

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

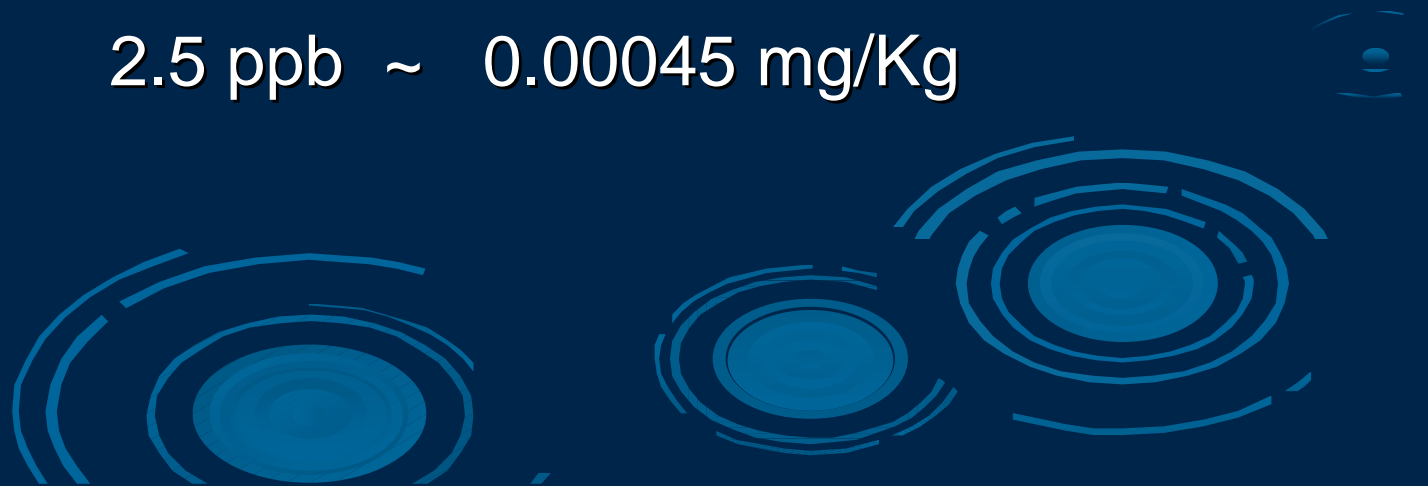
Concentration ~~~~~ Avg. Dose

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

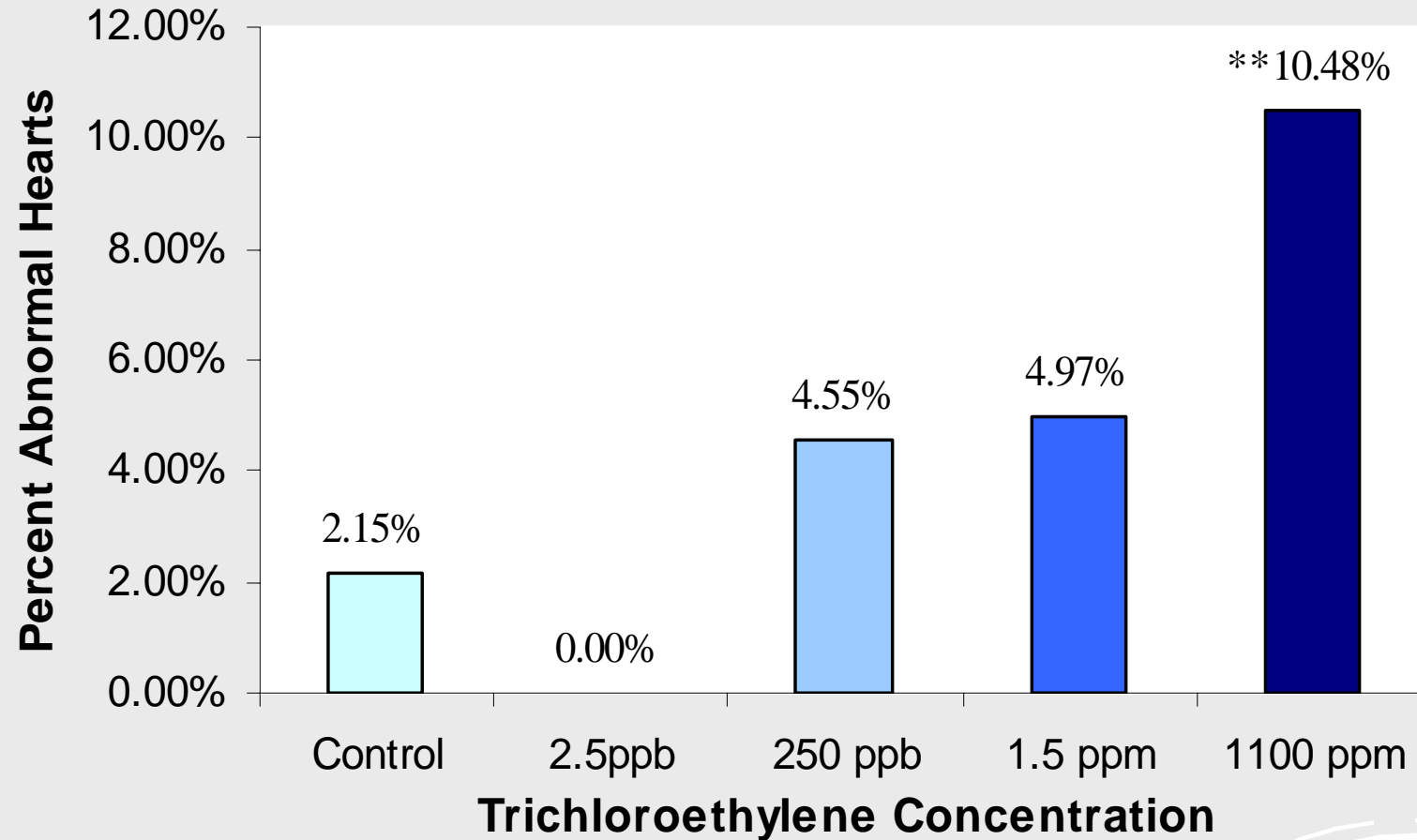
Dk Water Conc	No. of Maternal Rats	Total No. of Fetuses
1100 ppm	9	105
1.5 ppm	13	181
250 ppb	9	110
2.5 ppb	12	144
Control	55	606

