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NIOSH PERCHLOROETHYLENE REVIEW
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HSIA RESEARCH PROJECT

PERC: MOUSE LIVER TUMORS AND RISK ASSESSMENT

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Basic Information:

- **Perc increases incidence of hepatocellular carcinoma in B6C3F1 mice when administered orally or by inhalation.**
- **Generally accepted that metabolite trichloroacetic acid (TCA) is responsible.**
- **Perc and TCA are not considered genotoxic.**

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Mechanism of Action:

- **TCA is a classic peroxisome proliferator.**
- **Interacts with receptor PPARα.**
- **Peroxisome proliferation not directly responsible.**
- **Key factors: Increased Cell Proliferation**
  Reduced apoptosis (cell death)

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Peroxisome Proliferation and Humans:

- **Human cells have PPARα.**
- **DNA transcription much less effective.**
- **Cell proliferation, reduced apoptosis not seen *in vitro*.**
- **No increase in liver tumors despite therapeutic dose of potent peroxisome proliferator.**

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Usual Assumptions in Risk Assessment (with PBPK):

- **The same tumor incidence occurs in humans as in mouse at the same dose of TCA in the liver (LADD).**

Improved Assumptions:

- **Extent of increased cell proliferation/reduced apoptosis determines increase in tumors.**

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Sequence of Experiments:

1. **Inhalation Study (5-day)**

- **Perc at dose levels as in long term studies. Rat and B6C3F1 mouse.**
- **Establishes TCA level in blood/liver for given inhalation dose.**
- **Establishes cell proliferation (S-phase), apoptosis and PCoA (measure of peroxisome proliferation) at perc and TCA levels.**

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2. Drinking Water Study (14-day)

- B6C3F1 mouse, PPARα knockout mouse and wild-type SV129 equivalent.
- Dose levels to give blood TCA as in perc inhalation.
- Demonstrates effect of TCA alone vs perc>TCA.
- Will show role of PPARα.

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3. *In Vitro* Studies

- Hepatocytes from B6C3F1 mouse, PPARα knockout and wild-type mice, and human.
- Concentrations of TCA in culture medium to match levels in carcinogenicity study, and up to cytotoxic concentrations.
- Should demonstrate *in vitro* can replicate *in vivo* and put human response in a quantitative context.

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Application of Results

- **Mouse tumor incidence calibrated vs cell proliferation/ apoptosis.**
- **Human response read against that calibration and related to TCA concentration in medium.**
- **Equivalent human perc exposure calculated from TCA concentration in medium via PBPK model.**

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Progress

- **Inhalation study (Syngenta CTL) – complete.**
- **Drinking water study (Syngenta CTL) – prelim. complete, main study about to begin.**
- ***In Vitro* study (Indiana U.) – about to begin.**
- **Conclusion – 3 rd quarter 2003.**