TCE & Fetal Heart Development

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Why Study TCE?

- **Common Water Supply Contaminant**
  - World Wide reports of TCE contamination
  - NPL site in Tucson area

- **Epidemiology Studies**
  - Santa Barbara, CA
  - San Francisco, CA
  - Tucson AZ
Avian Studies

- Significant increase in heart defects in those treated with TCE or DCE
- Variety of heart defects
Mammalian Studies

- Sprague-Dawley Rats
  - Low spontaneous heart malformation rate
- Intrauterine exposure & Drinking water
  - Prepregnancy Only
  - Prepregnancy + Pregnancy
  - Pregnancy Only (GD 0-22)

- Significant ↑ in abnormal hearts

- Variety of heart malformations
Dose Response study

- Same methodologies as prior studies
  - Daily monitoring
  - Timed pregnancies
  - Drinking water exposure during entire pregnancy
  - Fetal heart removal & evaluation
## Concentration Equivalents

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Avg. Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,100 ppm</td>
<td>129.0 mg/Kg</td>
</tr>
<tr>
<td>1.5 ppm</td>
<td>0.218 mg/Kg</td>
</tr>
<tr>
<td>250 ppb</td>
<td>0.048 mg/Kg</td>
</tr>
<tr>
<td>2.5 ppb</td>
<td>0.00045 mg/Kg</td>
</tr>
</tbody>
</table>
# Trichloroethylene (TCE) Test Groups

<table>
<thead>
<tr>
<th>Conc</th>
<th>No. of Maternal Rats</th>
<th>Total No. of Fetuses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100 ppm</td>
<td>9</td>
<td>105</td>
</tr>
<tr>
<td>1.5 ppm</td>
<td>13</td>
<td>181</td>
</tr>
<tr>
<td>250 ppb</td>
<td>9</td>
<td>110</td>
</tr>
<tr>
<td>2.5 ppb</td>
<td>12</td>
<td>144</td>
</tr>
<tr>
<td>Control</td>
<td>55</td>
<td>606</td>
</tr>
</tbody>
</table>
Types of Heart Malformations

- Abnormal Looping
- Coronary Artery/Sinus
- Aortic Hypoplasia
- Pulmonary Artery Hypoplasia
- **Atrial Septal Defect (ASD)**
- Mitral Valve Defect
- Tricuspid Valve Defect
- **Ventricular Septal Defect (VSD):**
  - peri-membranous (subAortic)
  - muscular
- Atrio-Ventricular Septal Defect
- Pulmonary Valve Defect
- Aortic Valve Defect
% Abnormal Hearts

**Statistical Significance between control and treated groups**
% Litters with Abnormal Hearts

![Bar chart showing the percentage of litters with abnormal hearts at different trichloroethylene concentrations.]

- Control: 16.4%
- 2.5ppb: 0%
- 250 ppb: 44.4%
- 1.5 ppm: 38.5%
- 1100 ppm: *66.7%*

*Statistical Significance between control and treated groups*
Expected Effective Dose

Graph showing the predicted percentage of abnormal hearts against trichloroethylene concentration (in ppm). Key points include:

- 0% predicted abnormal hearts at 0 ppm
- 10% predicted abnormal hearts at 506 ppm
- 20% predicted abnormal hearts at 1061 ppm
- 30% predicted abnormal hearts at 1877 ppm
- 40% predicted abnormal hearts at 2692 ppm
- 50% predicted abnormal hearts at 3508 ppm
- 60% predicted abnormal hearts at 4323 ppm
- 70% predicted abnormal hearts at 4878 ppm

The point at 2692 ppm is marked as $ED_{50}$.
Result Differences

Fisher, et al
- 4.5% Fetuses w/ heart malformations
- 60 % Litters w/ malformations
- Water Controls: 2.9% fetuses w/ heart malformations
- Soybean Oil Control: 6.5 % fetuses w/ heart malformations

Dawson, et al
- 10.4% Fetuses w/ heart malformations
- 67 % Litters w/ malformations
- Water Controls: 2.2% fetuses w/ heart malformations
Differences Due to ???

- Method of delivery
- Timing of delivery

- Fisher, et al.
  - Daily Gavage in Soybean oil
  - Gestation Day 6-15

- Dawson, et al.
  - Continuously in Drinking Water
  - Gestation Day 0 to 22
TCE Effects on Gene Expression

- Treatment of Pregnant Dams from the onset of pregnancy

- Embryonic heart tissue collected Day 10-11 (E-11)
  - Several major cardiac developmental processes are underway

- Heart tissue:
  - RNA isolation
  - Subtractive Hybridization
  - Screening Assays
Gene Expression Results

160 Clones analyzed

Grouped by Functional Considerations:
- Housekeeping
- Stress Response
- Potential Developmental Processes
  - 9 cDNA specifically ID'd for heart
  - Shown to be sensitive to TCE exposure
Gene Expression after TCE Exposure

- Rat Serca-2 CA2+ ATPase
- Rat GPI-p137
- Expression of both were Decreased as the levels of exposure to TCE increased
Conclusions

TCE exposure in rats

- Increased cardiac malformations
  - Drinking Water Exposure during pregnancy
- Dose Response to TCE exposure
- Down Regulation of Serca2a and p137 genes

Goals: Continued Gene sequence evaluation

- Where altered levels of expression are producing cardiac malformations


Collier JM, Cover C, Selmin O, Johnson PD, Runyan R. Trichloroethylene Effects on Gene Expression During Cardiac Development. Accepted with revisions, *Toxicological Sciences*. 2002
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