EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF CHLOROFORM

Reproductive and Cancer Hazard Assessment Section (RCHAS)
Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency (Cal/EPA)
CHLOROFORM (CAS No. 67-66-3)

• Trichloromethane: CHCl₃

• Annual U.S. production over 500 million pounds

• By-product of water disinfection by chlorine

• Exposure may occur in the workplace, via consumption of contaminated water, or via exposure to vapor of contaminated water
PHARMACOKINETICS OF CHLOROFORM

• Absorbed by oral, inhalation, or dermal routes
• Rapid distribution throughout the body
  - Crosses placenta
  - Expected to appear in breast milk
• Metabolized by cytochrome P450-dependent pathways
• Non-metabolized chloroform excreted via exhalation
Non-DART Effects of Chloroform

Acute Effects:
• Anesthesia
• Liver necrosis
• Death

Chronic Effects:
• Neurological effects
• Cytotoxicity in liver, kidney, and nasal mucosa

Carcinogenicity:
• Proposition 65 carcinogen
Developmental Toxicity of Chloroform by Inhalation in the Rat (1a)

Schwetz et al., 1974 – 0, 30, 100, 300 ppm
  • Decreased pregnancy rate, litter size, fetal weight and length, altered sex ratio (300 ppm)
  • Increased gross anomalies (100 ppm)
  • Increased skeletal anomalies, decreased length (30 ppm)
  • Reduced maternal body weight (300 ppm)
Developmental Toxicity of Chloroform by Inhalation in the Rat (1b)

*Schwetz et al., 1974 – feed restricted control group*

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<thead>
<tr>
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<th>Feed restricted</th>
<th>300 ppm</th>
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<tbody>
<tr>
<td>Feed gd 12-13 (% ad lib control)</td>
<td>17%</td>
<td>4%</td>
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<tr>
<td>Pregnant/bred</td>
<td>8/8</td>
<td>3/20</td>
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<tr>
<td>Maternal wt gd 13 (% ad lib control)</td>
<td>72%</td>
<td>62%</td>
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<tr>
<td>Fetal weight at term (% ad lib control)</td>
<td>91%</td>
<td>60%</td>
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Developmental Toxicity of Chloroform by Inhalation in the Rat (2)

*Baeder & Hoffman, 1988 – 0, 30, 100, 300 ppm*
  - Decreased fetal length (30, 100, 300 ppm)
  - Decreased litters, and fetal weight (300 ppm)
  - Reduced maternal body weight (30, 100, 300 ppm)

*Baeder & Hoffman, 1991 – 0, 3, 10, 30 ppm*
  - Decreased fetal weight and length (30 ppm)
  - Increased ossification variations (3, 10, 30 ppm)
  - Reduced maternal body weights (10, 30 ppm)
Developmental Toxicity of Oral Chloroform in the Rat; by Gavage

*Thompson et al., 1974 – 0, 20, 50, 126 mg/kg-day*
  - Decreased fetal weights (126 mg/kg-day)
  - Decreased maternal weight gain (50, 126 mg/kg-day)

*Ruddick et al., 1983 – 0, 100, 200, 400 mg/kg-day*
  - Decreased fetal weight (400 mg/kg-day)
  - Decreased maternal weight gain (100, 200, 400 mg/kg-day)
Developmental Toxicity of Chloroform by Inhalation in the Mouse

*Murray et al., 1979 – 0, 100 ppm on gestation days 1-7, 6-15, or 8-15*

- Decreased pregnancy rate (days 1-7 or 6-15)
- Increased resorptions (days 1-7)
- Decreased fetal body weight and length (days 1-7 or 8-15)
- Increased cleft palate & retarded ossification of sternebrae (days 1-7 or 8-15)
- Decreased maternal weight gain (days 1-7 or 8-15)
Developmental Toxicity of Oral Chloroform in the Rabbit; by Gavage

*Thompson et al., 1974 – 0, 20, 35, 50 mg/kg-day*

- Decreased fetal weights (20, 50 mg/kg-day)
- Excess maternal death (50 mg/kg-day)
- Decreased maternal weight gain (50 mg/kg-day)
Developmental Neurotoxicity of Oral Chloroform in the Mouse; by Gavage

*Burkhalter and Balster, 1979* – 31.1 mg/kg-day, prior to mating, throughout gestation, lactation, and to pups

- Reduced postnatal weight gain (31.1 mg/kg-day)
- Lower scores for forelimb placement, postnatal days 5 and 7 (31.1 mg/kg-day)
- Maternal effects not discussed
Male Reproductive Toxicity of Chloroform in Mice

Inhalation Sperm Study

Land et al., 1979 & 1981 – 0, 400, 800 ppm (roughly 0, 450, 900 mg/kg-day)

• Abnormal sperm morphology

Gavage Continuous Breeding Study

NTP, 1988 – 0, 6.6, 15.9, 41.2 mg/kg-day

• No effects on fertility or sperm parameters

• Increased epididymal weight in F1 generation
Female Reproductive Toxicity of Chloroform (1)

*NTP, 1988 – 0, 6.6, 15.9, 41.2 mg/kg-day*
- Continuous breeding study in mice, by gavage
- No adverse reproductive effects

*U.S. EPA, 1980 – 0, 20, 38, 57, 81, 160 mg/kg-day*
- 90-day toxicity study in rats, drinking water
- No effects on ovaries or uterus

*Heywood et al., 1979 – 0, 15, 30 mg/kg-day*
- 7.5-year chronic study in dogs, by capsule
- No effects on ovaries or uterus
Female Reproductive Toxicity of Chloroform (2): Data From Developmental Toxicity Studies

Rats, inhalation
- Reduced pregnancy rate or complete resorption of litters
- Decreased litter size and/or increased resorption frequency

Mice, inhalation
- Reduced pregnancy rate and/or increased resorptions

Rats, oral
- No effects on live litter size or resorption frequency

Rabbits, oral
- Complete abortion of litters, not clearly related to dose
Summary of DART Effects Reported Following Chloroform Exposure

Developmental
  • Decreased pregnancy rate
  • Increased resorptions
  • Decreased fetal weight and length

Male Reproductive
  • Abnormal sperm

Female Reproductive
  • Decreased pregnancy rate
  • Increased resorptions and whole-litter abortions