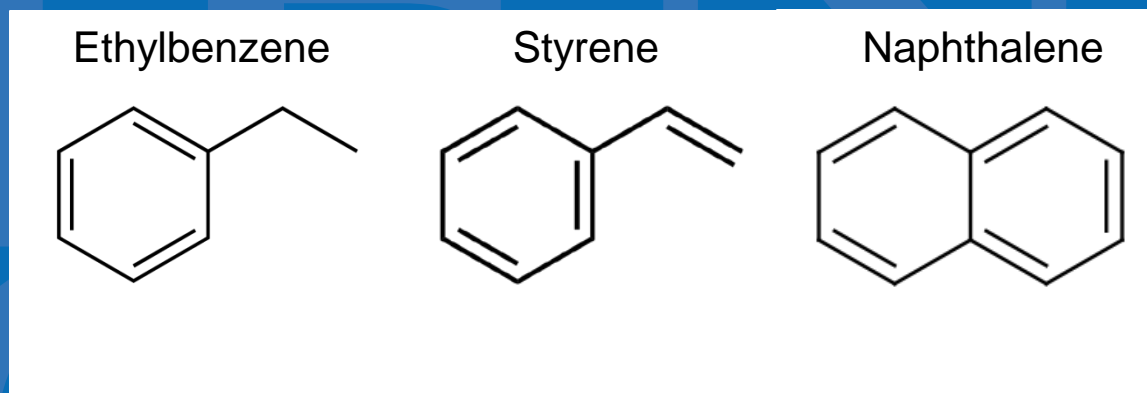


Mouse Lung Tumor Workshop: Background, Goals and Scope

George M. Woodall, PhD; Workshop Chair



The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Full Title:

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

Short Title:

Mouse Lung Tumor Workshop (MLTW)

Context for the Workshop

- Several chemical agents cause bronchiolar-alveolar adenomas and carcinomas (lung tumors) in mice.
- Three such agents are currently being assessed in the Integrated Risk Information (IRIS) Program within EPA:
 - Ethylbenzene
 - Naphthalene
 - Styrene
- Other chemicals have also been associated with causing similar tumors
 - Cumene
 - Coumarin
 - Fluensulfone
 - Benzene, and others

Goals of the Mouse Lung Tumor Workshop

- Identify the evidence, from multiple scientific disciplines, regarding formation of chemically-induced lung tumors in mice
- Discuss analysis and interpretation of the evidence within the context of the EPA Cancer Guidelines
- Discuss how such evidence informs human health assessments
- Identify commonalities, linkages, or differences between the evidence from various disciplines [and across the chemicals]

Scope of the MLTW

- This workshop will inform the development of IRIS assessments for chemicals where mouse lung tumors are an issue: **Ethylbenzene**, **Naphthalene**, and **Styrene**.
- EPA will not seek consensus, recommendations, or guidance during the workshop.
 - Application of a MOA framework to reach conclusions is not part of the scope of this meeting.
 - Identifying **Key Events** and whether they are **Necessary Elements** for application in a MOA are within the scope.
- Follow-on meetings may occur after the workshop to continue discussions related to the goals of the workshop

Organizational Structure for the MLTW

- Population/Individual Level - Evidence in humans at the population and individual level (**Session 1**)
 - Epidemiological evidence with the key chemicals
 - Pathology of human tumor formation
- Tissue Level - Review of mouse models to predict human tumor formation – pathology focused (**Session 2**)
 - Including issues of species/tissue concordance
- Mechanistic Level - Review the biological mechanisms and metabolism of the key/related chemicals to form toxic by-products (**Session 3**)
 - Key enzymatic processes
 - Areas of commonality, and differences
- Cellular/Subcellular Level - Genotoxicity, cytotoxicity, emerging molecular technologies (**Session 4**)

Pharmacokinetic & Pharmacodynamic Considerations

- PK: Do mice have a higher rate of creating the toxic moiety (or less capacity to detoxify) and are therefore “farther up” the dose-response curve?
- PD: Is there is something specific that makes the mouse lung different from or more sensitive than humans?
 - The underlying disease processes for tumor formation are complex
 - Chemicals may disrupt processes in multiple pathways; multiple combinations of disruption may result in disease
- Are the differences between species along a continuum or are they absolute?

Tissue & Cellular Specificity

- Localization

- What is the evidence that Clara cells in particular are transformed in mice?
- Do cells adjacent to Clara cells also become transformed (i.e., is there evidence that very local metabolism drives this effect)?
- What is the evidence in humans and other species?

