/person;
- "Residential II": 1.20 air changes/h, 8 m^2/person.

Room size: 24.1 m^2 – 72.3 m^3.

Temperature: 23±3°C – pressure controlled

Humidity monitored: 40-56 RH%

Air change: 0.5 to 12.2 per hour (Depending on environmental conditions)

Air filtration (dust, microparticles) – Low-emission / washable furniture

Fans to homogenize air

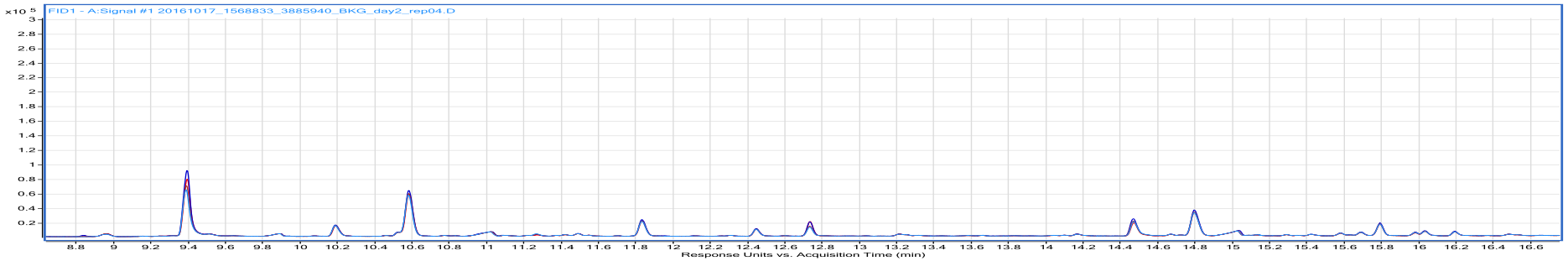
Background
- People in the room, not using any products

THS
- Actual use of THS

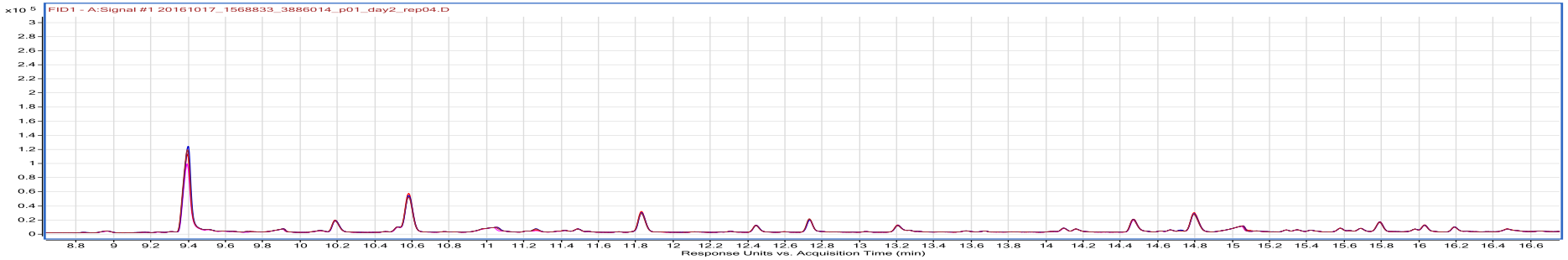
Data evaluation
- Comparison of THS vs. Background

How THS Environmental Aerosol is Different from Background?

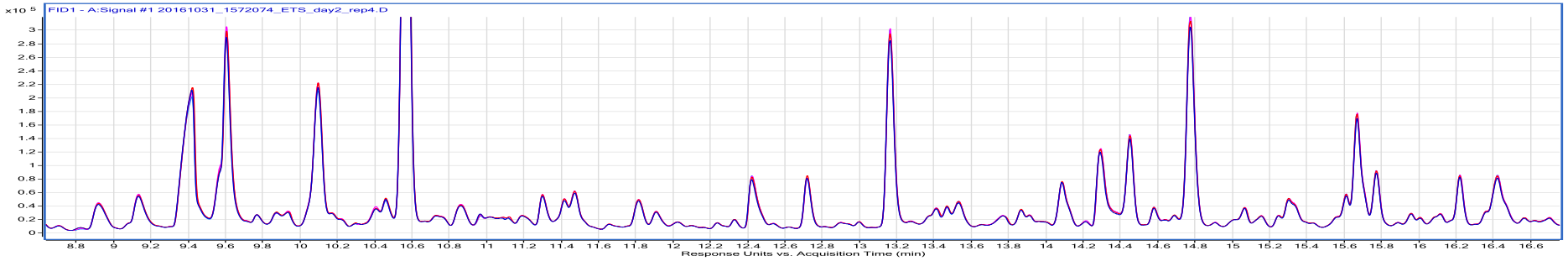
TVOC (ISO16006-2011) provides a broader view of chemical composition (bp 69-287°C)
Experimental conditions: 0.5 air change, 2 panelists, 12 products consumed during 2h



BKG
Overlay replicates 1-4
4-9 peaks above 2µg/m³

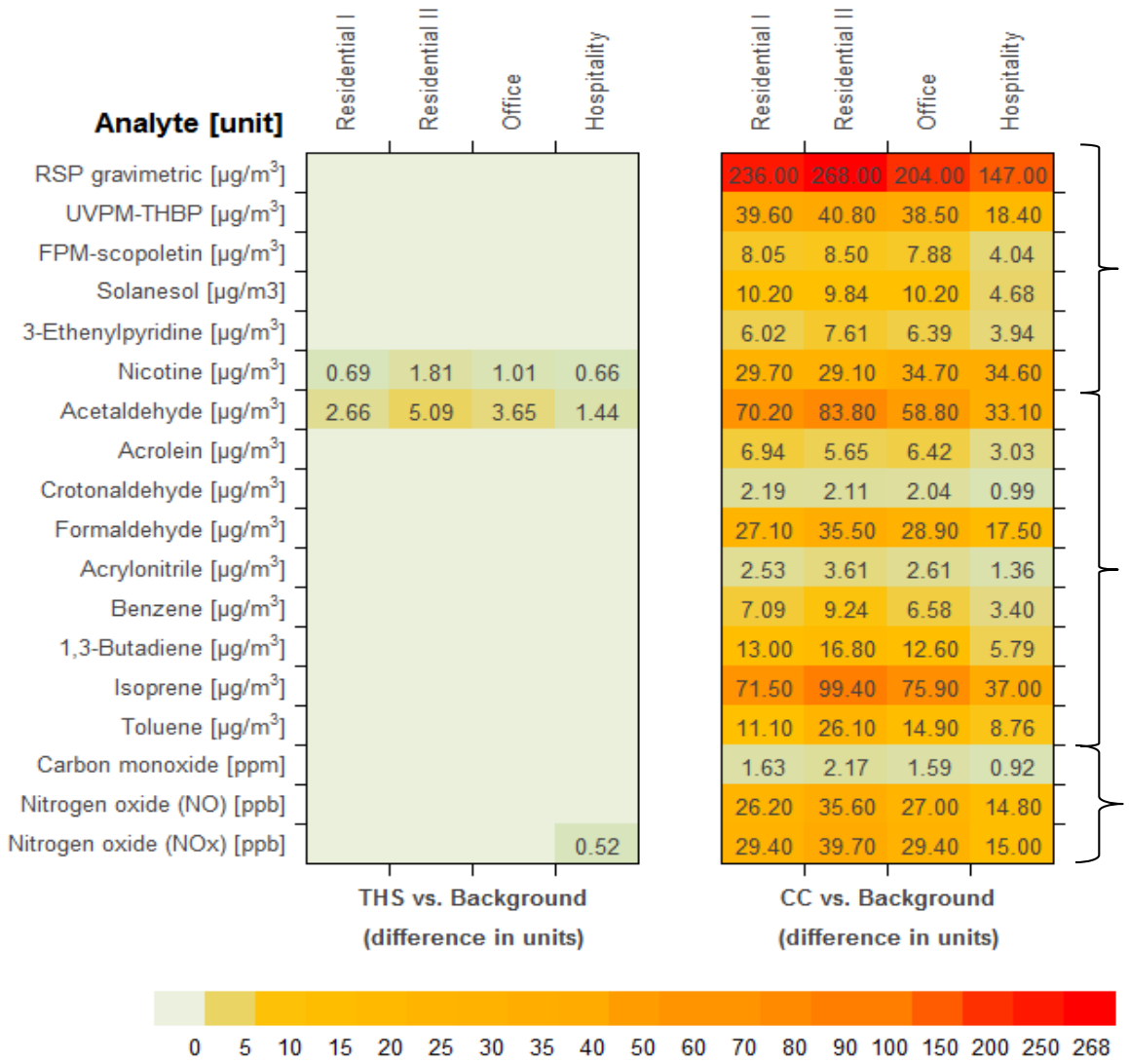


THS
Overlay replicates 1-4
4-10 peaks above 2µg/m³



ETS (cigarettes)
Overlay replicates 1-4
73-87 peaks above 2µg/m³

List of Measured Constituents (Indoor Air Chemistry)



PM2.5 & tobacco smoke-related chemical markers

Compounds selected based on:

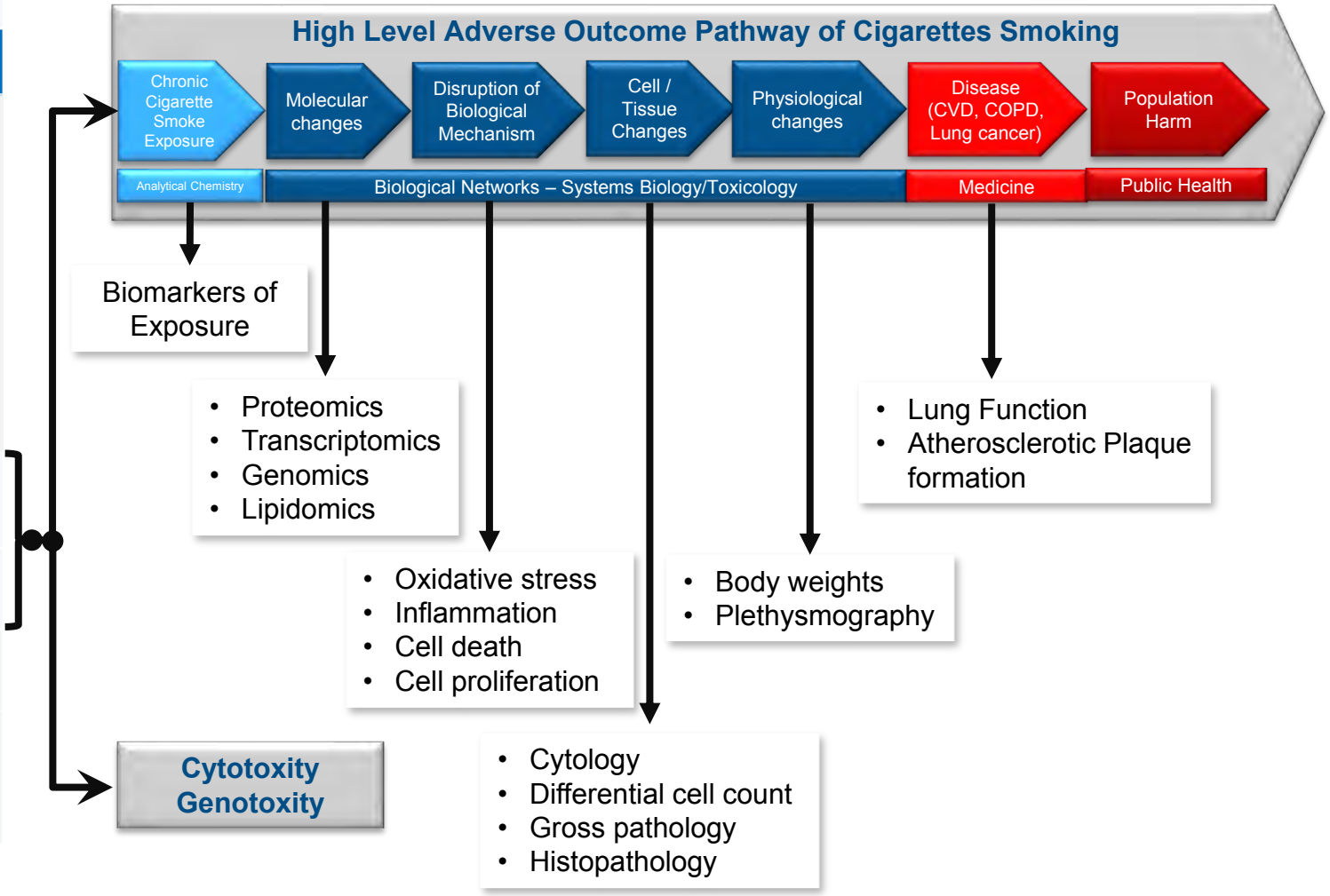
- Relevance for air quality
- Relative abundance in THS2.2 aerosol (i.e. the most abundant)

Gas-phase combustion marker

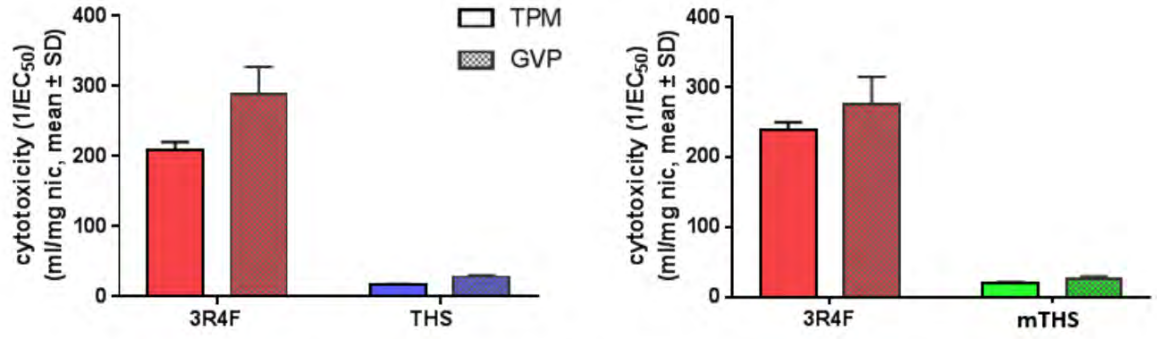
Non-clinical Evidence: Approach and Rationale

Assessment Strategy

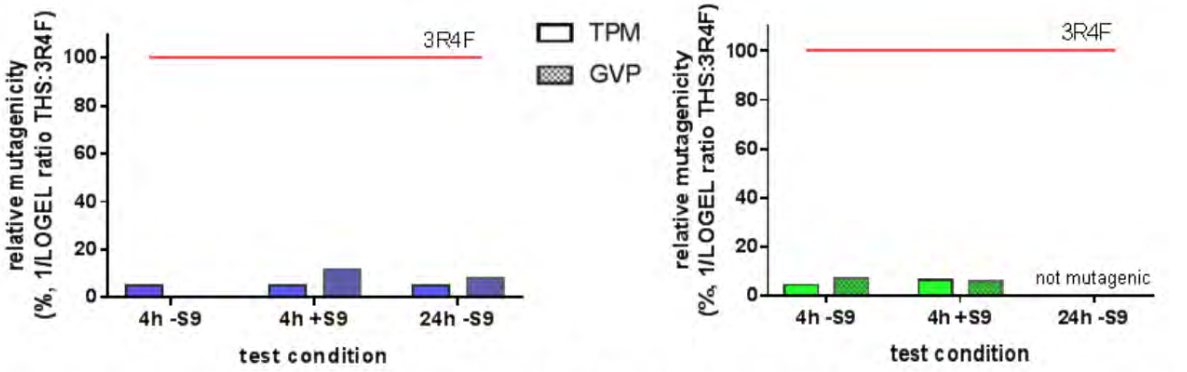
Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	Reduced Exposure and Reduced Risk in Humans
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion



In vitro Assessment of THS Aerosol



Cytotoxicity of 3R4F, THS and mTHS on nicotine basis.

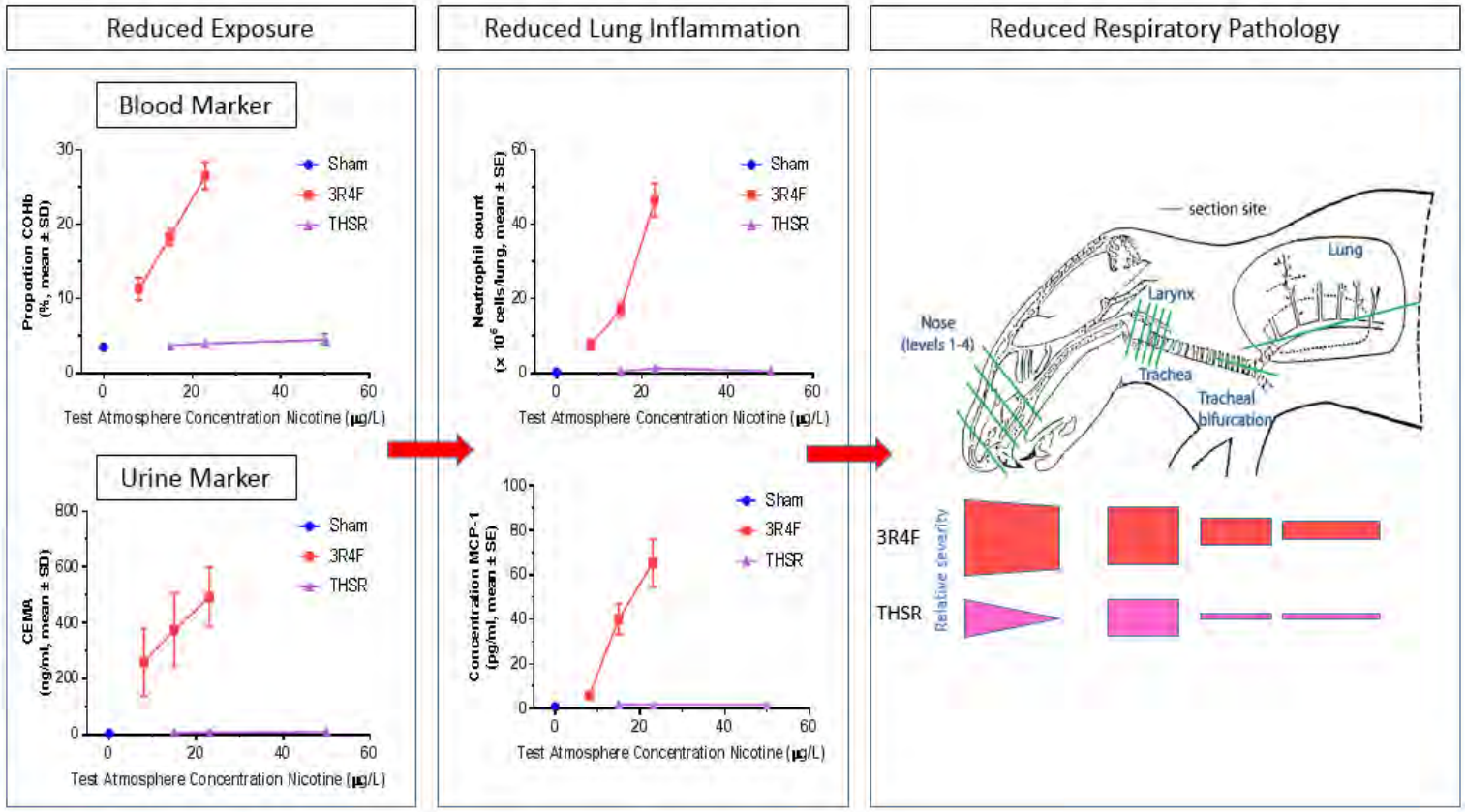


Percentage of relative mutagenicity reduction in THS (left panel) and mTHS (right panel, on a per item basis, calculated from LOGELs.

When repeat tests yielded different LOGEL ratios, the lowest value (most mutagenic) is shown.

- **Cytotoxicity assessment**
  - **Neutral Red Uptake (NRU) assay**
    - TPM from THS and menthol THS (mTHS) aerosols did not show mutagenic activity, over the dose range tested (up to 10mg/plate), in the different strains tested, while reproducible mutagenic responses were observed for the TPM from 3R4F smoke in strains TA98, TA100 and TA1537 in the presence of S9.
- **Genotoxicity Assessment**
  - **Ames bacterial mutagenicity assay (Ames assay)**
    - TPM from THS and mTHS aerosols did not show mutagenic activity, over the dose range tested (up to 10mg/plate), in the different strains tested, while reproducible mutagenic responses were observed for the TPM from 3R4F smoke in strains TA98, TA100 and TA1537 in the presence of S9.
  - **Mouse Lymphoma Assay (MLA)**
    - TPM of the THS aerosol was at least 9-14-fold less mutagenic than 3R4F smoke on a nicotine basis; GVP of THS aerosol was at least 8-fold less mutagenic than 3R4F smoke on an item basis (mutagenic responses with lowest observed genotoxicity level - LOGEL)

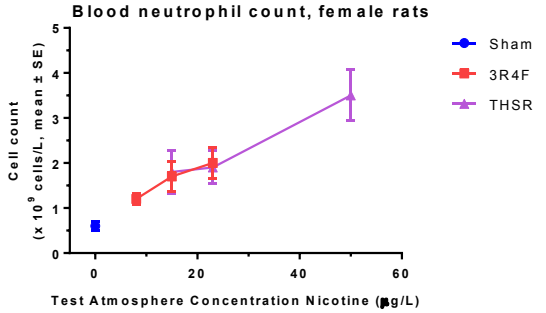
In vivo Assessment of THS Aerosol

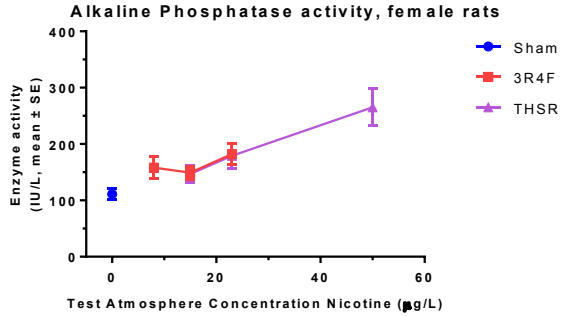


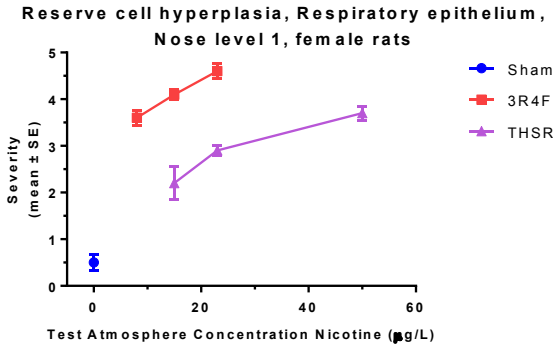
- OECD TG 413, Sub-chronic inhalation study on rats, according to OECD GLP
- Exposure to low, medium and high* concentration of THS aerosol and 3R4F smoke
- Characterization of:
  - Test atmosphere
  - Biomarkers of exposure
  - Systemic toxicity
  - Respiratory physiology
  - Lung inflammation
  - Histopathology of respiratory and non-respiratory tract organs

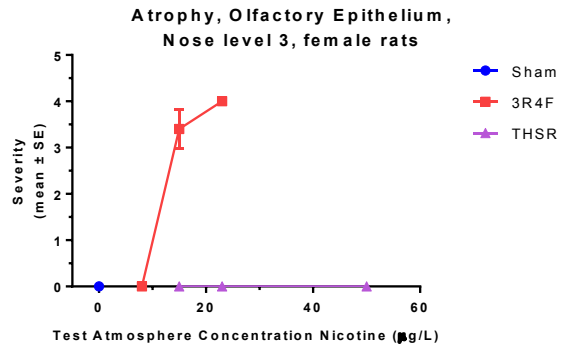
*50 µg/l nicotine (MTD for rats) corresponds to 13.6 mg/kg, daily dose; way above acute toxicity levels- or the nicotine amount from approx. 130 cig/day for a 60 kg human

