The IQOS Heating System

**Tobacco Products Scientific
Advisory Committee**

January 24, 2018

The IQOS Heating System

Tobacco Products Scientific Advisory Committee
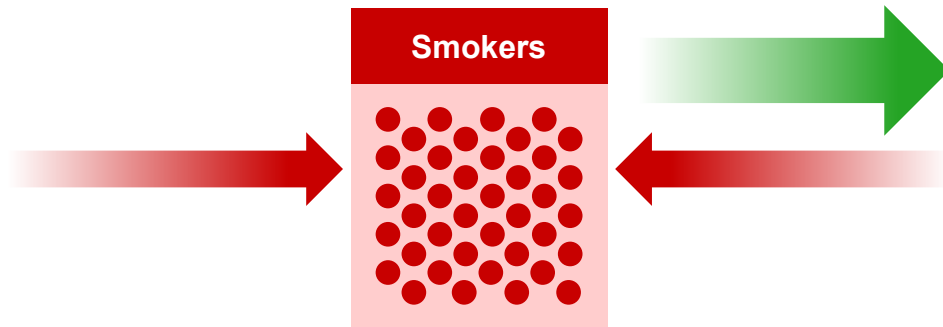
January 24, 2018

CC-1

Introduction

Moira Gilchrist, PhD

Vice President Scientific and Public Communications
Philip Morris International

CC-2
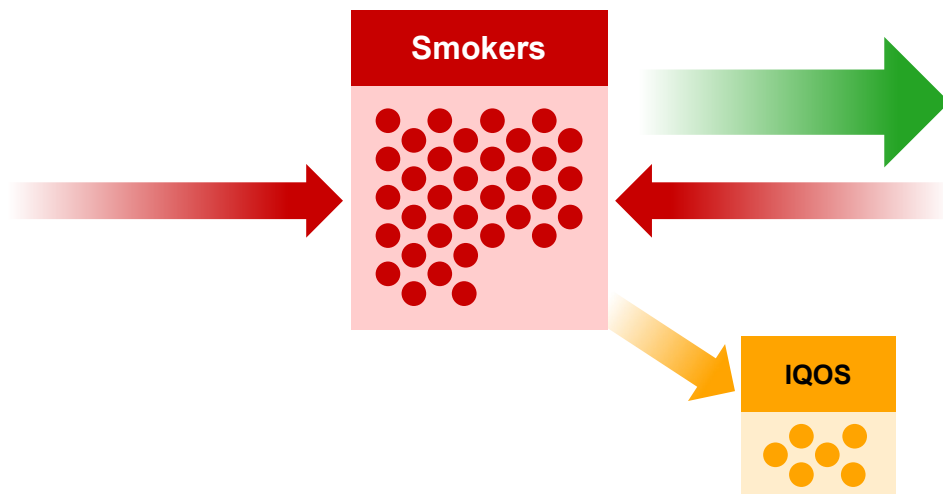
The Status Quo

Smokers

CC-3

Risk Continuum

Combustibles   **Cessation**

Highest Risk   **Lowest Risk**

CC-4

The IQOS Heating System

Heating Device

Charger

HeatStick

CC-5

The IQOS Opportunity

Smokers

IQOS

CC-6

911(g)(1) Modified Risk Products

…the applicant has demonstrated that such product, as it is actually used by consumers, will—

A Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

CC-7

911(g)(1) Modified Risk Products

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CC-8

911(g)(1) Modified Risk Products

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A Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

CC-9

Product Messages

AVAILABLE EVIDENCE TO DATE:
· The iQOS system heats tobacco but does not burn it.
· This significantly reduces the production of harmful and potentially harmful chemicals.
· Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.

SURGEON GENERAL'S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

1 **Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.**

CC-10

Product Messages

1. **Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.**

2. **Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.**

AVAILABLE EVIDENCE TO DATE:
Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

SURGEON GENERAL'S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

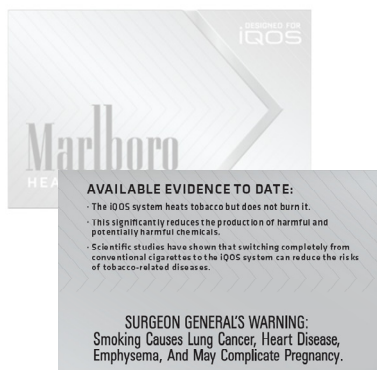CC-11

Product Messages

1. **Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.**
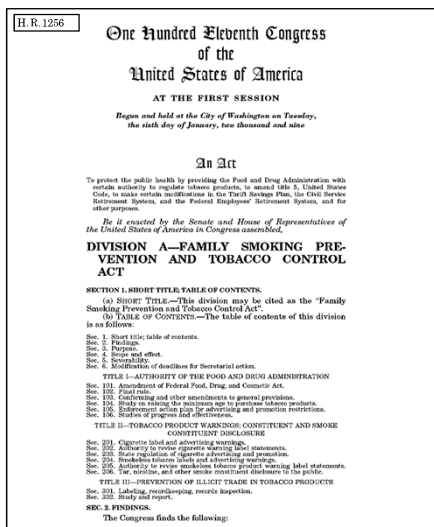
2. **Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.**

3. **Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.**

AVAILABLE EVIDENCE TO DATE:
· The iQOS system heats tobacco but does not burn it.
· This significantly reduces the production of harmful and potentially harmful chemicals.
· Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.

SURGEON GENERAL'S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

CC-12

Family Smoking Prevention and Tobacco Control Act

H.R. 1256

One Hundred Eleventh Congress
of the
United States of America

AT THE FIRST SESSION

*Begun and held at the City of Washington on Tuesday,
the sixth day of January, two thousand and nine*

An Act

To protect the public health by providing the Food and Drug Administration with certain authority to regulate tobacco products, to amend title 5, United States Code, to make certain modifications in the Thrift Savings Plan, the Civil Service Retirement System, and the Federal Employees' Retirement System, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

DIVISION A—FAMILY SMOKING PRE-
VENTION AND TOBACCO CONTROL
ACT

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This division may be cited as the "Family Smoking Prevention and Tobacco Control Act".
(b) TABLE OF CONTENTS.—The table of contents of this division is as follows:

"… to provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products"

-Sec. 3 (4) Purpose

CC-13

Presentation Agenda

Moira Gilchrist, PhD VP Scientific & Public Communications Philip Morris International	**IQOS System and Heating Technology**
Manuel Peitsch, PhD Chief Scientific Officer Philip Morris International	**Scientific Assessment of IQOS**
Antonio Ramazzotti VP Human Insights and Behavioral Research Philip Morris International	**Perception and Behavior**
Sarah Knakmuhs VP Heated Tobacco Products Philip Morris USA	**U.S. Commercialization and Controls**
Moira Gilchrist, PhD VP Scientific & Public Communications Philip Morris International	**Population Modeling and Conclusion**

CC-14

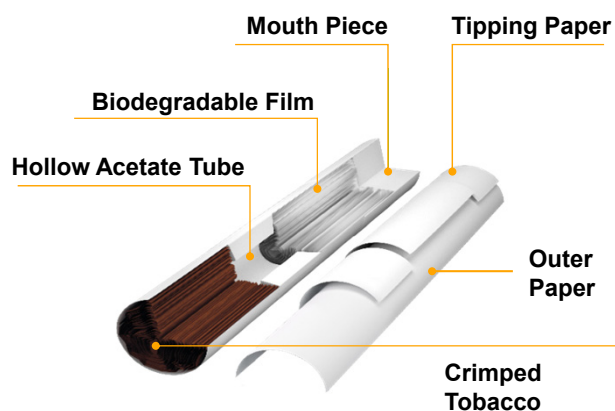# IQOS System and Heating Technology

Moira Gilchrist, PhD

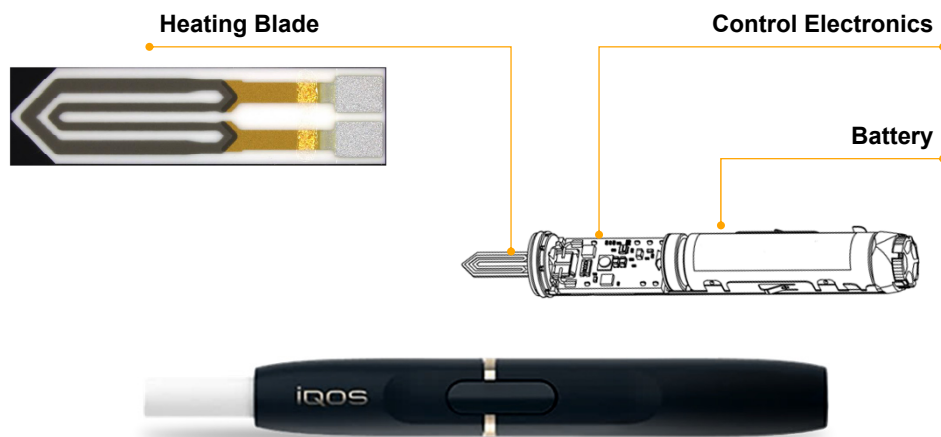Vice President Scientific and Public Communications
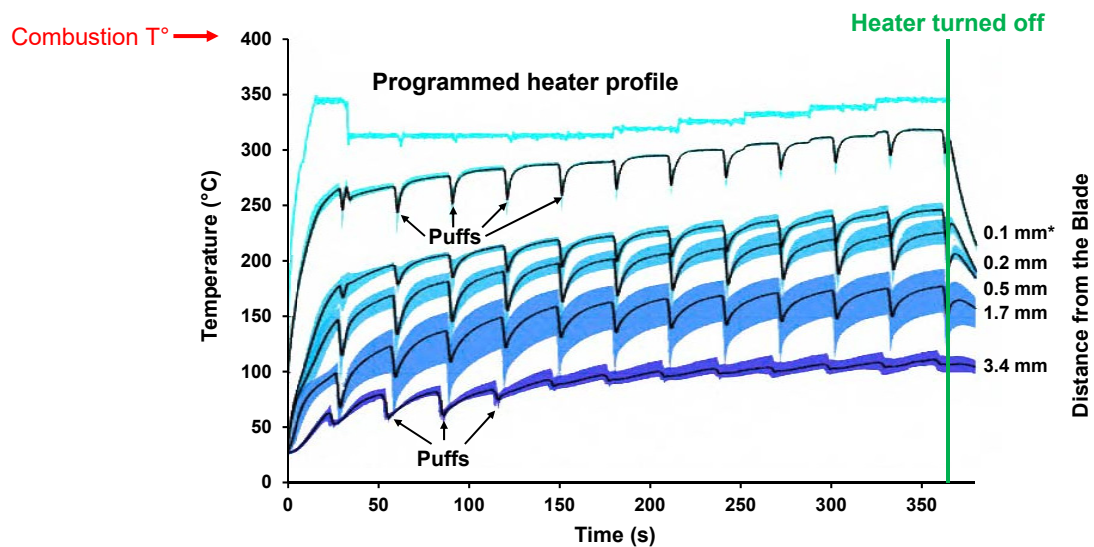Philip Morris International

CC-15

HeatStick Construction

Mouth Piece

Tipping Paper

Biodegradable Film

Hollow Acetate Tube

Outer Paper

Crimped Tobacco

CC-16

IQOS Holder and Heating Blade

Heating Blade

Control Electronics

Battery

iQOS

CC-17

IQOS Temperature Profile

Combustion T°

Heater turned off

Programmed heater profile

Temperature (°C)

Puffs

0.1 mm*
0.2 mm
0.5 mm
1.7 mm

3.4 mm

Distance from the Blade

Puffs

Time (s)

* Radial position of thermocouple relative to the surface of the heater

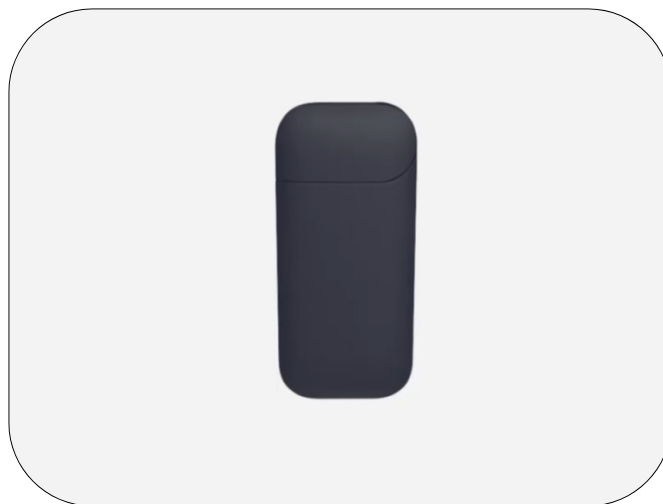CC-18

9

IQOS Charger

Battery

Electronics

Cradle for Holder
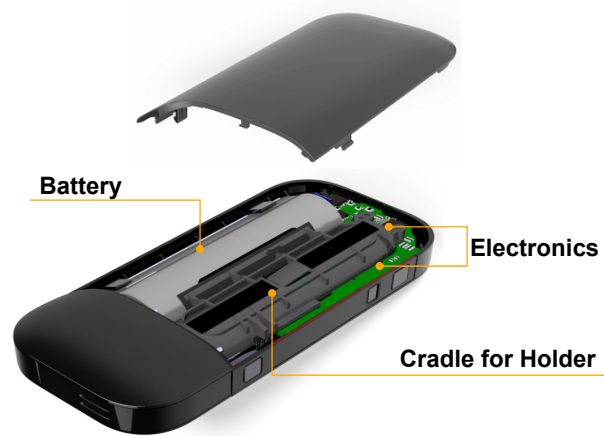
CC-19

IQOS Operation

CC-20

Scientific Assessment of IQOS

Manuel Peitsch, PhD

Chief Scientific Officer
Philip Morris International

CC-21

911(g)(1) Modified Risk Products

…the applicant has demonstrated that such product, as it is actually used by consumers, will—
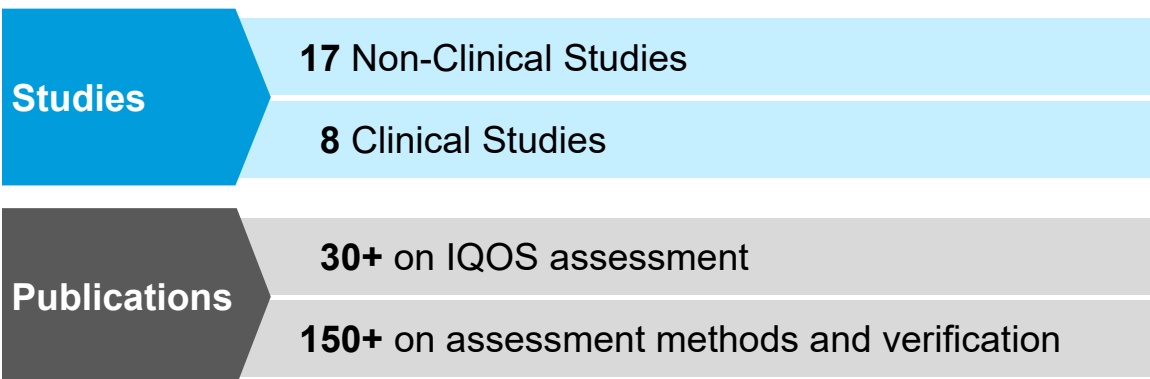
A Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products
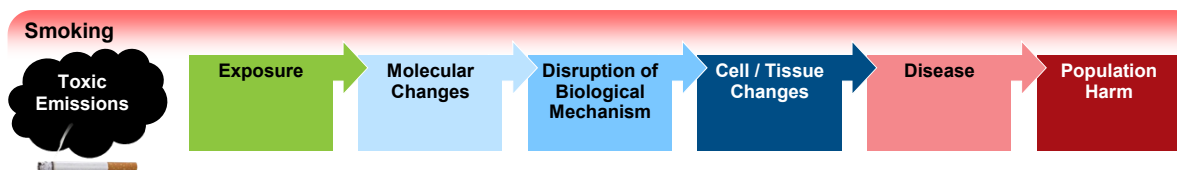
CC-22

Scientific Assessment

Studies

17 Non-Clinical Studies

8 Clinical Studies

Publications

30+ on IQOS assessment

150+ on assessment methods and verification

Hoeng *et al*. A Network-Based Approach to Quantify the Impact of Biologically Active Substances. *Drug Discov*. *Today* 2012; 17:413-418.
Sturla *et al*. Systems Toxicology: from basic research to risk assessment. *Chem. Res. Toxicol*. 2014; 27:314-329.
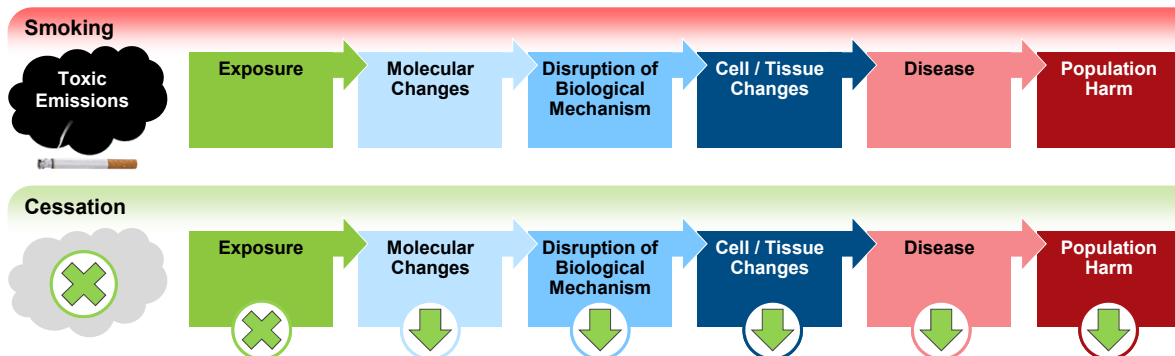
CC-23

Assessment Framework: Informed by Epidemiology

Smoking

Toxic Emissions → Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

The health risks of **smoking** are well established and supported by epidemiological evidence (IARC 2004, 2007)

CC-24

Assessment Framework: Informed by Epidemiology
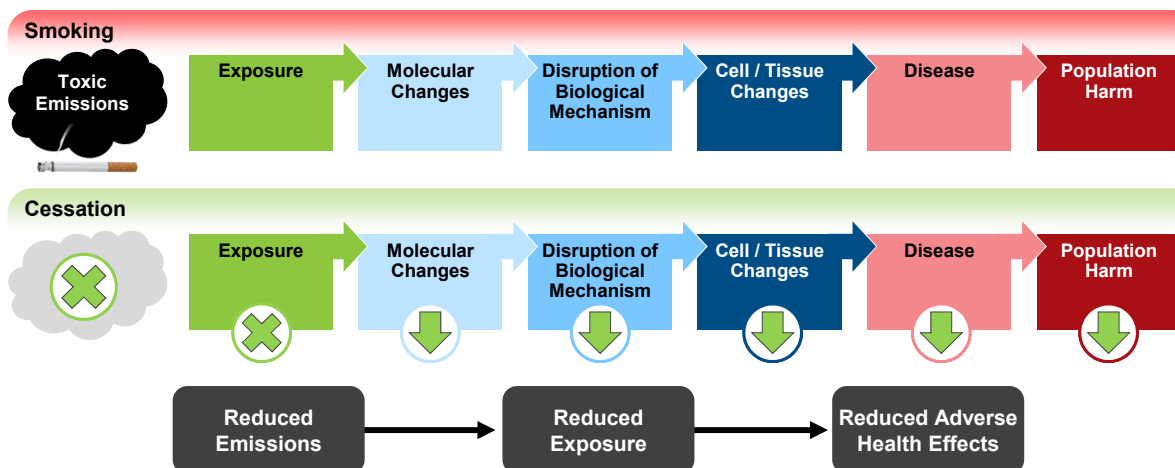
Smoking

Toxic Emissions → Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Cessation

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

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

CC-25

Assessment Framework: Informed by Epidemiology

Smoking

Toxic Emissions → Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Cessation

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Reduced Emissions → Reduced Exposure → Reduced Adverse Health Effects

