Integrating chemical, toxicological and clinical research to assess the potential of reducing health risks associated with cigarette smoking through toxicant regulation

Christopher Proctor, Christopher Shepperd, Kevin McAdam, Alison Eldridge and Clive Meredith

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Central question and overview of the presentation

Is there scientific evidence to suggest “reduced toxicant cigarettes” have a distinct place in a tobacco and nicotine risk continuum?

• The risk continuum
• Harmful and potentially harmful constituents in tobacco smoke
• Developing reduced toxicant prototype (RTP) cigarettes
• Chemistry
• Toxicology
• Clinical
• Implications for toxicant reduction regulations
sometimes a cigarette is just a cigarette

Chapter 7: Selective reduction
PREP: A product that (1) results in the substantial reduction in exposure to one or more tobacco toxicants and (2) can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects.

Reducing harm from tobacco use, Professor Ann McNeil and Professor Marcus Munafo, Journal of Psychopharmacology, October 3, 2012

Combustible tobacco products

Non-combustible tobacco products

Non-combustible nicotine products

Cigarettes
Cigars
Pipes

Chewing tobacco
Tobacco gum
Snus

E-cigarettes
NRTs

Most dangerous

Least dangerous
British American Tobacco “continuum of toxicant exposure”

- Conventional Cigarettes
- Reduced Toxicant Cigarettes
- Heat not Burn Cigarette-Like Devices
- Low-Toxicant Smokeless Tobacco
- Nicotine Products

Higher Exposure to Toxicants

Lower
The research challenge

• Develop “reduced toxicant prototype” cigarettes with substantially lower yields of as many toxicants as possible while maintaining reasonable sensory acceptability

• To do this develop new technologies capable of selectively reducing “priority toxicants”

• Evaluate whether these prototypes have the potential to reduce exposure compared to conventional cigarettes, and whether any reduce exposure is likely to be associated with reduced health risk to one or more diseases
Harmful and potentially harmful constituents of tobacco and tobacco smoke
Constructing a reduced toxicant prototype cigarette

Technologies:
Ion exchange resin (Branton et al, Chem. Centr J., 5, 15, 2011)
Split-tipping (Dittrich et al, Springer Plus, 3, 374, 2014)
Chemistry of the RTP

- **Aromatic Amines**
- **Nitrosamines**
- **Volatile Organics**
- **Saturated Carboxyls**
- **Semi Volatiles**
- **PAH's**
- **Other Carboxyls**
- **Phenols**
- **Miscellaneous**

Each category includes graphs showing data for different compounds, with labels indicating specific chemicals and data points for ISO, HCl, and WG9.
Creating a “cumulative toxicant index”

• We wanted to assess the “performance” of the RTP against a range of conventional cigarettes across a range of toxicants
• Used a database “Hoffman” analyte” yields measured at HCI of 120 commercial products from a variety of countries
• Normalised the median for each toxicant as 100, and scaled the yield for each product against this
• Summed the scaled values for all toxicants to give cumulative score
“Cumulative toxicant index” of a range of commercial cigarettes versus Reduced Toxicant Prototype cigarettes
In Vitro toxicology

- We conducted a battery of *in vitro* toxicological tests

- For the particulate matter collected for RTP and control we used the Ames test, mouse lymphoma assay, in vitro micronucleus test and Neutral Red assay

- Some reductions in bacterial mutagenicity and mammalian genotoxicity were seen in the RTP compared to control, consistent with lower levels of some toxicants such as heterocyclic amines and the dilution of PM resulting from the tobacco substitute sheet

(Crooks et al, The combination of two tobacco blend technologies to reduce tobacco smoke toxicant yields: Assessment in the Ames and *in vitro* micronucleus test, 10th International Conference on Environmental Mutagens, 2014, see www.bat-science.com/Library)
In vitro toxicology

Whole smoke cytotoxicity

Intercellular ROS

Glutathione
Computational toxicology

- We have a multi-staged approach to assessing toxicants through the use of computational toxicology
  - Margins of exposure (MOE)
  - Modes of Action (MOA)
  - Physiologically based pharmacokinetic modelling (PBPK)

Margin of exposure priority assignments for a reference cigarette, commercially-based control cigarette and a reduced toxicant prototype

<table>
<thead>
<tr>
<th>Smoke constituent</th>
<th>3R4F</th>
<th>Control cigarette</th>
<th>Reduced toxicant prototype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrolein</td>
<td>Top priority</td>
<td>Top Priority</td>
<td>Top Priority</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>Top priority</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Top priority</td>
<td>Top priority</td>
<td>Top Priority</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>Very high</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Isoprene</td>
<td>Very High</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Styrene</td>
<td>Very high</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Benzene</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>m- + p-Cresols</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>NNK</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Toluene</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>NNN</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Estimates of toxicant yields necessary to achieve a low priority assignment in modes of exposure calculations

<table>
<thead>
<tr>
<th>Compound</th>
<th>HCl* 3R4F yield µg/cig</th>
<th>MOE from HCl 3R4F (assuming 20 cigs daily)</th>
<th>Target µg/cig for 10,000 MOE (assuming 20 cigs per day and 100% retention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrolein</td>
<td>155</td>
<td>0.3</td>
<td>0.0046</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>68.1</td>
<td>2</td>
<td>0.011</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.146</td>
<td>6</td>
<td>0.000086</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>1534</td>
<td>45</td>
<td>6.9</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>1.37 (ISO)</td>
<td>460</td>
<td>0.063</td>
</tr>
<tr>
<td>Benzene</td>
<td>104</td>
<td>252</td>
<td>2.6</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>76.5</td>
<td>220</td>
<td>1.7</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>9.24 (ISO)</td>
<td>424</td>
<td>0.4</td>
</tr>
<tr>
<td>NNK</td>
<td>0.243</td>
<td>278</td>
<td>0.0067</td>
</tr>
<tr>
<td>NNN</td>
<td>0.276</td>
<td>2759</td>
<td>0.076</td>
</tr>
<tr>
<td>Benzo(a)pyrene</td>
<td>0.0162</td>
<td>16805</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Overview of chemistry and toxicology

- Can substantially reduce yields of some but not all toxicants compared to commercial cigarettes.

