APPENDIX E

OVERHEADS USED AT WORKSHOP

Michael Firestone

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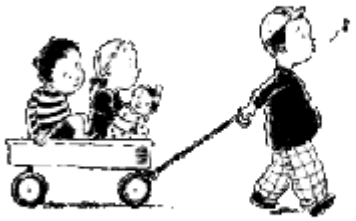


EPA's Perspective on Childhood Exposure Assessment - Current Practices and Future Needs

Michael Firestone, Ph.D., Science Director

United States Environmental Protection Agency

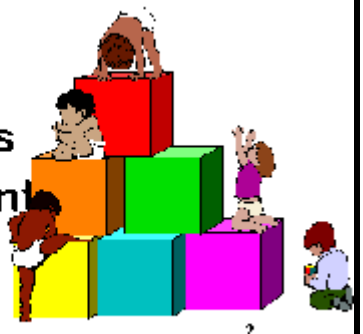
Office of Children's Health Protection - OCHP -

Our Mantra – Children are not little adults

- They eat and drink more for their size
- They play and act differently than adults
- Their bodies are still developing
- Children may be less able to metabolize and excrete certain toxic substances

Yes but …

- Newborns are not tiny toddlers
- Infants are not small adolescent



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Administrator Browner's Seven Step National Agenda to Protect Children's Health from Environmental Threats

1. Protective standards
2. Expand research on children's risks
3. New policies on childhood exposures
4. Expand Community Right-To-Know
5. Provide basic information to parents and care givers
6. Expand education efforts
7. Provide funding

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GOAL of this Presentation

I. Discuss EPA's exposure assessment needs with respect to considering the impact of developmental changes

II. Summarize current agency practices

III. Present some of EPA's ongoing activities and future needs

IV. Outline next steps

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I. EPA's Exposure Assessment Needs with respect to Considering the Impact of Developmental Changes

- Suggest and define specific early lifestages which EPA should consistently utilize when assessing exposure
- Provide the scientific rationale for these lifestages
- Identify related reseach needs

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II. Current Approaches for Childhood Exposure Assessments

- Assessments are conducted by EPA's program offices (Air and Radiation; Prevention, Pesticides & Toxic Substances; Water; Solid Waste/Superfund and 10 regions
- Executive Order 13045 http://www.epa.gov/children/whatwe/executiv.htm

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II. Current Approaches for Childhood Exposure Assessments

- EPA's Rule Writer's Guide to Executive Order 13045 http://www.epa.gov/children/whatwe/rrguide.pdf
- EPA Exposure Factors Handbook http://www.epa.gov/ncea/pdfs/efh/front.pdf
- Draft Child-Specific Exposure Factors Handbook

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II. Current Approaches for Childhood Exposure Assessments

Age Group Selection:

- Varies somewhat from program to program and case to case
- Often depends on data availability

e.g., Exposure Factors ndbook, Continuing Survey of Food Intake by Individuals, etc.

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II. Current Approaches for Childhood Exposure Assessments

Age Group Selection, continued:

- Often based on professional judgment about where children spend time and what activities they engage in

e.g., periods of increased mouthing of hands and objects

- May consider specific health concerns

e.g., age related differences in iron deficiency, cognitive impacts of methyl mercury due to fetal exposure

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II. Current Approaches for Childhood Exposure Assessments

Age Groups that are Sometimes Addressed in Agency Assessments Include:

- Fetus
- Infants
- Toddlers
- Children
- Adolescents

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II. Current Approaches for Childhood Exposure Assessments

Examples of How Exposure Data are Used to Represent the Different Age Groups :

- median values for 3 year olds used to represent ages 1 to 6 years
- time weighted averages of data for 1 to 2 years and 3 to 5 years used to represent 1 to 5 years

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IIIa. EPA's Ongoing Activities

- Child Specific Exposure Factors Handbook
- New Food and Water Consumption Data for Children through the Continuing Survey of Food Intake by Individuals
- Probabilistic Approaches to Aggregate Exposure and Cumulative Risk Assessment

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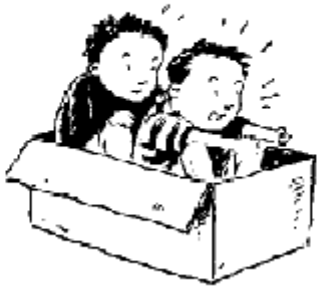
IIIa. EPA's Ongoing Activities

- Integration with Pharmacokinetic Information and Dose Metrics
- Children's Research Strategy (www.epa.gov/ncea/pdfs/draft21.pdf)



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IIIb. EPA's Future Needs

- Develop a set of early lifestages which should be assessed consistently throughout EPA (examples: Prenatal stages, newborn, infant, toddler, …)
- Define the characteristics expected to significantly impact exposure (examples: breastfeeding, crawling, dermal permeability, teething and associated oral behavior)

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IIIb. EPA's Future Needs

- Address how significantly exposure should vary (quantitatively and/or qualitatively) in order for EPA to consider the need for a special lifestage group
- How should EPA consider other factors such as sex, culture, geography in defining subgroups
- Identify key data gaps for which research can help reduce uncertainty

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IV. Next Steps

- Compile Workshop report
- EPA's Risk Assessment Forum will develop guidance based on output from the Workshop
- The guidance will be peer reviewed and submitted to EPA's Science Policy Council for approval

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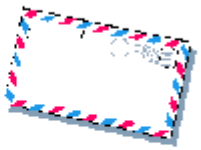
Contact Information



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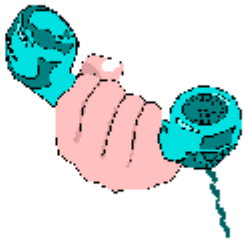

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Elaine Hubal

National Exposure Research Laboratory
U.S. Environmental Protection Agency

Exposure Assessments for Children: an Overview

Elaine A Cohen Hubal
National Exposure Research Laboratory, U.S. EPA,
Research Triangle Park, NC 27711

Risk Assessment Forum Workshop
Issues Associated with Selecting Age Groups for Assessing Exposure to Children
July 26-27, Washington D.C.

Definition of Human Exposure

The contact *at visible external boundaries* of an individual with a pollutant for a specific duration of time.

Exposure Assessment

Exposure assessments (half of a risk assessment) are developed to characterize "real-life" situations

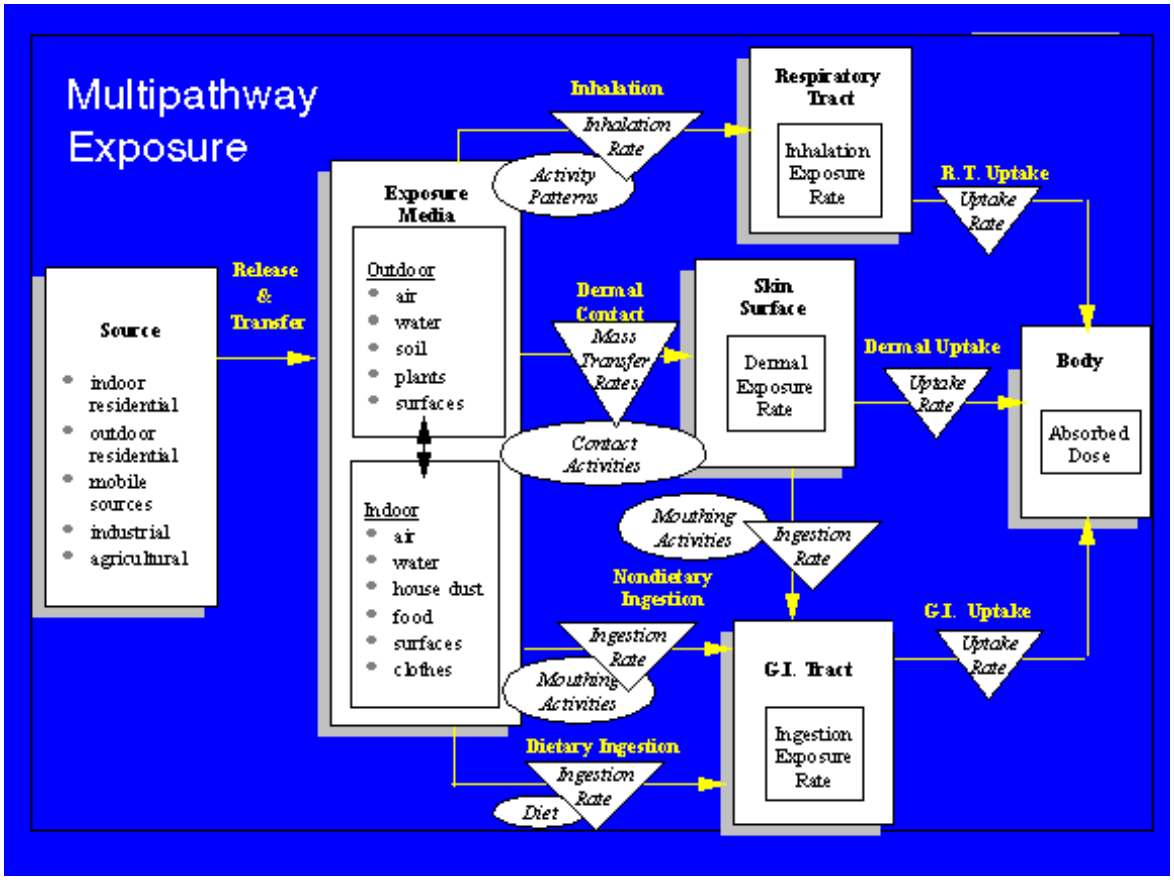
- Identify potentially exposed populations
- Identify potential exposure pathways
- Quantify the magnitude, frequency, and duration of chemical exposure

Direct Assessment

- **Measure receptor contact with chemical concentration in the exposure media over an identified period of time**
- **Personal monitoring techniques are used to directly measure exposure to an individual during monitored time intervals** (personal air, duplicate diet)
- **Biomarkers are an indicator of absorbed dose that resulted from direct exposure.**

Indirect Assessment

- To estimate exposure, use
  - **available information on concentrations of chemicals in exposure media,**
  - **information about when, where, and how individuals might contact the exposure media,**
  - **algorithms and a series of exposure factors (i.e., pollutant transfer, pollutant uptake)**
- Because of difficulty performing direct exposure assessments, indirect assessments are often used to perform the risk assessments required to make regulatory decisions.



