DOSSIER ON TITANIUM DIOXIDE
- PART 1 - NM 105
ANNEX 19

Series on the Safety of Manufactured Nanomaterials
No. 54

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Toxicokinetics, Metabolism and Distribution

TiO$_2$ NM-105 rutile/anatase (CAS N° 13463-67-7)

<table>
<thead>
<tr>
<th>Route</th>
<th>intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Rat Serum Albumin (RSA) 0.05% diluted (9:1) v/v in 10 x phosphate buffer pH 7.4. Volume: 1 ml/animal</td>
</tr>
<tr>
<td>Dose(s) used</td>
<td>10.5 mg/kg bw/d.</td>
</tr>
<tr>
<td></td>
<td>5 day cumulative dose: 52.5 mg/kg bw</td>
</tr>
<tr>
<td>Administration</td>
<td>Single (day 1) or repeated (on 5 consecutive days, day 1-5)</td>
</tr>
<tr>
<td>Sampling time</td>
<td>- Single admin: day 2 and day 90</td>
</tr>
<tr>
<td></td>
<td>- Repeated admin: day 6, 14, 30 and 90</td>
</tr>
<tr>
<td>Animals</td>
<td>Wistar Gender: male and female</td>
</tr>
<tr>
<td>Treated Groups</td>
<td>3-4 M + 2-3 F</td>
</tr>
<tr>
<td>Control</td>
<td>vehicle 3-4 M + 2-3 F</td>
</tr>
<tr>
<td>Statistical Methods</td>
<td>Describe statistical methods used.</td>
</tr>
<tr>
<td>Actual Dose(s)</td>
<td>Measured or actual doses/exposure concentrations achieved.</td>
</tr>
<tr>
<td>Excretion Routes</td>
<td>List all routes of excretion monitored in study (urine, faeces, exhaled air, etc.). Provide sampling times. For skin penetration studies, include details on measurement of skin residues.</td>
</tr>
<tr>
<td>Body Fluids Sampled</td>
<td>Blood sampling: - single admin (day 1): t=5, t=10, t=20, t=30 minutes,</td>
</tr>
<tr>
<td></td>
<td>- Repeated admin (day 5): t=1, t=2, t=4, and t=8 hour</td>
</tr>
<tr>
<td>Tissues Sampled</td>
<td>liver, spleen, kidneys, lung, brain, bone including bone marrow (femur),</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Ti</td>
</tr>
<tr>
<td>Metabolites CAS</td>
<td>List CAS numbers of all metabolites.</td>
</tr>
<tr>
<td>Results</td>
<td>Provide detailed results for all parameters; including percentage absorbed (bioavailability), half-life information, Km, Vmax, and similar measures (for skin penetration studies include flux and permeability coefficient). Also note the routes of elimination for each metabolite.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>NM 105 is rapidly distributed from the bloodstream to the organs with liver &gt; spleen &gt; lung &gt; kidney to a lesser extent</td>
</tr>
<tr>
<td></td>
<td>Its concentration declines between day 6 and 90 after administration in all</td>
</tr>
</tbody>
</table>
the organs although level of Ti remains above the control liver and spleen.

**Reliability**
Note the reliability of the study (for example, “Klimisch” code). Present a narrative clarifying the rationale for the reliability code.

**Reference**
Present full citation of the study summarised.

**General Remarks**
Use for any other comments necessary for clarification.

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**Results**

Major target organs following single administration: liver > spleen > lung > kidney to a lesser extent

Major target organs following repeated administration: liver > spleen > lung and kidney to a lesser extent. Significant accumulation in brain and heart compared to the control

NM 105 is removed from the blood within 8 h

Decline of Ti concentration between day 6 and 90 after administration in all the organs, indicative of excretion or redistribution of Ti to other organs. However, the level of Ti remain above the control in liver and spleen.

Ti tissue distribution (μg/g tissue) in male rats after repeated intravenous TiO₂ (NM-105) administration. Mean ±SD (n=4)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Day 6</th>
<th>Day 14</th>
<th>Day 30</th>
<th>Day 90</th>
<th>Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>μg TiO₂/g tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>283±36</td>
<td>213±33</td>
<td>166±35</td>
<td>51±39</td>
<td>0.08±0.05</td>
</tr>
<tr>
<td>Lung</td>
<td>11±1</td>
<td>7±2</td>
<td>2.78±0.72</td>
<td>0.54±0.35</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.2±0.4</td>
<td>0.90±0.06</td>
<td>0.41±0.20</td>
<td>0.07±0.03</td>
<td>&lt; LOD</td>
</tr>
<tr>
<td>Spleen</td>
<td>138±23</td>
<td>82±12</td>
<td>96±26</td>
<td>37±9</td>
<td>0.16±0.08</td>
</tr>
</tbody>
</table>