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
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Male Reproductive Toxicity

3 Epidemiologic Studies

Cross-sectional study in Zhejiang Province, China (Xiao et al., 1999 and 2001)

- Benzene, toluene, xylene (BTX) in blood and semen
- Semen parameters and indicators of sex gland function

Retrospective cohort study in Finland (Sallmén et al., 1998)

- Self-reported occupational exposure
- Time to pregnancy (TTP) as an indicator of fecundability

$$\text{FDR} = \frac{\text{fecundability}_{\text{exposed}}}{\text{fecundability}_{\text{unexposed}}}$$

Male Reproductive Toxicity

Nested case-control study in Finland (Taskinen et al., 1989)

- Paternal occupational exposure to xylene and other organic solvents, based mainly on job descriptions and reported solvent use
- Spontaneous abortion (SAB) or child with malformation

Male Reproductive Toxicity

Study	Sample & exposure	Findings
Xiao et al., 1999 & 2001	• 24 exposed (shoemaking, spray painting, paint manufacturing) • 37 unexposed (managers)	Blood xylene: ↓ semen γ-glutamyltransferase activity
Sallmén et al., 1998	282 men • 70 low/intermed exp. • 51 high/frequent exp.	Adjusted FDRs (95% C.I.) 0.75 (0.52, 1.09) 0.91 (0.61, 1.36)
Taskinen et al., 1989	SAB: 120 cases, 251 controls Malformations: 25 cases, 96 controls	SAB - high/freq. exp: Adj. OR = 1.6 (0.8, 3.2) Malformations: Crude OR = 1.6 (0.4, 5.7)

Female Reproductive Toxicity
2 Epidemiologic Studies

Retrospective cohort study in Finland (Sallmén et al., 1995)

- 1st trimester exposure based on descriptions of work
- TTP as an indicator of fecundability

$$\text{FDR} = \frac{\text{fecundability}_{\text{exposed}}}{\text{fecundability}_{\text{unexposed}}}$$

Cross-sectional study in China (Cho et al., 2001)

- Petrochemical industry exposures to benzene, toluene, styrene, and xylene
- Menstrual patterns

Female Reproductive Toxicity

Study	Sample	Findings
Sallmén et al., 1995	197 women • 31 low exposure • 10 high exposure	Adjusted FDRs 1.41 (0.91, 2.20) 0.93 (0.47, 1.84)
Cho et al., 2001	1,408 nulliparous, married women, age 20-40 years	Adjusted* OR for oligomenorrhea = 1.63 (1.04, 2.53) *not adjusted for exposure to other aromatic solvents

Developmental Toxicity

Outcomes

- Congenital malformations
- Spontaneous abortion (SAB)
- Birth weight
- Cord blood T cells

Congenital Malformations

4 epidemiologic studies

Case-control study of maternal exposure and neural tube defects (NTDs) in Texas (Lupo et al., 2011)

- Environmental BTEX (benzene, toluene, ethylbenzene, and xylene) for each mother's census tract
- Spina bifida & anencephaly

Nested case-control study of paternal occupational exposure in Finland (Taskinen et al., 1989)

- Exposure based on job descriptions, reported solvent use
- Any malformations from the Finnish register

Congenital Malformations

Case-control study of maternal laboratory occupational exposure in Finland (Taskinen et al., 1994)

- Exposure based on job descriptions, reported solvent use
- Any malformations recorded in the Finnish register

Cohort study of maternal laboratory work in Sweden (Axelsson et al., 1984)

- Exposure based on reported solvent use
- Minor and major malformations from the Swedish malformation register

Congenital Malformations

Study	Sample	Exposure	Findings
Lupo et al., 2011	533 spina bifida 303 anencephaly 3,695 controls	Environmental BTEX	n.s. ↑ risk of NTDs
Taskinen et al., 1989	25 cases 96 controls	Paternal occupational	Crude OR = 1.6 (0.4, 5.7)
Taskinen et al., 1994	36 cases 105 controls	Maternal laboratory work	No association

Spontaneous Abortion

6 Epidemiologic Studies

- Nested case-control study, Finland (Taskinen et al., 1989)
  - Paternal occupational exposure
- Case-control study, Finland (Taskinen et al., 1994)
  - Maternal occupational exposure
- Cohort study, Sweden (Axelsson et al., 1984)
  - Maternal laboratory solvent exposure

