Cumulative risk assessment of three aldehydes present in tobacco smoke: Application of Margin of Exposure (MOE) and Mode of Action (MOA) evaluations

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INTRODUCTION

In January 2012, the US Food and Drug Administration (FDA) outlined seven research priority areas relating to tobacco products (1). Research area three focused on “reducing toxicity and carcinogenicity of tobacco products and smoke”. This has been coupled with an increased interest in further characterising tobacco smoke toxicants both from the perspective of future regulatory frameworks aimed at monitoring or lowering toxicant levels and from the perspective of tobacco product development focused on selective toxicant reduction as part of broader harm reduction initiatives (2,3,4).

BACKGROUND

We have previously described the use of the Margin of Exposure (MOE) model as part of a quantitative risk assessment paradigm for tobacco smoke toxicants, in conjunction with the preparation of mode of action (MOA) reviews for individual tobacco smoke toxicants (5).

To generate a combined MOE assessment two assumptions are made: 1) the compounds are structurally similar and 2) that they share similar toxicological properties. The generation of MOAs reduces the number of assumptions made in combined MOE assessment by ensuring similar toxicological properties and lesion types are seen.

OBJECTIVES

This is the first study to investigate the potential application of MOA analysis to direct a cumulative risk assessment of tobacco smoke toxicants. To illustrate this process, a cumulative risk assessment for three saturated aldehydes, namely acetaldehyde, formaldehyde and propionaldehyde is presented here.

MARGIN OF EXPOSURE (MOE)

We propose the application of the MOE model, as described by the European Food Safety Authority (EFSA) guidelines (6). The MOE approach permits the analysis of both genotoxic and carcinogenic compounds. A MOE is a ratio between a benchmark dose (a reference point derived from either experimental or epidemiological dose-response data) and the specific human exposure. The view from EFSA is that a MOE greater than 10,000 may be considered a high priority for risk management actions (6).

CUMULATIVE MOE

A cumulative MOE can be calculated as the reciprocal of the sum of the reciprocals of the MOEs for each compound sharing a common MOA, following the formula below (9).

\[
\text{MOE}_{\text{total}} = \frac{1}{(1/\text{MOE}_1) + (1/\text{MOE}_2) + (1/\text{MOE}_3)}
\]

For each of the key events identified in the postulated MOA, a combined MOE has been calculated for the three aldehydes (Tables 1-5).

RESULTS

TABLE 1. GENOTOXICITY MOEs GENERATED FOR THE THREE ALDEHYDES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (16)</td>
<td>Micronuclei (human)</td>
<td>1.7</td>
</tr>
<tr>
<td>Formaldehyde (17)</td>
<td>Micronuclei (human)</td>
<td>0.1</td>
</tr>
<tr>
<td>Propionaldehyde (18)</td>
<td>Chromosome Aberrations (in vitro - CHO Cells)</td>
<td>12.3</td>
</tr>
</tbody>
</table>

\[
\text{MOE}_{\text{total}} = \frac{1}{(1/1.7) + (1/0.1) + (1/12.3)} = 0.09
\]

TABLE 2. CYTOTOXICITY MOEs GENERATED FOR THE THREE ALDEHYDES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (13)</td>
<td>Laryngeal Degeneration with Hyper/ Metaplasia of Epithelium (Female Rats)</td>
<td>1181</td>
</tr>
<tr>
<td>Formaldehyde (14)</td>
<td>Disarrangement of Respiratory Epithelium (Male Rats)</td>
<td>92.3</td>
</tr>
<tr>
<td>Propionaldehyde (15)</td>
<td>Nasal Atrophy (Male Rats)</td>
<td>1364</td>
</tr>
</tbody>
</table>

\[
\text{MOE}_{\text{total}} = \frac{1}{(1/1181) + (1/92.3) + (1/1364)} = 80.55
\]

TABLE 3. HYPER/METAPLASIA MOEs GENERATED FOR THE THREE ALDEHYDES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (16)</td>
<td>Laryngeal Squamous Hyper/Metaplasia with Keratinisation (Female Rats)</td>
<td>693</td>
</tr>
<tr>
<td>Formaldehyde (17)</td>
<td>Nasal Turbinate Squamous Metaplasia (Male &amp; Female Rats)</td>
<td>7.5</td>
</tr>
<tr>
<td>Propionaldehyde (15)</td>
<td>Squamous Metaplasia (Male rats)</td>
<td>12732</td>
</tr>
</tbody>
</table>

\[
\text{MOE}_{\text{total}} = \frac{1}{(1/693) + (1/7.5) + (1/12732)} = 7.42
\]

TABLE 4. TUMOUR MOEs GENERATED FOR THE THREE ALDEHYDES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (16)</td>
<td>Nasal Adenocarcinoma (Male Rats)</td>
<td>143</td>
</tr>
<tr>
<td>Formaldehyde (17)</td>
<td>Nasal Squamous Cell Carcinoma (Female Rats)</td>
<td>154</td>
</tr>
<tr>
<td>Propionaldehyde</td>
<td>NO DATA AVAILABLE</td>
<td></td>
</tr>
</tbody>
</table>

\[
\text{MOE}_{\text{total}} = \frac{1}{(1/143) + (1/154)} = 74.15
\]

CONCLUSION

In all instances, the cumulative MOEs are lower than 100 suggesting that these three saturated aldehydes (that are known to share a common MOA) are of very high priority for risk reduction research (19). This is the first attempt at generating a combined MOE assessment for a group of toxicants found in tobacco smoke, based on the available toxicological information. We propose the use of MOAs to group tobacco smoke toxicants as a first step towards a physiologically relevant cumulative risk assessment.

REFERENCES

1. Center for Tobacco Products, Food and Drug Administration 2013
6. EFSA meeting summary report EFSA/WHO international conference with support of ILSI Europe on risk assessment of compounds that are both genotoxic and carcinogenic. 16-18 November 2005. Brussels.
11. Center for Tobacco Products, Food and Drug Administration 2013