Evidence on the Developmental and Reproductive Toxicity of Xylene

February 25, 2013

Developmental and Reproductive Toxicant (DART) Identification Committee Meeting

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
**technical xylene** (*o-, m-, p*), CAS registry number 1330–20–7

**o-xylene**, *ortho-xylene*, *1,2-dimethylbenzene*, *2-xylene*; CAS registry number 95–47–6

**m-xylene**, *meta-xylene*, *1,3-dimethylbenzene*, *3-xylene*; CAS registry number 108–38–3

**p-xylene**, *para-xylene*, *1,4-dimethylbenzene*, *4-xylene*; CAS registry number 106–42–3
Human Exposure to Xylene

• Primarily to mixed xylenes, not isomers
• Inhalation:
  – Automobile exhaust
  – Cigarette smoke
  – Xylene-containing solvents
• Oral exposure to contaminated drinking water
• Dermal exposure to contaminated water, or to solvents in the workplace
Xylene Metabolism and Pharmacokinetics

• Absorption efficiencies:
  – Oral, 90%
  – Inhalation, 60-65%
  – Dermal, < 1%

• Distribution rapid; affinity for lipid-rich tissues

• Metabolism in liver, lung, and kidneys to excreted conjugates

• Radiolabelled xylene found in fetal tissues
Non-DART Toxicity of Xylene

• **Acute**
  – **Human**: low dose (1 - > 100 ppm) $\rightarrow$ mild excitation; higher doses (several thousand ppm) $\rightarrow$ sedation and narcosis
  – **Animal**: excitation followed by sedation, ataxia, altered visual and auditory evoked potentials, muscle spasms, labored breathing; rat 4-hr LC$_{50}$ = 6,500 ppm

• **Repeated dose**
  – **Animal**: hearing loss (> 800 ppm), impaired performance on neurobehavioral tests (100 ppm), ↓ body weight (500 – 800 mg/kg-day)

• **Cancer**
  – Insufficient human or animal data to determine carcinogenic potential
Male Reproductive Toxicity of Xylene in Animals; inhalation

• 1-gen reproductive toxicity study in rats
  – 0, 60, 250, 500 ppm
  – No ♂ reproductive or systemic toxicity
• 61-day study in ♂ rats
  – 0, 1000 ppm
  – No evidence of ♂ reproductive toxicity
• 7-day study in ♂ rats
  – 2X/day until animals lost righting reflex (no dose)
  – ↓ body weight on treatment day 7
  – ↓ absolute weights of ♂ reproductive organs
  – ↓ testosterone and epididymal sperm
Male Reproductive Toxicity of Xylene in Animals; i.p. injection

- ♂ Sprague Dawley rats given o-xylene by i.p. injection
  - 0, 0.5 or 1.5 ml/kg bw, daily, 2 days
  - ↑abnormal sperm in animals given 0.5 ml/kg and living at 24-30°C (no effect at 20-24°C)
Female Reproductive Toxicity of Xylene in Animals

• 1 one-generation rat study
  – Inhalation: 0, 60, 250, and 500 ppm
  – 6 hr/day; 131-days pre-mating, through lactation

• 12 studies with exposure restricted to gestation
  – 1 rat hormone levels after inhalation on GD 9 or 9-10, 0, 692 ppm
  – 11 developmental toxicity studies
    • 10 rat inhalation: concentrations 2.31-2000 ppm
      – 1/10 also tested mice and rabbits: 115, 231 ppm
    • 1 mouse gavage: 0, 0.52 - 4.13 mg/kg-day; GD 6-15
Female Reproductive Toxicity of Xylene in Animals, Results

- ↓progesterone and 17ß-estradiol in rats with 692 ppm xylene on GD 9-10
- Evidence of ↑embryo-fetal mortality, in some cases associated with excessive maternal mortality
  - Rabbits, inhalation: ↑embryo-fetal mortality (115 & 231 ppm)
  - Rats, inhalation (2 studies): ↑totally resorbed litters, ↓litter size, ↓implantation sites (692 & 784 ppm)
  - Mice, gavage: ↑resorptions at 3.1 mg/kg-day
Developmental Toxicity of Xylene in Animals

• 1 one-generation rat study
  – Inhalation: 0, 60, 250, and 500 ppm
  – 6 hr/day; 131-days pre-mating, through lactation

• 12 rat inhalation: concentrations 2.31-2000 ppm
  • 1 also looked at mice and rabbits: 115, 231 ppm

