A proposed bridging approach for the assessment of novel tobacco products

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R&D Centre
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Agenda

• Insight into BAT R&D

• Evolution of next generation products across the risk spectrum

• Multidisciplinary approach to demonstrate the reduced risk potential of next generation products

• Bridging data between product variants: a new requirement in the fast paced world of novel nicotine and tobacco products
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R&D at British American Tobacco

- Global R&D reach
- 1200 scientists and technologists
- > 50 scientific disciplines
- £0.5Bn R&D expenditure since 2013
- 2010–15, over 3000 patents filed, over 1800 granted
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 R&amp;D Live Centre at Global R&amp;D since 2011</td>
<td>Presentation of data at global scientific &amp; regulatory conferences and hosting of conferences on site</td>
<td>Over 180 publications since 2008</td>
<td>Website and Twitter feed dedicated to science</td>
</tr>
</tbody>
</table>
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BAT is investing in a range of products across the risk spectrum.
E-cigarettes have evolved rapidly

2013
- Disposable
- Rechargeable (cig-alike)
- Tank Modular
- Rechargeable (non-cig-alike)

2017
- Full (large-size) Modular
- Compact Modular
- Rechargeable (non-cig-alike)

Development of e-liquids
**Toxicants cause harm (not nicotine)**

*What is the source of toxicants in NGPs?*

<table>
<thead>
<tr>
<th>Source of Toxicants</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate number of compounds found in aerosol</td>
<td>&gt;6,500</td>
</tr>
<tr>
<td>Toxicants from burning tobacco</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxicants transferred from tobacco</td>
<td>Yes</td>
</tr>
<tr>
<td>Other potential sources of toxicants</td>
<td>Combustion / pyrolysis of cigarette paper</td>
</tr>
</tbody>
</table>
Toxicants cause harm (not nicotine)
What is the source of toxicants in NGPs?

<table>
<thead>
<tr>
<th></th>
<th>Cigarettes</th>
<th>THP</th>
<th>Vapour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate number of compounds found in aerosol</td>
<td>&gt;6,500</td>
<td>100-1000</td>
<td>10-100</td>
</tr>
<tr>
<td>Toxicants from burning tobacco</td>
<td>Yes</td>
<td>Trace</td>
<td>No tobacco</td>
</tr>
<tr>
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<tr>
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<td>Combustion / pyrolysis of cigarette paper</td>
<td>Thermal degradation of PG/VG &amp; flavours; leachables from device materials</td>
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</tr>
</tbody>
</table>
The mathematics of risk

Risk = exposure × longevity of use

Exposure = emissions × use
"While vaping may not be 100% safe, most of the chemicals causing smoking-related disease are absent and the chemicals which are present pose limited danger. It has been previously estimated that EC are around 95% safer than smoking. This appears to remain a reasonable estimate."

"Although it is not possible to quantify the long-term health risks associated with e-cigarettes precisely, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure."
E-cigarettes - a reduced risk product?

**REASONS WHY VAPING IS NOT AS BAD FOR YOU AS SMOKING TOBACCO**

1. The evidence so far shows that e-cigarettes are far safer than smoking.
2. E-cigarettes contain nicotine but not cancer causing tobacco.
3. Nicotine is addictive, but does not cause cancer.
4. There is no evidence that e-cigarettes harm bystanders.
5. Tobacco is the biggest cause of preventable death in the UK. Over 100,000 deaths per year.

LET'S BEAT CANCER SOONER
cruk.org

CANCER RESEARCH UK
E-cigarettes - a reduced risk product?

E-cigarettes aerosols induce lower oxidative stress in vitro when compared to tobacco smoke

Research Article

E-cigarettes aerosols induce lower oxidative stress in vitro when compared to tobacco smoke

Mark Taylor, Tony Carr, Oluwatobiloba Oke, Tomasz Jaunky, Damien Breheny, Frazer Lowe and Marianna Gaça

Research and Development Centre, British American Tobacco PLC, Southamporn, UK

ABSTRACT

Tobacco smoking is a risk factor for various diseases. The underlying cellular mechanisms are not fully characterised, but include oxidative stress, apoptosis, and necrosis. Electronic cigarettes (e-cigarettes) have emerged as an alternative to tobacco smoking. If e-cigarettes vapor contains significantly lower levels of toxins than cigarette smoke, but standardised methods to assay cellular responses to exposure are not well established. We investigated whether an aerosol generated from the electronic cigarette (e-cigarette) device would be toxic to cells. We measured the oxidative stress in human bronchial epithelial cells exposed to e-cigarette aerosol. The results showed that the e-cigarette aerosol did not induce oxidative stress in the bronchial epithelial cells. This suggests that e-cigarettes may be less harmful than traditional cigarettes.

