EPA
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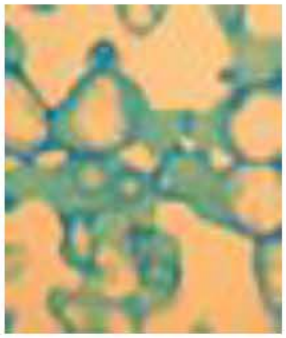
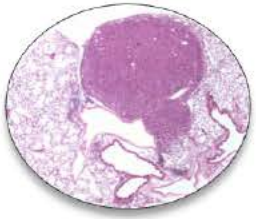
Environmental Protection
Agency



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.

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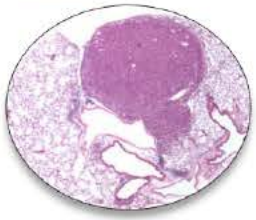

MLTW Session 2: Comparative Pathology

- 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*

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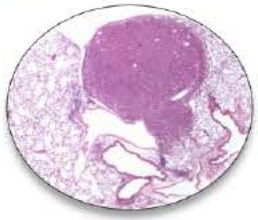
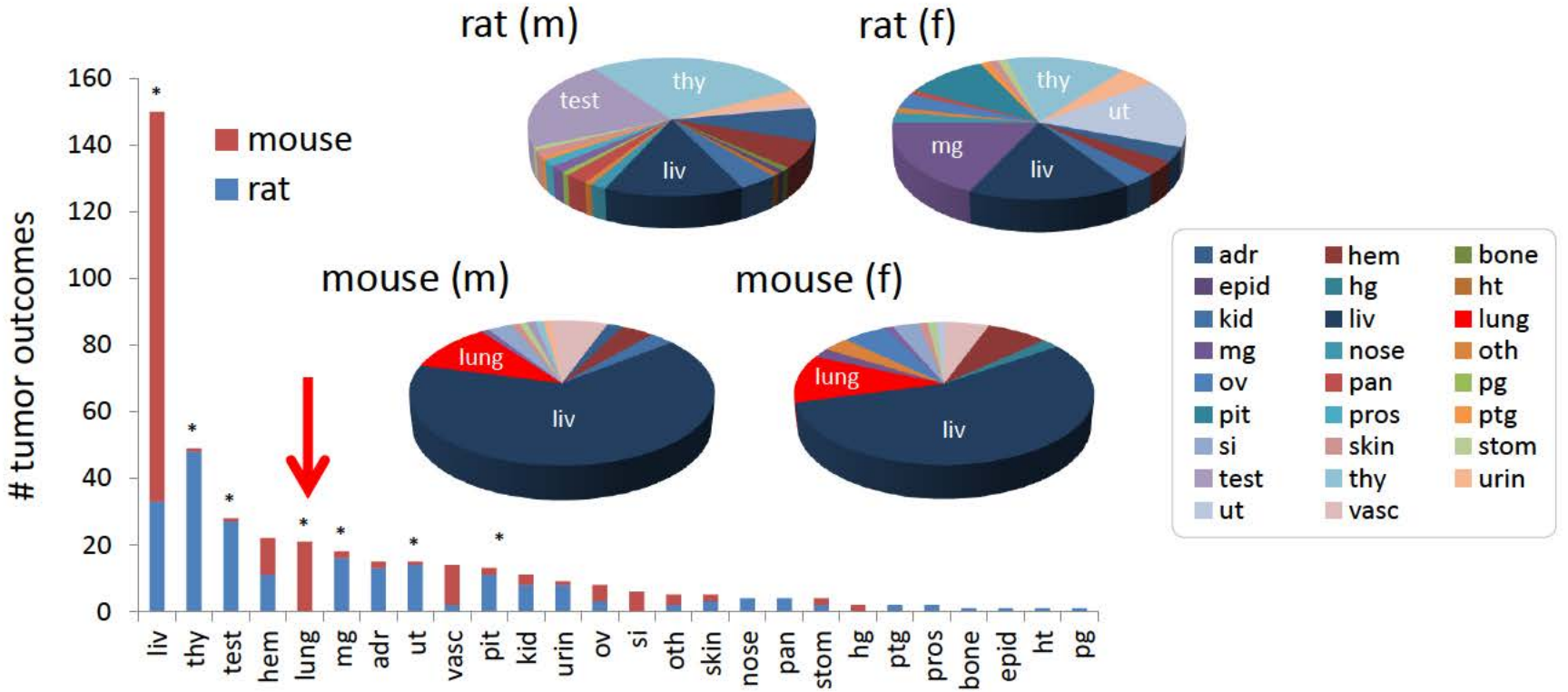
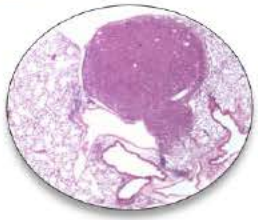


