Air Pollution
Effects on Children’s Health

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with thanks to: Gary Ginsberg, Ph.D.
Connecticut Dept. of Public Health
Topics To Cover

• Child-Adult Differences
  – Exposure Rates
  – Damage to Developing Organs
  – Immature Defense Mechanisms

• Sensitive Life Stages
  – In utero
  – Post-natal
  – Puberty

• Carcinogens in Early Life

• Implications for Risk Assessment and Standard-Setting
Child-Adult Differences

Children’s Predictable Exposures

- More food, more water/body weight
- Inhale more air per body weight and per lung surface area
- Toxicokinetic factors

Less Predictable Exposures

- Soil ingestion rate
- Swimming/bathtub water ingestion rate
- Unusual behaviors
  - Pica, glue sniffing, accidental poisoning
What is Toxicokinetics?

Toxicokinetics is essentially the study of "how a substance gets into the body and what happens to it in the body."

Four processes are involved in toxicokinetics.
• Absorption
• Distribution
• Biotransformation
• Excretion
Child-Adult Differences

- Faster Metabolism
- High Energy Demand
- High Caloric Needs
- High Ventilation Rate

Growth → Play Activities

5
## Child-Adult Differences: Ventilation

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Age Range (years)</th>
<th>Males</th>
<th>Females</th>
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<tr>
<td></td>
<td></td>
<td>Mean m$^3$/day</td>
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<td><strong>Long-term Exposures</strong></td>
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<tr>
<td>(All)</td>
<td>birth to &lt;1 year</td>
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<td></td>
<td>1 to &lt;2 years</td>
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<td>2 to &lt;3 years</td>
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<td>3 to &lt;6 years</td>
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<td>6 to &lt;11 years</td>
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<td>11 to &lt;16 years</td>
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<td><strong>Short-term Exposures</strong></td>
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<td>2 to &lt;3 years</td>
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<td>Lung Region</td>
<td>3-Month Old</td>
<td>Adult</td>
<td>Child/Adult Ratio</td>
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<td>Extra-thoracic</td>
<td>0.32</td>
<td>0.125</td>
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<td>Tracheobronchial (Upper)</td>
<td>0.22</td>
<td>0.07</td>
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<td>Tracheobronchial (Lower)</td>
<td>0.0084</td>
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<td>0.88</td>
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<tr>
<td>Pulmonary</td>
<td>0.00034</td>
<td>0.000026</td>
<td>13.1</td>
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</table>
More Child-Adult Differences

There are many physiological differences between children and adults

- Important immaturities in clearance pathways in first year of life
  - Liver metabolism
  - Renal clearance
- Internal dose of parent chemical often higher in very young children but metabolite may be lower
Why Should We Be Concerned About Greater Exposure Rate in Early Life?

• Acute effects that are not a chronic concern:
  – Irritation, neurological impacts

• Chronic effects from long or short-term exposure:
  – Chronic toxicity (non-cancer) – 30 to 70 yrs
    – Minimal chronic period of 7 yrs
  – Cancer – relevant exposure period – 70 yrs

Do we need to worry about brief exposures that are high?
Windows of Vulnerability: *In Utero*

- **Organ system development**
  - Critical windows of even a few days
    - Thalidomide – limb malformation
    - Fetal Alcohol Syndrome (FAS)

- **Brain development**
  - Irreversible neurotoxicity
    - Pesticides – affect nerve impulse transmission
    - Mercury – attacks neurons; don’t organize properly
    - Lead – prenatal period is the most sensitive
    - PCBs, perchlorate, PBDEs – affect thyroid function
Windows of Vulnerability: *In Utero*

- *In utero* Development
  - Hormone/endocrine imprinting in early life
    - DES (diethylstilbestrol): female reproductive tract abnormalities and cancer can result from in utero exposure
  - New evidence emerging
In Utero Vulnerability: Air Pollutants

• Los Angeles Studies
  – Higher CO and PM: 10-25% more pre-term births
    • 2500 births; Ritz, et al., 2007
  – Higher CO and ozone: 2-3x↑ heart defects
    • Effect most in 2nd month of pregnancy
    • 9000 babies; Ritz, et al., 2003
Post-Natal Vulnerability

- Modified organ function, maybe modified structure
- Lung – growth in surface area and branching during first 8-12 yrs
- Critical brain development
  - Lead example: impaired learning, reduced IQ
- Immune system development
  - Critical recognition of self vs. non-self
- Endocrine systems
  - Disruption of hormone levels
  - Early puberty?
Lead Inhibits the Propensity of Neural Stem Cells to Turn into Neurons

From Joel Schwartz April 2008
Figure 6-2.5 Restricted cubic splines and log-linear model for concurrent blood lead concentration. The dotted lines are the 95% confidence intervals for the restricted cubic splines.