- Concordance

- There is not always one to one correspondence across species for tumor type.
- Are mouse lung tumors a potential indicator for human tumors in the lung? In other tissues?
- Are these particular types of mouse lung tumors predictive of human tumor biology?

Mode of action: Definitions based on 2005 EPA Cancer Guidelines

- **Mode of action**

“a sequence of **key events** and processes, starting with **interaction of an agent with a cell**, proceeding through operational and anatomical changes, and **resulting in cancer formation.**”

[emphasis added]

- **Key event**

“an empirically observable precursor step that is itself a **necessary element** of the mode of action or is a biologically based marker for such an element.”

[emphasis added]

Mode of Action (MOA) and the MLTW

- MOA provides a useful framework for discussion of the data regarding formation of tumors via a set of **key events**.
- Slight Differences in Application:
 - US EPA Cancer Guidelines Approach: quantitative differences can be used to adjust dose-response
 - WHO/IPCS Approach: quantitative differences can be used to dismiss relevance
- Regardless of which approach is taken, the basic information needs are the same.

MOA Considerations

- Are MOA considerations chemical-specific, or do they apply across all the key chemicals?
 - Cruzan et al. (2013, 2012, 2009) propose that a common CYP-2F2 MOA applies to many chemicals causing mouse lung tumors.
 - Can data from multiple chemicals with the same purported MOA be used to bolster data gaps for other chemicals?
 - What weight of evidence (WOE) factors are important when considering whether a MOA is relevant (or not) in humans?
 - What factors should be considered when weighing whether a similar MOA is active for more than one chemical?

Resources Available for the MLTW

- **Session Abstracts:** This document provides context for and helps define the scope of the discussions. These materials will help participants engage in discussions from the beginning of the workshop and reduce the need for overview presentations at the workshop.
- **MLTW Project Page:** Located on the Health and Environmental Research Online (HERO) (<http://hero.epa.gov/mltw/>), the MLTW Project Page provides a list of relevant reference materials.

After the Workshop

- A **summary report** of the workshop proceedings will be developed.
- **Review articles** are anticipated to be developed for publication in peer-reviewed journals.
- **Post-workshop meetings** are anticipated to continue discussions related to the goals of the workshop.

Core Planning Team

- George Woodall
 - Team and Project Lead
 - NCEA-RTP
- Channa Keshava
 - Team and Project Co-Lead
 - (NCEA-IRIS;)
- Paul Reinhart
 - NCEA-RTP
- Nagu Keshava
 - NCEA-DC

Internal Planning Group

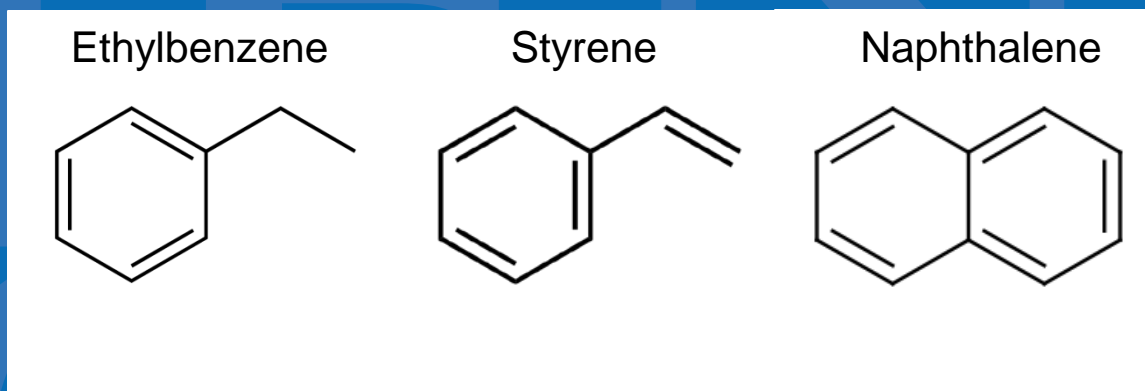
- Lyle Burgoon (NCEA-RTP – Molecular Toxicology)
- Weihsueh Chiu (NCEA-IRIS – Mechanisms)
- Glinda Cooper (NCEA-IRIS – Epidemiology)
- John Cowden (NCEA-RTP – Toxicology)
- Lynn Flowers (NCEA-IO – Toxicology; Naphthalene)
- Jason Fritz (NCEA-DC – Toxicity Pathways)
- Eva McLanahan (NCEA-RTP – PBPK)
- Reeder Sams (NCEA-RTP – Toxicology)
- Paul Schlosser (NCEA-DC – PBPK)
- Cheryl Scott (NCEA-DC – Epidemiology)
- Maria Spassova (NCEA-DC – Dose-response)
- Charles Wood (NHEERL – Pathology)
- Gloria Jahnke (NIEHS – Health Scientist; RoC)
- Ruth Lunn (NIEHS – Public Health; RoC)
- David Malarkey (NIEHS – Pathology)