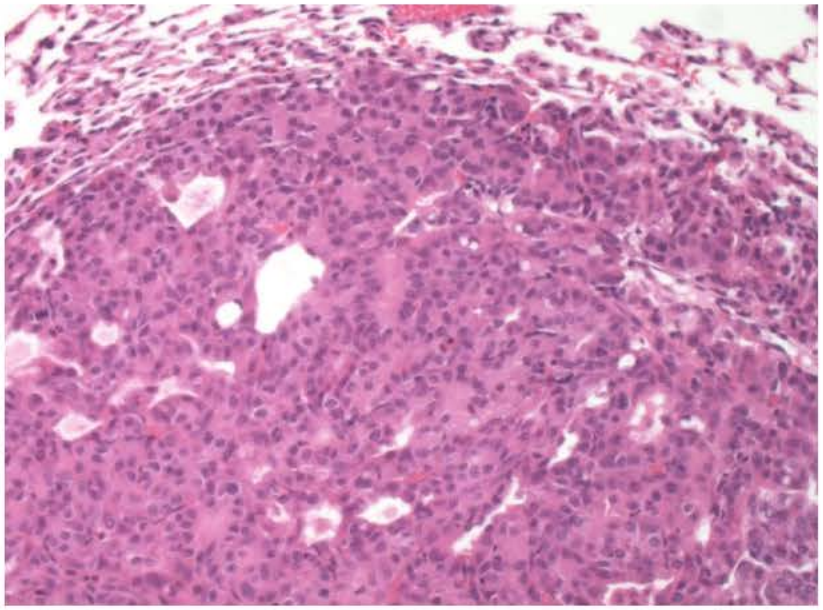
Lung tumors are common findings in mouse carcinogenicity studies

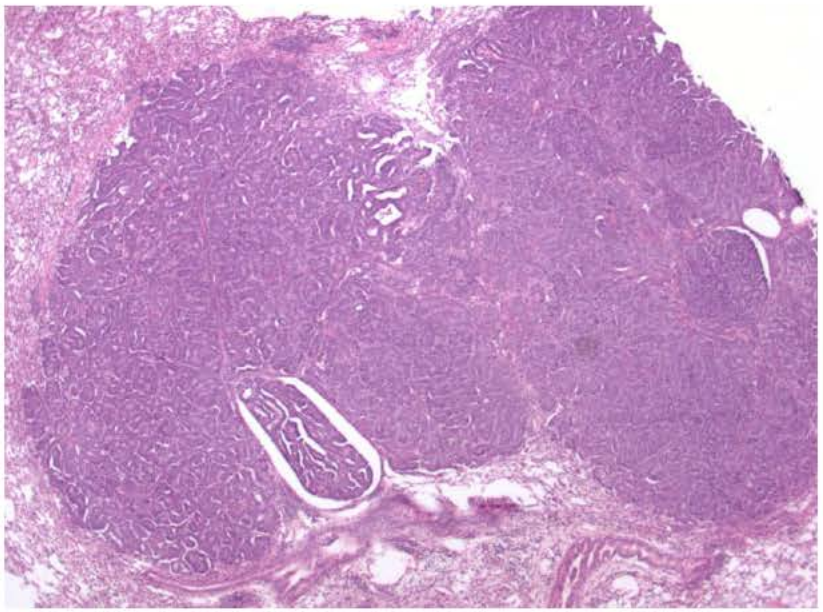


http://www.epa.gov/ncct/toxrefdb/

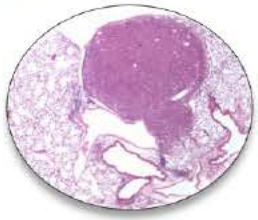


Mouse lung tumors have distinctive morphologic features



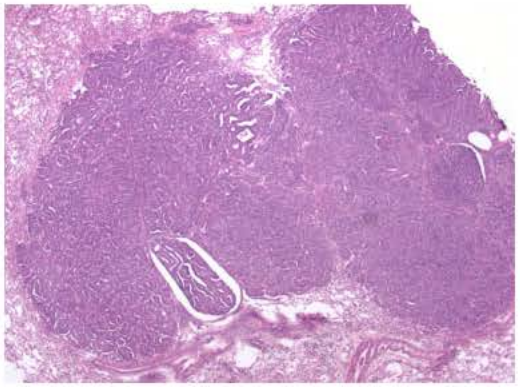


Mouse, Bronchiolo-alveolar adenoma (left) and carcinoma (right)

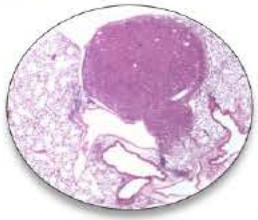


Mouse lung tumor incidence varies widely across strains

Strain	Incidence - control (%)	Incidence - induced (%)
A/J	71	100
CBA	18	60
C3H	14	36
DBA	9	25
C57Bl	7	57



