The IQOS Heating System

Tobacco Products Scientific Advisory Committee

January 24, 2018
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Introduction

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International
The Status Quo

Risk Continuum

Institute of Medicine, Clearing the Smoke, Assessing the Science Base for Tobacco Harm Reduction, 2001.
The IQOS Heating System

The IQOS Opportunity
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
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

Product Messages

Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.
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.
Family Smoking Prevention and Tobacco Control Act

"... 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

Presentation Agenda

<table>
<thead>
<tr>
<th>Moira Gilchrist, PhD</th>
<th>IQOS System and Heating Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP Scientific &amp; Public Communications</td>
<td>Philip Morris International</td>
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<tr>
<th>Manuel Peitsch, PhD</th>
<th>Scientific Assessment of IQOS</th>
</tr>
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<tr>
<td>Chief Scientific Officer</td>
<td>Philip Morris International</td>
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<tr>
<th>Antonio Ramazzotti</th>
<th>Perception and Behavior</th>
</tr>
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<tr>
<td>VP Human Insights and Behavioral Research</td>
<td>Philip Morris International</td>
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<thead>
<tr>
<th>Sarah Knakmuhs</th>
<th>U.S. Commercialization and Controls</th>
</tr>
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<tbody>
<tr>
<td>VP Heated Tobacco Products</td>
<td>Philip Morris USA</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Moira Gilchrist, PhD</th>
<th>Population Modeling and Conclusion</th>
</tr>
</thead>
<tbody>
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<td>VP Scientific &amp; Public Communications</td>
<td>Philip Morris International</td>
</tr>
</tbody>
</table>
IQOS System and Heating Technology

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International

HeatStick Construction
IQOS Holder and Heating Blade

IQOS Temperature Profile

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

Battery
Electronics
Cradle for Holder

IQOS Operation
Scientific Assessment of IQOS

Manuel Peitsch, PhD
Chief Scientific Officer
Philip Morris International

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
Scientific Assessment

<table>
<thead>
<tr>
<th>Studies</th>
<th>17 Non-Clinical Studies</th>
<th>8 Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publications</td>
<td>30+ on IQOS assessment</td>
<td>150+ on assessment methods and verification</td>
</tr>
</tbody>
</table>


Assessment Framework: Informed by Epidemiology

The health risks of smoking are well established and supported by epidemiological evidence (IARC 2004, 2007)
The health risks of smoking and the reversal of risks after quitting smoking are well established (IARC 2004, 2007)
Assessment Framework: Informed by Epidemiology

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

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
IQOS Does Not Emit Carbon-Based Solid Particles

IQOS Releases Less Toxicants than Cigarettes

* Under the Health Canada’s Intense Smoking Regime.


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.

Cigarette smoke
Carbon-based nanoparticles
Median diameter = 75 nm
Amount: 6x10^{11} particles ~= 0.7 mg*

Blank
(Air)

IQOS aerosol
No solid particles

IQOS Releases Less Toxicants than Cigarettes

<table>
<thead>
<tr>
<th>Variant</th>
<th>Number of toxicants</th>
<th>% of Reference Cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>&gt;92%</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>&gt;92%</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>&gt;92%</td>
</tr>
</tbody>
</table>

Health Canada’s Intense Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine
Non-targeted Differential Screening
Comparison of IQOS Aerosol and 3R4F Smoke

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

- **3R4F**
  - ca. 4330 constituents
  - \( \geq 100 \) ng/stick

- **IQOS Regular**
  - ca. 750 constituents
  - \( \geq 100 \) ng/stick

Constituents of toxicological concern:
- Glycidol (IARC 2A)
- 2-Furanemethanol (IARC 2B)
- 3-Monochloro-1,2-propanediol (IARC 2B)
- Furfural (IARC 3)