Peer Input Committee

- Channa Keshava (Core Team)
- Nagu Keshava (Core Team)
- Paul Reinhart (Core Team)
- George Woodall (Core Team)
- George Cruzan (Toxworks; Industry)
- Kathy Burns (ScienceCorps; NGO)
- John Budroe (OEHHA; State Agency)
- Joseph Haney (TCEQ; State Agency)
- Robert Keith (University of Denver)
- Mark Miller (Wake Forest University)
- Gary Stoner (University of Wisconsin)
- Ruth Lunn (NIEHS; Federal Agency)
- Barbara Parsons (FDA; Federal Agency)
- Linda Sargent (NIOSH; Federal Agency)

Mouse Lung Tumor Workshop: Workshop Logistics

Channa Keshava, PhD; Project Co-Lead



On-site Conveniences

- Beverage and food service:
 - Lakeside Café (across from the entry to the Auditorium)
 - Employee Store (behind Guard Desk on 2nd floor)
- Restrooms located on opposite side of main stairway, down a short hallway (on the left) past the telephones
- Direct other questions to the registration desk staff or a member of the Project Team
- Please wear visitor badges at all times!!

In Case of Emergency

- All on-site participants should muster in Area 8 (Visitors Parking Lot)
- Exiting the Building:
 - Go up the main staircase
 - Out the main doors
 - Proceed to the visitor's lot

Assembly Areas – Main Facility



Logistical Considerations

- The goal is to provide an open forum for informed discussion
 - This includes input (as time allows) from panelists, speakers and participants (attending in person or virtually)
- The times allotted after the individual presentations should focus on clarifications.
 - Tee-up more involved, open discussion topics for the end of Session discussions.
 - A “Parking Lot” for these discussion topics will be populated as the Sessions progress.

Discussion Ground Rules

- Discussion Order:
 - Session Co-chairs, Panelists and Speakers
 - Panelists and Speakers from other Sessions
 - General Audience Attendees
(alternating between on-site and virtual attendees)
- Discussions within each Session will be moderated by the Session Co-chairs.
 - Workshop Chair and Project Team will perform back-up as needed.
- All advance materials (MLTW Session Abstracts; HERO references, etc.) are “fair game” for inclusion into these discussions



Discussion Ground Rules: On-site Attendees

- Please use available microphones
- Please identify yourself (name and affiliation) prior to asking your question
- Please be considerate of time constraints and the other participants
 - Be as concise as possible (1-3 sentences) in your comments/questions.
 - Be specific; remember that wider ranging topics will be covered in the Session Summary discussions.

Discussion Ground Rules: Virtual Attendees

- On-site monitors will relay input from those participating via webinar.
 - Please be clear and concise so your question/comment can be relayed appropriately.
 - Type in questions/comments via the Q&A Pod.
 - Note any technical difficulties in the General Chat Pod.
 - All computer microphones and telephones will be on mute for the duration of the workshop.
 - Needed to avoid technical difficulties
 - If possible, use your computer speakers; there is a capacity limit for the phone connection.
 - Use the phone if you do not have a high-speed connection or lack computer speakers
- Call-in number:** (866) 299-3188
Conference Code: 919 541 3896#

Let's Get Started

Tuesday, January 7

- **Session 1:** Human Cancer – Epidemiology and Pathophysiology (10:00 – Noon)
- Lunch (Noon – 1:00)
- **Session 2:** Comparative Pathological Evidence (1:00 – 5:00)

Wednesday, January 8

- **Session 3:** Biological Mechanisms (8:30 – 11:30)
- Lunch (11:30 – 12:30)
- **Session 4:** Evidence for Cellular, Genetic, and Molecular Toxicity (12:30 – 3:30)
- **Workshop Summary Session** (3:30 – 5:00)