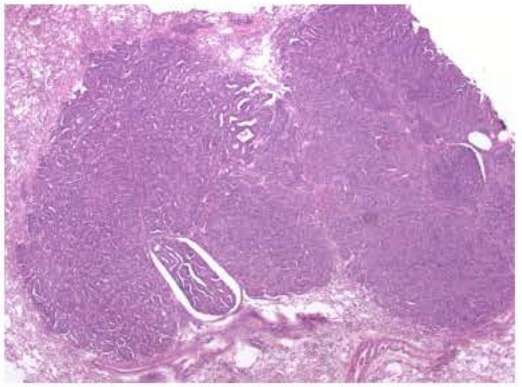
Hahn, Chapter 9, Toxicology of the Lung



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/

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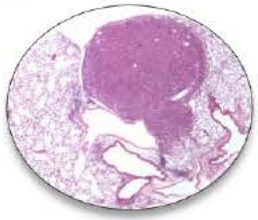
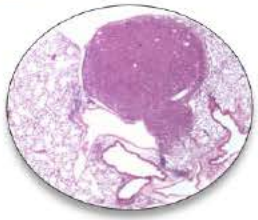


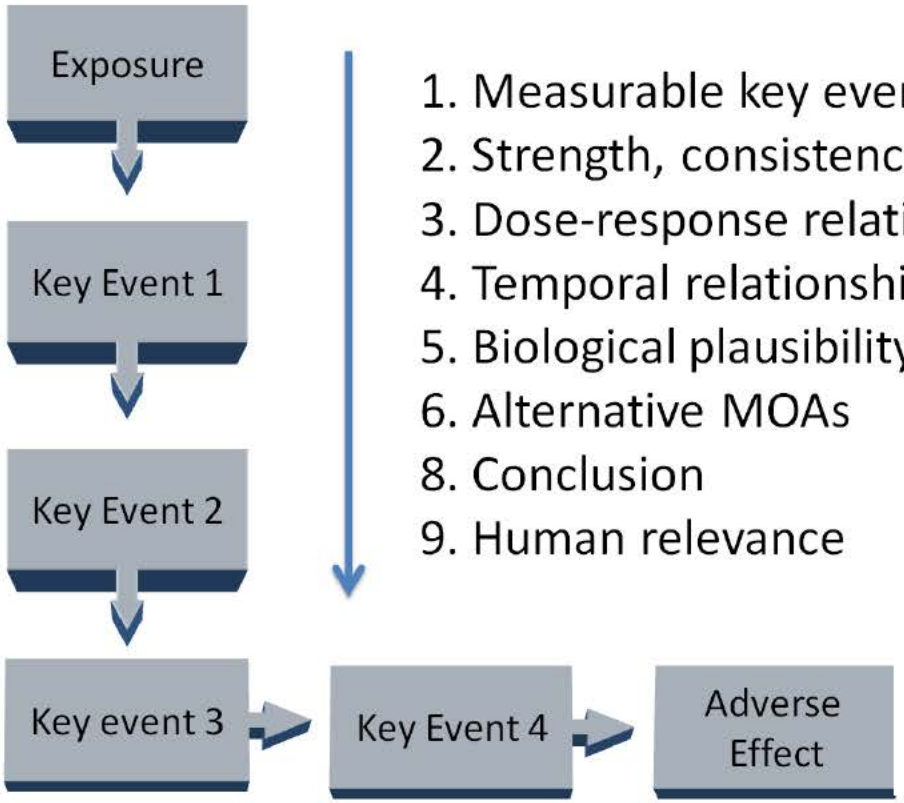
US EPA Guidelines for Cancer Risk Assessment (EPA/630/P-03-001F)

