Pre-natal and early life exposures, health significance in childhood (and later), and current reflections in policy

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Outline

I. Prenatal exposures and evidence of their significance
II. Related to discussion of "early life exposures"
III. What do we look for?
IV. Policy considerations

I. Prenatal exposures and their significance

- Environmental tobacco smoke provides a model
  - Presentation by Mark Anderson on this panel
- Agents
- Outcomes

Environmental tobacco smoke

- Well established relationships between ETS exposure during pre natal period and childhood diseases
- ETS: respiratory disease and asthma linked to pre-natal (maternal) and early childhood exposure
- Suggested significance of early exposure

(e. g. DiFranza 2004)

PCBs

- Epidemiology studies reported alterations in cognitive development and attention and motor deficits after pre-natal exposure
  - Stronger relationship than for post-natal
- Recent study: effect on thyroid hormone and premature differentiation of one type of brain cell
  - Mechanism for effects on brain development

PCB

- Studies of women exposed and their children show effects associated with pre-natal exposure (not post-natal or breast feeding) (e.g. Jacobson 2002)
- Later effects may be relevant as well
- Recent findings report sensitivity to organochlorine exposure and effects on semen quality in young men after puberty (Guo et al 2004)

PCBs

- Impact on brain cell differentiation varied by PCB congener
  - Not captured by the "toxicity equivalency factors" used to compare PCBs (Fritsche 2005)
- Previous study reported effects on thyroid hormone signaling
- Effects may be detected in childhood but deficits may extend throughout life

Methyl mercury

- Methyl mercury is a neurotoxicant
- Main exposure source is fish
  - transformed to "methyl" form in the environment and bioaccumulate in food chain
- Higher concentrations in fetal blood than mothers due to higher affinity to hemoglobin (Sakamoto 2004)

Perchlorate

- Drinking water contaminant from rocket fuel – estimated 11 million drink water with more than 4 ppb
- Interferes with uptake of iodide and thyroid hormones – concern for pregnant females
- Can lead to impacts on brain development of children
- Recent results show much greater concentrations in breast milk than would have been predicted – other exposure sources?

Perchlorate

- Keen debate over acceptable concentration
  - Levels from ~ 1 to 100 ppb suggested
  - Will determine cleanup cost
- Key issues:
  - Looking at "upstream" critical effect (i. e. interference with uptake of iodide) rather than illness
    - National Academy of Sciences and California EPA)
  - Representativeness (and ethics) of small human study used as basis for decision

Childhood leukemias

- Childhood leukemias most common cancer for children to age 15
- Several forms of leukemia
  - ALL (acute lymphocytic leukemia) is most common
  - AML (acute myeloid leukemia)
- Causes not known for 90%
- Increasing evidence that associated genetic changes arise before birth or in early neonatal (perinatal) period

Genetic evidence

- Particular patterns of changes or rearrangements in genes have been found to be typical of these cancers
- Recent results: these changes can already be seen in blood collected from newborns immediately after birth ("blood spots")
- This means that the changes occurred before birth

(Smith 2005) (McHale 2003)

Implications

- Other evidence suggests that both chemical and infectious agents may contribute to these changes
- Reflect both a change and a failure to repair change
- Latency for cancer can be ten years
- Maternal exposures and perinatal exposures likely to be important

Pesticides

- Evidence of effects of pre-conception exposure
  - In home use for insecticides; application by commercial applicator -> increased risk (Ma 2002)
- Recent study shows that effects in adults are based on cumulative exposure not high concentrations – could be of interest for children as well

Pesticides

- Results suggest that exposures to pesticides before birth or in the first year after birth, but not later, are associated with AML and ALL
- May be a particular fetal susceptibility

Pesticides

- Several studies show greater likelihood of childhood brain tumors with greater in home pesticide use including during pre natal period

Pesticides and fetal growth

- Home use pesticides (Columbia)
  - Chlorpyrifos and diazinon
  - Found in virtually all air samples in NYC
  - Found in most pregnant women; fetal blood had comparable levels
  - More exposure → reduced birth weight and growth
  - Before regulatory action was taken to reduce these in 1991
- No relationship in later births