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

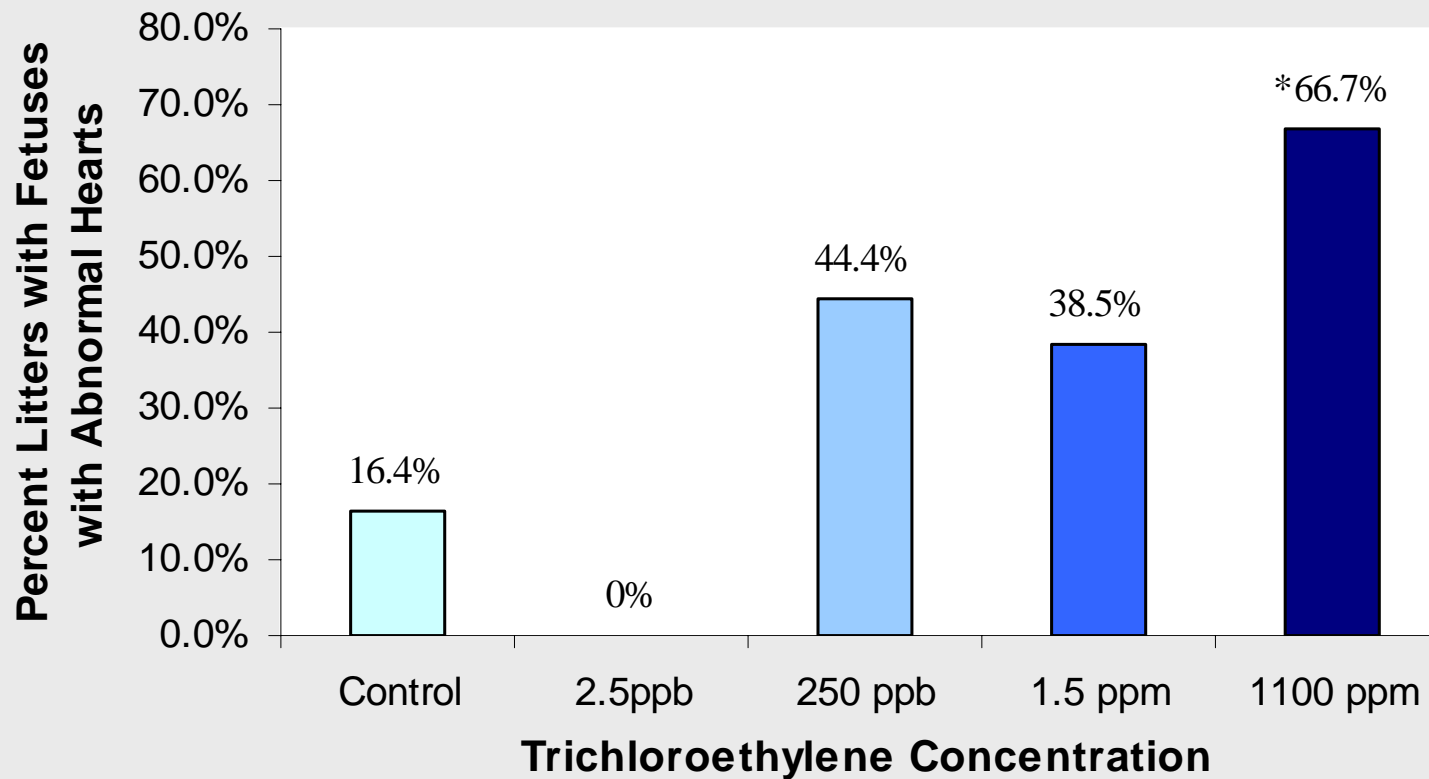


% Abnormal Hearts