The health risks of **smoking** and **the reversal** of risks **after quitting smoking** are well established (IARC 2004, 2007)
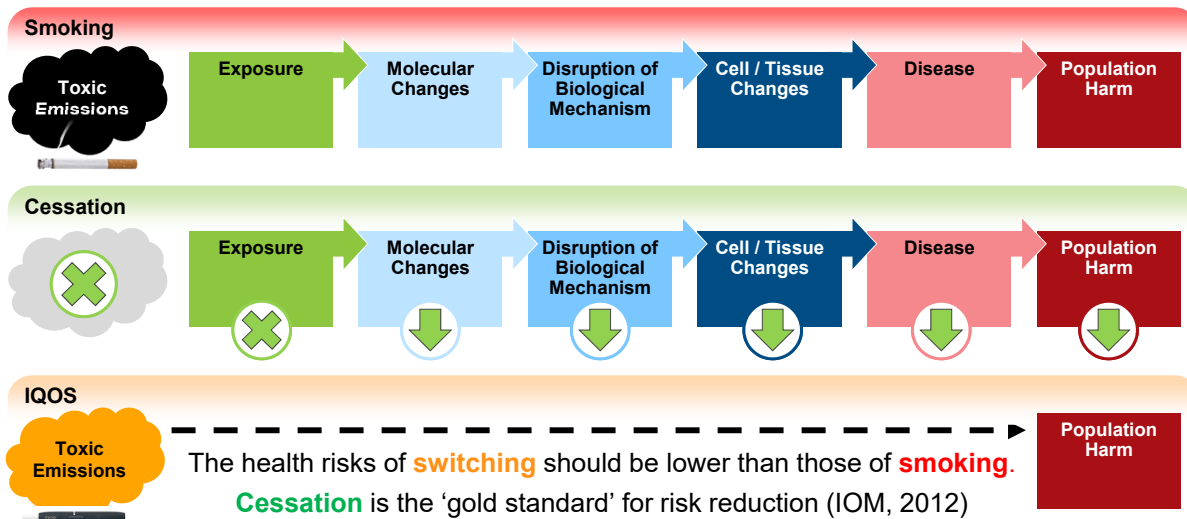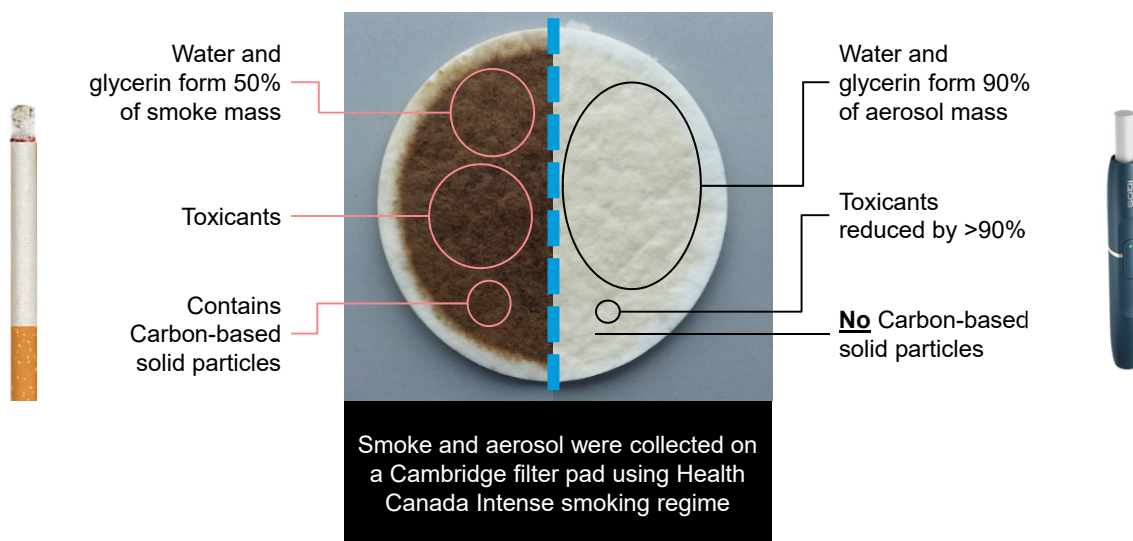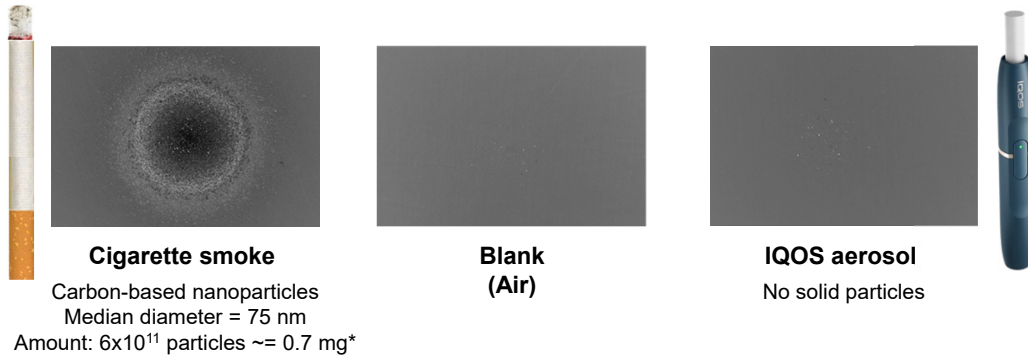
CC-26

Assessment Framework: Informed by Epidemiology

Smoking

| Toxic *Emissions* | Exposure → | Molecular Changes → | Disruption of Biological Mechanism → | Cell / Tissue Changes → | Disease → | Population Harm |

Cessation

| ⊗ | Exposure ⊗ | Molecular Changes ↓ | Disruption of Biological Mechanism ↓ | Cell / Tissue Changes ↓ | Disease ↓ | Population Harm ↓ |

IQOS

| Toxic Emissions | - - - - - - - - - - - - - - - → | Population Harm |

The health risks of **switching** should be lower than those of **smoking**. **Cessation** is the 'gold standard' for risk reduction (IOM, 2012)

CC-27

Differences Between IQOS Aerosol and Cigarette Smoke

Water and glycerin form 50% of smoke mass

Toxicants

Contains Carbon-based solid particles

Water and glycerin form 90% of aerosol mass

Toxicants reduced by >90%

No Carbon-based solid particles

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

CC-28

14

IQOS Does Not Emit Carbon-Based Solid Particles

Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm
Amount: 6×10^{11} particles $\sim= 0.7$ mg*

**Blank
(Air)**

IQOS aerosol
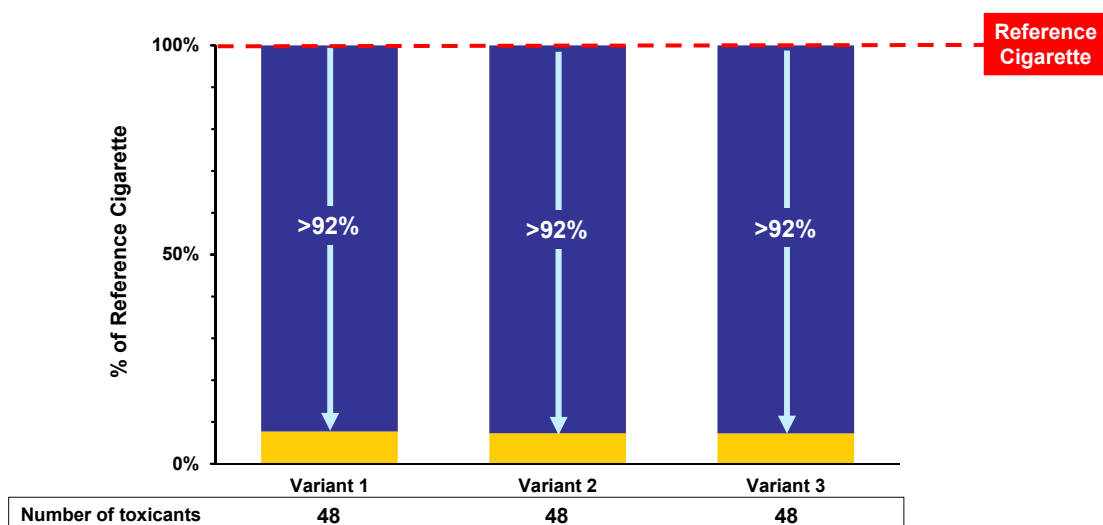
No solid particles

Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300º C to remove the volatile portion / collected material characterized by Electron Diffusive X-ray.

* Under the Health Canada's Intense Smoking Regime.
Pratte et al. 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*, 2017; 36:1115-1120
Cohen et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; 1907-1918. **CC-29**
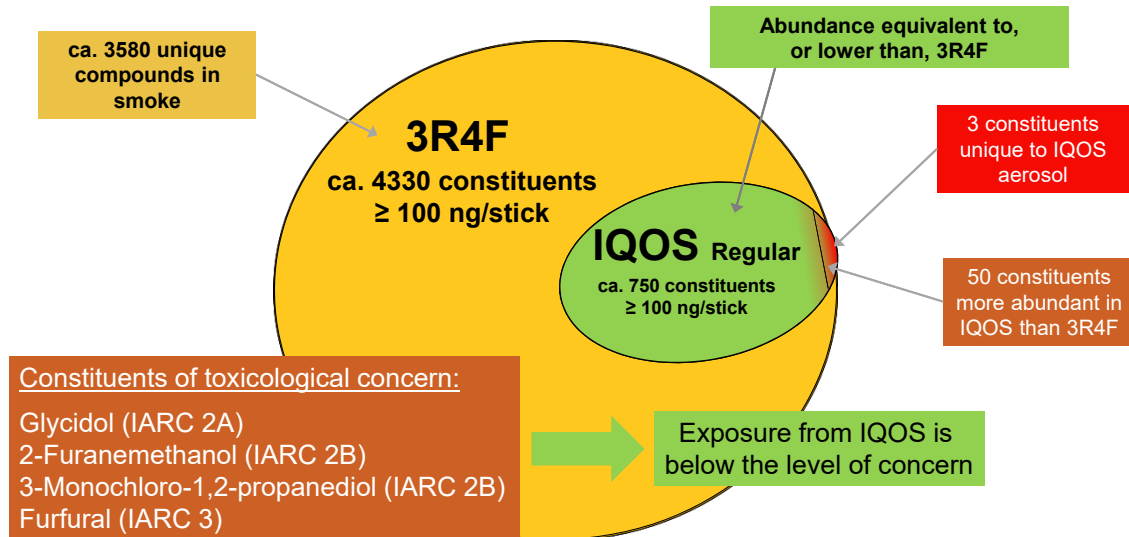
IQOS Releases Less Toxicants than Cigarettes

Reference Cigarette

% of Reference Cigarette

100%

50%

0%

>92%   >92%   >92%

	Variant 1	Variant 2	Variant 3
Number of toxicants	48	48	48

Health Canada's Intense Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine   **CC-30**

15

Non-targeted Differential Screening
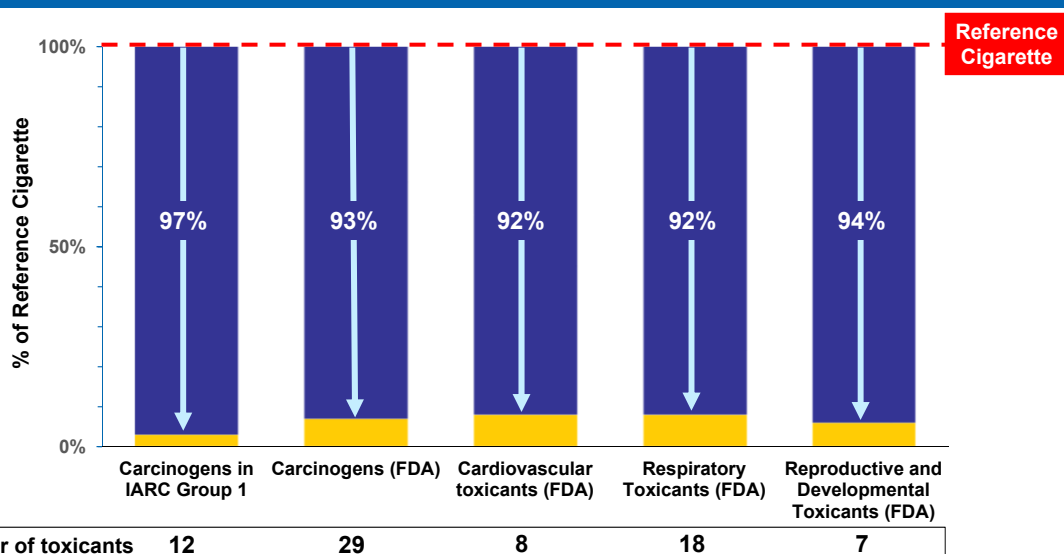**Comparison of IQOS Aerosol and 3R4F Smoke**

ca. 3580 unique compounds in smoke

Abundance equivalent to, or lower than, 3R4F

3R4F
ca. 4330 constituents ≥ 100 ng/stick

IQOS Regular
ca. 750 constituents ≥ 100 ng/stick

3 constituents unique to IQOS aerosol

50 constituents more abundant in IQOS than 3R4F

Constituents of toxicological concern:

Glycidol (IARC 2A)
2-Furanemethanol (IARC 2B)
3-Monochloro-1,2-propanediol (IARC 2B)
Furfural (IARC 3)

Exposure from IQOS is below the level of concern

This slide presents the results for the regular variant of the IQOS HeatStick characterization

CC-31

Reductions of Toxicants by Disease Category

Reference Cigarette

100%

% of Reference Cigarette

50%

97% 93% 92% 92% 94%

0%

Carcinogens in IARC Group 1 | Carcinogens (FDA) | Cardiovascular toxicants (FDA) | Respiratory Toxicants (FDA) | Reproductive and Developmental Toxicants (FDA)

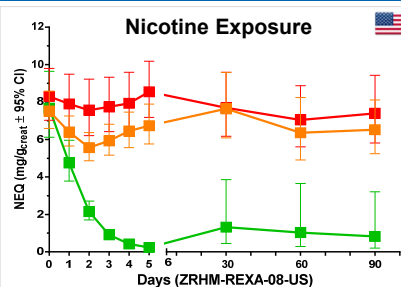| Number of toxicants | 12 | 29 | 8 | 18 | 7 |

Note: Intense Health Canada's Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

CC-32

16
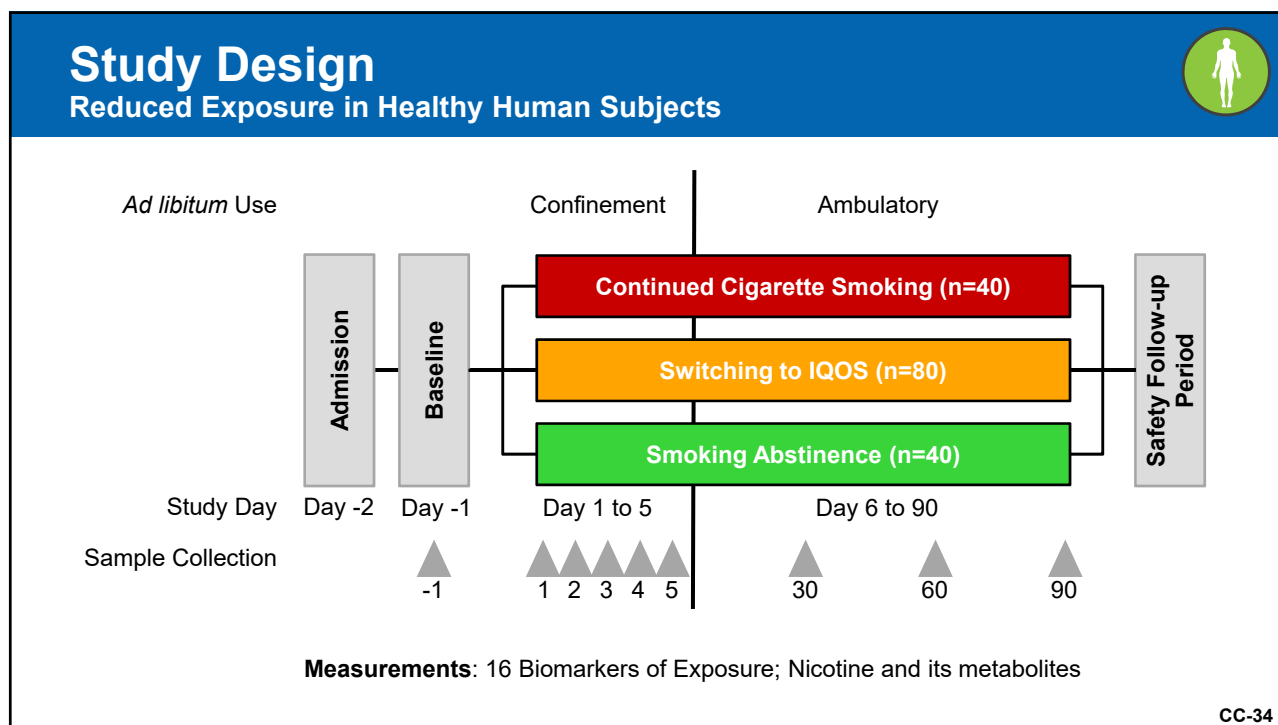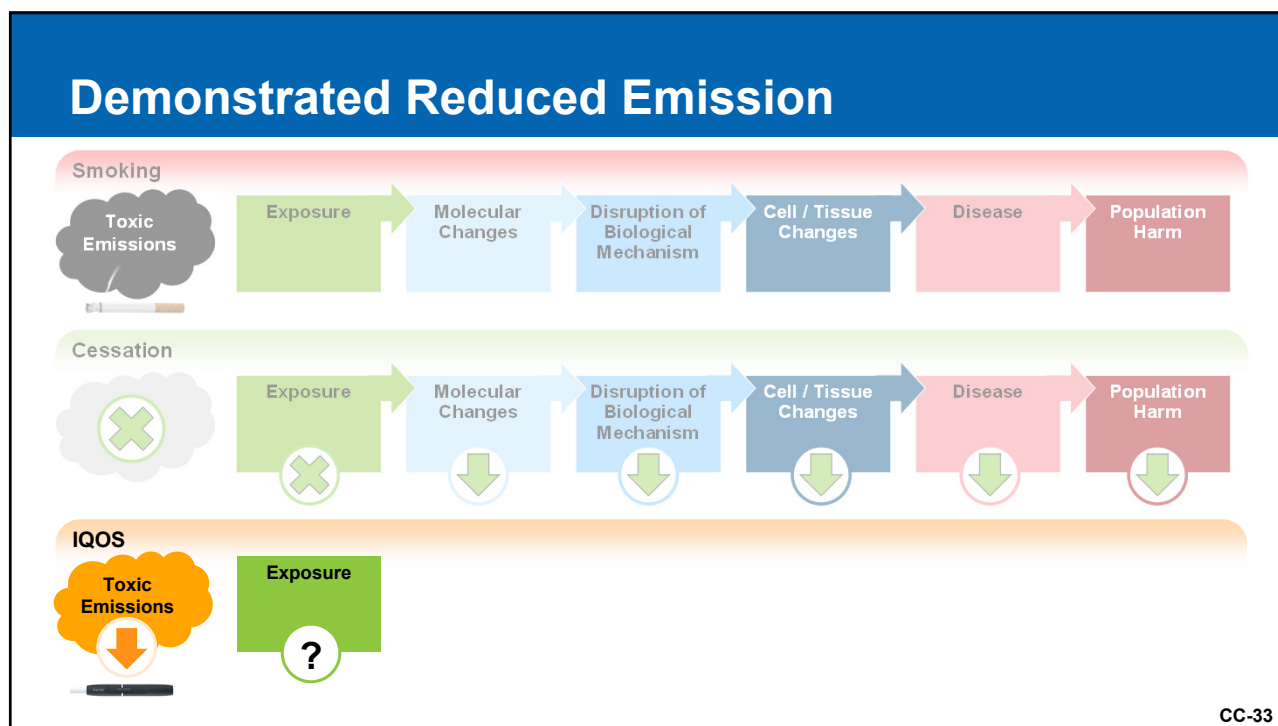
Smoker Acceptance of IQOS is Similar to Cigarettes

Nicotine Exposure

Smoking Satisfaction (mCEQ)
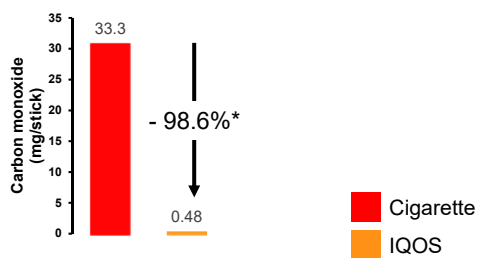
Product Use
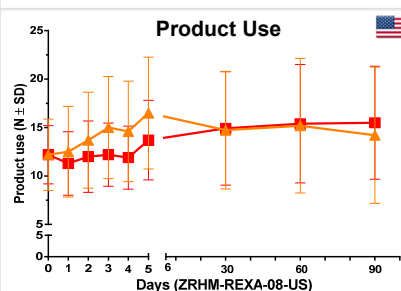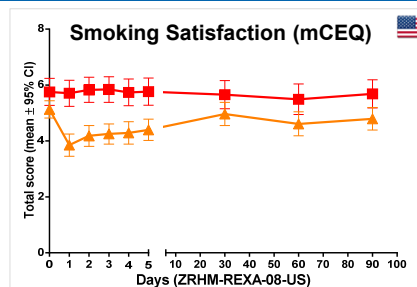
Cigarette
IQOS
Smoking Abstinence

CC-35

Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

33.3
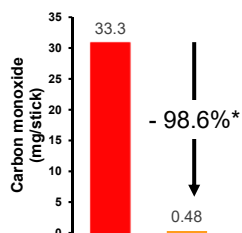- 98.6%*
0.48

Cigarette
IQOS

* On equivalent nicotine basis

CC-36

Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

- 98.6%*

Leads to

■ Cigarette
■ IQOS

* On equivalent nicotine basis

CC-37

Changes in Exposure to HPHCs with IQOS Use
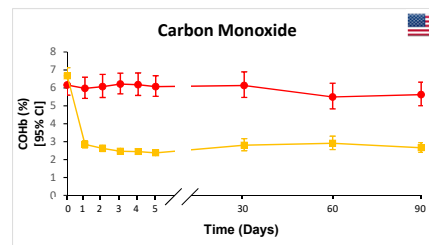## Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

- 98.6%*

Leads to

■ Cigarette
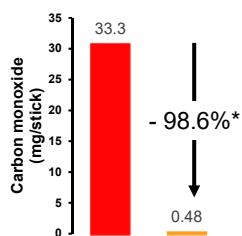■ IQOS
■ Smoking Abstinence

* On equivalent nicotine basis

CC-38

19

Changes in Exposure to HPHCs with IQOS Use
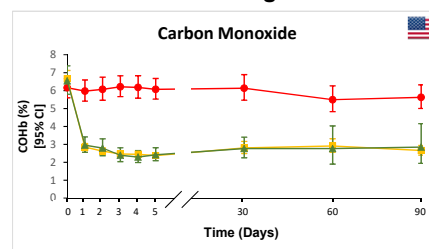**Reduced Exposure in Healthy Human Subjects**