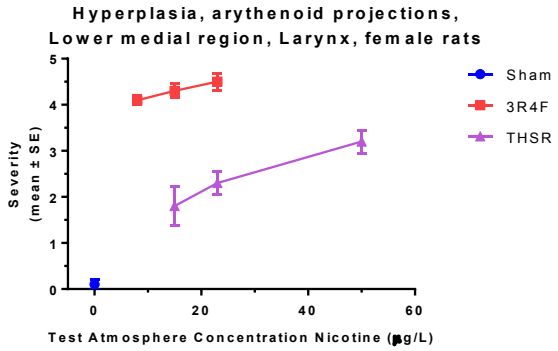
In vivo Assessment of THS aerosol

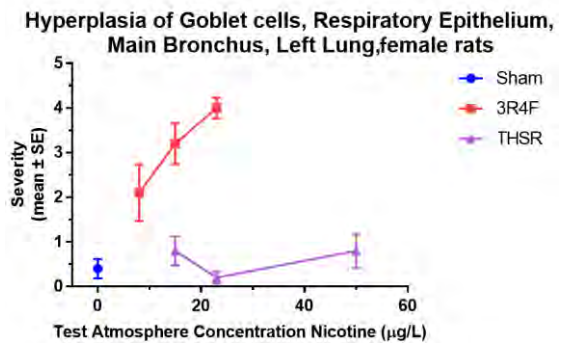












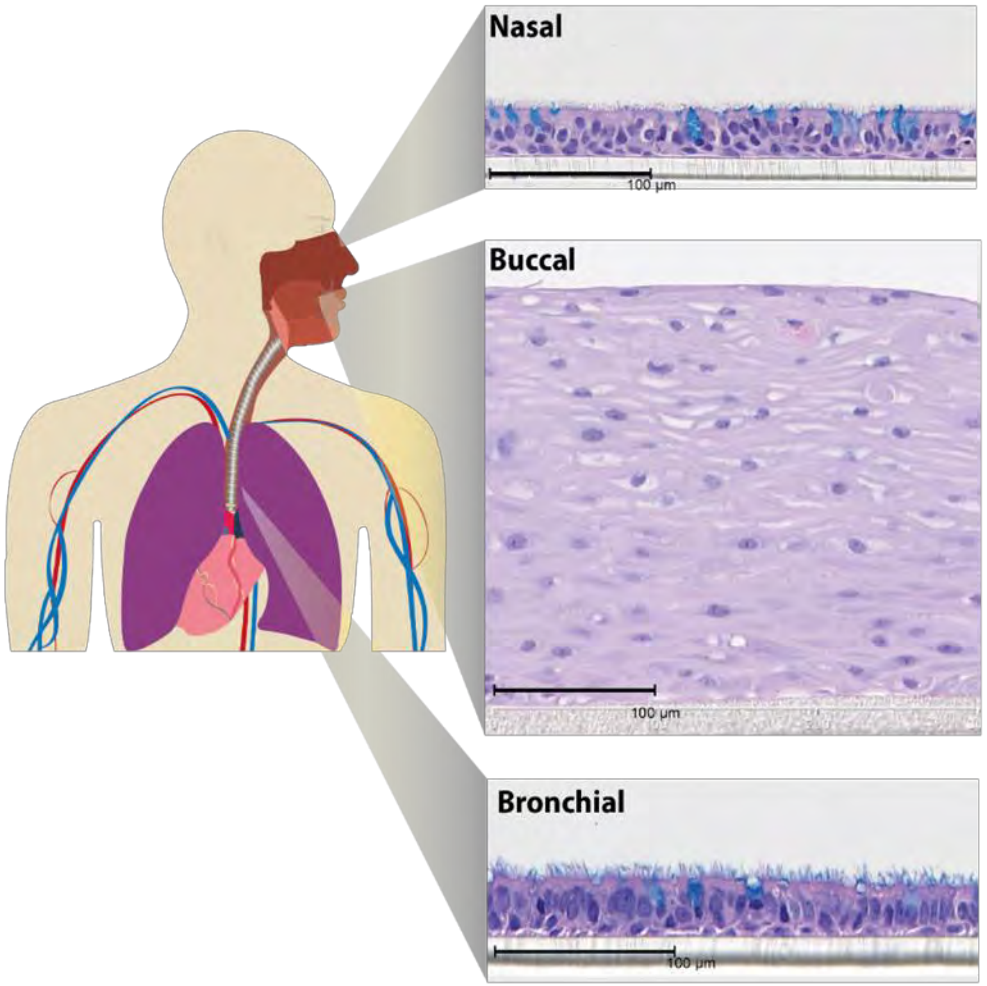
- Systemic toxicity effects
  - Nicotine concentration-dependent changes in THS aerosol and 3R4F smoke exposed rats – all adaptive changes
    - Higher blood neutrophil count
    - Higher liver enzyme activities, lower glucose and cholesterol
    - Higher liver and adrenal gland weight, lower thymus weight
- Histopathology of respiratory tract
  - Changes are of lower severity in THS-exposed rats compared with 3R4F smoke-exposed rats. THS aerosol causes:
    - Epithelial changes at nose level 1 and 2 only (hyperplasia and squamous metaplasia of respiratory epithelium)
    - Minimal to moderate hyperplastic epithelial changes
    - Minimal changes in epithelia from airways and bronchi
    - No lung inflammation

Systems Toxicology Evaluation of Organotypic Tissue Cultures Exposed to THS Aerosol

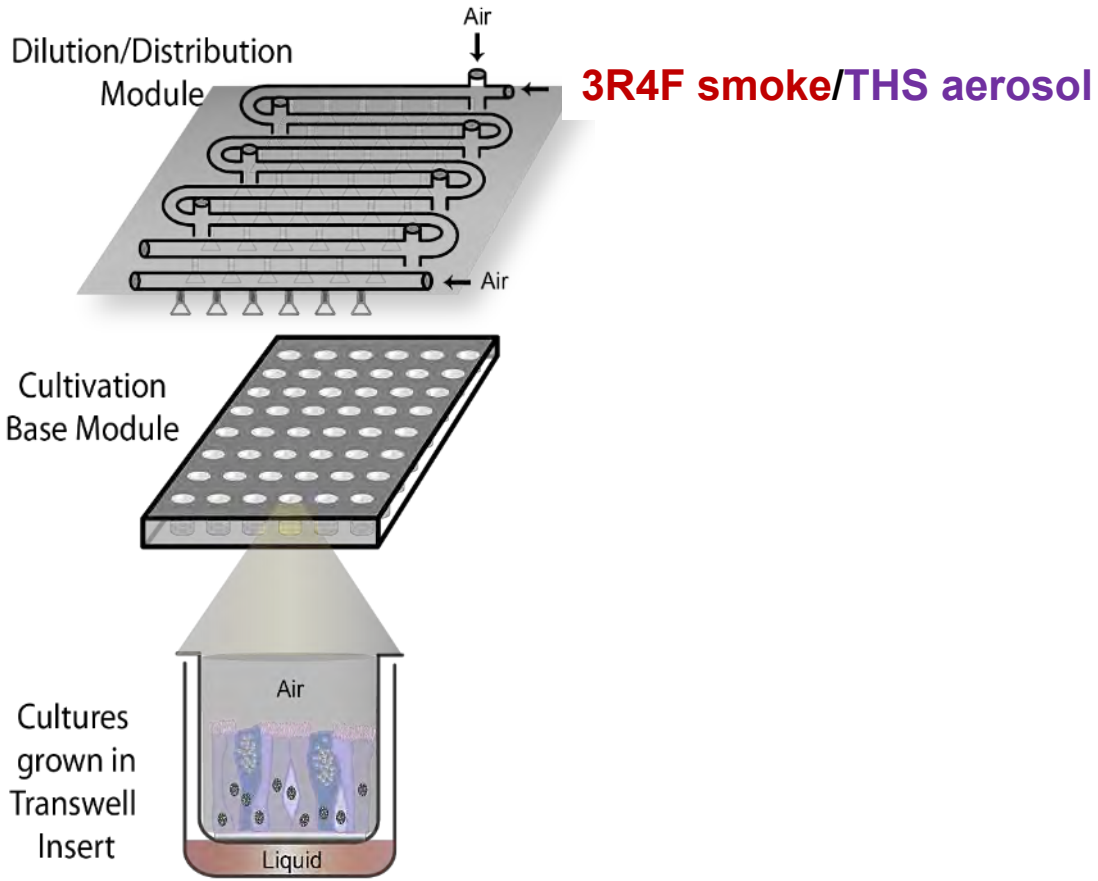
- *In vitro*, systems toxicology approach has been implemented to evaluate the impact of acute exposure of human organotypic airway epithelial tissues (nasal, bronchial, buccal) to THS.
- A total of 12-15 independent exposure runs per tissue type have been completed to evaluate the following toxicological endpoints:
  - Cytotoxicity
  - Histology
  - Secreted inflammatory mediators
  - Cytochrome P450 1A1/1B1 activity
  - Global gene expression changes

Studies using Human Organotypic Tissue Cultures: Whole Smoke/Aerosol Exposure

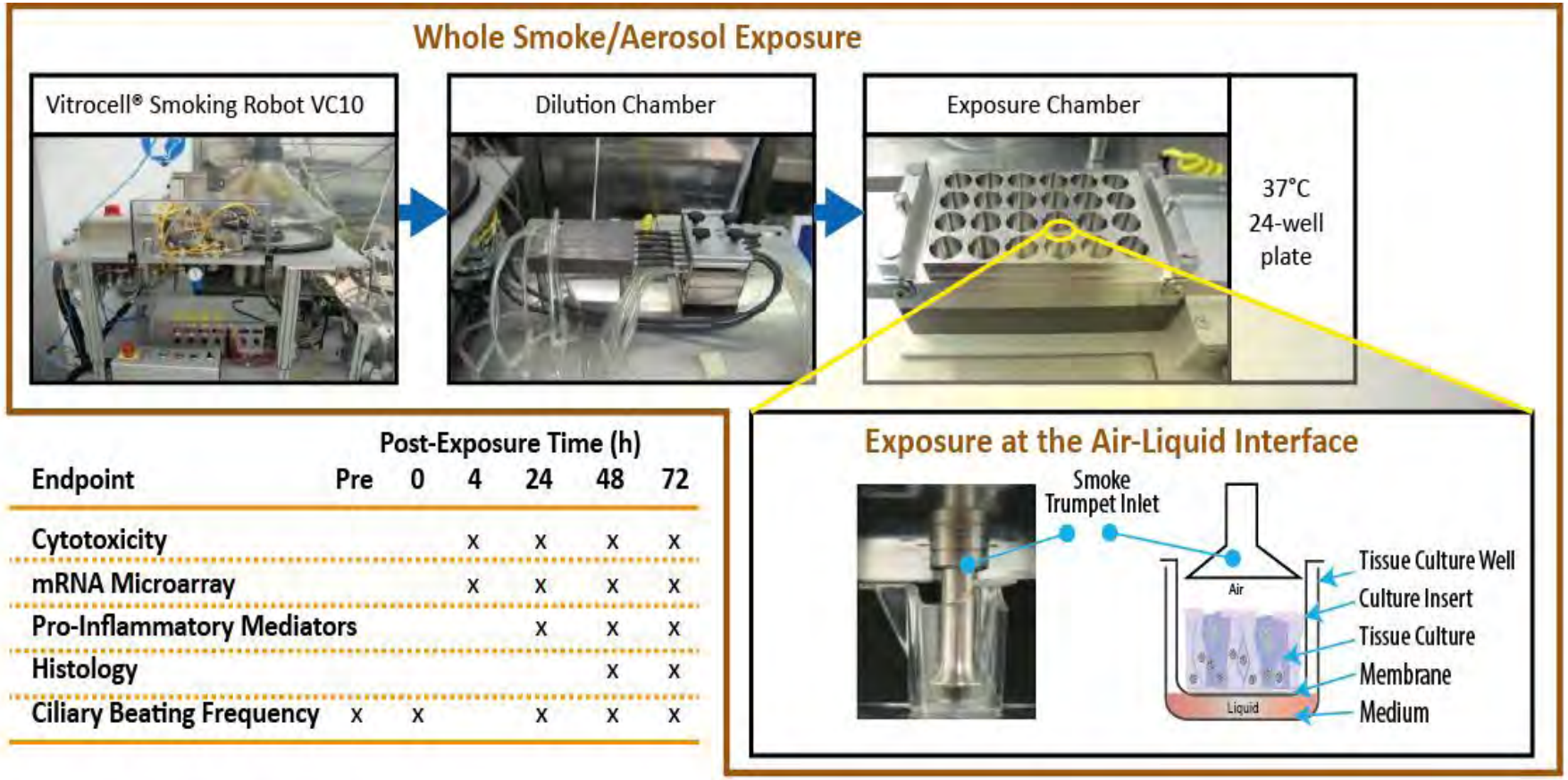
In Vitro Organotypic Culture System



***In vitro* Whole Smoke/Aerosol Exposure System**



Exposure Procedure and Study Design



Experimental Data Workflow

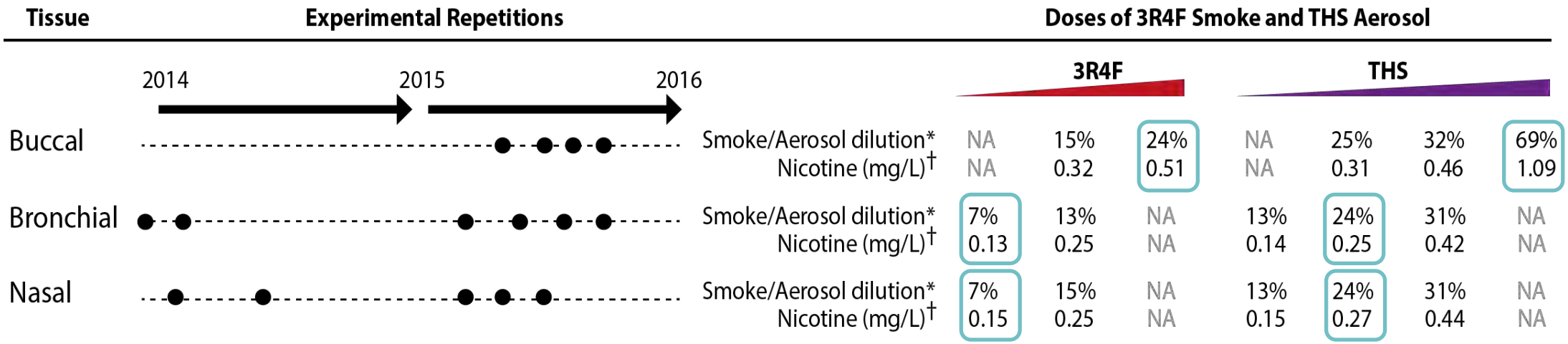
Upper panel: Organotypic cultures of human primary respiratory epithelial cells can be directly exposed to 3R4F smoke or THS aerosols using the Vitrocell® system.

Lower panel: The cells would be exposed to smoke/aerosols during different exposure times, then various endpoints were captured after different post-exposure times.

Majeed, S., et al. (2014). "Characterization of the Vitrocell(R) 24/48 in vitro aerosol exposure system using mainstream cigarette smoke." Chemistry Central Journal 8(1): 62.

Thorne, D., et al. (2013). "Characterisation of a Vitrocell(R) VC 10 in vitro smoke exposure system using dose tools and biological analysis." Chemistry Central Journal 7(1): 146

Exposure to THS Aerosol was Matched with Nicotine Concentrations of 3R4F Smoke



● 3 independent exposure-run was conducted for each item (3R4F and THS); except for those using bronchial cultures in 2014.

* Dilution refers to the percent 3R4F smoke or THS aerosol diluted with air in the Dilution/Distribution Module of the Exposure System.

† Nicotine concentration (mg/L) refers the corresponding concentration to the specific dilution of smoke/aerosol determined by trapping the diluted smoke/aerosol in the EXtrelut® 3NT column.

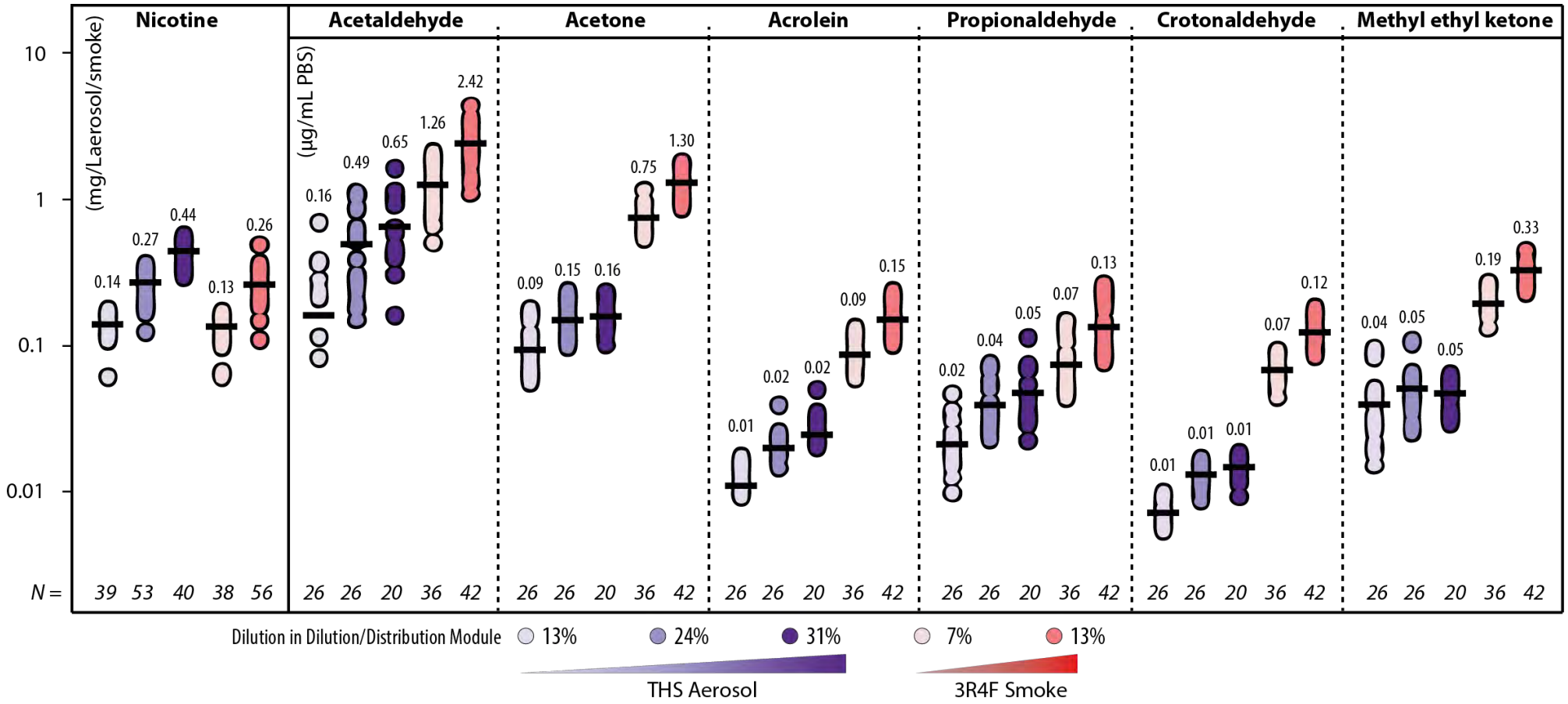
NA: not available (i.e., not tested).

Culture Type	Supplier	Cell Origin	Note
Buccal	EpiOral, MatTek, USA	46-male non-smoker	used for all experimental repetitions
Bronchial	EpiAirway, MatTek, USA	23-male non-smoker	used for experiment 1-2
	MucilAir, Epithelix, Switzerland	28-male non-smoker	used for experiment 3-6
Nasal	MucilAir, Epithelix, Switzerland	30-male non-smoker	used for all experimental repetitions

Doses taken for the comparative analysis of the transcriptome data

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

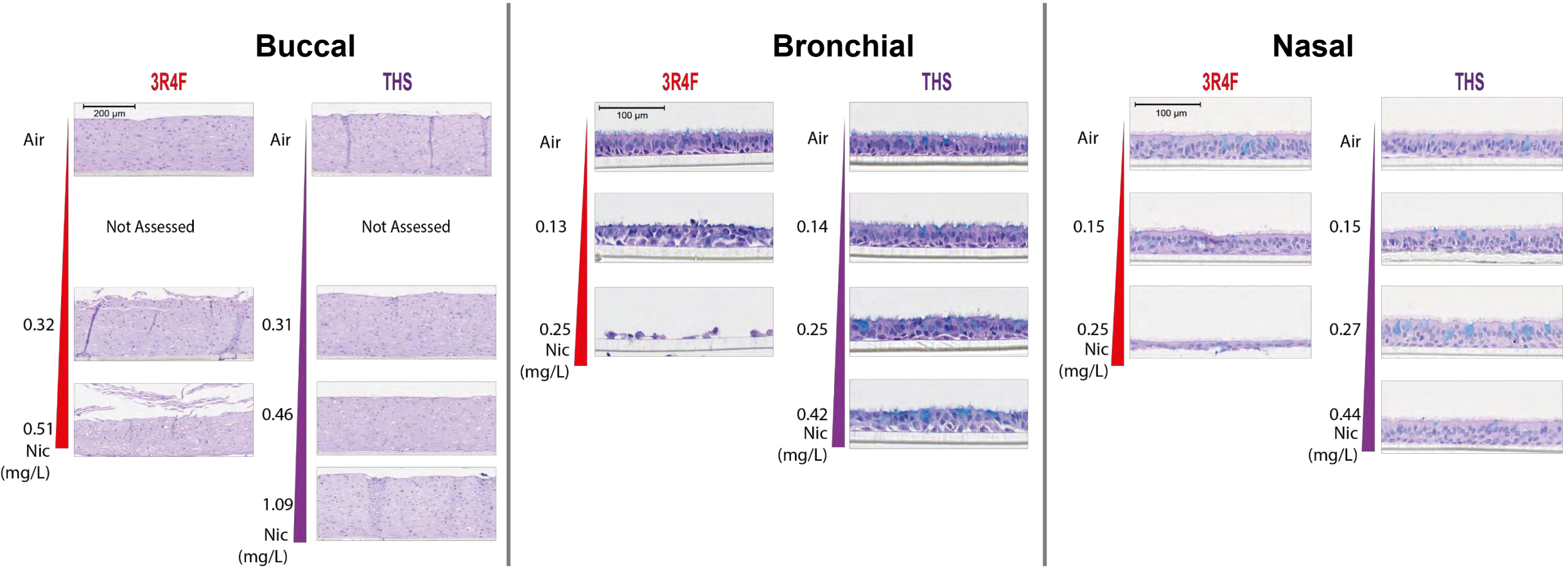
Exposure Characterization: Concentrations of Nicotine in Whole Smoke/Aerosol and Deposited Carbonyls in the Base Module of the Exposure System



Carbonyls were measured in phosphate buffered saline (PBS) following a 28 minute exposure to whole smoke or test aerosol (total ten sticks per item tested [a total of 110 puffs], each of them was smoked/aerosolized by applying a modified Heath Canada Intense (HCI) puffing protocol of 55 mL puff over 2 seconds, twice per minute with an 8 seconds pump exhaust time). Sample was injected to an HPLC instrument coupled with a tandem MS (HPLC-MS/MS) for the measurement of various carbonyls using an isotope dilution technique.

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

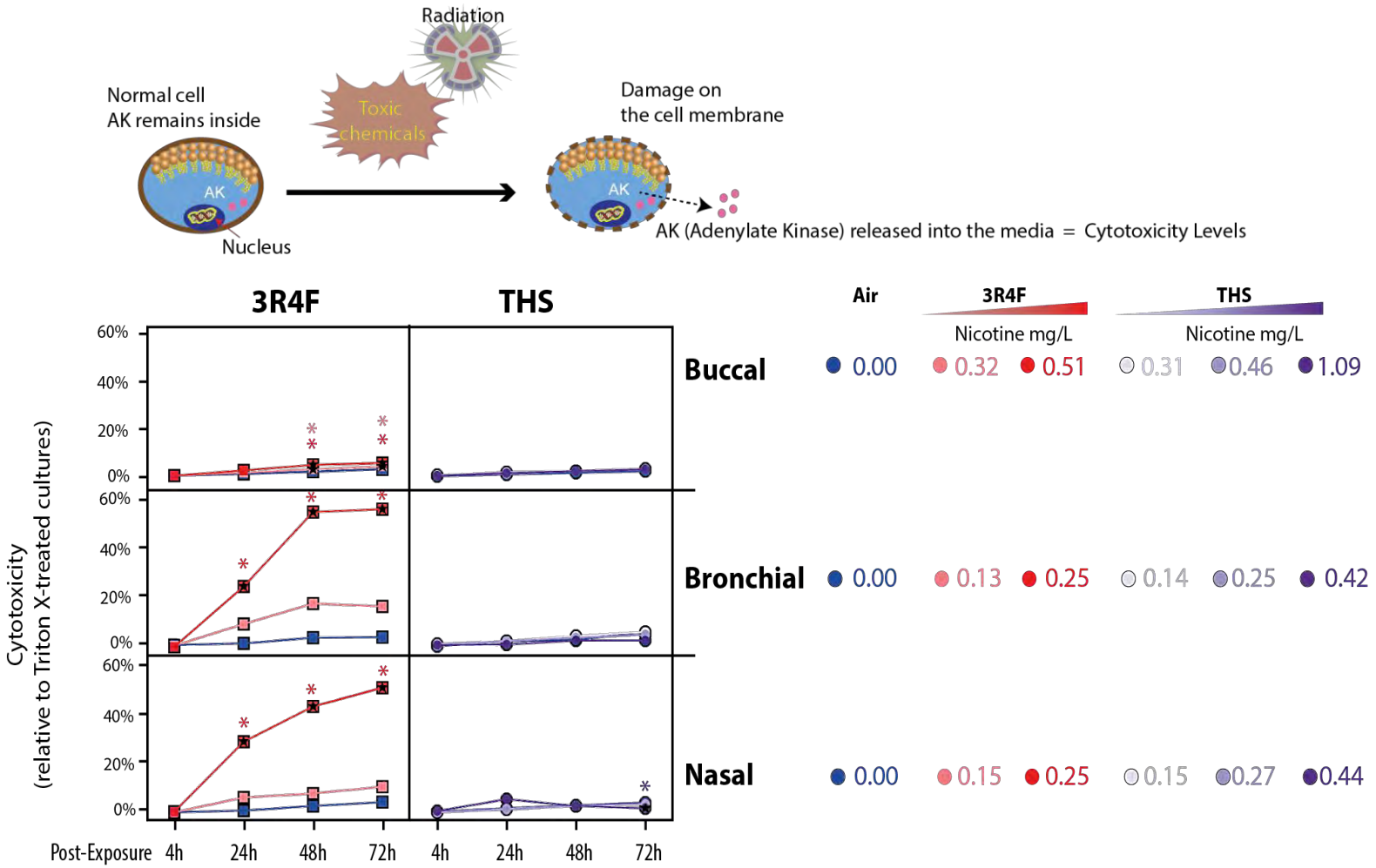
Impact of THS Aerosol and 3R4F Smoke Exposure on Organotypic Tissue Integrity



At equivalent nicotine concentrations, morphological changes in THS-exposed cultures were similar to the air control but 3R4F induced tissue damage in bronchial and nasal cultures (3R4F impacted only the apical epithelial layer of the buccal cultures).