(Whyatt 2005, 2004)

Children often more sensitive

- Research in several areas seeing that children are often more sensitive than adults
- Common mechanisms for this:
  - Interference with signaling
  - Development presents opportunity for defects (higher activity)
  - Defenses not available

May be no true "threshold"

- Current regulatory practice and toxicology assume there is a threshold for effects other than cancer
  - Threshold is a level at which no effects will occur
  - Allows setting a "safe" dose
- Increasing evidence this may not be the case, especially for a population
  - Lead results, methyl mercury, benzene
  - Suggests possible role for more precautionary approach

View of life stages

- Pre-natal phase is one key life stage
- Other phases also have other particular sensitivities
- Recent analyses suggest need to look at the vulnerabilities and susceptibilities at several life stages

Emerging themes

- Children are more sensitive
  - More opportunity due to growth/development
  - Importance of signaling, which can be disrupted
  - Lack of defenses
- Think of pre-natal and post-natal/early childhood together
- Consider factors relevant at different life stages and implications into adulthood
  - It is not only childhood illnesses that are relevant
- We have done almost nothing to address any of this

II. Early life exposure

- Term used to refer to pre-natal, perinatal, childhood exposures
  - Can be considered in terms of affecting a sensitive time period
- Consideration of "imprinting" or creation of functional changes that lead to disease later but do not create defects now
  - Includes disease in adulthood or even older age

Barker hypothesis

- People who "grew" differently from others more likely to get heart disease
  - Association of disease with low birth weight
  - Later: low birth weight followed by "compensatory" or "catch-up" weight gain
  - Thought to create unfavorable metabolic functioning that contributes to diabetes, heart disease, high blood pressure
  - Related to metabolism changes (Barker 2004)
- Now widely accepted (?)
- Recent report that results could be due to kidney effects (Moritz et al 2003)

Theory expanded to chemicals

- Chemicals can also cause low birth weight, impact fetal development
- This reason may also lead to the same kinds of adverse outcomes
- Research focus is very recent
- Causal mechanisms may be different
  - embryonic and fetal programming of physiological disorders in adulthood

(Lau and Rogers 2005)

NIEHS symposium

- Environmental agents cause functional deficits that do not become apparent until later in life
  - DES: altered gene expression in the uterus that is irreversible without any gross alterations in morphology
  - Possible role for in utero exposure to environmental estrogens in etiology of obesity
- Alterations in gene expression and imprinting due to in utero exposure to environmental agents →
  - alterations in developmental programming expressed as a permanently altered gland, organ or system potential
  - Animal is sensitized to be more susceptible to disease later in life

Reproductive toxicology

- Expanding beyond structural abnormalities
- Newer understanding includes "functional" teratology – extension beyond morphological examinations to include functional integrity of organ system.

Developmental plasticity

- Embodies idea that genetically based program can be modified in response to changing environmental conditions to shape the unique characteristics of each individual
- Development controlled by neural and hormonal signals
  - May allow individual to alter development in adaptive matter
  - Or may reflect limitations of development to buffer itself form environmental challenges

(Horton 2005)

Types of Results

- Occurrence of disease that would not otherwise have occurred in an individual
- Increased risk of a disease (higher prevalence) in a population
- Earlier onset or greater severity of a disease that would have occurred otherwise

(Heindel 2005)

Endocrine disruption as possible mechanism

- Disruption of development during a critical window
- To be discussed later
  - Presentation by Ted Schettler on this panel

Pesticide mixtures

- Parkinsons may result from insults during development
- Combined paraquat and maneb (mice)
  - loss of neurons
  - greater sensitivity to pesticides administered later
- Theory that agents with different modes of actions would reduce defense mechanism and increase vulnerability
- Greater damage → earlier or more severe disease

(Cory-Slechta et al 2005)

Cancer

EPA analysis shows higher cancer risk when exposure to chemical agents is earlier in life

- Reflected in children's supplement to the cancer risk assessment guidelines (proposed)

- Suggestion that fetal and perinatal hormonal factors that increase pool of stem cells could contribute - >
  - more potential for errant growth (Baik et al 2005)