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

- Cigarette
- IQOS
- Smoking Abstinence

Carbon monoxide (mg/stick): 33.3 → 0.48, - 98.6%*

Acrolein (µg/stick): 161 → 9.32, - 94.2%*

Leads to

Carbon Monoxide

Acrolein

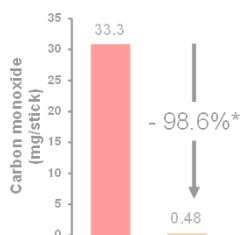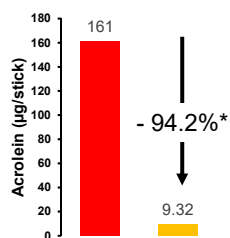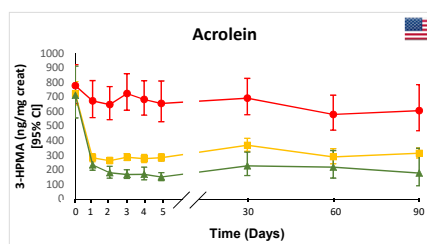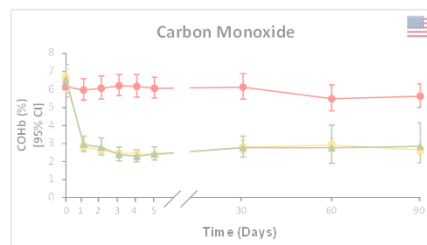* On equivalent nicotine basis

CC-39

Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

- Cigarette
- IQOS
- Smoking Abstinence

NNN (ng/stick): 274 → 7.74, - 97.2%*

NNK (ng/stick): 282 → 5.52, - 98.0%*

Leads to

NNN

NNK
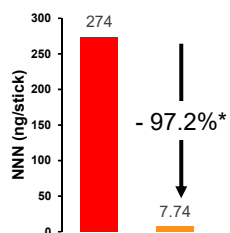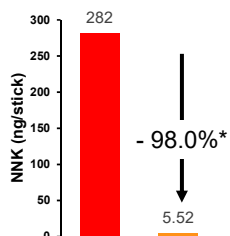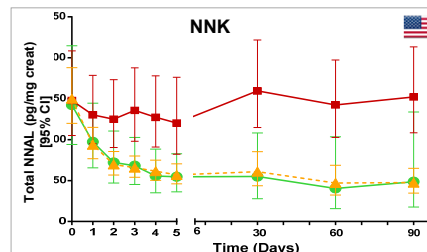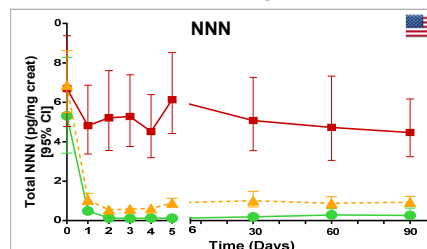
* On equivalent nicotine basis

CC-40

20

Reduced Exposure Compared to Cigarettes
Reduced Exposure in Healthy Human Subjects
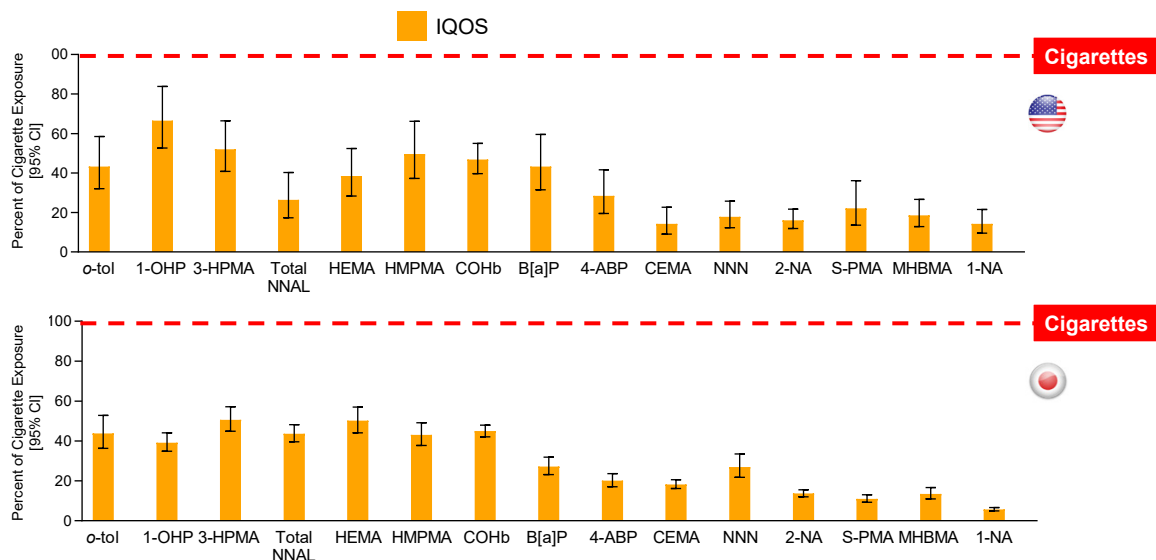
CC-41

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

CC-42

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

Switching to IQOS achieves almost 95% of the reduction achieved by smoking abstinence

CC-43

Demonstrated Reduced Exposure

CC-44
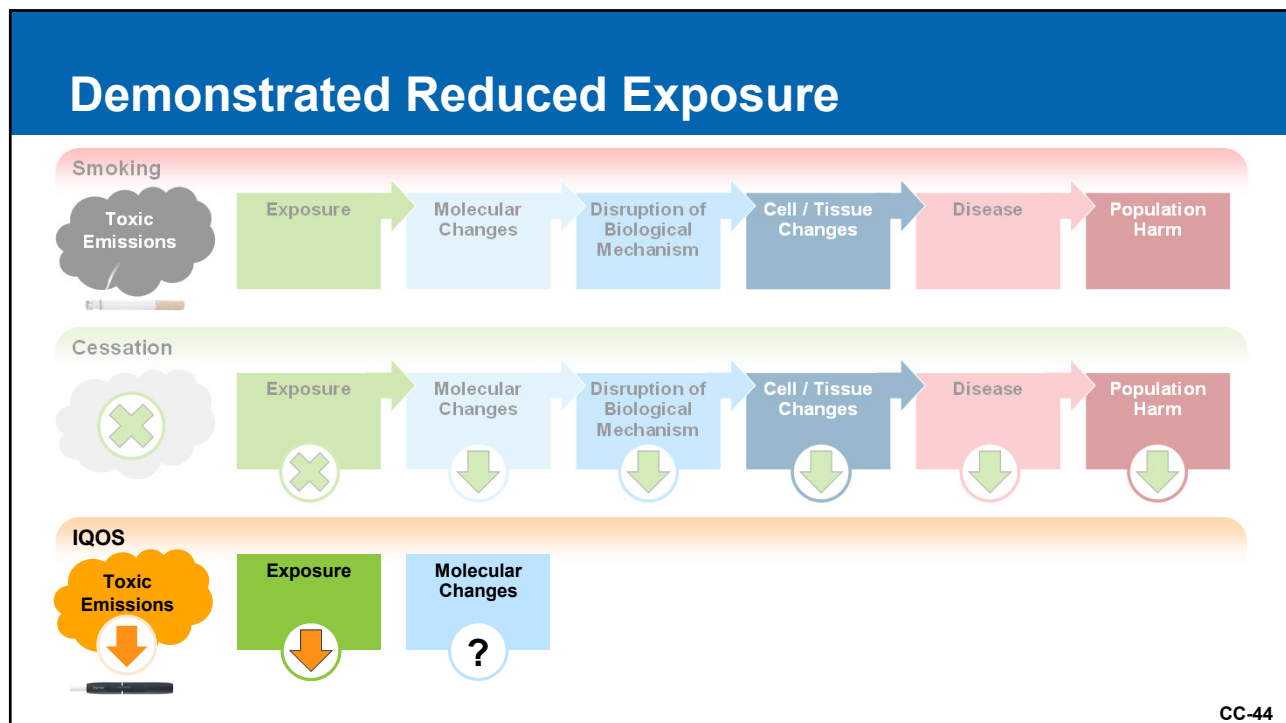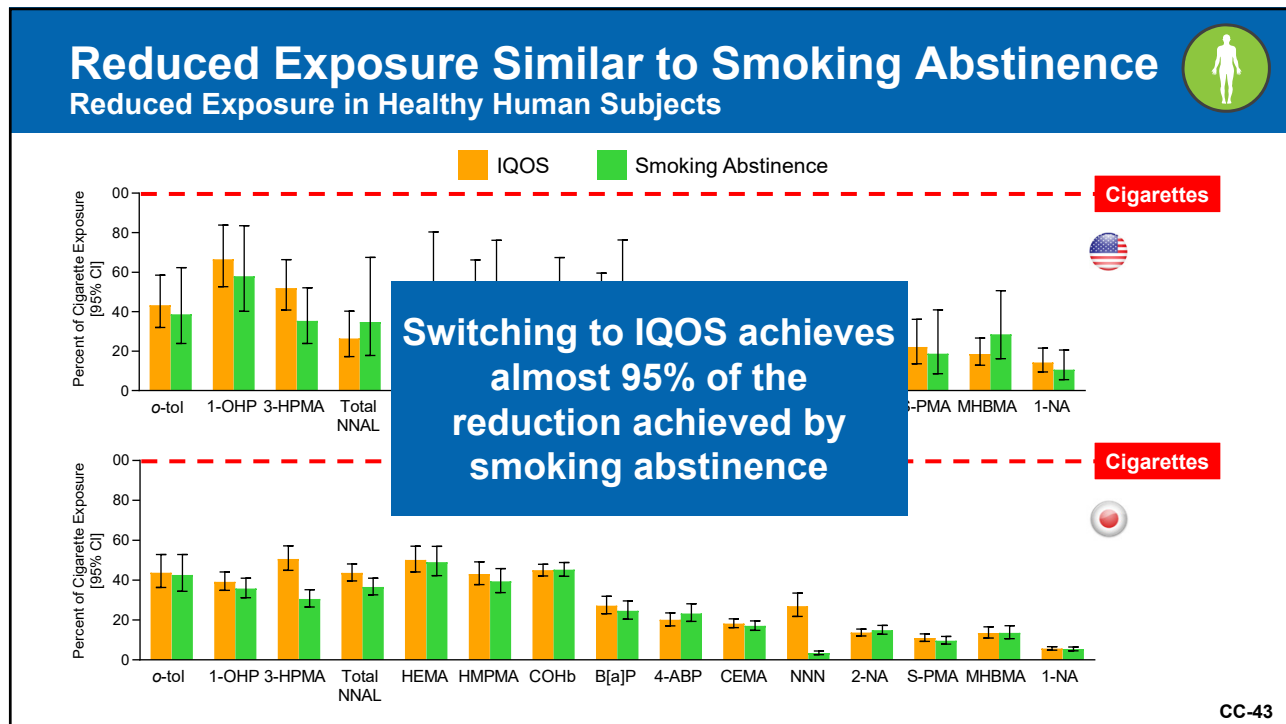
Switching Study in Apoe$^{-/-}$ Mouse Model

- 8 months duration (approximately 40% of lifetime)
- Concomitant analysis of CVD and COPD endpoints
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison

Group	Exposure		
Cigarette	3R4F		
IQOS Switching	3R4F	IQOS at equivalent nicotine concentration	
Cessation	3R4F	Fresh Air	
IQOS	IQOS at equivalent nicotine concentration		
Reference: Air	Fresh Air		

Start — Month 2 — Month 8
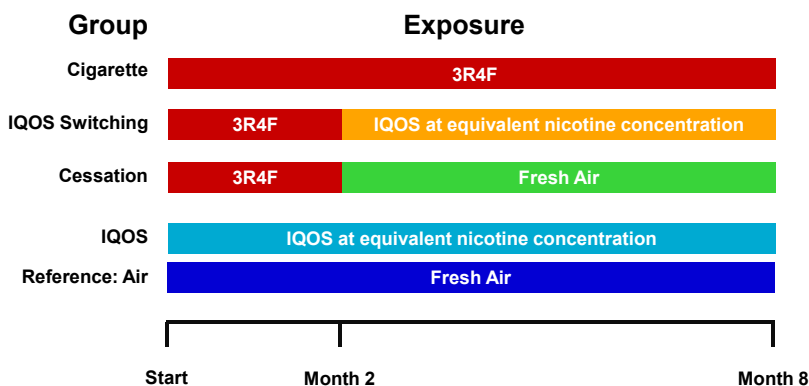
Use of animal model reviewed in: Lo Sasso *et al.* The Apoe$^{-/-}$ mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. *J. Transl. Med.,* 2016; 14:146.

CC-45

Reduced Molecular Changes in the Lung

Log2Ratio
-2 ———— 10

Reference Cigarette

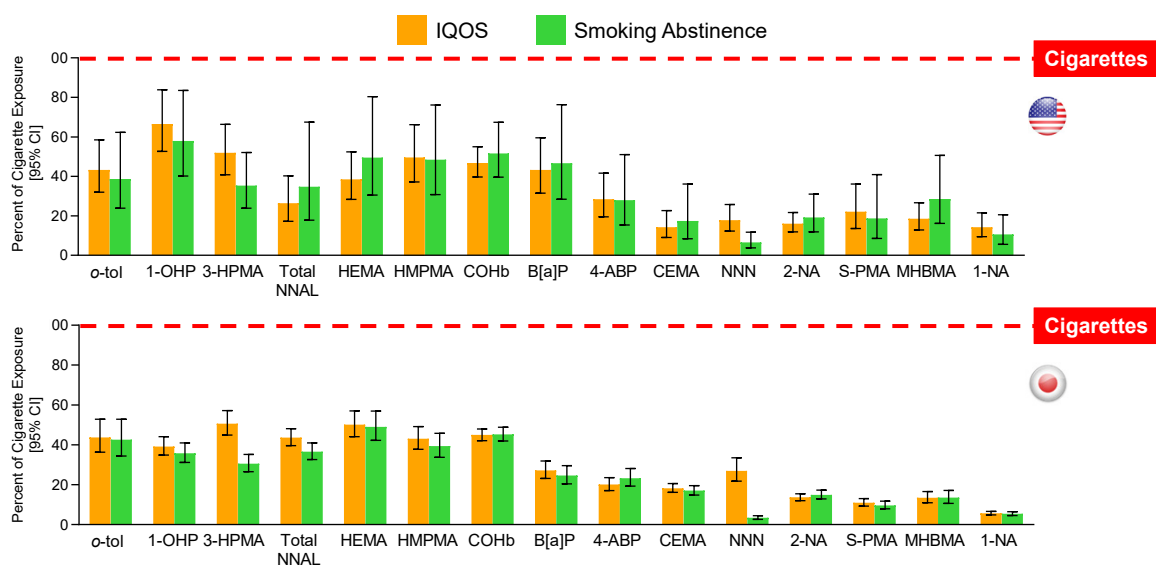| Time (months)	1	2	3	6	8
IgA	*	*		*	*
IL_1_alpha	*	*	*	*	*
IL_1_beta	*	*	*	*	*
IL_6	*	*	*	*	*
IL_7	*				
IL_10	*	*	*	*	*
IL_11	*	*			
IL_12p70		*			
IL_18	*	*	*	*	*
Insulin				*	*
IP_10	*	*	*		
KC_GRO	*	*	*	*	*
Leptin					
LIF	*	*	*	*	*
Lymphotactin	*	*	*	*	*
M_CSF_1	*	*	*	*	*
MCP_1	*	*	*	*	*
MCP_3	*	*	*	*	*
MCP_5	*	*	*	*	*
MDC	*	*	*	*	*
MIP_1_alpha	*	*	*	*	*
MIP_1_beta	*	*	*	*	*
MIP_1_gamma	*	*	*	*	*
MIP_2	*	*	*	*	*
MIP_2_beta	*	*	*	*	*
MMP_9	*	*	*	*	*
MPO	*	*	*	*	*

* p-value <0.05

Proteins in Bronchoalveolar Lavage Fluid

Reference Cigarette

Gene Expression in Lung Tissue at Month 8

Phillips *et al. Toxicological Sciences*, 2016;149:411-432.

CC-46

Reduced Molecular Changes in the Lung

Log2Ratio -2 ⟶ 10

Proteins in Bronchoalveolar Lavage Fluid — Gene Expression in Lung Tissue at Month 8

Time (months)	Ref. Cig. 1	Ref. Cig. 2	Ref. Cig. 3	Ref. Cig. 6	Ref. Cig. 8	IQOS Switch 3	IQOS Switch 6	IQOS Switch 8
IgA	*	*	*	*	*	*	*	*
IL_1_alpha	*	*	*	*	*	*		
IL_1_beta	*	*	*	*	*	*		
IL_6	*	*	*	*	*			
IL_7	*	*						
IL_10	*	*	*	*	*			
IL_11	*	*						
IL_12p70		*						
IL_18	*	*	*	*	*	*		
Insulin				*	*			
IP_10	*	*	*					
KC_GRO	*	*	*	*	*			
Leptin								
LIF	*	*	*	*	*	*		
Lymphotactin	*	*	*	*	*	*		
M_CSF_1	*	*	*	*	*	*		
MCP_1	*	*	*	*	*	*	*	
MCP_3	*	*	*	*	*	*		
MCP_5	*	*	*	*	*	*		
MDC	*	*	*	*	*	*		*
MIP_1_alpha	*	*	*	*	*	*		
MIP_1_beta	*	*	*	*	*	*		
MIP_1_gamma	*	*	*	*	*	*		*
MIP_2	*	*	*	*	*			
MIP_2_beta	*	*	*	*	*	*		*
MMP_9	*	*	*	*	*	*		
MPO	*	*	*	*	*	*	*	

* p-value <0.05

Reference Cigarette / IQOS Switch

Phillips *et al. Toxicological Sciences*, 2016;149:411-432. CC-47

Reduced Molecular Changes in the Lung

Log2Ratio -2 ⟶ 10

Proteins in Bronchoalveolar Lavage Fluid — Gene Expression in Lung Tissue at Month 8

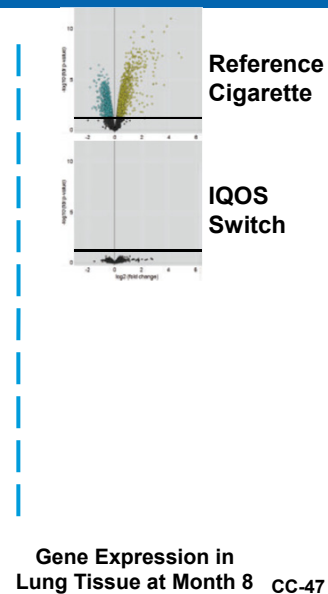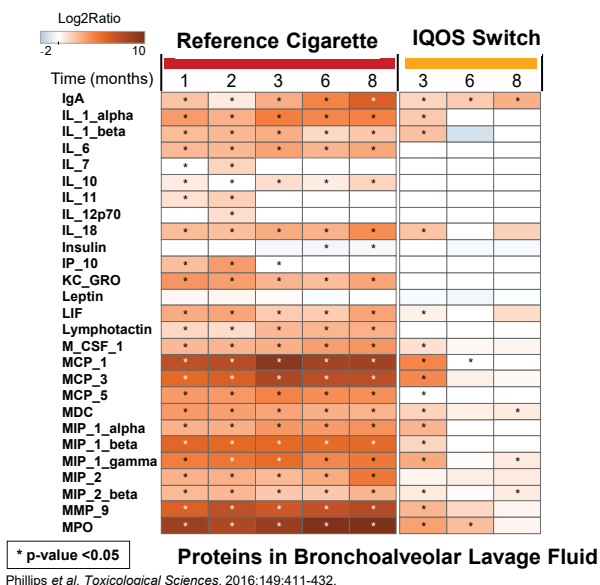| Time (months)	Ref. Cig. 1	Ref. Cig. 2	Ref. Cig. 3	Ref. Cig. 6	Ref. Cig. 8	IQOS Switch 3	IQOS Switch 6	IQOS Switch 8	Cessation 3	Cessation 6	Cessation 8
IgA	*	*	*	*	*	*	*	*	*	*	*
IL_1_alpha	*	*	*	*	*	*			*		
IL_1_beta	*	*	*	*	*	*			*		
IL_6	*	*	*	*	*						
IL_7	*	*									
IL_10	*	*	*	*	*						
IL_11	*	*									
IL_12p70		*									
IL_18	*	*	*	*	*	*			*		
Insulin				*	*						
IP_10	*	*	*								
KC_GRO	*	*	*	*	*						
Leptin											
LIF	*	*	*	*	*	*					*
Lymphotactin	*	*	*	*	*						
M_CSF_1	*	*	*	*	*	*			*		
MCP_1	*	*	*	*	*	*	*		*		
MCP_3	*	*	*	*	*	*			*	*	
MCP_5	*	*	*	*	*	*					
MDC	*	*	*	*	*	*		*	*		
MIP_1_alpha	*	*	*	*	*	*			*		
MIP_1_beta	*	*	*	*	*	*			*		
MIP_1_gamma	*	*	*	*	*	*		*	*		
MIP_2	*	*	*	*	*						
MIP_2_beta	*	*	*	*	*	*		*			
MMP_9	*	*	*	*	*	*			*	*	
MPO	*	*	*	*	*	*	*		*	*	

* p-value <0.05

Reference Cigarette / IQOS Switch / Cessation

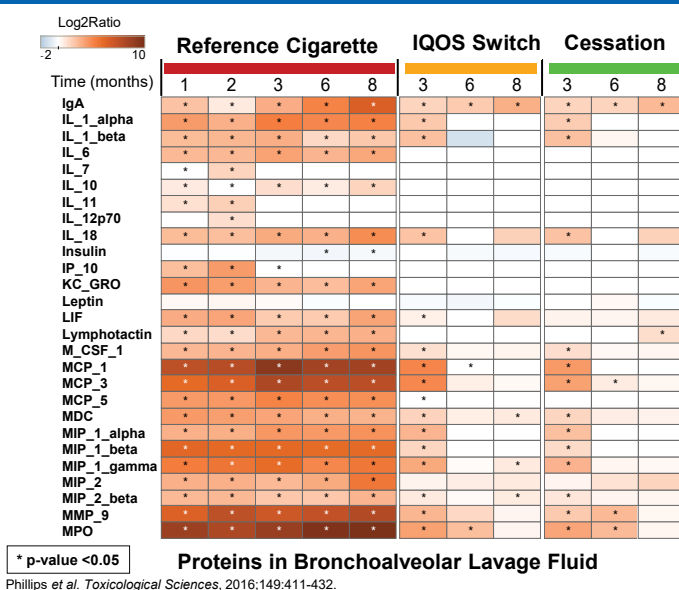Phillips *et al. Toxicological Sciences*, 2016;149:411-432. CC-48

Reduced Molecular Changes in the Lung

Time (months)	Reference Cigarette					IQOS Switch			Cessation			IQOS				
	1	2	3	6	8	3	6	8	3	6	8	1	2	3	6	8
IgA	*	*	*	*	*	*	*	*	*	*	*					
IL_1_alpha	*	*	*	*	*	*			*							
IL_1_beta	*	*	*	*	*	*			*							
IL_6	*	*	*	*	*											
IL_7	*	*														
IL_10	*	*	*	*	*											
IL_11	*	*														
IL_12p70		*														
IL_18	*	*	*	*	*	*			*							
Insulin				*	*								*			
IP_10	*	*	*													
KC_GRO	*	*	*	*	*											
Leptin																
LIF	*	*	*	*	*	*								*		
Lymphotactin	*	*	*	*	*						*					
M_CSF_1	*	*	*	*	*	*			*							
MCP_1	*	*	*	*	*	*	*		*							
MCP_3	*	*	*	*	*	*			*	*						
MCP_5	*	*	*	*	*	*										
MDC	*	*	*	*	*	*		*	*					*		
MIP_1_alpha	*	*	*	*	*	*			*							
MIP_1_beta	*	*	*	*	*	*			*							
MIP_1_gamma	*	*	*	*	*	*		*	*					*		
MIP_2	*	*	*	*	*									*		
MIP_2_beta	*	*	*	*	*	*		*	*					*		
MMP_9	*	*	*	*	*				*	*				*		
MPO	*	*	*	*	*	*	*		*	*						

Log2Ratio -2 ___ 10

* p-value <0.05

Proteins in Bronchoalveolar Lavage Fluid

Phillips *et al. Toxicological Sciences*, 2016;149:411-432.

