Developmental and Reproductive Toxicity of Methyl Isocyanate: Human Data

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Overview

• Exposure to methyl isocyanate (MIC) in Bhopal
  – Basis of the human studies

• Studies
  – Developmental effects
  – Female reproductive effects
  – Male reproductive effects

• Summary of human and animal findings
Exposure to MIC in Bhopal

• Accident in Bhopal, India on December 2-3, 1984 around midnight
• 30 metric tons of MIC escaped in one hour
• Gas spread like a cloud over a densely populated area, 40 km$^2$
  – ~100,000 people were severely or moderately exposed
  – ~400,000 people were mildly exposed
  – ~2500 – 5000 people died in the 1$^{st}$ 3 days
Exposure to MIC in Bhopal 2

- Mean MIC concentration in gas cloud estimated as 27 ppm
  - TLV is 0.02 ppm
- Additional contaminants unknown
- Exposed via respiratory tract, skin, ingestion of saliva
- Activity level influenced exposure
  - Running in panic to escape led to higher dose
Developmental Effects in Humans

- Eight studies of pregnancy outcome & neonatal mortality
  - Shilotri et al., 1986
  - Varma, 1987
  - Kanhere et al., 1987
  - Bhandari et al., 1990*
  - Kapoor, 1991*
  - Varma, 1991*
  - ICMR, 2001*
  - Dhara and Dhara, 2002

- Two studies of effects after birth in those exposed in utero
  - Ranjan et al., 2003
  - Mishra et al., 2009a

*Presented specific rates for early pregnancy loss
### Developmental Effects: Pregnancy Outcome

<table>
<thead>
<tr>
<th>Study Authors (Year)</th>
<th>Population (# Pregnant Women)</th>
<th>Spontaneous Abortion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhandari et al. (1990)</td>
<td>Severe affected areas (n=2566) Controls (n=1218)</td>
<td>24% 6%</td>
</tr>
<tr>
<td>Kapoor (1991)</td>
<td>Severe affected area (n=75) Controls (n=60)</td>
<td>27% 10%</td>
</tr>
<tr>
<td>Varma (1991)</td>
<td>Residence located within 1 km radius of Union Carbide plant (n=638)</td>
<td>59%</td>
</tr>
<tr>
<td>Indian Council of Medical Research (ICMR, 2001)</td>
<td>Area of residence: Severe affected (n=195)</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>Moderately affected (n=160)</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Mildly affected (n=30)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Control (n=36)</td>
<td>8%</td>
</tr>
</tbody>
</table>
Pregnancy Outcome – Spontaneous Abortion Rate over Five Years Following Gas Disaster

(Data from ICMR, 2001)
Developmental Effects
 – Neonatal Mortality

• Varma (1987) – Neonatal mortality in those born to exposed mothers was 14.2% compared to up to 3% in the controls

• Bhandari *et al.* (1990) – Perinatal and neonatal mortality significantly elevated \((p<0.001)\) in those exposed
Developmental Effects – Postnatal Manifestation

Ranjan et al. (2003) – Physical Growth

• Exposed in utero, measured during adolescence
• Covariance model: age, mother’s height and weight, father’s height and weight, and socioeconomic status
• Found significantly decreased size of males:
  – Weight*
  – Height*
  – Mid-arm circumference*
  – Head circumference*
• Study limited by small number of those exposed in utero

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Developmental Effects – Postnatal Manifestation

Mishra et al. (2009a) – Immune system

- Exposed in utero during the first trimester of pregnancy, immune system function examined 24 years later
- Blood parameters increased in those exposed:
  - B lymphocytes*
  - interleukin (IL) 2 *
  - interferon gamma (IFN-γ) *
  - IL-4 *
  - IL-10 *
  - Immunoglobulin (Ig) A *
  - IgG *
  - IgM *
  - IgE *

* p<0.001

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Female Reproductive Effects

• Two studies: Menstrual dysfunction, gynecological complaints not related to pregnancy outcome
  – Shilotri et al., 1986
  – Dhara and Dhara, 2002 (Medico Friend Circle Study)

• Three review articles: Reproductive health problems in exposed women continue
  – Varma and Varma, 2005
  – Sharma, 2005
  – Mishra et al., 2009b

• Eight studies: Pregnancy outcome (described above)
Pregnancy Outcome – Five Years Following Gas Disaster

Rate of Spontaneous Abortion
(Data from ICMR, 2001)

- Severely affected
- Moderately affected
- Mildly affected
- Control

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Male Reproductive Effects

• Two studies evaluated possible toxic effects on male reproduction: Semen analysis
  – Daniel et al., 1987: 18 exposed & 10 control men
  – Deo et al., 1987: 19 exposed men (no controls)
• Neither study found significant differences in sperm counts or other parameters measured
• Study limitations:
  – Samples collected 3-6 months after exposure.
  – No definite period of abstinence prior to semen collection
  – Lack of adequate (Daniel et al.) or any (Deo et al.) control for potential confounders (e.g., smoking, alcohol consumption)
  – Small sample numbers for parameters with large variations
Summary of Human Data

• Human data come from the gas disaster in Bhopal

• Multiple studies show adverse impacts on pregnancy outcome
  – These effects persisted over years following the accident

• Postnatal developmental effects seen in those exposed *in utero*
  – Effects on growth, immune function

• Clinicians in field report gynecological problems continue

• No adequate study of male reproductive effects

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Both animal and human studies demonstrate an effect on survival of the exposed conceptus:

- Fetal loss / Spontaneous abortion
- Neonatal mortality

Postnatal growth effects:

- Animals – Bone shortening
- Humans – Shorter stature
Integrative Evaluation
- Female Reproductive Effects

• Fetal loss and neonatal mortality in animal and human studies
  – May indicate an effect on female reproduction
  – Continued elevated rates years after exposure in human studies may indicate an effect mediated by female reproductive toxicity

• Both animal and human studies found decreases in placental weight

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Integrative Evaluation
- Male Reproductive Effects

• Animal data show reversible reduction in mating performance and loss of spermatozoa
  – With no dominant lethal effects

• Human studies were conducted too late to detect a transient effect on spermatogenesis

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ANY QUESTIONS?