Evidence of Developmental and Reproductive Toxicity of Chloroform in Humans

Developmental Toxicity in Humans

Eight epidemiologic studies

- One occupational cohort study of chloroform exposure in laboratory workers

- Seven studies of chloroform in drinking water
  - Three case-control studies
  - Three retrospective cohort studies
  - One prospective cohort study

Developmental Toxicity of Chloroform in Occupational Exposures

Wennborg et al., 2000

- Chloroform exposure before conception and spontaneous abortion OR = 2.3 (95% CI, 0.9 – 5.9)

- Previous spontaneous abortion OR = 2.2 (95% CI, 1.2 – 4.1)

Developmental Toxicity of Chloroform Exposure in Drinking Water in Humans

Kramer et al., 1992	Case-control	Intrauterine growth retardation	OR = 1.8 (95% CI, 1.1 – 2.9)
Waller et al., 1998	Prospective cohort	No effect	
King et al., 2000	Retrospective cohort	Stillbirth	RR = 1.66 (95% CI, 1.09 – 2.54)
Dodds and King, 2001	Retrospective cohort	Chromosomal abnormalities	RR = 1.9 (95% CI, 1.1 – 3.3)

Developmental Toxicity of Chloroform Exposure in Drinking Water in Humans (cont.)

Dodd et al., 2004	Case-control	Stillbirth	OR = 1.8 (95% CI 1.1 – 3.0) OR = 2.2, (95% CI, 1.0 – 4.8)
Infante-Rivard, 2004	Case-control	No effect	
Wright et al., 2004	Retrospective cohort	Lower birthweight Small for gestational age	-18 (95% CI, -26 to –10) OR = 1.11 (95% CI, 1.08 - 1.22)

Male Reproductive Toxicity of Chloroform in Humans

Occupational case report

Chang et al., 2001

- Very high levels of exposures – 8.5 ppm active sampling
  - may have been 450 ppm after overnight build up of levels
- Lower percentages of total motile sperm (26%)

Female Reproductive Toxicity of Chloroform in Humans

Occupational studies

- *Dahl et al., 1999*
  - No evidence of an effect on fertility
- *Wennborg et al., 2000*
  - Chloroform exposure before conception and spontaneous abortion OR = 2.3 (95% CI, 0.9 – 5.9)
  - Previous spontaneous abortion OR = 2.2 (95% CI, 1.2 – 4.1)

Summary of Effects Reported Following Chloroform Exposure in Humans

Developmental

- Decreased birth weight
- IUGR
- Increased stillbirths

Male Reproductive

- Lower percentages of total motile sperm

Female Reproductive

- Increased spontaneous abortions

Interpretation of Developmental Toxicity Data in Humans

Important factors to consider in these studies:

- Levels of chloroform exposure
- Sample size $\rightarrow$ power of study

Concordance of Human and Animal Data

Outcome	Human	Animal
<u>Developmental</u> - oral	↓ Fetal weight ↑ IUGR	↓ Fetal weight
- inhalation	↑ Spontaneous abortions ↑ Stillbirths	↑ Resorptions
<u>Male</u> - inhalation	↓ % Motile sperm	↑ Abnormal sperm morphology
<u>Female</u> - inhalation	↑ Spontaneous abortions	↑ Resorptions ↑ Whole litter abortions