Reference Cigarette

IQOS Switch

Cessation

IQOS

Gene Expression in Lung Tissue at Month 8 CC-49

Demonstrated Reduced Molecular Changes
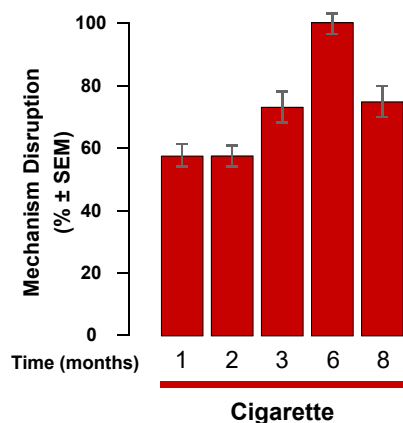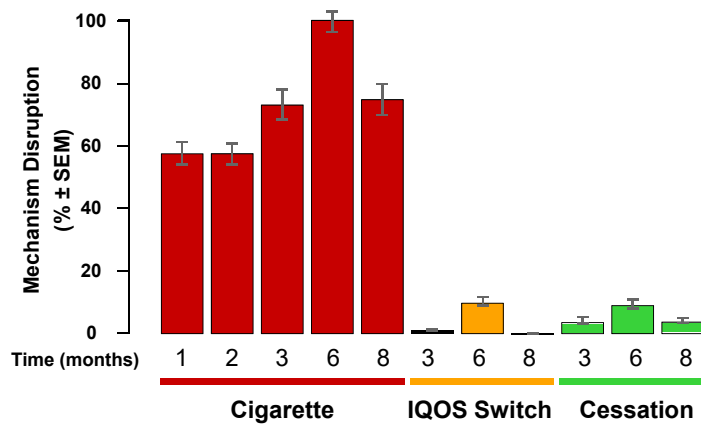
CC-50

1/24/2018

Reduced Effects on Disease Mechanisms

Lung Inflammation

CC-51

Reduced Effects on Disease Mechanisms

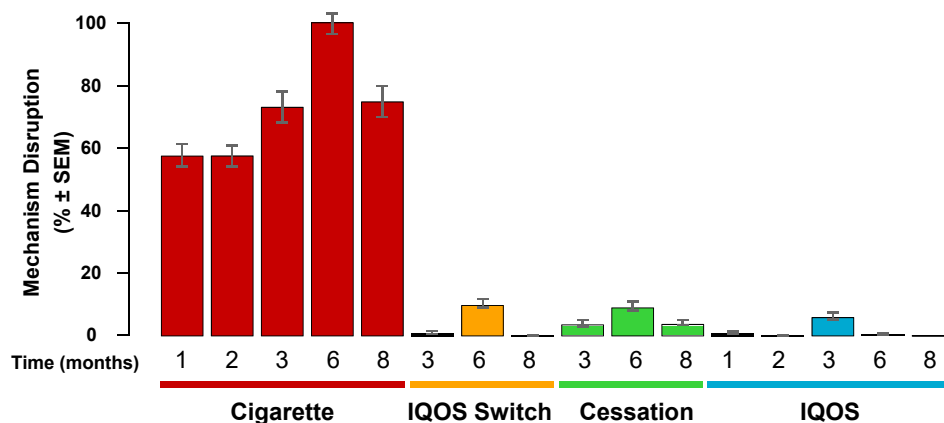## Lung Inflammation

CC-52

26

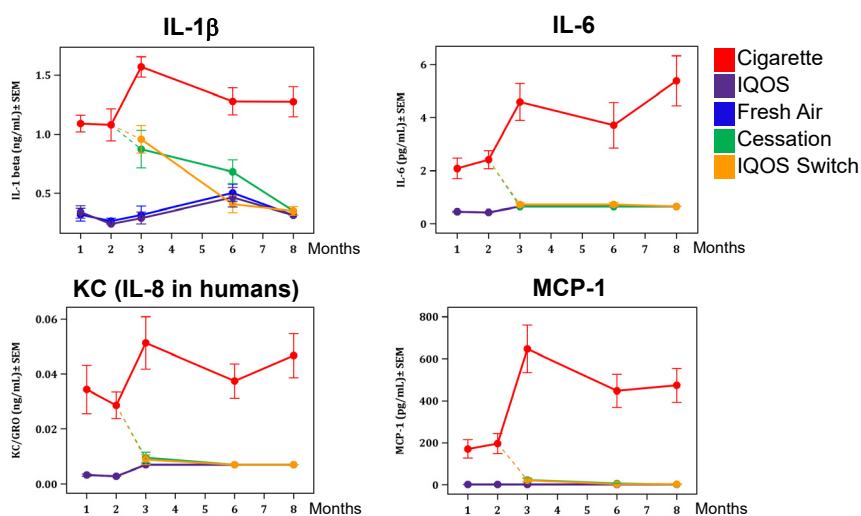# Reduced Effects on Disease Mechanisms
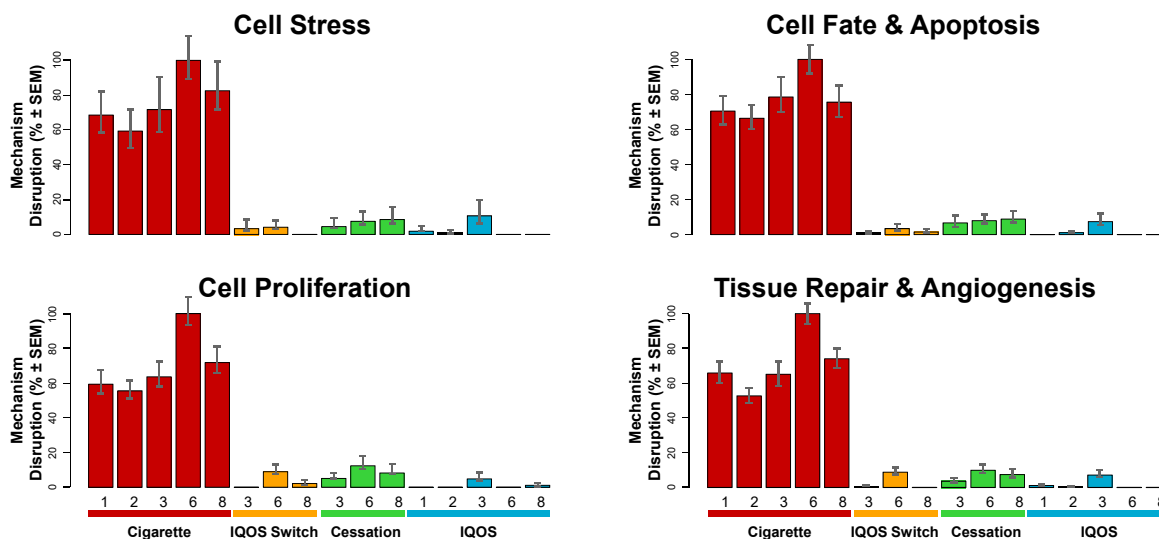
Lung Inflammation

CC-53

Specific Markers of Lung Inflammation

These changes in inflammation markers are all confirmed by the results from the A/J mouse dose response study at month 5.
Kuschner *et al.* Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. *Eur. Respir. J*, 1996; 9:1989–1994.

CC-54

Clinical Changes After 90 Days
Reduced Exposure in Healthy Human Subjects

Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to IQOS Effect at 3m [95%CI]
Lipid Metabolism	HDL-C	0.0 mg/dL [-5.77; 5.84]	↑	1.4 mg/dL [-2.3;5.0]
Inflammation	WBC	-0.94 10^9/L [-2.00; 0.13]	−	0.17 10^9/L [-0.47; 0.81]
Airway Impairment	FEV1	2.0 % pred [-3.37; 7.36]	↑	0.53 % pred [-2.79; 3.85]
Endothelial Dysfunction	sICAM-1	-9.9 % [-19.7;1.1]	↓	-10.6 % [-16.7; -4.0]
Oxidative Stress	8-epi-PGF2α	-8.5 % [-25.13; 11.8]	↓	-13.5 % [-23.6;-1.95]
Clotting	11-DTX-B2	-7.2 % [-37.7; 38.3]	↓	-3.6 % [-24.6; 23.3]

Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to IQOS Effect at 3m [95% CI]
Lipid Metabolism	HDL-C	6.4 mg/dL [2.5; 10.3]	↑	4.5 mg/dL [1.17, 7.88]
Inflammation	WBC	-0.41 10^9/L [-0.95; 0.14]	↓	-0.57 10^9/L [-1.04, -0.10]
Airway Impairment	FEV_1	1.94 % pred [-0.44; 4.31]	↑	1.91 % pred [-0.14, 3.97]
Endothelial Dysfunction	sICAM-1	-10.9 % [-17.8; -3.4]	↓	-8.7 % [-14.94;-2.05]
Oxidative Stress	8-epi-PGF$_{2α}$	-5.9 % [-17.1; 6.8]	↓	-12.7 % [-21.81;-2.55]
Clotting	11-DTX-B$_2$	-19.4 % [-30.1; -7.0]	↓	-8.98 % [-19.52, 2.94]

CC-57

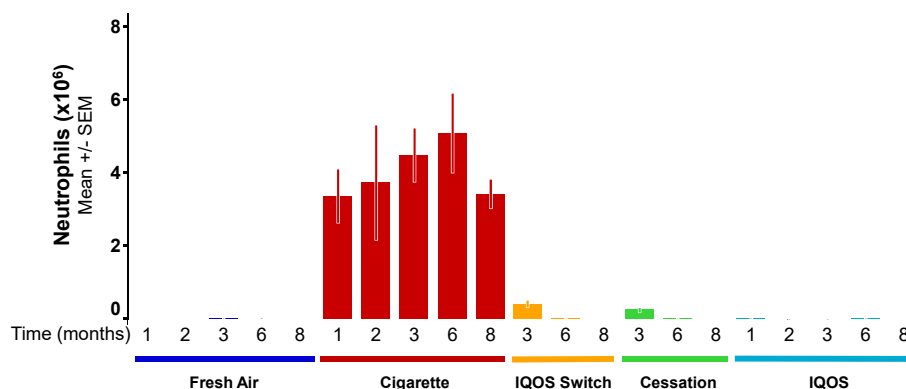# Demonstrated Reduced Disruption of Biological Mechanisms

CC-58

29
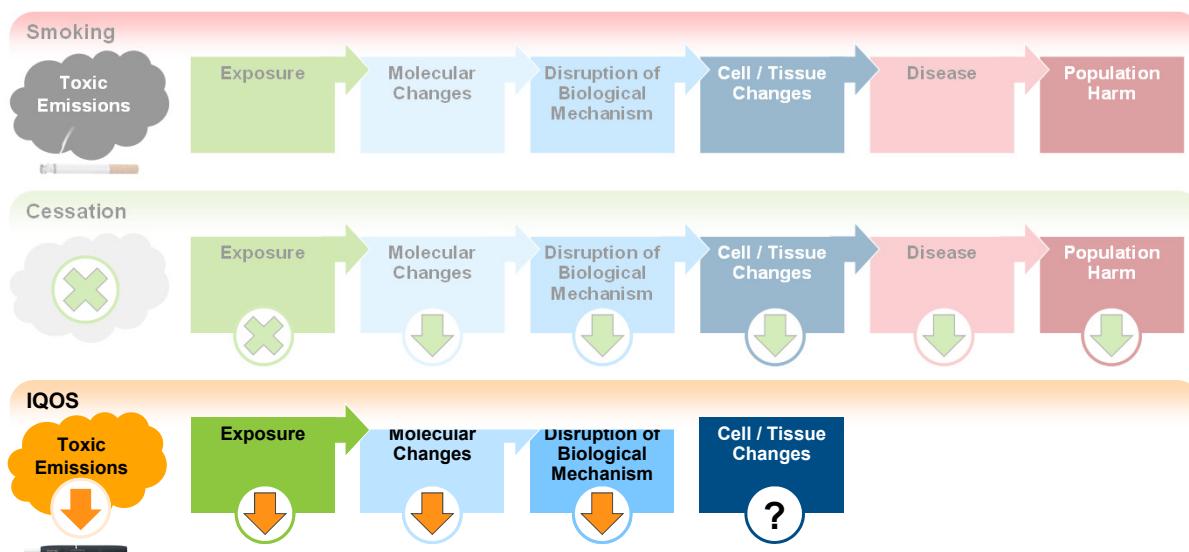
Reduces the Effects on Cells

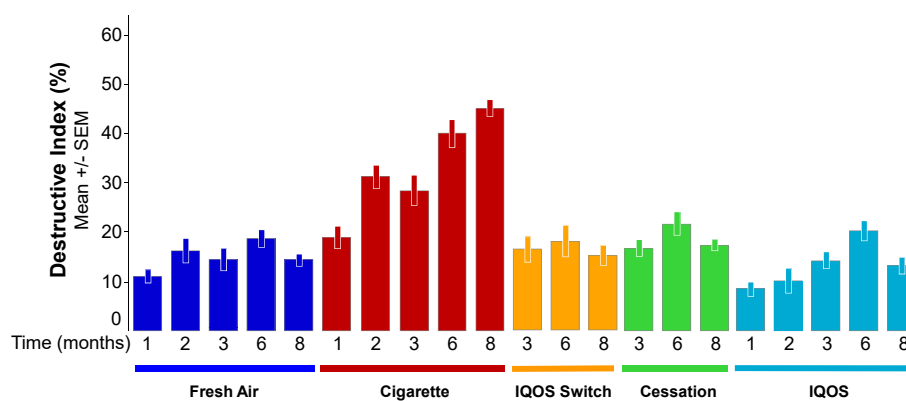**Inflammatory Lung Cells in Bronchoalveolar Lavage Fluid**

Phillips et al. *Toxicological Sciences*, 2016;149:411-432.
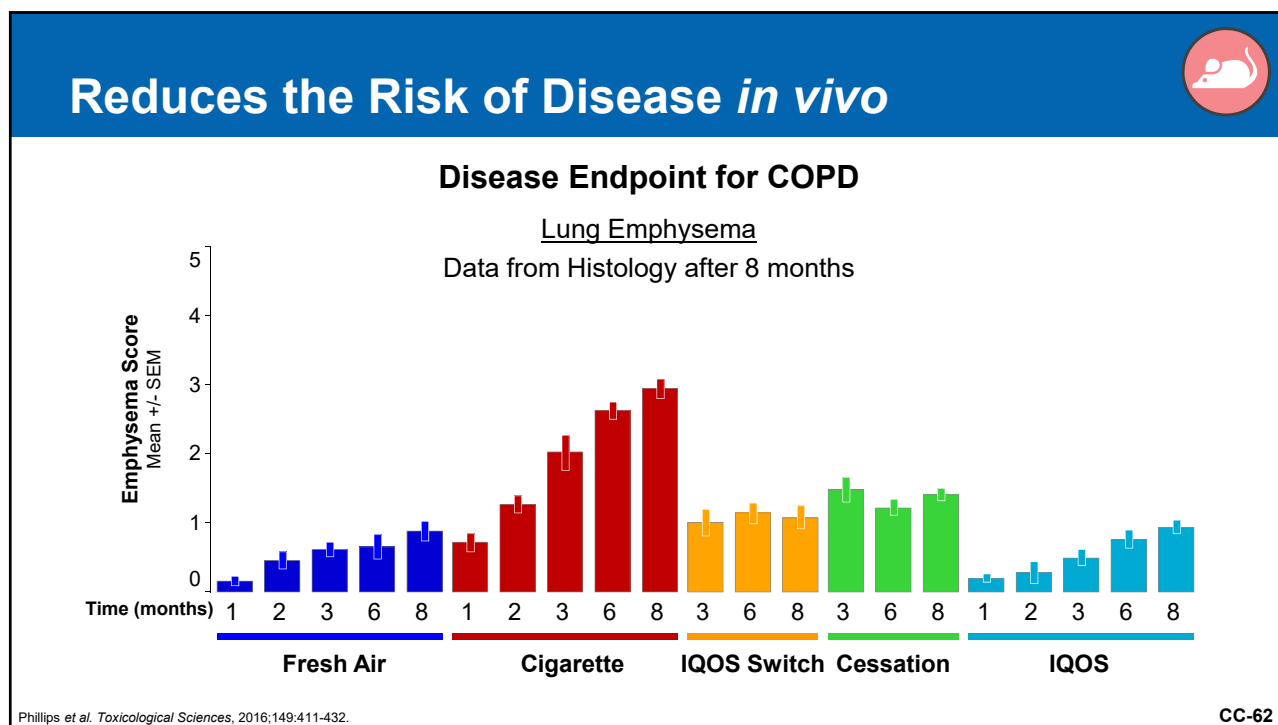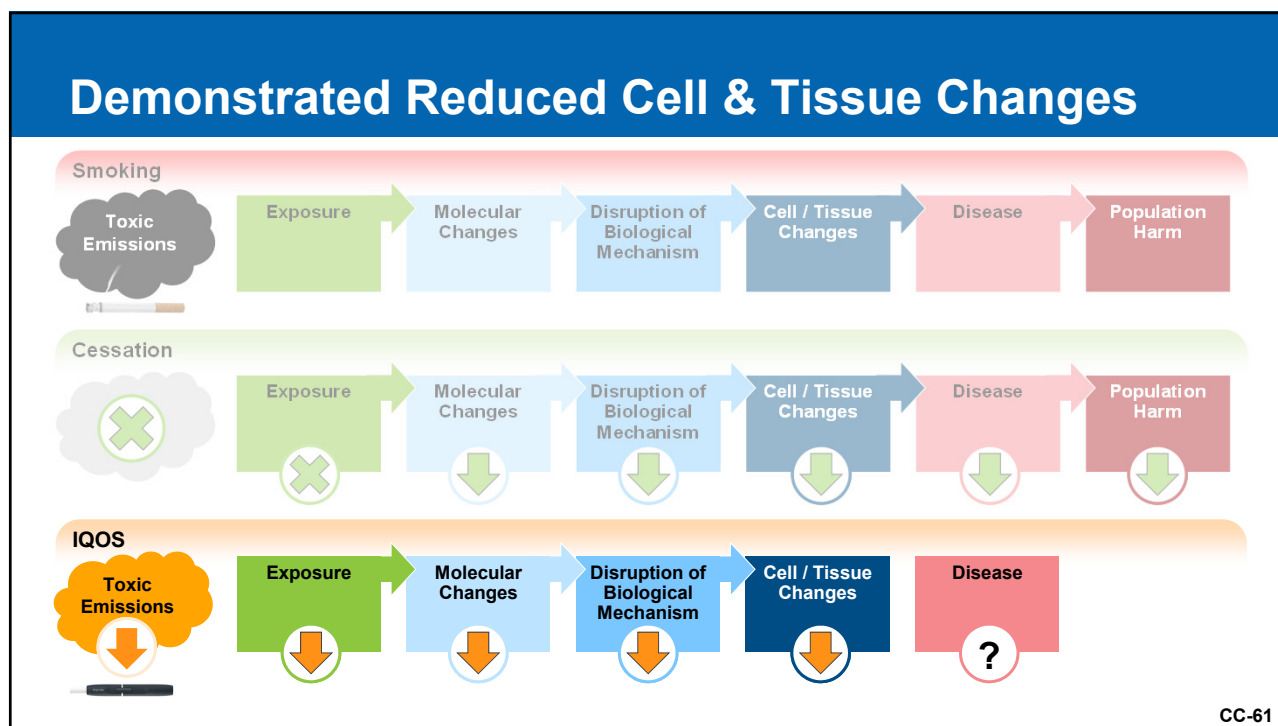
CC-59

Reduces the Effects on Tissues

Lung Tissue Destructive Index

Phillips et al. *Toxicological Sciences*, 2016;149:411-432.