Exposure Pathways

- In general terms, a pathway is defined as the course that a chemical takes from its source to the receptor's portal of entry.
- To specifically evaluate potential for exposure, pathways are defined here by the exposure medium and the route of exposure.
- The pathway crosses the environmental medium with the human activity that leads to exposure
- Examples:

  Indoor air → Inhalation

  Turf → Dermal contact

Exposure Factors

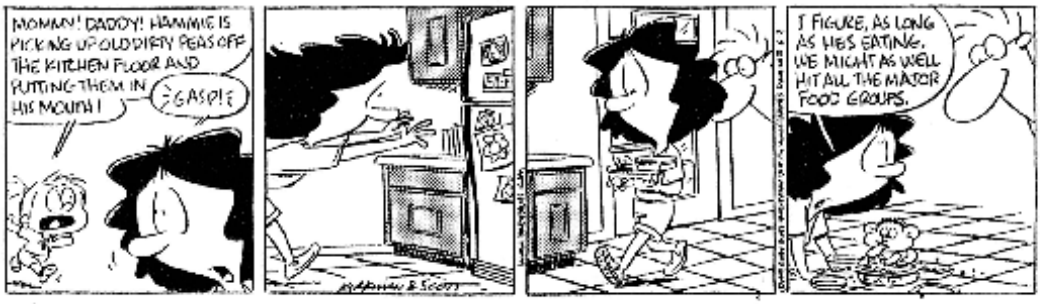
Indirect exposure assessments require data on the following exposure factors:

- Contaminant concentrations in the exposure media in the environment where the individual spends time
- Contact rates of the individual with the exposure media
- Contaminant transfer efficiency from the contaminated medium to the portal of entry
- Contaminant uptake rates through portal of entry
- Human activities

Characteristics of Children that Influence Exposure

- Physiological characteristics
- Behavioral characteristics
  - Development (motor capacity, mouthing)
  - Physical Activities
  - Diet and eating habits
- Other characteristics
  - Gender
  - Socioeconomic Status
  - Race/ethnicity

Baby Blues



Characteristics of Children that Influence Exposure

- Physiological characteristics
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Exposure Algorithms

- For each route, the algorithm mathematically expresses exposure as a function of
  - chemical concentration in the exposure medium
  - contact rate
  - rate of transfer from the exposure medium to the portal of entry
  - exposure duration
- Aggregrate assessments include all three exposure routes: inhalation, dermal contact, and ingestion
- Ingestion can be divided into two subroutes, dietary and non-dietary ingestion.

Children's Activity Pattern Data

- **Microenvironment**

  The location the child occupies

- **Macroactivity**

  General activities such as watching TV, eating dinner, taking a shower

- **Microactivity**

  Detailed actions that occur within a general activity, such as hand-to-surface and hand-to-mouth behavior

Inhalation Exposure

For each microenvironment/macroactivity (me/ma), inhalation exposure over the 24-hr period is defined as

$$E_{inhale\_me/ma} = C_{air\_me} \times IR_{ma} \times ED_{me/ma}$$

C_{air_me} = air concentration measured in the microenvironment (mg/m^3)

IR_{ma} = child's respiration rate for the macroactivity (m^3/h)

ED = time spent in that me/ma over the 24-hour period (h/24h)

Exposure over the 24-hr period is the sum of all of the me/ma exposures.

Inhalation: Data Requirements

- Definition of important me/ma for inhalation exposure
- Air concentration in each microenvironment
- Inhalation rate for each me/ma
  - Estimated for each macroactivity based on child's age and weight
- Amount of time child spends in each me/ma over 24-hrs
  - Questionnaires designed to collect this data

Macroactivity Data

- Macroactivity information for an individual contains at least one complete day of sequential location/activity data for each discrete major behavior. There are 9 studies that recorded such data, but only 4 include data on children.
- Data from all 9 studies contained in CHAD; a relational database using a common set of codes for activities, locations, intensity levels, and questionnaire information.
- Limitations of existing macroactivity data:
  - Location information not sufficient to assess dermal exposure
  - Activity codes are much too broadly defined and ignore many child-oriented behaviors

Dermal Exposure - Macroactivity Approach

For each me/ma, dermal exposure over the 24-hour period is defined as

$$E_{dermal\_me/ma} = C_{surface} \times TC_{der} \times ED$$

$C_{surface}$	= transferable surface residue loading measured in the microenvironment ($\mu g/cm^2$)
TC_{der}	= dermal transfer coefficient for the me/ma (cm^2/h)
ED	= time spent in the me/ma over a 24-hr period (h/24h)

Dermal: Data Requirements

- Definition of important me/ma for dermal exposure
- Transferable surface loading in each microenvironment
- Time child spends in each me/ma over 24-hrs
  Questionnaires designed to collect this data
- Transfer coefficient for each me/ma
  Data need to be generated experimentally

Macroactivity Data

- Macroactivity information for an individual contains at least one complete day of sequential location/activity data for each discrete major behavior. There are 9 studies that recorded such data, but only 4 include data on children.
- Data from all 9 studies contained in CHAD; a relational database using a common set of codes for activities, locations, intensity levels, and questionnaire information.
- Limitations of existing macroactivity data:
  - Location information not sufficient to assess dermal exposure
  - Activity codes are much too broadly defined and ignore many child-oriented behaviors

Dermal Exposure - Microactivity Approach

For each microactivity, dermal exposure over the 24-hour period is defined as

$$E_{dermal\_me/ma} = C_{surface} \times TC_{der} \times ED$$

$C_{surface}$ = transferable surface residue loading measured in the microenvironment ($\mu g/cm^2$)

TE = transfer efficiency, fraction transferred from surface to skin (unitless)

SA = area of surface that is contacted (cm^2/event)

EF = event frequency over a 24-hr period (events/24h)

Dermal: Data Requirements

- Data on important microactivities that lead to contact with objects/surfaces
- Residue loadings for the objects/surfaces contacted
- Fraction of residue transferred from surface to skin during contact event
- Surface area of objects/surfaces contacted
- Number of contact events over 24-hours

Microactivity Data

- Approaches to gathering data
  - Real-time hand recording
  - Videotaping
- Comparing results among studies is difficult due to differences in
  - Ages of children
  - Reported summary statistics
  - Categories of body parts and objects contacted
- Limitations
  - Few data sets, small sample sizes
  - Require knowledge on important contact parameters

Non-dietary Ingestion Exposure

For each microactivity resulting in non-dietary ingestion, exposure over the 24-hour period is defined as

$$E_{nding/mi} = C_x \times TE_{xm} \times SA_x \times EF$$

x	= hand or object that is mouthed
C_x	= contaminant loading on hand or object ($\mu g/cm^2$)
TE_{xm}	= transfer efficiency, fraction transferred from x to mouth (unitless)
SA_x	= area of x that is contacted by the mouth (cm^2/event)
EF	= mouthing event frequency over a 24-hr period (events/24h)

Non-dietary Ingestion Data Requirements

Information required to asses non-dietary exposure from surface-to-mouth activities

- Data on important microactivities that lead to object/surface-to-mouth ingestion
- Residue loadings for the objects/surfaces mouthed
- Fraction of residue transferred from surface to mouth during mouthing event
- Surface area of objects/surfaces contacted by mouth
- Number of mouthing events over 24-hours

Non-dietary Ingestion Data Requirements

Information required to asses non-dietary exposure from hand-to-mouth activities

- Data on important microactivities that lead to hand-to-mouth ingestion
- Residue loadings on the hands
- Fraction of residue transferred from hand to mouth during mouthing event
- Surface area of hand contacted by mouth
- Number of mouthing events for each me/ma over 24-hours

Dietary Ingestion

- Exposure is estimated by summing contributions from:
  - Chemical residue on the food prior to handling in the residence
  - Pesticide transferred to the food during contact with contaminated surfaces
  - Pesticide transferred from surface to hand to food during handling and eating
- Algorithms and data requirements similar to those for non-dietary ingestion with addition of information on:
  - Concentrations of contaminant in foods coming into house
  - How food is handled

Exposure Scenarios

- For any given pathway there are a set of associated exposure scenarios
- Exposure scenarios combine
  - **Source** (application method, residential use of a consumer product)
  - **Population** (age group, geographic location, SES)
  - **Timeframe** (acute, short term, chronic)
  - **Microenvironment** (indoors and outdoors at home, indoors and outdoors at daycare/school, indoor and outdoor other, in transit)
  - **Macroactivity** (active play, quiet play, sleeping, eating)

Exposure Pathways vs Exposure Scenarios

- Systematically identify potential exposure pathways to frame exposure assessments
- Identify exposure scenarios to specify values of exposure factors and to estimate distribution of exposure by any given pathway
- To identify exposure scenarios, need identify appropriate age/developmental benchmarks for categorizing children

Research Needs

To improve the database available to assess children's exposures, three areas of research are required.

- Identification of appropriate age/developmental benchmarks for categorizing children in exposure assessments
- Development and improvement of methods for monitoring children's exposures and activities
- Collection of physical activity data for children (especially young children) required to assess exposure by all routes

Summary

- Activity patterns provide information about when, where, and how individuals might contact exposure media.
- Contact rates, transfer efficiencies, and uptake rates are all a function of activity patterns.
- To guide field studies and select scenarios for exposure assessment, it is critical to develop relevant age/developmental based milestones for children

Kimberly Thompson

Harvard Center for Risk Analysis

Note: the charts and illustrations shown on pages E-36, E-37, E-40 through E-45, E-48, E-49, and E-50 also appear in Appendix H of this document.

