

Children's Environmental Health



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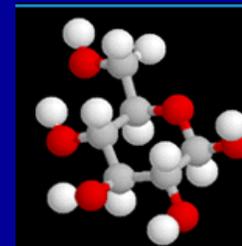
Why Is It Important To Improve Risk Assessment for Children?

- Role of environmental agents in the overall etiology of birth defects is largely unknown, with estimates of 3-25% of all birth defects due to some type of environmental interaction
- Data uncertainties have been identified by EPA from chemically induced prenatal carcinogens, autism, etc.



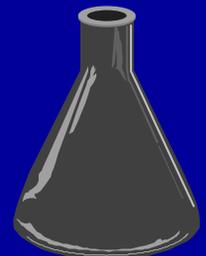
Chemical Universe

- **Approximately 75,500 chemicals listed by EPA**
- **Most of these chemicals have not been tested for developmental toxicity**
- **For example, High Production Volume (HPV) Chemicals**
 - **Chemicals produced at >1 million lbs/year**
 - **Approximately 3,000 chemicals identified internationally**
 - **23% tested for both reproductive and developmental toxicity**
 - **43% have inadequate data bases**

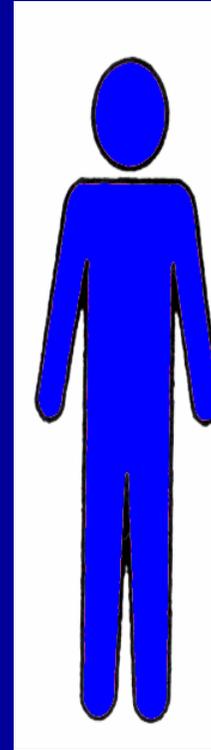
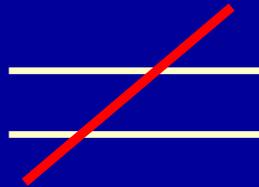


Chemical Universe (continued)

- Chemicals are known to cause developmental defects and neurobehavioral changes
 - Summary databases have listed over 900 agents as known animal developmental toxicants (4,000 entries)
 - 50 of the agents have sufficient human exposure information to be listed as known human developmental toxicants



Children Are Not Just Tiny Adults



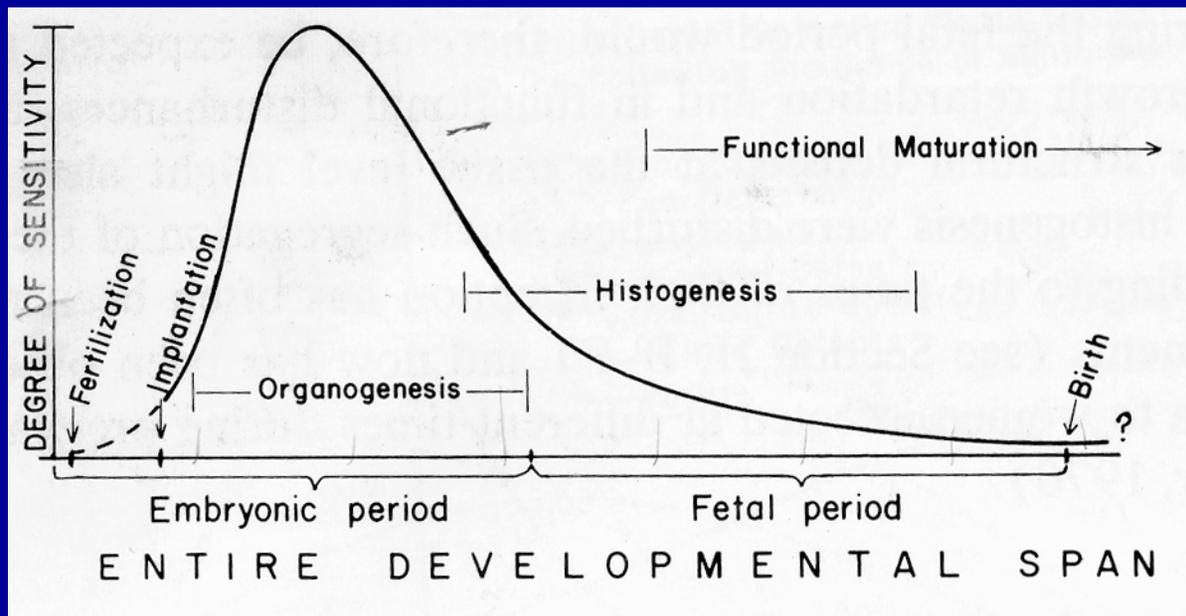
Reasons for Susceptibility of Children to Toxicity

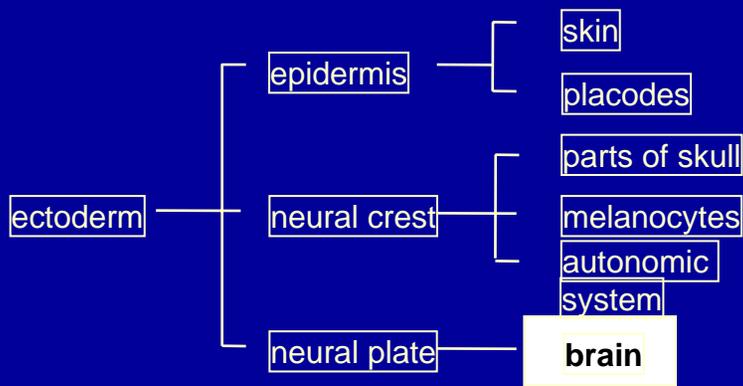
- Toxicity considerations
- Exposure considerations