CC-60

Demonstrated Reduced Cell & Tissue Changes

Smoking

Toxic Emissions

| Exposure | Molecular Changes | Disruption of Biological Mechanism | Cell / Tissue Changes | Disease | Population Harm |

Cessation

| Exposure | Molecular Changes | Disruption of Biological Mechanism | Cell / Tissue Changes | Disease | Population Harm |

IQOS

Toxic Emissions

| Exposure | Molecular Changes | Disruption of Biological Mechanism | Cell / Tissue Changes | Disease ? |

CC-61

Reduces the Risk of Disease *in vivo*

Disease Endpoint for COPD

Lung Emphysema
Data from Histology after 8 months

Emphysema Score Mean +/- SEM

Time (months): 1 2 3 6 8 | 1 2 3 6 8 | 3 6 8 | 3 6 8 | 1 2 3 6 8

Fresh Air | **Cigarette** | **IQOS Switch** | **Cessation** | **IQOS**

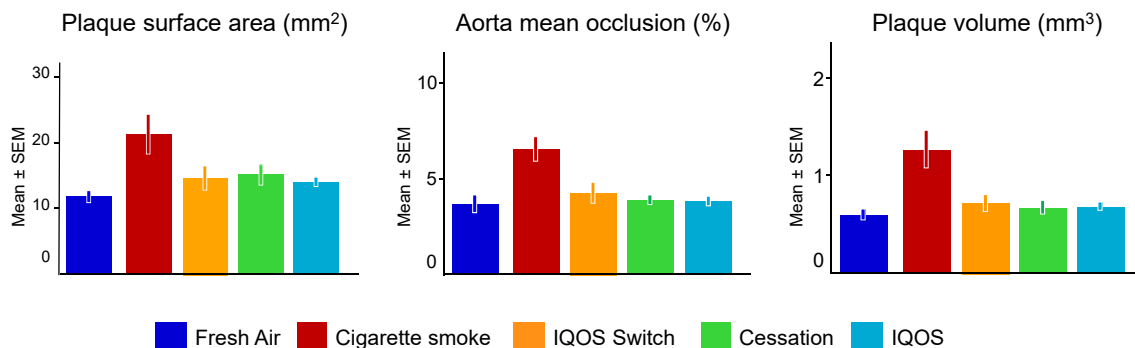Phillips *et al. Toxicological Sciences*, 2016;149:411-432.

CC-62

Reduces the Risk of Disease *in vivo*

Disease Endpoint for CVD

Atherosclerotic Plaque in the Aortic Arch

Data from µCT at month 7

Plaque surface area (mm^2)   Aorta mean occlusion (%)   Plaque volume (mm^3)

Mean ± SEM

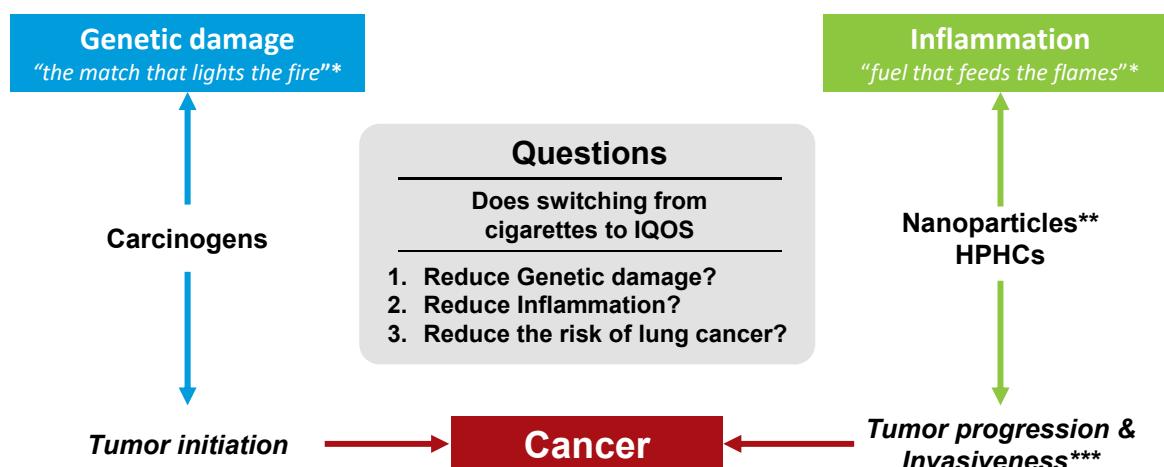■ Fresh Air ■ Cigarette smoke ■ IQOS Switch ■ Cessation ■ IQOS

Phillips *et al. Toxicological Sciences*, 2016;149:411-432.
Poussin *et al.* 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*, 2016; 339:73-86.

CC-63

How Cigarette Smoke Causes Cancer

Genetic damage
*"the match that lights the fire"**

Inflammation
*"fuel that feeds the flames"**

Carcinogens

Questions

Does switching from cigarettes to IQOS

1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

Nanoparticles**
HPHCs

Tumor initiation → **Cancer** ← *Tumor progression & Invasiveness****

* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357:539–45.
** You *et al.* Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623
*** Rothwell *et al.* Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; **377:**31–41.

CC-64

Genetic Damage is Reduced by IQOS

Does Switching to IQOS Reduce Genetic damage?

Evidence from IQOS Assessment

Genetic damage
*"the match that lights the fire"**

↑↓

Carcinogens

↑↓

Tumor initiation

Reduced Emission of Carcinogens

Reduced Exposure to Carcinogens

Reduced Genotoxicity

Reduced DNA Damage

Reduced Exposure Response

Reduced Genetic Damage

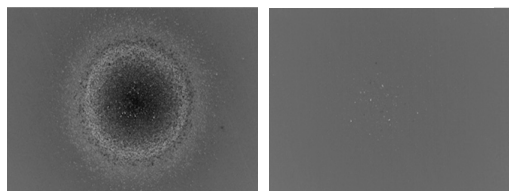* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357**:**539–45.

CC-65

Nanoparticles Deposit in the Lung

Cigarette Smoke

Carbon-based nanoparticles 6×10^{11} particles $\sim= 0.7$ mg*

IQOS Aerosol

No solid particles

Lung Deposition after 6 months

Cigarette smoke (600 mg/m^3 TPM)

Corresponding concentration of IQOS aerosol

Apoe-/- mice exposed for 6 months, 3h/day and 5days/week.
You et al. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623

CC-66

33

Inflammatory Markers in Smokers' Lungs

Table 2. – Mean bronchoalveolar lavage (BAL) cell concentrations in smokers and nonsmokers

Cell type	BAL concentration $\times 10^3$ cells·mL^{-1}		F statistic	p-value
	Smokers (n=14)	Nonsmokers (n=16)		
Macrophage	524±219	220±98	25.1	0.0001
Neutrophil	12.9±13.3	2.1±1.6	10.6	0.003
Lymphocyte	7.3±7.5	14.8±17.7	2.2	1.15
Eosinophil	0.9±1.7	1.1±1.3	0.1	0.75
Epithelial	1.5±1.4	2.1±2.1	1.0	0.33

Values are presented as mean±SD. Statistics quoted are by discriminant analysis. Overall model Hotelling's statistic = 1.7; p=0.0001. Critical Bonferoni alpha (n tests=5) = 0.01.

Table 3. – Bronchoalveolar lavage (BAL) supernatant cytokine and total protein (TP) concentration differences between smokers and nonsmokers

BAL constituent	Smokers (n=14)	Nonsmokers (n=16)	F statistic	p-value
IL-1β pg·mL^{-1}	1.2±0.7	0.5±0.4	14.3	0.0007
IL-6 pg·mL^{-1}	5.3±3.2	1.9±1.0	17.3	0.0003
IL-8 pg·mL^{-1}	32.8±15.9	18.2±11.5	8.4	0.007
TNF-α pg·mL^{-1}	2.5±7.9	0.2±0.2	1.4	0.25
MCP-1 pg·mL^{-1}	36.7±28.3	13.0±7.7	10.4	0.003
TP µg·mL^{-1}	75.8±27.7	87.2±56.5	0.4	0.50

Values are presented as mean±SD. IL-1β: Interleukin-1β (nondetectable in one nonsmoker); IL-6: interleukin-6 (detected in all subjects); IL-8: interleukin-8 (detected in all subjects); TNF-α: tumour necrosis factor-α (detectable in seven nonsmokers and two smokers); MCP-1: macrophage chemoattractant protein-1 (nondetectable in one nonsmoker and three smokers). Statistics quoted are by discriminant analysis. Overall model Hotelling's statistic=1.34; p<0.002. Critical Bonferoni alpha value (n tests=6) = 0.008.

Kuschner *et al.* Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. *Eur. Respir. J*, 1996; 9:1989–1994.
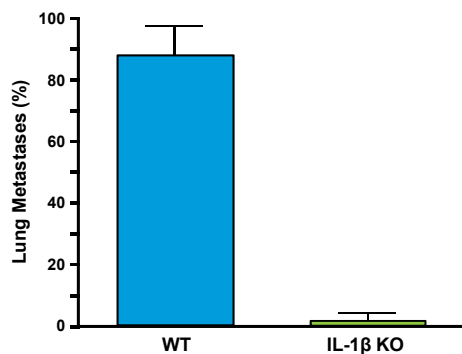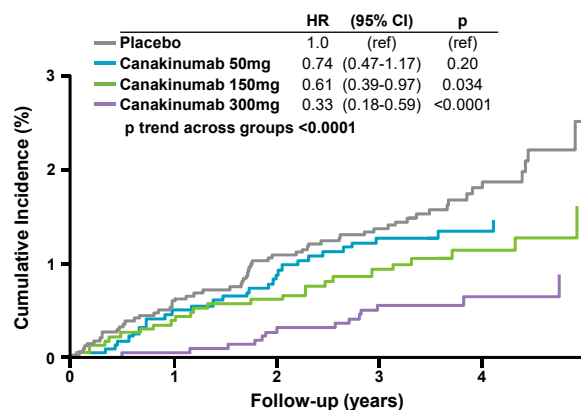
CC-67

Inflammation and Cancer
The Role of Interleukin-1β in Cancer

Animal Studies*
Lung Metastases (%)

Human Study (CANTOS)**
Lung Cancer Cumulative Incidence (%)

	HR	(95% CI)	p
Placebo	1.0	(ref)	(ref)
Canakinumab 50mg	0.74	(0.47-1.17)	0.20
Canakinumab 150mg	0.61	(0.39-0.97)	0.034
Canakinumab 300mg	0.33	(0.18-0.59)	<0.0001

p trend across groups <0.0001

*   Voronov *et al*. IL-1 is required for tumor invasiveness and angiogenesis. *PNAS* 2002; 100:2645-2650.
** Ridker *et al*. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis. *Lancet* 2017; 390:1833-1842.
Krelin *et al*. Interleukin-1β–Driven Inflammation Promotes the Development and Invasiveness of Chemical Carcinogen–Induced Tumors. *Cancer Res*. 2007: 67:1062-1071.
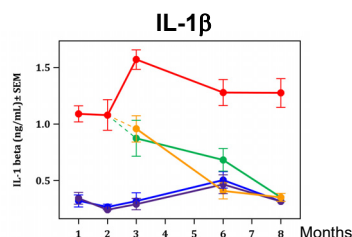
CC-68

Inflammation is Reduced by IQOS

Evidence from IQOS Assessment

Does Switching to IQOS Reduce Inflammation?
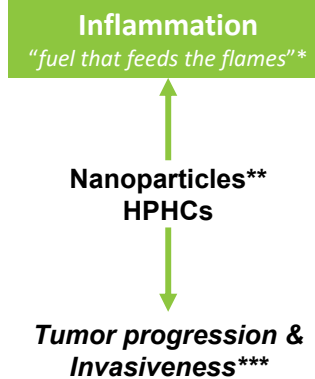
Reduced Emission of HPHCs and No carbon-based nanoparticles

Reduced Exposure to HPHCs

No Exposure to nanoparticles

Reduced Lung Inflammation

IL-1β

Reduced Inflammation

Inflammation
"fuel that feeds the flames"*

Nanoparticles** HPHCs

Tumor progression & Invasiveness***

IL-1 beta (ng/mL)± SEM
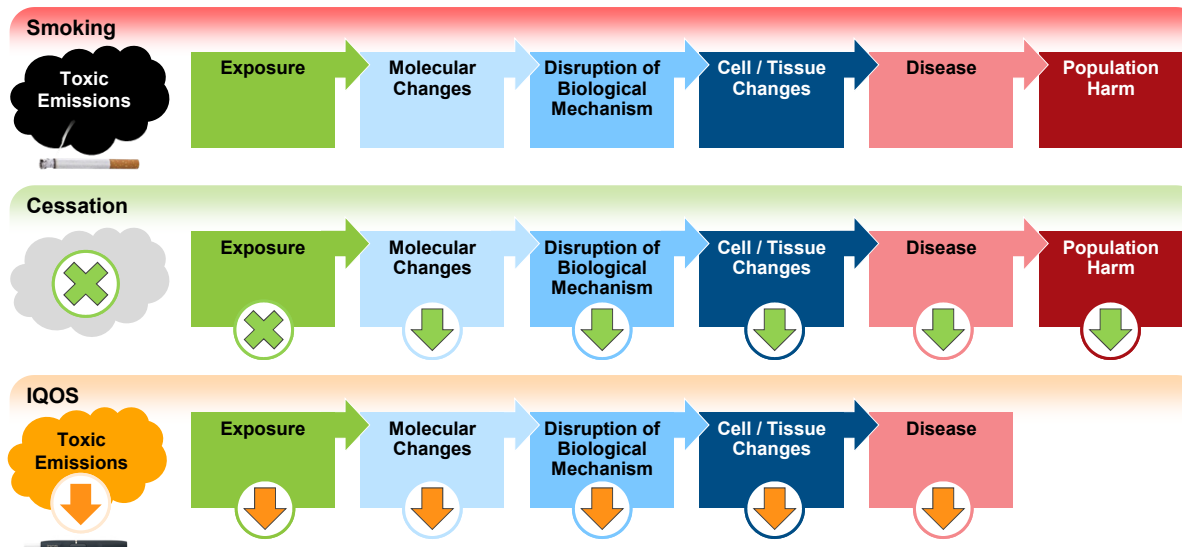
1 2 3 4 5 6 7 8 Months

* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357**:**539–45.
** You *et al*. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623
*** Rothwell *et al*. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; **377:**31–41.

CC-69

Demonstrated Reduced Disease

Smoking

Toxic Emissions

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Cessation

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

IQOS

Toxic Emissions

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease

CC-70

35

Summary of Totality of Evidence

IQOS

Toxic Emissions	Exposure	Molecular Changes	Disruption of Biological Mechanism	Cell / Tissue Changes	Disease
90-95% less Toxicants	90-95 % of Abstinence	90-95% of Cessation	90-95% of Cessation	90-95% of Cessation	90-95% of Cessation
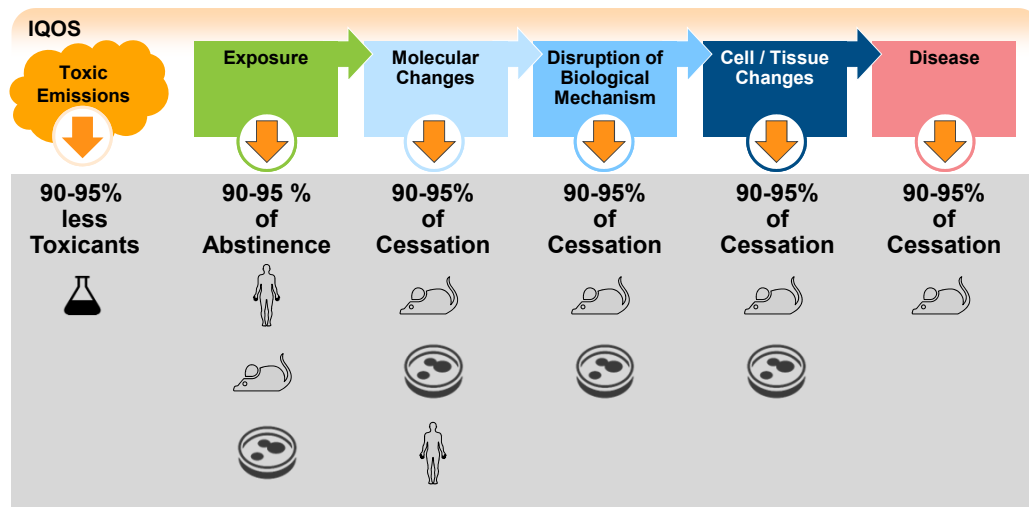
CC-71

Demonstrate a Benefit to the Health of the Population as a Whole …

Toxic Emissions	Exposure	Molecular Changes	Disruption of Biological Mechanism	Cell / Tissue Changes	Disease	Population Harm
						?
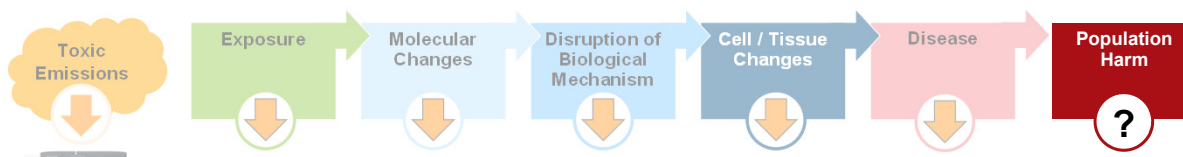
CC-72

Consumer Perception and Behavior

Antonio Ramazzotti

Vice President Human Insights and Behavioral Research
Philip Morris International

CC-73

911(g)(1) Modified Risk Products

…the applicant has demonstrated that such product, as it is actually used by consumers, will—
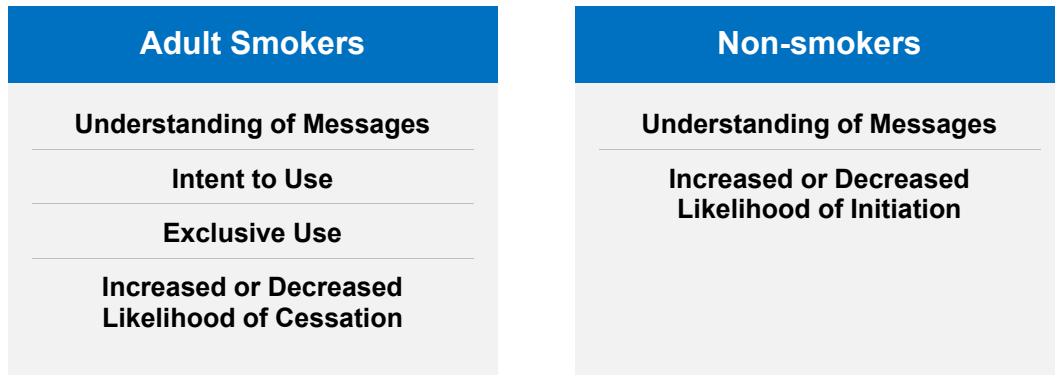
A — Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B — Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

CC-74

Who Will Use IQOS and to What Degree?