- 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/

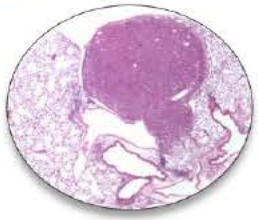


Weight-of-evidence criteria for evaluating a cancer mode of action

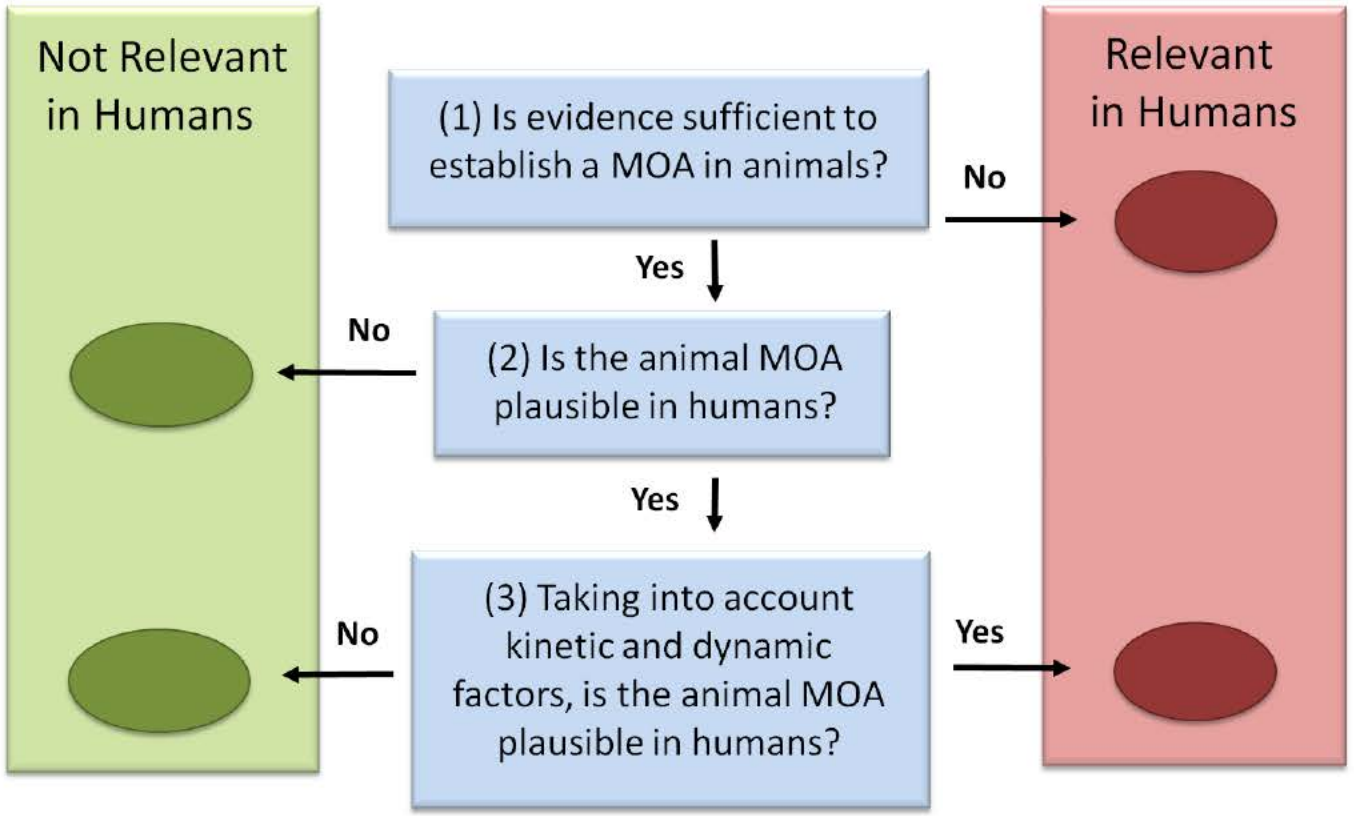


Boobis et al 2006

http://www.epa.gov/cancerguidelines/

