Electronic cigarettes:
Pre-clinical and clinical assessment

Dr Chris Proctor
Chief Scientific Officer, British American Tobacco

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I declare that this work was fully funded by British American Tobacco (Investments) Ltd and that myself and my co-workers were full time employees of British American Tobacco (Investments) Ltd for the duration of the research.
AGENDA

1. Background
2. Assessing the risk profile of e-cigarettes
3. Product bridging
4. Summary
E-cigarettes have evolved rapidly
## An open approach to R&D

<table>
<thead>
<tr>
<th>Visitors</th>
<th>Conferences</th>
<th>Publications</th>
<th>Social Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 1500 visitors to our</td>
<td>Presentation of data at global scientific &amp; regulatory conferences and hosting</td>
<td>Over 180 publications since 2008</td>
<td>Website and Twitter feed dedicated</td>
</tr>
<tr>
<td>R&amp;D Live Centre at Global</td>
<td>of conferences and hosting of conferences on site</td>
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<td>to science</td>
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<td>R&amp;D since 2011</td>
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</table>
Our global credibility for assessing e-cigarettes (1):
Presentations at regulatory meetings

**US, FDA**

**US, National Academy of Sciences**
Our global credibility for assessing e-cigarettes (2):

Publications

Accepted


Submitted (under review)

- Murphy J et al. Assessing modified risk tobacco and nicotine products: Description of the scientific framework and assessment of a closed modular electronic cigarette. Reg Tox Pharma (Submitted)
In the UK there is a growing consensus on e-cigarette harm reduction potential

Kevin Fenton, Public Health Director of Health and Wellbeing: “The wider body of evidence consistently finds that e-cigarettes are less harmful than smoking”

E-cigarettes: an evidence update
“The current best estimate is that e-cigarettes are around 95% less harmful than smoking”

Nicotine without smoke: tobacco harm reduction
Promote e-cigarettes widely as substitute for smoking says new RCP report

Electronic cigarettes (also known as vapourisers)
“Compared to tobacco products, electronic cigarettes are significantly safer”
Consumer safety testing of e-cigarettes

What do we need to know?

- **eLiquid**
  - What’s in the liquid?

- **Device**
  - What’s the device made of?
  - Does it conform to electrical safety?

- **Product**
  - What’s in the vapour?
  - How stable is the product over time?
  - How is it used?

## A three-step scientific journey to substantiate reduced risk

<table>
<thead>
<tr>
<th>01</th>
<th>EMISSIONS</th>
<th>02</th>
<th>EXPOSURE</th>
<th>03</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical studies in laboratories using smoking/vaping machines comparing NGPs with conventional cigarettes.</td>
<td>Studies demonstrating switching to NGPs results in lower exposure to toxicants by making comparisons with continued smoking and quitting.</td>
<td>Studies demonstrating changes on switching to NGPs on biomarkers of biological effect, supported by toxicology, systems science, modelling and post market studies.</td>
<td></td>
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<tr>
<td>Provides evidence of reduced hazard and RRP potential.</td>
<td></td>
<td></td>
<td>Provides evidence to reduce risk at both the individual and population level.</td>
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</tbody>
</table>
A three-step scientific journey to assess the risk profile of e-cigarettes

01 EMISSIONS
- Untargeted emissions
- Targeted emissions
- Environmental emissions

02 EXPOSURE
- Puffing behaviour
- Average daily consumption
- Clinical PK
- Clinical BoE

03 RISK
- Clinical BoBE
- Risk perception
- Post market surveillance

REDUCED TOXICITY IN LAB MODELS
- in vitro reg tox
- in vitro disease models
- in vitro systems science

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>TOBACCO PRESENT</th>
<th>AEROSOL FORMATION MECHANISM</th>
<th>NUMBER OF COMPOUNDS IN AEROSOL</th>
<th>TYPICAL NUMBER OF TOXICANT TYPES</th>
<th>HPHC FORMATION MECHANISMS</th>
<th>UNTARGETED EMISSIONS²</th>
</tr>
</thead>
</table>
| CIGARETTE | Yes | Combustion & pyrolysis of tobacco | >7000 | 100–150 | • Transfer from tobacco  
• Pyrosynthesis of tobacco | |
| ENDS | No | Vaporisation of e-liquid | 10–100 | <5 | • Poorly stewarded e-liquids (eg. containing contaminants, CMRs)  
• Thermal degradation of humectants (‘Dry wicking’)  
• Extractables & Leachables from device during storage or heating | |

Key findings:
Studies show that consumer behaviour with ENDS is in-line with CORESTA recommended method N° 81 (CRM81): 55mL puff volume/3 s puff duration/30s interval between puffs

6. Prasad et al., in preparation;
E-cigarette has reduced levels of toxicants relative to cigarettes*

*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products

Substantial reductions in toxicant levels observed versus cigarettes for all regulatory lists under these test conditions

E-cigarette has reduced toxicity relative to cigarettes (1)*

OECD* TG 471: Bacterial Reverse Mutation Test, S. typhimurium TA98

Exposure to reference cigarette smoke caused mutations in a dose dependent manner; e-cigarettes gave no response


E-cigarettes gave no response even after 900 puffs


*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products
E-cigarettes have reduced responses in disease relevant models

Substantial reductions in responses in tests relevant to oxidative stress, CVD, genotoxicity, tumour promotion and cytotoxicity vs. cigarettes

*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products
Irritancy assessment of aerosols*
Comparison of cytotoxicity after cigarette and e-cigarette exposure using EpiAirway™

