Report on the NTP Technical Reports
Peer Review Panel Meeting
May 22, 2014

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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 9-10, 2014
• NTP conducts rodent toxicity and cancer studies on agents of public health concern to identify potential hazards for human health

• NTP technical reports describe the methods, results, and NTP conclusions as “levels of evidence” for carcinogenic activity under the specific conditions of the study
Levels of Evidence of Carcinogenic Activity

**Clear evidence:** Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy

**Some evidence:** Chemical-related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence

**Equivocal evidence:** Marginal increase of neoplasms that may be chemical related

**No evidence:** No chemical related increase in neoplasms

**Inadequate study:** Major limitations preclude interpretation
• Bromodichloroacetic acid (TR-583)
  – F344/NTac Rats and B6C3F1/N Mice

• Indole-3-Carbinol (TR-584)
  – Harlan Sprague Dawley Rats and B6C3F1/N Mice

• Green Tea Extract (TR-585)
  – Wistar Han Rats and B6C3F1/N Mice

• Cimstar 3800 (TR-586)
  – Wistar Han Rats and B6C3F1/N Mice
Technical Reports Peer Review Panel

- Hillary Carpenter III, PhD, Minnesota Department of Health, Retired (Panel Chair)
- Michael W. Conner, DVM, Theravance, Inc
- Michelle V. Fanucchi, PhD, University of Alabama
- Charles R. Mahrt, DVM, MS, PhD, Eli Lilly and Company
- Jon C. Mirsalis, PhD, SRI International
- Gary H. Perdew, PhD, Pennsylvania State University
- Karen Regan, DVM, Research Pathology Services, LLC
- Sonya Sobrian, PhD, Howard University (BSC Liaison)
Charge to the Panel

• Review and evaluate the scientific and technical elements of the study and its presentation

• Determine whether the study’s experimental design, conduct, and results support the NTP’s conclusions regarding the carcinogenic activity and toxicity of the substance tested
Bromodichloroacetic acid (TR-583)

- Drinking water disinfection by-product
- The panel recommended accepting the conclusions (6 yes, 0 no, 0 abstentions) with following changes:
  - Recommended equivocal evidence instead of some evidence based on tumors of the brain and within the oral cavity of male rats
  - Recommended equivocal evidence instead of some evidence based on tumors of the brain in female rats

<table>
<thead>
<tr>
<th>Sex/Species</th>
<th>Level of Evidence</th>
<th>Neoplastic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Rats</td>
<td>Clear Evidence</td>
<td>Malignant mesothelioma and the combined incidences of epithelial tumors of the skin</td>
</tr>
<tr>
<td>Female Rats</td>
<td>Clear Evidence</td>
<td>Fibroadenoma and carcinoma of the mammary gland</td>
</tr>
<tr>
<td>Male Mice</td>
<td>Clear Evidence</td>
<td>Hepatocellular carcinoma and hepatoblastoma and increased incidences of adenoma or carcinoma (combined) of the Harderian gland</td>
</tr>
<tr>
<td>Female Mice</td>
<td>Clear Evidence</td>
<td>Hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma</td>
</tr>
</tbody>
</table>
**Indole-3-Carbinol (TR-584)**

- Dietary supplement; Breakdown product from consumption of cruciferous vegetables
- The panel recommended accepting the conclusions as written (4 yes, 2 no, 0 abstentions)

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<tbody>
<tr>
<td>Male Rats</td>
<td>No Evidence</td>
<td>75, 150, 300 mg/kg</td>
</tr>
<tr>
<td>Female Rats</td>
<td>Some Evidence</td>
<td>Malignant uterine neoplasms (primarily adenocarcinoma)</td>
</tr>
<tr>
<td>Male Mice</td>
<td>Clear Evidence</td>
<td>Liver neoplasms (hepatocellular adenoma, hepato cellular carcinoma, and hepatoblastoma)</td>
</tr>
<tr>
<td>Female Mice</td>
<td>No Evidence</td>
<td>62.5, 125, 250 mg/kg</td>
</tr>
</tbody>
</table>
Green Tea Extract (TR-585)

• Botanical dietary supplement

• The panel recommended accepting the conclusions with one edit (5 yes, 1 no, 0 abstentions)
  – Panel recommended that neoplasms of the female mouse tongue were not supportive of equivocal evidence, but were considered no evidence

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<th>Sex/Species</th>
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<tr>
<td>Male and Female Rats</td>
<td>No Evidence</td>
<td>100, 300, 1000 mg/kg</td>
</tr>
<tr>
<td>Male and Female Mice</td>
<td>No Evidence</td>
<td>30, 100, 300 mg/kg</td>
</tr>
</tbody>
</table>

Non-neoplastic lesions of the liver, glandular stomach, small intestine (duodenum, ileum, and jejunum), nose, lung, heart, and spleen in male and female rats; bone marrow of female rats; the nose, mandibular lymph node, and bone marrow of male and female mice; and the liver of male mice
• A metal working fluid used as lubricant and coolant

• The panel recommended accepting the conclusions (6 yes, 0 no, 0 abstentions) with one change:
  – Panel recommended the granular cell tumors of the brain to be considered as no evidence instead of equivocal evidence in male rats

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<tr>
<td>Male Rats</td>
<td>Equivocal Evidence</td>
<td>Prostate gland adenoma or carcinoma</td>
</tr>
<tr>
<td>Female Rats</td>
<td>Equivocal Evidence</td>
<td>Squamous cell papilloma or keratoacanthoma of the skin, Uterine adenocarcinoma or mixed malignant Mullerian tumor</td>
</tr>
<tr>
<td>Male Mice</td>
<td>No Evidence</td>
<td>10, 30, or 100 mg/m³</td>
</tr>
<tr>
<td>Female Mice</td>
<td>Some Evidence</td>
<td>Follicular cell carcinoma of the thyroid, Alveolar/bronchiolar adenoma or carcinoma</td>
</tr>
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</table>
Other Topics from the Review Meeting

• Change in Rat Stocks
  – F344/NTac to Wistar Han to Harlan Sprague Dawley

• Extended Evaluation of the Uterus
  – Indole-3-Carbinol, Green Tea Extract, Cimstar 3800

• Molecular Analysis
  – BDCA: Mammary Neoplasms (Female Rat) and Liver Neoplasms (Mice)
  – Indole-3-Carbinol: Liver tissue (Female Rat; 3-months)
Next Steps

- Comments reviewed by NTP staff
- Draft Technical Report edited (with QA report findings)
- NTP Technical Reports to be published in 2015
Questions