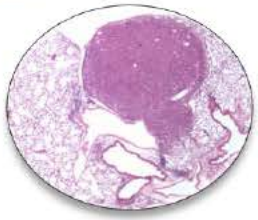


EPA/IPCS Human Relevance Framework

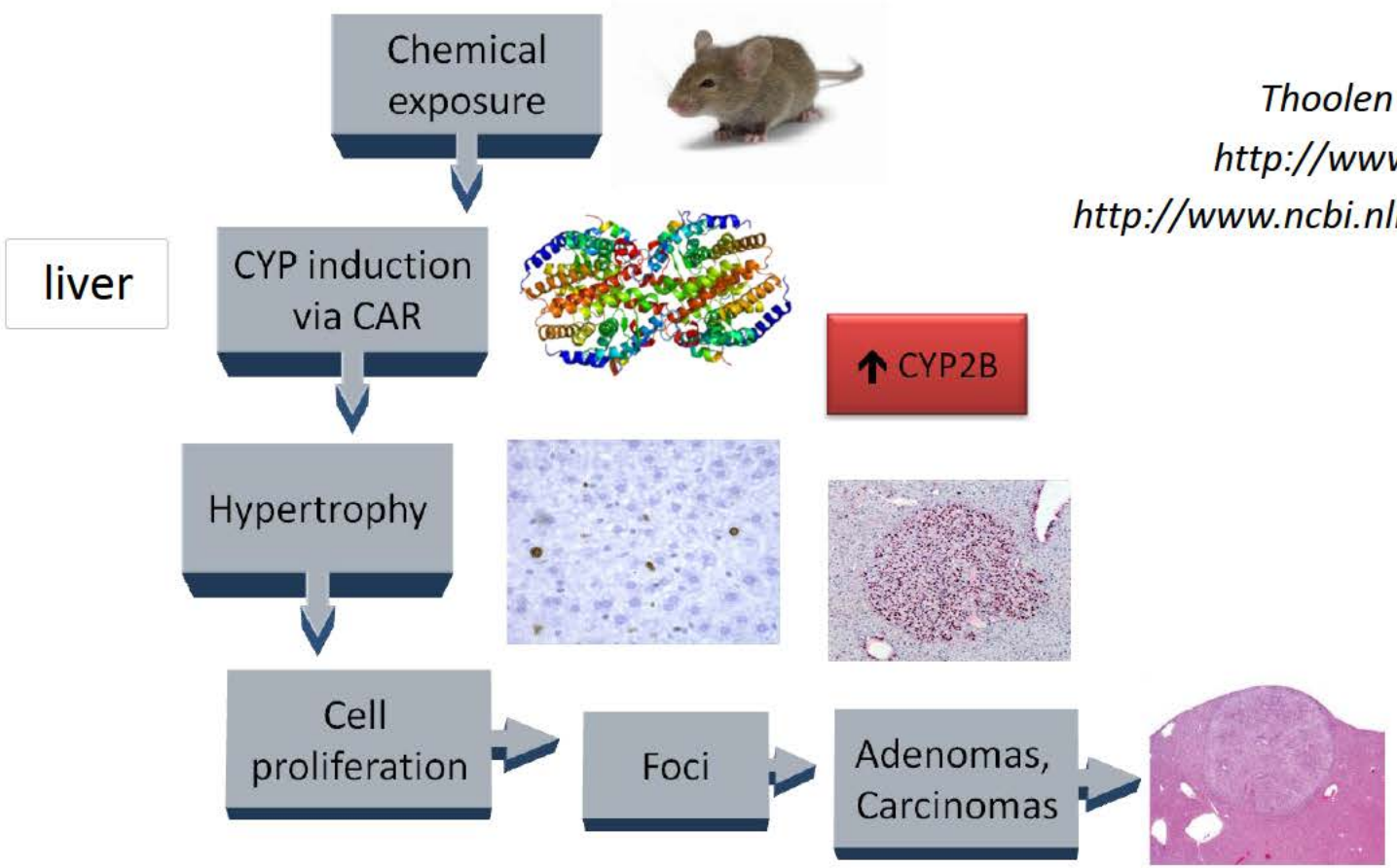


Boobis et al 2006

http://www.epa.gov/cancerguidelines/



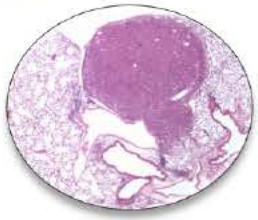
Example Mode of Action: Receptor-mediated mitogenicity



