Children Matter: Using a Lifecourse Approach to Understanding Safety Assessment Needs for Children

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Conflict of Interest

Dr. Faustman has no conflicts of interest
Children Are Not Just Tiny Adults

Faustman, 2016
Outline

● Introducing Concepts of Life Course Analysis
  A. Use of Risk Assessment Frameworks Across Life Stage
  B. Building upon Social Ecological Models of Development
     - How do we organize our data across lifestage?
     - How do we analyze our data across lifestage?
     - Example from our EPA-NIEHS funded Children’s Health Centers
        ▪ Importance of Community Based Participatory Research (CBPR)
        ▪ Need for Temporal Assessment and Evaluation to identify exposures and response and identifying effectiveness of interventions.

● Next steps for Life Course Models
Overall Framework for Assessing the Effects of a Toxicant on Development

Risk Assessment

Exposure Assessment
- Exposure
  - Inhalation
  - Oral
  - Dermal

Toxicokinetics
- Absorption
- Distribution
- Metabolism
- Elimination

Toxicodynamics
- Adolescent
- Child
- Newborn
- Conceptus
- Organ, Tissues
- Cellular
- Organelle
- Molecular

Risk Characterization

Outcome
- Normal Parameters
- Developmental Disorder
  - Lethality
  - Growth Retardation
  - Malformation
  - Altered Function

Faustman, 2016
Child Specific Behaviors Can Result in Child Specific Exposures
Children’s Activities That Impact Exposures As a Function of Developmental Age (from USEPA, 2003b)

Age Related Consumption of Foods and Beverages As a Ratio of Intake to Body Weight

Lawrie 1998
DMTP in Urine: National Survey Children Higher Than Adults

Faustman, 2016
Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (Final)

Notice:
EPA announced the release of the final document in the February 5, 2006 Federal Register Notice.

A major issue facing the Agency is how to consistently consider age-related changes in behavior and physiology when assessing childhood exposure and potential dose to environmental contaminants. Key to this issue is how to capture those changes in an assessment of risks from exposure to environmental contaminants.

Contact: Risk Assessment Forum Staff, 202-564-6483, or riskforum@epa.gov

Background
This final document, Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (Final), is intended to provide guidance to EPA scientists on selecting age groups to consider when assessing childhood exposure and potential dose to environmental contaminants. A consistent set of childhood age groups, supported by an underlying scientific rationale, will improve agency exposure and risk assessments for children and will assist the Agency in implementing various regulatory initiatives. In addition, these age groups will guide future analyses of exposure factors data as well as new research and data collection efforts.

History/Chronology
- Jul 2000 Risk Assessment Forum sponsored workshop identified the needs for this guidance.
- Dec 2003 Guidance document is submitted for public comment.
- May 2004 External Peer Review of this Guidance document (see related link).
- June 2006 EPA released the final report.

Next Steps
This is the Final Document.
Combined Approaches for NCS Exposure Assessment

- Questionnaire/Diary/Observation
- “True” Exposure (or Dose)
- Environmental Measurements
- Biological Measurements

Scale: Community Household Individual

Life Stage: NCS, 2010
Need to Consider Both Exposure and Toxicological Differences across Life Stage
Overall Framework for Assessing the Effects of a Toxicant on Development

Risk Assessment

- Exposure Assessment
- Toxicity Assessment
- Risk Characterization

Exposure
- Inhalation
- Oral
- Dermal

Toxicokinetics
- Absorption
- Distribution
- Metabolism
- Elimination

Toxicodynamics
- Adolescent
- Child
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Cell Signaling
- Cellular
- Organelle
- Molecular

Outcome
- Normal Parameters
- Developmental Disorder
  - Lethality
  - Growth Retardation
  - Malformation
  - Altered Function

Faustman, 2016
Initial Appearance of Organs during Gestation in Humans Can Define Windows of Sensitivity

Fig. 78. Schematic illustration of the sensitive or critical periods in human development with regard to teratogens. Black denotes highly sensitive periods. From Moore, K. L., "The Developing Human." Saunders, Philadelphia, 1973.
Key Processes of Neurodevelopment

Faustman, 2016
Sensitive Life-Stage and Region Specific Neurodevelopmental Processes

Faustman et al 2006
Nervous System Development in Humans and Rodents

Evolution of cytochrome P450 isoforms in the human liver.