A. R. Iskandar, et al. ALTEX. 2016; A. R. Iskandar, et al. Toxicology in vitro. 2017, 39, 29-51; F. Zanetti, et al. Chem Res Toxicol. 206, 29, 1252-1269

Impact of THS Aerosol and 3R4F Smoke Exposure on the Organotypic Tissue Cytotoxicity



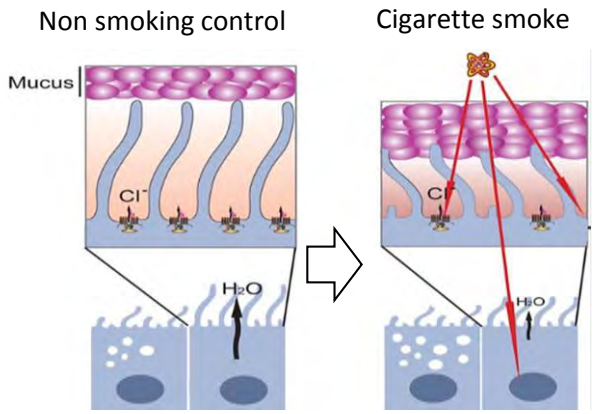
A dose-dependent cytotoxicity effect (derived from the adenylate kinase levels released into the media) was observed in the bronchial and nasal cultures for both 3R4F smoke and THS aerosol exposure with a clear difference in magnitude at equivalent nicotine concentrations.

Less toxicity was observed in buccal cultures following THS aerosol and 3R4F smoke exposure in all concentrations tested.

* P-value ≤ 0.05, as compared with the air control. N = 9 – 16 per group (aggregated data from the experimental repetitions throughout the study period)

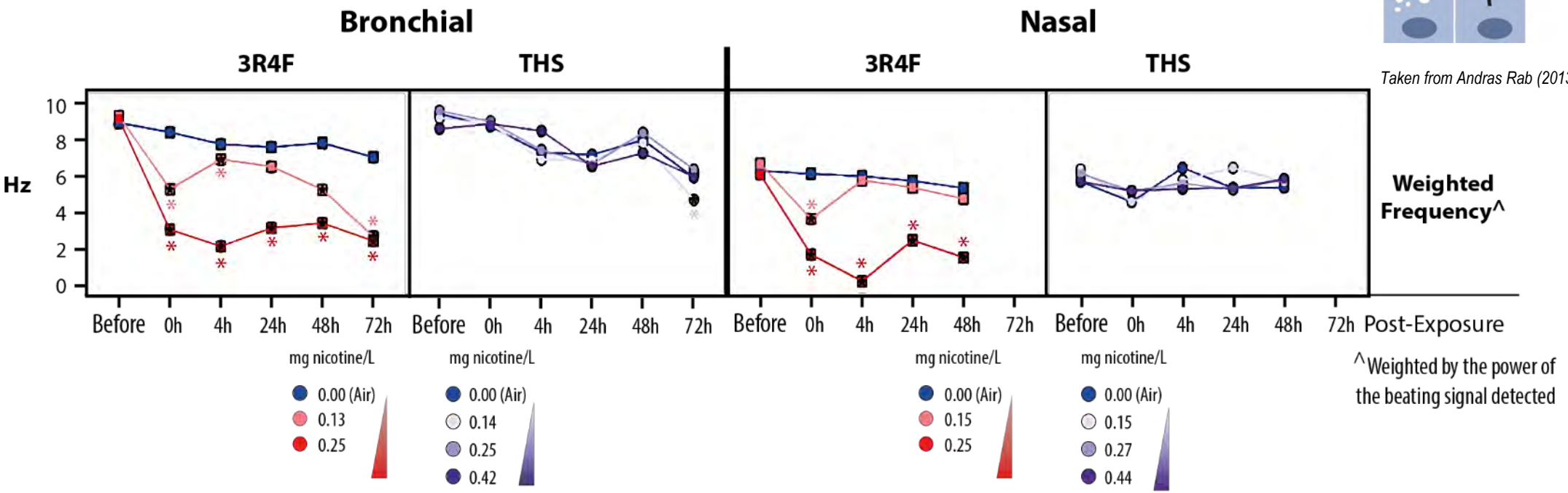
A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Impact of THS Aerosol and 3R4F Smoke Exposure on the Ciliary Beating Function of Bronchial and Nasal Cultures



Taken from Andras Rab (2013)

The mucociliary clearance provides defense mechanism for respiratory tract. The clearance rate correlates to the ciliary beating frequency (CBF). Normal CBF was reported to be at ~8.4 ± 1.6 Hz in the nasal biopsy (Jorissen, M. and A. Bessems (1995). Acta Otolaryngol 115(1): 66-70.)



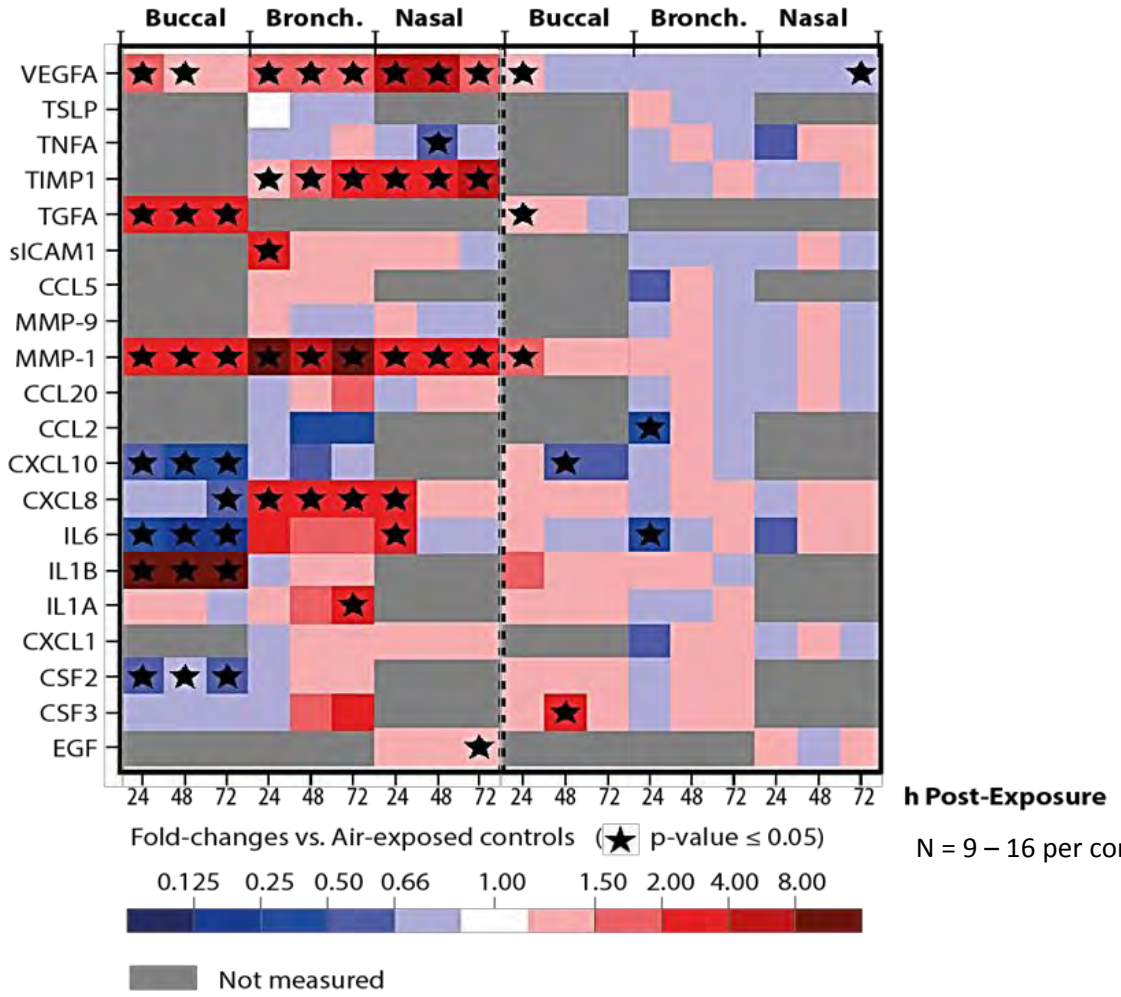
* P-value ≤ 0.05, as compared with the air control. N = 3-12 per group (aggregated data from the experimental repetitions throughout the study period)

3R4F smoke exposure substantially reduced the ciliary beating frequency, without recovery after 72 h post-exposure. Whereas, THS aerosol exposure elicited less impact on the frequency of ciliary beating.

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Levels of Secreted Pro-inflammatory Mediators following Exposure to THS Aerosol as Compared with 3R4F Smoke at Similar Nicotine Concentrations

	3R4F	THS	
Buccal	0.51	0.46	mg nic/L
Bronchial	0.13	0.14	mg nic/L
Nasal	0.15	0.15	mg nic/L



The basolateral media of the cultures were collected at various time points post-exposure and subjected to Luminex-based analysis of the pro-inflammatory mediator levels.

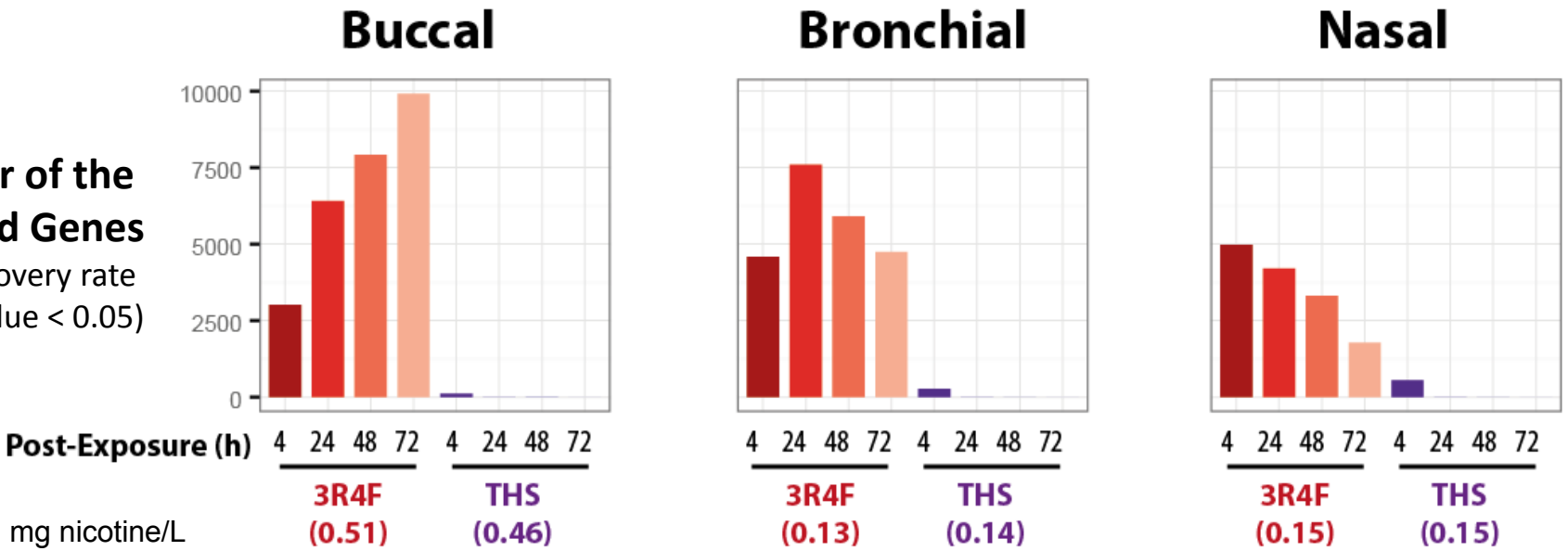
At similar nicotine concentrations, for each culture, greater secretion of pro-inflammatory mediators was detected in the medium of tissue cultures following 3R4F smoke as compared with THS aerosol exposure.

N = 9 – 16 per contrast (aggregated data from the experimental repetitions throughout the study period)

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Alteration in Gene Expression following THS Aerosol and 3R4F Smoke Exposure for 28 min: Global Transcriptome Changes

Number of the Differentially Expressed Genes
(FDR, false discovery rate -adjusted p-value < 0.05)



N = 9 – 15 per contrast (aggregated data from the experimental repetitions throughout the study period)

For all the three cultures, lower number of genes was significantly altered following THS aerosol exposure as compared with 3R4F smoke at similar nicotine concentrations. THS aerosol exposure resulted mainly in transient effects: alterations in the gene expression were primarily observed at 4 h post-exposure.

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Impacted Biological Processes following THS Aerosol and 3R4F Smoke Exposure for 28 min: A Network-based Analysis of the Transcriptomes

Transcriptome Data

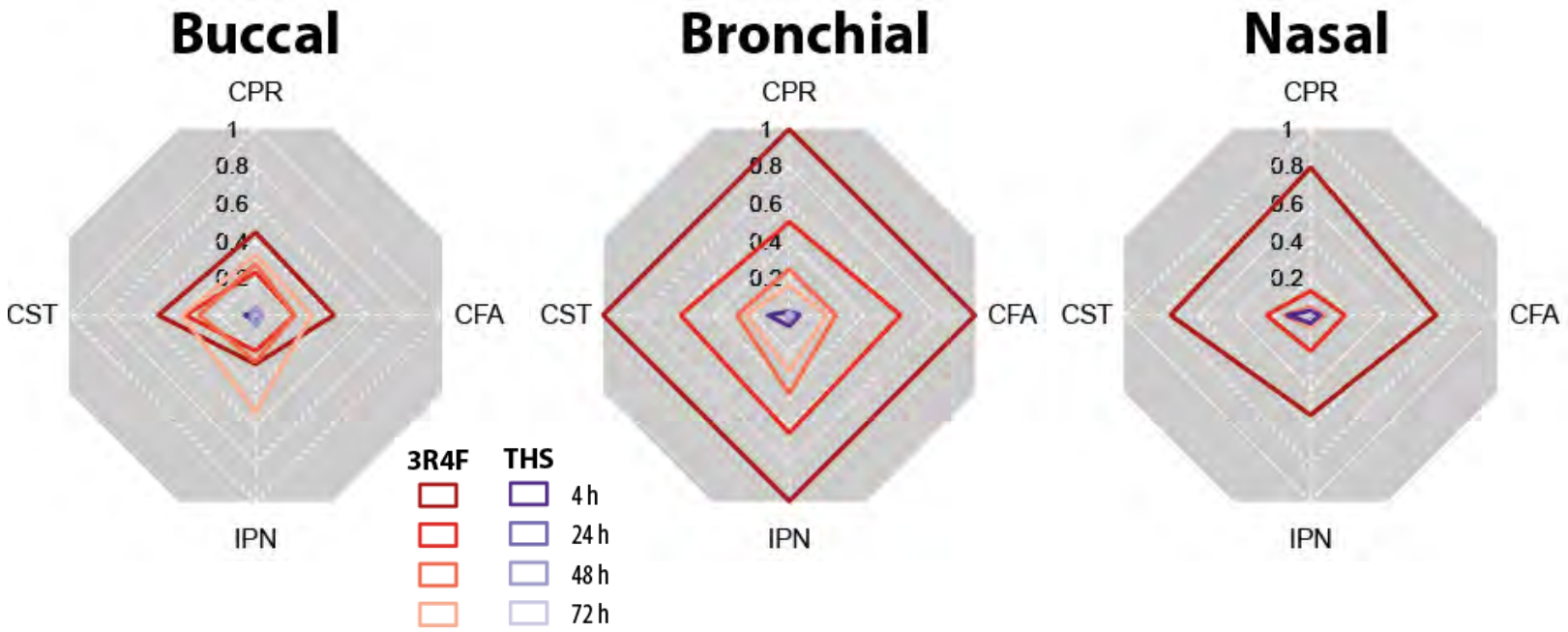
↓

Impact on 29 Causal Biological Network Models*

↓

Perturbation at the Network Category:
- **Cell Stress (CST)**
- **Cell Proliferation (CPR)**
- **Cell Fate (CFA)**
- **Inflammatory Process Networks (IPN)**

*Network Perturbation Amplitude (NPA) was computed as compared with the air controls (the NPA methodology is described in F. Martin, A. Sewer, M. Talikka, Y. Xiang, J. Hoeng and M. C. Peitsch, BMC bioinformatics, 2014, 15, 238).

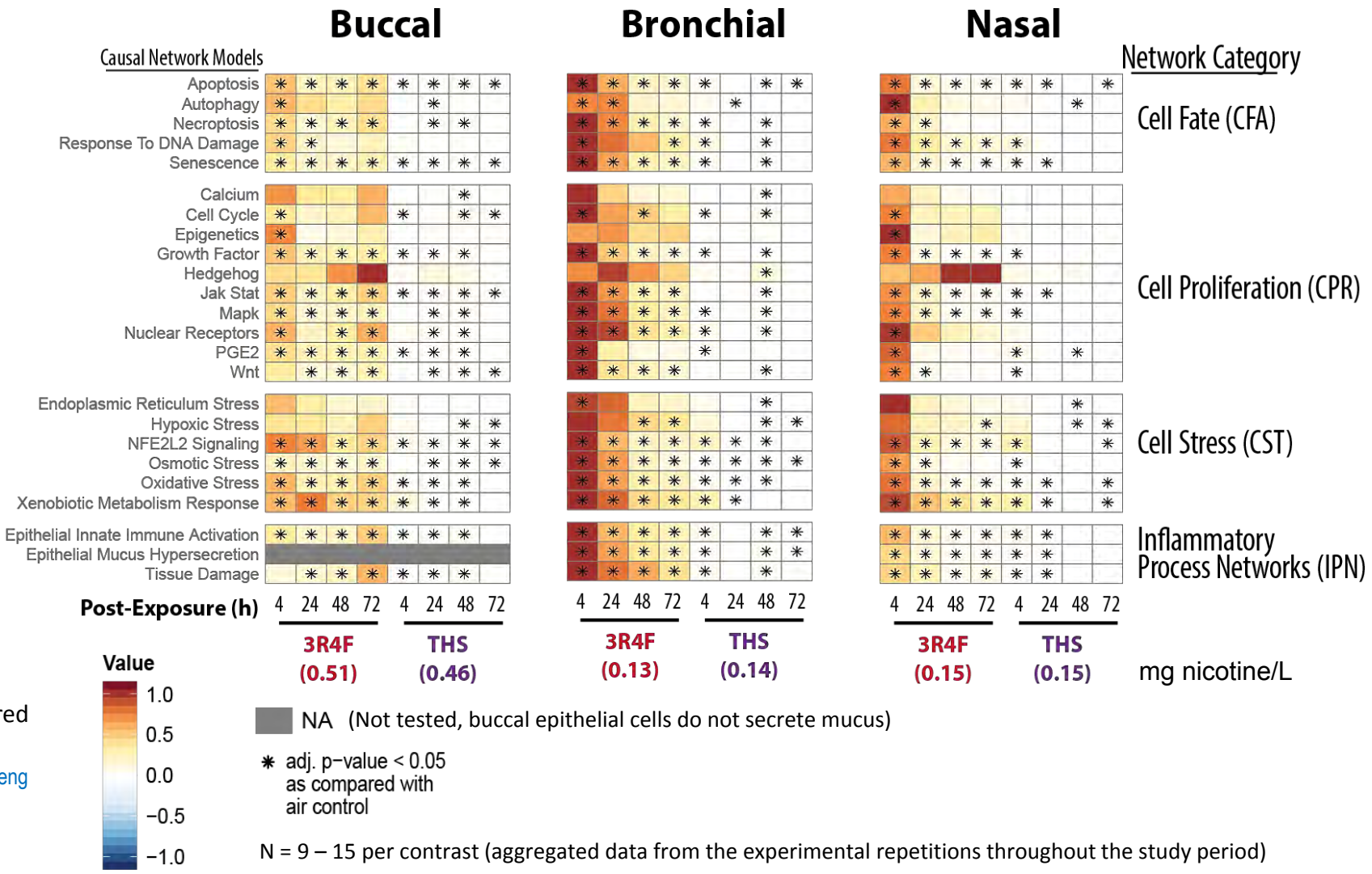


For all three culture types, 3R4F smoke exposure clearly impacted all four biological network categories. At similar nicotine concentrations, THS aerosol exposure resulted in only limited biological effects, which is to be expected because THS aerosol contains over 90% lower levels of measured HPHCs than 3R4F smoke.

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Impacted Biological Processes following THS Aerosol and 3R4F Smoke Exposure for 28 min: A Network-based Analysis of the Transcriptomes (Cont.)

Reduced impact was observed following THS aerosol exposure as compared with 3R4F smoke at similar nicotine concentrations. THS aerosol exposure elicited transient perturbations in the various biological network models (primarily observed at 4 h post-exposure).