Reasons for Susceptibility of Children to Toxicity- Toxicological Considerations

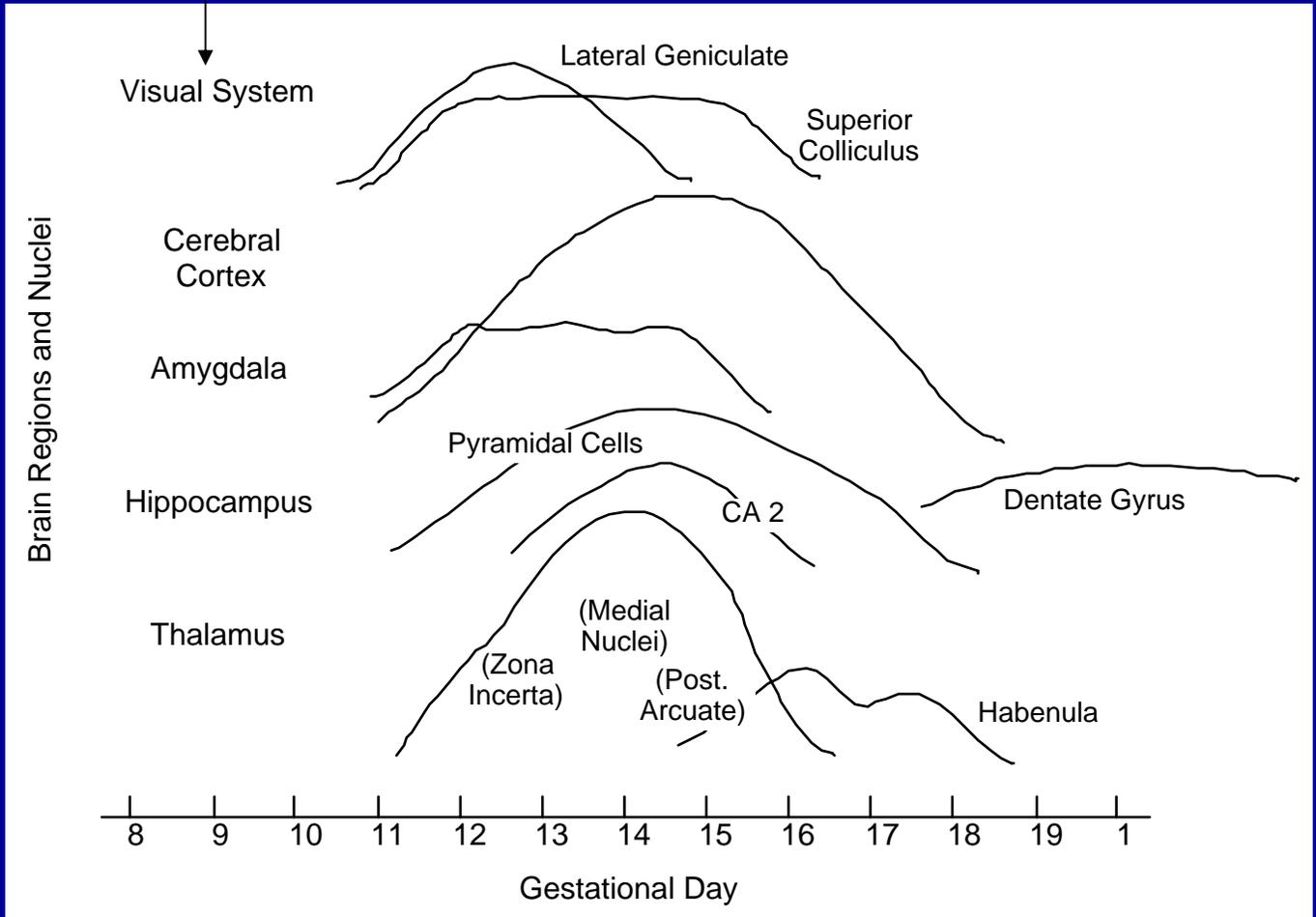
- Temporal differences in susceptibility
- Dose response considerations
- Genetic susceptibility

 <p>Pre differentiation Period</p>	<p>Usually Not Susceptible to Teratogenesis</p>
 <p>Period of Early Differentiation</p>	<p>Highly Susceptible to Teratogenesis</p>
 <p>Period of Advanced Organogenesis</p>	<p>Increasingly Resistant to Teratogenesis With Increasing Age</p>





Profiles of peak neuroepithelial cell proliferation within specific brain regions and nuclei throughout gestation

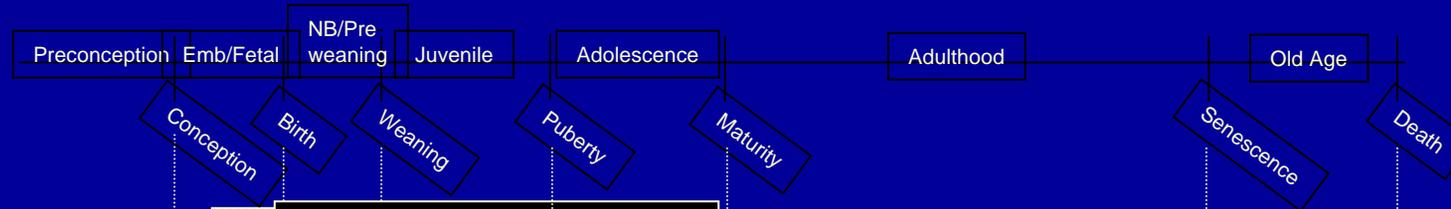


Determination of Most Sensitive Brain Regions and Time Periods

Regions of Rodent Brain Development	Gestational/Postnatal Age																		
	9	10	11	12	13	14	15	16	17	18	19	20	21	22	1	2	3	4	5
midbrain																			
proliferation			■	■	■	■	■	■	■	■									
differentiation					■	■	■	■	■	■									
apoptosis																	■	■	■
neocortex																			
proliferation					■	■	■	■	■	■	■	■							
differentiation						■	■	■	■	■	■	■	■	■					
apoptosis																		■	■
cerebellum																			
proliferation													■	■	■	■	■	■	■
differentiation																■	■	■	■
apoptosis																■	■	■	■
glial proliferation																■	■	■	■

Developmental Toxicity Endpoints in Standard Toxicity Testing Protocols

Life Stages



Study Designs:

Prenatal Developmental Toxicity Study

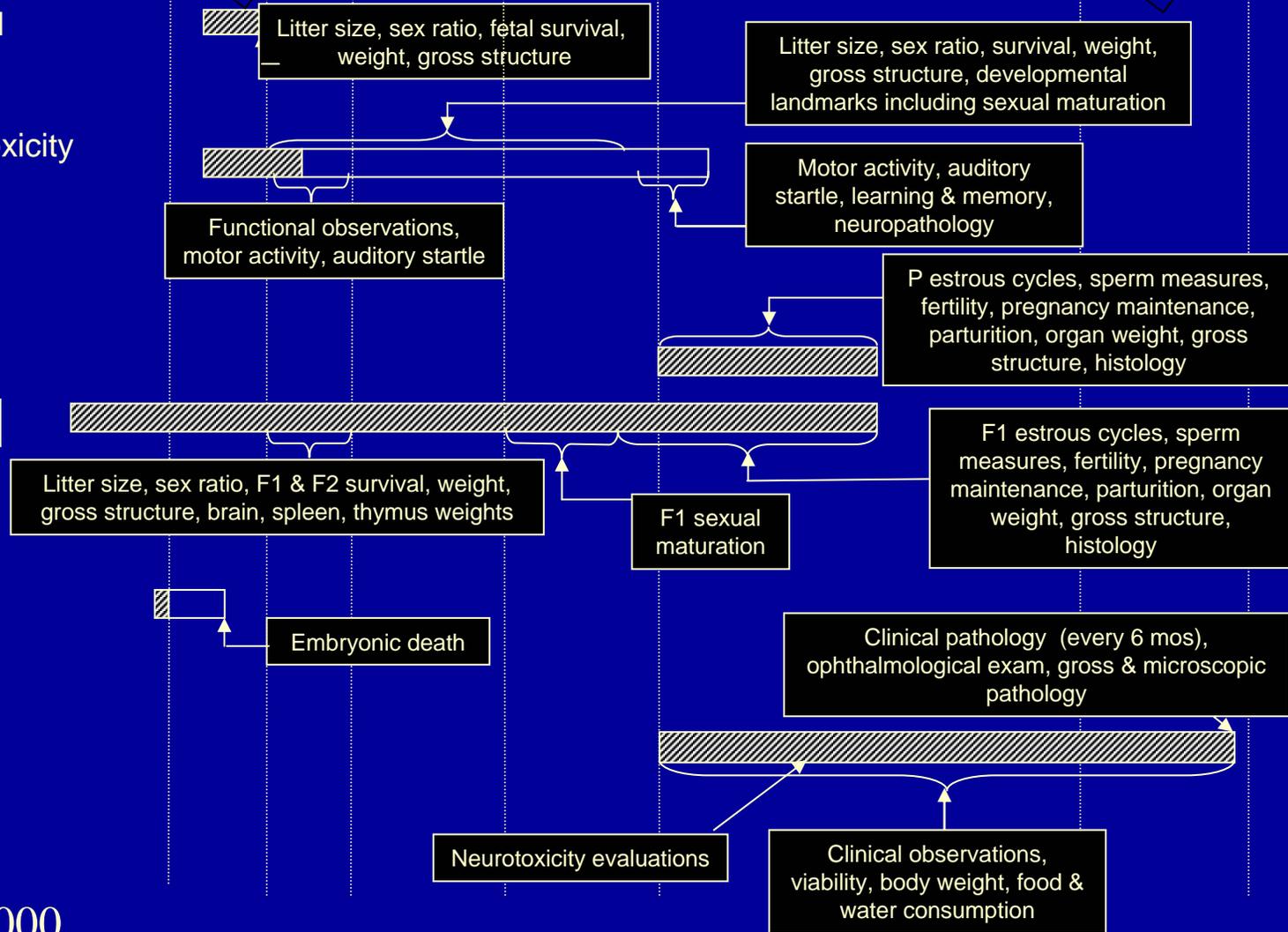
Developmental Neurotoxicity Study

Reproduction and Fertility Study



Dominant Lethal

Subchronic/chronic



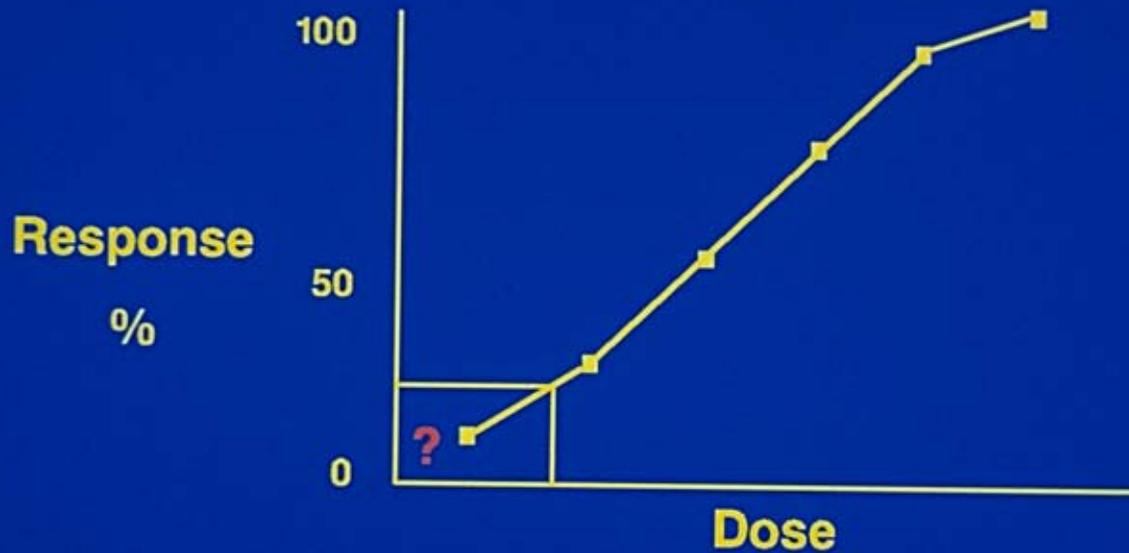
Reasons for Susceptibility of Children to Toxicity- Toxicological Considerations

- Temporal differences in susceptibility

- **Dose response considerations**

- Genetic susceptibility

Dose-Response Curve



Changing Types and Incidences (%) of Malformations in Rat Embryos Irradiated on Different Days of Gestation

Gestation Day	Dose (R)			
	25	50	100	200
8	none	none	none	no survivors
9	Eye (6)	Eye (72)	Eye (90)	Eye (100)
		Brain (9)	Brain (41)	Brain (78)
10		Eye (11)	Eye (75)	Eye (94)
			Brain (8)	Brain (19)
11			none	Eye (100)
				Brain (54)

Reasons for Susceptibility of Children to Toxicity- Toxicological Considerations

- Temporal differences in susceptibility
- Dose response considerations
- **Genetic susceptibility**



SO WHAT'S WRONG WITH RELEASING HARMLESS AMOUNTS OF KRYPTON GAS INTO THE ATMOSPHERE?..

Reasons for Issues of Geno-Phenotype are Especially Relevant for Defining Susceptibility to Developmental Toxicants

- Age dependent differences in gene expression
- Potential for differences in maternal vs. conceptual genotype
- Combinations of the above factors may be significant

Examples of Geno-Phenotype Issues Relevant for Developmental Toxicity

- **Methemoglobinemia**
 - Fetal forms Hb
 - Methemoglobin reductase polymorphisms
- **Organophosphates**
 - Polymorphisms of paraoxonase 1
 - Age and form specific expression