Cresteil 1998
Metabolic Scheme for CP

Chlorpyrifos Oxon (CP-oxon) → PON-1 and B-esterases → Diethylphosphate (DEP) → CYP 2B6, IA2 and CYP3A4 (at high conc.) → Chlorpyrifos (CP) → CYP 2C19 and CYP3A4 (at low conc.) → Diethylthiophosphate (DETP) → 3,5,6-trichloro-2-pyridinol (TCP) → Sulfate or glucuronide conjugates

Faustman et al. (2006)
PON1 Levels Are Low in Children

- PON1 levels plateau at 6 to more than 24 months of age
- May not reach adult levels until 5-7 yr
  (Karen Huen, Nina Holland—UC Berkeley)

Developmental onset of PON1 activity in individual children

Risk Assessment Framework Across Life Stage

- Pre-natal
- Post-natal
- Infant
- Adolescent

RISK ASSESSMENT

- Toxicokinetics
- Toxicodynamics
- Cell Signaling
- Outcome
- Population

Incorporating Population Level Sustainability Factors, Polymorphism and Variability Data

Normal Parameters
- Developmental Disorder
- Lethality
- Growth Retardation
- Malformation
- Altered Function

Faustman, 2016
Spectrum of Reproductive Toxicity Evaluations

Adapted from Kimmel et al, 2000
Ability of Experimental Systems to Assess and Predict Neurodevelopmental Toxicity across Multiple Levels of Biological COMPLEXITY

Faustman, 2016
Extending our Life Stage Framework

Faustman, 2016

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
Life Course Considerations for Epigenetics

Multiple Sources: K. Sabon et al, 2014; D. Foley et al, 2009
Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals
**Risk Assessment Approaches**

**NOAEL Approach**

\[
\text{NOAEL} = \text{“Safe Dose” (RFD)}
\]

\[
\text{Uncertainty Factors} = \text{“Safe Dose” (RFD)}
\]

**Benchmark Dose Approach**

\[
\frac{\text{BMD}_x}{\text{Uncertainty Factors}} = \text{“Safe Dose” (RFD)}
\]

\[
X = \text{Response Level}
\]
Two Approaches Frequently Used for Identifying Critical Effects

NOAEL-No Observed Adverse Effect Level
● Exposure level at which there are no statistically or biologically significant increases in observed adverse effects between exposed population and control population.

BMD-Benchmark Dose
● Modeling of the dose response for adverse endpoints and identification of effect levels. For example identification of the dose that results in a 10% change and the 95% confidence limit on that dose
Guidelines for Uncertainty (Safety) Factors

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average  →  Sensitive human</td>
<td>10x</td>
</tr>
<tr>
<td>Animal  →  Human</td>
<td>10x</td>
</tr>
<tr>
<td>LOAEL  →  NOAEL</td>
<td>10x</td>
</tr>
<tr>
<td>Data base inadequacies</td>
<td>10x</td>
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</tbody>
</table>
Additional Factors to Consider

- Food Quality Protection Act (FQPA)
- Child Specific Uncertainty Factor
- Age Adjustment Factors
Framework to Describe Assessment of the Effects of a Toxicant on Development

Faustman, 2016
### Adverse Effects of Developmental Stage-Specific Exposures on Various Organ Systems

<table>
<thead>
<tr>
<th>Age Span</th>
<th>Preconception</th>
<th>Preimplantation</th>
<th>Embryonic Age</th>
<th>Fetus</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td>Agent: Folic Acid</td>
<td>Agent: Folic Acid</td>
<td>Agent: Retinoic acid, valproic acid, arsenic</td>
<td>Agent: Lead</td>
<td>Agent: Pesticides</td>
<td>Agent: High-dose ionizing radiation</td>
<td>Agent: Ethanol</td>
<td></td>
</tr>
<tr>
<td>Outcome: ▼ rate of NTDs</td>
<td>Outcome: ▼ rate of NTDs</td>
<td>Outcome: ▲ NTDs</td>
<td></td>
<td>Outcome: ▼ Intelligence, ▲ behavioral problems</td>
<td>Outcome: Parkinson-like decline in dopaminergic neurons in adulthood</td>
<td>Outcome: Brain tumors and meningiomas</td>
<td>Outcome: Delayed puberty</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td>Agent: Dioxin (TCDD)</td>
<td>Agent: Phthalates</td>
<td>Agent: Dioxin</td>
<td>Agent: Dioxin</td>
<td>Agent: Dioxin</td>
<td></td>
<td>Agent: Ethanol</td>
<td></td>
</tr>
<tr>
<td>Outcome: ▼ Fertility in female rats</td>
<td>Outcome: ▼ AGD, malformations</td>
<td>Outcome: ▼ Hydrenephrosis in rats</td>
<td>Outcome: ▼ Hydrenephrosis in rats</td>
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<td>Outcome: Delayed puberty</td>
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</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Agent: Maternal smoking</td>
<td>Agent: Maternal exposure to angiotensin inhibitors</td>
<td>Agent: Dioxin</td>
<td>Agent: Dioxin</td>
<td></td>
<td></td>
<td>Agent: Ethanol</td>
<td></td>
</tr>
<tr>
<td>Outcome: ▼ Birth weight, ▲ Diabetes, osteoporosis</td>
<td>Outcome: ▼ T3/T4 levels in infant and juvenile rats</td>
<td></td>
<td></td>
<td>Outcome: ▼ Hydrenephrosis in rats</td>
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</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Agent: Methylmercury</td>
<td>Agent: Maternal smoking</td>
<td>Agent: Methoxychlor, heptachlor</td>
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<td></td>
<td></td>
<td>Agent: Ethanol</td>
<td></td>
</tr>
<tr>
<td>Outcome: ▼ Heart rate variability in children</td>
<td>Outcome: ▼ Th1 immune capability, ▲ Th2 response in rats</td>
<td>Outcome: ▼ Cell-mediated immunity in male rats</td>
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<td></td>
<td>Outcome: Delayed puberty</td>
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<tr>
<td><strong>Cardiac</strong></td>
<td>Agent: Methylmercury</td>
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<tr>
<td><strong>Immune</strong></td>
<td>Agent: Maternal smoking</td>
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<td>Agent: Air particulates</td>
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<td>Outcome: ▼ Collagen deposition in airway walls, ▼ Postnatal hypoxic response</td>
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<td>Outcome: ▼ Respiratory mortality</td>
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<tr>
<td><strong>Respiratory</strong></td>
<td>Agent: X-rays, urethan</td>
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<td>Agent: Inorganic arsenic</td>
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<tr>
<td>Outcome: Cancer in offspring of male mice</td>
<td></td>
<td>Outcome: Adrenal tumors in male offspring, ovarian and lung tumors in female offspring</td>
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</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>Agent: Inorganic arsenic</td>
<td></td>
<td>Agent: Ionizing radiation</td>
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<tr>
<td>Outcome: Adrenal tumors in male offspring, ovarian and lung tumors in female offspring</td>
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<td>Outcome: Leukaemia</td>
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</tbody>
</table>
# Integrated child-life stages for NICHD Pediatric Terminology as mapped to existing medical terminologies

