A Framework for Considering the CYP2F2 MOA Hypothesis & Relevance of Mouse Lung Tumors to Humans

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US EPA Mouse Lung Tumor Workshop
January 7-8, 2014
Research Triangle Park, NC

General Principles

- Animal lung tumor findings are considered to be relevant to evaluations of human cancer risk – of the known human carcinogens, lung tumors are the most common in both humans and animals
- The reliance on a MOA that counters the basic assumption of human relevance of animal tumor findings requires the establishment of sufficient and valid evidence for a species-specific cancer response by rigorous hypothesis testing

Experimental Needs for a Hypothesized Cancer MOA

- Identification of species-specific key precursor event(s) with strong evidence they do not operate in humans
- Identification of the active agent(s) and source (metabolic pathway and organ)
- Dose-response concordance for sustained key event and tumor induction
- Consistent key event-tumor response relationship for chemicals operating by the hypothesized MOA
- Cancer and mechanistic data on major metabolites are captured in the hypothesis
- Characterization of human variability and susceptibility
- Consistently negative epidemiological findings
- Human biomarker data are consistent with the hypothesized MOA

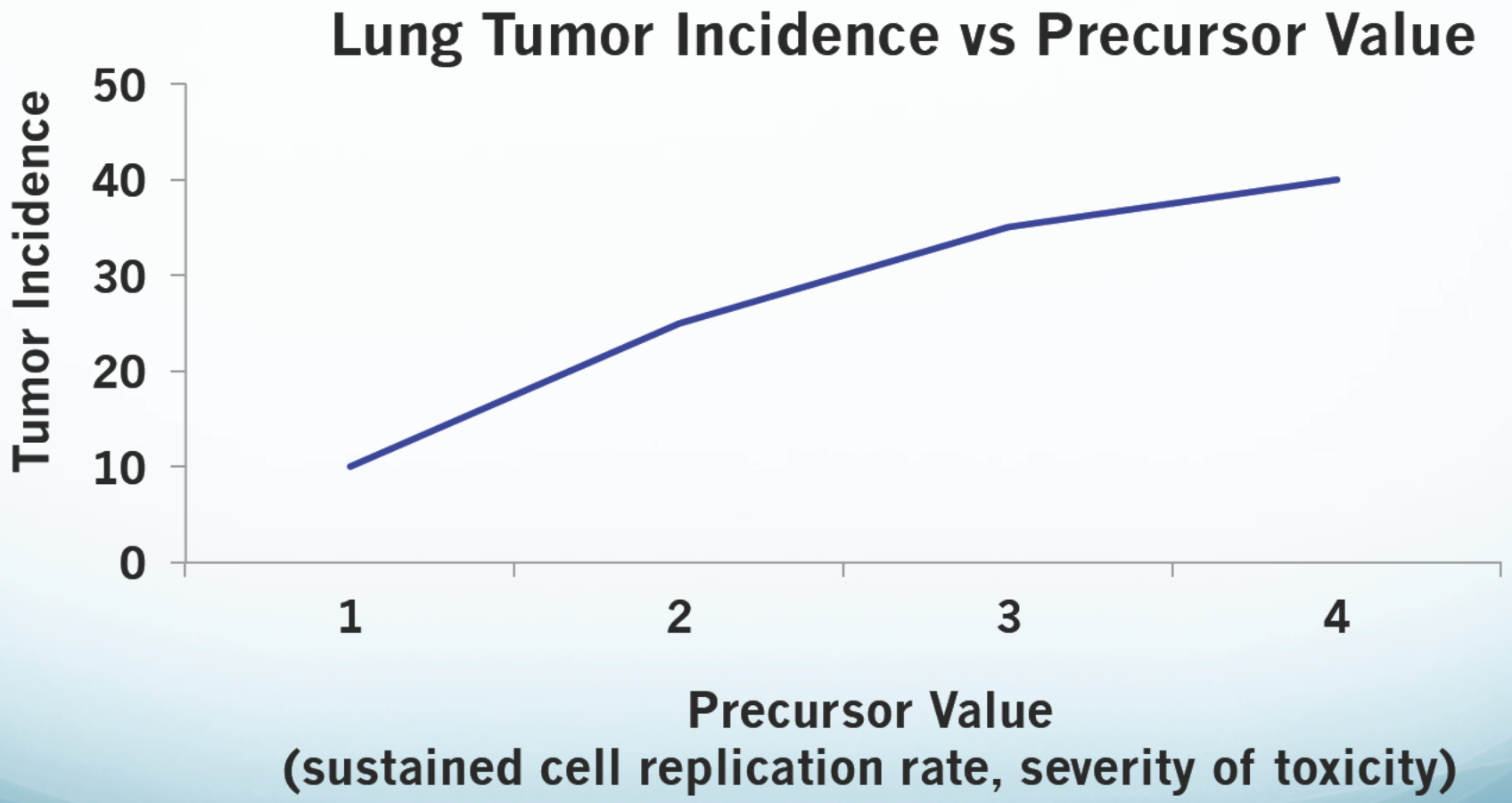
Pharmacokinetic Issues

- Route of exposure affects tissue dosimetry
- Characterization of lung dosimetry & systemic distribution of key metabolites with repeated exposures
  - Relative role of CYP2E1 and CYP2F2-mediated metabolism in the lung (Clara cells) and liver: target tissue metabolism vs systemic circulation
  - Stability of reactive/toxic intermediates
  - Lung dosimetry in CYP2F2 and CYP2E1 knockout mice
- Characterization of human variability in expression of key metabolizing enzymes and in lung dosimetry
  - Genetic differences
  - Age/life stage
  - Effect of other exposures – medication, occupational
- Characterization of the kinetics and tissue/organ distribution of ring oxidation enzymes in humans

Pharmacodynamic Issues and Needs

- Characterization of events critical for induction of lung cytotoxicity and carcinogenicity
  - Identification of key event(s) predictive of lung tumor response in mice – GSH depletion, ROS, protein binding, topoisomerase inhibition, genotoxicity, etc., or multiple metabolic pathways and processes
  - Identification of reactive intermediate(s): protein or DNA adducts in mice or human
  - Sustained vs transient toxicity and cell proliferation
- Characterization of tumors induced by the agent or its metabolites
  - Frequencies and types of oncogene/tumor suppressor gene mutations
- 2-year carcinogenicity studies of ethylbenzene, styrene, and naphthalene in CYP2F2 and CYP2E1 KO mice

Consistency in Key Precursor Event-Tumor Response Relationship for Chemicals Operating by the Hypothesized MOA



MOA for other sites, other chemicals that induce lung tumors in mice, and analogs

- Mechanism for nasal respiratory and olfactory epithelium tumors induced in rats by naphthalene, but not by stryene or ethylbenzene. Also naphthalene induced nasal lesions in mice (inflammation, olfactory metaplasia, respiratory epithelial hyperplasia), but no tumor response
- Ethylbenzene: kidney tumors in male and female rats, lung tumors in male mice (only), liver tumors in female mice
- Benzene (gavage): induces lung tumors in mice (not in rats) and is metabolized predominantly by CYP2F2 in the mouse lung
- Trichloroethylene: metabolized by CYP2E1, causes Clara cell necrosis and lung tumors in mice
- Analogs:
  - 4-methylstyrene (gavage): negative in rats and mice
  - α-methylstyrene (inhalation): rat kidney tumors and mouse liver tumors