Implications

- Early exposures have important effects that are often worse than later exposures
  - Children's illnesses but also adult illnesses
  - Loss of potential, increased risk or severity
- Existing tools and approaches do not capture this
- Need to think more carefully about how to assess children's environments and reduce exposures

III. What do we look for?

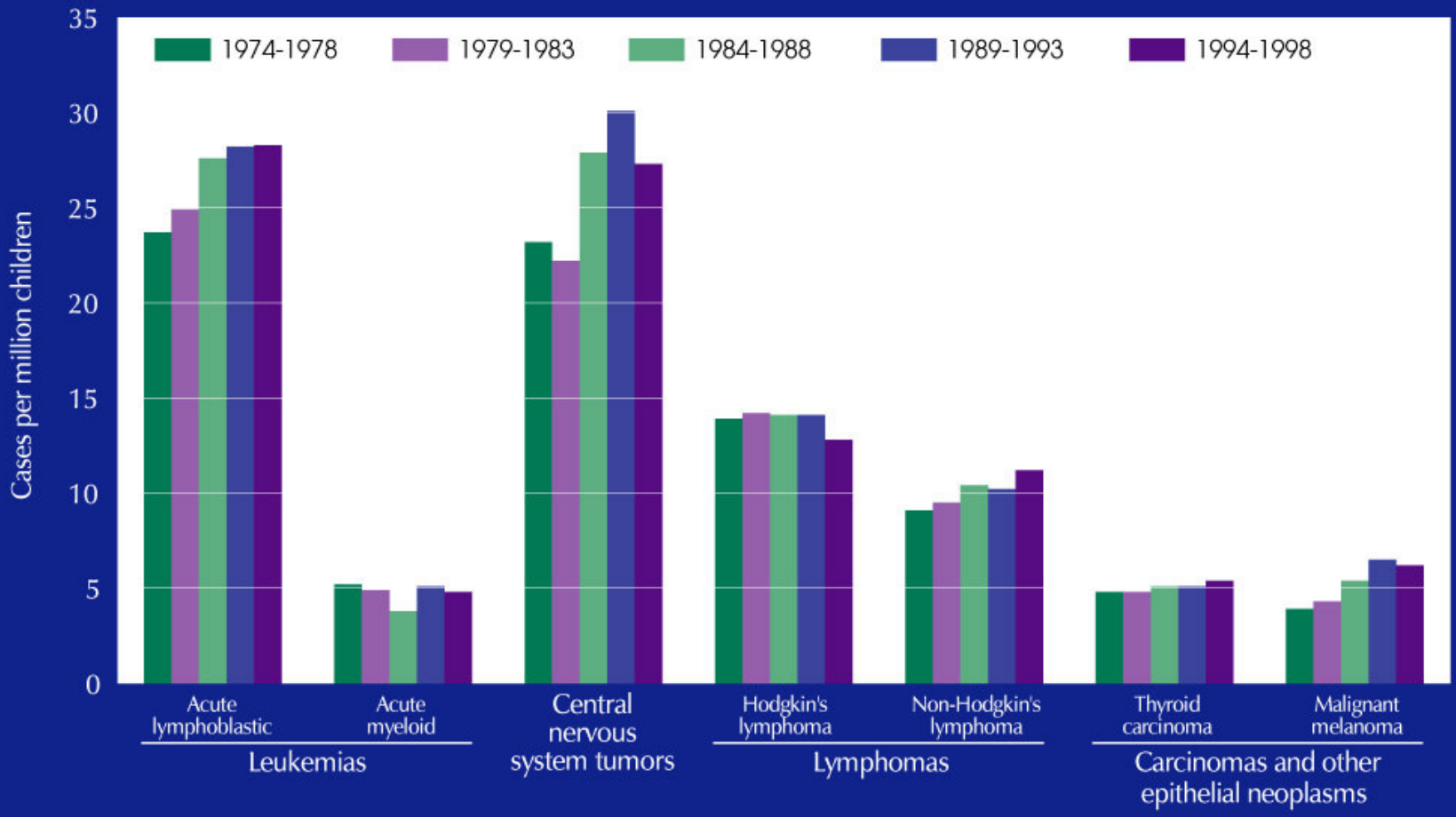
- We need to think about these issues more systematically
- Beyond individual studies to better understanding the processes likely to be affected
- Then what?
  - More detailed risk assessment OR
  - Precautionary approaches