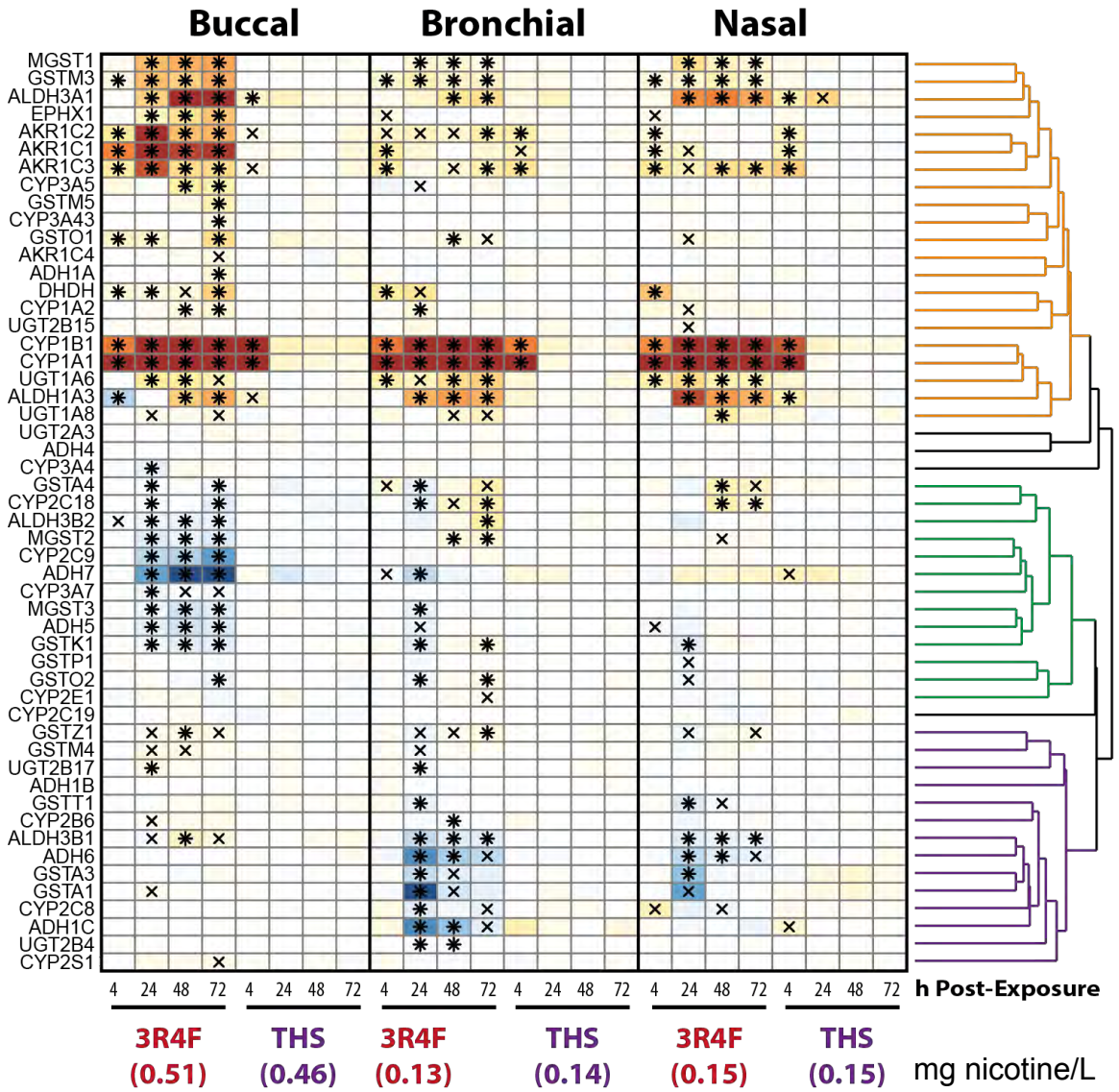


N = 9 – 15 per contrast (aggregated data from the experimental repetitions throughout the study period)

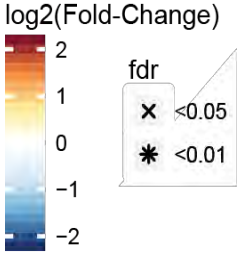
Color in the heatmap represents the value of the Network Perturbation Amplitude (NPA) as compared with the air controls (the NPA methodology is described in F. Martin, A. Sewer, M. Talikka, Y. Xiang, J. Hoeng and M. C. Peitsch, BMC bioinformatics, 2014, 15, 238).

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Alterations of Xenobiotic Metabolism Gene Expression following THS Aerosol and 3R4F Smoke Exposure



Reduced alteration in genes regulating xenobiotic metabolism ("Metabolism of Xenobiotics by Cytochrome P450" gene set from KEGG) was observed following THS aerosol exposure as compared with 3R4F smoke exposure, in the buccal, bronchial, and nasal organotypic cultures. Alterations in these genes following THS aerosol exposure were primarily observed at the earlier post-exposure time point (4 h).

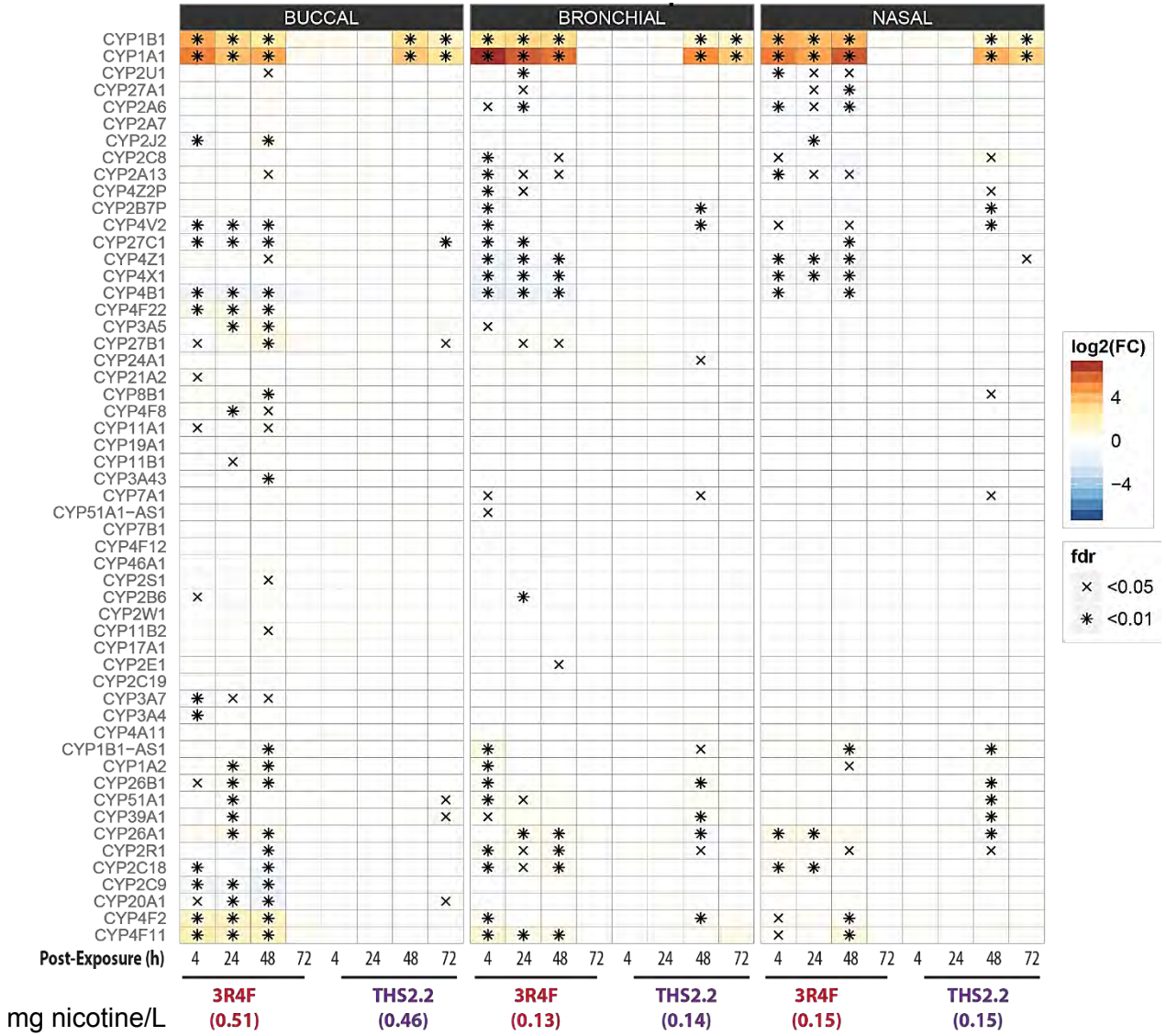


N = 9 – 15 per contrast (aggregated data from the experimental repetitions throughout the study period)
Fdr, false discovery rate

Gene clustering based on the pair-wise correlation between the fold-changes and the clustering results are shown as a dendrogram (clusters are marked in different color).

A.R. Iskandar, B. Titz, A. Sewer, P. Leroy, T. Schneider, F. Zanetti, C. Mathis, A. Elamin, S. Frentzel,, W. Schlage, F. Martin, N.V. Ivanov, M.C. Peitsch, and J. Hoeng, submitted to Toxicology Research (under revision April 2017)

Alterations of Cytochrome P450 (CYP) Gene Expression following THS Aerosol and 3R4F Smoke Exposure



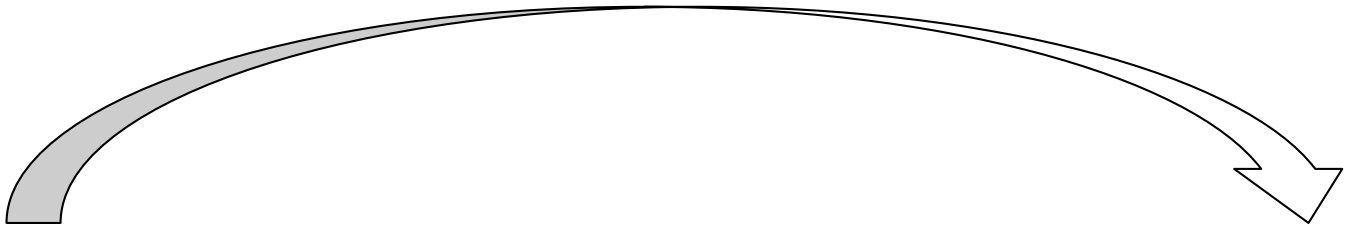
At the similar nicotine concentrations for a given culture, the impact of THS aerosol exposure on the CYP gene expression was minimal as compared with 3R4F smoke exposure in the human buccal, bronchial, and nasal organotypic cultures.

FC, fold changes
FDR, false discovery rate

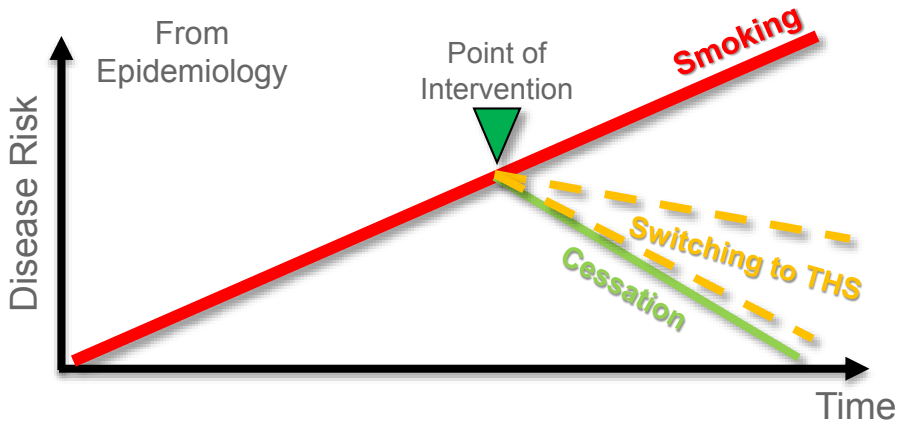
N = 9 – 15 per contrast (aggregated data from the experimental repetitions throughout the study period)
Fdr, false discovery rate

From Risk Assessment Framework to *in vivo* Study Design

Animal Model: ApoE-KO mouse – concomitant analysis of CVD and COPD endpoints



Assessment Framework



Note: The descriptions in the chart are for illustrative purposes only

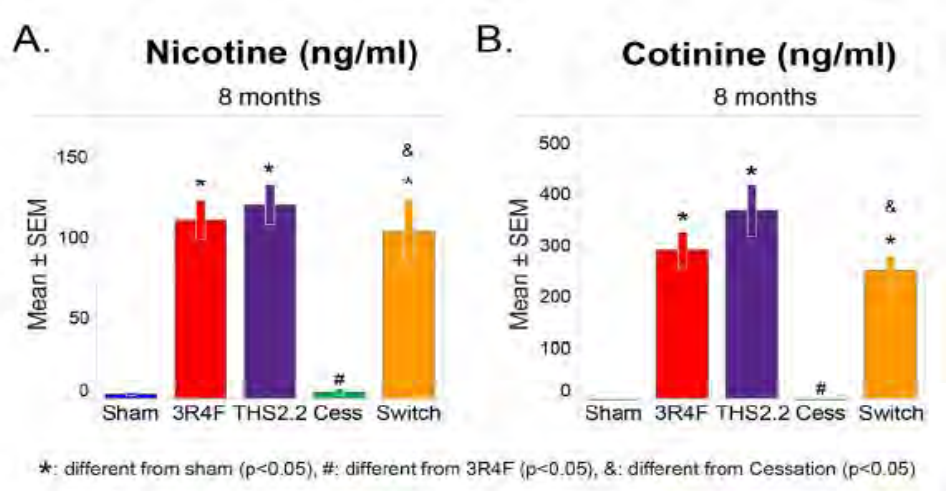
Group	Exposure
Cigarette	3R4F
Cessation	3R4F → Air
Switching	3R4F → THS
Candidate MRTP	THS
Reference: Air	Air

Start — Month 2 — Month 8

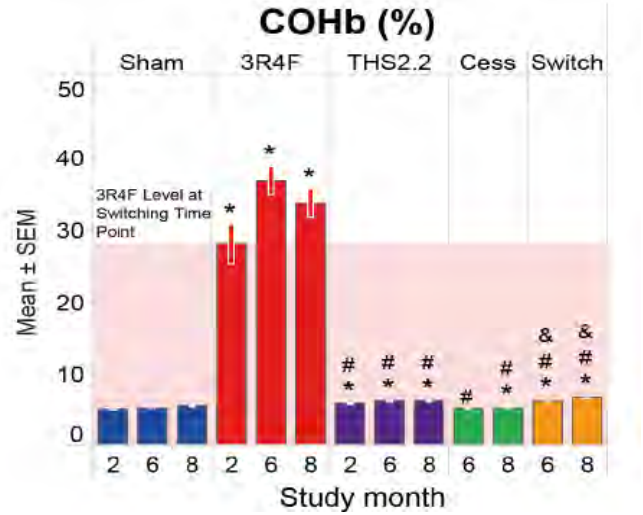
Phillips *et al.* (2015) An 8-Month Systems Toxicology Inhalation/Cessation Study in Apo e-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared with Conventional Cigarettes. Toxicological Sciences, in press

Non-clinical Evidence for Reduced Exposure and Harm to the Lung

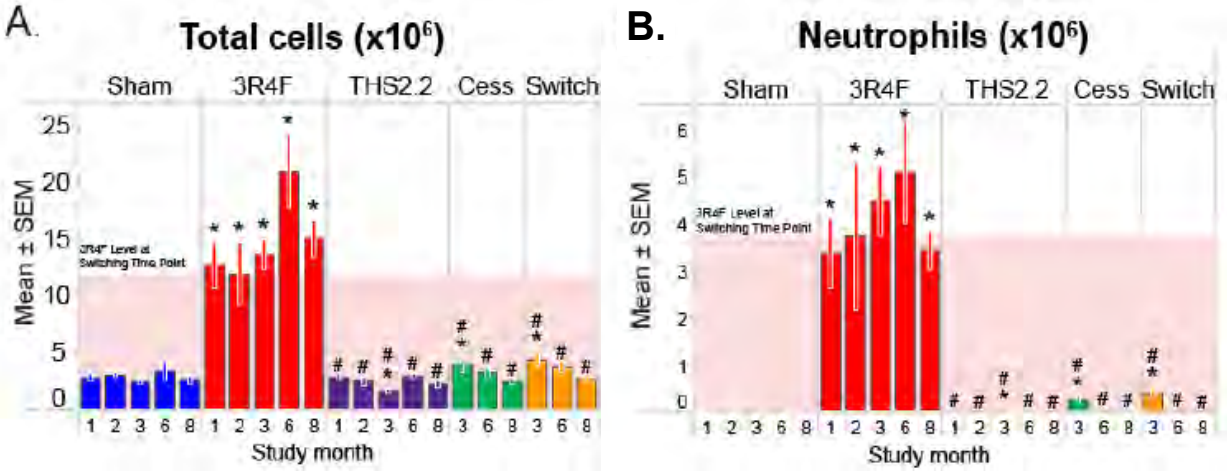
Blood: Biomarkers of Exposure



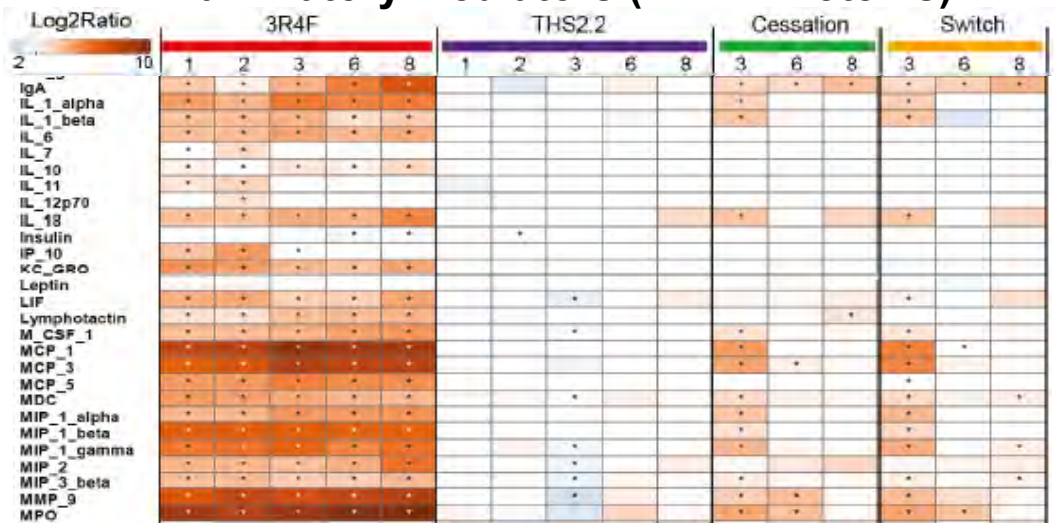
C.



Inflammatory Lung cells (BALF)

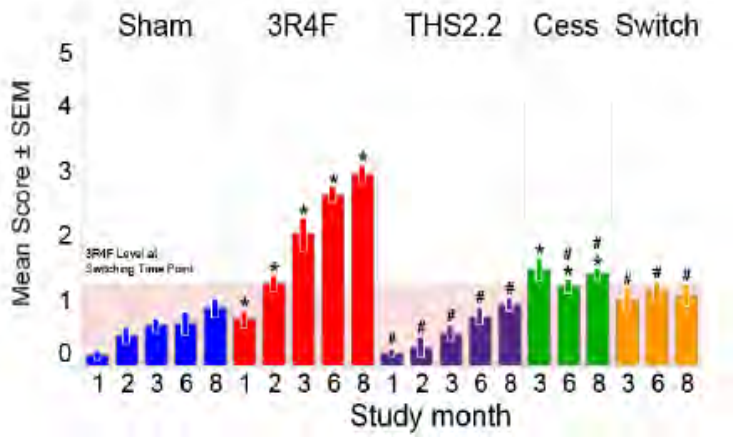


Inflammatory Mediators (BALF Proteins)

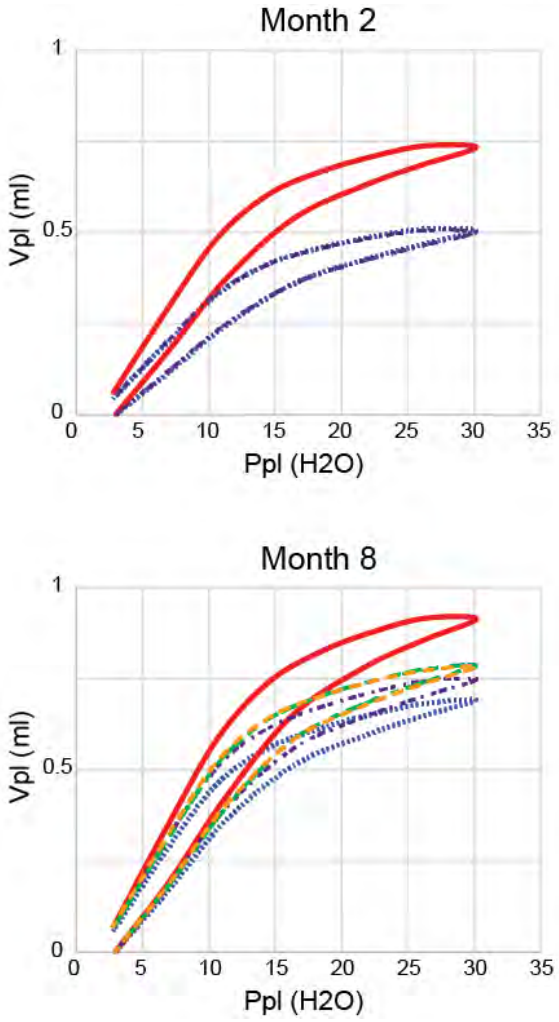


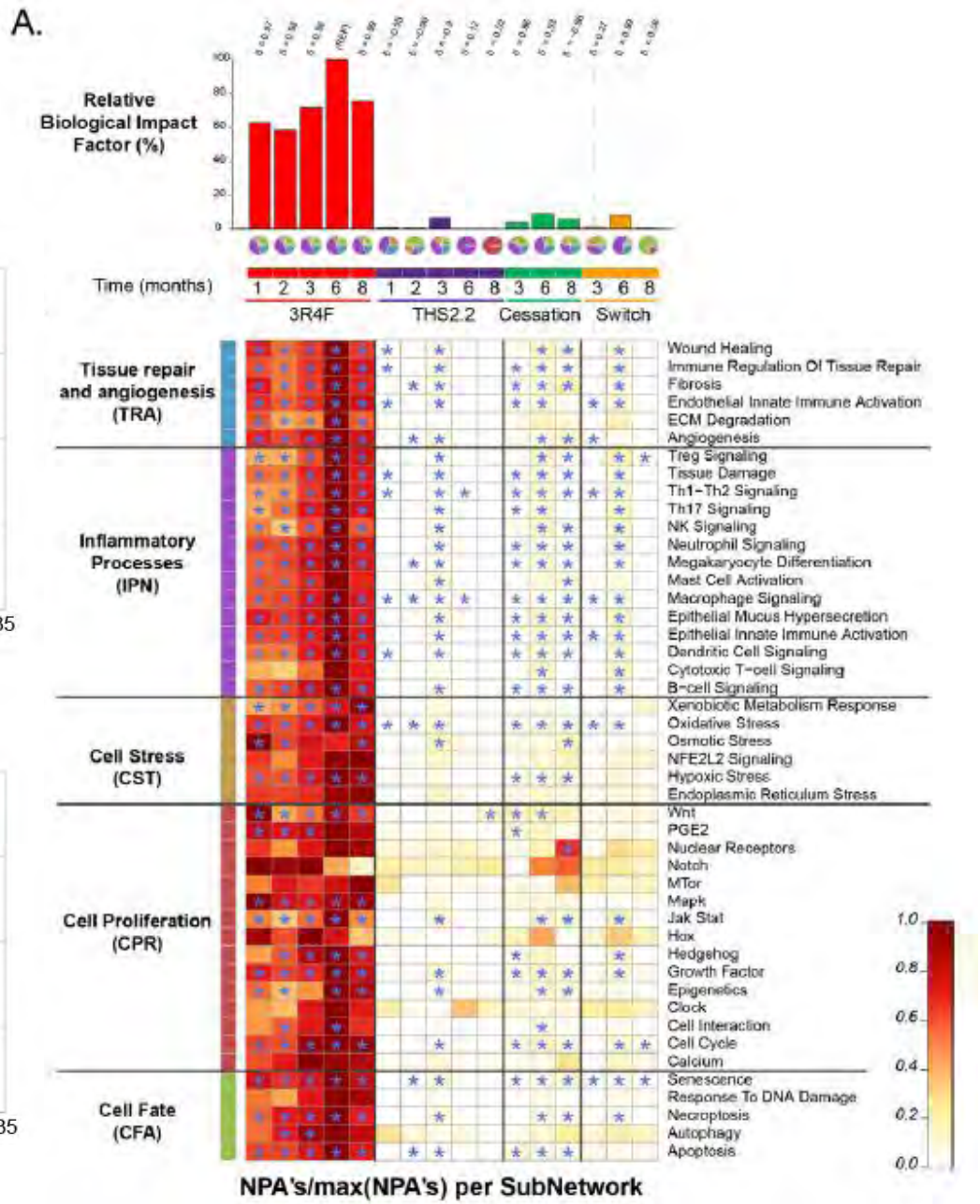
Non-clinical and Mechanistic Evidence for Reduced Risk in the Lung

