4-N-Nitrosomethylamino-1-(3-pyridyl)-1-butanone (NNK) and N-Nitrosonornicotine (NNN): Risk Assessment of two tobacco-specific nitrosamines (TSNAs)

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Table 1. Summary of MOEs for NNK

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study Details</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drinking water, Male Rats</td>
<td>Lung or nasal tumours</td>
<td>278</td>
</tr>
<tr>
<td>2</td>
<td>Subcutaneous injection 20 weeks, Male &amp; Female Rats</td>
<td>Lung or nasal tumours</td>
<td>801 – 15,069</td>
</tr>
<tr>
<td>3</td>
<td>Intrapulmonary injection 7 weeks, Female Mice</td>
<td>Lung tumours</td>
<td>3,439</td>
</tr>
<tr>
<td>4</td>
<td>Single intraperitoneal injection, Female Mice</td>
<td>Lung adenomas</td>
<td>89,544</td>
</tr>
</tbody>
</table>

Taking the MOEs generated from the chronic study (5), which would be considered the most relevant for a smoking exposure scenario, suggest NNK to be a high priority for risk management actions. However, no inhalation studies are currently available for NNK and route of exposure extrapolation is required.

Table 2. Summary of MOEs for NNN

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study Details</th>
<th>Endpoint</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Subcutaneous injection 20 weeks, Male &amp; Female Rats</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>Intrapulmonary injection 7 weeks, Female Mice</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>Intragastric instillation 78 weeks, Male &amp; Female Rats</td>
<td>Lung tumours</td>
<td>13,632 – 19,655</td>
</tr>
<tr>
<td>9</td>
<td>Intragastric injection 25 weeks, Male Rats</td>
<td>N/A</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The majority of MOEs generated for NNN are above 10,000, including MOEs from a route of exposure extrapolation is required.

The key events in our postulated mode of action (MOA) for both NNK and NNN involve metabolic activation, DNA damage and genotoxicity (mutation) leading to cell proliferation and tumours, as follows:

1) Transport into the target tissue
2) Metabolic activation of NNK or NNN to a reactive intermediate
3) DNA adduct formation by reactive species
4) Mutation in critical gene(s)
5) Cell proliferation (assumed)
6) Tumour development

Figure 3. Flow diagram of QRA framework

Figure 4. A summary of the key events in the postulated MOA for NNK and NNN

The postulated MOA was used to inform assay selection for further testing. Genotoxicity and mutagenicity of NNN and NNK was assessed in vitro.

REFERENCES