Changes in Children's Exposure as a Function of Age and Relevance of Age Definitions for Exposure and Risk Assessment

EPA Technical Workshop

Kimberly M. Thompson, Sc.D.

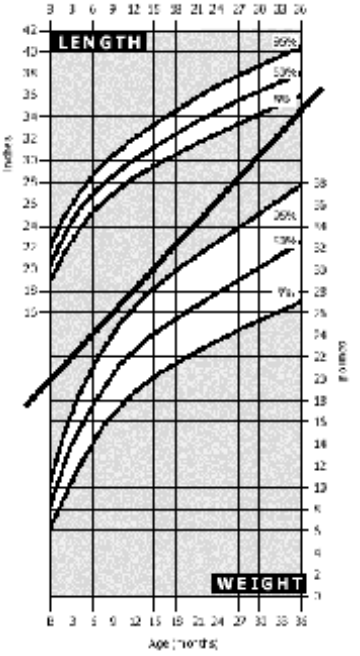
Harvard School of Public Health

Key Issues

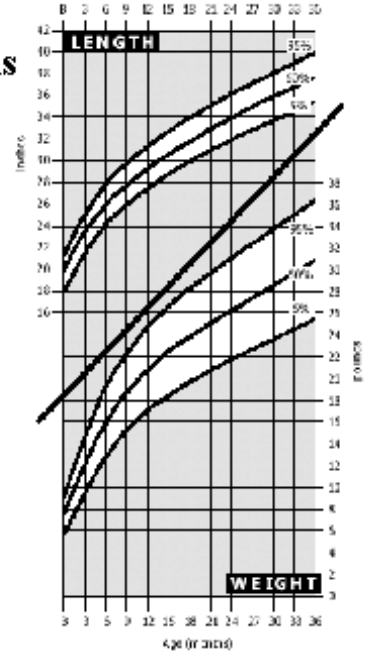
- **Childhood - distinct phase of life**
- **Growth - transition from birth to adulthood (physical, social, behavioral, psychological)**
- **Some things common to all (e.g., teething)**
- **Some specific to children with certain characteristics (e.g., kids with fair skin)**
- **Some specific to child-activity patters (e.g., kids that swim)**

Physical changes (birth - 3 years)

Boys

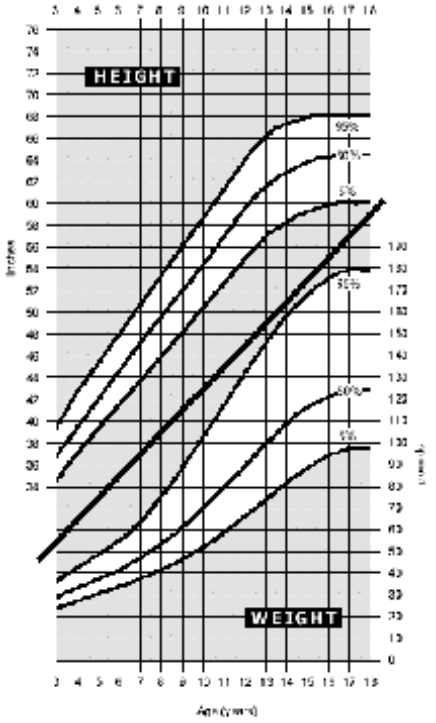


Girls

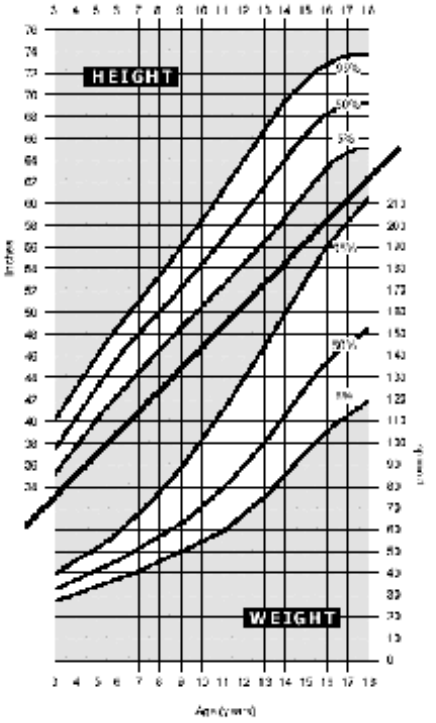


Physical changes (3-18 years)

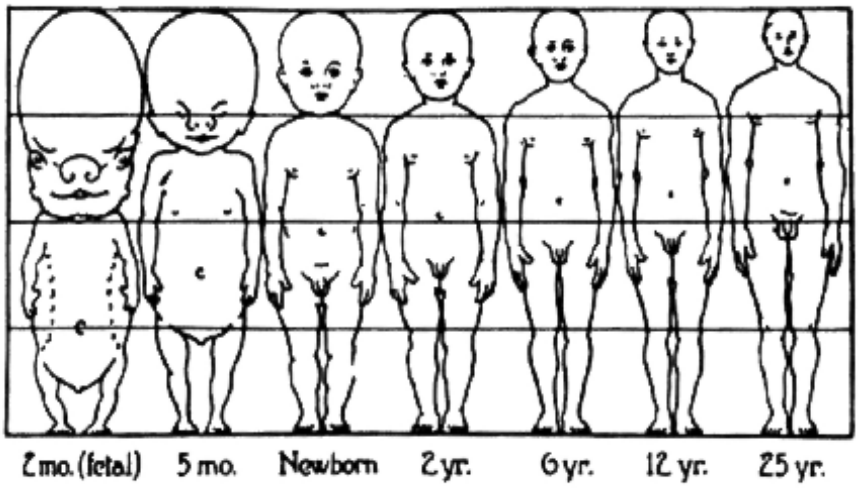
Girls



Boys



Physical changes



Developmental milestones (birth - 6 years)

- Charts available
- Categories (personal-social, fine motor-adaptive, language, gross motor)
- May have different significance for physicians and exposure/risk assessors
- Continuous changes, growth spurts, measurements at discrete time points
- Qualitative and quantitative differences

Working with what we have

- Existing exposure data
  - use a wide array of age categories
  - may not be representative of the children of interest or concern
- As a result
  - analysts must pull together data from different databases to create modeled children, but avoid "hypothetical" children that could not exist
  - significant data gaps may exist

Exposure Equations

- 7 Equations given, based on Hubal *et al.* (2000)
- Routes: Ingestion (dietary, non-dietary), inhalation, and dermal
- Plus equation to go from exposure to dose (Pharmacokinetics and pharmacodynamics are <u>not</u> covered in this meeting)

Objectives

- Characterize
  - the availability of data for use in exposure equations and the age categories used
  - the extent to which the data are accessible and the age categories could be modified
  - the current quantification of variability among children of similar ages and uncertainty in the data
- Use
  - primarily the EPA's Child-Specific Exposure Factors Handbook (CSEFH)
  - a few other studies from the peer-reviewed literature

Tables

- Summarize
  - exposure factor
  - original source
  - age category used, and when available the number of subjects in each
  - general assessment of (1) data quality based on the criteria and judgments (EPA's CSEFH)
  - extent of generalization (as judged by author)

Figures

- **Summarize**
  - **exposure factor (linked to the table) for 3 different age ranges (a=birth to 1 month by days, b=birth to 3 years by month, and c=birth to 21 years by year)**
  - **an "x" under a specific age indicates that the study reported measurements for children at that age**
  - **a bar between endpoints of a range indicates that the study reported measurements between that range**

