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

Concentration ~~~~~~~ Avg. Dose

1,100 ppm ~~~~129.0 mg/Kg

1.5 ppm ~~~~ 0.218 mg/Kg

250 ppb ~~ 0.048 mg/Kg

2.5 ppb ~ 0.00045 mg/Kg

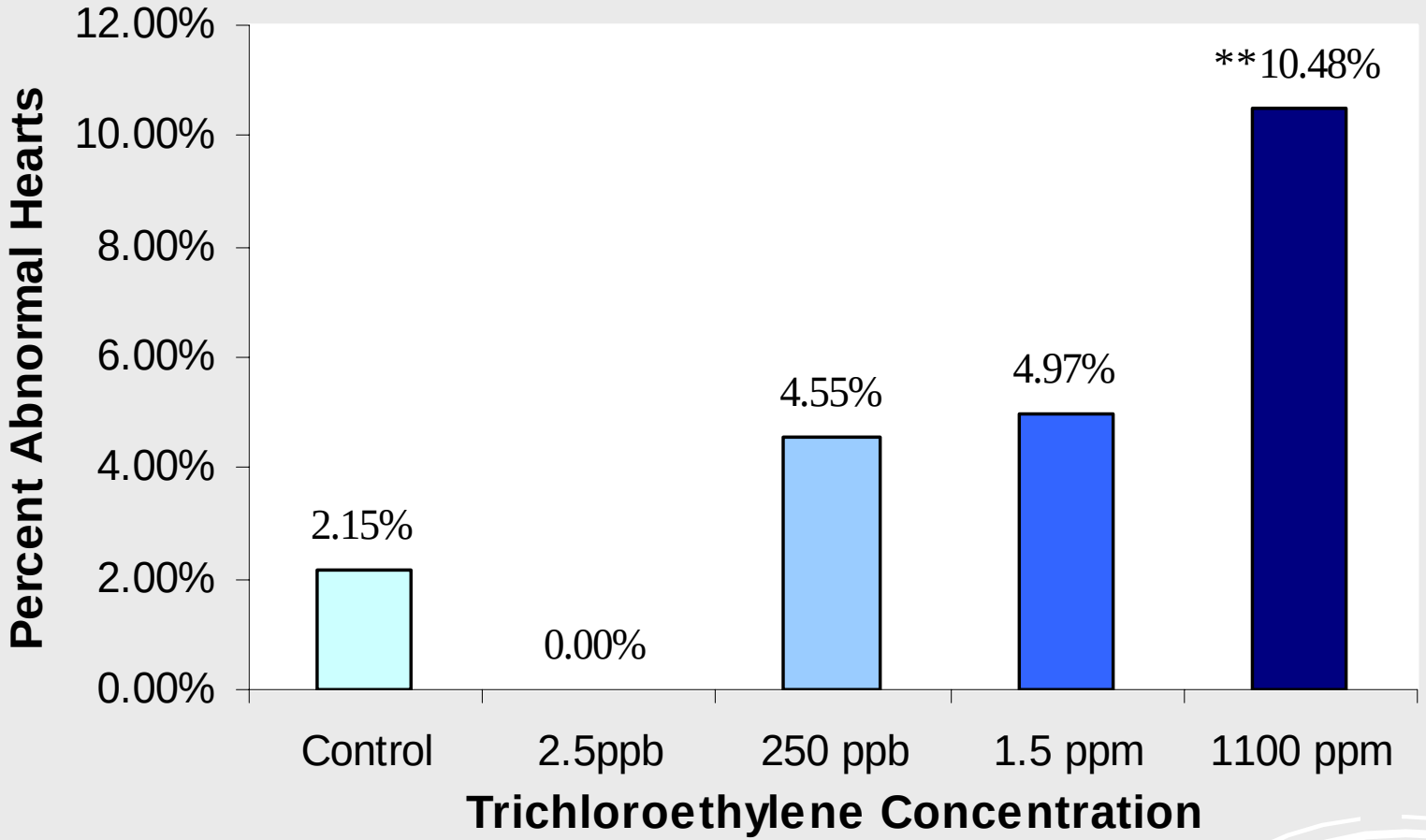
Trichloroethylene (TCE) Test Groups

Dk Water Conc	No. of Maternal Rats	Total No. of Fetuses
1100 ppm	9	105
1.5 ppm	13	181
250 ppb	9	110
2.5 ppb	12	144
Control	55	606