Abundance equivalent to, or lower than, 3R4F

3 constituents unique to IQOS aerosol

50 constituents more abundant in IQOS than 3R4F

Exposure from IQOS is below the level of concern

---

Reductions of Toxicants by Disease Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Toxicants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogens in IARC Group 1</td>
<td>12</td>
</tr>
<tr>
<td>Carcinogens (FDA)</td>
<td>29</td>
</tr>
<tr>
<td>Cardiovascular toxicants (FDA)</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory Toxicants (FDA)</td>
<td>18</td>
</tr>
<tr>
<td>Reproductive and Developmental Toxicants (FDA)</td>
<td>7</td>
</tr>
</tbody>
</table>

% of Reference Cigarette

- Carcinogens in IARC Group 1: 97%
- Carcinogens (FDA): 93%
- Cardiovascular toxicants (FDA): 92%
- Respiratory Toxicants (FDA): 92%
- Reproductive and Developmental Toxicants (FDA): 94%

Note: Intense Health Canada’s Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine
Demonstrated Reduced Emission

Study Design
Reduced Exposure in Healthy Human Subjects

Ad libitum Use

Confinement

Ambulatory

Continued Cigarette Smoking (n=40)

Switching to IQOS (n=80)

Smoking Abstinence (n=40)

Safety Follow-up Period

Study Day
Day -2
Day -1
Day 1 to 5
Day 6 to 90

Sample Collection
-1
1 2 3 4 5
30 60 90

Measurements: 16 Biomarkers of Exposure; Nicotine and its metabolites
Smoker Acceptance of IQOS is Similar to Cigarettes

Nicotine Exposure

Product Use

Smoking Satisfaction (mCEQ)

Changes in Exposure to HPHCs with IQOS Use

Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

* On equivalent nicotine basis
Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Leads to

- 98.6%*

Exposure is Significantly Reduced After Switching to IQOS

Carbon Monoxide

* 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

Leads to

- 98.6%*

- 94.2%*

Leads to

* On equivalent nicotine basis

Exposure is Significantly Reduced After Switching to IQOS

Carbon Monoxide

Acrolein

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

HPHCs are Drastically Reduced in IQOS Aerosol

Leads to

- 97.2%*

- 98.0%*

Leads to

* On equivalent nicotine basis

Exposure is Significantly Reduced After Switching to IQOS

NNN

NNK
Reduced Exposure Compared to Cigarettes
Reduced Exposure in Healthy Human Subjects

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

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

Demonstrated Reduced Exposure

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette</td>
<td>3R4F</td>
</tr>
<tr>
<td>IQOS Switching</td>
<td>3R4F IQOS at equivalent nicotine concentration</td>
</tr>
<tr>
<td>Cessation</td>
<td>3R4F Fresh Air</td>
</tr>
<tr>
<td>IQOS</td>
<td>IQOS at equivalent nicotine concentration</td>
</tr>
<tr>
<td>Reference: Air</td>
<td>Fresh Air</td>
</tr>
</tbody>
</table>

Start | Month 2 | Month 8


Reduced Molecular Changes in the Lung

<table>
<thead>
<tr>
<th>Proteins in Bronchoalveolar Lavage Fluid</th>
<th>Log2Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td></td>
</tr>
<tr>
<td>IL-1 alpha</td>
<td></td>
</tr>
<tr>
<td>IL-1 beta</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>IL-7</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
</tr>
<tr>
<td>IL-11</td>
<td></td>
</tr>
<tr>
<td>IL-12p70</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>IFN-10</td>
<td></td>
</tr>
<tr>
<td>KC_GRO</td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
</tr>
<tr>
<td>LIF</td>
<td></td>
</tr>
<tr>
<td>Lymphotactin</td>
<td></td>
</tr>
<tr>
<td>M_CSF_1</td>
<td></td>
</tr>
<tr>
<td>MCP_1</td>
<td></td>
</tr>
<tr>
<td>MCP_3</td>
<td></td>
</tr>
<tr>
<td>MCP_5</td>
<td></td>
</tr>
<tr>
<td>MDC</td>
<td></td>
</tr>
<tr>
<td>MIP_1_alpha</td>
<td></td>
</tr>
<tr>
<td>MIP_1 beta</td>
<td></td>
</tr>
<tr>
<td>MIP_1 gamma</td>
<td></td>
</tr>
<tr>
<td>MIP_2</td>
<td></td>
</tr>
<tr>
<td>MIP_2 beta</td>
<td></td>
</tr>
<tr>
<td>MMP_3</td>
<td></td>
</tr>
<tr>
<td>MPO</td>
<td></td>
</tr>
</tbody>
</table>