Body weight

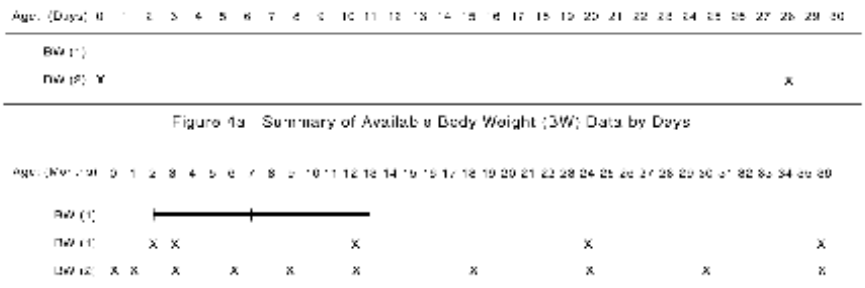


Figure 4a Summary of Available Body Weight (BW) Data by Days

Figure 4b Summary of Available Body Weight (BW) Data by Months

Figure 4c Summary of Available Body Weight (BW) Data by Years

X = Recorded at specific age

— = Recorded within age range

Skin surface area

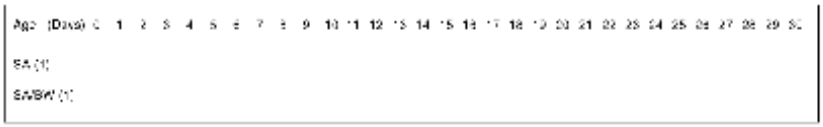


Figure 5a Summary of Available Surface Area (SA) Data by Days

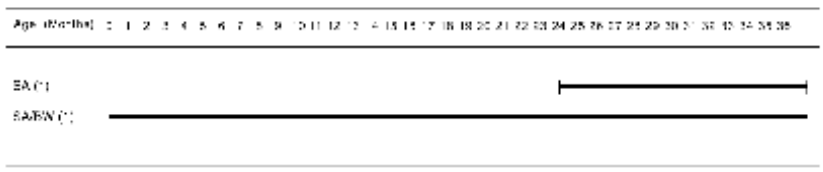


Figure 5b Summary of Available Surface Area (SA) Data by Months

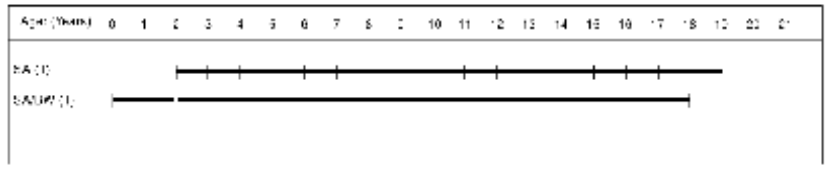


Figure 5c Summary of Available Surface Area (SA) Data by Years

= Reported adult age range

Food intake

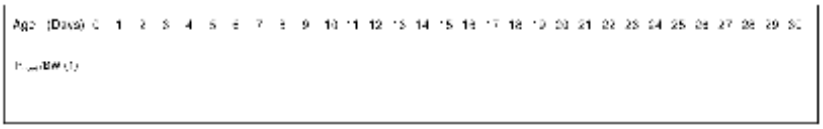


Figure 6a Summary of Available Ingestion Rate (IR) of Food Data by Days

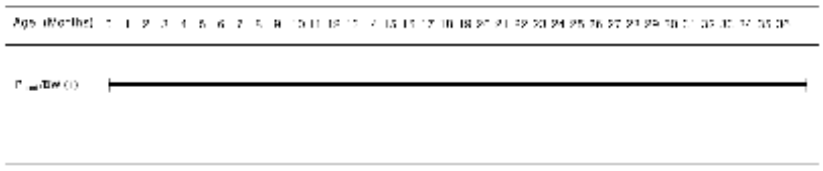


Figure 6b Summary of Available Ingestion Rate (IR) of Food Data by Months

Figure 6c Summary of Available Ingestion Rate (IR) of Food Data by Years

= Reported adult age range

Water consumption

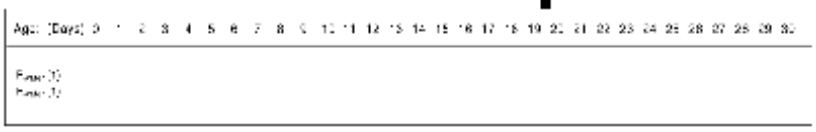


Figure 7a. Summary of Available Ingestion Rate (IR) of Water Data by Days

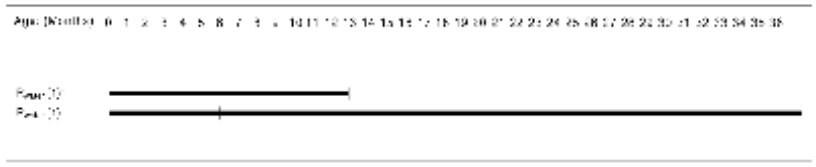


Figure 7b. Summary of Available Ingestion Rate (IR) of Water Data by Months

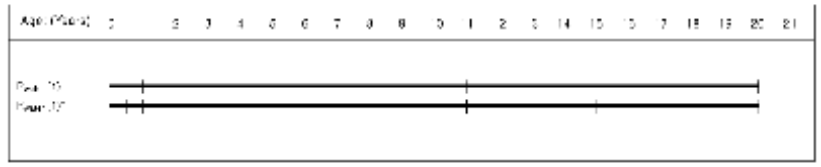


Figure 7c. Summary of Available Ingestion Rate (IR) of Water Data by Year

'Reported for R_{water} and $IR_{water/BW}$

= Reported within age range

Breast milk ingestion

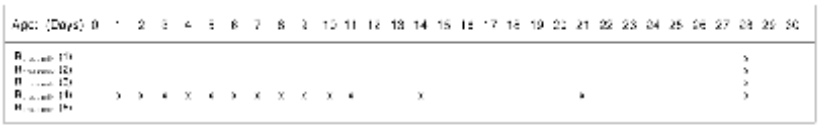


Figure 8a. Summary of Available Ingestion Rate (IR) of Breast Milk Data by Days

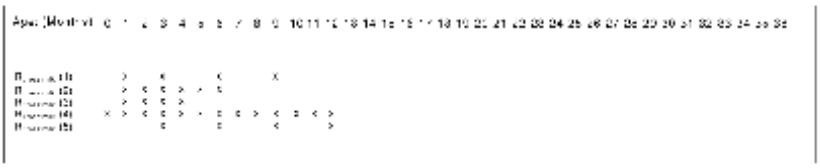


Figure 8b. Summary of Available Ingestion Rate (IR) of Breast Milk Data by Months

Figure 8c. Summary of Available Ingestion Rate (IR) of Breast Milk Data by Years

X = Reported associated age

Fish consumption

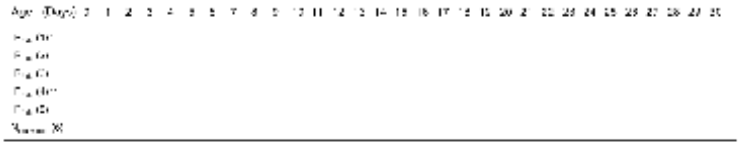


Figure 8a Summary of Available Ingestion Rate (IR) of Fish Consumption Data by Days

Figure 8b Summary of Available Ingestion Rate (IR) of Fish Consumption Data by Months

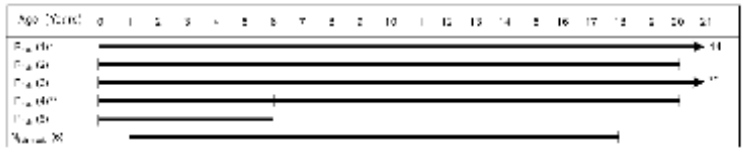


Figure 8c Summary of Available Ingestion Rate (IR) of Fish Consumption Data by Years

= Reported at this age range

Soil ingestion

Figure 10a Summary of Available Ingestion Rate (IR) of Soil Ingestion Data by Days

Figure 10b Summary of Available Ingestion Rate (IR) of Soil Ingestion Data by Months

Figure 10c Summary of Available Ingestion Rate (IR) of Soil Ingestion Data by Years

X = Reported at specific age

= Reported at this age range

Other non-dietary ingestion

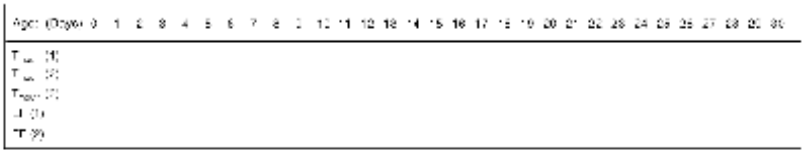


Figure 11a Summary of Available Other Non-Dietary Ingestion Data by Days

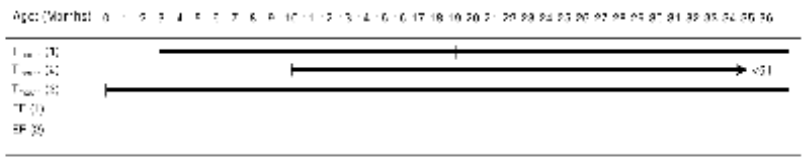


Figure 11b Summary of Available Other Non-Dietary Ingestion Data by Days

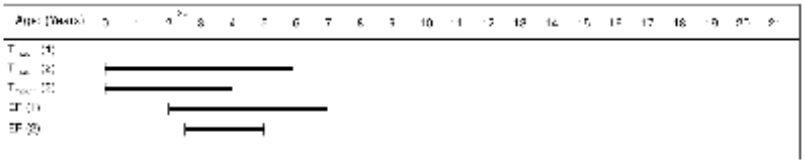


Figure 11c Summary of Available Other Non-Dietary Ingestion Data by Days

Inhalation

Figure 12a Summary of Available Inhalation Rate Data by Days

Figure 12b Summary of Available Inhalation Rate Data by Months

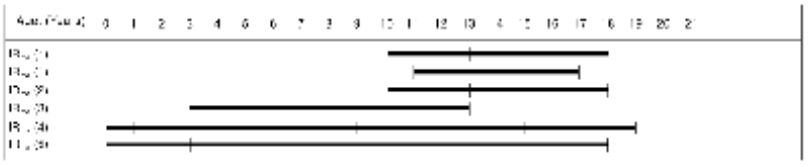


Figure 12c Summary of Available Inhalation Rate Data by Years

Dermal contact

Figure 13a. Summary of Available Dermal Contact Data by Days

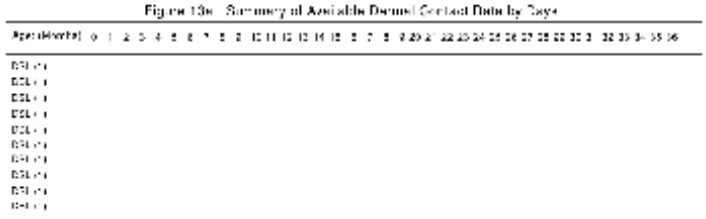


Figure 13b. Summary of Available Dermal Contact Data by Months

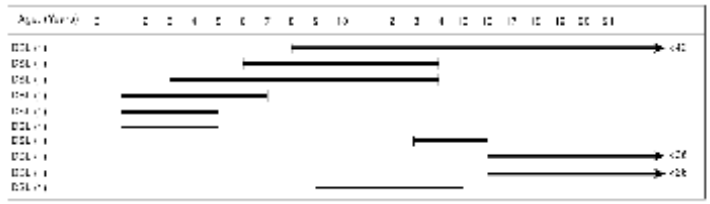


Figure 13c. Summary of Available Dermal Contact Data by Years

Time/activity patterns

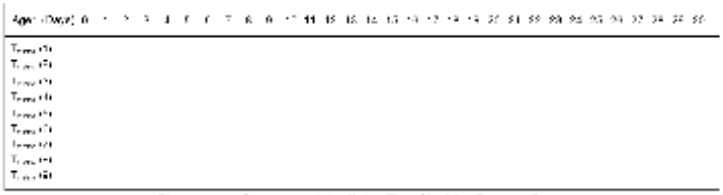


Figure 14a. Summary of Available Time/Activity Data by Days

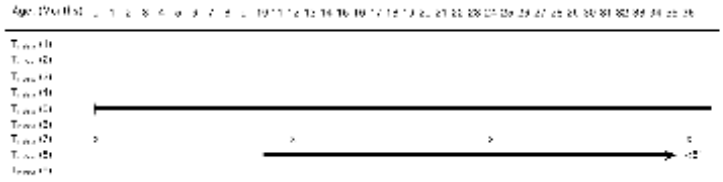


Figure 14b. Summary of Available Time/Activity Data by Months

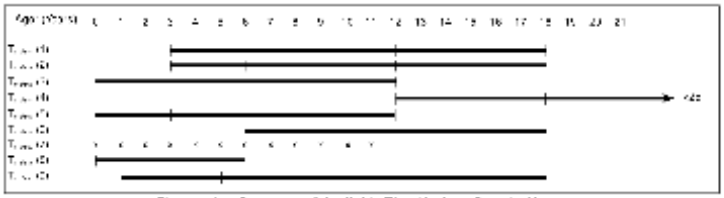


Figure 14c. Summary of Available Time/Activity Data by Years

Synthesis and observations

- **Lack of representative/available data for the individual, population, temporal and/or spatial scale of interest**
- **Know relatively more about easily observable anatomical exposure factors (weight) than behavioral not-easily observable factors (non-dietary consumption)**

