An Integrated Assessment Approach for Candidate Modified Risk Tobacco Products

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

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

Offering adult smokers satisfying products that reduce risk

- Smoking is addictive and causes a number of serious diseases

- Worldwide it is estimated that more than one billion people will continue to smoke in the foreseeable future*

- Successful harm reduction requires that current adult smokers be offered a range of Reduced Risk Products so that consumer acceptance can be best fulfilled

Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced-Risk Products ("RRPs") is the term we use to refer to products that have the potential to reduce individual risk and population harm in comparison to smoking combustible cigarettes
Risk Framework for MRTP Assessment

Conceptual depiction of the cumulated risk of smoking and the effect of cessation over time. These represent the two boundaries for the assessment of an MRTP:

1. comparing switching to an MRTP with continued smoking, and
2. benchmarking switching against smoking cessation (gold standard).

Note that the straight lines used in this figure are for illustration purposes only as the accumulation of disease risk and the reduction upon cessation and switching to an MRTP follow different trajectories for specific diseases.
Chronic exposure to cigarette smoke affects a number of biological networks associated with smoking-related diseases in a causal chain of events known as Adverse Outcome Pathways.
### The MRTP assessment program

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<th>Assessment Steps</th>
<th>Evidence Levels</th>
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<td>Reduced Population Harm</td>
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<td>Consumer Perception and Behavior Assessment</td>
<td>Reduced Exposure &amp; Risk</td>
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<td>Systems Toxicology Assessment</td>
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<td>Standard Toxicology Assessment</td>
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<td>Aerosol Chemistry and Physics</td>
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<td>Product Design and Control Principles</td>
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Seven steps of assessment lead to five Levels of Evidence.

Taken together, these Levels of Evidence are the *totality-of-the-evidence* used to demonstrate that a candidate MRTP is indeed a reduced-risk product.
Systems Toxicology is:

- the integration of the classic toxicology paradigm with the quantitative analysis of many molecular and functional changes occurring across multiple levels of biological organization.
- aimed at developing a detailed mechanistic as well as dynamic understanding of toxicological processes. (Research)
- enabling inter-species and system translation.
- part of a new paradigm for risk assessment. (Product Assessment)

In vitro assessment of e-liquids: a framework

In vitro assessment of e-liquids: methods
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In vivo: the OECD(+) Study Design Concept

- Follows OECD Testing Guidelines such as TG 412, TG 413, TG 451, TG 453, etc.
- Supplement study arms with additional animals for non-conventional endpoints such as:
  - Transcriptomics (e.g. Affymetrix or RNAseq)
  - Genomics and epigenomics
  - Proteomics
  - Metabolomics and Lipidomics
- Exploratory Research:
  - Identify biological networks perturbed by exposure → Mode of Action and Pathway of Toxicity
- Product Assessment:
  - Apply Network Perturbation Amplitudes and Pathway Analysis to quantify biological impact of exposure.

In vivo: Switching studies in Animal Models


Note: CC is a 3R4F reference combustible cigarette.
Sample study results obtained with *iQOS*

**Heated Tobacco Products**

- Platform 1: *iQOS*
- Platform 2
- Platform 3
- Platform 4

**Nicotine-Containing Products**

Note: Reduced-Risk Products ("RRPs") is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. The products depicted are subject to ongoing development and therefore the visuals are illustrative and do not necessarily represent the latest stages of product development.
Average reductions in formation of harmful or potentially harmful constituents for *iQOS* compared to levels measured in smoke from the 3R4F reference cigarette*

* Aerosol collection with Intense Health Canada's Smoking Regime (55 mL puff volume, 2 second puff duration, 30 second interval puff);
* Comparison on a per-stick basis;
* Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter.
Indoor Air Quality

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

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

- iQOS is not a source of Environmental Tobacco Smoke
- Levels of 16 substances are the same as background measurements
- Nicotine is detectable (1.8 µg/m$^3$) but at levels 275 fold lower than EU occupational exposure limits$^1$
- Acetaldehyde is detectable (5 µg/m$^3$) but at levels 40 fold lower than EU indoor exposure limits$^2$

### Category

<table>
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<tr>
<th>Category</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Environmental Tobacco Smoke Markers</td>
<td>6 substances</td>
</tr>
<tr>
<td>Carbonyls</td>
<td>4 substances</td>
</tr>
<tr>
<td>Volatile Organic Compounds</td>
<td>5 substances</td>
</tr>
<tr>
<td>Inorganics</td>
<td>3 substances</td>
</tr>
</tbody>
</table>

Total of 18 substances measured

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$^1$ European Agency for Safety and Health at Work Directive 2006/15/EC

$^2$ The Index Project, Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU, EC, Joint Research Center, Institute for Health and Consumer Protection, January 2005
Reduced Toxicity

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

- Cytotoxicity: ≈ 90% reduction
- Bacterial Mutagenicity: Under conditions of test, iQOS aerosol not mutagenic as opposed to smoke from reference cigarette
- Mammalian Genotoxicity: ≈ 95% reduction

Comparison on a per-nicotine basis
Note: These data alone do not represent a claim of reduced exposure or reduced risk.
Source: PMI Research and Development
Compare *iQOS* with Continued Smoking and Cessation in Mouse Model: Impact on Disease Endpoints

**Disease endpoint for COPD**

**Lung Emphysema**

After 8 months

**Disease endpoint for CVD**

**Atherosclerotic Plaque**

After 8 months

Note: These data alone do not represent a claim of reduced exposure or reduced risk. CC is a 3R4F reference combustible cigarette. Cess. is Cessation, Switch. is Switching to iQOS. COPD is chronic obstructive pulmonary disease, CVD is cardiovascular disease.

Source: PMI Research and Development
Smokers used the products \textit{ad libitum}. Smokers randomized to cigarettes or iqOS were free to use the product as often as they wished.

Note: These data alone do not represent a claim of reduced risk.
Source: PMI Research and Development
Registered on clinicaltrials.gov: NCT 01959932
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Assessing a Product’s Potential to Contribute to Tobacco Harm Reduction

HARM REDUCTION = REDUCED-RISK PRODUCT X PRODUCT ACCEPTANCE AND USAGE

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

For more information visit www.pmiscience.com
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Source: Philip Morris International R&D

Data generated and analyzed by:
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