Pulmonary emphysema



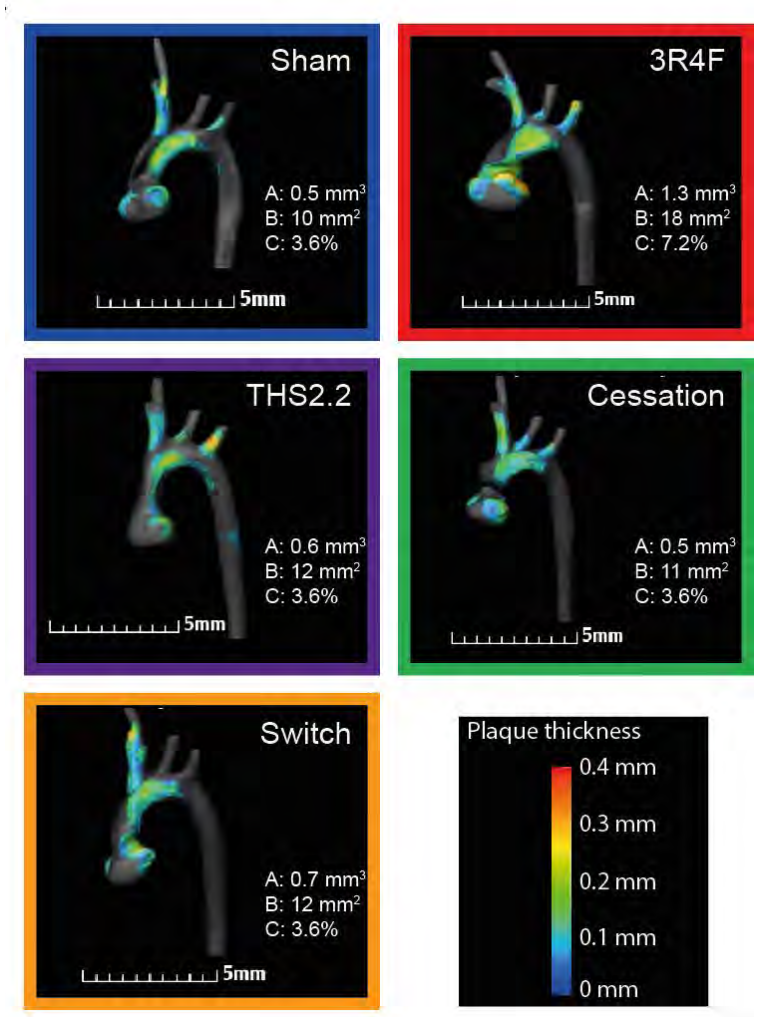
Lung function

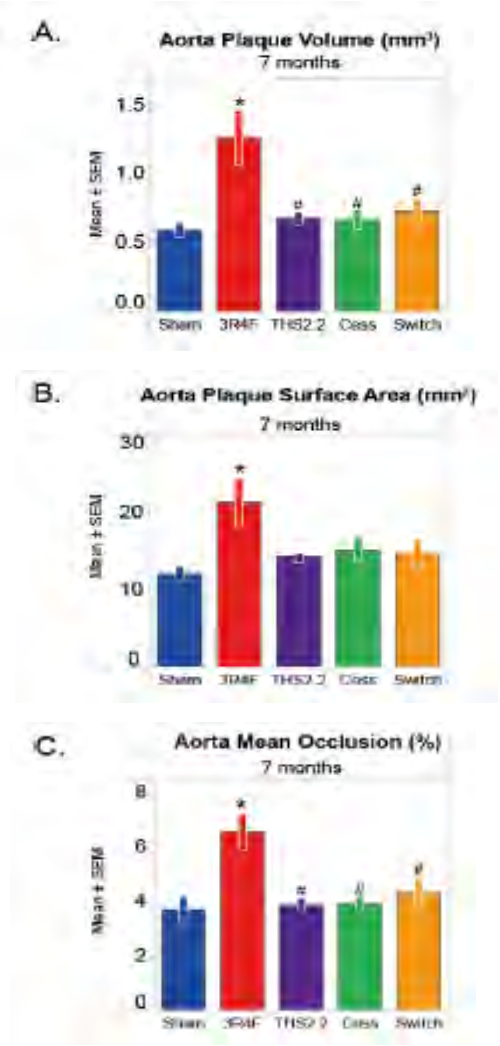




Non-clinical Evidence for Reduced Risk of Atherosclerosis

in situ aortic arch plaque measurements (µCT)





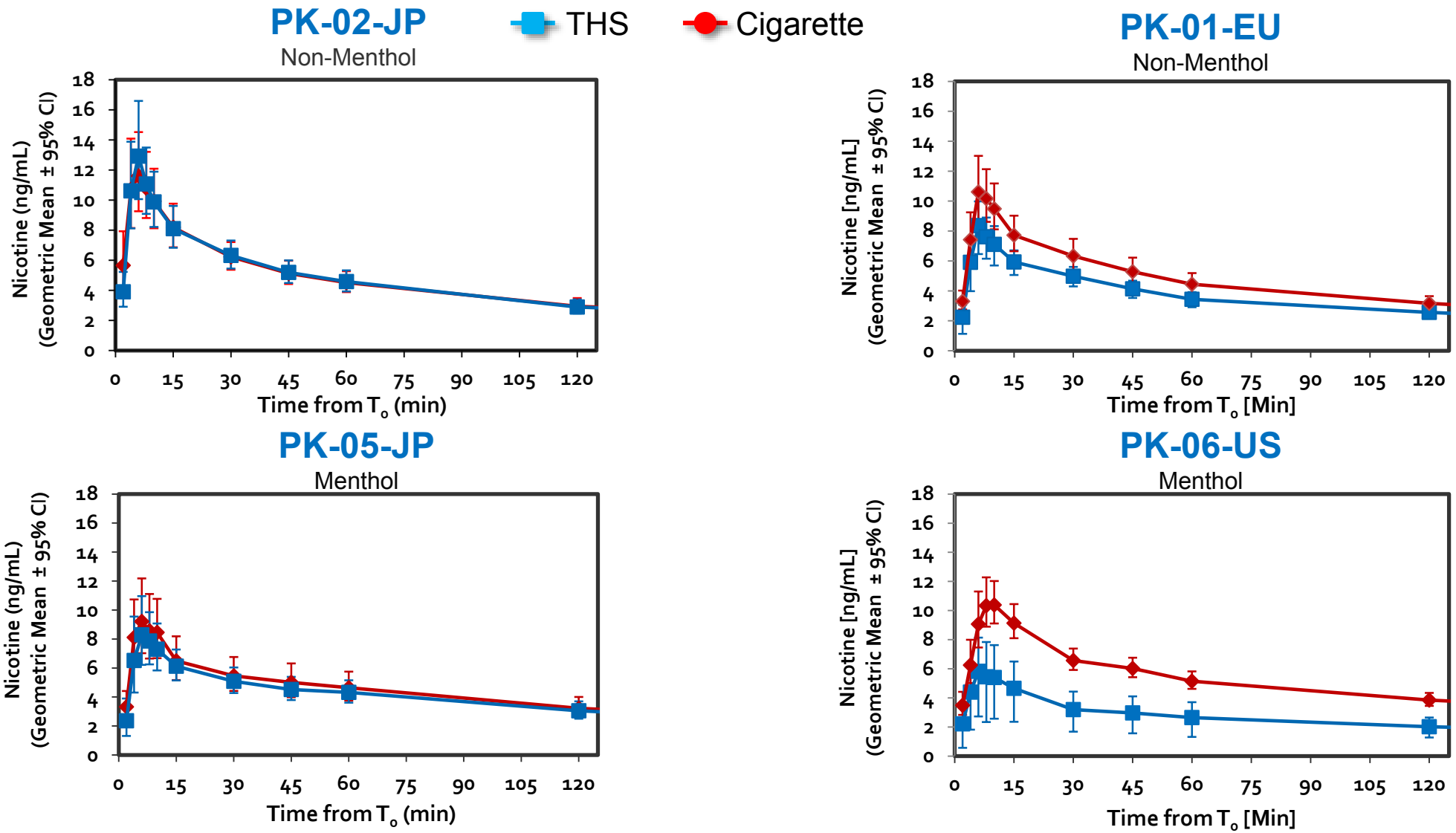
Clinical Evidence for Reduced Exposure: Approach and Rationale

Assessment Strategy

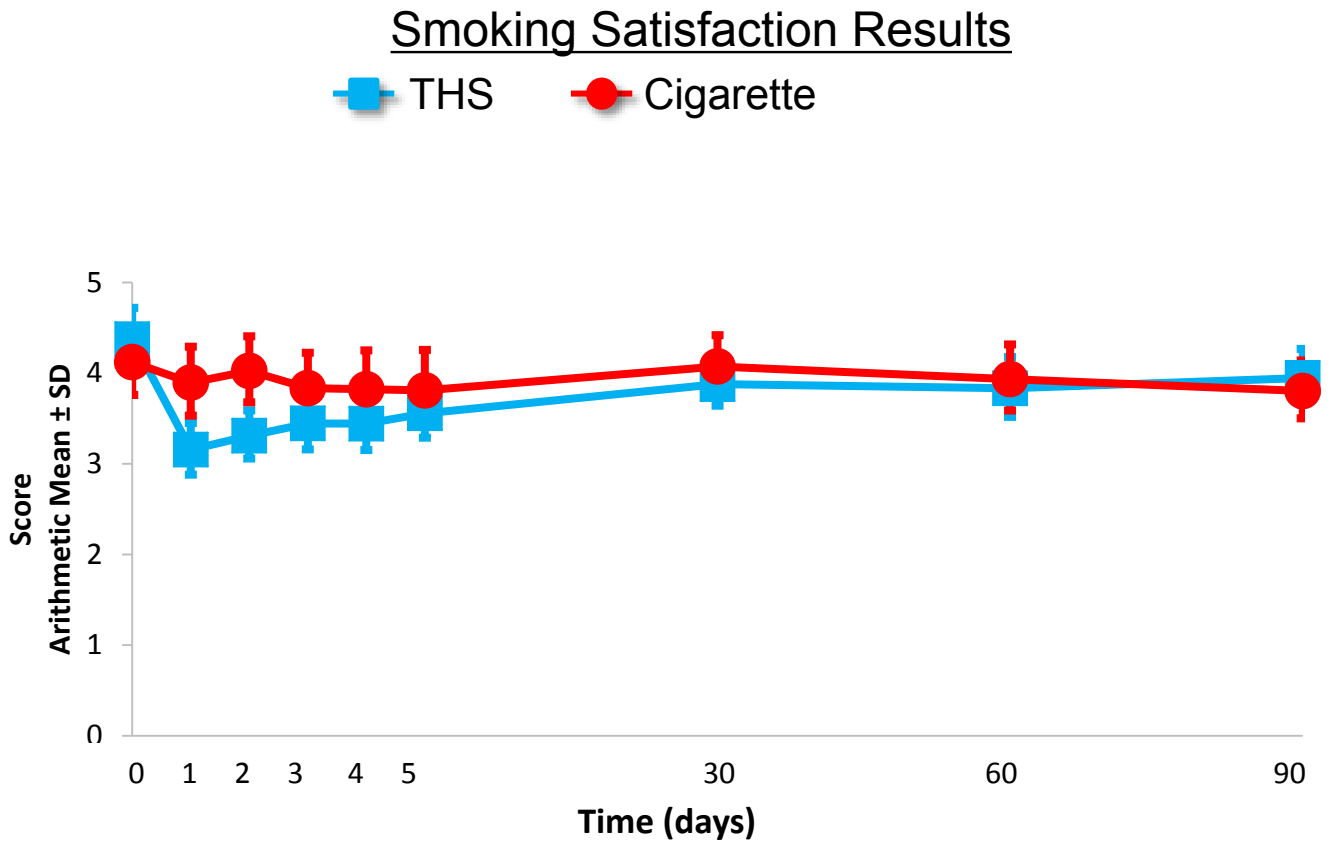
Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	PK Studies
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion

- PK/PD studies are performed to assess how close the pharmacokinetic profile of nicotine delivered by THS is to that delivered by cigarettes, as this is an important factor to facilitate switching by adult smokers.

PK Study Results – Japan, US and EU



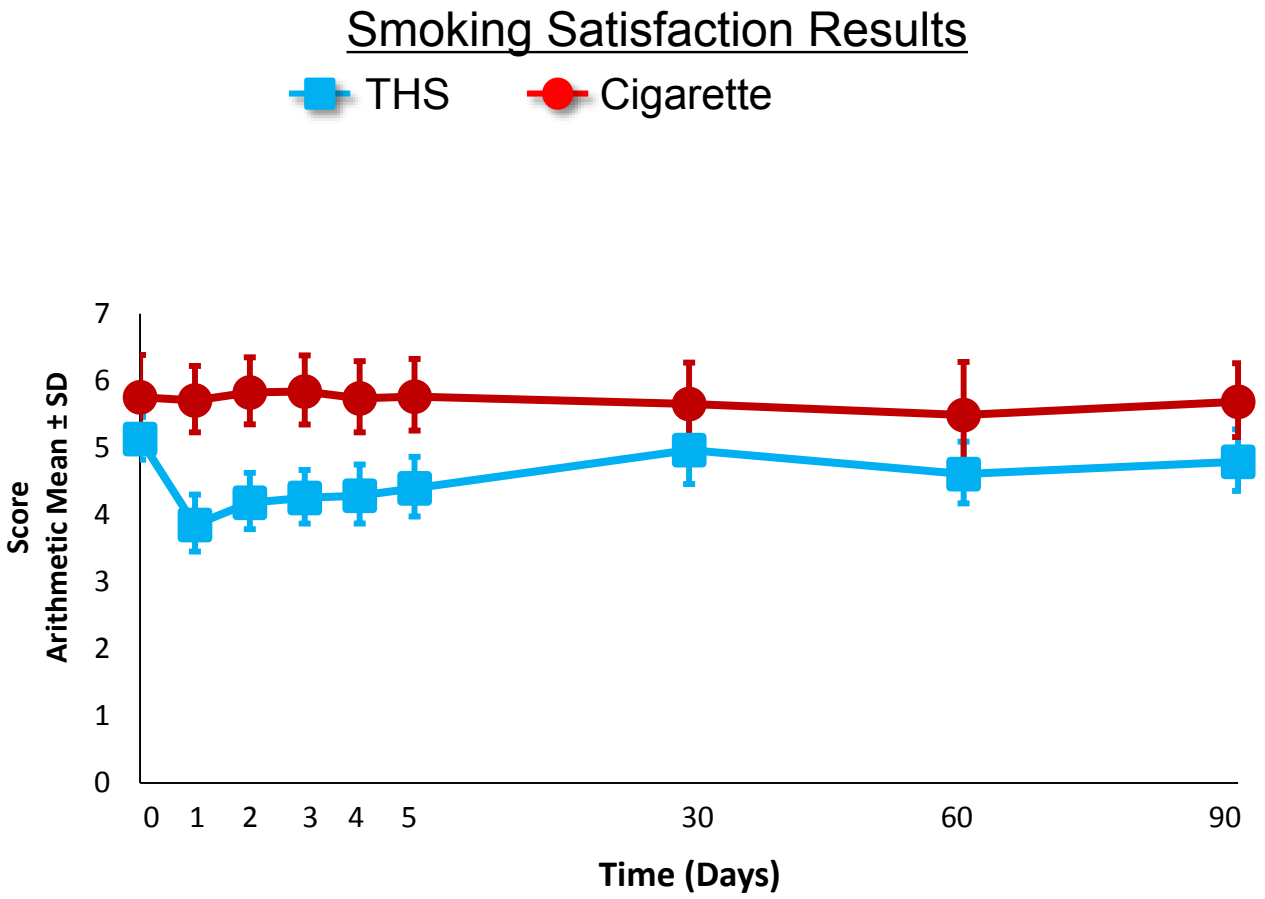
Smoking Satisfaction Results (3 months study - Japan)



Product acceptance (MCEQ)

- Similar level of psychological reward, enjoyment of respiratory tract sensation and smoking satisfaction for THS 2.2 and CC at Day 90
- Similar level of aversion for THS 2.2 and CC, stable during the study
- Similar level of craving after 5 days of exposure.

Smoking Satisfaction Results (3 months study - U.S.)



Product acceptance (MCEQ)

- Slightly lower level of smoking satisfaction for THS 2.2 vs CC at Day 90
- Similar level of aversion for THS 2.2 and CC, stable during the study
- Comparable levels of psychological reward, enjoyment of respiratory tract sensation
- Slightly lower level of craving after 5 days of exposure for THS 2.2 vs CC

Clinical Evidence for Reduced Exposure: Approach and Rationale

Assessment Strategy

Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	Reduced Exposure
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion

Biomarkers of Exposure (BoExp) were selected based on the following criteria:

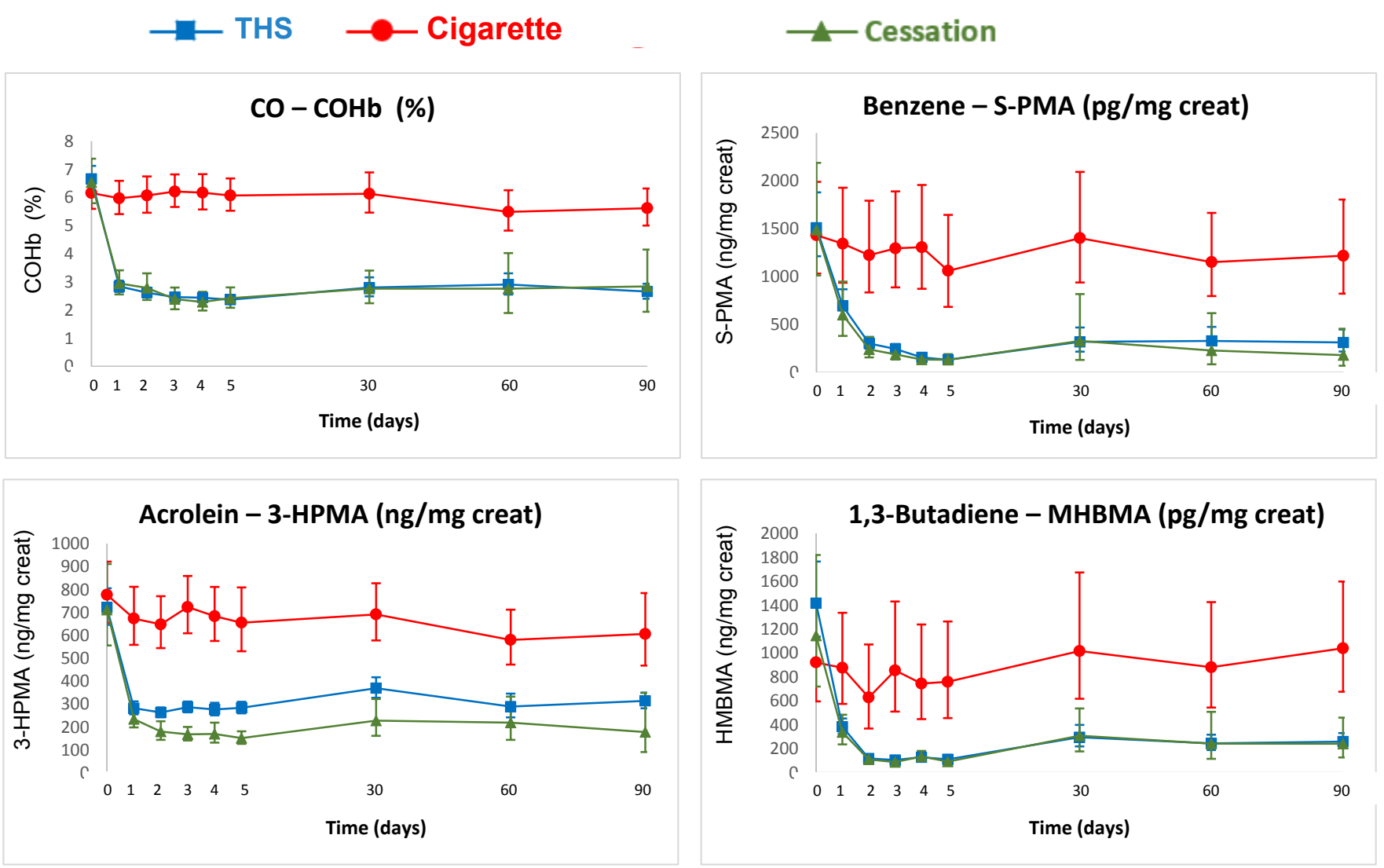
1. BoExp is **specific to the source** of exposure with other sources being minor or non-existent
2. BoExp is **easily detectable** using reliable, reproducible, precise analytical methods
3. BoExp reflects a **specific toxic exposure** or is a **reliable surrogate** of exposure to an HPHC.
4. BoExp represents a set of HPHCs as listed by the **FDA**[1] and **WHO**[2]
5. BoExp ensures assessment of both **gas and particulate phase** of the THS aerosol
6. BoExp include a broad **variety of chemical classes** and **organ toxicity classes**[3]
7. BoExp spread across various **formation temperatures**

[1] FDA (2012). Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act.
[2] WHO Study Group on Tobacco Product Regulation, A. DL, et al. (2008). The Scientific Basis of Tobacco Product Regulation. Second Report of a WHO Study Group. W. S. G. o. T. P. Regulation. Geneva, Switzerland, World Health Organization
[3] carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential)

THS: Reduced Exposure (US Clinical Data)

Adult smokers used the products *ad libitum*

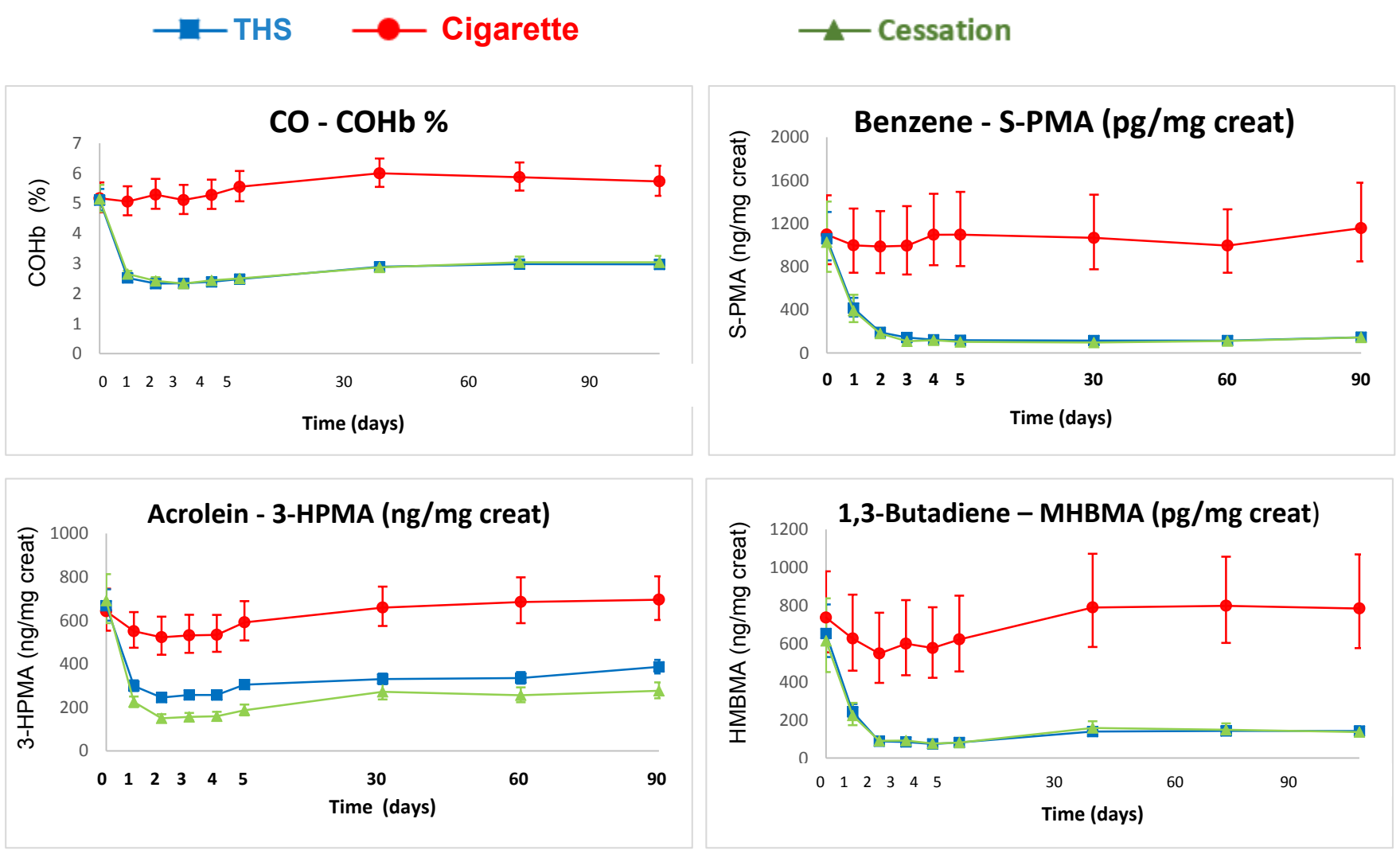
Adult smokers randomized to cigarettes or THS were free to use the product as often as they wished, in confinement (5 days) and then ambulatory (86 days)



THS: Reduced Exposure (Japan Clinical Data)

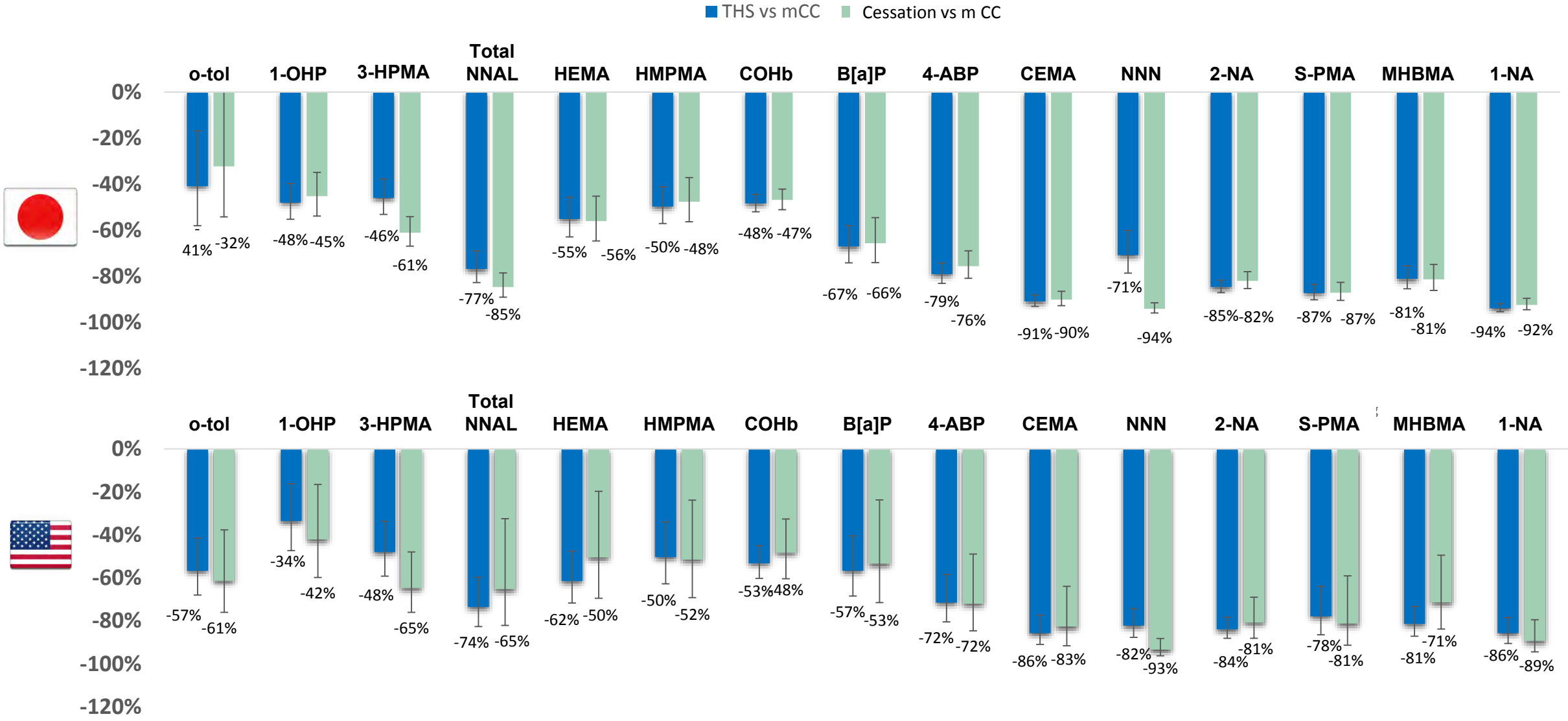
Adult smokers used the products *ad libitum*

Adult smokers randomized to cigarettes or THS were free to use the product as often as they wished, in confinement (5 days) and then ambulatory (85 days)



Clinical Evidence for Exposure Reduction (Japan and US)

% Reduction in Biomarkers of Exposure After Switching for Three Months



Clinical Evidence for Reduced Risk: Approach and Rationale

Assessment Strategy

Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	Reduced Risk in Humans
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion

- Smoking-related diseases cover a broad range of disease pathways, biological processes, physiological systems and mechanisms of action
- There is no single biomarker which can be easily used to quantify the potential risk for smoking related diseases.
- Therefore a set of markers which are effected by smoking, are linked to smoking related disease and are reversible after smoking cessation is needed to characterize the risk reduction potential of an RRP in the absence of epidemiological evidence.