<table>
<thead>
<tr>
<th>Age Span</th>
<th>In Utero</th>
<th>Preterm</th>
<th>0-1 month</th>
<th>1-12 months</th>
<th>1-2 years</th>
<th>2-5 years</th>
<th>5-11 yrs</th>
<th>12-21 yrs</th>
</tr>
</thead>
</table>

### SNOMED
- **Infants**
  - Newborn
  - Infant child
- **Child**
  - Pre-school
  - Preteen

### CDC
- **Infants** (0-1 yrs)
- **Toddlers** (1-2 yrs)
- **Toddlers** (2-3 yrs)
- **PreSchooler** (3-5 yrs)
- **Middle childhood** (6-8 yrs)
- **Middle childhood** (9-11 yrs)
- **Early Adolescence** (12 to 14 yrs)

### AAP
- **Infancy: Prenatal - 1 year**
- **Early Childhood: 1 year - 4 years**
- **Childhood: 5 - 10 years**
- **Adolescence: 11 – 21 years**

### CDISC
- **In Utero**
  - Preterm newborn infants
  - Term newborn infants 0-27 days
- **Infant And Toddler** (28 Days - 23 Months)
- **Children (2-11 yrs)**
- **Adolescents (12 to 18-19 yrs)**

### ICH-E11
- **Fetal Stage**
  - Preterm Neonatal Stage
  - Term Neonatal Stage
- **Infancy Stage** (28 days - 12 months)
- **Toddler Stage** (13 months - 2 yrs)
- **Early Childhood** (2-5 yrs)
- **Middle childhood** (6-11 yrs)
- **Early Adolescence** (12 to 18 yrs)
- **Late Adolescence** (19-21 yrs)

### EPA
- **6 <1 month**
- **2 <2 months**
- **6 <6 months**
- **6 <6 months**
- **0 <12 months**
- **2 <3 years**
- **3 <8 years**
- **0 <11 years**
- **11 <10 years**
- **10 <21 years**

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**Hirschfeld NCS, 2010**
Multiple, Interacting Influences Affect Children’s Health including Chemical and Non-Chemical Stressors

IOM, 2004
A New Life Course Based Model of Children’s Health and Its Influences

Source: Children’s Health, Nation’s Health, IOM report, 2004

FIGURE 2-2 A new model of children’s health and its influences.
• Importance of early exposures
• Complexity of factors affecting development
• Complexity of Environmental Exposures
• Need to consider these across multiple stages of development and at difference levels of assessment
• Need for framework for evaluating risks
• Need for Life Course Frameworks for incorporating both chemical and non-chemical stressors
Acknowledgements

- The NIEHS, EPA funded Center for Children’s Environmental Health Risks Research (RD-83170901, 5P01ES-09601)
- National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN267200700023C
- US Environmental Protection Agency Biomarkers grant (RD-83273301) and contract (2W-2296-NATA)
- EPA funded Predictive Toxicology Center (USEPA STAR grant RD-83573801)