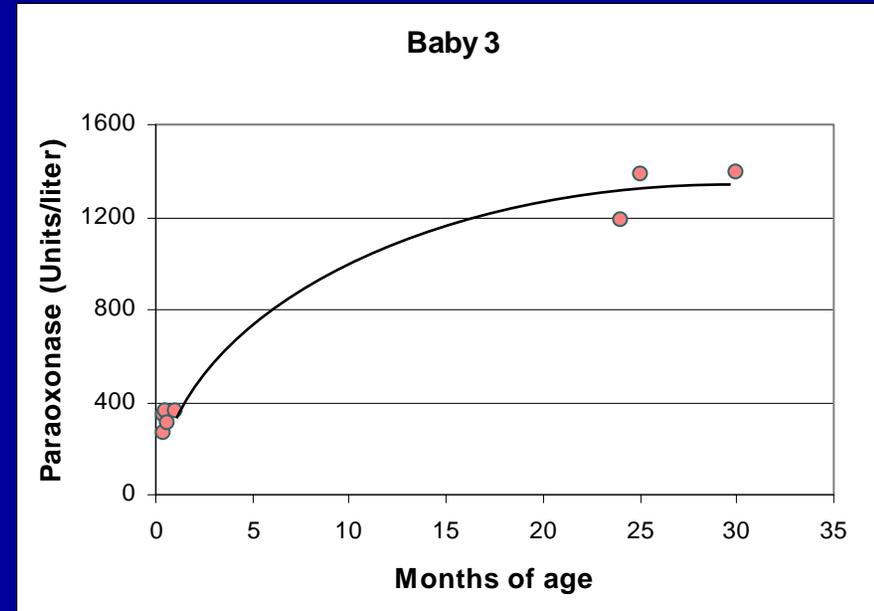
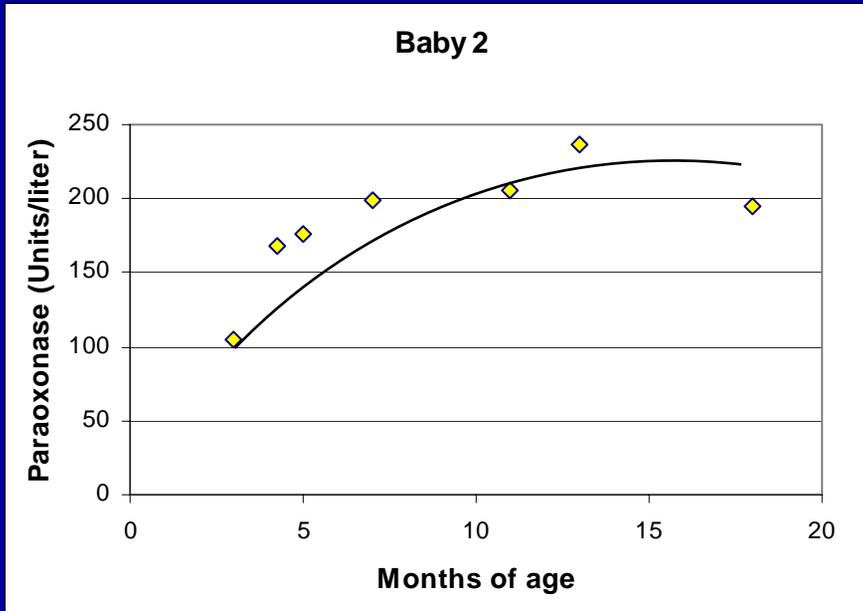
Paraoxonase Polymorphisms: Role in Defining Susceptibility to the Developmental Neurotoxicity of Organophosphates