* p-value <0.05

Reduced Molecular Changes in the Lung

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

* p-value <0.05

References:

1/24/2018
Reduced Molecular Changes in the Lung

Proteins in Bronchoalveolar Lavage Fluid

Gene Expression in Lung Tissue at Month 8

Demonstrated Reduced Molecular Changes
Reduced Effects on Disease Mechanisms

Lung Inflammation

Mechanism Disruption (% ± SEM)

Time (months)

Cigarette

Reduced Effects on Disease Mechanisms

Lung Inflammation

Mechanism Disruption (% ± SEM)

Time (months)

Cigarette  IQOS Switch  Cessation
Reduced Effects on Disease Mechanisms

Lung Inflammation

Specific Markers of Lung Inflammation

### Reduced Effects on Disease Mechanisms

**Cell Stress**

**Cell Fate & Apoptosis**

**Cell Proliferation**

**Tissue Repair & Angiogenesis**

### Clinical Changes After 90 Days of Cessation

**Reduced Exposure in Healthy Human Subjects**

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>0.0 mg/dL [-5.77; 5.84]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.94 10^9/L [-2.00; 0.13]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>2.0 % pred [-3.37; 7.36]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-9.9 % [-19.7; 1.1]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-8.5 % [-25.13; 11.8]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
<td>-7.2 % [-37.7; 38.3]</td>
</tr>
</tbody>
</table>

**Smoking Abstinence:**

- Changes in Clinical Risk Endpoints after 3 months are small but relevant.
- Changes are in the expected direction upon cessation.
### Clinical Changes After 90 Days
**Reduced Exposure in Healthy Human Subjects**

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to IQOS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>0.0 mg/dL [-5.77; 5.84]</td>
<td>1.4 mg/dL [-2.3; 5.0]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.94 x 10^9/L [-2.00; 0.13]</td>
<td>0.17 x 10^9/L [-0.47; 0.81]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>2.0 % pred [-3.37; 7.36]</td>
<td>0.53 % pred [-2.79; 3.85]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-9.9 % [-19.7; 1.1]</td>
<td>-10.6 % [-16.7; -4.0]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-8.5 % [-25.13; 11.8]</td>
<td>-13.5 % [-23.6; -1.95]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
<td>-7.2 % [-37.7; 38.3]</td>
<td>-3.6 % [-24.6; 23.3]</td>
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<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to IQOS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>6.4 mg/dL [2.5; 10.3]</td>
<td>4.5 mg/dL [1.17; 7.88]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.41 x 10^9/L [-0.95; 0.14]</td>
<td>-0.57 x 10^9/L [-1.04; -0.10]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>1.94 % pred [-0.44; 4.31]</td>
<td>1.91 % pred [-0.14; 3.97]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-10.9 % [-17.8; -3.4]</td>
<td>-8.7 % [-14.94; -2.05]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-5.9 % [-17.1; 6.8]</td>
<td>-12.7 % [-21.81; -2.55]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
<td>-19.4 % [-30.1; -7.0]</td>
<td>-8.98 % [-19.52; 2.94]</td>
</tr>
</tbody>
</table>

### Demonstrated Reduced Disruption of Biological Mechanisms

- **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
  - ?
Reduces the Effects on Cells