Adult Smokers	Non-smokers
Understanding of Messages	**Understanding of Messages**
Intent to Use	**Increased or Decreased Likelihood of Initiation**
Exclusive Use	
Increased or Decreased Likelihood of Cessation	

CC-75

PBA Studies to Develop and Assess IQOS Messages

6
qualitative and quantitative studies to develop and assess IQOS communications

Phase 1
Developing the most appropriate product messages

- Comprehension
- Intent to Use
- Risk Perception

3 Studies

Phase 2
Assessing Labeling and Advertising

- Comprehension
- Intent to Use
- Risk Perception
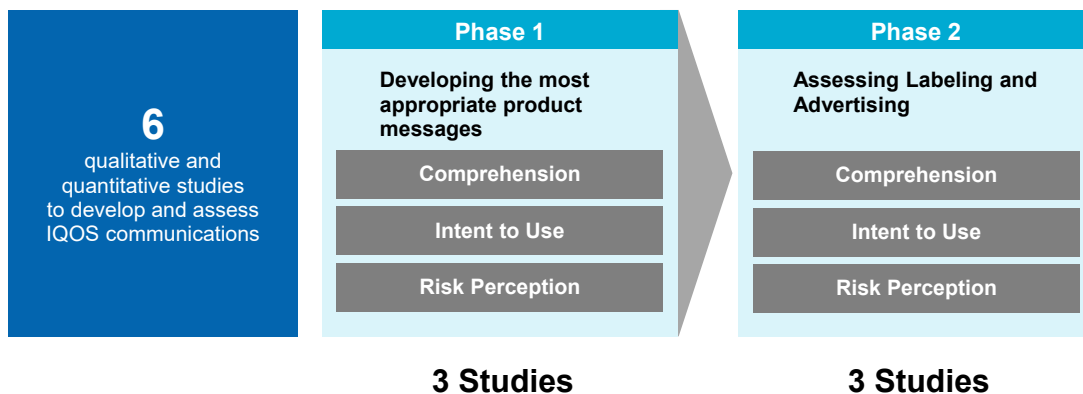
3 Studies

CC-76

Product Messages (On a Tested Pack)

AVAILABLE EVIDENCE TO DATE:
Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

SURGEON GENERAL'S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

1. Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

2. Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

3. Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.
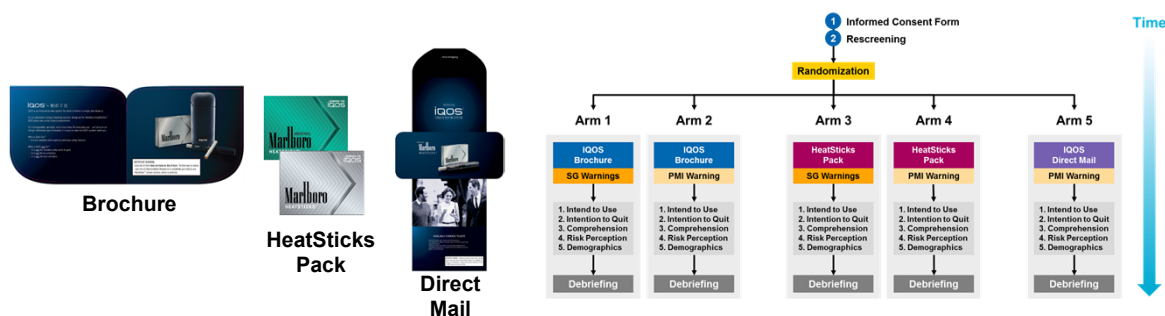
CC-77

Study Design
IQOS Communication Studies

Five arms, experimental studies, describing responses to materials on comprehension, intent to use, change in intention to quit and risk perception

≈ 2,200 enrolled participants in each study
- Five subject groups: adult smokers with and without intention to quit, adult former smokers, adult never smokers and LA-25 Adult Never Smokers
- Sample was balanced, by subject group, sex, age group and city

Conducted in 4 US cities

Brochure

HeatSticks Pack

Direct Mail

1. Informed Consent Form
2. Rescreening

Randomization

Time

Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
IQOS Brochure	IQOS Brochure	HeatSticks Pack	HeatSticks Pack	IQOS Direct Mail
SG Warnings	PMI Warning	SG Warnings	PMI Warning	PMI Warning
1. Intend to Use 2. Intention to Quit 3. Comprehension 4. Risk Perception 5. Demographics	1. Intend to Use 2. Intention to Quit 3. Comprehension 4. Risk Perception 5. Demographics	1. Intend to Use 2. Intention to Quit 3. Comprehension 4. Risk Perception 5. Demographics	1. Intend to Use 2. Intention to Quit 3. Comprehension 4. Risk Perception 5. Demographics	1. Intend to Use 2. Intention to Quit 3. Comprehension 4. Risk Perception 5. Demographics
Debriefing	Debriefing	Debriefing	Debriefing	Debriefing

CC-78

Tested Product Message
Reduced Risk of Harm

HeatSticks Pack *with SG's Warnings*		HeatSticks Pack *with PMI Warning*

AVAILABLE EVIDENCE TO DATE:
Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

SURGEON GENERAL'S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

AVAILABLE EVIDENCE TO DATE:
Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

IMPORTANT WARNING:
· Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
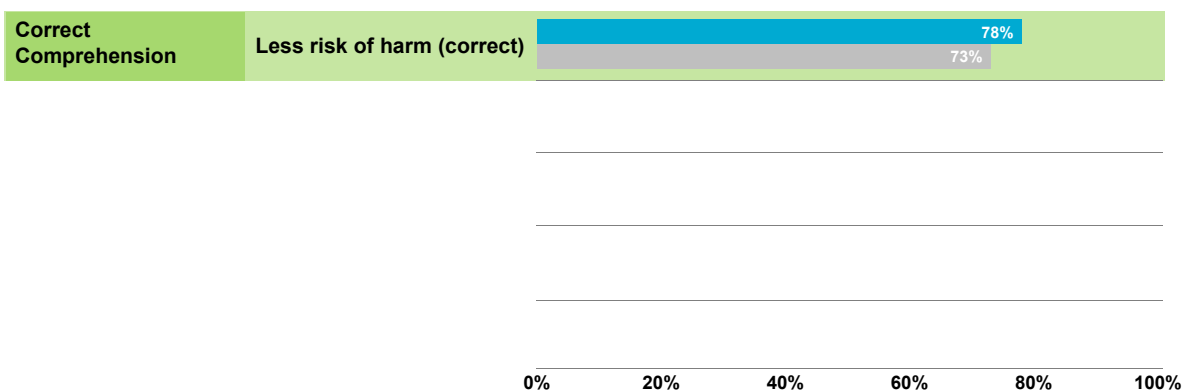· HeatSticks™ contain nicotine, which is addictive.

CC-79

The Majority Understood that IQOS Presents Less Risk of Harm, but is Not Risk Free

IQOS Communication Study - Reduced Risk of Harm

■ **HeatSticks Pack PMI Warning n=380**   ■ **HeatSticks Pack SG's Warnings n=376**

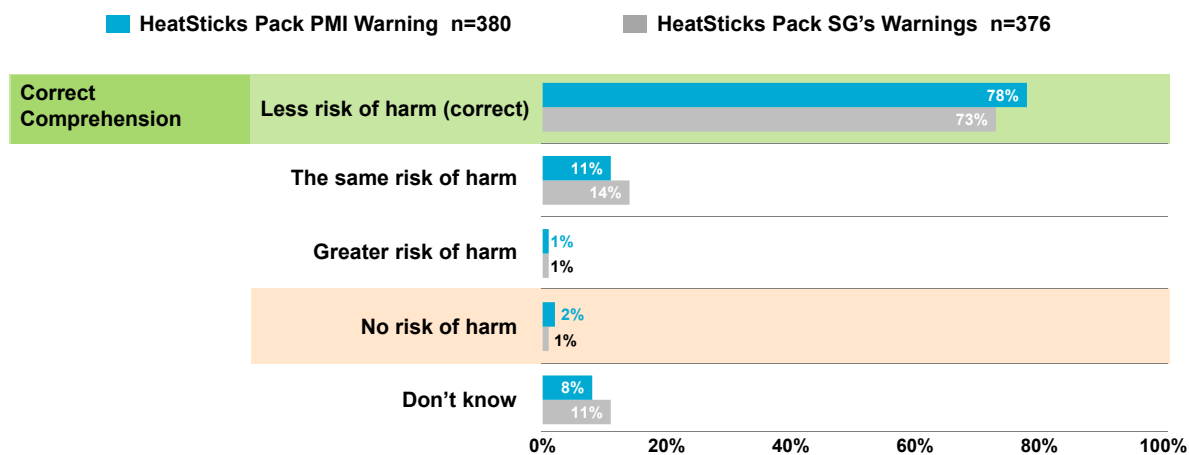| Correct Comprehension	Less risk of harm (correct)	
	78%	
	73%	

0%   20%   40%   60%   80%   100%

THS-PBA-05-RRC2-US

CC-80

Only 1% and 2% Misunderstood that IQOS Presents "No Risk of Harm"
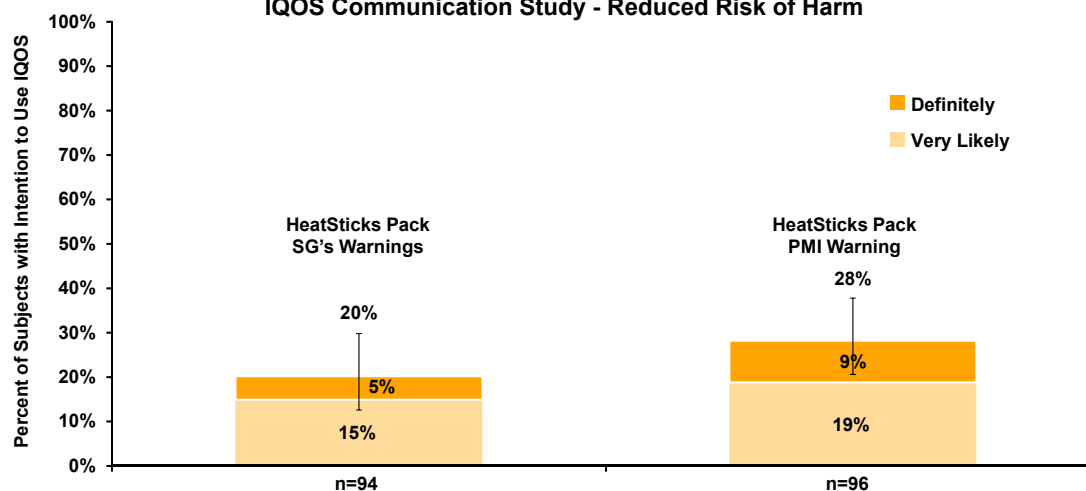
IQOS Communication Study - Reduced Risk of Harm

■ HeatSticks Pack PMI Warning n=380   ■ HeatSticks Pack SG's Warnings n=376

Correct Comprehension	Less risk of harm (correct)	78% / 73%
The same risk of harm	11% / 14%
Greater risk of harm	1% / 1%
No risk of harm	2% / 1%
Don't know	8% / 11%

0% 20% 40% 60% 80% 100%

THS-PBA-05-RRC2-US

CC-81

Substantial Intention to Use IQOS Among Adult Smokers with No Intention to Quit

IQOS Communication Study - Reduced Risk of Harm

Percent of Subjects with Intention to Use IQOS

■ Definitely
■ Very Likely

HeatSticks Pack SG's Warnings — 20% (Definitely 5%, Very Likely 15%), n=94

HeatSticks Pack PMI Warning — 28% (Definitely 9%, Very Likely 19%), n=96

* Error bars show 95% confidence intervals for the 'very likely' and 'definitely' categories combined.
THS-PBA-05-RRC2-US
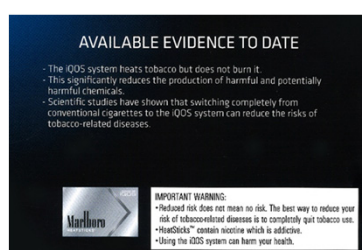
CC-82

41

Study Design
Actual Use Study

Single group, observational study, *ad libitum* use of IQOS and cigarettes, reported on a stick-by-stick basis
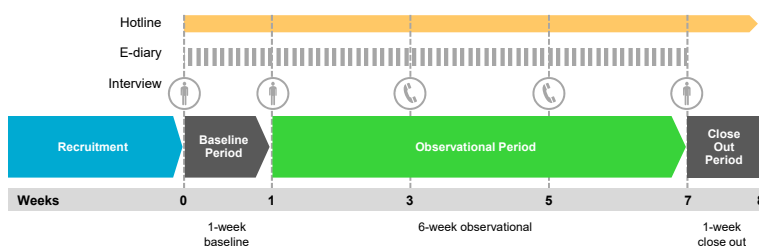
1,336 enrolled participants
Quota sampling approximating the distribution of US adult smokers population by sex, age, race and income (CDC, 2012)

Conducted in 8 US geographic areas

IQOS brochure shown to participants contained a reduced risk product message

AVAILABLE EVIDENCE TO DATE
- The iQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.

Marlboro

IMPORTANT WARNING:
- Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- HeatSticks™ contain nicotine which is addictive.
- Using the iQOS system can harm your health.

1-week baseline, 6-week observational and 1-week close out period

Hotline
E-diary
Interview

Recruitment | Baseline Period | Observational Period | Close Out Period

Weeks | 0 | 1 | 3 | 5 | 7 | 8
1-week baseline | 6-week observational | 1-week close out
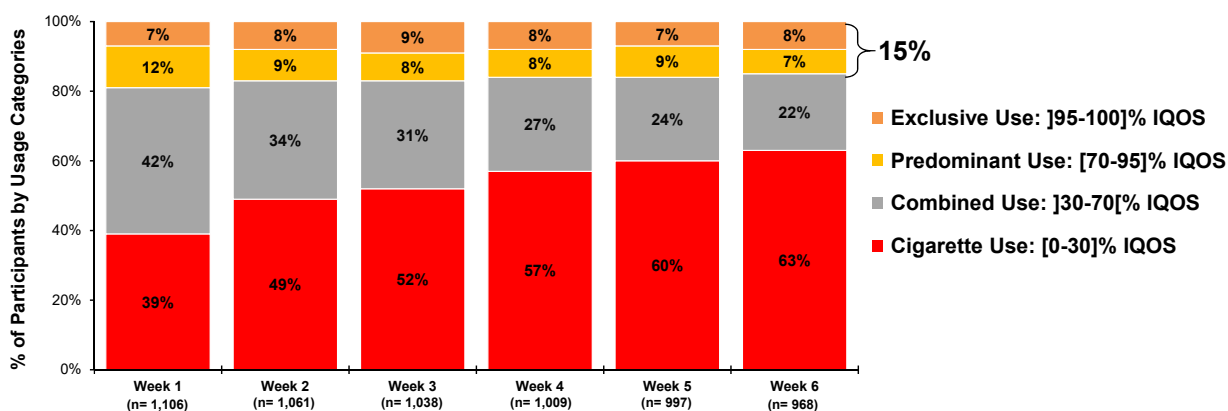
THS-PBA-07-US

CC-83

15% of U.S. Adult Daily Smokers Switched from Cigarettes to IQOS

IQOS and Cigarettes Use: Observational Period
Actual Use Study

% of Participants by Usage Categories

|	Week 1 (n= 1,106)	Week 2 (n= 1,061)	Week 3 (n= 1,038)	Week 4 (n= 1,009)	Week 5 (n= 997)	Week 6 (n= 968)
Exclusive Use:]95-100]% IQOS	7%	8%	9%	8%	7%	8%
Predominant Use: [70-95]% IQOS	12%	9%	8%	8%	9%	7%
Combined Use:]30-70[% IQOS	42%	34%	31%	27%	24%	22%
Cigarette Use: [0-30]% IQOS	39%	49%	52%	57%	60%	63%

15%

THS-PBA-07-US

CC-84

No Increase in IQOS and Cigarettes Consumption Between Baseline and Observational Period
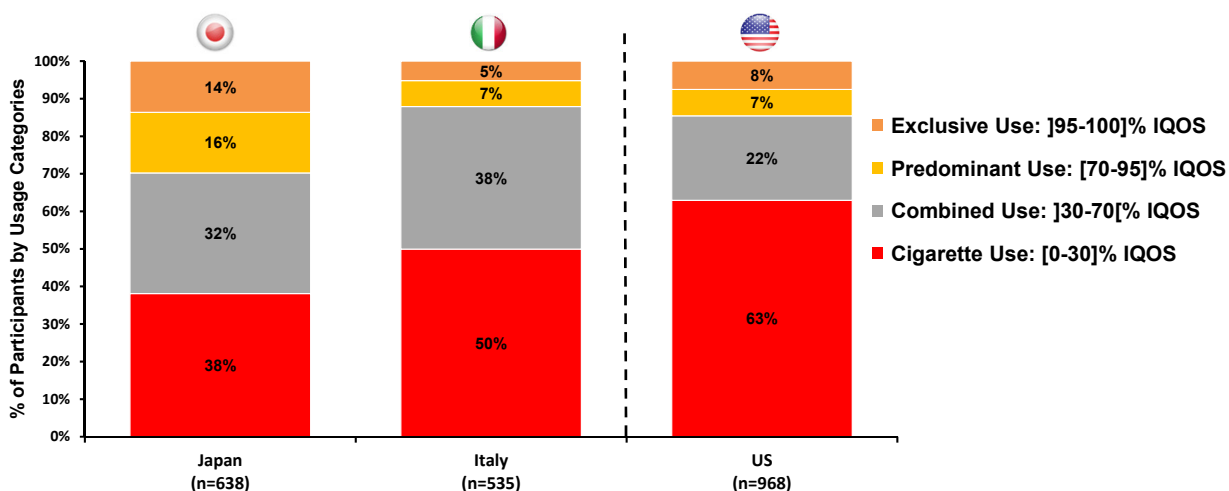
Actual Use Study: IQOS + Cigarette Consumption

Exclusive or Predominant IQOS Use
n=141

Combined IQOS Use
n=217
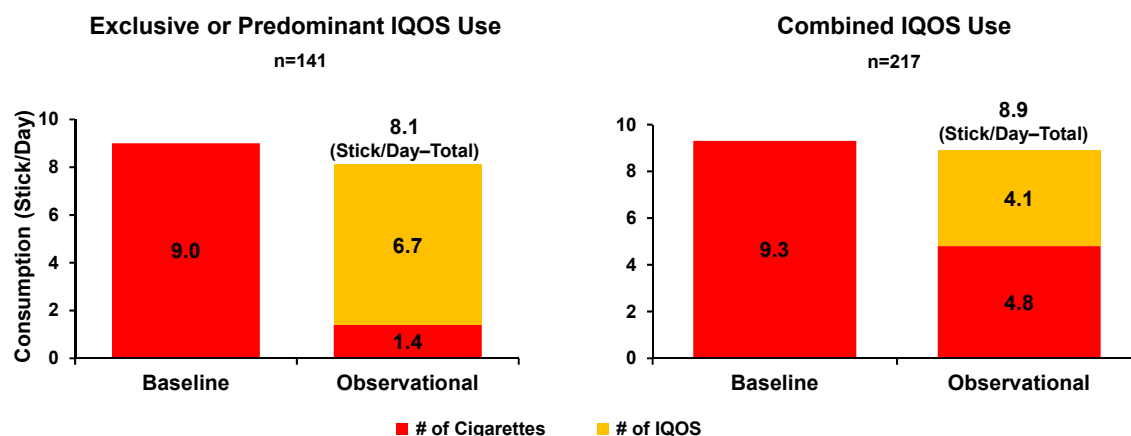
THS-PBA-07-US

CC-85

Between 12% and 30% of Participants Switched to IQOS

IQOS Usage Patterns

- Exclusive Use:]95-100]% IQOS
- Predominant Use: [70-95]% IQOS
- Combined Use:]30-70[% IQOS
- Cigarette Use: [0-30]% IQOS

WOT

CC-86

43

Post-market Data Show Exclusive Use is the Most Common Behavior Among IQOS Purchasers

% of Participants by Usage Categories

Japan (n=6,925)
- 72%
- 8%
- 9%
- 11%

Italy (n=4,197)
- 61%
- 13%
- 11%
- 15%

- Exclusive Use:]95-100]% IQOS
- Predominant Use: [70-95]% IQOS
- Combined Use:]30-70[% IQOS
- Cigarette Use: [0-30]% IQOS
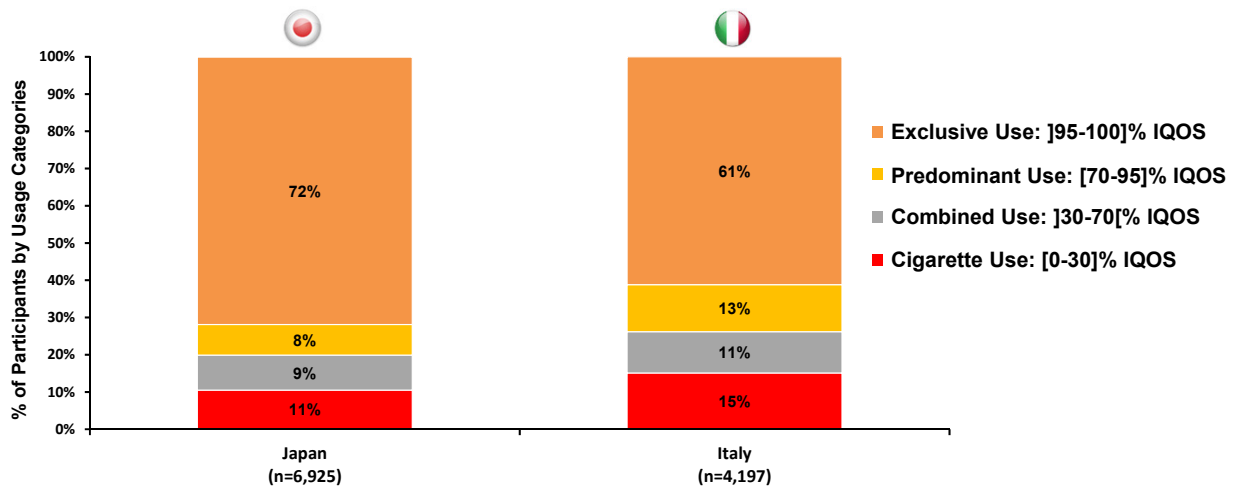
Consumer Panels, August 2017

CC-87

Increased Awareness and Repeated Communication Lead to Higher Switching Rates

Exclusive Use at Week 3 by Month of IQOS Purchase - Japan

% Exclusive Use: >95% IQOS

- Sept 2015: 35%
- Nov 2015: 49%
- Jan 2016: 56%
- Mar 2016: 61%

Month of IQOS Purchase

Source: Consumer Panel Japan, March 2016

CC-88

Who Will Use IQOS and to What Degree?

