Mouse Lung Tumor Workshop

Session 3: Biological Mechanisms

Co-Chairs: Paul Schlosser | *US EPA*

Ron Melnick | *Ron Melnick Consulting*

Panelists: Tim Fennell | *Research Triangle Institute*

Kathy Burns | *ScienceCorps LLC*

Ernest Hodgson | *North Carolina State University*

Also presenting: George Cruzan | *ToxWorks*

Laura Van Winkle | *University of California, Davis*

John Lipscomb | *U.S. EPA*

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.

Session 3 Goals

- Discuss biological mechanisms, including ADME, & relevance to potential MOAs
- Mechanistic data for ethylbenzene, naphthalene, and styrene, as they relate to the formation of mouse lung tumors
- Other mouse lung tumorigens
- Differences in mechanisms between mice and other species (especially rats and humans), and between chemicals
  - Quantitative: Rate of key metabolite production
  - Qualitative: Metabolites produced only in mice?

Session 3 Agenda / Format

8:30 am	Session Overview -Paul Schlosser
8:35 am	CYP2F2 Mode of Action Hypothesis and Evidence -George Cruzan
8:55 am	A Framework for Considering the CYP2F2 MOA Hypothesis & Relevance of Mouse Lung Tumors to Humans –Ron Melnick
9:05 am	Clarifying Q&A
9:15 am	Pharmacokinetics and Pharmacodynamics of Ethyl benzene -Ernest Hodgson
9:25 am	Clarifying Q&A
9:30 am	Pharmacokinetics and Pharmacodynamics of Naphthalene -Laura Van Winkle
9:40 am	Clarifying Q&A
9:45 am	Pharmacokinetics and Pharmacodynamics of Styrene -Tim Fennell
10:00 am	Clarifying Q&A
10:10 am	**Break**
10:30 am	Related Chemicals: CYP2F2 Substrates & Other Mouse Lung Tumorigens -Paul Schlosser
10:40 am	Clarifying Q&A
10:45 am	Integration of Cross Cutting Issues -John Lipscomb
10:55 am	Open Session Discussion
11:30 am	**Lunch**

Session 3 Topics

1. Use of ADME to inform differences between effects in the lung and other tissues within the mouse, and differences between species/strains
   a. Contribution of species and tissue differences in metabolism (especially enzyme profiles and metabolites) to tumor formation.
   b. Metabolites with cytotoxic, genotoxic, clastogenic, mitogenic, or epigenetic activity.
   c. Metabolic pathways in mice and in the human lung: similarities, differences, and where comparative data do not exist.
   d. Route of exposure differences (e.g., dietary versus inhalation) related to key effects leading to lung tumor formation.
   e. Potential for metabolism in the liver to contribute to effects elsewhere in the body (e.g., nasal effects for naphthalene). First-pass effect considerations.

Session 3 Topics (continued)

2. Mechanisms and resulting pathology in the context of potential to develop mouse lung tumors
   a. Time course of key pathologic effects for lung tumorigenesis in the mouse for known lung tumorigens
   b. Tumorigens known or suspected of inducing lung epithelial cell cytotoxicity, stress leading to regenerative proliferation, hyperplasia, genotoxicity, and/or other molecular events leading to tumor formation
   c. Morphologic criteria for cytotoxicity
   d. Evidence for mitogenicity in lung epithelial cells & the potential to distinguish mitogenicity from cytotoxicity
   e. Downstream events that could distinguish a cytotoxic tumorigen vs. a non-tumorigen or genotoxic tumorigen