What we have now (data)

- Example from America's Children and the Environment 2003
- Representation of key topics for environment and health for children
  - Project to identify and represent children's environmental health
  - These measures are about childhood cancer and hazardous air pollutants as they relate to cancer risks
  - Shows the very limited data available
  - Not adequate to show the more subtle issues we are discussing today (as yet)

Measure D6a

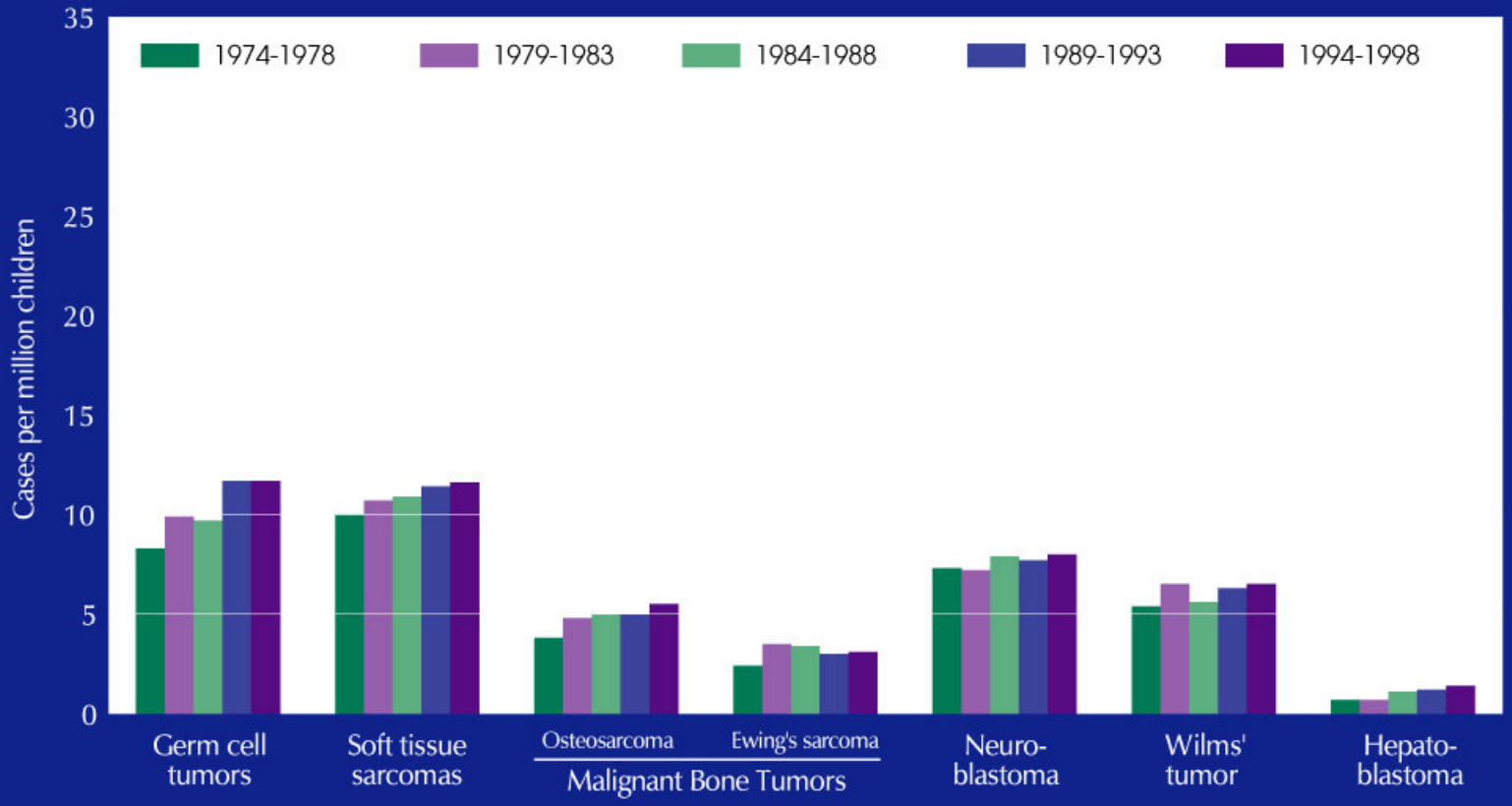
Cancer incidence for children under 20 by type