Adult Smokers
Understanding of Messages
Intent to Use
Exclusive Use
Increased or Decreased Likelihood of Cessation

Non-smokers
Understanding of Messages
Increased or Decreased Likelihood of Initiation

CC-89

Minimal Interference on Intention to Quit All Tobacco among Adult Smokers with the Intention to Quit
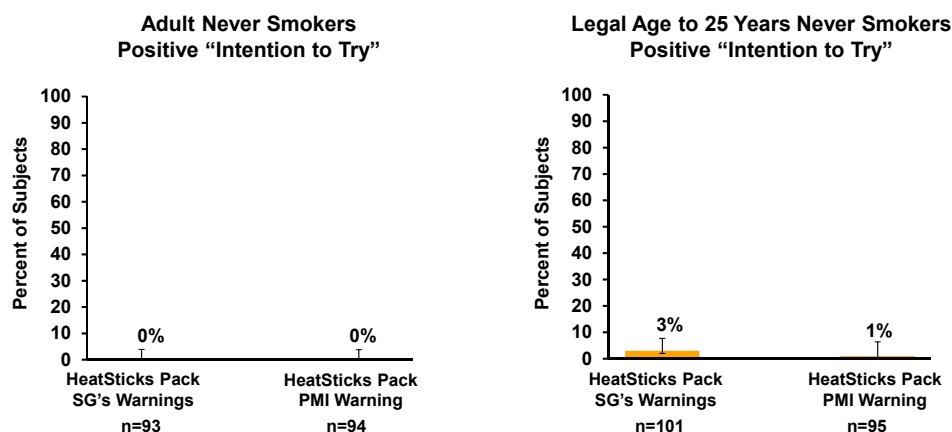
HeatSticks Pack SG's Warnings

HeatSticks Pack PMI Warning

Percent of Subjects with Intention to Quit All Tobacco

- Pre-Exposure n=96: 84%
- Post-Exposure n=96: 82%
- Pre-Exposure n=94: 87%
- Post-Exposure n=94: 90%
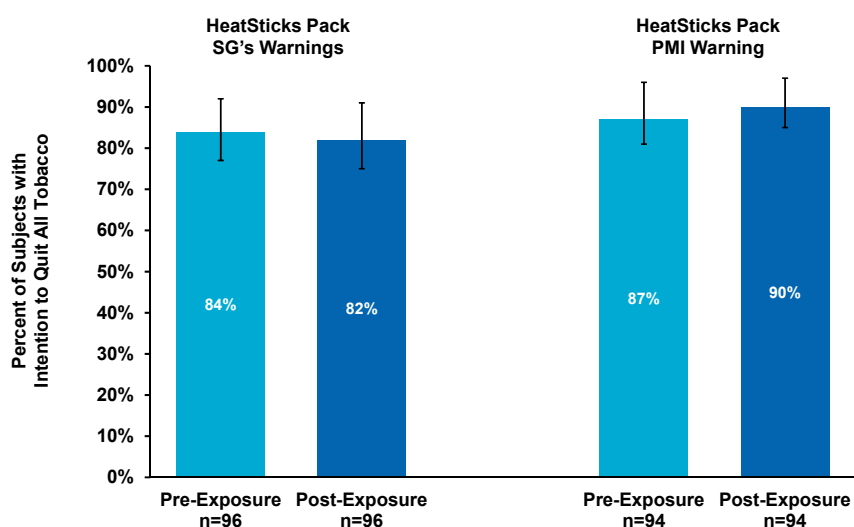
THS-PBA-05-RRC2-US

CC-90

Low Levels of Intent to Use Among Adult Never Smokers and LA-25 Never Smokers

IQOS Communication Study - Reduced Risk of Harm

Adult Never Smokers
Positive "Intention to Try"

Percent of Subjects

0%
HeatSticks Pack
SG's Warnings
n=93

0%
HeatSticks Pack
PMI Warning
n=94

Legal Age to 25 Years Never Smokers
Positive "Intention to Try"

Percent of Subjects

3%
HeatSticks Pack
SG's Warnings
n=101

1%
HeatSticks Pack
PMI Warning
n=95

Positive Intention to Try IQOS is the sum of *% Very Likely* and *% Definitely* responses
Error bars show 95% confidence intervals for the 'very likely' and 'definitely' categories combined
THS-PBA-05-RRC2-US

CC-91

Low Levels of Intent to Use Among Adult Former Smokers

IQOS Communication Study - Reduced Risk of Harm
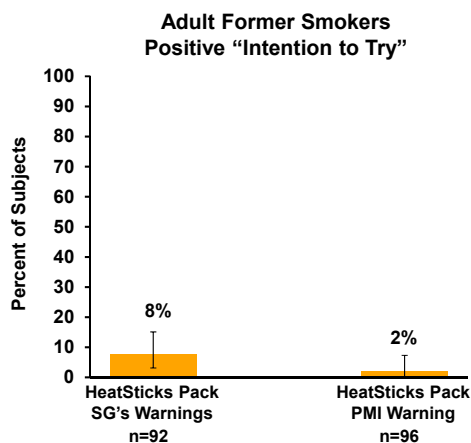
Adult Former Smokers
Positive "Intention to Try"

Percent of Subjects

8%
HeatSticks Pack
SG's Warnings
n=92

2%
HeatSticks Pack
PMI Warning
n=96

Positive Intention to Try IQOS is the sum of *% Very Likely* and *% Definitely* responses
Error bars show 95% confidence intervals for the 'very likely' and 'definitely' categories combined
THS-PBA-05-RRC2-US

CC-92

911(g)(1) Modified Risk Products

…the applicant has demonstrated that such product, as it is actually used by consumers, will—

A Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

CC-93

U.S. Commercialization and Controls

Sarah Knakmuhs

Vice President, Heated Tobacco Products
Philip Morris USA

CC-94

Tobacco Harm Reduction in the U.S.

FDA U.S. FOOD & DRUG ADMINISTRATION

"For the first time…the federal government …is able to bring science-based regulation to the manufacturing, marketing, and distribution of tobacco products."

- Former FDA Commissioner Margaret A. Hamburg, M.D., September 19, 2013

CC-95

IQOS in the U.S.

IQOS®
TOBACCO HEATING SYSTEM

FOR USE EXCLUSIVELY
WITH MARLBORO HEATSTICKS®

CC-96

Behavior Change – IQOS Use

| Device Usability | Charging & Cleaning | Taste & Experience |
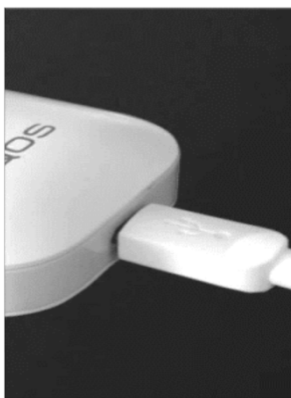
CC-97

PM USA Marketing Approach for IQOS

	Awareness	Trial	Conversion
Objective	Introduce IQOS	Explain Product & Encourage Trial	Support Exclusive Switching
	Intended Audience = U.S. Adult Smokers		
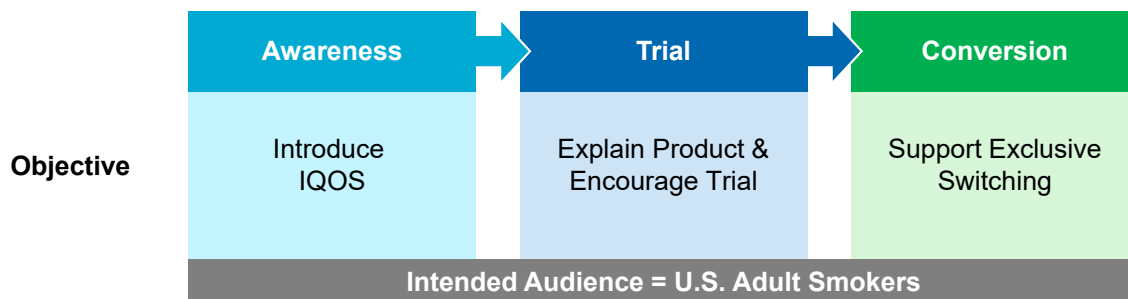
CC-98

Build Awareness for IQOS

Print Advertising

Direct Mail

Email

AVAILABLE EVIDENCE TO DATE
Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

CC-99

Electronic Age Verification

Data Entry	Validation	Authentication
Consumer inputs data for age and identity	Match inputs with identity on electronic databases	Consumer answers questions to confirm identity
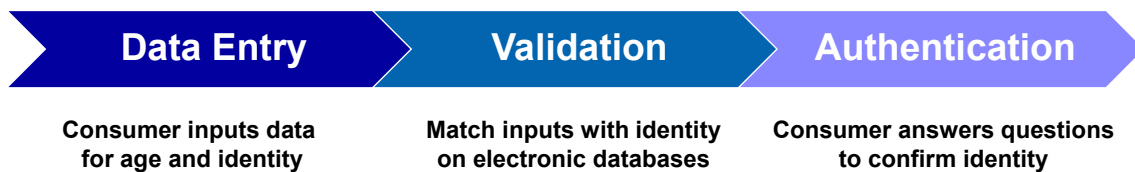
CC-100

Opportunities for Trial of IQOS

Individual Engagements

Consumer Events

Retail

CC-101

Trial of IQOS

Verification

Confirm age and
identity via
government issued ID

Confirmation

Confirm
smoking status

Guided Trial

Provide overview
and perform
guided trial

CC-102

IQOS Support

Device Troubleshooting

HeatStick Availability

Personal Support

CC-103

PM USA Marketing Approach for IQOS

	Awareness	Trial	Conversion
Objective	Introduce IQOS	Explain Product & Encourage Trial	Support Exclusive Switching
Examples	Direct Mail Print Media	Consumer Events Retail Engagement	Customer Care Personal Support

Intended Audience = U.S. Adult Smokers

CC-104

Post-market Surveillance

Surveillance	Studies
• U.S. call center • IQOS product safety summary • Literature reviews • Regulatory reporting systems (FDA/HHS/WHO) • National poison data system	• Cross-sectional surveys • Longitudinal cohort study

Adverse Events **Product Misuse**	**Consumer Perception & Behavior** **Self-Reported Health Measures***
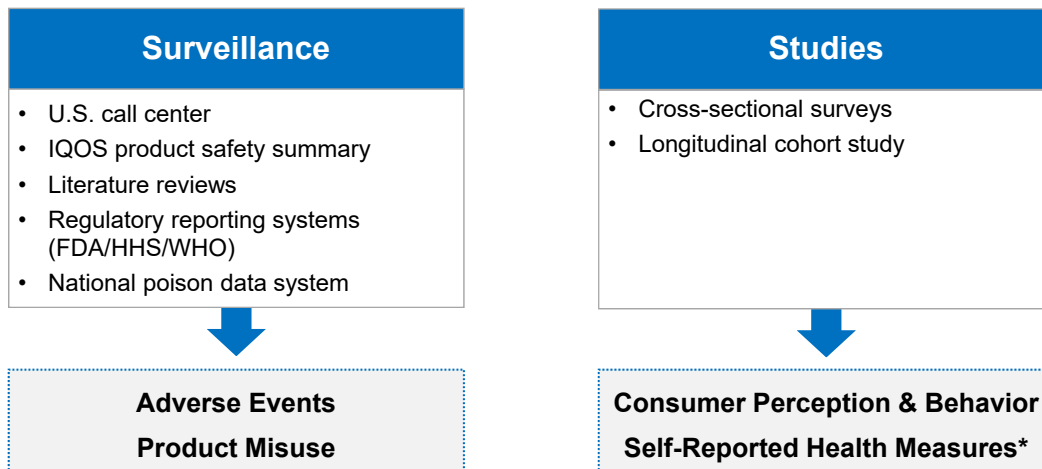
*For Longitudinal Cohort Study

CC-105

IQOS in the U.S.

CC-106

Population Modeling and Conclusion

Moira Gilchrist, PhD

Vice President Scientific and Public Communications
Philip Morris International

CC-107

The PMI Population Health Impact Model

Prevalence Component

Epidemiological Risk Component

Weitkunat R et al, A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product. *Regulatory Toxicology and Pharmacology* (2016).
Lee, P, et al, Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. *Regulatory Toxicology and Pharmacology* (2017). **CC-108**

The Prevalence Component

Prevalence Component

Hypothetical population based on publicly available databases and scientific literature

Transition probabilities

✅ **Validated**
using published smoking statistics

CC-109

The Epidemiological Risk Component

Epidemiological Risk Component

Hypothetical population risk estimates

Ischemic heart disease, lung cancer, stroke, and COPD

✅ **Validated**
using estimates from the Surgeon General's Report

CC-110

The PMI Population Health Impact Model
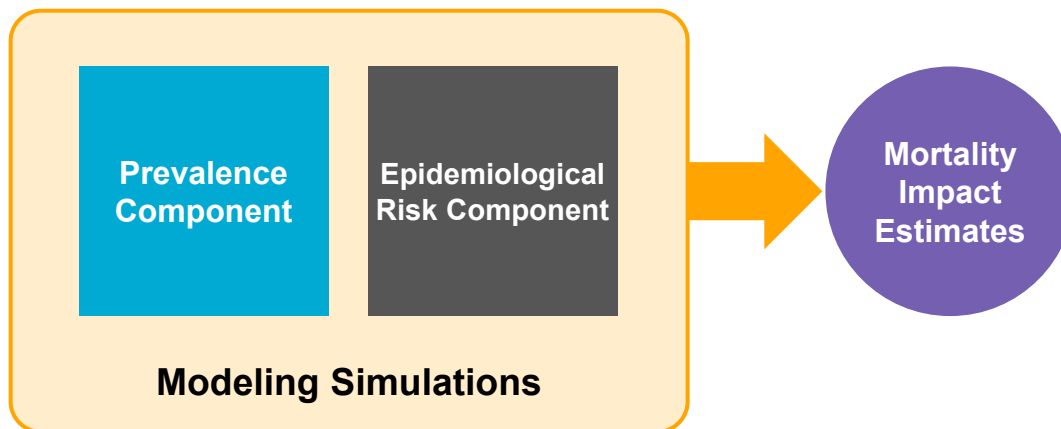
Prevalence Component

Epidemiological Risk Component

Modeling Simulations

Mortality Impact Estimates

Weitkunat R et al, A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product. *Regulatory Toxicology and Pharmacology* (2016).
Lee, P, et al, Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. *Regulatory Toxicology and Pharmacology* (2017). **CC-111**

Benefit to the U.S. Population as a Whole

90% of cessation benefit

15% switching

90,155 **Smoking-related deaths averted**
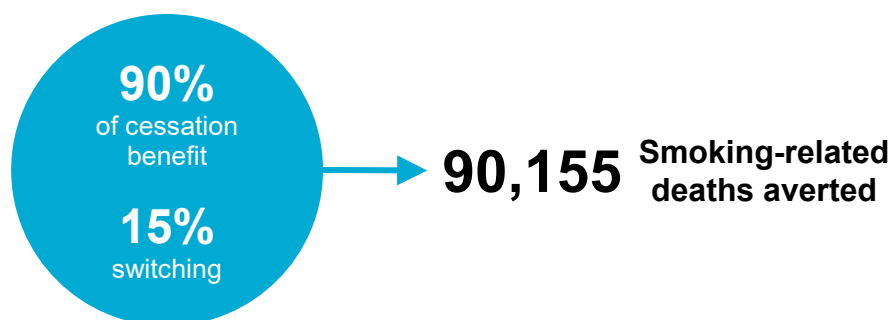
CC-112

911(g)(1) Modified Risk Products

…the applicant has demonstrated that such product, as it is actually used by consumers, will—

(A) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

(B) Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

CC-113

The IQOS Opportunity

CC-114

The IQOS Opportunity

- **Millions fewer smokers**

- **Reduced harm and tobacco-related disease**

- **An important step forward**

CC-115

The IQOS Heating System

Tobacco Products Scientific Advisory Committee

January 24, 2018

CC-116

Tobacco Products Scientific Advisory Committee

Sponsor slides shown

January 24, 2018

Non-targeted Differential Screening
Comparison of IQOS Aerosol and 3R4F Smoke
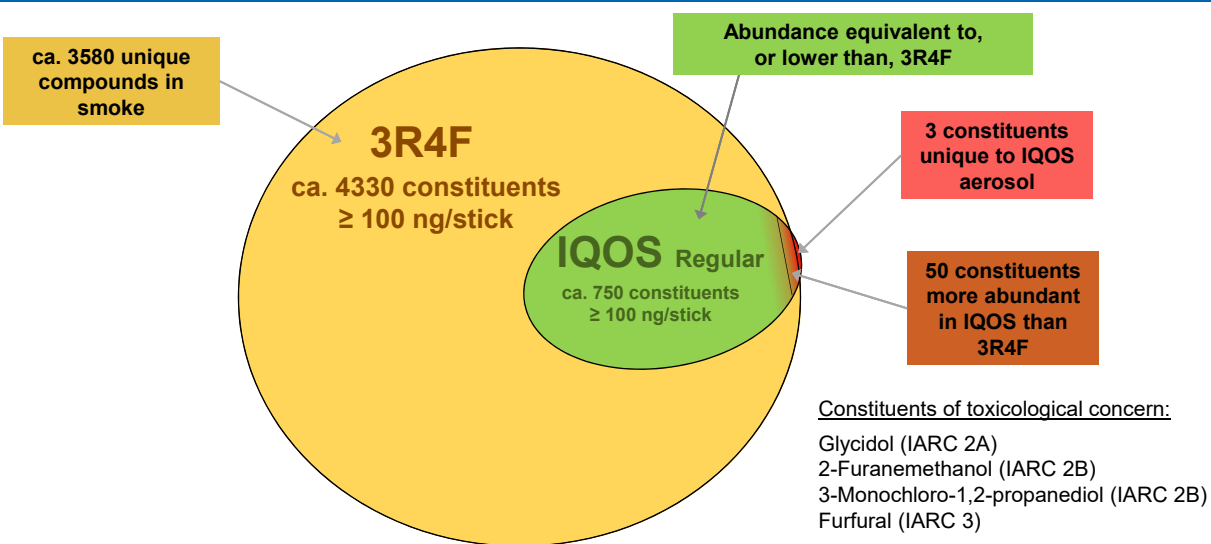
ca. 3580 unique compounds in smoke

Abundance equivalent to, or lower than, 3R4F

3R4F
ca. 4330 constituents ≥ 100 ng/stick

3 constituents unique to IQOS aerosol

IQOS Regular
ca. 750 constituents ≥ 100 ng/stick

50 constituents more abundant in IQOS than 3R4F

Constituents of toxicological concern:

Glycidol (IARC 2A)
2-Furanemethanol (IARC 2B)
3-Monochloro-1,2-propanediol (IARC 2B)
Furfural (IARC 3)

This slide presents the results for the regular variant of the IQOS HeatStick characterization

AC-28

Results
Ames: IQOS Regular

- TPM from IQOS Regular is not mutagenic

- TPM from 3R4F is mutagenic in the presence of S9 in TA98, TA100, and TA1537
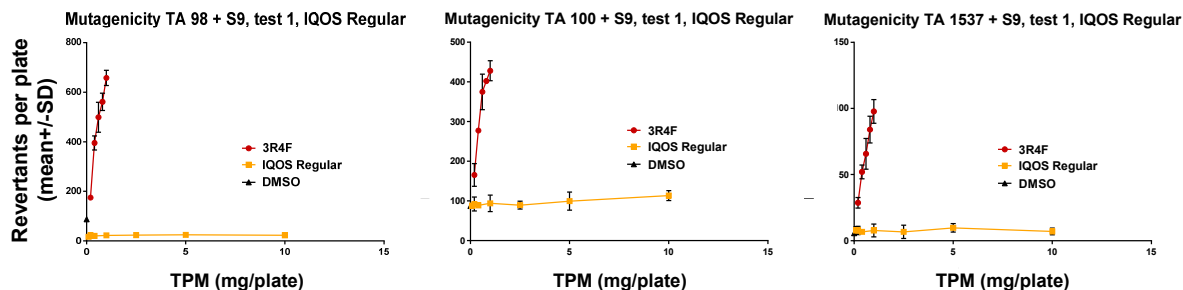
Study report BSR_SR_RLS-ZRH-2015-253, pages 22, 26 and 38 , Tables 12, 16 and 28

SD-37

Results
Mouse Lymphoma Assay (MLA) - IQOS Regular

Relative Mutagenicity expressed as lowest observable genotoxic effect levels (LOGELs)
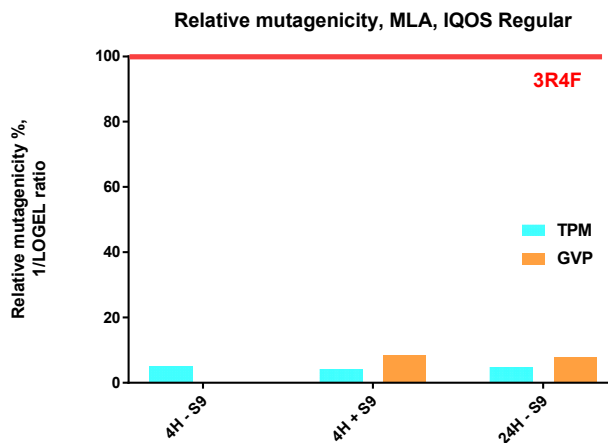
Reference: Study report RLS-ZRH-2015-252_Study_Report_MLA_2of2, pages 153, 154 and 155 , Tables 123, 124, 125, 126, 127 and 128, MRTPA section 6.1.2.2.3.2, Tables 3 and 4

SD-21

Summary of Demographics and Subject Characteristics – Main Sample: Race, Ethnicity and Education Level
IQOS Communication Study (Reduced Risks of Harm Claim)