Exposure factors reviewed and equations that use them

Factor	Quality	Extent of generalization	"X" Denotes Used in Equation Number 1	2	3	4	5	6	7
BW	H	H							X
SA	H	M							
SA/BW									
IR_{food}/BW	H/L	M					X		
IR_{water}	H	H					X		
IR_{water}/BW									
$IR_{human milk}$	M	L					X		
IR_{fish}	H/L	M					X		
IR_{fish}/BW									
$N_{fish meals}$	H/L	M							
IR_{soil}	M	L					X		
T_{mouth}		M/L							
$EF_{mouthing}$		M/L						X	
IR_{ms}	M	M	X						
DSL	L	L			X				
$T_{ms/ms}$	M	M	X	X					

H=high, M=medium, L=low, H/L=high for average/low for long-term and upper-percentiles
M/L= medium for average/low for long-term and upper-percentiles

Exposure factors in equations that did not occur in the review

Factor	"X" Denotes Used in Equation Number						
	1	2	3	4	5	6	7
DTC_{der}		X					
EF_{dermal}			X				
TE_{dermal}			X				
SA_{dermal}			X				
W_T				X			
$TE_{S/F}$				X			
$EF_{S/F}$				X			
$SA_{S/F}$				X			
$TE_{H/F}$				X			
$EF_{H/F}$				X			
$SA_{H/F}$				X			

Synthesis and observations

- **Lack of representative/available data for the individual, population, temporal and/or spatial scale of interest**
- **Know relatively more about easily observable anatomical exposure factors (weight) than behavioral not-easily observable factors (non-dietary consumption)**

Data available from birth to 30 days

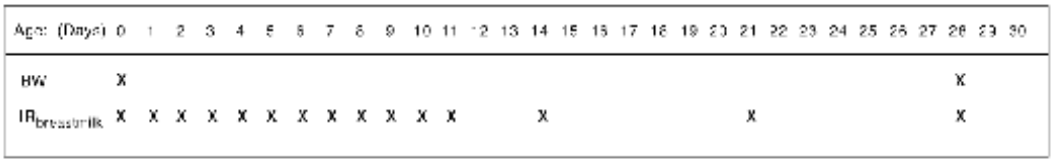


Figure 15. Data Available for Ages 0 to 30 Days for Exposure Factors Used in Equations 1, 2, 3, 5, and 6

X = Reported at specific age

Data available from birth to 3 years

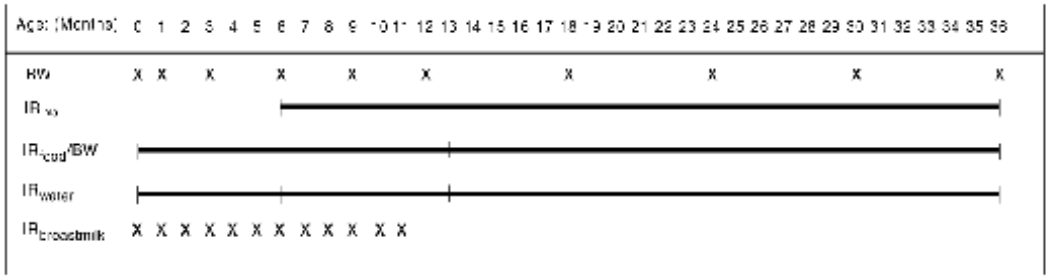


Figure 16. Data Available for Ages 0 to 36 Months for Exposure Factors Used in Equations 1, 2, 3, 5, and 6

X = Reported at specific age

= Reported within age range

Data available from birth to 21 years

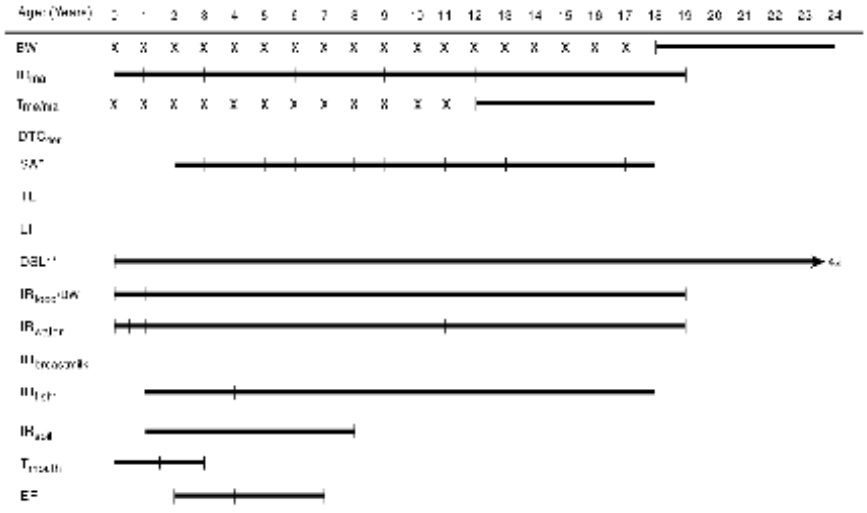


Figure 17. Data Available for Ages 0 to 24 Years for Exposure Factors Used in Equations 1, 2, 3, 5, and 6

* Total body surface area
** Limited data; depends on activity

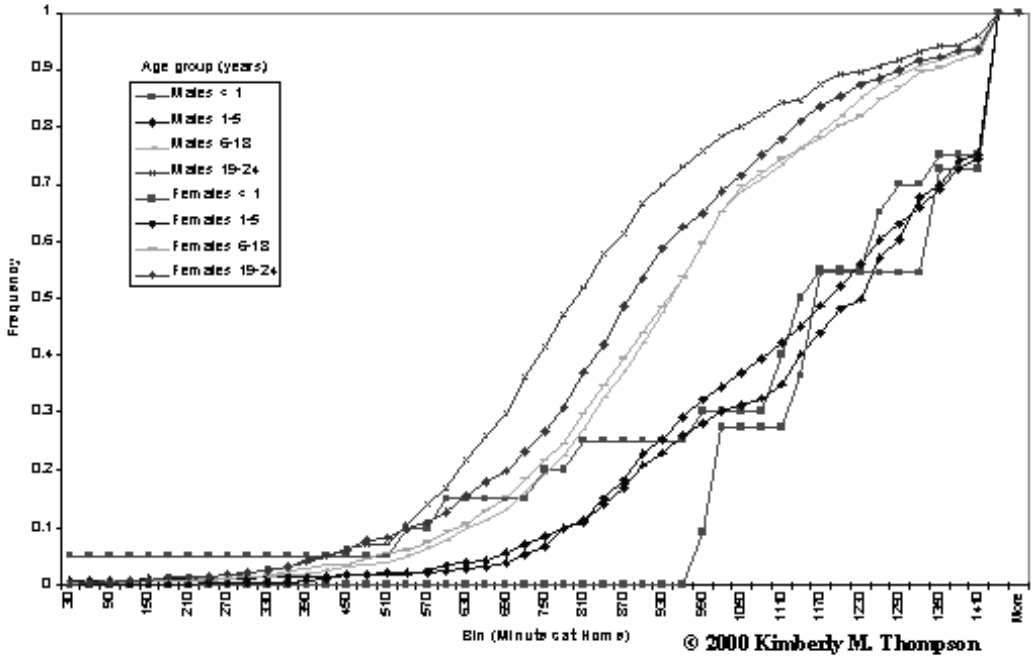
X = Records at specific age

— = Records within age range

Challenges

- **Significant data gaps for children's exposure factors**
  - **Breast milk consumption**
  - **Food handling practices**
  - **Fish intake rates**
  - **Soil intake**
  - **Soil adherence**
  - **Relationships between microactivities, macroactivities, and microenvironments**
  - **Correlation between exposure and growth**
- **Demands for aggregate exposure and cumulative risk assessment**

Time spent at home according to NHAPS data (Source: The LifeLine™ Project)



Children

Photograph courtesy of Children's Hospital, Boston, MA

Discussion issues

- What is the ideal approach to preparing childhood exposure assessments that reflect changes in children's behavior and anatomy over time?
- Is the existing exposure information adequate to implement the ideal approach, if not, what additional information is needed?
- What short term studies could be conducted to supply the necessary information or provide additional guidance?
- What longer term research may be needed to achieve the ideal approach to preparing childhood exposure assessments?