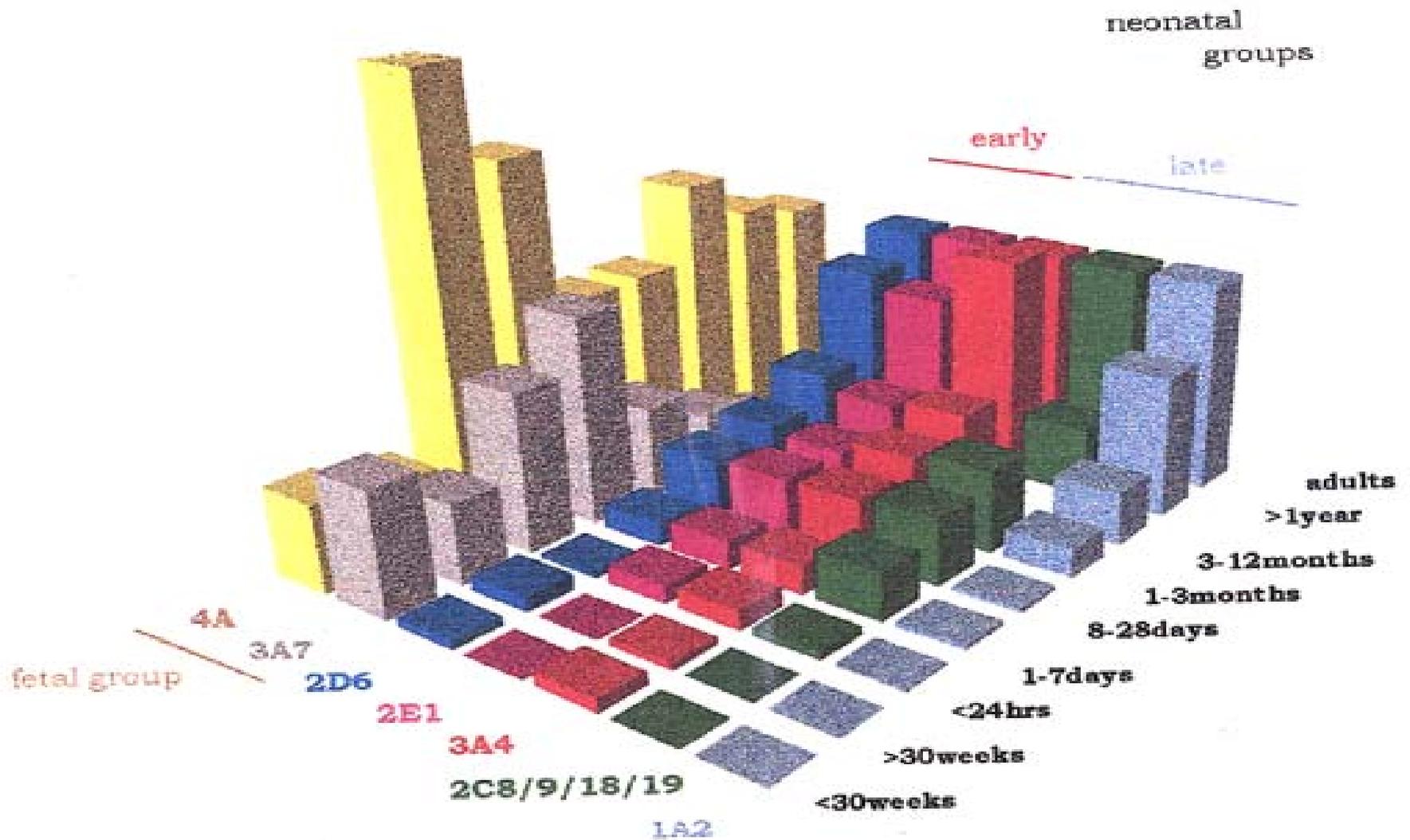
Lucio G. Costa and Clement E. Furlong

Center for Child Environmental Health Risks Research
University of Washington



Time Course of PON1 Appearance in Infants



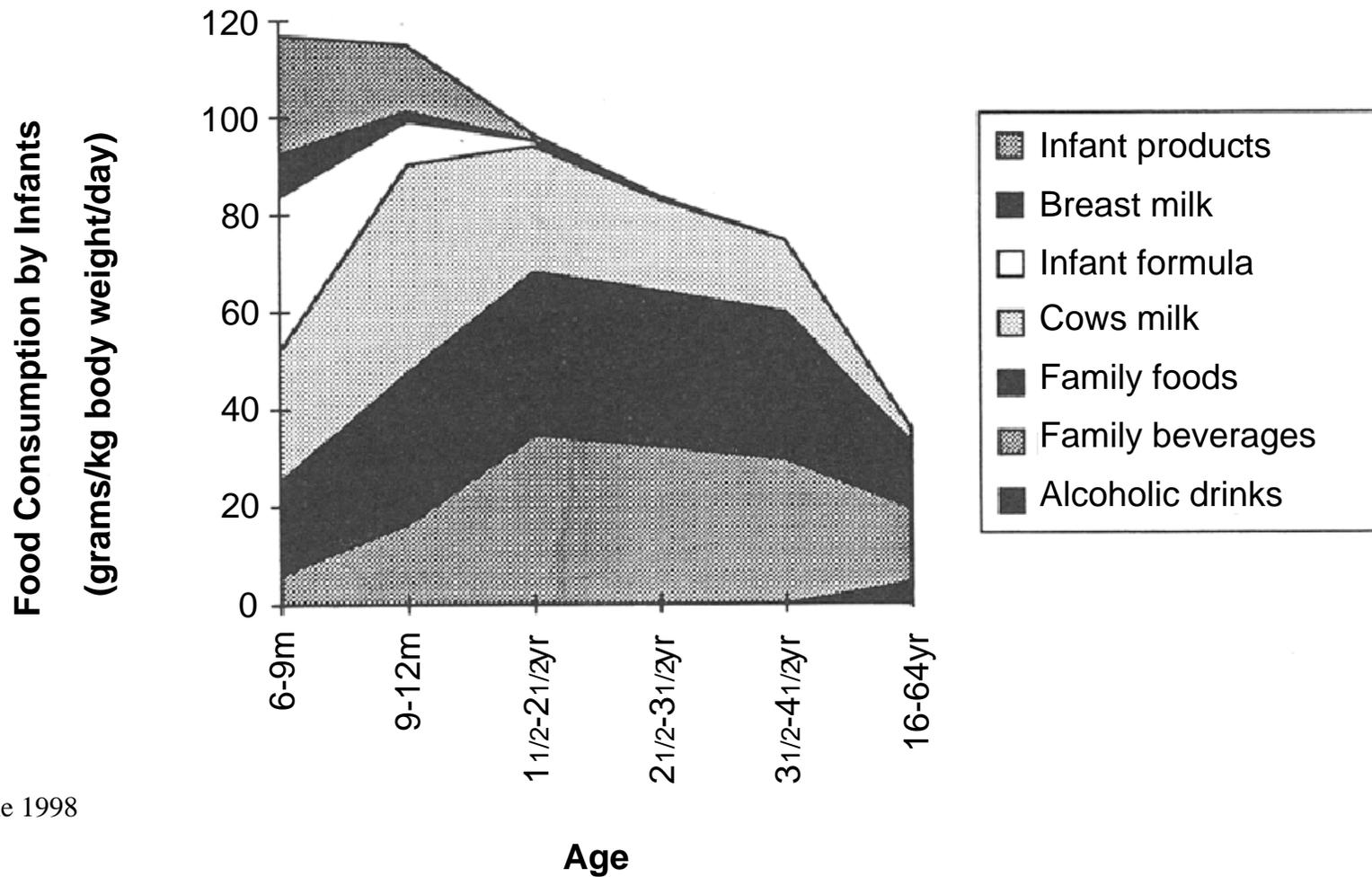


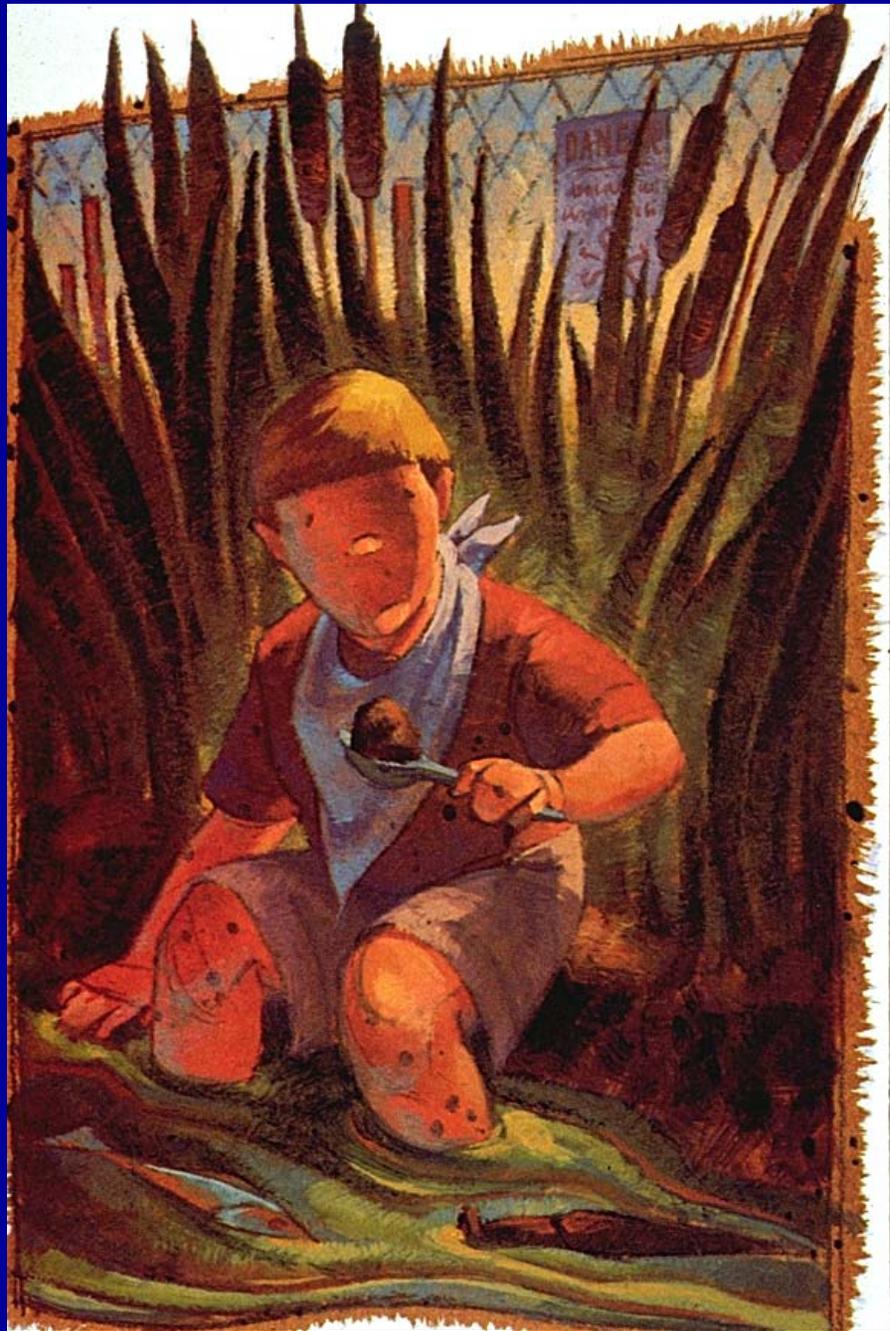
Evolution of cytochrome P450 isoforms in the human liver.

