EXTENSION OF THE MARGIN OF EXPOSURE (MOE) APPROACH FOR THE PRIORITISATION OF TOBACCO SMOKE TOXICANTS

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INTRODUCTION

Tobacco smoke contains over 6,000 constituents [1], approximately 150 of which have known associated toxicological effects and can be termed toxicants [2]. We have previously presented the margin of exposure (MOE), as a tool for the initial prioritisation of individual tobacco smoke toxicants [3]. The application of the MOE calculation is a useful approach for tobacco smoke toxicants with data sets which meet our criteria for inclusion. For toxicants without such data sets, it has not been possible to calculate an MOE, thus preventing prioritisation.

OBJECTIVES

- Investigate the options available to extend the MOE data selection criteria, to allow inclusion of a wider range of data sets.
- Outline the process by which additional data sets can be included to generate alternative points of departure (PoDs) and ultimately MOEs.
- Apply this extended approach to a set of example toxicants and critique the utility of the new MOE approach.

SELECTION CRITERIA CONSIDERATIONS

To be able to extend the MOE approach, it was imperative that a structured approach was established to determine the most appropriate studies. To do this, it was necessary to identify the key variables within a toxicological study impacting the relevance of any given data set, specifically to the prioritisation of individual tobacco smoke toxicants.

Based on the initial examination, it was concluded that the following are key criteria:

1. Species – human epidemiological data would be the gold standard, however, these data sets are very rare for single toxicant exposure, as they are often confounded by other exposures and/or do not contain data on multiple doses. In general, data sets from rodent toxicity studies are most often used.
2. Route of Exposure – for tobacco smoke toxicants the ideal route of exposure is via inhalation. Any other route must be considered sub-optimal for tobacco smoke related MOE calculations.
3. Lesion Type – lesions should be relevant to those associated with tobacco smoke toxicants, i.e. focused initially on lung, then followed by cardiovascular lesions (as determined by the three main smoke related diseases; cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD)) and/or the key events identified by the postulated mode of actions (MOAs).
4. Study Length – studies should ideally be of a chronic length, i.e. studies of over 104-weeks or greater should be the gold standard, whereas a single dose or acute study (i.e. four weeks) would be considered sub-optimal.
5. Point of Departure (PoD) – the gold standard would be a data set which has multiple doses and produces a dose-response curve, allowing for benchmark dose analysis; sub-optimal would be the use of an alternative PoD, i.e. a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) value.
6. Read across – the last resort for toxicants where still no suitable data exist, would be to use data sets from structurally similar toxicants.

For each of these key criteria, the merits for inclusion of an additional data set should be reviewed on a case-by-case basis. Most critical of all is to ensure that any MOE generated from data sets not meeting the original criteria should be coupled with clear detailed narratives highlighting the limitations of these MOEs. These ball park MOEs are important in allowing the initial prioritisation of these toxicants to help steer whether they are investigated further using our proposed qualitative risk assessment (QRA) framework [4].

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Table 1. Summary of Examples MOEUs using the Extended Approach

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Species</th>
<th>Route of Exposure</th>
<th>Lesion Type</th>
<th>Study Length</th>
<th>Suitable for BMDL Analysis</th>
<th>PoD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>Human</td>
<td>Inhalation</td>
<td>Lung lesions concurrently with MOA</td>
<td>Chronic (104 weeks)</td>
<td>Yes</td>
<td>Chronic (104 weeks)</td>
</tr>
<tr>
<td>NKK</td>
<td>Rats</td>
<td>Drinking Water</td>
<td>Lung lesions - concurrently with MOA</td>
<td>Sub-Chronic (13 weeks)</td>
<td>Yes</td>
<td>Chronic (104 weeks)</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>Mice</td>
<td>Gavage</td>
<td>Lung lesions - not concurrently with MOA</td>
<td>Acute (6 weeks)</td>
<td>Yes</td>
<td>Chronic (104 weeks)</td>
</tr>
</tbody>
</table>

As can be seen in the table above, there are positive (dark blue) and negative (light blue) aspects to each of the studies used for MOE assessment. This clearly illustrates the need to handle each data set on a case-by-case basis and to select as relevant a data set for each individual toxicant as possible. It also shows the potential for an innovative approach with each of the MOE assessments, to explain the positive and negative aspects of the data sets included, as well as the overall confidence in the final MOE prioritisation.

DISCUSSION

The original criteria we set out for MOE assessment of individual tobacco smoke toxicants significantly restricted the types of data which could be included [3]. It was important that the key data sets were variable, to enable the extended process to be mapped. This process flow now allows the interpretation of the relative suitability and quality of a wide range of data sets in a systematic manner, which ultimately aids in the interpretation of the MOE assessment.

Importantly, our expansion of the criteria for MOE calculations now enables evaluation and prioritisation of toxicants for which the original data sets precluded assessment by BMDs. Although the majority of these new MOE assessments cannot be considered as gold standard, they are important in providing an initial indication of the priority of the toxicant, as well as helping to focus further research as part of our QRA framework.

REFERENCES