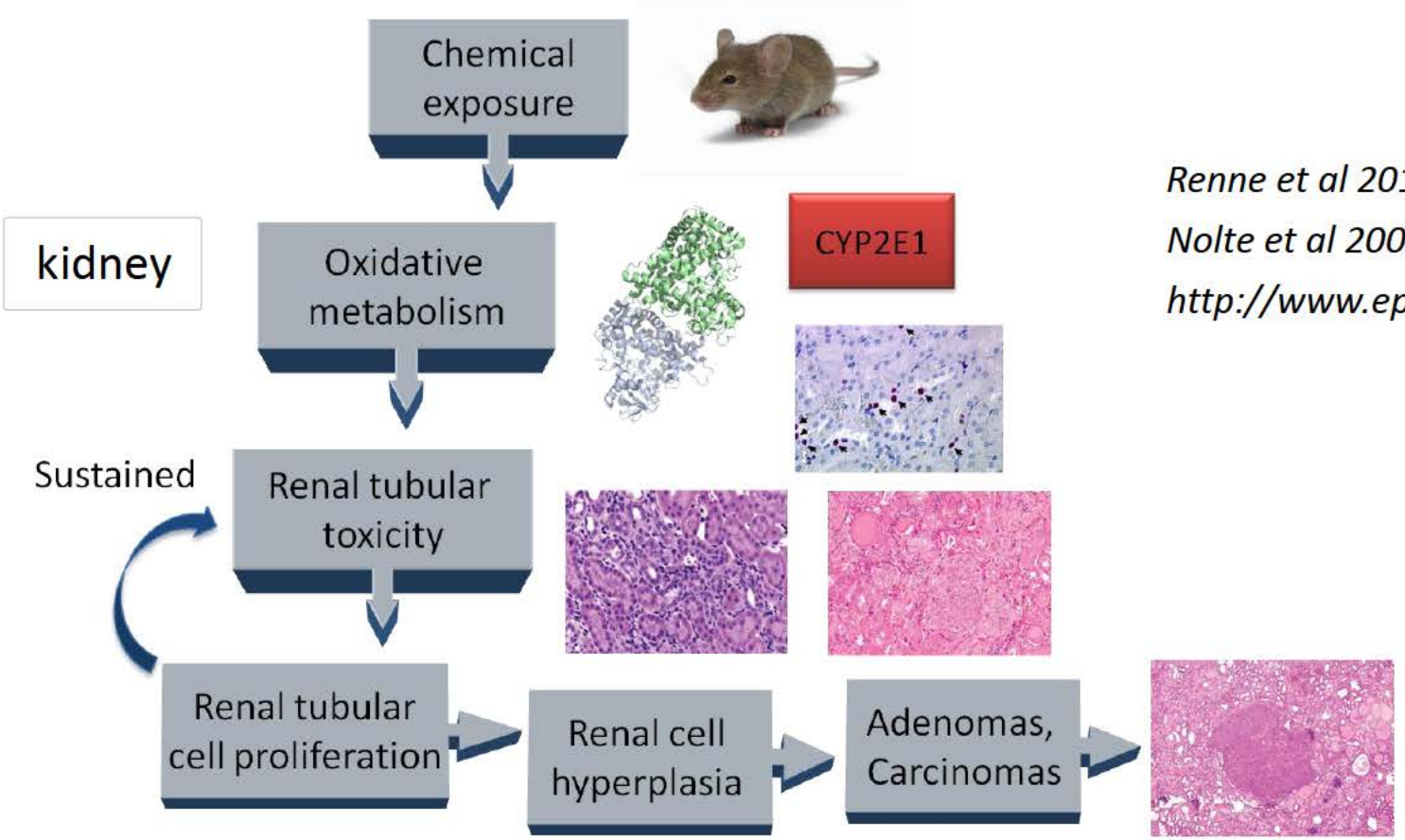
Thoolen et al 2010

http://www.epa.gov

http://www.ncbi.nlm.nih.gov



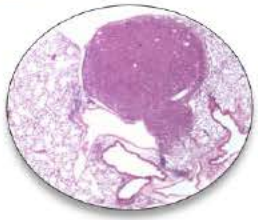
Example Mode of Action: P450-mediated cytotoxicity



Renne et al 2012

Nolte et al 2005

http://www.epa.gov



Proposed Mode of Action: CYP2F2-mediated cytotoxicity

Chemical exposure

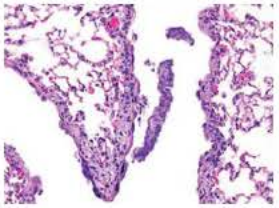
Renne et al 2009

Cruzan et al 2012

lung

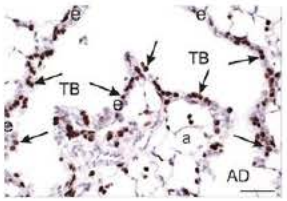
Oxidative metabolism

CYP2F2 (Clara cell)



Sustained

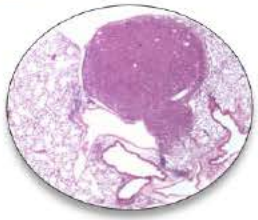
Terminal bronchiolar (TB) cell toxicity



TB epithelial cell proliferation

TB epithelial hyperplasia

Adenomas, Carcinomas



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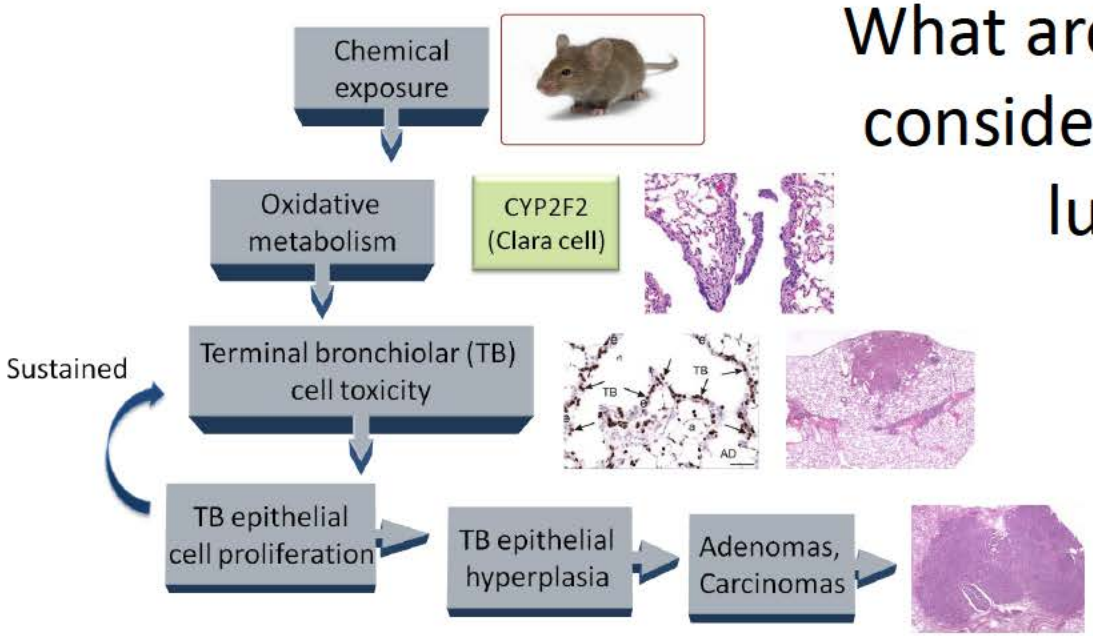
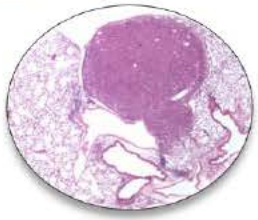
Mode of Action

What are strain and model considerations for mouse lung tumors?





