State-of-the-Science Workshop on Chemically-induced Mouse Lung Tumors: Applications to Human Health Risk Assessments

Session 2: Comparative Pathology

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.
MLTW Session 2: Comparative Pathology

• Co-chairs
  – Charles Wood  ○ US EPA
  – Mark Miller  ○ Wake Forest School of Medicine

• Panelists
  – Gary Boorman  ○ Covance, Inc.
  – Arun Pandiri  ○ Experimental Pathology Laboratories, Inc.
  – Laura Van Winkle  ○ University of California, Davis

• Other presenter
  – Dan Krewski  ○ University of Ottawa
Lung tumors are common findings in mouse carcinogenicity studies.
Mouse lung tumors have distinctive morphologic features

Mouse, Bronchiolo-alveolar adenoma (left) and carcinoma (right)
Mouse lung tumor incidence varies widely across strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>Incidence - control (%)</th>
<th>Incidence - induced (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/J</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td>CBA</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>C3H</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>DBA</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>C57Bl</td>
<td>7</td>
<td>57</td>
</tr>
</tbody>
</table>

_Hahn, Chapter 9, Toxicology of the Lung_
Mouse lung tumors are often cited in EPA risk assessments

US EPA CARC (2006): Mouse lung tumor outcomes cited in the cancer classification for 27/465 compounds. Of these...

- 19 (70%) were classified as Likely/Probable human carcinogens.
- 17 (63%) had a linear extrapolation method applied for risk assessment.
- 1 (4%) had an accepted lung tumor MOA.

http://www.epa.gov/pesticides/carlist/
US EPA Guidelines for Cancer Risk Assessment (EPA/630/P-03-001F)

- Released in 2005 to provide the framework for determining the mode(s) of action by which a chemical induces cancer
  - **Mode of Action:** Key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer
  - **Key Event:** Measurable precursor step that is a necessary element of the mode of action or a biologically based marker for such an element

http://www.epa.gov/cancerguidelines/
Weight-of-evidence criteria for evaluating a cancer mode of action

1. Measurable key events
2. Strength, consistency, specificity
3. Dose-response relationship
4. Temporal relationship
5. Biological plausibility, coherence
6. Alternative MOAs
8. Conclusion
9. Human relevance

Boobis et al 2006
http://www.epa.gov/cancerguidelines/
EPA/IPCS Human Relevance Framework

Not Relevant in Humans

(1) Is evidence sufficient to establish a MOA in animals?

Yes \rightarrow

(2) Is the animal MOA plausible in humans?

Yes \rightarrow

(3) Taking into account kinetic and dynamic factors, is the animal MOA plausible in humans?

No \leftarrow

No \leftarrow

Yes \rightarrow

Relevant in Humans

Boobis et al 2006

http://www.epa.gov/cancerguidelines/
Example Mode of Action: Receptor-mediated mitogenicity

Chemical exposure

CYP induction via CAR

Hypertrophy

Cell proliferation

Foci

Adenomas, Carcinomas

Thoolen et al 2010
http://www.epa.gov
Example Mode of Action: P450-mediated cytotoxicity

Chemical exposure → kidney → Renal tubular toxicity → Renal tubular cell proliferation → Renal cell hyperplasia → Adenomas, Carcinomas

CYP2E1

Renne et al 2012
Nolte et al 2005
http://www.epa.gov
Proposed Mode of Action: CYP2F2-mediated cytotoxicity

1. Chemical exposure
2. Oxidative metabolism
3. CYP2F2 (Clara cell)
4. Terminal bronchiolar (TB) cell toxicity
5. TB epithelial cell proliferation
6. TB epithelial hyperplasia
7. Adenomas, Carcinomas

Renne et al 2009
Cruzan et al 2012
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Mode of Action

What are strain and model considerations for mouse lung tumors?
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Mode of Action
Are lung cytotoxicity, proliferation, and hyperplasia consistent findings for the compounds of interest?
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Human Relevance
What are the features of lung tumors in mice compared to other species?
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Human Relevance
What are cell of origin considerations for mouse lung tumors?
Chemical exposure → Oxidative metabolism → CYP2F2 (Clara cell) → Sustained → Terminal bronchiolar (TB) cell toxicity → TB epithelial cell proliferation → TB epithelial hyperplasia → Adenomas, Carcinomas → Human Relevance → What are tissue and species concordance issues for mouse lung tumors?
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- Comparative lung pathology  ◦ G. Boorman
- Mouse lung tumor model considerations  ◦ M. Miller
- Rodent lung tumors in NTP studies  ◦ A. Pandiri
- Species differences in compound responses and cell of origin considerations  ◦ L. Van Winkle
- Species and site concordance  ◦ D. Krewski
- Open discussion