Types of Heart Malformations

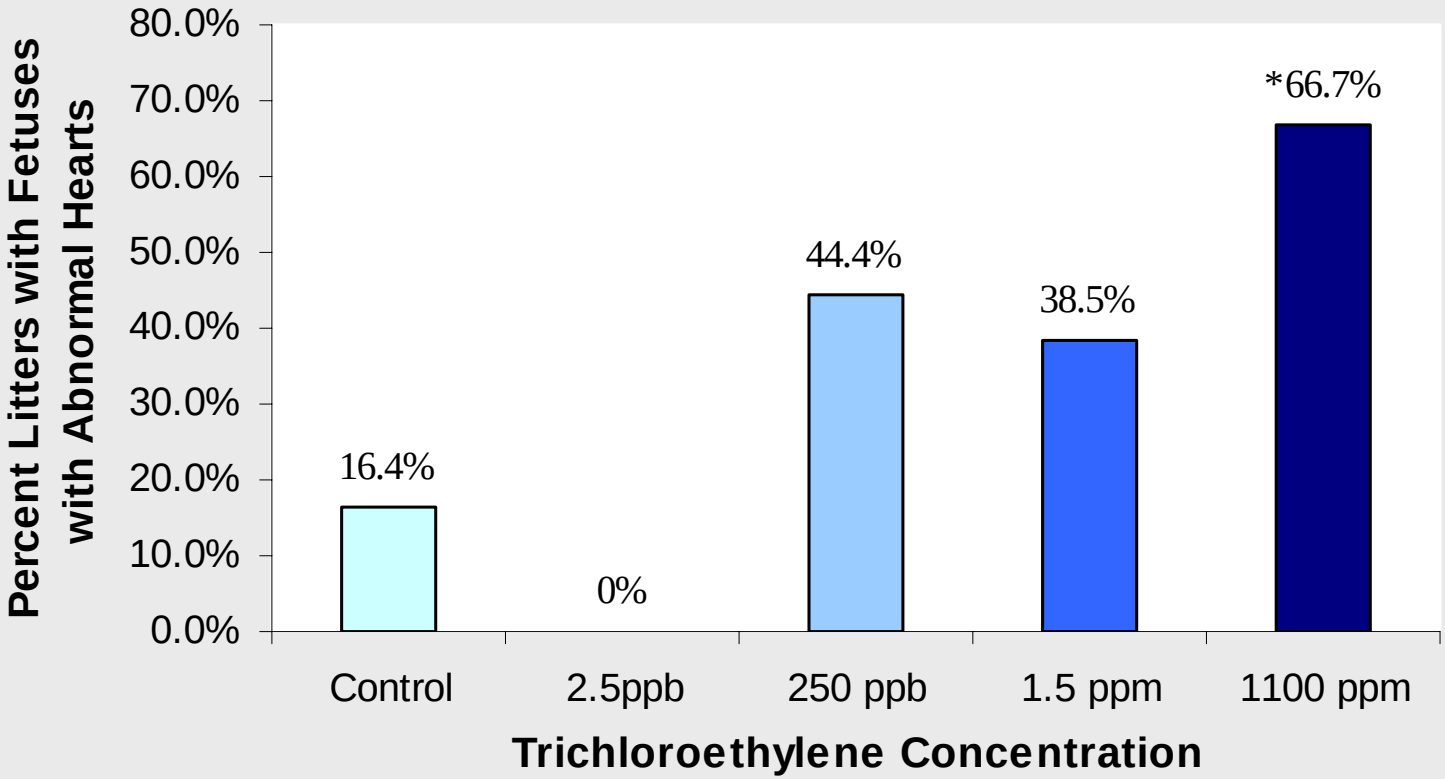
- Abnormal Looping
- Coronary Artery/Sinus
- Aortic Hypoplasia
- Pulmonary Artery Hypoplasia
- Atrial Septal Defect (ASD)
- Mitral Valve Defect
- Tricuspid Valve Defect
- Ventricular Septal Defect (VSD):
- -peri-membranous (subAortic)
- -muscular
- Atrio-Ventricular Septal Defect
- Pulmonary Valve Defect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