The Effects of Smoking Cessation are Well Known and Can be Measured

	Clinical Effects	Functional and Molecular Changes
1 week	• Abstinence symptoms start (craving, anxiety etc.)	• Blood pressure and pulse rate decrease • Carboxyhemoglobin decreases to normal level
1 month	• Circulation improves - walking becomes easier • Cough or wheeze decreases • Phlegm production decreases	• Platelet function improved, e.g. changes in clotting • Oxidative stress reduced, e.g. changes in 8-epi-prostaglandin-$F_{2\alpha}$
3 months	• Reduced presence and severity of respiratory symptoms	• Some molecular cardiovascular markers improved: - white blood cells count decreases - HDL (“good” cholesterol) increases
1 year	• Improved respiratory symptoms in COPD • Coronary heart disease and heart attack risk reduces 30 to 50%.	• Improved inflammatory biomarkers • Arrest in decline of lung function (FEV_1)

**US DHHS 1990, 2004 and 2008; Gratziou 2009; Haustein 2001; Drelser 2006; Yanbaeva 2007; Zevin 1999*

Smokers Health Profile as Defined by PMI

Endpoint	Link to Smoking-Related Disease		Timeframe of Reversibility
HDL-C	Cardio-Vascular	Lipid Metabolism	3 months
WBC		Inflammation	6-12 weeks
sICAM-1		Endothelial Dysfunction	4 weeks
11-DTX-B_2		Clotting	2-4 weeks
8-epi-$PGF_{2\alpha}$		Oxidative Stress	1-2 weeks
COHb		Acute Effect	1-7 days
FEV_1		Respiratory	6-12 months
Total NNAL		Genotoxicity	3 months

Clinical Evidence for Reduced Risk of Harm: Results to Date

Disease Pathway	Marker	Cessation Effect at 3m	mTHS Effect at 3m
Lipid Metabolism	HDL-C	6.4 mg/dL	4.5 mg/dL
Inflammation	WBC	-0.41 10^9/L	-0.57 10^9/L
Airway Impairment	FEV_1	1.93 % pred	1.91 % pred
Endothelial Dysfunction	sICAM-1	10.9 % reduction	8.7 % reduction
Oxidative Stress	8-epi-$PGF_{2\alpha}$	6.0 % reduction	12.7 % reduction
Clotting	11-DTX-B_2	19.4 % reduction	9.0 % reduction

Disease Pathway	Marker	Cessation Effect at 3m	mTHS Effect at 3m
Lipid Metabolism	HDL-C	0.0 mg/dL	1.4 mg/dL
Inflammation	WBC	-0.94 10^9/L	-0.17 10^9/L
Airway Impairment	FEV1	1.95 % pred	0.49 % pred
Endothelial Dysfunction	sICAM-1	9.9 % reduction	10.6 % reduction
Oxidative Stress	8-epi-PGF2α	8.5 % reduction	13.5 % reduction
Clotting	11-DTX-B2	7.2 % reduction	3.6 % reduction

Consumer Perception and Behavior Evidence: Approach and Rationale (Example)

Assessment Strategy

Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	Reduced Exposure and Reduced Risk in Humans
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion

1. Effect on Tobacco Use Behavior among Adult Smokers

- The likelihood that adult smokers will
  - Switch from CC to THS
  - Use THS in conjunction with CC
  - Switch back to CC
- The likelihood that adult smokers motivated to quit would instead switch to THS

2. Effect on Tobacco Use Initiation among Adult Non-Smokers

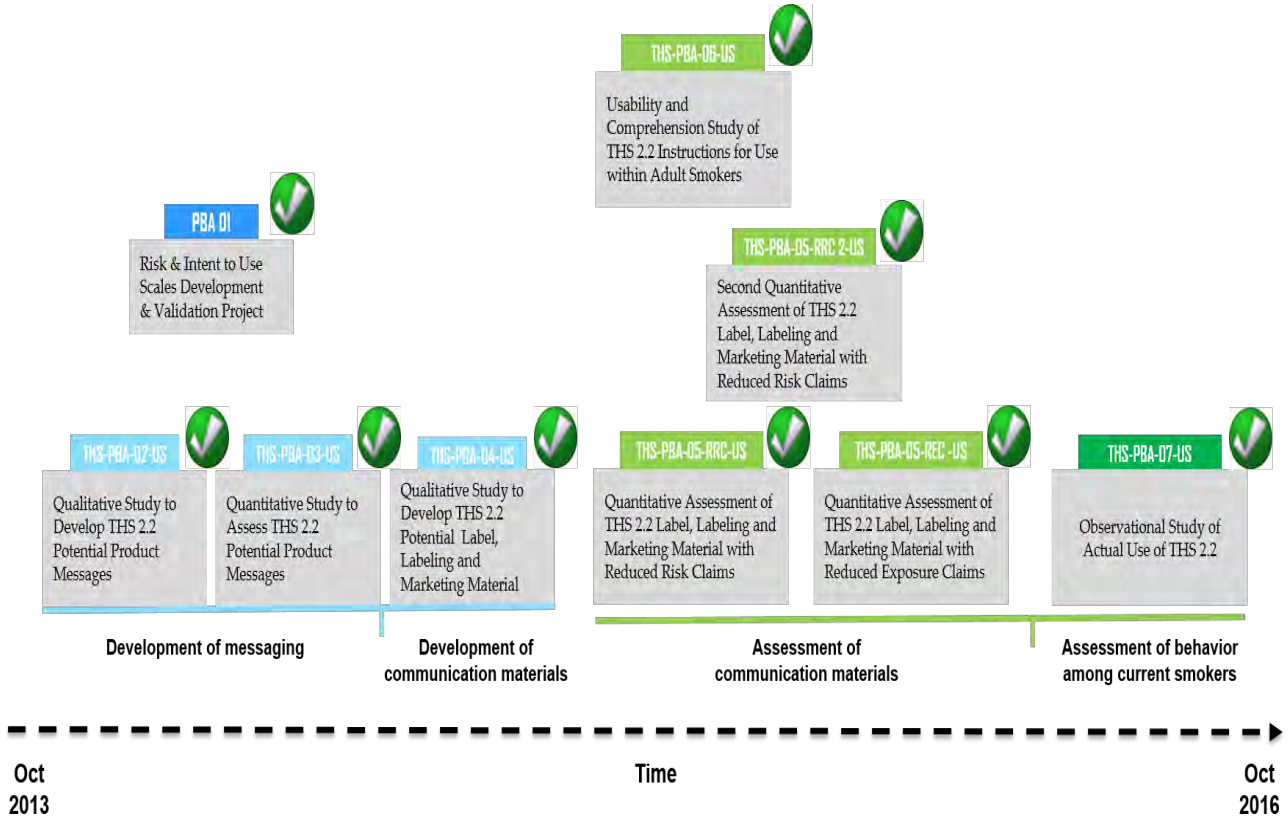
- The likelihood that adult never and former smokers will initiate use of THS

3. Effect on Consumer Understanding and Perceptions

- Comprehension of the information concerning modified exposure/risk claims
- Perception about the health risks of using THS in comparison to CC, NRTs and cessation

Pre-market Evidence on THS Perception and Behavior Assessment

- Approximately 10,000 participants involved in U.S. studies
- Significant percentage of adult smokers – between 20% and 39% – intended to use THS, depending on the type of tested materials and modified risk message
- Less than 6.4% of adult former smokers and less than 1.1% of adult never smokers (including young adult never smokers below 25) expressed an intention to use THS
- Adult consumers correctly understood the modified risk communications, including that THS is not without risk
- Actual use study showed that a sizable proportion of adult smokers can predominantly or exclusively switch to THS



Consumer Perception and Behavior Evidence: Approach and Rationale (Example)

Assessment Strategy

Assessment Layers	Evidence Levels
Post-Market Studies & Surveillance	Reduced Population Harm
Consumer Perception and Behavior Assessment	Correct Product Understanding of Benefit, Usage and impact among different populations
Clinical Studies	Reduced Exposure and Reduced Risk in Humans
Systems Toxicology Assessment	Reduced Risk in Laboratory Systems
Pre-Clinical Toxicology Assessment	Reduced Toxicity
Aerosol Chemistry and Physics	Reduced Formation
Product Design and Controls	Absence of Combustion

- This step includes a population health impact model designed to estimate the potential long-term public health impact of introducing an RRP in the market.
- PMI has initiated post-market studies including safety surveillance, cross-sectional surveys to monitor prevalence and cohort studies to monitor usage patterns of THS in Japan.

Post-Market Assessment in Japan

- Japan was the first country in which the product has been marketed nation-wide.

- The following epidemiological studies are currently being conducted, also providing information of prevalence and product use.

  - Four annual cross-sectional surveys (P1-PMX-01-JP): covering population representative and THS users samples. Recruitment into these is done in four waves per year with n=1,200 and n=500 per wave, respectively.

  - A longitudinal cohort study (P1-PMC-01-JP): following 2,000 THS users and 2,000 cigarette smokers, recruited over a period of 4 years (500 participants per group and year), for up to 5 years.

Cross-sectional Surveys (P1-PMX-01-JP) - Objectives

- General Population Sample
  - Describe patterns of use of tobacco/nicotine products
  - Estimate prevalence of use of tobacco/nicotine products
  - Describe current frequency and consumption
  - Describe interest in quitting/stopping
  - Estimate initiation, relapse, re-initiation and quitting of manufactured or roll-your-own cigarettes or THS

- THS Users Sample, in addition to the above:
  - Self-reported aesthetic changes
  - Frequency and type of misuse of THS and/or HeatSticks
  - Product satisfaction as assessed with Modified Cigarette Evaluation Questionnaire (mCEQ)
  - Perception of the health risk associated with cigarettes and THS as assessed with the Perception of Risk Instrument – Global (PRI-G)

Longitudinal Cohort Study (P1-PMC-01-JP) - Objectives

- Describe patterns of use of tobacco/nicotine products
- Identify intra-individual product use trajectories over time
- Describe cessation rates of tobacco/nicotine products
- Identify and assess the motivations for quitting tobacco use and to characterize the quit attempts.
- User characterization
- Assess subjective effects (e.g. urge to smoke, product reinforcement and self-observed aesthetic improvements)
- Assess perception of risk associated with tobacco/nicotine products
- Assess the strength of nicotine dependence
- Describe rates of self-reported signs, symptoms and diagnoses
- Summarize number of health related events (hospitalizations)
- Assess coughing

Post-Market Assessment in Japan

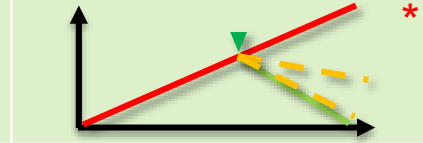
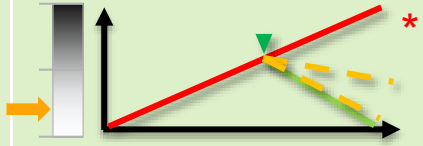
- The first survey and cohort study waves have been completed in March 2017
- The population-based survey included 631 (51.7%) women and 589 men, with a mean age of 54 years
- The estimated population prevalence of smoking was 17% (95% CI: 15-19%; 27.6% in men and 7.3% in women)
- The mean number of cigarettes smoked per day was 15.9 in men and 13.6 in women

- Most participants in the THS user survey (n=487, 97.4%) had previously initiated tobacco product use with cigarettes
- Currently, more than half used THS exclusively (n=281, 56.2%), while 27.6% (n=138) used THS and cigarettes, and 11% (n=55) used more than two products
- The mean number of HeatSticks used per day was 15.9 in men and 15.2 in women

Totality-of-the-Evidence for THS

REDUCED-RISK PRODUCT

PRODUCT ACCEPTANCE AND USAGE

Assessment Layers	Evidence Levels	Risk Framework	Evidence for Reduced Exposure	Evidence for Reduced Toxicity	Evidence for Reduced Risk	
Consumer Perception and Behavior	**VI.** Adopted by Adult Smokers & Undestood by All	Risk Perception 	PBA-05-REC-US PBA-07-US		PBA-05-RRC-US PBA-05-RRC2-US PBA-07-US	Red. Risk and Exp. messages Understood
Clinical	**V.** Reduced Exposure & Reduced Risk in Humans	 *	REXC studies REXA studies		REXA Studies	Demonstrated
Systems Toxicology	**IV.** Reduced Risk in Laboratory Systems	 *	Animal model of disease study; *In vitro* studies	Animal model of disease study; *In vitro* studies	Animal model of disease study	Demonstrated
Pre-Clinical Toxicology	**III.** Reduced Toxicity		*In vivo* studies	*In vitro* studies; *in vivo* studies	Pulmonary endpoints *in vivo*	Demonstrated
Aerosol Chemistry	**II.** Reduced Formation		Aerosol Characterization; Indoor Air Quality			Demonstrated
Product Design and Controls	**I.** Absence of Combustion		Product Design Principles; Combustion Control			Demonstrated
			Demonstrated	Demonstrated	Demonstrated	

*Note: The descriptions in the chart are for illustrative purposes only.

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

TOX/2017/25 Annex C

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature

Reserved Business

Presentation from British American Tobacco

Redacted as indicated to remove slides containing data provided in confidence

Secretariat
May 2017

©British American Tobacco (Investments) Limited 2015. All rights reserved. No part of these materials may be reproduced in any form or by any means without the prior written consent of British American Tobacco (Investments) Limited and no responsibility or liability is accepted for any third party reliance on any data contained herein. The data and information used in these materials has been compiled from a number of sources.

Presentation to the Independent Scientific Advisory Committees on Toxicity (COT), Cancer (COC) and Mutagenicity (COM):

Evaluation of the heat not burn tobacco product: iFuse (iFU1.0)

Dr Christopher Proctor | Chief Scientific Officer, British American Tobacco

Tuesday 16th May 2017

Agenda

- Scientific design rationale and product overview
- Aspects relating to the product
- Exposure
- Health Effects
- Summary

Scientific design rationale of iFuse (iFU1.0)

- Our mission is to create a portfolio of next generation products that smokers will want to switch to, with the aim of reducing the harms caused by smoking

- Tobacco harm reduction outlined by Institute of Medicine as ‘decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use’ [Stratton *et al,* 2001]

Harm Reduction = Modified risk tobacco products X Number of smokers who switch

- Thus, iFuse was designed to be as low risk as possible with maximum consumer relevance relative to a cigarette

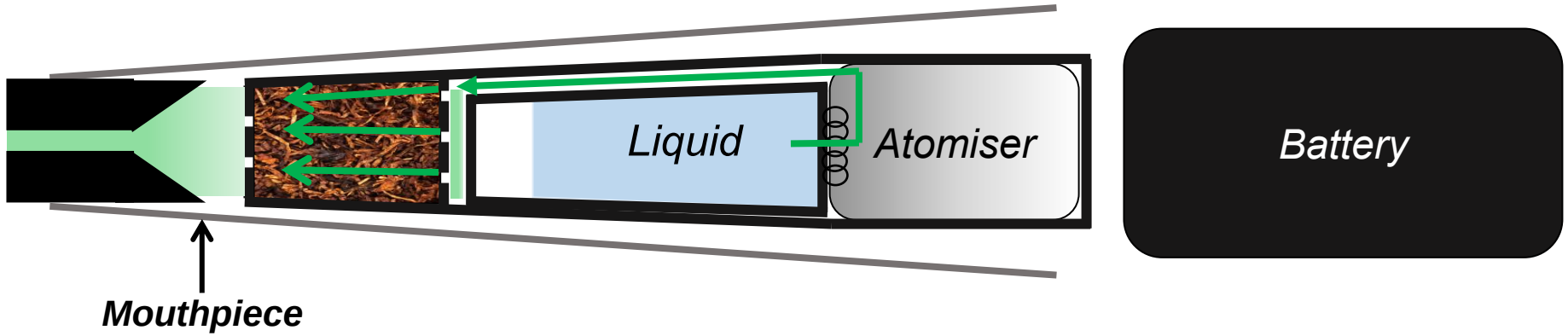
iFuse (iFU1.0) is a Tobacco Heating Product

1. Tobacco Section
2. Formulation
3. KENT Neopod
4. iFuse Device
5. iFuse (IFU1.0)

This slide has been redacted as it contains confidential information

How iFuse works

The liquid is aerosolised by an atomiser, forming a vapour which passes through the tobacco section. The tobacco imparts a sensory flavour to the aerosol.



Heating and chemical process during use of iFuse

IFU1.0 does not combust tobacco

- Combustion of tobacco in a cigarette occurs at >900°C [Baker *et al*, 2006], creating smoke which contains >7,500 compounds [Perfetti *et al,* 2013] of which, around 100 are known as toxicants [Fowles *et al*, 2003]

- iFuse aerosol formed via three process:
  - ➢ Heating of the liquid formulation by an atomiser to vaporise the nicotine formulation into an aerosol (ca. 250°C)
  - ➢ Passage of the warm aerosol (ca. <50°C) through the tobacco section. Volatilises flavour compounds from the tobacco
  - ➢ Elution of volatilised flavour compounds into the tobacco vapour from the tobacco plug

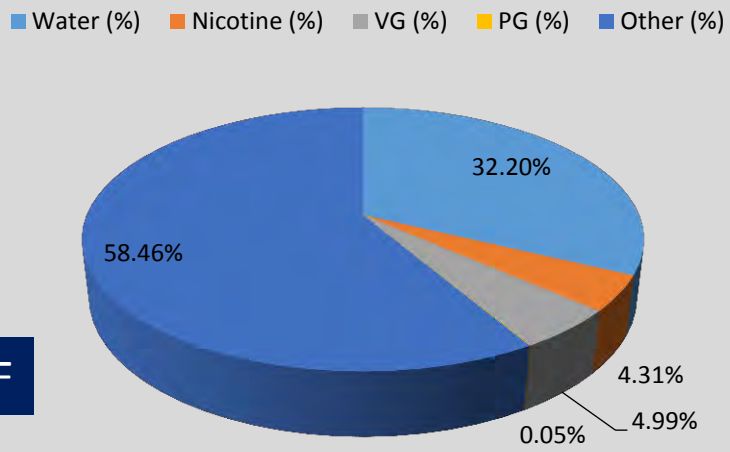
- As iFuse operates at temperatures substantially less than 900°C, no combustion occurs

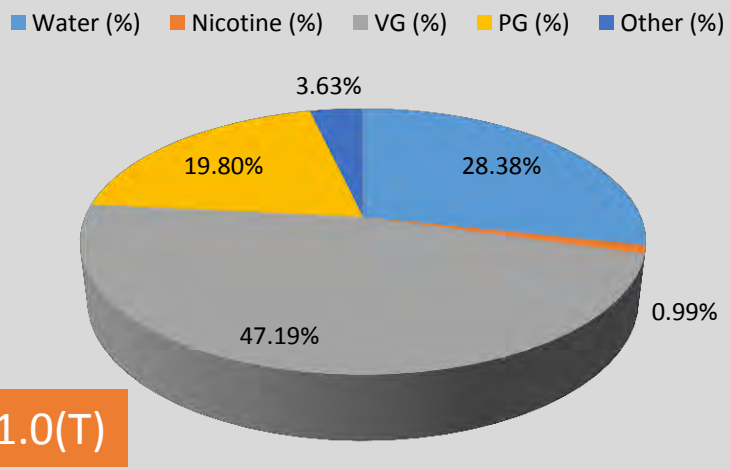
- Volatile tobacco flavours are eluted from the tobacco into the aerosol, substantially improving the sensory performance [Poynton *et al*, 2017]

