

# Evidence on the Developmental and Reproductive Toxicity of Xylene

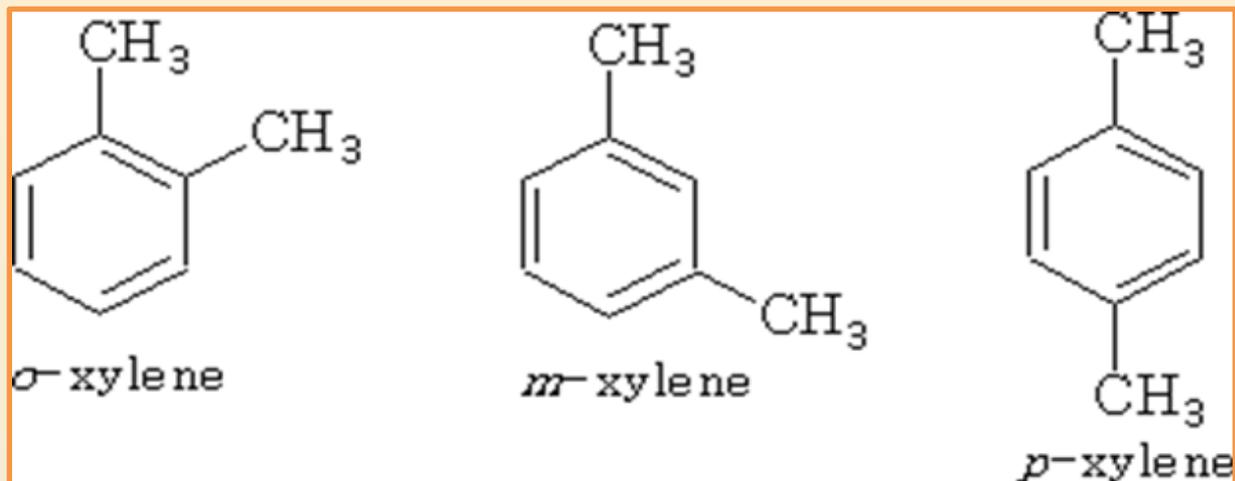
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Developmental and Reproductive Toxicant (DART) Identification Committee Meeting



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) → mild excitation; higher doses (several thousand ppm) → sedation and narcosis
  - Animal: excitation followed by sedation, ataxia, altered visual and auditory evoked potentials, muscle spasms, labored breathing; rat 4-hr LC<sub>50</sub> = 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  $17\beta$ -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)

Reference	Highest dose tested	Lowest effective dose	Notations
Hass & Jacobson (1993)	200 ppm	200 ppm	↑♂ bw, rat
Hass et al. (1995 & 1997)	500 ppm	No effect	rat
Hudak & Ungvary (1978)	230 ppm	No effect	rat
Litton Bionetics (1978)	400 ppm	No effect	rat
Biodynamics (1983)	500 ppm	500 ppm	↓♀ fw, rat
Mirkova (1983)	115 ppm	11.5 ppm	↓ fw, rat
Saillenfait et al. (2003)	2000 ppm	500 ppm	↓ fw, o-xylene, rat
Ungvary et al. (1980)	692 ppm	346 ppm	↓ fw, o-xylene, rat
Ungvary & Tatrai (1985)	784 ppm	115 ppm	↓♀ fw, rabbit
Rosen et al. (1986)	1615 ppm	No effect	rat
Marks et al. (1982)	3.10 mg/kg-day (oral)	2.06 mg/kg-day	↓ fw, mouse

# Developmental Toxicity of Xylene in Animals, Structural Abnormality (Skeletal Anomalies)

Reference	Highest dose tested	Lowest effective dose	Notations
Biodynamics (1983)	500 ppm	No effect	rat
Litton Bionetics (1978)	400 ppm	No effect	rat
Saillenfait et al. (2003)	2000 ppm	2000 ppm	rat, skeletal anomalies
Hass and Jakobsen (1993)	200 ppm	200 ppm	rat, skeletal anomalies
Hudak & Ungvary (1978)	230 ppm	230 ppm	rat, skeletal anomalies
Ungvary & Tatrai (1985)	784 ppm	58 ppm rats 231 ppm mice	rat and mouse skeletal anomalies
Ungvary et al. (1980)	692 ppm	35 ppm	rat, skeletal anomalies
Marks et al. (1982)	3.10 mg/kg-day (oral)	2.06 mg/kg-day	mouse, combined anomalies

# 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