Inflammatory Lung Cells in Bronchoalveolar Lavage Fluid

Reduces the Effects on Tissues

Lung Tissue Destructive Index
Demonstrated Reduced Cell & Tissue Changes

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

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

Reduces the Risk of Disease *in vivo*

Disease Endpoint for COPD
- Lung Emphysema
- Data from Histology after 8 months

Reduces the Risk of Disease *in vivo*

**Disease Endpoint for CVD**
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at month 7

<table>
<thead>
<tr>
<th>Plaque surface area (mm²)</th>
<th>Aorta mean occlusion (%)</th>
<th>Plaque volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>Fresh Air</td>
<td>Cigarette smoke</td>
<td>IQOS Switch</td>
</tr>
</tbody>
</table>

Data from µCT at month 7

**How Cigarette Smoke Causes Cancer**

- Genetic damage: "the match that lights the fire"**
- Inflammation: "fuel that feeds the flames"*

**Questions**
Does switching from cigarettes to IQOS?

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

- Carcinogens
- Nanoparticles** HPHCs
- Tumor initiation
- Tumor progression & Invasiveness***

Genetic Damage is Reduced by IQOS

Does Switching to IQOS Reduce Genetic damage?
- Genetic damage: "the match that lights the fire"**
- Carcinogens
- Tumor initiation

Evidence from IQOS Assessment
- Reduced Emission of Carcinogens
  - Reduced Exposure to Carcinogens
  - Reduced Genotoxicity
  - Reduced DNA Damage

Reduced Genetic Damage


Nanoparticles Deposit in the Lung

Cigarette Smoke
- Carbon-based nanoparticles
- 6x10^{11} particles ~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.
Inflammatory Markers in Smokers’ Lungs

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

<table>
<thead>
<tr>
<th>Cell type</th>
<th>BAL concentration x10^6 cells·mL^(-1)</th>
<th>F statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>(n=14)</td>
<td>(n=16)</td>
<td></td>
</tr>
<tr>
<td>Macrophage</td>
<td>524±219</td>
<td>220±98</td>
<td>25.1</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>12±9·13·3</td>
<td>2·1±1±6</td>
<td>10.6</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>7±3±7·5</td>
<td>14±8±17·7</td>
<td>2.2</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.9±1·7</td>
<td>1.1±1±3</td>
<td>0.1</td>
</tr>
<tr>
<td>Epithelial</td>
<td>1.5±1·4</td>
<td>2·1±2·1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>BAL constituent</th>
<th>Smokers (n=14)</th>
<th>Nonsmokers (n=16)</th>
<th>F statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β pg·mL^(-1)</td>
<td>1.2±0.7</td>
<td>0.5±0.4</td>
<td>14.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>IL-6 pg·mL^(-1)</td>
<td>5.3±3.2</td>
<td>1.9±1.0</td>
<td>17.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>IL-8 pg·mL^(-1)</td>
<td>32±8±15.9</td>
<td>18±2±11.5</td>
<td>8.4</td>
<td>0.007</td>
</tr>
<tr>
<td>TNF-α pg·mL^(-1)</td>
<td>2.6±7.9</td>
<td>0.2±0.2</td>
<td>1.4</td>
<td>0.25</td>
</tr>
<tr>
<td>MCP-1 pg·mL^(-1)</td>
<td>36.7±28.3</td>
<td>13±0±7.7</td>
<td>10.4</td>
<td>0.003</td>
</tr>
<tr>
<td>TP µg·mL^(-1)</td>
<td>75±27.7</td>
<td>87±2±56.5</td>
<td>0.4</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD. IL-1β: Interleukin-1β (non-detectable 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 (non-detectable in one nonsmoker and three smokers). Statistics quoted are by discriminant analysis. Overall model Hotelling’s statistic=1.34; p<0.002. Critical Bonferroni alpha value (n tests=6) = 0.008.


Voronov et al. Interleukin-1β (IL-1β) is required for tumor invasiveness and angiogenesis. PNAS 2002; 100:2645-2650.


Kuren et al. Interleukin-1β-Driven Inflammation Promotes the Development and Invasiveness of Chemical Carcinogen-Induced Tumors. Cancer Res. 2007; 67:1062-1071.