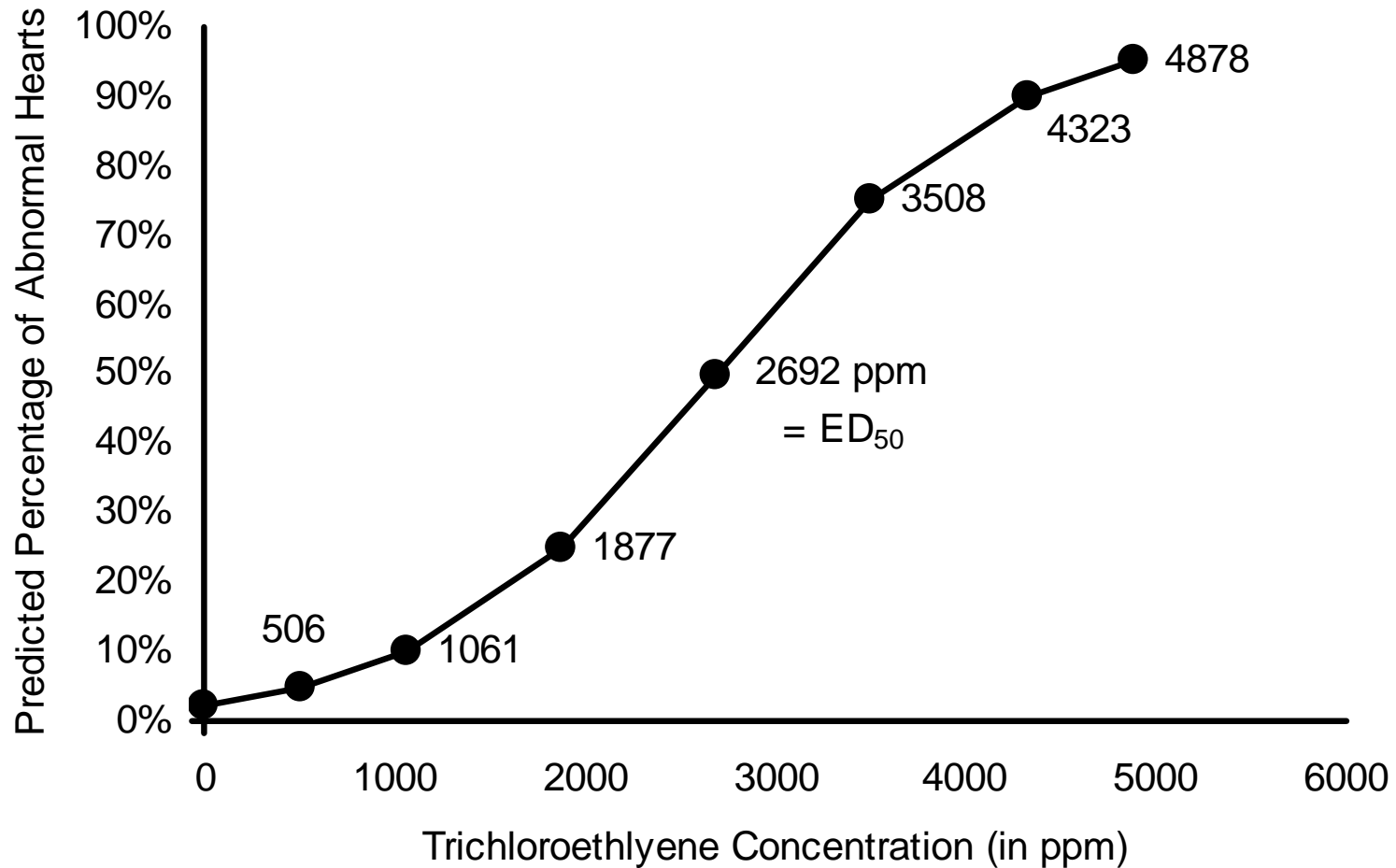
**Statistical Significance between control and treated groups