Behavioral question 1

- Does it make sense to think about childhood behavioral development as a series of discrete events which lend themselves to characterization using age group "bins?" Alternatively, should exposure assessors be thinking in terms of a continuum of behavioral development that contributes to an exposure function over all ages? If so, how would one pursue this later approach? When existing information is not adequate to construct an exposure function that reflects continuous behavioral development, a consistent, default approach using age group "bins" may be needed. In such cases, what "bins" serve as a reasonable surrogate for the continuous function? How would one characterize the uncertainties that arise from the use of such "bins?"

Behavioral question 2

- **What are the most important developmental milestones in children's behavior? For each milestone, what is the range of ages during which the behaviors are typically observed? How much variability is there among children with respect to the age of onset and the age of abandonment (if applicable) for these behaviors? Are the observed changes in behavior associated with these milestones likely to affect children's exposure to environmental contaminants? If so, how?**

Behavioral question 3

- **For those behaviors that are likely to have an important impact on exposure, is there existing exposure information that is representative of the behavior? Comment on the existing information including some indication of accessibility and quality. If such information is not available, is there exposure information that could serve as a reasonable surrogate? Comment on this information including some indication of accessibility and quality.**

Behavioral question 4

- For those behaviors that are represented in existing exposure information, compare the age groups identified for the developmental milestone in question 2 with the age groups in the existing exposure information. Were the age groups reported in the exposure information based on consideration of child developmental milestones, are they an artifact of study/survey design and/or responses, or are they based on the expert judgment of the study investigator?

Behavioral question 5

- For those behaviors where the age groups reported in the exposure information are not aligned with the age groups defined by the developmental milestone, what is the best approach to representing the appropriate age groups in an exposure assessment? The issue of alignment is compounded when attempting to aggregate exposure across multiple routes (e.g., dermal, inhalation, and ingestion). For example, exposure information may be available to characterize children's inhalation exposure at a particular stage of development while such information may be lacking to characterize exposure by the dermal and ingestion routes. Under these circumstances, what is the best approach to characterizing childhood aggregate exposure?

Anatomical question 1

- **Does it make sense to think about childhood anatomical development as a series of discrete events which lend themselves to characterization using age group "bins?" Alternatively, should exposure assessors be thinking in terms of a continuum of anatomical development that contributes to an exposure function over all ages? If so, how would one pursue this later approach? When existing information is not adequate to construct an exposure function that reflects continuous anatomical development, a consistent, default approach using age group "bins" may be needed. In such cases, what "bins" serve as a reasonable surrogate for the continuous function? How would one characterize the uncertainties that arise from the use of such "bins?"**

Anatomical question 2

- **What are the most important developmental milestones for anatomical changes related to physical growth in children? For each milestone, what is the range of ages during which the characteristics are typically observed? How much variability is there among children with respect to the age of onset for the characteristics ? Are the observed characteristics associated with these milestones likely to affect children's exposure to environmental contaminants? If so, how?**

Anatomical question 3

- **For those anatomical characteristics that are likely to have an important impact on exposure, is there existing exposure information that is representative of the characteristics? Comment on the existing information including some indication of accessibility and quality. If such information is not available, is there exposure information that could serve as a reasonable surrogate? Comment on this information including some indication of accessibility and quality.**

Anatomical question 4

- **For those characteristics that are represented in existing exposure information, compare the age groups identified for the developmental milestone in question 2 with the age groups in the existing exposure information. Were the age groups reported in the exposure information based on consideration of child developmental milestones, are they an artifact of study/survey design and/or responses, or are they based on the expert judgment of the study investigator?**

Anatomical question 5

- **For those behaviors where the age groups reported in the exposure information are not aligned with the age groups defined by the developmental milestone, what is the best approach to representing the appropriate age groups in an exposure assessment? The issue of alignment is compounded when attempting to aggregate exposure across multiple routes (e.g., dermal, inhalation, and ingestion). For example, exposure information may be available to characterize children's inhalation exposure at a particular stage of development while such information may be lacking to characterize exposure by the dermal and ingestion routes. Under these circumstances, what is the best approach to characterizing childhood aggregate exposure?**

James Walker

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

Empirical Evidence of Multiple Critical Developmental Periods in Children

Dr. James T. Walker
Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment-Wash. Office

Introduction

- It has been hypothesized that developing children undergoing rapid growth, during exposures to xenobiotics, are highly susceptibility to adverse health effects.
- So, I initiated a program in NCEA to model and characterize growth in children, so that I could determine when the periods of rapid growth occurred.
- I set out to develop empirical mathematical models for describing the postnatal growth and development of normal human organs and tissues.
- If one were to define a "critical developmental period" as the age when an organ reaches a peak growth velocity, then there is some empirical evidence that children have multiple critical growth periods as they develop from birth to maturity.

Modeling Serial Height Data from the Fels Longitudinal Growth Study

- Recently, my wife and I introduced and published the WWHLA[(1)] growth model. This is empirical model that we used for describing serial height data of 80 children (40 males and 40 females), who participated in the Fels Longitudinal Growth Study[(2)].
- These were white children from the US.
- As is shown in Slides #1, 2, 3, and 4, the model fitted their growth data extremely well.
- Six growth spurts were observed during different developmental periods in these children.

Fels Longitudinal Growth Study

(Cont'd)

- The spurts were named according to the period when they reached their peak height velocity (PHV): neonatal (NS), infantile (IS), early-childhood (ES), middle-childhood (MS), late-childhood (pre-pubertal) (LS), and pubertal (PS) (See Slide #5).
- The ages at PHV for the different spurts varied, depended on a child's gender and whether they were an early, average, or late developer.
- The mean ages at PHV and their standard deviations for the 80 Fels children are shown in Slide #6.
- These ages represent developmental milestones for height growth in a typical Fels child.

Modeling Serial Height Data from the First Zurich Longitudinal Growth Study

- We decided to validate the model by fitting it to serial height data of 8 children (4 males and 4 females), who were randomly selected from individuals from the First Zurich Longitudinal Growth Study.
- These children were from Zurich, Switzerland.
- Slides #7, and 8 show how well the model fitted these data.
- Distinct growth spurts are evident in the growth curves of the Zurich children.

First Zurich Longitudinal Growth Study
(Cont'd)

- As an example, Slide #9 shows the growth spurts that were identified in the height curve of a female participant from the Zurich Study.
- Like the Fels children, the ages at PHV varied for the these children, depending on their gender and whether they were an early, average, or late developer.
- The mean ages at PHV and their standard errors for the 4 males and 4 females are shown in Slide #10.
- These ages are almost the same as those that were found in the Fels study.

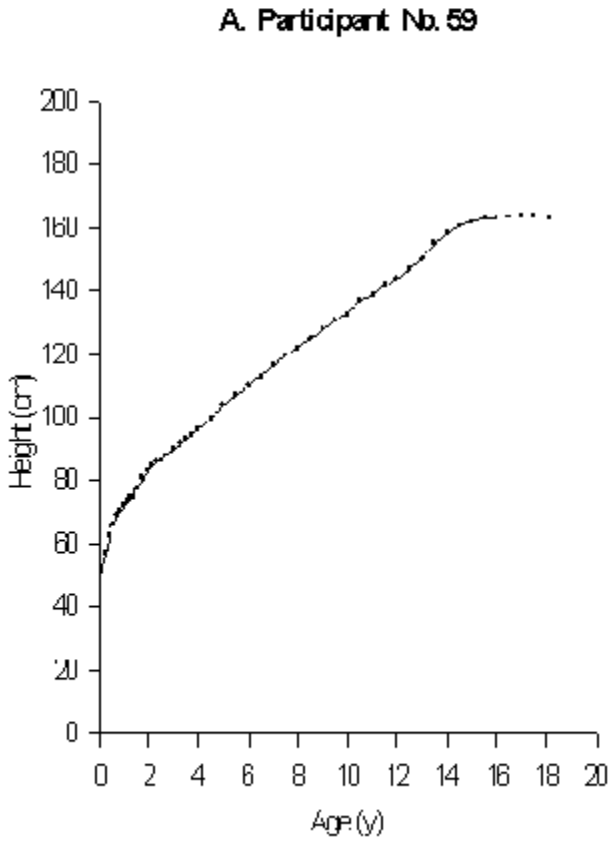
Modeling Kidney and Liver Weight Growth Data

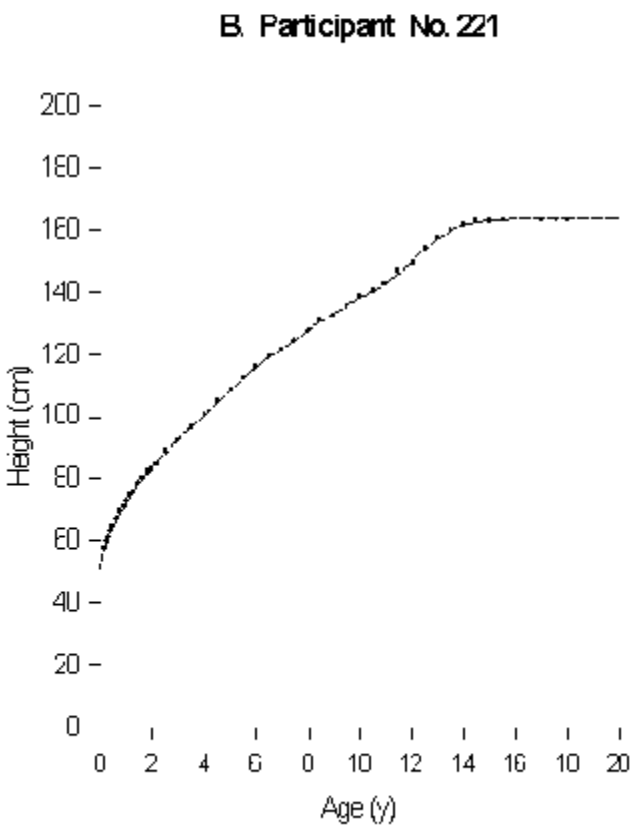
- There is also evidence that other human organs undergo multiple growth spurts.
- Japanese organ weight data from autopsies were evaluated using a modified form of the WWHLA growth growth.
- Slide #11 and 12 show that the model identified several growth spurts, as these organs matured from birth to maturity.