SOURCE: National Cancer Institute, Surveilliance, Epidemiology, and End Results Program

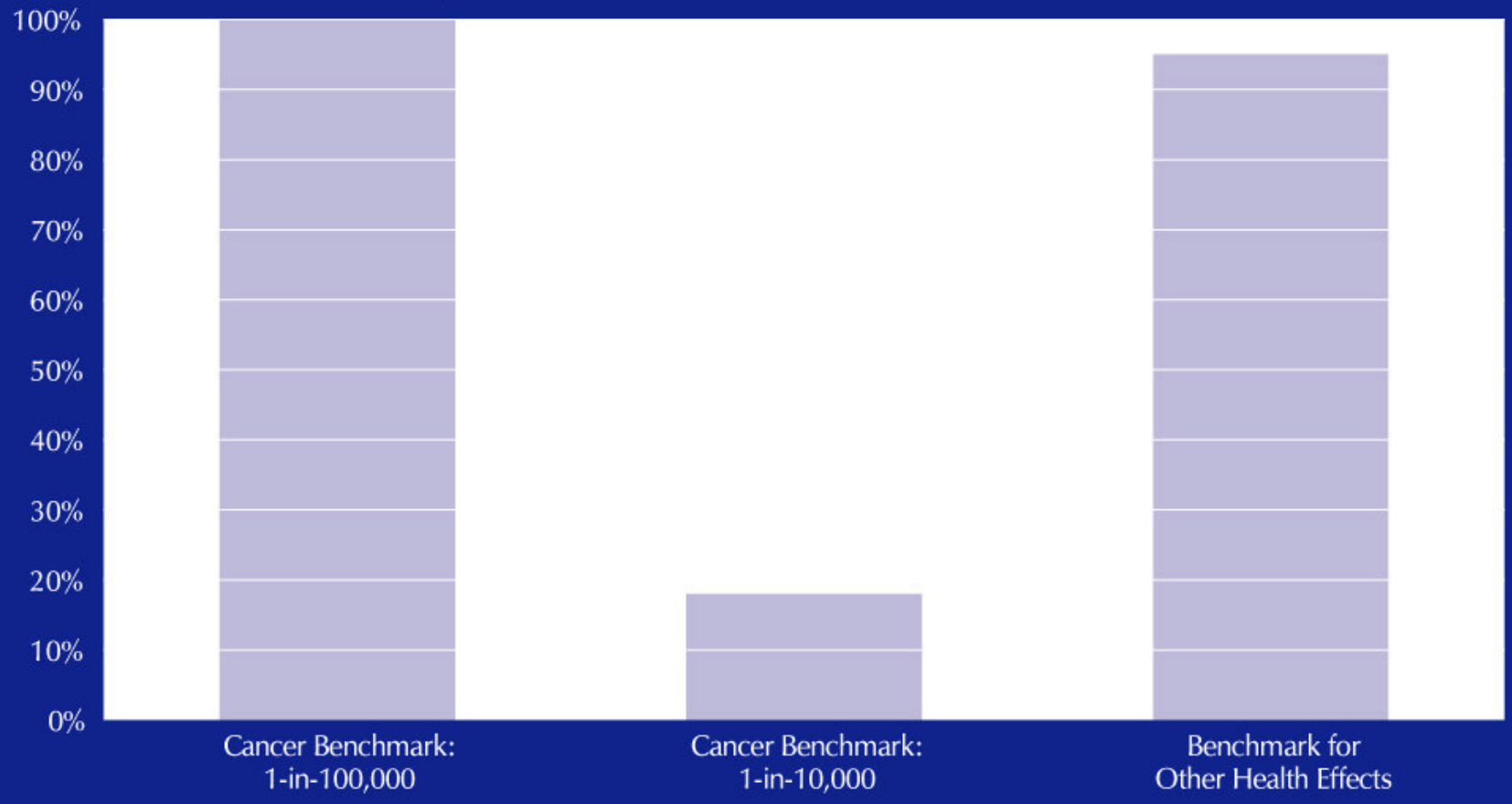
Measure D6b

Cancer incidence for children under 20 by type



SOURCE: National Cancer Institute, Surveilliance, Epidemiology, and End Results Program