Spontaneous Abortion

- Case-control study in Finland (Lindbohm et al., 1990)
  - Maternal occupational exposure to organic solvents
- Case-control study in Santa Clara County (Windham et al., 1991)
  - Solvent exposure, including occupational and non-occupational
- Retrospective cohort study in U.S. semiconductor industry (Swan et al., 1995)
  - Maternal occupational exposures in semiconductor fabrication

Spontaneous Abortion

Study	Sample	Exposure	Findings
Taskinen et al., 1989	120 cases 251 controls	Likely paternal occupational	n.s. ↑ risk of SAB
Taskinen et al., 1994	206 cases 329 controls	Maternal lab work	Expos. ≥ 3d/wk in 1st trimester: Adjusted OR = 3.1 (1.3, 7.5)
Axelsson et al., 1984	556 pregnancies 194 exposed 20 SAB	Maternal lab work	No association
Lindbohm et al., 1990	73 cases 167 controls	Maternal occupational	Adjusted OR = 1.3 (0.4, 4.5)

Spontaneous Abortion

Study	Sample	Exposure	Findings
Windham et al., 1991	626 cases, 1,300 matched controls (9 cases, 12 controls exposed)	Occupational and other	Crude OR = 1.6 (0.66, 3.8)
Swan et al., 1995	506 current & 385 former employees	Semiconductor fabrication	2nd, 3rd exposure levels, vs. unexposed, Adjusted RR = 2.31 (1.39, 3.58)

Birth weight

Case-control study of maternal occupational exposure (Taskinen et al., 1994)

Cohort study of maternal laboratory solvent exposure (Axelsson et al., 1984)

Retrospective cohort study of traffic-related air pollution (including BTEX), Los Angeles County (Ghosh et al., 2012)

- Term low birth weight (LBW)
- Exposure assessed throughout pregnancies

Birth weight

Study	Sample	Exposure	Findings
Taskinen et al., 1994	Not reported	Maternal lab work	Exposure ≤ 2 days a week assoc. w/ ↑ birth weight
Ghosh et al., 2012	8,181 term LBW, 370,922 normal weight infants	3rd trimester (m+p)-xylenes o-xylene	Adjusted ORs 1.03 (1.01-1.06) 1.03 (1.01-1.05)

Umbilical cord blood T cells

Cross-sectional study of exposure to volatile organic compounds (VOCs) in relation to cytokine secretion profile of cord blood T cells (Lehman et al., 2002)

- 85 healthy, full-term neonates
- Cord blood T cell function analyzed
- Possible VOC exposure and family atopy history assessed
- VOCs sampled continuously in homes for 4 weeks after birth
- (m+p)-xylene: ↑ cytokine-producing T cells (unadjusted)
- No associations with xylene in multivariate analyses

Summary of Epidemiologic Evidence for Reproductive and Developmental Toxicity of Xylene

- **Multiple Exposures a Concern for All Endpoints**
- **Male Reproductive Toxicity**
  - 3 studies; 1 finding of ↓ semen γ-glutamyltransferase activity (prostate function)
- **Female Reproductive Toxicity**
  - ↑ oligomenorrhea in 1 of 2 studies (not including embryo/fetal viability)
- **Developmental Toxicity**
  - Malformations: 0 of 4 studies found effects
  - SAB: ↑ risk in 2 of 6 studies
  - Birth weight: ↑ BW w/ ≤ 2 days/wk exposure in 1 study, ↑ risk LBW in 1 air pollution study
  - No effect in 1 study of umbilical cord blood T cells

Summary of Animal Evidence for Reproductive and Developmental Toxicity of Xylene

- **Male Reproductive Toxicity**
  - 1/3 inhalation studies reported effects; study limited by lack of quantitative dosing
  - 1 i.p. study found ↑ abnormal sperm only in treated animals kept between 24 and 30°C
- **Female Reproductive Toxicity**
  - 1 inhalation study ↓ progesterone and 17ß-estradiol
  - ↓ embryo-fetal viability in 2/12 inhalation studies, and 1 oral study; interpretation complicated by excessive maternal mortality
- **Developmental Toxicity**
  - ↓ embryo-fetal viability (as above)
  - ↓ birth or fetal weight in 7/11 studies
  - ↑ minor skeletal or total anomalies in 6/8 studies
  - evidence of neurobehavioral effects in 3/4 studies

Questions?