Animal Studies*
Lung Metastases (%)**

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

* Voronov et al. IL-1β is required for tumor invasiveness and angiogenesis. PNAS 2002; 100:2645-2650.
Kuren et al. Interleukin-1β-Driven Inflammation Promotes the Development and Invasiveness of Chemical Carcinogen-Induced Tumors. Cancer Res. 2007; 67:1062-1071.
Inflammation is Reduced by IQOS

Evidence from IQOS Assessment

- Reduced Emission of HPHCs and No carbon-based nanoparticles
  - Reduced Exposure to HPHCs
  - No Exposure to nanoparticles

Does Switching to IQOS Reduce Inflammation?

- Inflammation "fuel that feeds the flames"
  - Nanoparticles**
  - HPHCs

Tumor progression & Invasiveness***

Reduced Lung Inflammation


Demonstrated Reduced Disease

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

CC-69

CC-70
Demonstrate a Benefit to the Health of the Population as a Whole …
Consumer Perception and Behavior

Antonio Ramazzotti
Vice President Human Insights and Behavioral Research
Philip Morris International

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
Who Will Use IQOS and to What Degree?

<table>
<thead>
<tr>
<th>Adult Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding of Messages</td>
<td>Understanding of Messages</td>
</tr>
<tr>
<td>Intent to Use</td>
<td>Increased or Decreased Likelihood of Initiation</td>
</tr>
<tr>
<td>Exclusive Use</td>
<td></td>
</tr>
<tr>
<td>Increased or Decreased Likelihood of Cessation</td>
<td></td>
</tr>
</tbody>
</table>

PBA Studies to Develop and Assess IQOS Messages

**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

6 qualitative and quantitative studies to develop and assess IQOS communications
Product Messages (On a Tested Pack)

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.

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
Tested Product Message
Reduced Risk of Harm

HeatSticks Pack with SG’s Warnings

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.

HeatSticks Pack with PMI Warning

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.

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

IQOS Communication Study - Reduced Risk of Harm

<table>
<thead>
<tr>
<th></th>
<th>HeatSticks Pack PMI Warning</th>
<th>HeatSticks Pack SG’s Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct Comprehension</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>Less risk of harm (correct)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Correct Comprehension</th>
<th>Less risk of harm (correct)</th>
<th>The same risk of harm</th>
<th>Greater risk of harm</th>
<th>No risk of harm</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>78%</td>
<td>14%</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Percent of Subjects with Intention to Use IQOS

- HeatSticks Pack SG’s Warnings
  - Definitely: 20%
  - Very Likely: 19%
- HeatSticks Pack PMI Warning
  - Definitely: 9%
  - Very Likely: 15%
  - Very Likely: 28%

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

* Error bars show 95% confidence intervals for the ‘very likely’ and ‘definitely’ categories combined.
Study Design
Actual Use Study

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

Single group, observational study, ad libitum use of IQOS and cigarettes, reported on a stick-by-stick basis

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 2 3 4 5 6

1-week baseline
6-week observational
1-week close out

IQOS brochure shown to participants contained a reduced risk product message

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

IQOS and Cigarettes Use: Observational Period
Actual Use Study

% of Participants by Use Categories

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

Baseline Observational Consumption (Stick/Day–Total)

# of Cigarettes
# of IQOS

Between 12% and 30% of Participants Switched to IQOS

IQOS Usage Patterns

% of Participants by Usage Categories

Exclusive Use: [95-100]% IQOS
Predominant Use: [70-95]% IQOS
Combined Use: [30-70]% IQOS
Cigarette Use: [0-30]% IQOS
Post-market Data Show Exclusive Use is the Most Common Behavior Among IQOS Purchasers

% of Participants by Usage Categories

Japan (n=6,925)
- Exclusive Use: 72%
- Predominant Use: 8%
- Combined Use: 9%
- Cigarette Use: 11%

Italy (n=4,197)
- Exclusive Use: 61%
- Predominant Use: 13%
- Combined Use: 11%
- Cigarette Use: 15%