This slide has been redacted as it contains confidential information

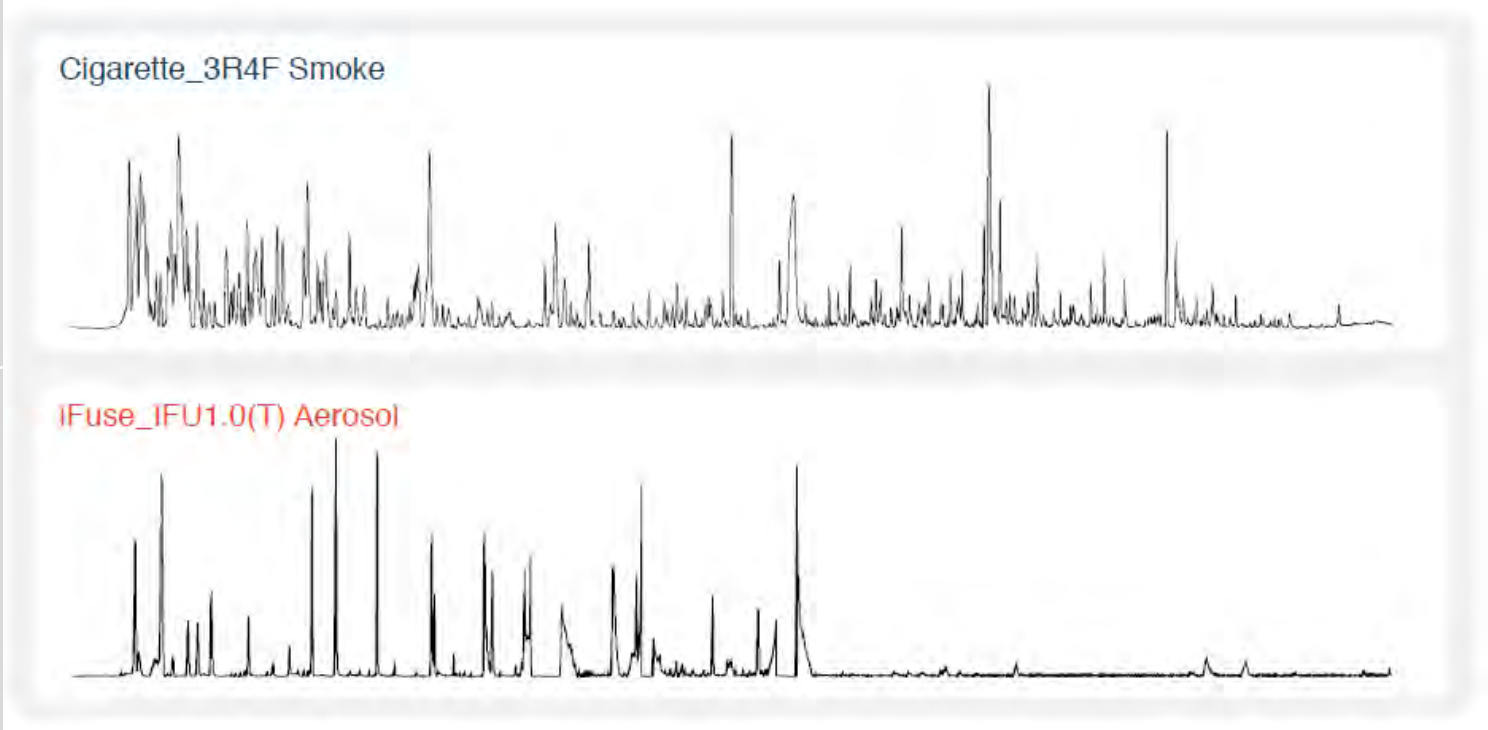
Exposure: Chemical analysis of mainstream aerosol and untargeted emissions

Mainstream aerosol composition[a]





Untargeted analysis[b]



The chromatograms of 3R4F and iFU1.0(T) were performed using different methods and are for complexity representation only

[a]Murphy *et al*, 2017; [b]Poynton *et al* 2017

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

This slide has been redacted as it contains confidential information

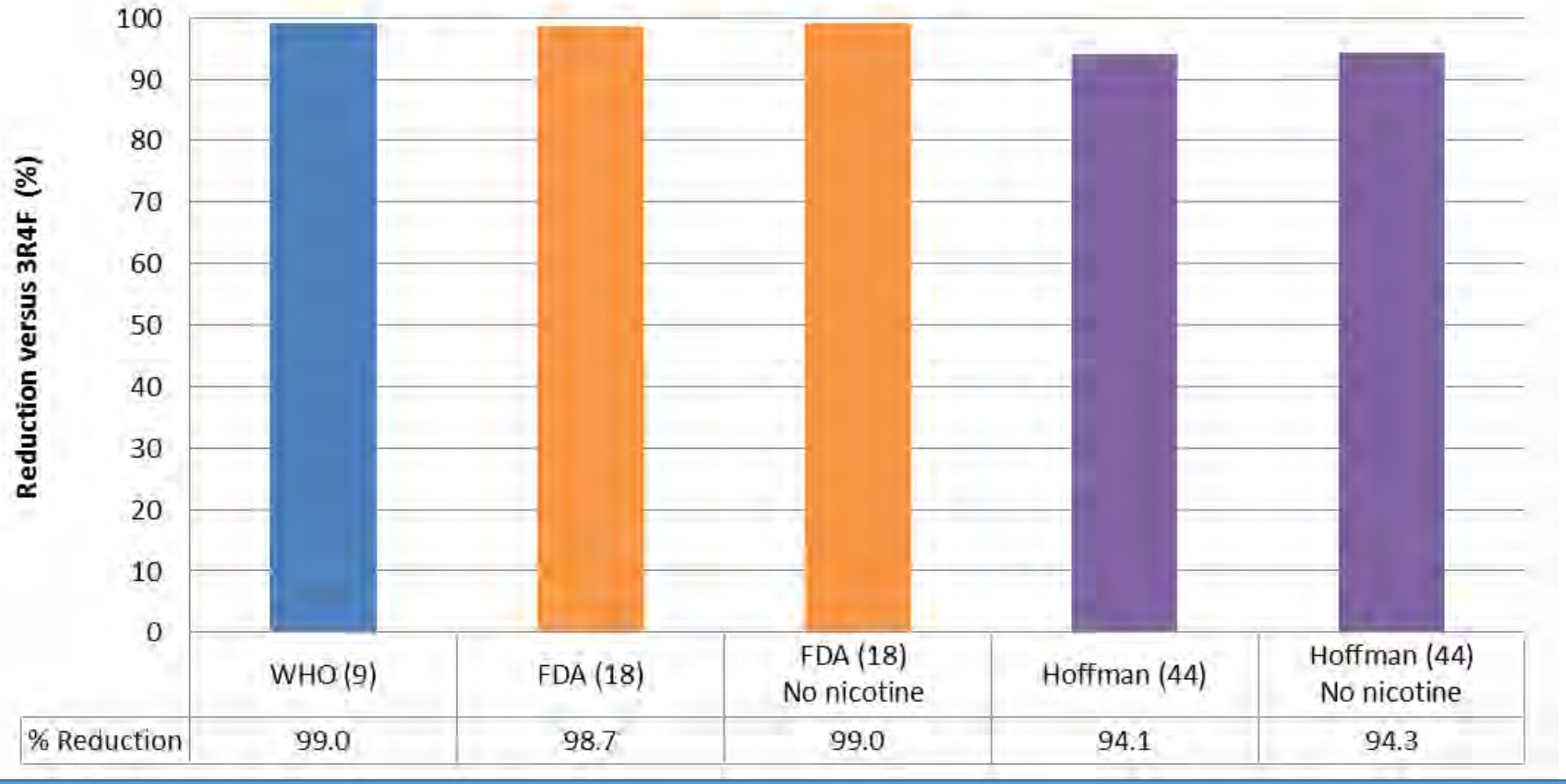
This slide has been redacted as it contains confidential information

This slide has been redacted as it contains confidential information

This slide has been redacted as it contains confidential information

Exposure: Chemical analysis of targeted emissions [Poynton *et al,* 2017]

Average per puff reductions relative to scientific reference cigarette (3R4F)



All toxicants within groups are reduced to similar levels as the average reduction

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

Exposure: Chemical analysis of environmental emissions[a]

Assessment of Indoor air Quality

	Measured values			
	Baseline	**LSR**	**DMS**	**IFU1.0**
VOCs (µg.m^{-3})				
Isoprene	17	191	255	17
Benzene	1	16	21	1
Toluene	2	29	32	2
TVOC	72	298	312	69
Carbonyls (µg.m^{-3})				
Formaldehyde	16	33	43	18
Acetaldehyde	8	100	118	9
Other (µg.m^{-3})				
Nicotine	1.3	28	33	0.79
3-ethenyl pyridine	0.2	9	8	0.24
CO (ppm)	nd	1.4	1.4	nd
NO (ppb)	12	30	22	4
NO_2 (ppb)	8	11	11	8
NO_X (ppb)	20	41	33	12

Values with subtracted baseline yields		
LSR	**DMS**	**IFU1.0**
174	238	0
15	20	0
27	30	0
226	240	-3
17	27	2
92	110	1
26.7	31.7	-0.51
8.8	7.8	0.04
1.4	1.4	0
18	10	-8
3	3	0
21	13	-8

iFU1.0(T)≥ LSR or DMS

iFU1.0(T) > Baseline

iFU1.0(T) ≤ Baseline

[a]Murphy et al, 2017

Toxicants in environmental emissions of IFU1.0(T) were substantially reduced relative to cigarette smoke and in many cases were similar or lower than those measured at baseline (ie. no product usage)

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

Exposure: Assessment of air quality

	Measurement	DMS	LSR	iFU1.0(RS)
Inhaled aerosol	MMD[a] (nm)	262 ± 23	271 ± 26	590 ± 47
	GSD[b]	1.4	1.41	1.65
	99.7%'ile (nm)	95 - 713	97 - 760	131 - 2,650
Indoor air quality	$PM_{1.0}$	510	572	3
	MMD[a] (nm)	229 ± 11	237 ± 18	169 ± 40
	GSD[b]	1.48	1.48	1.81

[a]MMD = Mass Median diameter; [b]GSD = Geometric standard deviation;

- iFU1.0(RS) and cigarette smoke inhaled aerosol in respirable range
- 99.7% inhaled aerosol for iFU1.0(RS) was above 100nm
- DMS and LSR cigarette inhaled aerosol were similar, with a small percentage sub 100nm
- Indoor air quality aerosol particulate matter ($PM_{1.0}$) for iFU1.0(RS) aerosol is substantially reduced (99%) relative to DMS and LSR cigarette smoke
- Particulate matter ($PM_{1.0}$) in iFU1.0(RS) aerosol is not significantly different from baseline

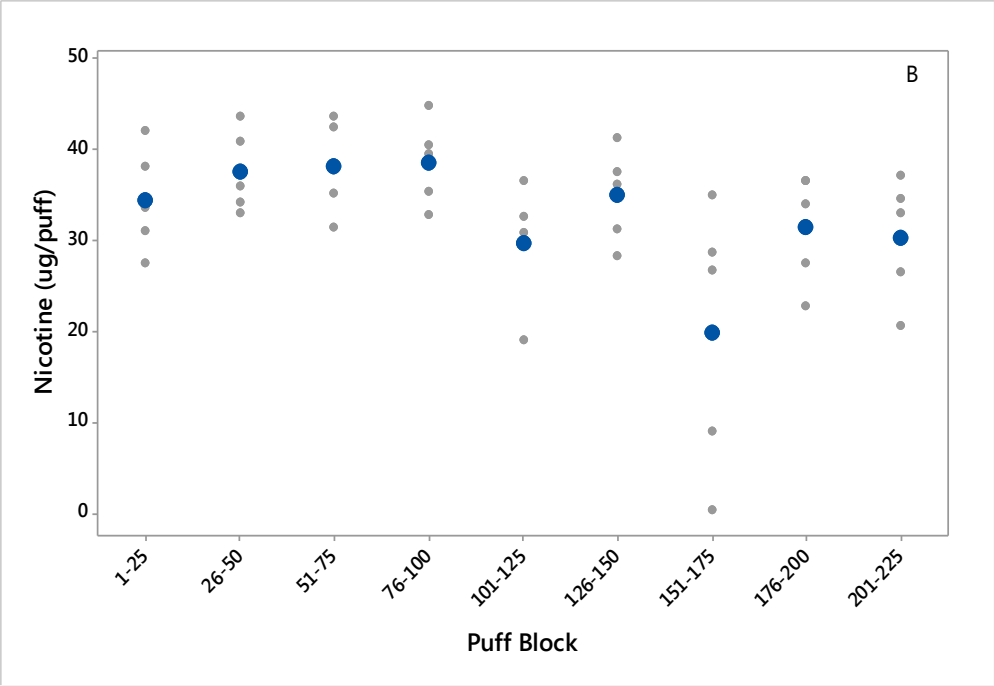
Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

This slide has been redacted as it contains confidential information

Exposure: Nicotine levels calculated from machine yields

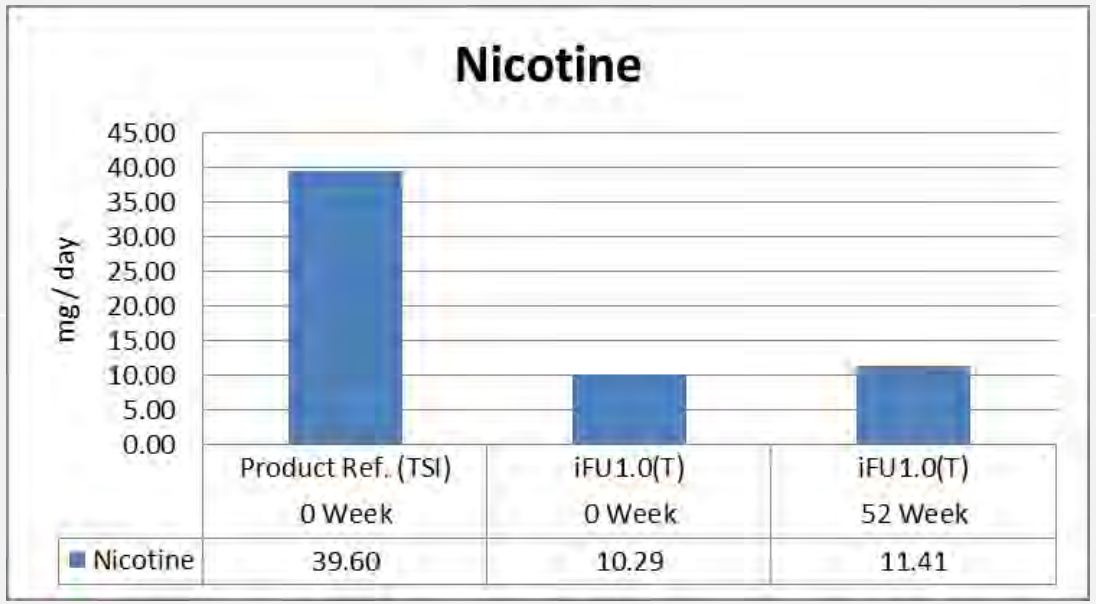
Nicotine delivered by iFU1.0(T) ug/puff

Consistent nicotine delivery across life of the Neopod



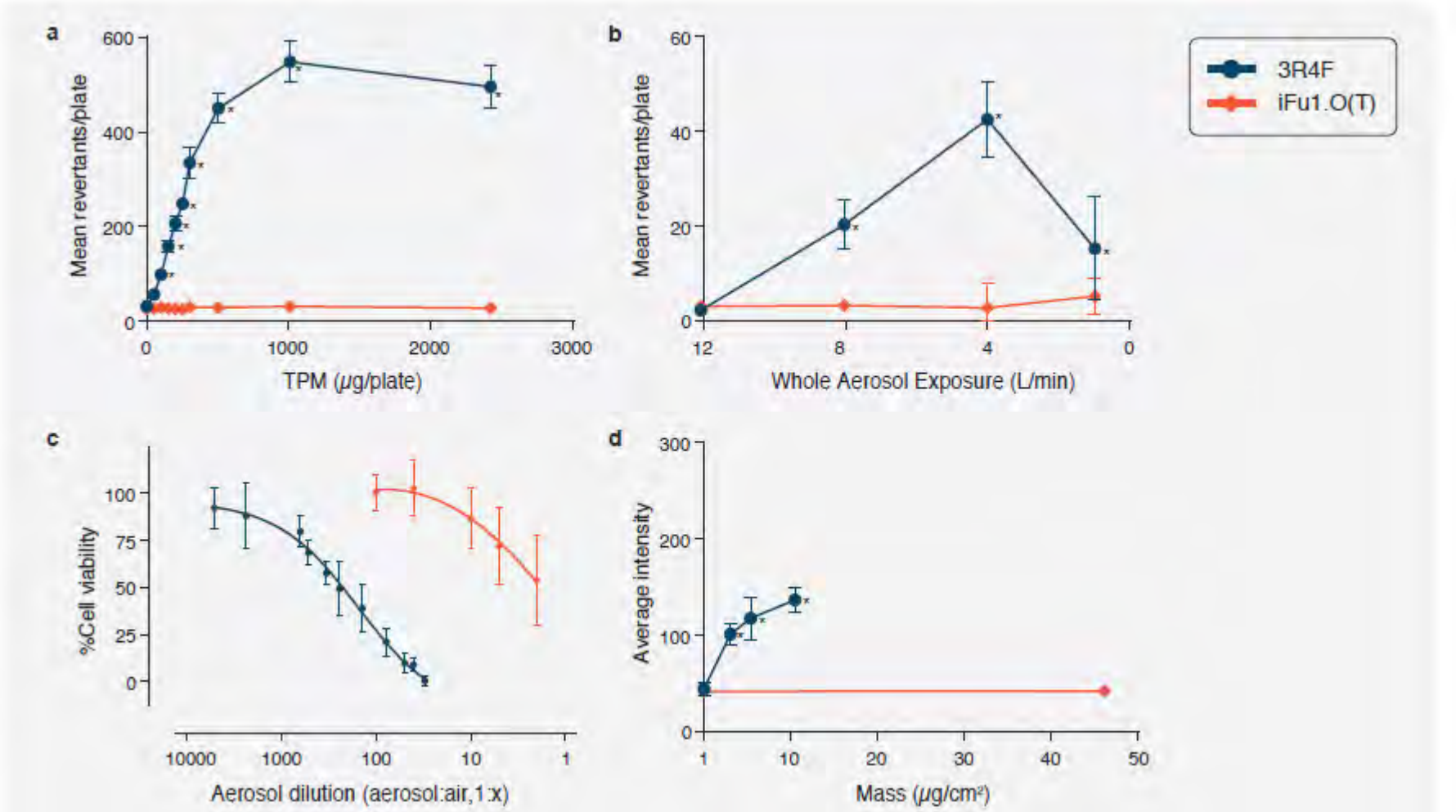
Daily nicotine exposure

Nicotine exposure based on 40 cigarettes / day or 350 puffs of IFU1.0 / day



- IFU1.0 delivers nicotine consistently across the life of the Neopod
- IFU1.0 delivers less nicotine than smoking

Health effects:
in vitro toxicological assessment



Mutagenicity assessment using (a) TPM and (b) WA in the Ames test. (c) Cytotoxic response using WA in a cell viability assay. (d) DNA double-strand breaks assessed by the γ-H2AX assay.
Breheny *et al* (2017)

Responses from iFU1.0(T) emissions in tests compared to 3R4F smoke:

- No *in vitro* mutagenicity or DNA damage
- Reduced levels of cytotoxicity

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

This slide has been redacted as it contains confidential information

Systemic toxicity assessment

Systemic Toxicity	Risk assessment of iFU1.0(T) relative to cigarettes	References
Hepatotoxicity	-"Active smoking is causally associated with liver cancer" -Reduction in possible drivers in IFU1.0 emissions relative to cigarette smoke • Toxicant emissions were >95% reduced* • No mutagenicity or cell transformation responses	US Surgeon General (2014) Poynton et al (2017) Breheny *et al*. (2017)
Cardiovascular toxicity	-"Smoking tobacco is causally related to almost all major forms of CVD" -Reduction in possible drivers in IFU1.0 emissions relative to cigarette smoke • No combustion • CO emissions were at levels similar to air blank	US Surgeon General (2014) Poynton et al (2017)

*COMPARISON OF SMOKE FROM A 3R4F REFERENCE CIGARETTE (APPROX. 9 MG TAR) AND VAPOUR FROM IFUSE, IN TERMS OF THE 9 HARMFUL COMPONENTS THE WORLD HEALTH ORGANISATION RECOMMENDS TO REDUCE IN CIGARETTE SMOKE.

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

Sensitisation:
A two phased approach to measuring sensitisation potential

Additive screen

Respiratory sensitisers

Respiratory sensitisers are excluded, based on their identification in the following sources.

- European Chemicals Agency (ECHA) Classifications & Labelling (C&L) database
- Assessment of published toxicity data collated by BIBRA on all ingredients
- Xaver Baur, 'A compendium of causative agents of occupational asthma.' Journal of Occupational Medicine and Toxicology, 2013, 8:15
- World Allergy Organisation, list of Sensitizing Agents, inducers of Occupational Asthma, Hypersensitivity Pneumonitis and Eosinophilic Bronchitis. Available at

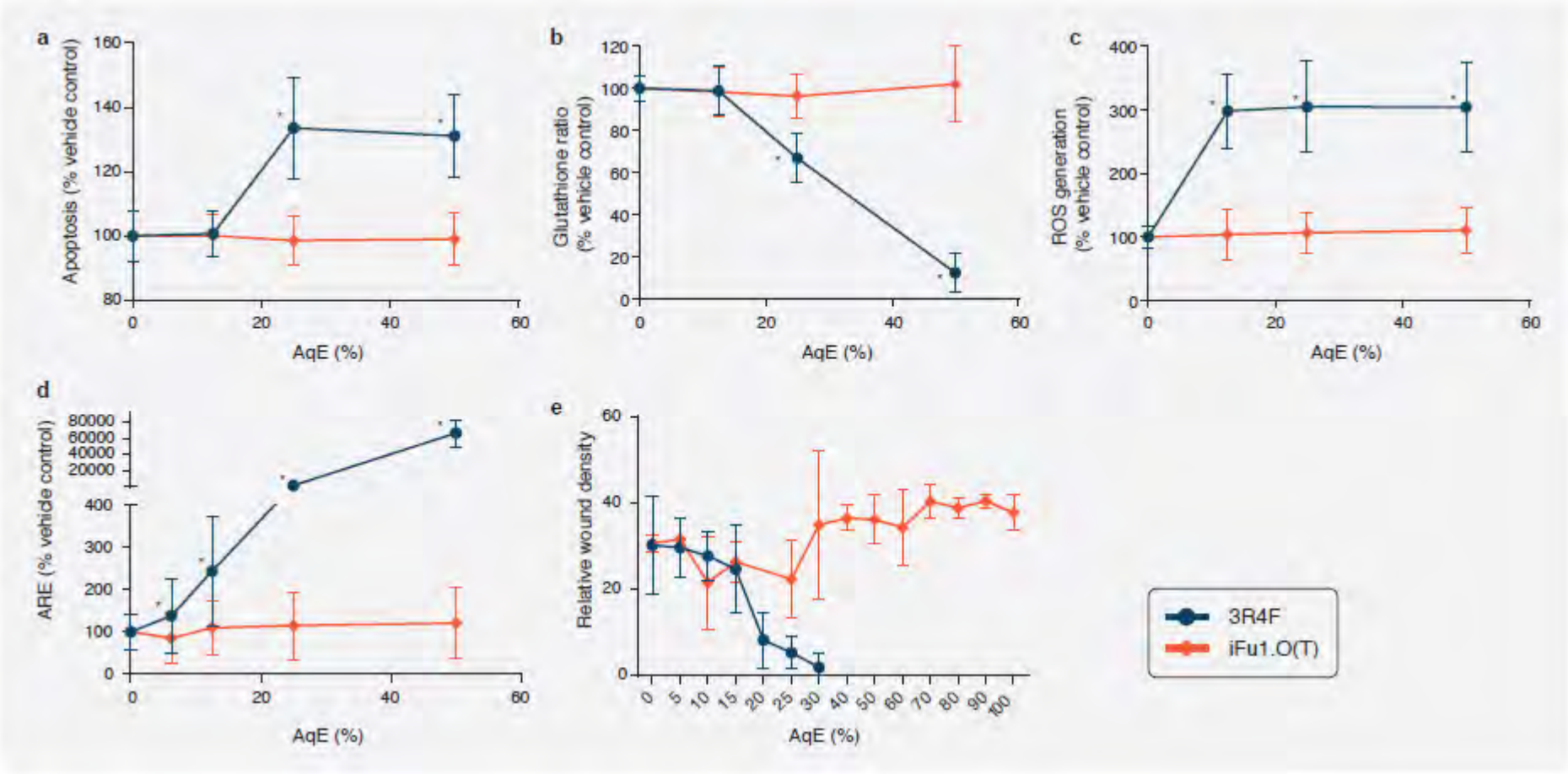
http://www.worldallergy.org/professional/allergic_diseases_center/occupational_allergens/

Contact sensitisers

Contact sensitisers are identified in the following sources:

- European Chemicals Agency (ECHA) Classifications & Labelling (C&L) database
- Assessment of published toxicity data collated by BIBRA on all ingredients
- DEREK report
- IFRA standards
- EU Cosmetics Directive
- Any identified contact sensitisers are risk assessed using the process summarised in Appendix XX of dossier.

A 21st century toxicology approach:
in vitro disease modelling oxidative stress and endothelial wound healing



In vitro biological effect of exposure to AqE from a 3R4F reference cigarette and a iFU1.0(T)*.

(**a**) apoptotic response

(**b**) GSH:GSSG ratio

(**c**) generation of intracellular oxidant species

(**d**) and ARE activation in lung epithelial H292 cells.

(**e**) Wound healing rates in HUVEC monolayers.