Reasons for Susceptibility of Children to Toxicity- Exposure Considerations

- Varied types and frequency of childhood exposures
- Age-specific behaviors
- Toxicokinetic considerations

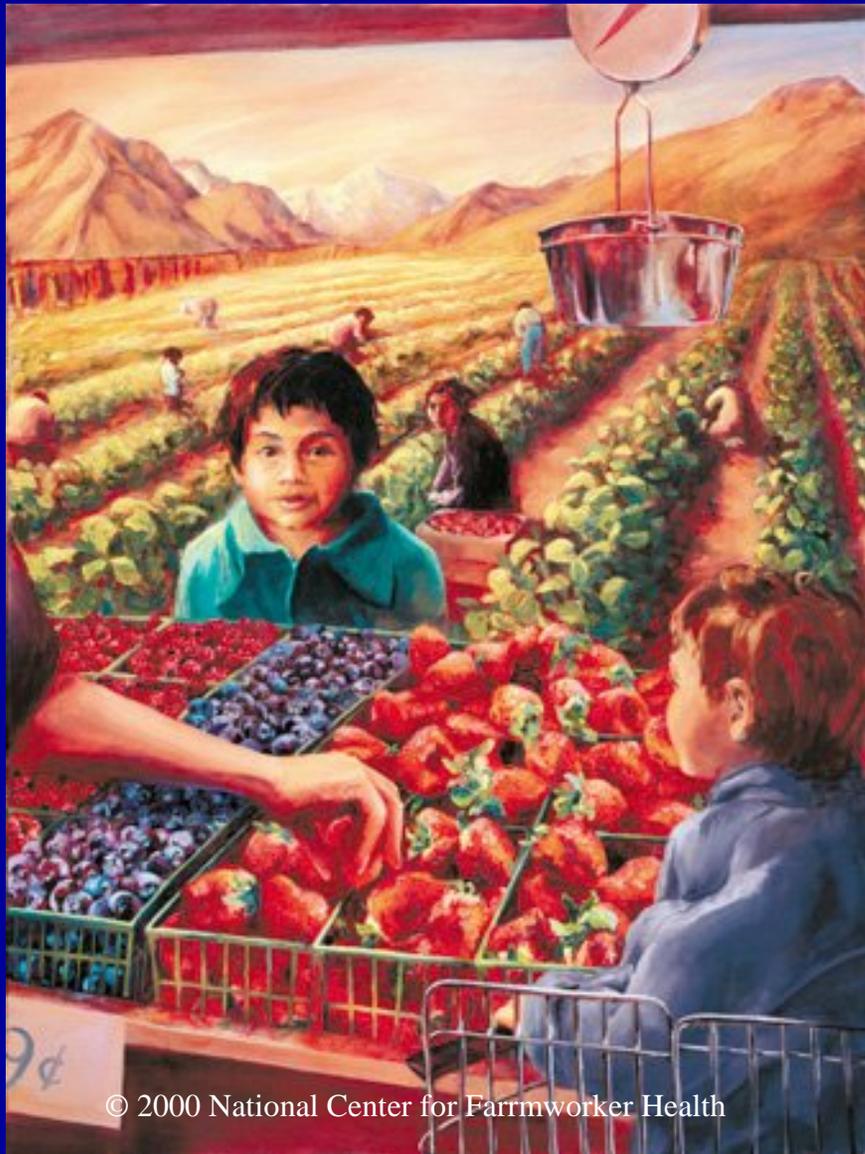
Age Related Consumption of Foods and





Reasons for Susceptibility of Children to Toxicity- Exposure Considerations

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Evaluation and use of a new GPS instrument to characterize children's time-location in pesticide exposure assessment studies

Kai Elgethun
Center for Child Environmental
Health Risks Research
External Advisory Committee Meeting
11 June 2002