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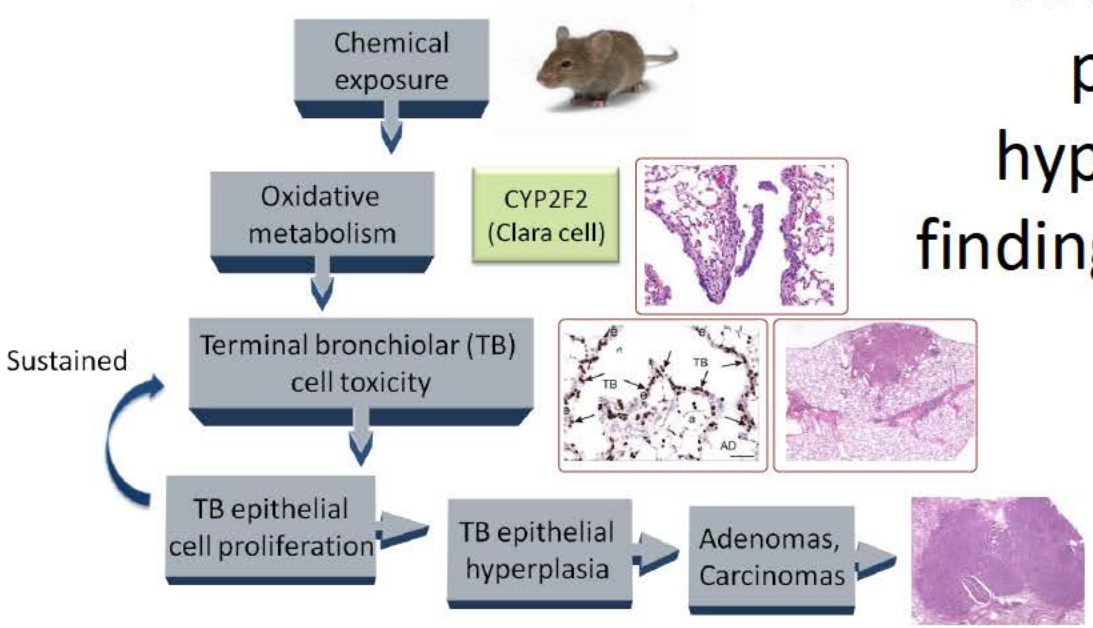
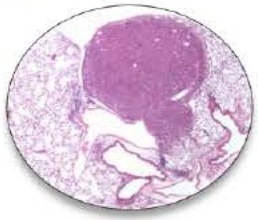


Mode of Action

Are lung cytotoxicity, proliferation, and hyperplasia consistent findings for the compounds of interest?



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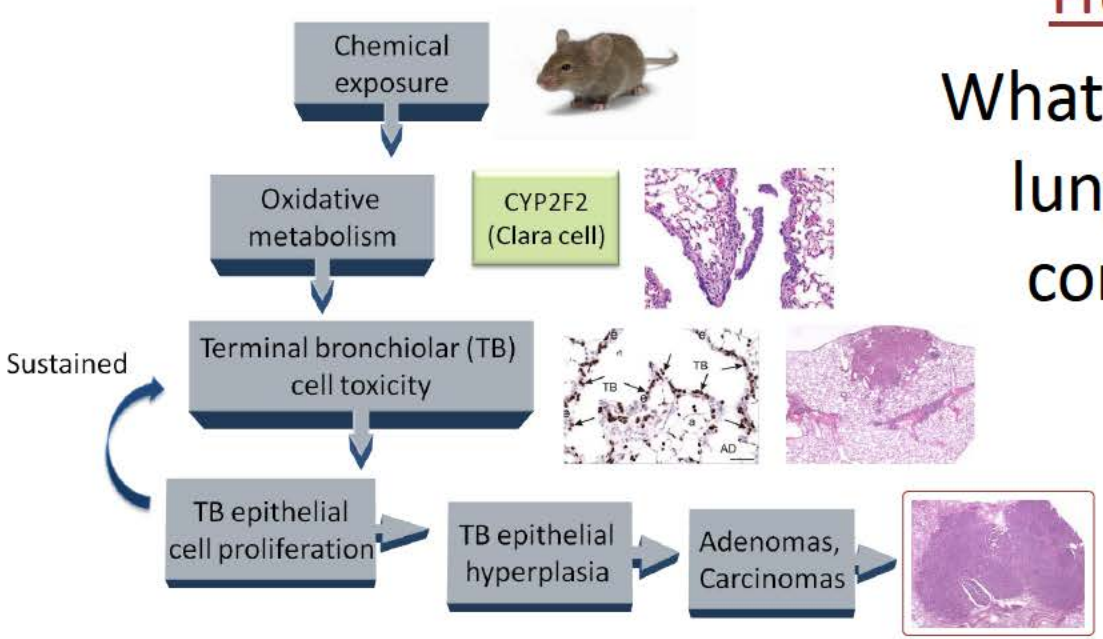
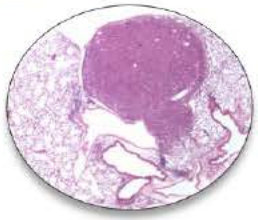


Human Relevance

What are the features of lung tumors in mice compared to other species?