• 1 mouse oral: 0, 0.52, 1.03, 2.06, 2.58, 3.10, 4.13 mg/kg-day; GD 6-15

• 1 rat dermal, biochemical endpoints: 0, 100, 200, and 2000 mg/kg bw-day, GD 1-20
Developmental Toxicity of Xylene in Animals, Manifestations

• Viability –
  – Rabbits, inhalation: ↑embryo-fetal mortality (115 & 231 ppm, GD 7-20)*
  – Rats, inhalation (2 studies): ↑totally resorbed litters, ↓litter size, ↓implantation sites (692 & 784 ppm, GD 7-14 or 15)
  – Mice, oral: ↑resorptions at 3.10 mg/kg-day, GD 6-15*

• Growth –

• Structural Abnormality –

• Functional Deficits –

*associated with excessive maternal mortality
## Developmental Toxicity of Xylene in Animals, Growth (Fetal or Birth Weight)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Highest dose tested</th>
<th>Lowest effective dose</th>
<th>Notations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hass &amp; Jacobson (1993)</td>
<td>200 ppm</td>
<td>200 ppm</td>
<td>↑♂ bw, rat</td>
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<tr>
<td>Hass et al. (1995 &amp; 1997)</td>
<td>500 ppm</td>
<td>No effect</td>
<td>rat</td>
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<tr>
<td>Hudak &amp; Ungvary (1978)</td>
<td>230 ppm</td>
<td>No effect</td>
<td>rat</td>
</tr>
<tr>
<td>Litton Bionetics (1978)</td>
<td>400 ppm</td>
<td>No effect</td>
<td>rat</td>
</tr>
<tr>
<td>Biodynamics (1983)</td>
<td>500 ppm</td>
<td>500 ppm</td>
<td>↓♀ fw, rat</td>
</tr>
<tr>
<td>Mirkova (1983)</td>
<td>115 ppm</td>
<td>11.5 ppm</td>
<td>↓ fw, rat</td>
</tr>
<tr>
<td>Saillenfait et al. (2003)</td>
<td>2000 ppm</td>
<td>500 ppm</td>
<td>↓ fw, o-xylene, rat</td>
</tr>
<tr>
<td>Ungvary et al. (1980)</td>
<td>692 ppm</td>
<td>346 ppm</td>
<td>↓ fw, o-xylene, rat</td>
</tr>
<tr>
<td>Ungvary &amp; Tatrai (1985)</td>
<td>784 ppm</td>
<td>115 ppm</td>
<td>↓♀ fw, rabbit</td>
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<tr>
<td>Rosen et al. (1986)</td>
<td>1615 ppm</td>
<td>No effect</td>
<td>rat</td>
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<tr>
<td>Marks et al. (1982)</td>
<td>3.10 mg/kg-day (oral)</td>
<td>2.06 mg/kg-day</td>
<td>↓ fw, mouse</td>
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## Developmental Toxicity of Xylene in Animals, Structural Abnormality (Skeletal Anomalies)

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<tr>
<td>Hass and Jakobsen (1993)</td>
<td>200 ppm</td>
<td>200 ppm</td>
<td>rat, skeletal anomalies</td>
</tr>
<tr>
<td>Hudak &amp; Ungvary (1978)</td>
<td>230 ppm</td>
<td>230 ppm</td>
<td>rat, skeletal anomalies</td>
</tr>
<tr>
<td>Ungvary &amp; Tatrai (1985)</td>
<td>784 ppm</td>
<td>58 ppm rats, 231 ppm mice</td>
<td>rat and mouse skeletal anomalies</td>
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<tr>
<td>Ungvary et al. (1980)</td>
<td>692 ppm</td>
<td>35 ppm</td>
<td>rat, skeletal anomalies</td>
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<tr>
<td>Marks et al. (1982)</td>
<td>3.10 mg/kg-day (oral)</td>
<td>2.06 mg/kg-day</td>
<td>mouse, combined anomalies</td>
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Developmental Toxicity of Xylene in Animals, Functional Deficits (neuro-behavioral)

**Rotarod** (Hass & Jakobsen, 1993; Hass et al., 1995)
- ↓ Rotarod times for ♀ pups, 200 ppm
- No significant effect, 500 ppm

**Air-Righting reflex** (Hass et al., 1995)
- Delayed acquisition of air-righting reflex, 500 ppm

**Open Field** (Hass et al., 1995)
- No effect, 500 ppm

**Morris Water Maze** (Hass et al., 1995 & 1997)
- ↑ swim time in Morris Water Maze, ♀, 500 ppm

**Locomotor Activity, Acoustic Startle** (Rosen et al., 1986)
- No effect, 1615 ppm p-xylene