% 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

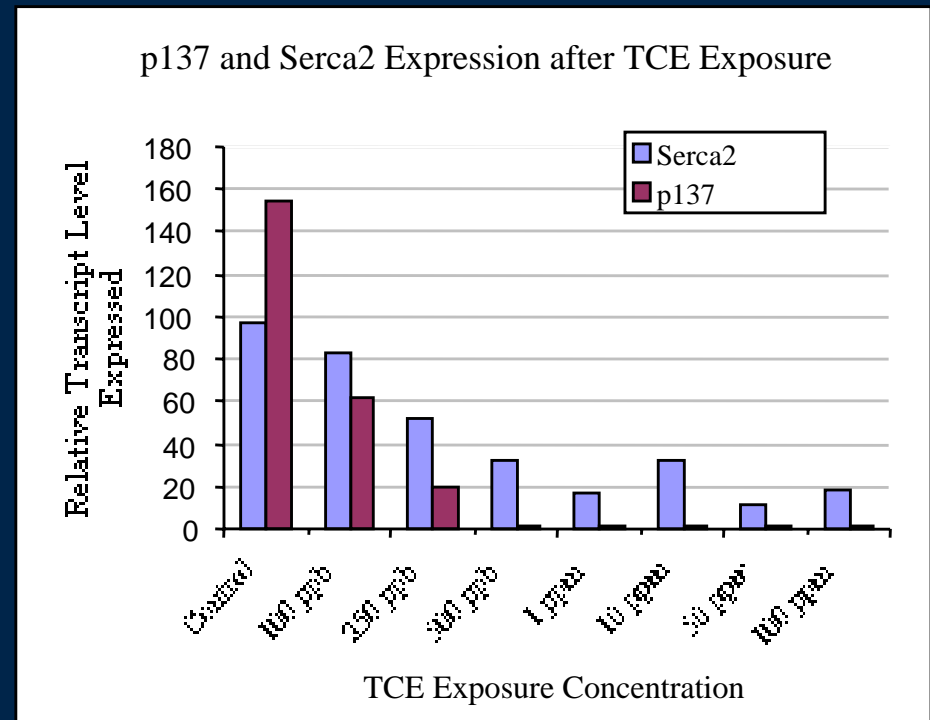


Gene Expression Results

- 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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