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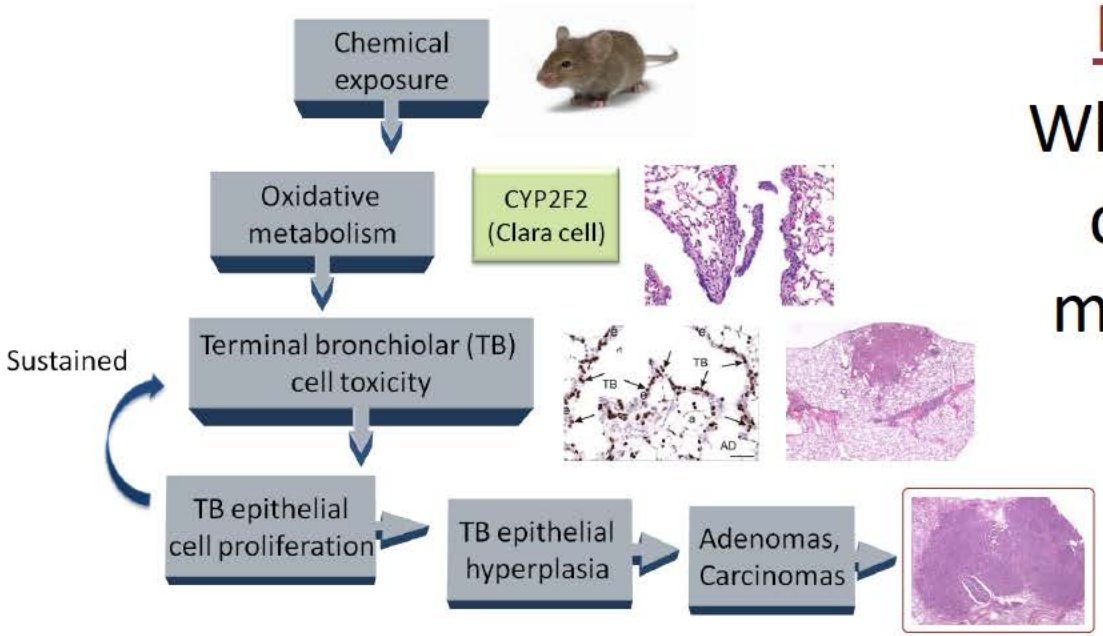
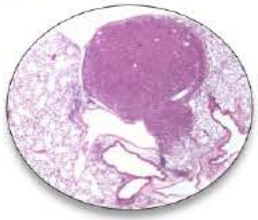


Human Relevance

What are cell of origin considerations for mouse lung tumors?



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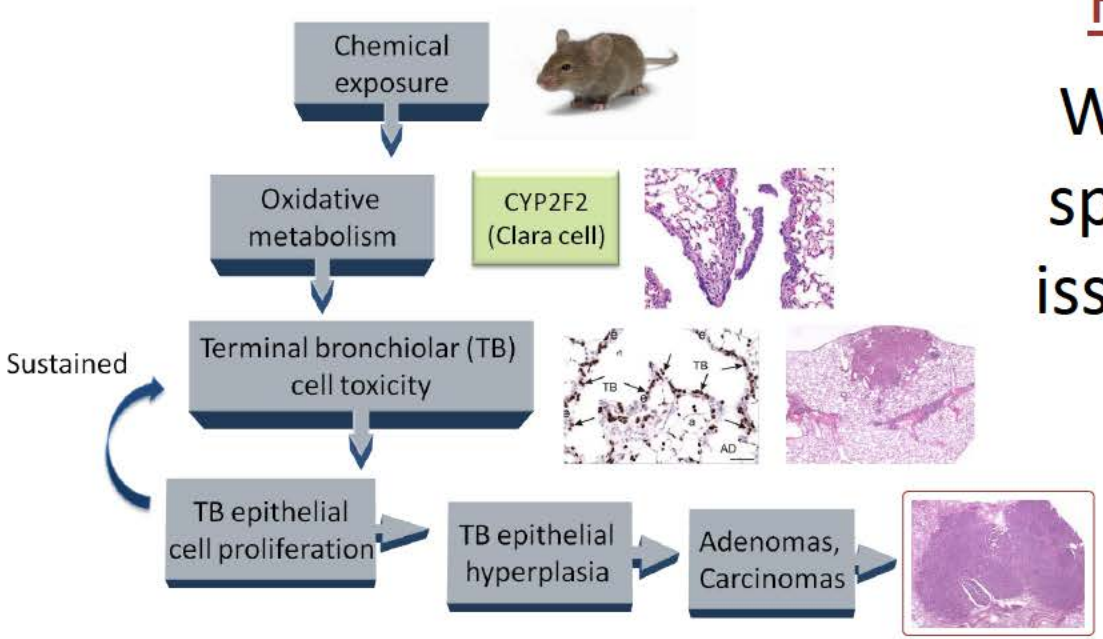

Human Relevance

What are tissue and species concordance issues for mouse lung tumors?

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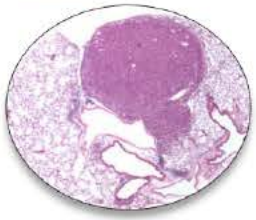

MLTW Session 2: Comparative Pathology

- 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

http://www2.epa.gov/aboutepa/about-epa-region-4-southeast