Time-location: an important piece of the exposure puzzle



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Bil Keane



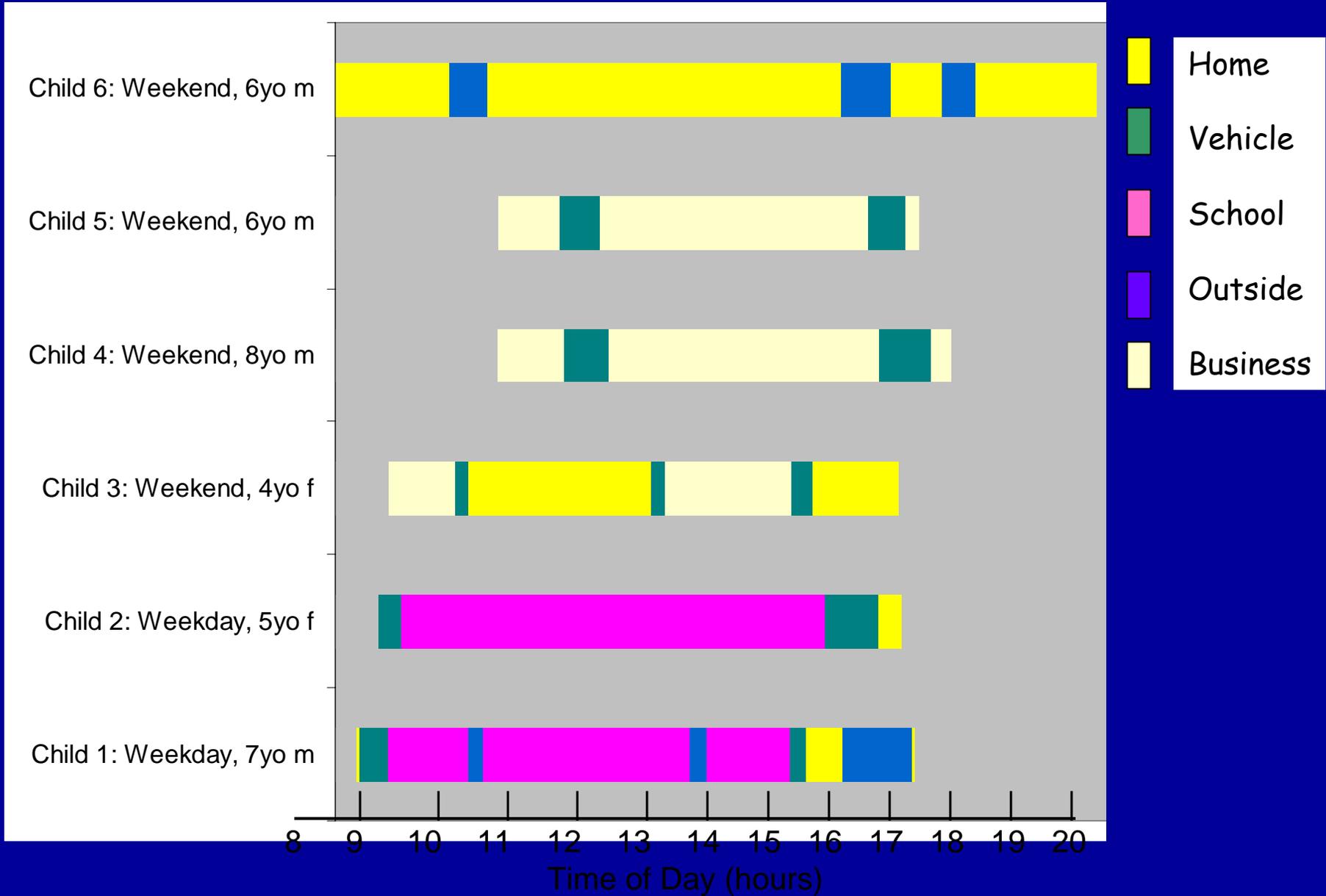
Child wearing GPS-PAL in a vest.
Dashed lines indicate location of components inside the vest