	Arm				
Assessment	1 N=378	2 N=375	3 N=376	4 N=380	5 N=374
Race					
White, n (%)	292 (77.7)	288 (77.0)	281 (75.3)	287 (75.5)	286 (76.7)
Black, n(%)	60 (16.0)	57 (15.2)	64 (17.2)	63 (16.6)	65 (17.4)
Asian, n(%)	5 (1.3)	6 (1.6)	4 (1.1)	5 (1.3)	2 (0.5)
Other, n (%)	19 (5.0)	23 (6.1)	24 (6.4)	25 (6.6)	20 (5.3)
Missing, n	2	1	3	0	1
Ethnicity					
Hispanic or Latino, n (%)	52 (13.8)	55 (14.7)	51 (13.7)	64 (16.8)	46 (12.3)
Not Hispanic or Latino, n (%)	324 (86.2)	319 (85.3)	322 (86.3)	316 (83.2)	327 (87.7)
Missing, n	2	1	3	0	1
Education level					
Some high school or less, n (%)	18 (4.8)	25 (6.7)	13 (3.5)	21 (5.5)	9 (2.4)
High school graduate, n (%)	55 (14.6)	39 (10.4)	54 (14.5)	57 (15.0)	58 (15.5)
Some college, n (%)	134 (35.6)	156 (41.7)	147 (39.4)	148 (38.9)	147 (39.4)
College graduate, n (%)	132 (35.1)	119 (31.8)	125 (33.5)	129 (33.9)	124 (33.2)
Advanced degree, n (%)	37 (9.8)	35 (9.4)	34 (9.1)	25 (6.6)	35 (9.4)
Missing, n (%)	2	1	3	0	1

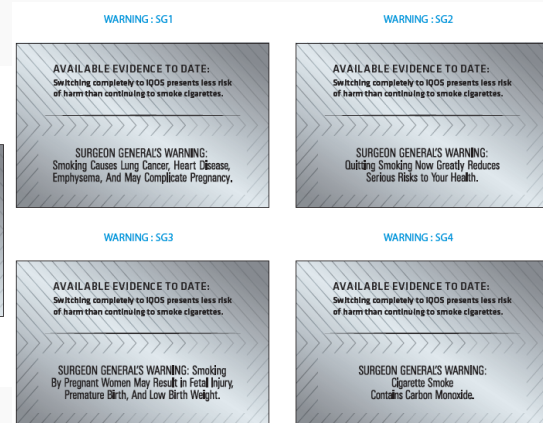LA = state legal smoking age
THS-PBA-05-RRC2-US

PB-438

How HeatSticks are Consumed According to "Usage Categories": By Product Types Used (Menthol, Regular)
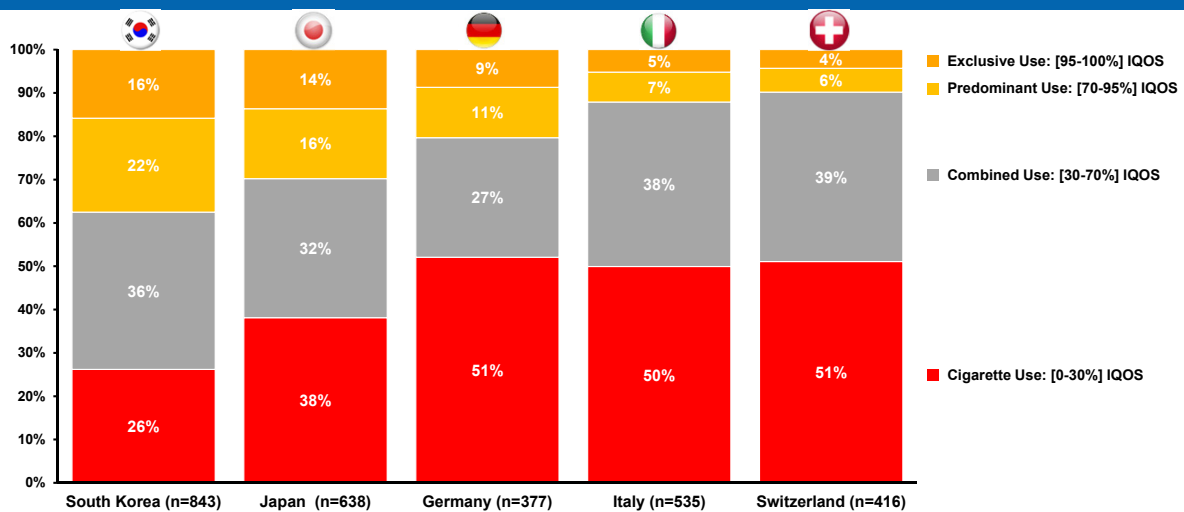### Actual Use Study
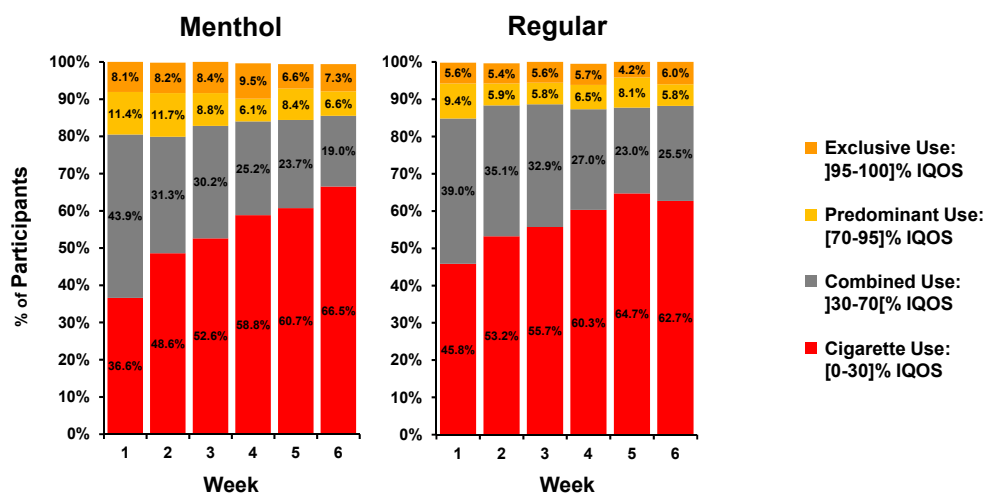
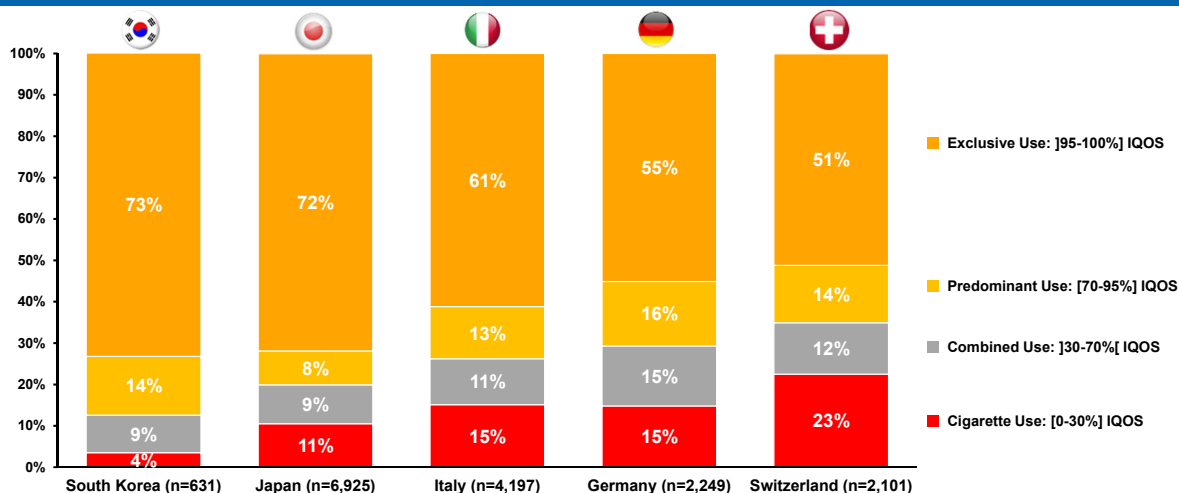THS-PBA-07-US

PB-603

IQOS HeatStick Pack (RRC2)

UC-100

IQOS and Cigarettes Use: End of the Observational Period
Whole Offer Test Studies

	South Korea (n=843)	Japan (n=638)	Germany (n=377)	Italy (n=535)	Switzerland (n=416)
Exclusive Use: [95-100%] IQOS	16%	14%	9%	5%	4%
Predominant Use: [70-95%] IQOS	22%	16%	11%	7%	6%
Combined Use: [30-70%] IQOS	36%	32%	27%	38%	39%
Cigarette Use: [0-30%] IQOS	26%	38%	51%	50%	51%

WOT
Total in any specific week could be lower than 100% given "no CC or Tobacco Sticks use" option WOT

IQ-14

IQOS In Market Usage Patterns
Post-Market Consumer Panel Surveys

Legend:
- Exclusive Use:]95-100%] IQOS
- Predominant Use: [70-95%] IQOS
- Combined Use:]30-70%[IQOS
- Cigarette Use: [0-30%] IQOS

	South Korea (n=631)	Japan (n=6,925)	Italy (n=4,197)	Germany (n=2,249)	Switzerland (n=2,101)
Exclusive Use	73%	72%	61%	55%	51%
Predominant Use	14%	8%	13%	16%	14%
Combined Use	9%	9%	11%	15%	12%
Cigarette Use	4%	11%	15%	15%	23%

Consumer Panel Surveys. August 2017

IQ-15

Exposures Are Below the Levels of Concern from *in vivo* Studies

Compound	Quantities in IQOS Aerosol [µg/Stick]	IARC Class	Exposure level without tumors *in vivo*	Delivered dose *in vivo* [mg/kg/day]	Human Equivalent Concentration (HEC)[4] [µg/kg/day]	Ratio IQOS/HEC exposure to 40 Sticks
Glycidol[1]	5.71	2A	3 ppm	0.896	144.6	1/39
2-Furanemethanol[2]	39.18	2B	2 ppm	0.499	80.5	1/3
3-Monochloro-1,2-propanediol	9.94	2B	NA	NA	NA	NA
Furfural[3]	31.08	3	400 ppm	89.539	12099.9	1/584

NA: No inhalation toxicity data available, but positive in Ames test
1. Japan Bioassay Research Center, 2003. Summary of Inhalation Carcinogenicity Study of Glycidol in F344 Rats. http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/Glycidol_Rats.pdf
2. NTP, 1999b. Toxicology and carcinogenicity studies of furfuryl alcohol (CAS no. 98-00-0) in F344/n rats and B6C3F mice (inhalation studies).Natl. Toxicol. Program Tech. Rep. Ser. 482, 1-248.
3. R. Cary, S. Dobson, N. Gregg. 2-Furaldehyde. World Health Organization International Program on Chemical Safety. World Health Organization (WHO), 2000.
4. FDA, 2005. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Food and Drug Administration, Washington, DC. http://www.fda.gov/cder/guidance.

ER-51

Retail

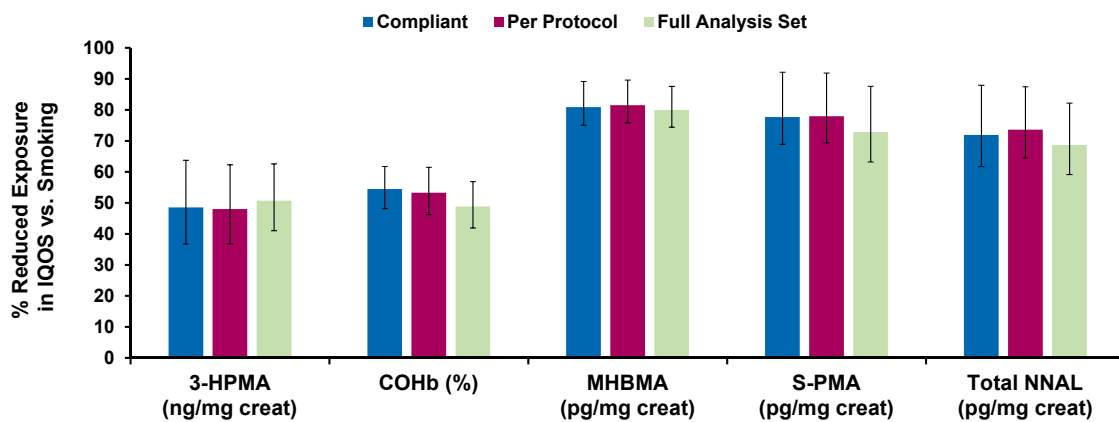| Entry	Guided Trial	Purchase
Confirm age and identity via government issued ID	Confirm smoking status	Register for Database and Support

UC-87

Impact of Dual Use
3 months Reduced Exposure Study in the US

**Robust Exposure Reduction following IQOS use at 3 month in all analysis populations.**

Legend: ■ Compliant ■ Per Protocol ■ Full Analysis Set

Y-axis: % Reduced Exposure in IQOS vs. Smoking (0–100)

X-axis categories: 3-HPMA (ng/mg creat), COHb (%), MHBMA (pg/mg creat), S-PMA (pg/mg creat), Total NNAL (pg/mg creat)

3-hydroxypropylmercapturic acid (3-HPMA), Monohydroxybutenyl mercapturic acid (MHBMA), and S-phenylmercapturic acid (S-PMA) in 24-hour urine (concentration adjusted for creatinine), and carboxyhemoglobin (COHb) in blood

DP-8

No Increase in IQOS and Cigarettes Consumption Between Baseline and Observational Period

Actual Use Study: IQOS + Cigarette Consumption
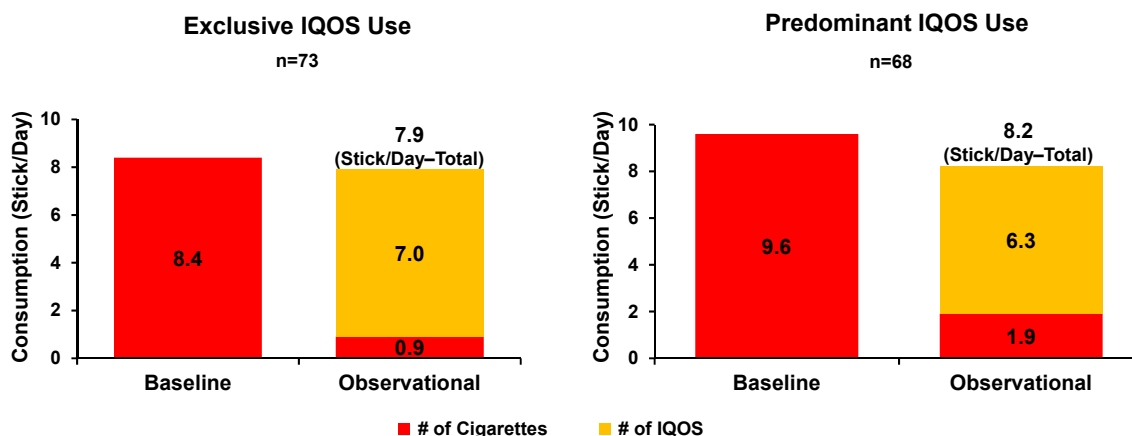
THS-PBA-07-US

XX-1

Selection of Study Population
Actual Use Study

- **Inclusion Criteria: Each subject had to meet the following criteria to be eligible for the study:**
  - ‣ a) 18 years of age or above according to the minimum LA, whichever was higher
  - ‣ b) Current daily smokers of regular and/or menthol CC with no intention of quitting within the next 30 days
  - ‣ A current daily smoker was defined as an individual who had smoked at least 100 cigarettes in his/her lifetime and was currently smoking at least 1 regular or menthol CC (no brand restrictions) per day (disregarding religious fasting). Participants who intended to quit smoking within the next 30 days were excluded from the study, because they did not intend to remain smokers for the entire duration of the study
  - ‣ c) Individuals who signed an ICF and were able to understand the information provided in the ICF
  - ‣ d) Individuals available and interested in participating in an 8 week study about tobacco
  - ‣ e) Individuals with positive intention to use the iQOS system
  - ‣ f) Individuals currently living in the United States (US)
- **Exclusion Criteria: Subjects who met any of the following criteria were excluded from the study:**
  - ‣ a) Pregnant or breastfeeding women (based on self-reported status)
  - ‣ b) Women of childbearing potential who were not using adequate means of contraception (self-reported)
  - ‣ c) Individuals with no proof of age (photo identity document (ID), such as passport, driver's license)
  - ‣ d) Individuals who had started smoking within the last 30 days
  - ‣ e) Individuals who were not able to read and speak English
  - ‣ f) Individuals employed in the fields of market research, marketing, advertising, media or journalism, law, manufacturers or distributors of tobacco products, or who were health care providers
  - ‣ g) Individuals who had taken part in a consumer or clinical study within the past 3 months
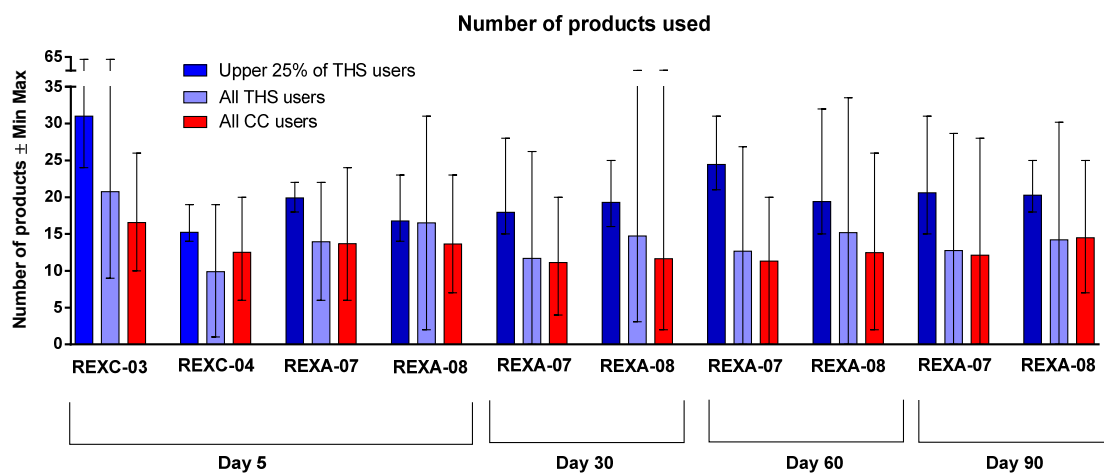
THS-PBA-07-US

PB-97

Extent of Exposure to Investigational Product (PP)
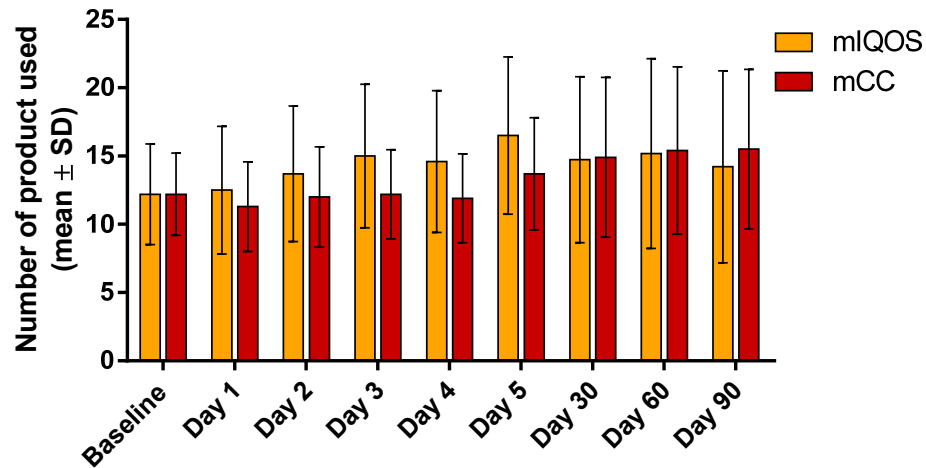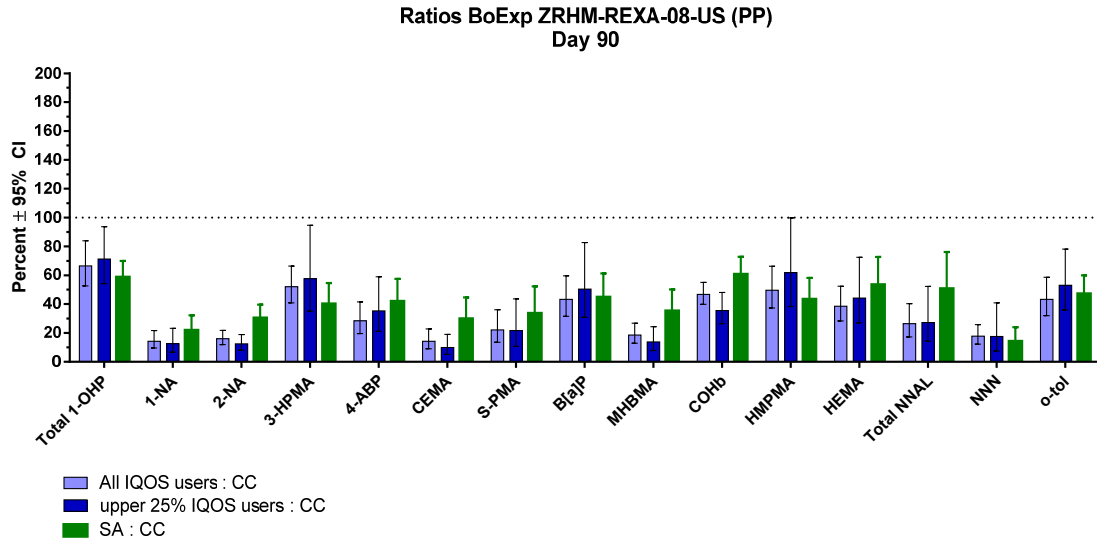

SD-1135

Product Use Per Day – IQOS and CC

REXC-03, REXC-04: Studies with 5 Days of Exposure in Confinement
REXA07, REXA08: 3 Month Reduced Exposure Studies in an Ambulatory Setting

TC-52

BoExp Ratios – Day 90
3 Months Reduced Exposure Study in an Ambulatory Setting (US)

Ratios BoExp ZRHM-REXA-08-US (PP)
Day 90

Legend:
- All IQOS users : CC
- upper 25% IQOS users : CC
- SA : CC

TC-58