No cytotoxicity with e-cigarette exposed EpiAirway™


*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products
Comparing transcriptional perturbations in MucilAir™

48, 854 genes/ RNA features screened

3R4F 8197 significant genes/RNA features
Vype ePen 49 significant genes/RNA features
Vype ePen* 113 significant genes/RNA features

RNA-seq data mapped onto 131 pathway-focussed gene sets with specific biological function and disease processes

Toxicogenomics – RNA-seq differential gene expression

* X2 nicotine dose


*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products
Adverse Outcome Pathways (AOPs)
Describes a sequential chain of causally linked events at different levels of biological organisation, that lead to an adverse effect

Collaboration to Support AOP Build
Two AOPs (BAT/PMI/SELVENTA)

Oxidative Stress Leading to Hypertension
https://aopwiki.org/aops/149

EGFR Activation Leading to Decreased Lung Function
https://aopwiki.org/aops/148
Nicotine exposure: PK studies

**Key findings**

- 1st study: Smokers (naïve ENDS users) have reduced nicotine uptake with ENDS in comparison to cigarettes
- 2nd study: Smokers (experienced vapers) may adapt their puffing behaviour and therefore have similar nicotine uptake with ENDS in comparison to cigarettes

Clinical study design to assess exposure from e-cigarettes use in comparison to smoking and cessation

- 5 day, randomised forced switch, confinement study
- Typically 30 subjects/arm
- Measure Biomarkers of Exposure (BoE) levels in ENDS users relative to smoking and cessation
- Cessation arm objectives (i) maximum effect comparator and (ii) baseline for confounders

<table>
<thead>
<tr>
<th>Subject</th>
<th>Original product</th>
<th>Randomisation to Switch product</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>Cigarette</td>
<td>Cigarette</td>
<td>●</td>
</tr>
<tr>
<td>Smoker</td>
<td>Cigarette</td>
<td>ENDS</td>
<td>●</td>
</tr>
<tr>
<td>Smoker</td>
<td>Cigarette</td>
<td>Cessation</td>
<td>●</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker Cigarette</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Smoker ENDS</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Smoker Cessation</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tbody>
</table>

● = Sampling point

Public Health clinical studies on e-cigarettes

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Roswell Park Cancer Institute$^{23}$</th>
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<tbody>
<tr>
<td>COHb (CO)</td>
<td>63–75%</td>
</tr>
<tr>
<td>NNAL (NNK)</td>
<td>57–64%</td>
</tr>
<tr>
<td>3-HPMA (Acrolein)</td>
<td>49–56%</td>
</tr>
</tbody>
</table>


**Conclusions**

- Solus ENDS use can reduce exposure to selected carcinogens and toxicants to similar levels as cessation
- Exposure reductions with dual use are lower than solus use
Population risk: studies in post market surveillance

<table>
<thead>
<tr>
<th>ER ESTIMATES</th>
<th>X</th>
<th>POPULATION USAGE</th>
<th>=</th>
<th>POPULATION RISK IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess Risk (ER) estimates determined from pre-clinical and <strong>clinical</strong> assessment</td>
<td>Usage of products assessed across population:</td>
<td>Dynamic model\textsuperscript{24,25} to assess population risk impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk estimates calculated for:</td>
<td>• Smoking</td>
<td>• Never smokers and Nicotine Replacement Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solus ENDS use</td>
<td>• Dual use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dual use</td>
<td>• Non smokers</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>with respect to never smokers</td>
<td>• Quitting</td>
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</tbody>
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\textsuperscript{24.} Hill & Camacho (2017) Reg Tox Pharma 86, pp.265-278.  
Conundrum: can we bridge data between product variants in the fast paced world of next generation products?

Yes – this is happening today in the world of ‘similar’ and ‘bio-similars’

Modified pharma industry approach to bridging could be applied in the nicotine and tobacco product context

Foundation datasets on the original product variant (‘reference’) can be added to on a “need” basis to allow bridging to the new variant (‘similar’)

Product bridging
Proposed principles of product bridging

<table>
<thead>
<tr>
<th>FOUNDATIONAL DATASET</th>
<th>BRIDGING CRITERIA</th>
<th>BRIDGING DATASET</th>
<th>ANALYSIS</th>
<th>BRIDGING DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATA A</td>
<td>Has exposure changed?</td>
<td>DATA A</td>
<td>Has exposure changed?</td>
<td>New product (&quot;Similar&quot;) can be bridged</td>
</tr>
<tr>
<td>DATA B</td>
<td>Has aerosol chemistry changed?</td>
<td>DATA A</td>
<td>Has exposure changed?</td>
<td>NO</td>
</tr>
<tr>
<td>DATA C</td>
<td></td>
<td>DATA A</td>
<td>Has aerosol chemistry changed?</td>
<td>NO</td>
</tr>
<tr>
<td>DATA D</td>
<td></td>
<td>DATA A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATA E</td>
<td></td>
<td>DATA A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATA F</td>
<td></td>
<td>DATA A</td>
<td></td>
<td></td>
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Original product ("Reference") Foundation dataset

Q? New product ("Similar") Bridging dataset A
SUMMARY

• Scientific framework established to substantiate risk reduction potential of e-cigarettes
• Pre-clinical assessment shows that e-cigarettes have the potential to reduce risk relative to cigarettes
• All data is being published in peer review literature
• A workable framework for bridging data between product variants is required
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