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.

ASSESSMENT OF THE GLO™ TOBACCO HEATING PRODUCT: TRADITIONAL AND 21ST CENTURY TOXICOLOGY APPROACHES

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Summary

• Novel Tobacco Products – Risk Continuum

• Tobacco Heating Product - glo™

• Investigating the Risk Reduction Potential – In vitro assays
Increasing acknowledgement of the risk continuum model

Our portfolio approach supports the risk continuum

These modellings do not necessarily mean that our products are less harmful than cigarettes.
In 2017 the UK Independent Scientific Committee on Toxicity (COT) were asked by the UK Department of Health and Public Health England to study data on Tobacco Heating Products. They concluded:

“As the exposure to compounds of concern in the aerosol is reduced compared to conventional cigarette smoke, it is likely that there is a reduction in risk, though not to zero, to health for smokers who switch completely to heat-not-burn tobacco products” UK COT, Dec 12, 2017.

Tobacco Heating Product- glo™

- **Device - glo™**
- **Consumable - Neostik™**
- No ash is formed during consumption as there is no combustion
- Aerosol generated mainly by evaporation and distillation

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Eaton *et al.* 2017 – Regulatory Toxicology and Pharmacology
Different Aerosol to Cigarette Smoke

OVER 60 YEARS HERITAGE IN TOBACCO SCIENCE HAS LED TO GLO: A PRODUCT WITH CONTROLLED TOBACCO HEATING

Cigarettes burn tobacco at around 900°C. Glo heats tobacco up to a maximum of 250°C.

Glo produces a much simpler aerosol containing less compounds than cigarettes.

## Outline of products and *in vitro* toxicology studies

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Technique</th>
<th>Cell/Bacterial System</th>
<th>Metabolic activation</th>
<th>Guideline/Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotoxicity</strong></td>
<td><strong>Neutral red uptake assay (NRU)</strong></td>
<td>BALB/c 3T3 mouse fibroblasts</td>
<td>None</td>
<td>ICCVAM (NIH Publication No. 07-4519)</td>
</tr>
<tr>
<td><strong>Mutation</strong></td>
<td><strong>Bacterial reverse mutation (Ames) assay (TPM)</strong></td>
<td><em>Salmonella typhimurium</em> TA98 TA100 TA1535 TA1537 TA102</td>
<td>±S9</td>
<td>OECD 471</td>
</tr>
<tr>
<td></td>
<td><strong>Bacterial reverse mutation (Ames) assay (WA)</strong></td>
<td><em>Salmonella typhimurium</em> TA98 TA100 TA1535 TA97 TA102</td>
<td>+S9</td>
<td>OECD 471#</td>
</tr>
<tr>
<td></td>
<td><strong>Mouse Lymphoma Assay (MLA)</strong> (In vitro gene mutation assay at the <em>tk</em>&lt;sup&gt;+&lt;/sup&gt; locus)</td>
<td>Mouse lymphoma L5178Y cells</td>
<td>±S9</td>
<td>OECD 490</td>
</tr>
</tbody>
</table>
Glo induced significantly less cytotoxicity than the 3R4F reference cigarette

Thorne D*, Breheny D, Proctor C and Gaca M (2018) 
Assessment of a novel tobacco heating product THP1.0(T). Part 6: In vitro toxicology: mutagenicity, cytotoxicity and tumour promoting activity. Reg Tox Pharm

Assessment of a novel tobacco heating product THP1.0(T). Part 4: In vitro dosimetric and cytotoxic assessment of a novel tobacco heating product. Reg Tox Pharm
Mutagenic response can be observed for cigarette smoke in TA98, TA100 and TA1537. Glo was deemed non-mutagenic under all test conditions.

Mutagenic response can be observed for cigarette smoke in TA98, TA100. Glo was deemed non-mutagenic under all test conditions.

3R4F was mutagenic across all treatment conditions. Glo was non-mutagenic in all test conditions and did not exceed the global evaluation factor.

3R4F induced a concentration-dependent response and was positive at all concentrations tested. Glo was negative in this assay.
Contemporary Screening Approach - TPM
High Content Screening (HCS)
Multi-parametric assessment of 10+ endpoints using Cellomics platform

• The use of automated robotics platforms for in vitro toxicological screening complements traditional testing approaches. HCS technology is based around automated fluorescence microscopy in combination with advanced imaging processing and analysis tools, which together can provide quantitative information as a first-level description of complex cellular events.

• Multiparametric toxicity and oxidative stress endpoints were used to assess in vitro biological responses elicited after exposure to TPM from gloTM, and the reference tobacco product 3R4F, in human bronchial epithelial cells.

• High-content screening was used to assess 10 endpoints after 4 and 24 h exposures.

• A luciferase-based reporter gene assay was used to assess antioxidant response element (ARE) transcriptional activation in stably transfected H292 cells after 6 and 24 h exposures.
Contemporary Screening Approach - TPM
High Content Screening (HCS)
Multi-parametric assessment of 10+ endpoints using Cellomics platform

- 3R4F was positive in all endpoints assessed using a HCS approach.

- Glo was negative for each HCS endpoint, apart from activation of the antioxidant response element. However, the data showed a significantly higher response to TPM generated from 3R4F than from glo at both timepoints tested.
Conclusion

- Glo has significantly reduced levels of harmful constituents when compared to a 3R4F reference cigarette

- *In vitro* assays have enabled the biological assessment of glo. These studies indicate that glo has the potential to confer reduced risk of disease compared to cigarette smoking

- All data published in peer review journals
References


• Gee, J., et al., Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users, Regulatory Toxicology and Pharmacology (2017), http://dx.doi.org/10.1016/j.yrtph.2017.08.005

• Murphy, J., et al., Assessment of tobacco heating product THP1.0. Part 9: The placement of a range of next-generation products on an emissions continuum relative to cigarettes via pre-clinical assessment studies, Regulatory Toxicology and Pharmacology (2017), https://doi.org/10.1016/j.yrtph.2017.10.001
Thank you for your attention