Related Chemicals: CYP2F2 Substrates & Other Mouse Lung Tumorigens

- Methylene chloride
- Benzene
- Fluensulfone
- Trichloroethylene

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Methylene chloride: Toxicity

- B6C3F1 mice:
  - Liver & lung tumors
  - Transient but not sustained Clara cell vacuolation and lung cell proliferation – effects appear to be CYP2E1-mediated
  - No overt cytotoxicity at tumorigenic levels
  - Cancer risk thought due to GST-mediated mutagenic metabolites
- F344 (& S-D) rats: mammary tumors
- Humans: occupational exposure associated with several cancers, including brain, liver, biliary tract, non-Hodgkin lymphoma, and multiple myeloma

Methylene chloride: Metabolism

- CYP-mediated Metabolism
  - **Assumed** to be exclusively CYP 2E1
  - Rat lung ~ 3.5% of mouse lung; human ~ 0 (n.d.)
  - Metabolism by other CYPs (including 2F2) not evaluated
  - Appears to cause short-term bronchiolar cell vacuolation and Clara cell proliferation
  - But then protective depression of CYP activity occurs (in mouse), so response not sustained
  - Not known if tumors originate from Clara cells
- GST-mediated Metabolism
  - Leads to reactive metabolites
    - Assumed to not distribute outside tissue of production
    - Thought causative for lung tumors
  - Rat lung ~ 14% of mouse lung; human ~ 5%
- MOA relevant to rats and humans, but sensitivity:
  mouse >> rat > human (quantitative difference)

Benzene: Toxicity

Oral

- Multi-site carcinogen in rats & mice
- Lung tumors in mice but not rats

Inhalation

- Lung cancer in CD-1 and CBA/Ca mice
  - 10- or 16-week exposures w/ life-time observation
  - Or 1-week on / 2-week off intermittent (CD-1)
- Genotoxicity observed (Big Blue Mouse)
- Some epi studies show increases in lung cancer among benzene-exposed workers

Role of Clara cells?

Benzene: Metabolism & Distribution

- Both 2E1 and 2F2 are active in the mouse lung for benzene, ~ equal activity
- 2B1 known to catalyze benzene (rat only?)
- 2F1 active in human lung, ~ 2E1 in human lung, but that activity is very low
- 2E1 metabolites can circulate from liver to lung
- Benzene oxide (2E1 metabolite) increases tumors in newborn mouse assay
- Does 2F2 produce different/ring-open benzene metabolites?
- Is differential sensitivity of mouse lung to ***oral*** benzene due to 2F2, or higher total metabolism (including liver)?

Fluensulfone: Toxicity

CD-1 Mice:

- Alveolar/bronchiolar adenomas
  - Significant + in females
  - Non-significant (+) in males
- Bronchiolar hyperplasia: + in both sexes
- Clara cells are "likely origin of the bronchiolar epithelial hyperplasia and adenomas"*

Wistar Rat:

- Negative for cancer
- Proliferative response ??

Humans: ?

Mutagenicity: Negative in a range of tests (in vitro & mouse bone marrow micronucleus

*Strupp et al. (2012). Toxicol. Sci. 128:284-94

Fluensulfone: Metabolism

- Lung metabolism
  - Significant with mouse microsomes
    - ~ 20% of microsomal metabolism via CYP 2F2
    - ~ 5% due to CYP 2E1
    - ~ 75% of microsomal metabolism by other path
  - No elimination with human microsomes
  - Rat metabolism: not tested
  - Cytosolic metabolism: not tested
  - Active metabolite: unknown
- While 2F2-mediated lung metabolism occurs in the mouse, other pathways could cause cancer

Trichloroethylene: Toxicity

- Lung tumors in mice, but not rats or hampsters
  - Acute toxicity mostly to Clara cells:
    - Vacuolation and replication
    - Aneuploidy in some systems
  - Uncertain if tumors originate with Clara cells, but no evidence of toxicity in other cell types
- Liver tumors in mice (inhalation & oral)
- Kidney tumors in rats (inhalation and oral)
  - Small "N"s, but rare tumor
  - Consistent with human observations
- Limited evidence: lymphohematopoietic cancers in rats & mice, and testicular tumors in rats
- Humans
  - Strongest epi for kidney cancer
  - Limited evidence for non-Hodgkin lymphoma & liver cancer

Trichloroethylene: Metabolism

- Key metabolite: chloral hydrate (CH)
- CYP2E1-mediation significant
  - Metabolism reduced in 2E1-knockout mice
- Vmax/Km:
  - rat 2E1 > rat 2F4 > mouse 2F2 > human 2E1
  - In-vivo activity also depends on expression
  - CH is not 2F2-specific
  - Differences are quantitative
- Limited CH production from human lung microsomes (5 of 8 were N.D.)
  - Consistent with low 2E1 in human lung