RNA-SEQ based toxicogenomics comparison of airway cells exposed to Vype™ ePen vapour and cigarette smoke

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CONFLICT OF INTEREST STATEMENT

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

- E-cigarettes & Vype e-Pen
- 21st Century toxicology
- *In vitro* RNA-seq toxicogenomics
- Conclusions and perspectives
E-cigarettes have evolved rapidly

Development of e-cigarettes

Vype ePen
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”
Assessment strategy for 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

Core elements of our *in vitro* assessment programme for e-cigarettes

*in vitro* reg tox  *in vitro* disease models  *in vitro* systems science

**Systems biology: 21st century toxicology**

*In vitro* relevant models, non-animal, human clinical
Unbiased high density, high throughput, top down
Mode of action

<table>
<thead>
<tr>
<th>Biology</th>
<th>Bioinformatics</th>
<th>Perturbations (Tox)</th>
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<tbody>
<tr>
<td>A biological system is a network of genes, proteins, lipids, metabolites and cells in an equilibrium</td>
<td>The networks of genes, proteins, metabolites interactions can be modelled with computer-based tools</td>
<td>The equilibrium of a system is perturbed by a toxic stress and can be measured by combining tox end points, OMICs and bioinformatics</td>
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Experimental design: 3D primary cells aerosol exposure system

MucilAir™

Exposure chamber

Smoke engine RM20S

Air

Media
Experimental workflow for e-cigarette RNA-sequencing work

Haswell et al., Sci Reports (2017)
Reduced biological impact of e-cigarette aerosol vs cigarette smoke

Haswell et al., Sci Reports (2017)
Functional enrichment analyses of e-cigarette aerosol and cigarette smoke

Haswell et al., Sci Reports (2017)
Mapping genes contributing to tobacco-related adverse events

AOP: EGFR activation leading to decreased lung function

Enrichment analysis tools against known disease mechanisms/events

Luettich et al., App in vitro Tox (2017)
Our comprehensive peer-reviewed contribution on e-cigarette risk assessment

Accepted

- Cunningham, A et al. (2016). Development, validation and application of a device to measure e-cigarette users' puffing topography. Scientific Reports 6, 35071; doi: 10.1038/srep35071.
- Taylor, M et al. (2016). E-cigarette aerosols induce lower oxidative stress in vitro when compared to tobacco smoke. Toxicology Mechanisms and Methods 26: 465-476; DOI: 10.1080/15376551.2016.1222473
SUMMARY

Scientific framework established to substantiate risk reduction potential of e-cigarettes

*In vitro* toxicogenomics shows reduced effect of e-cigarette aerosols

- *In vitro* omics offer an unbiased coverage of the biological changes
- Limited impact of e-cigarette on global airway transcriptome
- Provided information on mechanism of action based on impacted pathways
- Changes can be matched against key disease events mapped in AOPs

All data are being published in peer review literature
THANK YOU

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