NIOSH PERCHLOROETHYLENE REVIEW
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HSIA RESEARCH PROJECT

PERC: MOUSE LIVER TUMORS AND RISK ASSESSMENT

Paul H. Dugard

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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 – 3rd quarter 2003.