2. A framework for the assessment of reduced risk tobacco and nicotine products

Fraser Lowe, Ian M Fearon, Oscar Camacho, Emmanuel Minet and James J Murphy
Content

- Lessons learned from tobacco harm reduction through reduced toxicant prototype cigarettes
- Preliminary results from novel products across the risk spectrum
- Consumers: making the switch to reduced risk tobacco & nicotine products
- Creating a global approach with common goals
Introduction

- Tobacco products used on global scale with current estimates at 1.4bn adult smokers worldwide

- Epidemiology shows cigarette smoking to be the cause of many human diseases

- Tobacco harm reduction is being considered by some regulators (eg. FDA)

- Starting point.....reduce consumer exposure to toxicants while maintaining acceptability
1956-2012: Tobacco harm reduction through Reduced Toxicant Prototype (RTP) cigarettes

Chemical characterisation | in vitro regulatory toxicology | in vitro disease modelling

Chemistries were significantly reduced which led to reductions in vitro.
Biomarkers of Exposure Biomarkers of biological effect (BoBE)

Toxicant reductions were substantial enough to reduce biomarkers of exposure but not biological effect – greater toxicant reductions are required.
British American Tobacco’s risk spectrum

- Conventional Cigarettes
- Tobacco-Heating Products
- Low-Toxicant Smokeless Tobacco
- Electronic Cigarettes
- Licensed Medicinal Products

Exposure to toxicants range from high to low.
## Product descriptions

<table>
<thead>
<tr>
<th>Product</th>
<th>Schematic</th>
<th>Aerosol formation</th>
<th>Aerosol condensate</th>
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</thead>
</table>
| E-cigarette                   | ![E-cigarette schematic](image)
|                               |           | Heating of formulation containing nicotine           | ![E-cigarette condensate](image) |
| Tobacco Heating Product       | ![THP schematic](image)
|                               |           | Heating of tobacco                                    | ![THP condensate](image) |
Rationale for a framework to assess the risk reduction potential of tobacco & nicotine products

- Built on the foundations of chemical and toxicological studies
- *in vitro* models are extremely useful for early stage screening and assessing products in a fast paced industry
- Laboratory data are important but clinical biomarker studies required to demonstrate individual risk reduction
- Population studies required to understand real world use and assess population effects
- New scientific disciplines and approaches (AOP, ‘omics etc) used to connect the studies
10 steps to substantiating the risk reduction potential of tobacco & nicotine products

**TYPE OF STUDY**
- Post-market surveillance
- Consumer perception study
- Systems Science
- Biomarker of effect study
  - *in vitro* models of disease
  - Exposure and pharmacokinetic studies
  - Computational toxicology
  - *in vitro* regulatory toxicology
  - Chemical and physical characterisation
  - Product design stability

**PURPOSE**
- Population risk reduction
- Individual risk reduction
  - Toxicant exposure reduction
  - Stewardship science
Novel products = novel chemistries

- Tobacco smoke is a complex mixture:
  - >6,000 identified compounds
  - 150 compounds classed as “tobacco smoke toxicants”
  - Multiple ‘toxicant lists (eg. WHO, FDA etc.)

- Reduced toxicant yields possible:
  - Control of product chemistry
  - Absence of pyrolysis / combustion
  - Absence of tobacco

- Need to plan for unknown compounds produced from new products
Dual approach to chemistry

Toxicant measurements

Chemical characterisation

in silico computational toxicology
Our latest results...

<table>
<thead>
<tr>
<th>Reference cigarette</th>
<th>Prototype Tobacco Heating Product</th>
<th>E-cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>100*</td>
<td>8*</td>
<td>5*</td>
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</table>

*Number of peaks as a percentage of the response from the reference cigarette (GC-GC-MS scans)
Chemistry reductions driving reduced responses *in vitro*

- **Mutagenicity (Particulate matter)**
  - No observed mutagenicity for prototype tobacco heating product or e-cigarette under these test conditions

- **Mutagenicity (Whole aerosol)**
  - Significant reductions in cytotoxicity for THP and E-cigarette versus reference cigarette

- **Cytotoxicity (Whole aerosol)**

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**in vitro toxicology**
in vitro Models of disease

- Adverse Outcome Pathway approach linking toxicant exposure to disease end points
- Based on ‘Toxicity testing in the 21st Century’

1. Toxicant Exposure
   - Inflammation & Oxidative Stress
     - Lung Airway cell response
     - DNA Damage
     - Altered endothelial repair
   - Toxicant exposure reduction
   - Lung Tissue remodelling
   - Cell transformation
   - Endothelial dysfunction

   COPD
   Cancer
   CVD

1. Ankley et al., 2010
2. Andersen et al., 2007
**in vitro Models of disease**

- Models capable of assessing products across the risk spectrum

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1. **Ankley et al., 2010**
2. **Andersen et al., 2007**
Promising preliminary results...

**Inflammation & Oxidative stress**

- THP and e-cigarettes showed:
  - greatly reduced reductions in oxidative stress versus reference cigarette
  - no genotoxic responses under these test conditions

**DNA damage**
Promising preliminary results...

**Altered endothelial repair**
- E-cigarette and THP show less endothelial dysfunction
- Significant reduction in tumor promotion observed with E-cigarette and THP versus reference cigarette

**Cell transformation**

*in vitro models of disease*
- 3-D lung model system using epigenetic markers (μRNA)
- Increased (i) perturbations and (ii) inflammatory markers for reference cigarette in comparison to cigarettes
Risk reduction potential of new products*

- Dependent on the reduced toxicity of the product

- Dependent on the number of people who switch from cigarettes

Harm reduction = Reduced risk x Number who switch

*Clive Bates (former director of Action on Smoking & Health, UK), E-cig summit, 2013
Convincing consumers to switch

- Different nicotine kinetics with different novel products
- Some products beginning to show efficacy profiles similar to cigarettes

*Amalgamation of data from multiple studies*
Population effects model*

Deborah Arnott (ASH)* “…The number of ex-smokers who are staying off tobacco by using electronic cigarettes is growing, showing just what value they can have. But the number of people who wrongly believe that vaping is as harmful as smoking is worrying. The growth of this false perception risks discouraging many smokers from using electronic cigarettes to quit and keep them smoking instead which would be bad for their health and the health of those around them…”

*Deborah Arnott, Chief Executive of Action on Smoking and Health (ASH), UK
Consolidated approach required to assessing products

Public Health England

E-cigarettes: an evidence update
A report commissioned by Public Health England

"There has been an overall shift towards the inaccurate perception of EC being as harmful as cigarettes over the last year in contrast to the current expert estimate that using EC is around 95% safer than smoking."

Center for Tobacco Products

"From 2011 to 2014 e-cigarette use among high school students increased nearly 800%"
How do we quantify risk?

Weight of evidence approach
- Phased approach
- Review data in totality

Data Integration
- Integrate responses - test product v control
- Individual & population level

Delphi panel approach*
- Panel of experts
- Weighting given to each dataset

*Reproduced from Nutt et al. (2014) *Eur Addict Res*
Towards a greater consensus on reduced risk products

- Product standards
- Harmonisation of approaches
- Agreement on methodologies and standardisation across the various study types
- Transparency of datasets through publication
- Cross functional working with regulators, academia, industry and public health scientists
Take home messages

- Evolution of consumer relevant reduced risk tobacco and nicotine products
- Preliminary data shows that these products have the potential to reduce risk versus cigarettes
- Series of integrated studies over time required to substantiate reduced risk
- Common product standards and industry testing platform required
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