- *In vitro* toxicology gives mixed results, but generally suggest this could result in some lower toxicological activity in some assays and little to suggest increase toxicology.

- Computational toxicology MOAs suggest that for some toxicants reducing the yields sufficiently to classify the levels of low priority may be impossible to achieve.
Clinical studies

• Two key clinical studies, built on a series of clinical studies determining the value of biomarkers of exposure

• First was a short term switching study focused on evaluating whether reduced HCl chemistry yields translated to reduced biomarkers of exposure toxicant yields in human volunteers
  
  (Shepperd et al, Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes, Reg Pharm Tox, 66, 1, 147, 2013)

• Second was a 6 month switching study focused on BOE and BOBE
Study Design

140 smokers supplied with control product for 2 weeks; baseline biomarker measures in clinic; 70 switched to RTP, 70 to visually different control (from cork to white tipping)

Clinical visits for sample collection/biomarker analysis at 1, 2, 3 and 6 months. Ambulatory visits to collect further supplies of cigarettes

Ex- and never smokers provide background levels of biomarkers of exposure and biological effect
Consumption data (baseline & on-study)

Observed consumption change initiated:

- Increased consumption monitoring (electronic diaries) and added questionnaire
- Set-up of independent Data Safety Monitoring Board (DSMB)
- Addition of post-study monitoring of cigarette consumption
Reasons for smoking more cigarettes
Scored (4-point scale) pre-set questions

The study cigarettes don’t last as long as my usual brand
I sometimes smoke one study cigarette soon after another
Study cigs. may be less harmful than my usual brand
I was in company of friends
The cigarettes are free of charge
The study cigarettes are very satisfying
The study cigarettes taste good
Being on the study
Work/job reasons such as stress, longer working hours
The study cigarettes are not very satisfying
I was on holiday
The study cigarettes taste bad
I am trying to smoke less
My lifestyle has changed
My usual brand may be less harmful than the study cigs.
Other people smoked some of these given cigarettes
The study cigarettes last longer as my usual brand

RTP (n=54)
Control (n=43)
**Consumption data (baseline, on-study & POST-STUDY)**

<table>
<thead>
<tr>
<th>Cigarettes Per Day</th>
<th>CONTROL</th>
<th>RTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean CPD per smoking group

- **CONTROL**
  - Baseline
  - On-study
  - Post-study

- **RTP**
  - Baseline
  - On-study

Each error bar is constructed using a 95% confidence interval of the mean.

= Clinical confinement
Biomarkers of effective dose

Acrylonitrile BoE in urine – half life around 8 hours

Acrylonitrile haemoglobin adduct – body residence time around 120 days
Biomarkers of Exposure

Nicotine

Acrolein

NNK

4-aminobiphenyl
Urinary mutagenicity

Each error bar is constructed using a 95% confidence interval of the mean
Biomarkers of biological effect
Conclusion of clinical studies

- Switching volunteers from a conventional cigarette to a reduced toxicant prototype can result in sustained reductions in exposure to some toxicants, as measured by biomarkers of exposure.

- Clinical designs of long term switching studies can cause changes in daily consumption.

- Some biomarkers of biological effect clearly distinguish smokers and non-smokers.

- We didn’t see clear changes in BOBE in this 6 months switching study – neither increases related to increased consumption nor decreases related to lower toxicant yields.

- Greater toxicant reduction may be necessary than can be achieved through modifying cigarettes.
“Cumulative toxicant index” comparing a range of commercial cigarettes, reduced toxicant prototype cigarettes, tobacco heating systems and e-cigarettes
Is there scientific evidence to suggest “reduced toxicant cigarettes” have a distinct place in a tobacco and nicotine risk continuum?
Implications for the regulation of tobacco and tobacco smoke toxicants

Potential toxicant regulations:

FDA could set product standards related to yields of toxicants

WHO’s TobReg proposed a complex scheme of toxicant monitoring across a complete country/market followed by limits on nine toxicants

   NNK and NNN limited at median of the dataset
   Acetaldehyde, acrolein, benzene, benzo [a] pyrene, 1,3-butadiene,
   carbon monoxide and formaldehyde limited at 125% of the median

(or against limits identified from either an international dataset or a Canadian brands dataset)

Results of our market surveys

Market A – Mixed tobacco blend, low filter charcoal incidence
Market B – Mixed tobacco blend, high filter charcoal incidence
Market C – Predominantly flue-cured blend
Market D – Predominantly US blended cigarettes
Determining the potential public health impact of toxicant regulations

• Tobacco smoking causes a wide range of diseases and it is exposure to toxicants in tobacco smoke

• The epidemiology typically shows dose-response relationships, and reductions in risk following cessation

• Our studies suggest limited scope for reducing health risks substantially by modifying toxicants in cigarettes, but there are important limitations to our studies

• More research on which toxicants, or combinations of toxicants, are the drivers of smoking-related diseases, and the dynamic range of their actions, remains important

• Research evaluating the effects of tobacco heating devices and e-cigarettes may provide insights
Acknowledgements

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