Percentage of children living in counties where estimated hazardous air pollutant concentrations were greater than health benchmarks in 1996



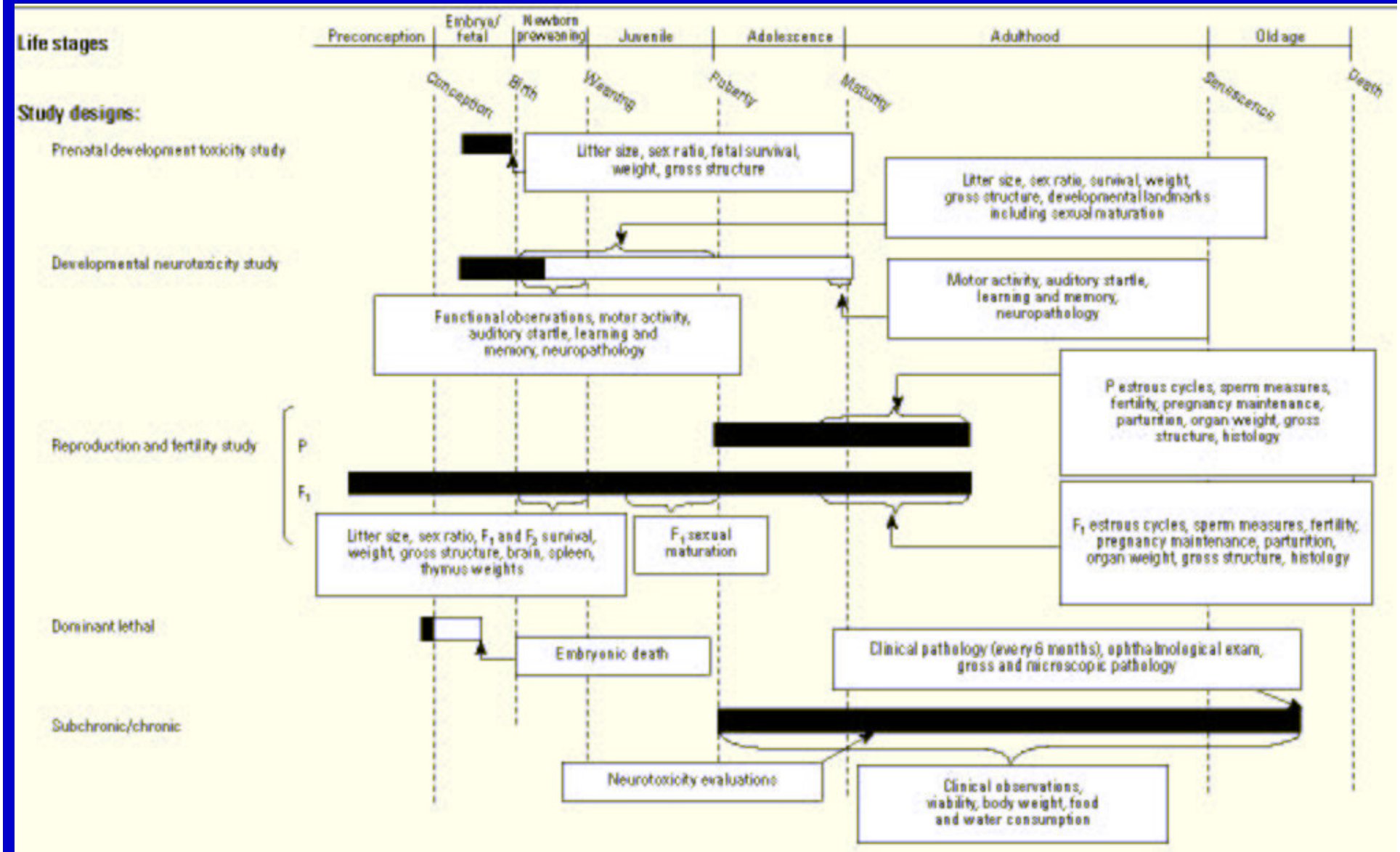
SOURCE: U.S. Environmental Protection Agency, National Air Toxics Assessment