Conclusions

- This presentation has demonstrated that children have at least six critical periods of height growth as they develop.
- Soft organs, such as the kidneys and liver, also experience multiple postnatal growth spurts.
- These critical periods of growth represent developmental milestones that should be considered in assessing risks to children.
- It is during these rapid periods of growth when the total doses to organs and tissues in children are expected to be the highest (See Slides #13 and 14)

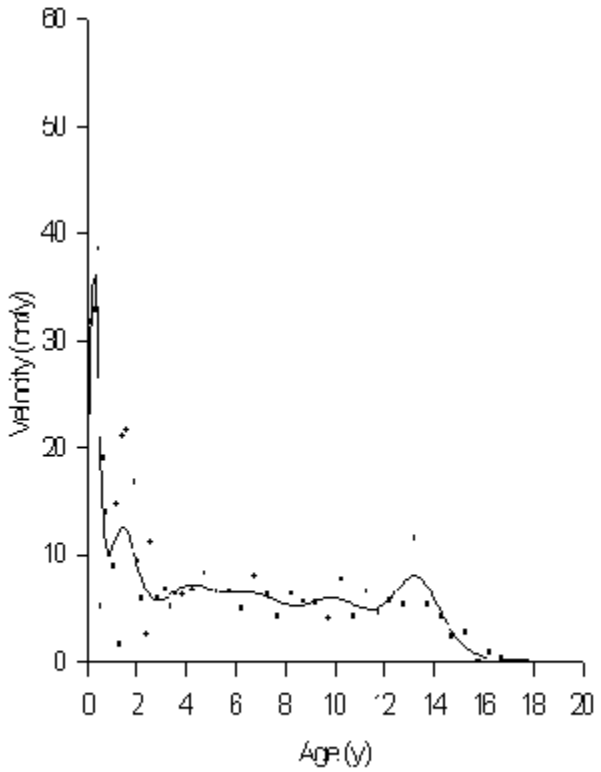
Height Displacement Curves of Two Females from the Fels Longitudinal Growth Study (dots=observed;line=predicted)--Slide #1



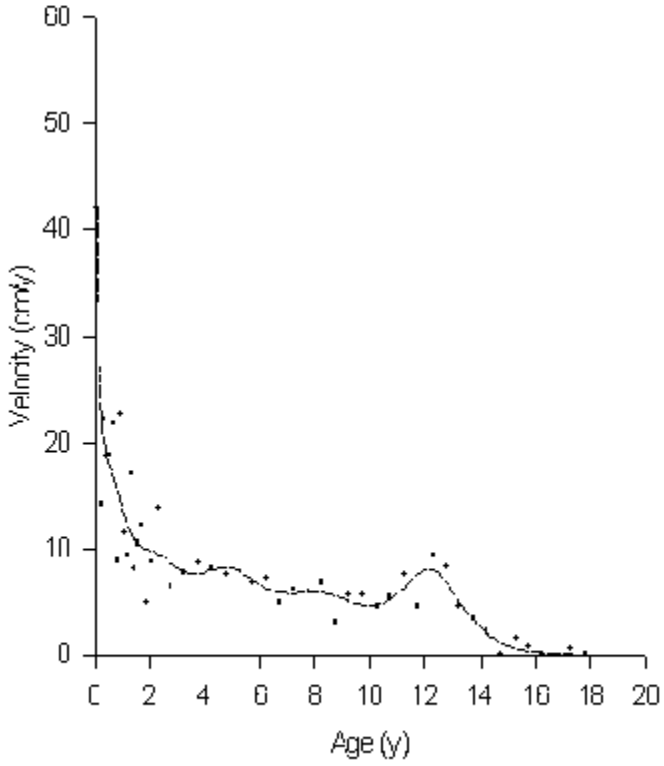


Height Velocity Curves for the Two Females found in Slide #1 (dots=observed;line=predicted)--Slide #2

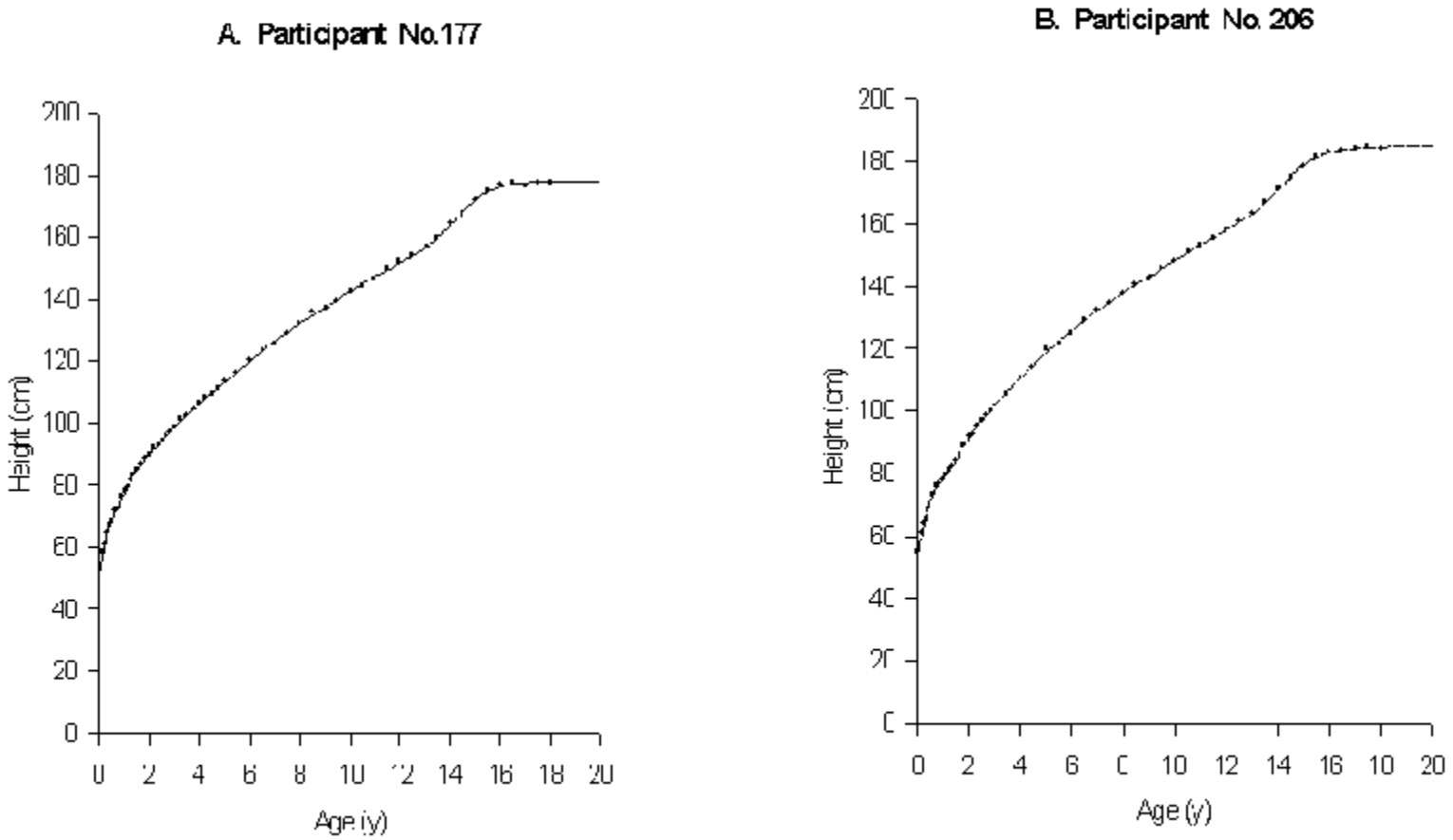
A Participant No. 59



B. Participant No. 221

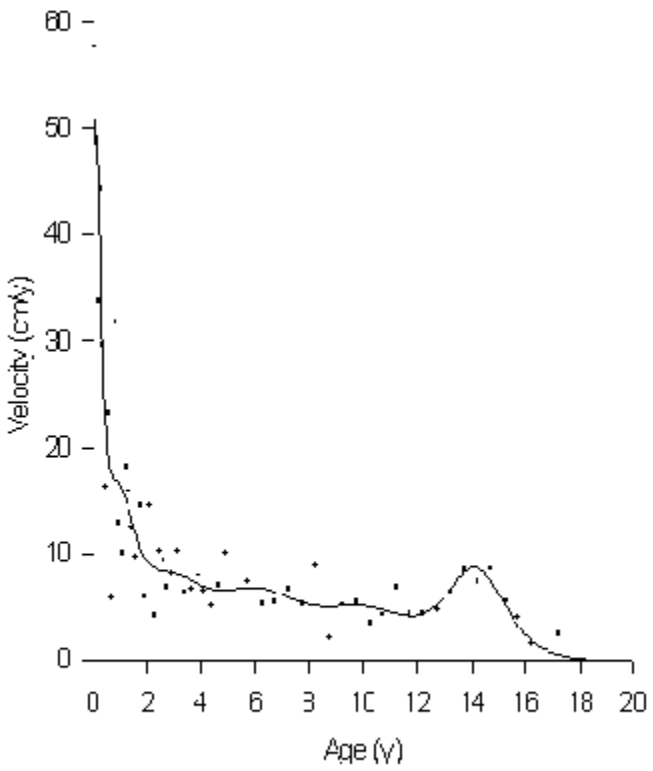


Height Displacement Curves of Two Males from the Fels Longitudinal Growth Study (dots=observed;line=predicted)--Slide #3

