Draft NTP Technical Report TR574 on Pyrogallol

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Pyrogallol – Background

• Natural decomposition by-product of plant tannins
  - Soil, tea, smoked fish/meat, tobacco smoke, industrial waste (sawmills, instant coffee, rubber, coal)

• Use in manufacture and consumer products
  - Dyes: hair, fur, wool, leather, surgery sutures
  - Corrosion inhibitor: boilers, semiconductor, microchips
  - Fine arts photographic developer
  - Historic use as topical antipsoriatic (2%-10%)
Pyrogallol – Nomination

- By private individuals
- Frequent occurrence in natural and manufactured products, including hair dyes
- Lack of carcinogenicity data
Pyrogallol – Study Design

- Genetic toxicity studies (in vitro and in vivo)
- Contact hypersensitivity
- 90-day studies
- 2-year studies

- Dermal route
  - Occupational dermal exposure is the most common route in humans
Pyrogallol – Genetic Toxicity Studies

• Bacterial gene mutation tests (in vitro)
  ▪ With metabolic activation: positive in 3 strains
  ▪ Without metabolic activation:
    ▪ Equivocal in two *S. typhimurium* strains
    ▪ Positive in one *E. coli* strain

• B6C3F1/N mice micronucleus test
  ▪ 90-day dermal (peripheral blood erythrocytes)
    ▪ Equivocal in males, negative in females
  ▪ 3-day intraperitoneal (bone marrow reticulocytes)
    ▪ Negative in males
Pyrogallol – Contact Hypersensitivity Study

- 0, 0.125%, 0.25%, 0.5%, 1.0%, 2.5%, 5%, 10%, 25% and 50% w/v
  - Female BALB/c mice

Findings:
- Weak Sensitizer
  - Positive at 0.5% in Local Lymph Node Assay
  - Negative in Mouse Ear Swelling Test
- Strong Irritant at all doses
Pyrogallol – 90-Day Dermal Studies

- 5 doses at max concentration
  - F344/N rats: 0, 9.5, 18.75, 37.5, 75, 150 mg/kg
  - B6C3F1/N mice: 0, 38, 75, 150, 300, 600 mg/kg

- Findings:
  - All animals survived, no significant changes in body weight
  - Site of application irritation, inflammation, hyperkeratosis and hyperplasia - Both species and at all doses
  - Low incidence of site of application ulcers (≥ 150 mg/kg)
## Rat – 90-Day Non-neoplastic SOA Lesions

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0</th>
<th>9.5</th>
<th>18.75</th>
<th>37.5</th>
<th>75</th>
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<td><strong>F344/N Males</strong></td>
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<tr>
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<td>10** (1.0)</td>
<td>10** (1.0)</td>
<td>10** (1.0)</td>
<td>10** (1.5)</td>
<td>10** (1.4)</td>
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<tr>
<td></td>
<td>0</td>
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<td>10** (1.3)</td>
<td>10** (1.7)</td>
<td>10** (2.2)</td>
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</tr>
<tr>
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<td>0</td>
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<td>9** (1.2)</td>
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<td>10** (1.9)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
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<td><strong>F344/N Females</strong></td>
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<td>10</td>
<td>10</td>
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<td>10</td>
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<td>Squamous Hyperplasia</td>
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<td>10** (1.3)</td>
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<td>Hyperkeratosis</td>
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<td>10** (2.1)</td>
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<td>0</td>
<td>8** (1.0)</td>
<td>10** (1.5)</td>
<td>9** (1.8)</td>
<td>10** (2.0)</td>
<td>10** (1.8)</td>
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</tbody>
</table>

** Significantly different (P≤0.01) from vehicle control group by Fisher exact test

Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
Pyrogallol – 2-Year Dermal Studies

• 0, 5, 20, 75 mg/kg rats and mice

• Dose rationale:
  – Doses ≥ 150 mg/kg were too high for a 2-year study due to the increase in the severity of chronic active inflammation and the presence of ulcers.
  – Use of 38 mg/kg was discussed but upon pathology review of the skin lesions, 75 mg/kg was selected as a sufficiently challenging high dose for a 2-year study.
  – Lesions were seen as low as 10 mg/kg, therefore 5 mg/kg was selected as the lowest dose for the 2-year study.
Pyrogallol – 2-Year Dermal Studies

- 0, 5, 20, 75 mg/kg rats and mice

- Findings:
  - Survival and body weights of treated rats and male mice not different from controls
  - Decreased survival and weight gain in 75 mg/kg female mice
  - Non-neoplastic lesions at application site, same as 13-week
    - Both species
    - At all doses for most lesions
  - Mice had more types of lesions than rats (sebaceous gland hyperplasia, fibrosis, pigmentation), and outside app. site
    - Mammary gland hyperplasia in 75 mg/kg female mice
  - Treatment-related site of application tumors in mice (not in rats)
### Mice – 2-yr Study SOA Tumors

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0</th>
<th>5</th>
<th>20</th>
<th>75</th>
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<tbody>
<tr>
<td><strong>B6C3F1/N Males</strong></td>
<td>N</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Squamous Cell Papilloma</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>2 (4%)</td>
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<td>Historical Controls</td>
<td>same route/vehicle:</td>
<td>0/200 (0%)</td>
<td>1/1150 (0.1%)</td>
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<tr>
<td><strong>B6C3F1/N Females</strong></td>
<td>N</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>0***</td>
<td>0</td>
<td>0</td>
<td>4* (8%)</td>
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<tr>
<td>Historical Controls</td>
<td>same route/vehicle:</td>
<td>1/348 (0.3%)</td>
<td>1/1198 (0.2%)</td>
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</tr>
<tr>
<td></td>
<td>all routes/vehicles:</td>
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</table>
Pyrogallol – Conclusions

- Under the conditions of these 2-year dermal studies, there was:
  - No evidence of carcinogenic activity of pyrogallol in male or female F344/N rats administered 5, 20, or 75 mg/kg.
  - There was equivocal evidence of carcinogenic activity of pyrogallol in male B6C3F1/N mice based on increased incidences of squamous cell papilloma of the skin at the site of application.
  - There was some evidence of carcinogenic activity of pyrogallol in female B6C3F1/N mice based on increased incidences of squamous cell carcinoma of the skin at the site of application.
  - Dermal administration of pyrogallol caused increased incidences of nonneoplastic lesions of the skin at the site of application in male and female rats and mice; skin adjacent to the site of application in male and female mice; and mammary gland in female mice.