Source: Lanphear et al. (2005).
Post-Natal Effects of Ozone on Respiratory Tract

• Monkey model – Plopper, et al. 2007
  – Newborn monkey model for asthma
  – Combined exposure to HDMA and ozone
    • Intermittent ozone exposure: 0.5 ppm, 8 hr/day
    • 5 days on, 9 days off for first 6 months of life
    • 6 months to evaluate recovery
  – Structure and function of the airways changed

HDMA = House Dust Mite Allergen
Difference in size of a bronchial of an infant monkey after various exposures

FA = Filtered Air
HDMA = House Dust
Mite Allergen
O₃ = Ozone
Carcinogen Susceptibility

• Good mechanistic grounds for heightened neonatal sensitivity to mutagens
  – Cell division rates are higher
  – Longer timeframe for tumor to be expressed

![Figure 1.B](image)

Change in Liver Weight (g) with Age
(Derived from equations in Haddad, et al., 1999)
Cancer Vulnerability in Early Life

- Animal cancer bioassays begin at 6 weeks of age
  - Miss juvenile and *in utero* periods
- Isolated studies in 1960s thru 1990s in juvenile animals showed:
  - Surprisingly high potency per exposure period
  - Haber Law not true
    - \( \text{(Dose x Time} \neq \text{constant toxicity)} \)
  - Cannot pro-rate exposure over lifetime
Chemicals Which Show Early Life Cancer Vulnerability

- Mutagens
  - Nitrosoamines
  - BaP
  - Benzidine
  - Vinyl chloride
- Non-mutagens
  - DDT, dieldrin, tamoxifen
## MLEs of Cancer by Sex and Age Compared to Adult Rates at Similar Dosage

<table>
<thead>
<tr>
<th>Sex and age group</th>
<th>Maximum likelihood estimate</th>
<th>95% LCL</th>
<th>95% UCL</th>
<th>Arithmetic mean</th>
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<tbody>
<tr>
<td>Male animals</td>
<td></td>
<td></td>
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<tr>
<td>Fetal period</td>
<td>25</td>
<td>15.6</td>
<td>42</td>
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<tr>
<td>Birth–weaning</td>
<td>57</td>
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<td>90</td>
<td>59</td>
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<td>Weaning–60-days</td>
<td>5.0</td>
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<tr>
<td>Female animals</td>
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<td></td>
</tr>
<tr>
<td>Fetal period</td>
<td>1.77</td>
<td>1.05</td>
<td>2.9</td>
<td>1.83</td>
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<tr>
<td>Birth–weaning</td>
<td>4.4</td>
<td>3.3</td>
<td>6.0</td>
<td>4.5</td>
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<tr>
<td>Weaning–60-days</td>
<td>0.82</td>
<td>0.50</td>
<td>1.29</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Data are maximum likelihood estimates and confidence limits of cancer inductions per dose/(body weight$^{0.75}$-day) relative to comparably dosed adults (nine compounds, 153 tumor incidence observations).

**MLE** = Maximum Likelihood Estimate

Hattis, et al., EHP 113: 509-516, 2005
Implications for Risk Assessment & Standard Setting
Framework for Early Life Cancer Risk Assessment

Implementation Option 1: Pro-Rating

10x higher potency * early life dose * 2/70 yrs
+ 3x higher potency * older child dose * 13/70 yrs
+ 1x potency * adult dose * 55/70 yrs

Total Lifetime Cancer Risk
Implementation Option 2: Additive

1x Potency * Early Life (0-2) Dose

+  

1x Potency * Adult Dose

Total Lifetime Cancer Risk

Each window of vulnerability receives adult slope factor without pro-rating. For example: Vinyl Chloride in Drinking Water

• Risk for continuous lifetime exposure in adulthood is 2.1E-05/ug/L
• Risk for continuous lifetime exposure from birth is 4.2E-05/ug/L
Outstanding Issues with Cancer Vulnerability

• **Mutagens vs. non-mutagens**
  – Only address mutagens quantitatively?
    • Non-mutagens on a case-by-case basis
  – Apply default to non-mutagen potency based upon limited data currently available?
  – Treat mutagens and non-mutagens alike?
  – Any carcinogen with low dose linear potency basis – assume mutagen-like vulnerability in early life?

• **Need to apply exposure and kinetics factors for vulnerability windows to the risk estimate**
Inhalation Risk Equation Adjustments for Early Life: Dose Approach

Modifying the adult risk equation for a MUTAGENIC toxic air contaminant

• 0-2 year-old critical period
  – Inhalation rate/body wt = 1.25 m³/kg/day

• Adult Exposure for 30 years
  – Inhalation rate/body wt = 0.286 m³/kg/day
  – Pro-rate for 30/70 yrs = 0.123 m³/kg/day

• Child/Adult Dose Adjustment Factor
  – 1.25/0.123 = 10.2
  – Lifetime cancer risk = (10.2*CSF)+(1*CSF) = 11.2*CSF

CSF = Cancer Slope Factor
Risk Equation Adjustments (continued)

- **Non-Mutagens**
  Adjustment factor = 2.3
  \[(CSF\times 10.2/8) + (CSF\times1)\]

- **Non-Carcinogens**
  Minimum chronic period = 7 yrs
  - Inhalation rate for 0-7 yrs = 1.1 m³/kg/day
  - Adult = 0.286 m³/kg/day (not prorated)
  Adjustment Factor = 1.1/0.286 = 3.8
Summary

• Children represent critical stages of chemical vulnerability due to:
  – Greater dose rate
  – Toxicokinetics
  – Vulnerability for some endpoints

• Initial steps now possible for incorporating children’s exposures and vulnerabilities into risk assessment