% Abnormal Hearts



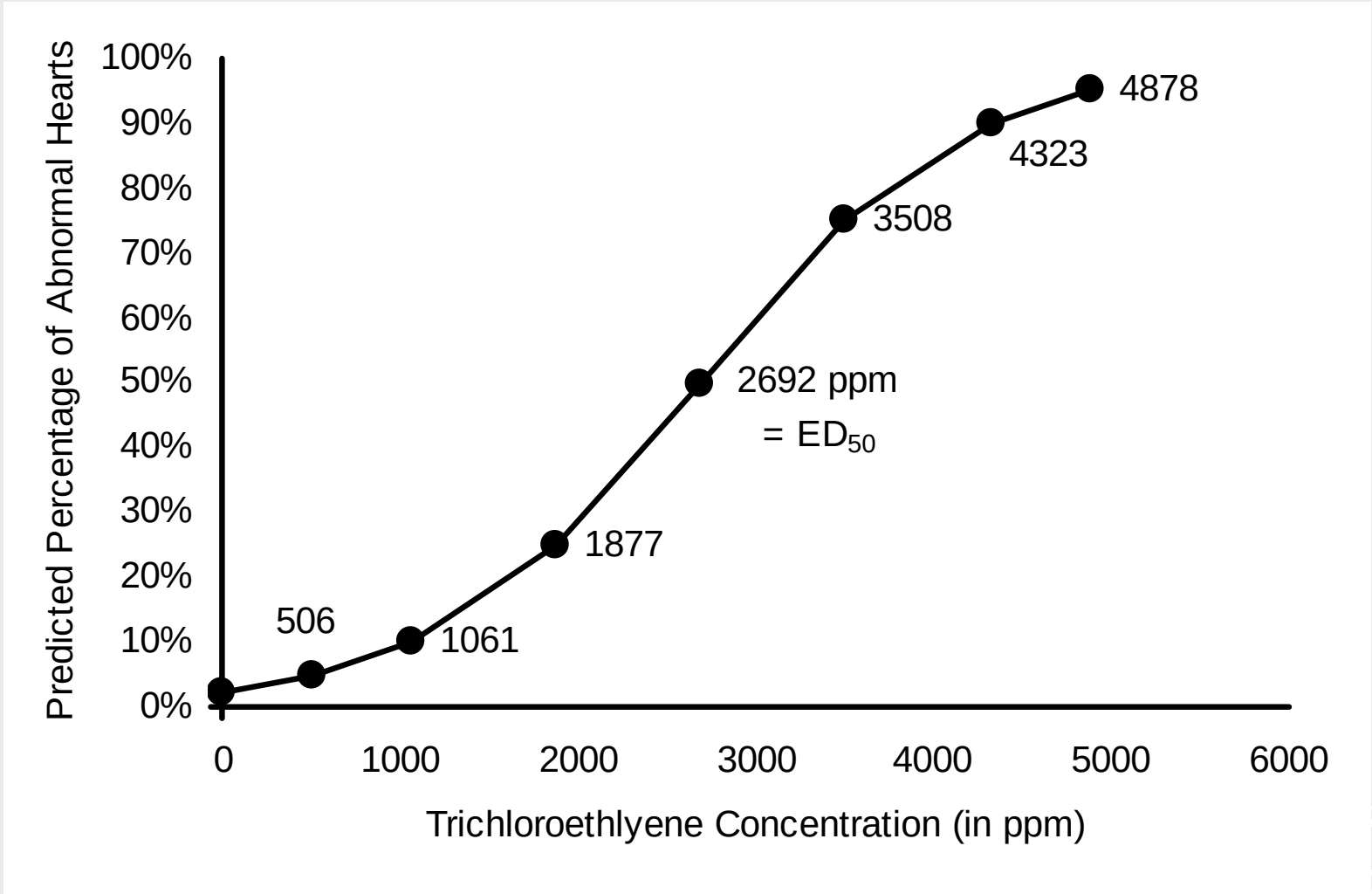
**Statistical Significance between control and treated groups

% Litters with Abnormal Hearts



*Statistical Significance between control and treated groups

Expected Effective Dose



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

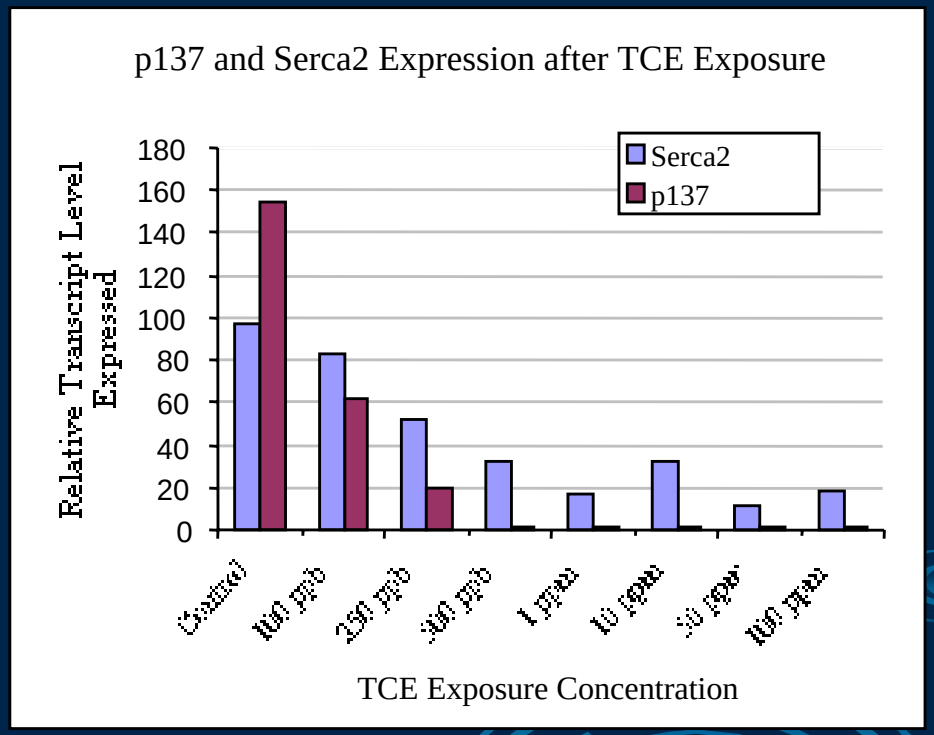
Gene Expression Results

- 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

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