Research Article

Comparative Tumor Promotion Assessment of e-Cigarette and Cigarette Aerosols Using the In Vitro Bhas 42 Cell Transformation Assay

Dwayne Brophy, Corina Balaban, Oluwatobiloba Oke, Tomas Jaunky and Marianna Gaça

ABSTRACT

We assessed the tumour promoting potential of cigarette and e-cigarette aerosols using the in vitro Bhas 42 cell transformation assay. The results showed that e-cigarette aerosols were less tumour promoting than cigarette aerosols.

Research Article

Reduced biological effect of e-cigarette smoke evaluated in vitro using normalized nicotine dose and RNA-seq-based toxicogenomics

Linsey E. Hennell, Andrew Baxter, Amika Banerjee, Ivan Verstreken, Jessica Mishuganova, Jason Adamson, David Thorne, Marianna Gaça & Emmanuel Minet

ABSTRACT

E-cigarettes aerosols induce lower oxidative stress in vitro when compared to tobacco smoke.

To cite this article: Mark Taylor, Tony Carr, Oluwatobiloba Oke, Tomasz Jaunky, Damien Breheny, Frazer Lowe & Marianna Gaça (2016) E-cigarettes aerosols induce lower oxidative stress in vitro when compared to tobacco smoke, Toxicology Mechanisms and Methods, 26.6, 460-470, DOI: 10.1080/19400513.2016.1222473

To link to this article: http://dx.doi.org/10.1080/19400513.2016.1222473
Need for product assessment

• Novel tobacco and nicotine products have rapidly increased in popularity over the last 5 years

• Mainly driven by rapid innovation with new products and e-liquids introduced to the market place that have constantly evolved to meet smokers’ needs

• Potential frameworks for assessing the individual- and population-level risks associated with product introduction
  • FDA PMTA/MRTP
  • TPD2

• These mandate submission of data package prior to marketing/approval
Stewardship of e-cigarettes
Requirements of and additional to TPD2

e-Liquid
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?

Stewardship of e-cigarette flavours
S. Costigan and C. Meredith
Regul Toxicol Pharmacol
72: 361–369, 2015
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Reduced risk substantiation

• TPD2 provides a regulatory standard which all manufacturers must meet

• Greater datasets are required if you want to go further
  • exposure reduction assessment
  • risk reduction assessment

• These datasets may need to be submitted to regulators where mandated but may also be consumer-facing
10 steps to substantiating the risk reduction potential of tobacco & nicotine products

- Population risk reduction
  - 10) Post-market surveillance
- Individual risk reduction
  - 9) Consumer perception study
  - 8) Biomarker of effect study
  - 7) Systems Science
- Toxicant exposure reduction
  - 6) In vitro models of disease
  - 5) Exposure and pharmacokinetic studies
  - 4) Computational toxicology
- Stewardship science
  - 3) In vitro regulatory toxicology
  - 2) Chemical and physical characterisation
  - 1) Product design stability
Conundrum

How do regulators, public health scientists and product manufacturers keep innovating and improving novel products to ensure that smokers start to use and keep using these new products, while allowing their timely safety assessment and approval?
Hypothetical scenario

- Product has demonstrated reduced-risk potential and is on the market
Hypothetical scenario

- Innovation drives down toxicant emissions, potentially enhancing the risk reduction
- Ideally:
Hypothetical scenario

• Innovation drives down toxicant emissions, potentially enhancing the risk reduction
• Practically:

3-year research package
6-month regulatory approval

How do we reduce this time, while maintaining safety?
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Pharma approach to the issue

- Many drug regulators allow ‘bridging’ studies to bring existing foreign medicines to new market

“....provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients for their benefit....”
Can a derivation of this model be applied to nicotine and tobacco products?

• Assumptions:
  
  • e-cigarettes are a reduced risk product
  
  • chemical emissions are the key determinants of risk
  
  • a reduced risk product needs to be on the market to be a reduced risk product
  
  • there is a fundamental need for stewardship
Can a derivation of this model be applied to nicotine and tobacco products?
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Summary

• Product innovation necessary to drive incremental increases in performance

• Public health potential of novel products requires rapid product assessment to place products on market

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

• Foundation datasets can be added to on a “need” basis to allow bridging to a novel product
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