Risk assessment approaches

- Intensive science approach
- Analysis by Daston, Faustman et al 2004
- Looks at needs for research at each life stage
- The diagram shows types of studies that are relevant

Elements to consider

- Life stages
- Differences in biochemical, molecular, cellular, organ related processes
- Differences in kinetics:
  - Slower clearance from blood
  - Slower elimination
  - More absorption


Life stages
Preconception
Embryo/ fetal
Newborn preweaning
Juvenile
Adolescence
Adulthood
Old age
Conception
Birth
Weaning
Puberty
Maturity
Senescence
Death
Study designs:
Prenatal development toxicity study
Litter size, sex ratio, fetal survival, weight, gross structure
Litter size, sex ratio, survival, weight, gross structure, developmental landmarks including sexual maturation
Developmental neurotoxicity study
Motor activity, auditory startle, learning and memory, neuropathology
Functional observations, motor activity, auditory startle, learning and memory, neuropathology
Reproduction and fertility study
P
F1
P estrous cycles, sperm measures, fertility, pregnancy maintenance, parturition, organ weight, gross structure, histology
F1 estrous cycles, sperm measures, fertility, pregnancy maintenance, parturition, organ weight, gross structure, histology
Litter size, sex ratio, F1 and F2 survival, weight, gross structure, brain, spleen, thymus weights
F1 sexual maturation
Dominant lethal
Embryonic death
Clinical pathology (every 6 months), ophthalmological exam, gross and microscopic pathology
Subchronic/chronic
Neurotoxicity evaluations
Clinical observations, viability, body weight, food and water consumption

WHO / Europe Env Agency

- Questions to consider:
  - Does assessment include reproductive and early developmental stages?
  - Did tests consider adequately sensitive endpoints (i. e. impact on learning)
  - Have long term effects of early life exposure been assessed?
  - Were exposure patterns at different stages assessed?
  - Did models reflect children, consider ALL sources, and reflect real world conditions?

(Tamburlini et al 2002)

Precautionary approaches

- Being discussed in Europe to address children's environmental health
- Alternative to science intensive risk assessment approaches

IV. Policy needs

1. Environmental standards that reflect children
2. Focus on upstream processes that lead to increased disease or risk
3. Address "missing" chemicals
4. Address "missing" environments
5. Think about cumulative exposures/risks

Environmental health standards

- Don't have standards for very many substances now
  - A few (six) air pollutants,
  - More (86) drinking water pollutants (including microbes and disinfection byproducts),
  - Pesticide practices
- Need to address children in setting standards
- FIFRA (pesticides) and Safe Drinking Water Act have elements that begin this

Focus on process or disease?

- More upstream biological changes or processes may be useful to study or address (rather than waiting for disease)
  - More preventive approach
  - Disease may be MUCH later
  - Children's research center results have been key – integrated approaches

Add missing chemicals

- Many recently discovered threats not adequately understood or controlled
  - Phthalates
  - PBDEs
  - Pesticides
- Need to assess systematically

Add missing environments

- Children's environments not well addressed
  - Homes
  - Child care
  - Schools
  - Vehicles
  - Products
- Not one is addressed well nationally

Think about cumulative impacts

- See common mechanisms
- See some evidence that differing mechanisms add up to more effect
- Still assessing chemicals and impacts one at a time

Conclusion

- Children are not a subpopulation
  - Virtually everyone starts out as a child
- Need to understand that the health of children is fundamental to the health of the population
- Early exposures matter more – greater benefit to prevent them
- Late impacts can be severe