What is “Developmental” About “Developmental Neurotoxicology”

David C. Bellinger
Boston Children’s Hospital
Harvard Medical School
Harvard School of Public Health
Boston, MA, USA
## What We (Think We) Know About Children and Chemicals

### Neurodevelopmental Effects

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Little or None</th>
<th>Some</th>
<th>Considerable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little or None</td>
<td>waste sites</td>
<td>manganese</td>
<td></td>
</tr>
<tr>
<td></td>
<td>incinerators</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>solvents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some</td>
<td>cadmium</td>
<td>OPs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dioxins</td>
<td>arsenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phthalates</td>
<td>PBDEs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bisphenol A</td>
<td>inorganic Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFAAs</td>
<td>PAHs</td>
<td></td>
</tr>
<tr>
<td>Considerable</td>
<td>Elemental Hg</td>
<td>fluoride</td>
<td>lead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MeHg PCBs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Little or None: Waste sites, incinerators, solvents, manganese
- Some: Cadmium, dioxins, phthalates, bisphenol A, PFAAs, OPs, arsenic, PBDEs, inorganic Hg, PAHs
- Considerable: Elemental Hg, fluoride, lead, MeHg, PCBs
Elements of a Developmental Perspective

1. Early stages of development shape and constrain the way in which subsequent development unfolds (developmental cascades)

2. Elements of a child’s developmental system influence the form and severity of adverse effects of neurotoxicant exposure (effect modifiers)

3. Early-life neurotoxicant exposure becomes an element of the context within which a child’s subsequent development occurs (neurotoxicant exposure as an effect modifier itself in later life)
1. Early stages of development shape and constrain the way in which subsequent development unfolds: “developmental cascades”

- Childhood Lead exposure
  - IQ
  - Executive function
  - Impulse control
  - Ability delay
  - Gratification

- Criminal activity

- School achievement
- ADHD, Conduct Disorder, substance abuse, injury
2. Form and severity of adverse effects of neurotoxicants influenced by other elements of the developmental system

- Co-exposures to other neurotoxicants (i.e., mixtures)
- Prenatal stress
- Nutrition
- Extent to which child-rearing environment fosters optimal development
  - effects of lead more pronounced on disadvantaged children
  - animal data suggest possible remediation strategies
3. Early-life neurotoxicant exposure reduces resilience to meet later neurological challenges

• reduces CNS “reserve capacity” available in adulthood
  • recovery from a photothrombotic stroke in hind limb parietal sensorimotor cortex slower in rats with early lead exposure (beam walking and proprioceptive limb placing)

• produces epigenetic changes eventually expressed as altered gene expression in adulthood
  • rats exposed to lead only as newborns show delayed overexpression, as adults, of the gene encoding the β-amyloid precursor protein

• accelerating neurodegenerative processes associated with aging
Conclusions

• Early-life exposure to neurotoxicants can affect myriad aspects of a child’s neurodevelopment;
  – adversities evident in childhood are only earliest stage of their unfolding; need to consider downstream effects
  – a lifespan approach necessary to appreciate full range of morbidities and burden associated with them; delayed neurotoxicity
• Exposure-related adversities responsive to context in which development occurs
  – suggests that viewing the adversities as “permanent” unduly pessimistic, ignoring possibilities of remediation by environmental manipulation
• Early-life exposure is, itself, a risk modifier, forming part of the context that determines the impacts of later physiologic and pathologic CNS events;
  – a child exposed early to a neurotoxicant likely to respond differently to a later insult than a child not similarly exposed