Increased Awareness and Repeated Communication Lead to Higher Switching Rates

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

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

Source: Consumer Panel Japan, March 2016
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

---

Minimal Interference on Intention to Quit All Tobacco among Adult Smokers with the Intention to Quit

- **HeatSticks Pack SG’s Warnings**
  - Pre-Exposure: n=96
    - 84%
  - Post-Exposure: n=96
    - 82%

- **HeatSticks Pack PMI Warning**
  - Pre-Exposure: n=94
    - 87%
  - Post-Exposure: n=94
    - 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”

<table>
<thead>
<tr>
<th>HeatSticks Pack</th>
<th>SG’s Warnings</th>
<th>PMI Warning</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeatSticks Pack</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>SG’s Warnings</td>
<td>n=93</td>
<td>n=94</td>
<td></td>
</tr>
</tbody>
</table>

Legal Age to 25 Years Never Smokers
Positive “Intention to Try”

<table>
<thead>
<tr>
<th>HeatSticks Pack</th>
<th>SG’s Warnings</th>
<th>PMI Warning</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeatSticks Pack</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>SG’s Warnings</td>
<td>n=101</td>
<td>n=95</td>
<td></td>
</tr>
</tbody>
</table>

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

Low Levels of Intent to Use Among Adult Former Smokers

IQOS Communication Study - Reduced Risk of Harm

Adult Former Smokers
Positive “Intention to Try”

<table>
<thead>
<tr>
<th>HeatSticks Pack</th>
<th>SG’s Warnings</th>
<th>PMI Warning</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeatSticks Pack</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>SG’s Warnings</td>
<td>n=92</td>
<td>n=96</td>
<td></td>
</tr>
</tbody>
</table>

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
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

U.S. Commercialization and Controls

Sarah Knakmuhs
Vice President, Heated Tobacco Products
Philip Morris USA
Tobacco Harm Reduction in the U.S.

“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

IQOS in the U.S.
Behavior Change – IQOS Use

Objective

Introduce IQOS

Explain Product & Encourage Trial

Support Exclusive Switching

Intended Audience = U.S. Adult Smokers
Build Awareness for IQOS

Print Advertising
Direct Mail
Email

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
Opportunities for Trial of IQOS

Individual Engagements

Consumer Events

Retail

---

Trial of IQOS

**Verification**
- Confirm age and identity via government issued ID

**Confirmation**
- Confirm smoking status

**Guided Trial**
- Provide overview and perform guided trial
IQOS Support

Device Troubleshooting
HeatStick Availability
Personal Support

PM USA Marketing Approach for IQOS

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
Post-market Surveillance

**Surveillance**
- U.S. call center
- IQOS product safety summary
- Literature reviews
- Regulatory reporting systems (FDA/HHS/WHO)
- National poison data system

**Studies**
- Cross-sectional surveys
- Longitudinal cohort study

**Adverse Events**
- Product Misuse

**Consumer Perception & Behavior**
- Self-Reported Health Measures*

*For Longitudinal Cohort Study

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IQOS in the U.S.

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Population Modeling and Conclusion

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International

The PMI Population Health Impact Model

Prevalence Component

Epidemiological Risk Component


The Prevalence Component

- Hypothetical population based on publicly available databases and scientific literature
- Transition probabilities

Validated using published smoking statistics

The Epidemiological Risk Component

- Hypothetical population risk estimates
- Ischemic heart disease, lung cancer, stroke, and COPD

Validated using estimates from the Surgeon General’s Report
The PMI Population Health Impact Model

- Prevalence Component
- Epidemiological Risk Component

Modeling Simulations

Mortality Impact Estimates

Benefit to the U.S. Population as a Whole

90% of cessation benefit
15% switching

90,155 Smoking-related deaths averted

References:

CC-111
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

The IQOS Opportunity
The IQOS Opportunity

- Millions fewer smokers
- Reduced harm and tobacco-related disease
- An important step forward

The IQOS Heating System

Tobacco Products Scientific Advisory Committee

January 24, 2018