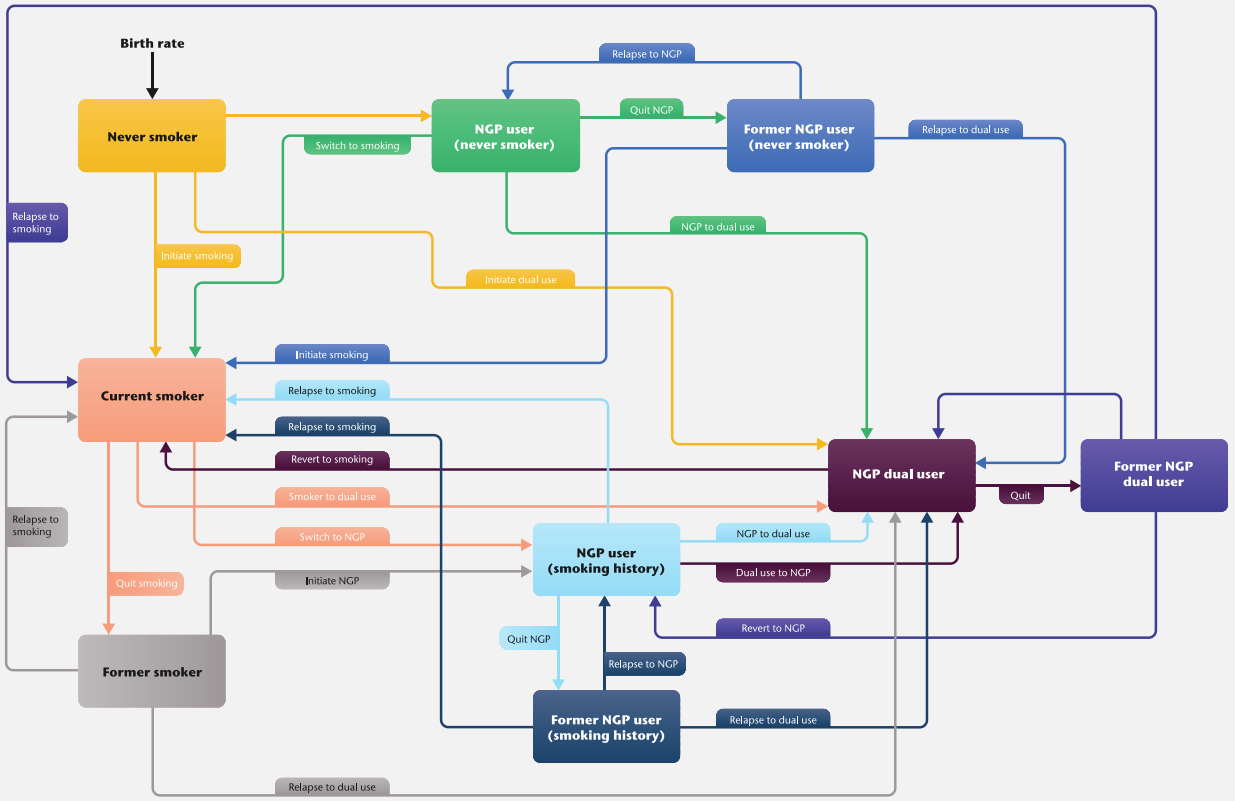
*Breheny *et al* (2017)

Significant reductions were observed with iFU1.0(T) when compared to 3R4F scientific reference tobacco product across all *in vitro* biological tests

Data shows comparative analysis between iFuse 1.0 and a reference cigarette; these qualities do not necessarily mean the iFuse 1.0 product produces less adverse health effects than other tobacco products.

POPULATION RISK
STUDIES IN POST MARKET SURVEILLANCE

ER ESTIMATES	X	POPULATION USAGE	=	POPULATION RISK IMPACT
Excess Risk (ER) estimates determined from pre-clinical and clinical assessment Risk estimates calculated for: • Smoking • Solus NGP* use • Dual use with respect to never smokers and Nicotine Replacement Therapy *NGP = Next Generation Product		Usage of products assessed across population: • Smoking • Solus NGP use • Dual use • Non smokers • Quitting		Dynamic model [1,2] to assess population risk impact



[1] Hill *et al* (2017)
[2] Model design to meet FDA expectations (FDA 2012)

Misuse considerations

Misuse consideration	Mitigation
Accidental exposure	Failure Mode Effect Analysis Leak test User instructions Warning label Maximum nicotine concentration 18 mg/ml maximum formulation volume 1.2ml Instructions on spillage or swallowing Manufacturing QC process
Routes of exposure	Oral Dermal
Child exposure	Warning label Instructions on spillage or swallowing. Website requires age approval Purchase in shop requires age approval
Potential for deliberate misuse	Maximum nicotine concentration 18 mg/ml maximum formulation volume 1.2ml Warning label Neopod only compatible with iFuse device
Potential for overdose	Adverse event monitoring in PMS (UK and Romania)

This slide has been redacted as it contains confidential information

This slide has been redacted as it contains confidential information

References

- Baker *et al* (2006) Progress in Energy and Combustion Science. Volume 32, Issue 4, 2006, Pages 373–385
- Breheny *et al* (2017) Food and Chem Tox (Accepted)
- Coresta (2015) https://www.coresta.org/sites/default/files/technical_documents/main/CRM_81.pdf (Accessed 20th March 2017)
- FDA (2012) http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf. (*Accessed 20th April 2017*).
- Fowles et al (2003) Tobacco Control, 12(4), 424-30.
- Hill *et al* (2017) Reg Tox Pharm (Accepted)
- Murphy *et al* (2017) Reg Tox Pharm (Submitted)
- Perfetti et al (2013) The Chemical Components of Tobacco and Tobacco Smoke, Second Edition, CRC Press, Boca Raton.
- Poynton *et al* (2017) Food and Chem Tox (Accepted)
- Stratton *et al* (2001) Clearing the smoke: assessing the science base for tobacco harm reduction. Washington, DC: National Academy Press.
- US Surgeon General (2014)

bat-science.com

@BAT_Sci

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Joint COT, COM and COC discussion on the toxicological evaluation of novel heat-not-burn tobacco products: Evaluation of data provided against Committees' data requirements and summary of peer-reviewed published literature

Reserved Business

Details of Literature search

The following search terms were used:

- *Neopod, iFuse, Heatstick, Heet*, Electrically + heated + tobacco + product, EHTP, "heat-not-burn", IQOS, THS + PMI, "tobacco heating system", "electrically heated" + tobacco, "modified risk tobacco product", Mrtp, "British American Tobacco" + rtp, "British American Tobacco" + prototype*

Total no. of papers retrieved (for screening) = 127

No of papers selected[1] (based on abstract screen only) = 86

These were categorised as those:

(i) cited either in the current presentations or in a scoping document taken to the COT/COC/COM (n=17)

(ii) new papers not previously cited in scoping documents. These were further divided into those where the abstract reports data on HNB products that are either IQOS or iFuse (or versions of) (n=49), or

(iii) abstract does not specify whether the evaluated HNB product is IQOS or iFuse (or versions of) (n=20)

NB. Due to time constraints, a full paper screen to confirm the relevance of selected papers was not conducted, but is expected to take place at a later date.

PHE-Supported Imperial College Toxicology Unit
May 2017

[1] 41 papers were excluded for following reasons: did not evaluate HNB; evaluate HNB produced by other tobacco companies; provides no experimental data (unless considered as potentially relevant review)

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Table D1. Papers published by PMI (on PMI's IQOS and related products i.e. earlier versions)

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Ansari et al (2016)	Comprehensive systems biology analysis of a 7-month cigarette smoke inhalation study in C57BL/6 mice.	Sci Data.;3:150077	26731301			X
Elamin et al (2016)	Quantitative proteomics analysis using 2D-PAGE to investigate the effects of cigarette smoke and aerosol of a prototypic modified risk tobacco product on the lung proteome in C57BL/6 mice.	J Proteomics.; 145:237-45	27268958			X
Frost-Pineda et al (2008a)	12-week clinical exposure evaluation of a third-generation electrically heated cigarette smoking system (EHCSS) in adult smokers.	Regul Toxicol Pharmacol.;52(2):111-7	18619511		X	
Frost-Pineda et al (2008b)	Environmental tobacco smoke (ETS) evaluation of a third-generation electrically heated cigarette smoking system (EHCSS).	Regul Toxicol Pharmacol.;52(2):118-21	18639603		X	
Frost-Pineda et al (2008c)	Short-term clinical exposure evaluation of a third-generation electrically heated cigarette smoking system (EHCSS) in adult smokers.	Regul Toxicol Pharmacol.;52(2):104-10	18640172		X	
Gonzalez-Suarez et al (2016)	In Vitro Systems Toxicology Assessment of a Candidate Modified Risk Tobacco Product Shows Reduced Toxicity Compared to That of a Conventional Cigarette.	Chem Res Toxicol.;29(1):3-18	26651182	X		
Haziza et al (2016a)	Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement.	Regul Toxicol Pharmacol.;81: 489-499	27693654		X	
Haziza et al (2016b)	Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland.	Regul Toxicol Pharmacol.;81 Suppl 2:S139-S150	27816672	X		
Haziza et al (2016c)	Biomarker of exposure level data set in smokers switching from conventional cigarettes to Tobacco Heating System 2.2, continuing smoking or abstaining from smoking for 5 days.	Data Brief.;10:283-293	27995164		X	

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Iskandar et al (2017a)	3-D nasal cultures: Systems toxicological assessment of a candidate modified-risk tobacco product.	ALTEX.;34(1):23-48.	27388676	X		
Iskandar et al (2017b)	A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified-risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures.	Toxicol In Vitro.;39:29-51	27865774	X		
Kogel et al (2014)	A 28-day rat inhalation study with an integrated molecular toxicology endpoint demonstrates reduced exposure effects for a prototypic modified risk tobacco product compared with conventional cigarettes.	Food Chem Toxicol.;68:204-17.	24632068			X
Kogel et al (2015)	Biological impact of cigarette smoke compared to an aerosol produced from a prototypic modified risk tobacco product on normal human bronchial epithelial cells.	Toxicol In Vitro.;29(8):2102-15	26277032			X
Kogel et al (2016)	Evaluation of the Tobacco Heating System 2.2. Part 7: Systems toxicological assessment of a mentholated version revealed reduced cellular and molecular exposure effects compared with mentholated and non-mentholated cigarette smoke.	Regul Toxicol Pharmacol.;81 Suppl 2:S123-S138	27818347		X	
Lo Sasso et al (2016a)	Effects of cigarette smoke, cessation and switching to a candidate modified risk tobacco product on the liver in Apoe -/- mice--a systems toxicology analysis.	Inhal Toxicol.;28(5):226-40	27027324	X		
Lo Sasso et al (2016b) (Review)	The Apoe(-/-) mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction.	J Transl Med.;14(1):146	27207171		X	
Lüdicke et al (2017a)	Reduced Exposure to Harmful and Potentially Harmful Smoke Constituents With the Tobacco Heating System 2.1.	Nicotine Tob Res.;19(2):168-175	27613951		X	

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Lüdicke et al (2017b)	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. [Epub ahead of print]	28177489		X	
Lüdicke et al (2017c)	Effects of Switching to the Menthol Tobacco Heating System 2.2, Smoking Abstinence, or Continued Cigarette Smoking on Clinically Relevant Risk Markers: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 2).	Nicotine Tob Res. [Epub ahead of print]	28177498		X	
Marchand et al (2017)	Nicotine Population Pharmacokinetics in Healthy Adult Smokers: A Retrospective Analysis	Eur J Drug Metab Pharmacokinet. [Epub ahead of print]	28283988		X	
Martin et al (2016)	Evaluation of the tobacco heating system 2.2. Part 9: Application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2.	Regul Toxicol Pharmacol.;81 Suppl 2:S151-S157	27845159		X	
Martin Leroy et al (2012)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: A one-month, randomized, ambulatory, controlled clinical study in Poland.	Regul Toxicol Pharmacol.;64(2 Suppl):S74-84	22951349		X	
Mitova et al (2016)	Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality.	Regul Toxicol Pharmacol.;80:91-101	27311683		X	
Moennikes et al (2008)	Reduced toxicological activity of cigarette smoke by the addition of ammonia magnesium phosphate to the paper of an electrically heated cigarette: subchronic inhalation toxicology.	Inhal Toxicol.;20(7):647-63	18464053		X	
Mottier et al (2016)	Validation of selected analytical methods using accuracy profiles to assess the impact of a Tobacco Heating System on indoor air quality.	Talanta. 2016 Sep 1;158:165-78	27343591		X	

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Munjal et al (2009)	Heart rate variability increases with reductions in cigarette smoke exposure after 3 days.	J Cardiovasc Pharmacol Ther.;14(3):192-8	19592602		X	
Oviedo et al (2016)	Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with mentholated and non-mentholated cigarette smoke.	Regul Toxicol Pharmacol.;81 Suppl 2:S93-S122	27818348	X		
Patskan & Reininghaus (2003)	Toxicological evaluation of an electrically heated cigarette. Part 1: Overview of technical concepts and summary of findings.	J Appl Toxicol.;23(5):323-8	12975771		X	
Phillips et al (2015)	A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product.	Food Chem Toxicol.;80:328-45	25843363			X
Phillips et al (2016a)	An 8-Month Systems Toxicology Inhalation/ Cessation Study in Apoe-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes.	Toxicol Sci.;149(2):411-32	26609137	X		
Phillips et al (2016b)	An 8-Month Systems Toxicology Inhalation/ Cessation Study in Apoe-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes.	Toxicol Sci. 2016 Jun;151(2):462-4	27225756	X		
Picavet et al (2016)	Comparison of the Pharmacokinetics of Nicotine Following Single and Ad Libitum Use of a Tobacco Heating System or Combustible Cigarettes.	Nicotine Tob Res.;18(5):557-63	26438645		X	
Poussin et al (2016a)	Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells.	Toxicology.;339:73-86	26655683	X		

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Poussin et al (2017b)	Crowd-sourced verification of computational methods and data in systems toxicology: A case study with a heat-not-burn candidate modified risk tobacco product	Chem Res Toxicol; 30(4):934-945	28085253			X
Pratte et al (2016)	Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette.	Hum Exp Toxicol. [Epub ahead of print]	27932538		X	
Roemer et al (2004)	Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions.	Toxicology.;195(1):31-52.	14698566		X	
Roemer et al (2008)	Reduced toxicological activity of cigarette smoke by the addition of ammonium magnesium phosphate to the paper of an electrically heated cigarette: smoke chemistry and in vitro cytotoxicity and genotoxicity.	Toxicol In Vitro.;22(3):671-81	18261880		X	
Roethig et al (2005)	Short-term exposure evaluation of adult smokers switching from conventional to first-generation electrically heated cigarettes during controlled smoking.	J Clin Pharmacol.;45(2):133-45.	15647405		X	
Roethig et al (2007)	Short-term clinical exposure evaluation of a second-generation electrically heated cigarette smoking system.	J Clin Pharmacol.;47(4):518-30	17389561		X	
Roethig et al (2008)	A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation electrically heated cigarette smoking system.	J Clin Pharmacol.;48(5):580-91	18319361		X	
Schaller et al (2016a)	Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol.	Regul Toxicol Pharmacol.;81 Suppl 2:S27-S47	27720919	X		
Schaller et al (2016b)	Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol.	Regul Toxicol Pharmacol.;81 Suppl 2:S48-S58	27793747		X	

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Schorp et al (2012)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 1: Non-clinical and clinical insights.	Regul Toxicol Pharmacol.;64(2 Suppl):S1-10	22940435		X	
Schramke et al (2006)	The mouse lymphoma thymidine kinase assay for the assessment and comparison of the mutagenic activity of cigarette mainstream smoke particulate phase.	Toxicology. 2006;227(3):193-210	16963170		X	
Sewer et al (2016)	Evaluation of the Tobacco Heating System 2.2 (THS2.2). Part 5: microRNA expression from a 90-day rat inhalation study indicates that exposure to THS2.2 aerosol causes reduced effects on lung tissue compared with cigarette smoke.	Regul Toxicol Pharmacol.;81 Suppl 2:S82-S92	27866933	X		
Smith et al (2016) (Review)	Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program.	Regul Toxicol Pharmacol.;81 Suppl 2:S17-S26	27450400		X	
Stabbert et al (2003)	Toxicological evaluation of an electrically heated cigarette. Part 2: Chemical composition of mainstream smoke.	J Appl Toxicol.;23(5):329-39.	12975772		X	
Stabbert et al (2003)	Analysis of aromatic amines in cigarette smoke.	Rapid Commun Mass Spectrom.;17(18):2125-32	12955743		X	
Szostak et al (2017)	Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke.	Food Chem Toxicol.;101:157-167	28111298		X	
Terpstra et al (2003)	Toxicological evaluation of an electrically heated cigarette. Part 4: Subchronic inhalation toxicology.	J Appl Toxicol.;23(5):349-62	12975774		X	
Tewes et al (2003)	Toxicological evaluation of an electrically heated cigarette. Part 3: Genotoxicity and cytotoxicity of mainstream smoke.	J Appl Toxicol.;23(5):341-8	12975773		X	
Titz et al (2016)	Effects of Cigarette Smoke, Cessation, and Switching to Two Heat-Not-Burn Tobacco Products on Lung Lipid Metabolism in C57BL/6 and Apoe-/- Mice-An Integrative Systems Toxicology Analysis.	Toxicol Sci.;149(2):441-57	26582801	X		

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Tricker et al (2009)	Comparison of environmental tobacco smoke (ETS) concentrations generated by an electrically heated cigarette smoking system and a conventional cigarette.	Inhal Toxicol.;21(1):62-77	18951229		X	
Tricker et al (2012a)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 3: Eight-day randomized clinical trial in the UK.	Regul Toxicol Pharmacol.;64(2 Suppl):S35-44	22940436		X	
Tricker et al (2012b)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan.	Regul Toxicol Pharmacol.;64(2 Suppl):S54-63	22940437		X	
Tricker et al (2012c)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: Eight-day randomized clinical trial in Korea.	Regul Toxicol Pharmacol.;64(2 Suppl):S45-53	22951346		X	
Tricker et al (2012d)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-Day randomized clinical trial of a menthol cigarette in Japan.	Regul Toxicol Pharmacol.;64(2 Suppl):S64-73	22951347		X	
Unverdorben et al (2007)	Effects of levels of cigarette smoke exposure on symptom-limited spiroergometry.	Prev Cardiol.;10(2):83-91.	17396059		X	
Unverdorben et al (2008)	Effects of different levels of cigarette smoke exposure on prognostic heart rate and rate--pressure-product parameters.	J Cardiovasc Pharmacol Ther.;13(3):175-82	18628485		X	
Unverdorben et al (2010)	Acute effects of cigarette smoking on pulmonary function.	Regul Toxicol Pharmacol.;57(2-3):241-6	20233598		X	
Urban et al (2012)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 8: Nicotine bridging--estimating smoke constituent exposure by their relationships to both nicotine levels in mainstream cigarette smoke and in smokers.	Regul Toxicol Pharmacol.;64(2 Suppl):S85-97	22943848		X	
van der Toorn et al (2015)	Aerosol from a candidate modified risk tobacco product has reduced effects on chemotaxis and transendothelial migration compared to combustion of conventional cigarettes.	Food Chem Toxicol.;86:81-7	26432920	X		

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
van der Toorn et al (2015)	A prototypic modified risk tobacco product exhibits reduced effects on chemotaxis and transendothelial migration of monocytes compared with a reference cigarette.	Food Chem Toxicol.;80:277-86	25839901	X		
Weitkunat et al (2015)	A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product.	Regul Toxicol Pharmacol;72(1):87-93	25819932			X
Werley et al (2008)	Smoke chemistry, in vitro and in vivo toxicology evaluations of the electrically heated cigarette smoking system series K.	Regul Toxicol Pharmacol.;52(2):122-39	18590791		X	
Wong et al (2016)	Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke.	Regul Toxicol Pharmacol. 2016 Nov 30;81 Suppl 2:S59-S81	27793746	X		
Zanetti et al (2016a)	Systems Toxicology Assessment of the Biological Impact of a Candidate Modified Risk Tobacco Product on Human Organotypic Oral Epithelial Cultures.	Chem Res Toxicol.;29(8): 1252-69	27404394	X		
Zanetti et al (2017b)	Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A 3-day repeated exposure study.	Food Chem Toxicol.;101:15-35.	28025120		X	
Zenzen et al (2012)	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior.	Regul Toxicol Pharmacol.;64(2 Suppl):S11-34	22922180		X	

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Table D2. Papers published by BAT (on BAT iFuse and related products i.e. earlier versions)

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on iFuse or related versions	Product not specified
Hill & Camacho (2017)	A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes.	Regul Toxicol Pharmacol.;86:265-278	28342844	X		
Kulasekaran et al (2015)	Preliminary Evaluation of a New German Translated Tobacco Quality of Life Impact Tool to Discriminate Between Healthy Current and Former Smokers and to Explore the Effect of Switching Smokers to a Reduced Toxicant Prototype Cigarette.	Nicotine Tob Res.;17(12):1456-64	25914263			X
Lowe et al (2013) (Review)	Lung cancer biomarkers for the assessment of modified risk tobacco products: an oxidative stress perspective.	Biomarkers.;18(3):183-95.	23530763			X
Shepperd et al (2013a)	Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes.	Regul Toxicol Pharmacol.;66(1):147-62	23537587			X
Shepperd et al (2013b)	A single-blinded, single-centre, controlled study in healthy adult smokers to identify the effects of a reduced toxicant prototype cigarette on biomarkers of exposure and of biological effect versus commercial cigarettes.	BMC Public Health.;13:690	23895296			X
Shepperd et al (2015)	Changes in levels of biomarkers of exposure and biological effect in a controlled study of smokers switched from conventional cigarettes to reduced-toxicant-prototype cigarettes.	Regul Toxicol Pharmacol.;72(2):273-91	25957570			X

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Table D3. Papers published by other organisations (on PMI IQOS and related products i.e. earlier versions)

Author and Year	Title	Journal details	PMID	Cited in scoping document taken to Committees or Joint meeting presentations	New	
					Reports data on IQOS or related versions	Product not specified
Dayan (2016)	Investigating a toxic risk (self-inflicted) the example of conventional and advanced studies of a novel Tobacco Heating System.	Regul Toxicol Pharmacol.;81 Suppl 2:S15-S16	27483981		X	
Protano et al (2016)	Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system.	Ann Ig.;28(2):109-12	27071321		X	
Scherer et al (2010)	Determination of methyl-, 2-hydroxyethyl- and 2-cyanoethylmercapturic acids as biomarkers of exposure to alkylating agents in cigarette smoke.	J Chromatogr B Analyt Technol Biomed Life Sci.;878(27):2520-8	20227354		X	

Table D4. Papers published by other organisations

Author/ Year	Title	Journal details	PMID	Cited in scoping document taken to Committee/ or Joint meeting presentations	New	
					Reports data on IQOS or iFuse and related versions	Product not specified or potentially relevant review
Caputi (2016) (Review)	Heat-not-burn tobacco products are about to reach their boiling point.	Tob Control. 2016 Aug 24. pii	27558827			X
Carter et al (2009) (Review)	Abuse liability assessment of tobacco products including potential reduced exposure products.	Cancer Epidemiol Biomarkers Prev.;18(12):3241-62	19959676			X
Kamada et al (2016).	Acute eosinophilic pneumonia following heat-not-burn cigarette smoking.	Respirol Case Rep.;4(6):e00190	28031826			X

This is a paper for discussion.
It does not represent the views of the Committee and should not be quoted, cited or reproduced.

Author/ Year	Title	Journal details	PMID	Cited in scoping document taken to Committee/ or Joint meeting presentations	New	
					Reports data on IQOS or iFuse and related versions	Product not specified or potentially relevant review
Kleinstreuer (2013) (Review)	Lung deposition analyses of inhaled toxic aerosols in conventional and less harmful cigarette smoke: a review.	Int J Environ Res Public Health.; 10(9):4454-85	24065038			X
Levy et al (2017) (Review)	A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products.	Addiction.;112(1):8-17.	27109256			X
Lopez et al (2016)	Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers.	Drug Alcohol Depend.;169:33-40	27768968			X
Poland &, Teischinger (2017).	Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk.	Nicotine Tob Res [Epub ahead of print]	28371856			X
Solyst (2012) (Review)	Toward a comprehensive policy on nicotine delivery products and harm reduction.	Food Drug Law J. 2012;67(4):393-404, i.	24640613			X

Table D5. Additional relevant published studies cited in the manufacturer's presentations/dossier (not captured in the literature search)

Company	Author/ Year	Title	Status/ Journal
PMI	Iskandar et al (2017)	n/a	Submitted to Toxicological Research (under revision April 2017)
BAT	Breheny et al (2017).	*Redacted as pre-publication reference*	Food and Chemistry Toxicology. Accepted
	Forster & McAughey (2017).	*Redacted as pre-publication reference*	Reg Tox Pharm. Submitted
	Forster et al (2017).	*Redacted as pre-publication reference*	Reg Tox Pharm. Submitted.
	Murphy et al (2017a).	*Redacted as pre-publication reference*	Reg Tox Pharm. Submitted.
	Murphy et al (2017b).	*Redacted as pre-publication reference*	Reg Tox Pharm. Submitted.
	Poynton et al (2017b).	*Redacted as pre-publication reference*	Food and Chemistry Toxicology. Accepted