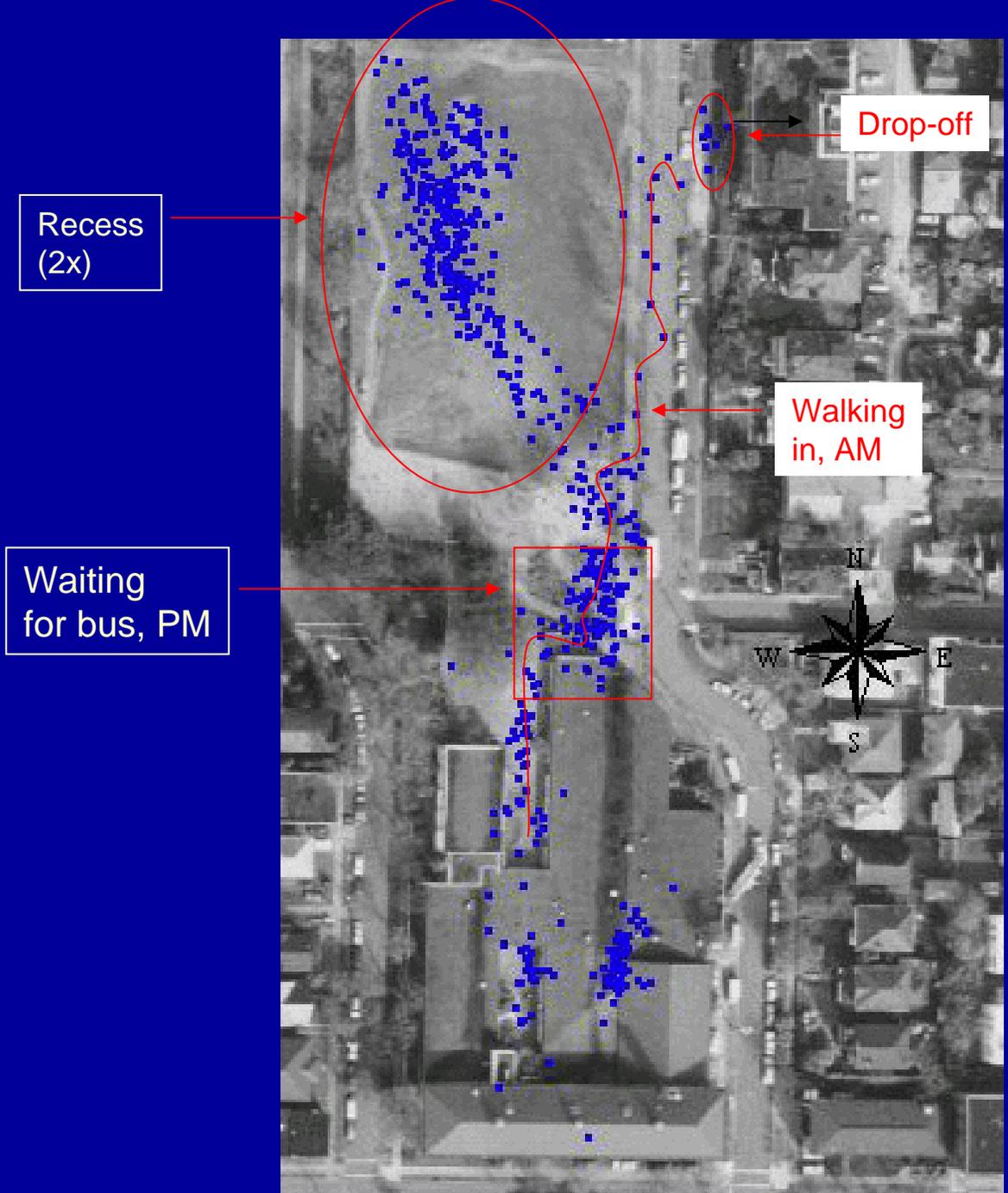
Clothing does not block reception



Resolution:
Capability to differentiate between distinct areas inside & outside

Children: where they spent their time



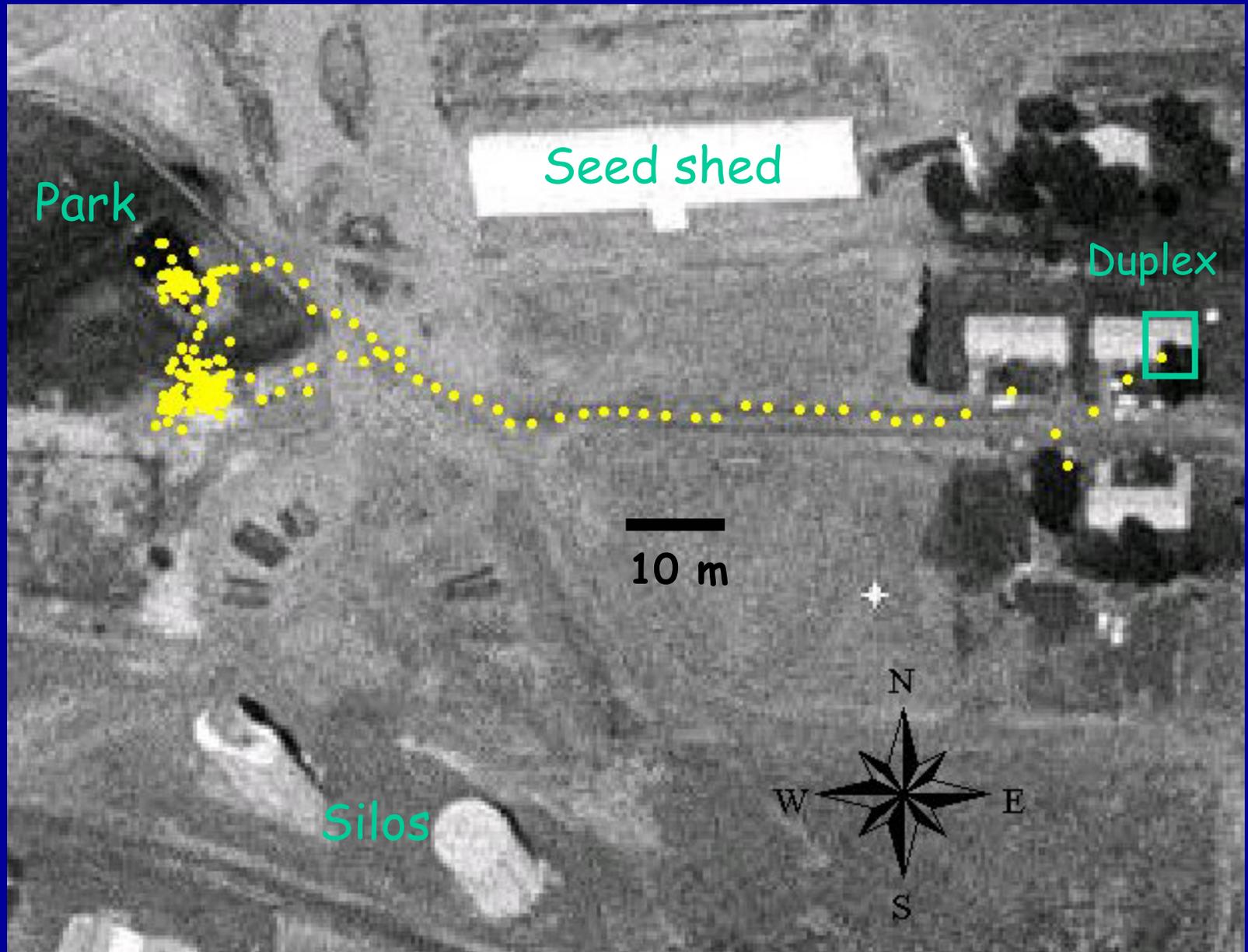


Path traveled by one child on a weekday during school hours

20 m

6 hrs shown here

5-31-02 Drift study, child 3, 1 hour GPS data



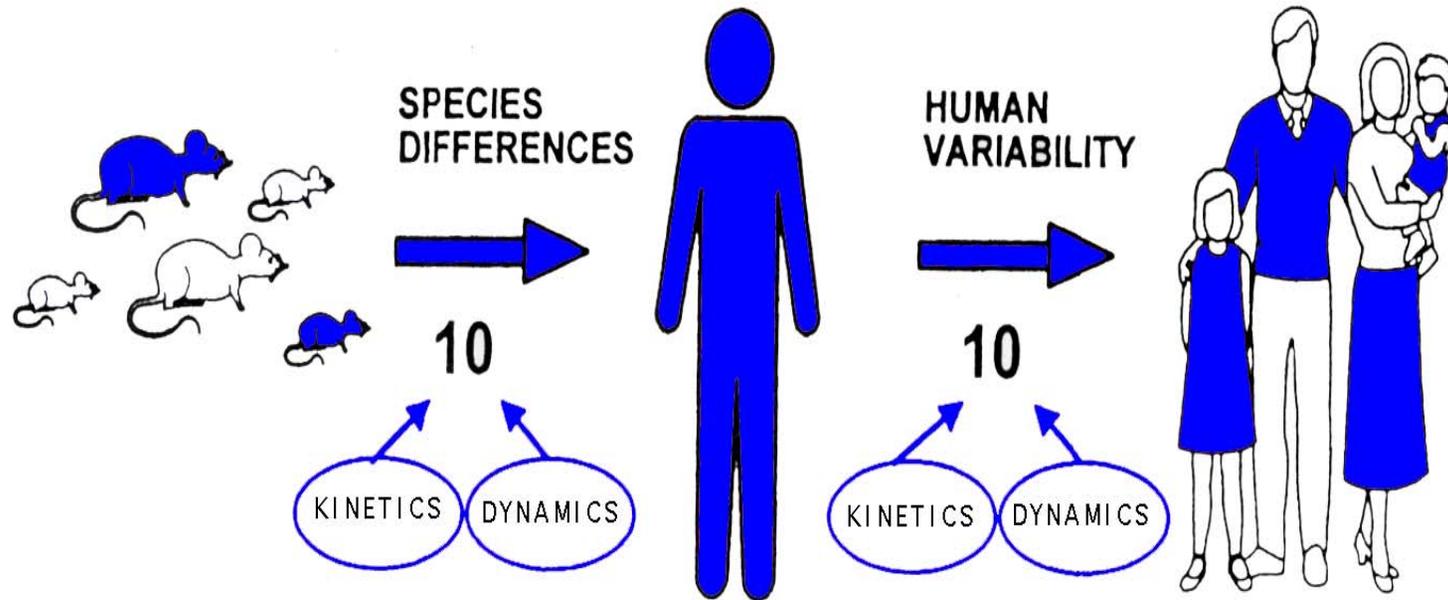
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Toxicokinetic and Toxicodynamic Considerations Inherent in Inter-species and Inter-individual Extrapolations



New Directions in Children's Health Risk Research

- Exposure Factors Handbook
- Childhood Cancer
- Autism
- Children's Risk Assessment Framework
- National Cohort Study

Promise:
Increased Understanding of
Children= Improved Risk Assessment

