Children’s Health Issues and Green Chemistry

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Currently Very Large Data Gaps In:

- Toxicity by lifestage at exposure
  - pharmacodynamic and pharmacokinetic aspects
- Exposure across lifestages

Regulatory agencies most often working with inadequate data on risk from early life exposures

“Green Chemistry” must address how we can fill these very large gaps in knowledge
Typical Chronic Rodent Bioassays: Dosing Periods and Critical Windows

- **In Utero**
- Postnatal & Juvenile
- Standard chronic dosing regimen

- conception
- birth
- 6-8 wks
- 2 years
- 3 years

OEHHA, 2009
CYP450 in Human Liver Differs by Lifestage

Cresteil T *Food Additives and Contaminants* 1998; 15 Sup. 45-51
Peripuberty:
A time of cellular growth and differentiation in reproductive organs and mammary gland

Window of Susceptibility
Nervous System Development is Determined by Multiple Processes.

Rice and Barone, 2000
Nervous system tumors in male and female rats treated with a single dose of N-ethylnitrosourea at different ages during gestation or after birth (birth ~ GD23)

No. tumors/offspring

Fitted values

Birth

days since conception

(data from Donovan, 1999 and Naito et al., 1981 (normalized))
Green Chemistry - Prioritize Chemicals with Children in Mind

- Prioritizing chemicals in commerce
  - Consider toxicities where early-life exposure important.
    - E.g., Developmental, Neuro-, Endocrine, Immuno-, etc
  - Consider children’s exposures – higher intake rates
- Utilize available databases (U.S.EPA, Cal/EPA, Canada, REACH, Literature survey)
- Improve existing and develop new QSAR models for specific endpoints of concern for children
Improve Knowledge of Children’s Exposures

- Which chemicals go into what products?
- Predictive models for exposure potential (persistence, bioaccumulation, absorption, etc)
- Expand biomonitoring of cord blood, breast milk
- Exposure simulation models for chemicals in household/personal care products
  - Modify existing screening tools to address children’s pathways of exposure including breast milk, hand-to-mouth transfer, etc.
Need kid-focused toxicological screening tools

Predictive tools that focus on early lifestages

- Toxicological screening assays that include developmental toxicity pathways
  - Efforts to develop rapid high-throughput assays that adequately consider early lifestages
  - Genomics, proteomics to evaluate developmental pathways
  - In silico models
    - EPA’s Virtual Embryo under development
    - Birth Defects Systems Manager website (http://systems analysis.louisville.edu) microarray database of teratogens

- Green Chemistry program needs to use results from newer testing paradigms.
“Scientific Frontiers in Developmental Toxicology and Risk Assessment” (NRC, 2000).

- Many basic signaling pathways used in development across wide-range of species (fruit fly, roundworm, zebrafish, frog, chick, mouse, human), e.g.,
  - Hedgehog signaling pathway
  - Apoptosis pathway
  - Integrin pathway
  - Cadherin pathway

If chemical interferes with basic developmental signaling pathway, prudent to view as a red flag for potential developmental toxicity.

Need to bring knowledge of signaling pathways to bear in green chemistry decisions.
Challenges Abound – e.g., Developmental Neurotoxicology

- *How do you mimic the processes in vivo that must be orchestrated temporally and spatially for normal brain development?*
  - Raises serious challenges for evaluating tens of thousands of chemicals in commerce
  - Recent journal issue devoted to high throughput and complementary model screens for neurotoxicology
    - *Neurotoxicology and Teratology 32(1), 2010*
  - Describes available models/screens and strengths and weaknesses