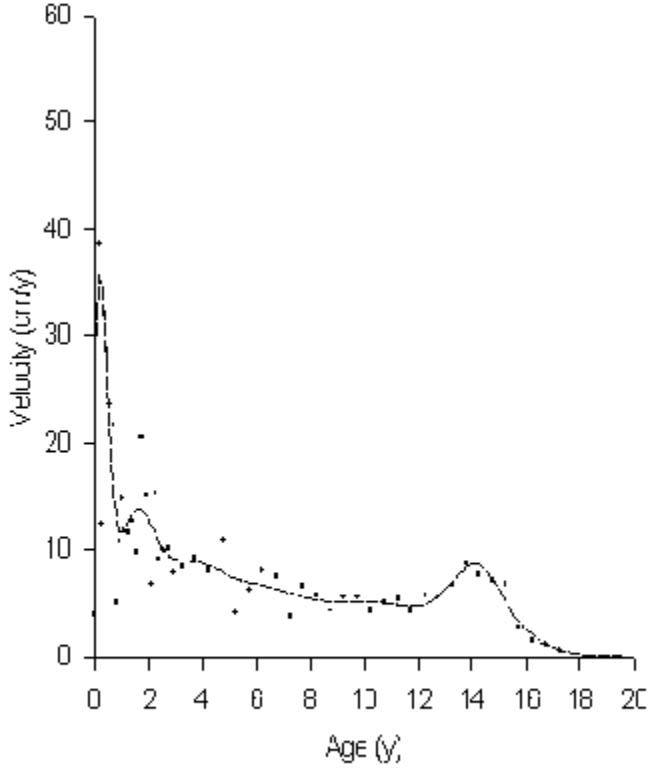


Height Velocity Curves for the Two Males found in Slide #3 (dots=observed;line=predicted)--Slide #4

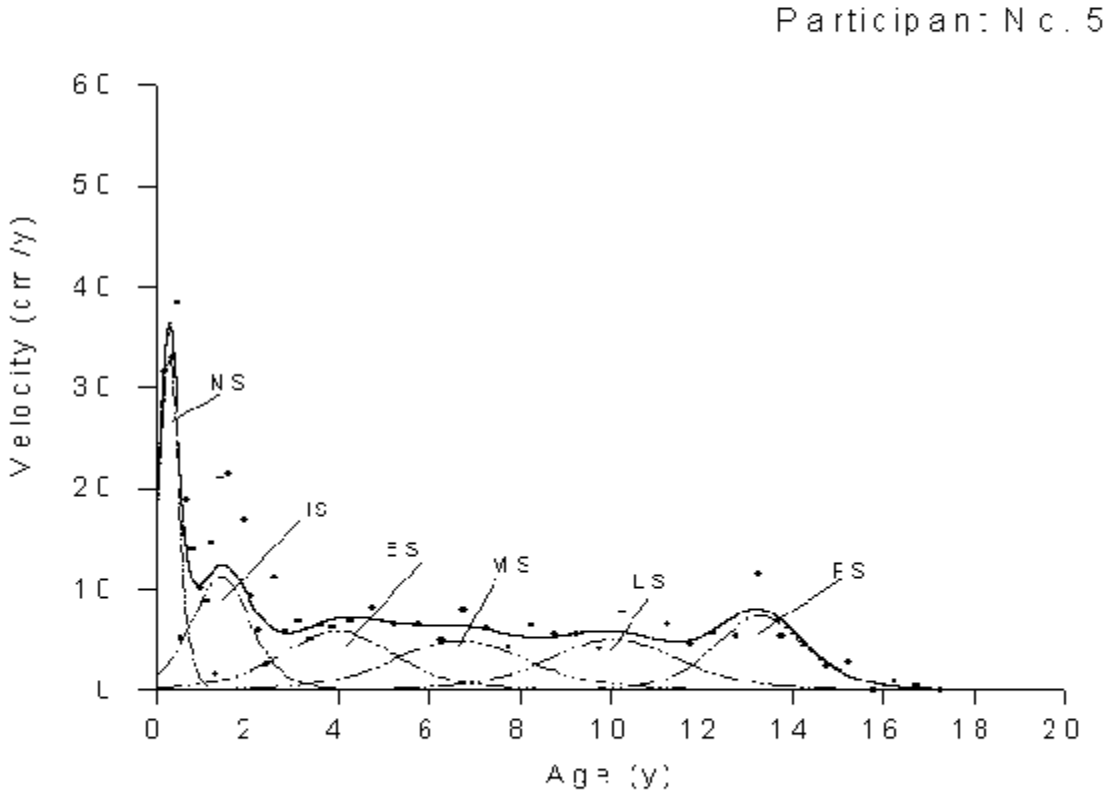
A. Participant No. 177



A. Participant No. 206



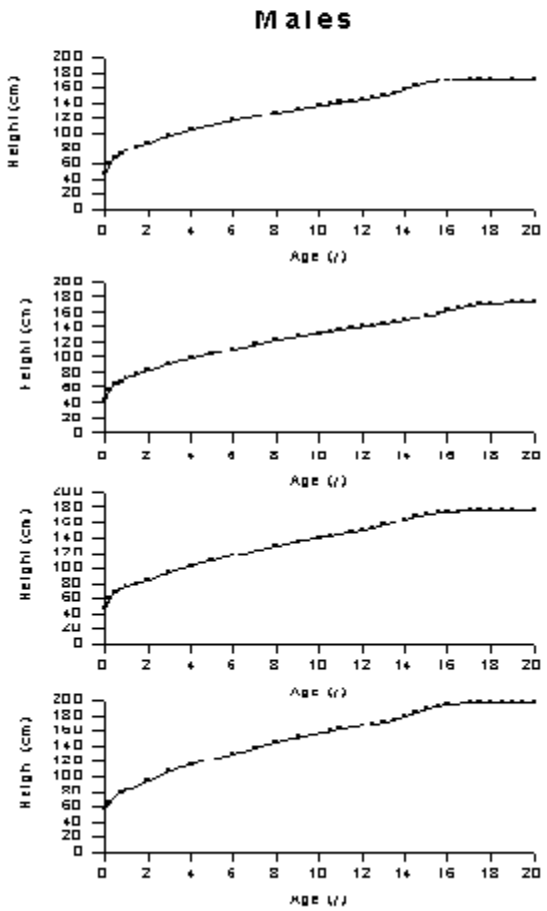
Individual Growth Spurts Identified from the Growth Curve of Fels Participant No. 59--Slide #5

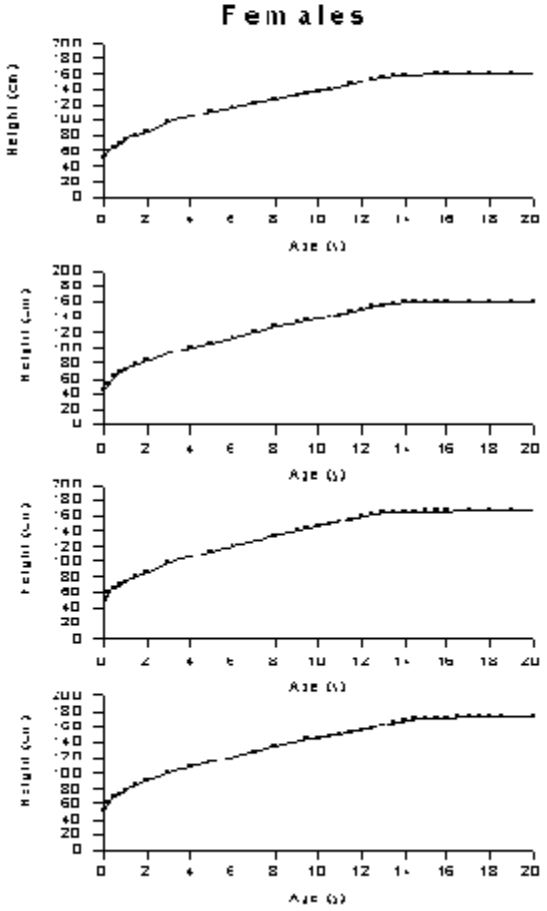


Critical Developmental Periods found from Fitting Growth Curves of 80 Fels Children--Slide #6

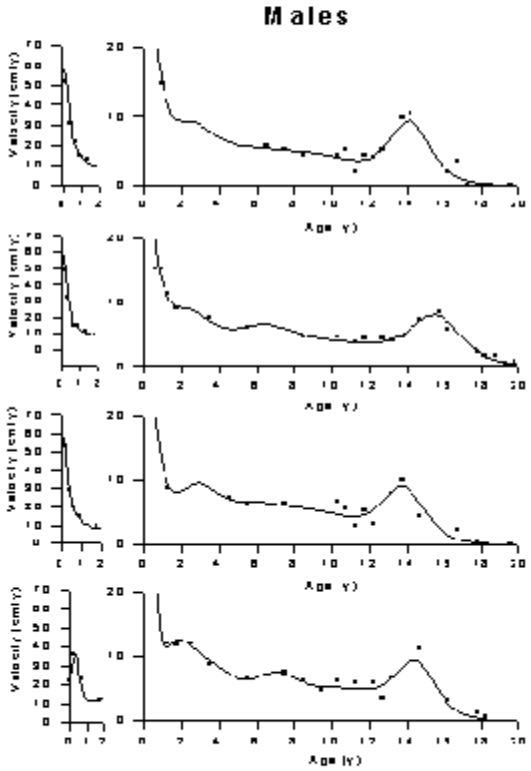
	Females		Males	
Critical Periods	Mean Age at PHV (y)	Std. Dev.	Mean Age at PHV (y)	Std. Dev
Neonatal	0.0650	0.1132	0.0535	0.0853
Infantile	0.9209	0.2922	0.8939	0.3249
Early-Childhood	2.7606	0.3688	2.5981	0.6098
Middle-Childhood	5.7744	0.8116	6.0456	0.5703
Late-Childhood	8.6577	1.0709	10.288	0.6710
Pubertal	12.048	0.9697	14.007	0.8443

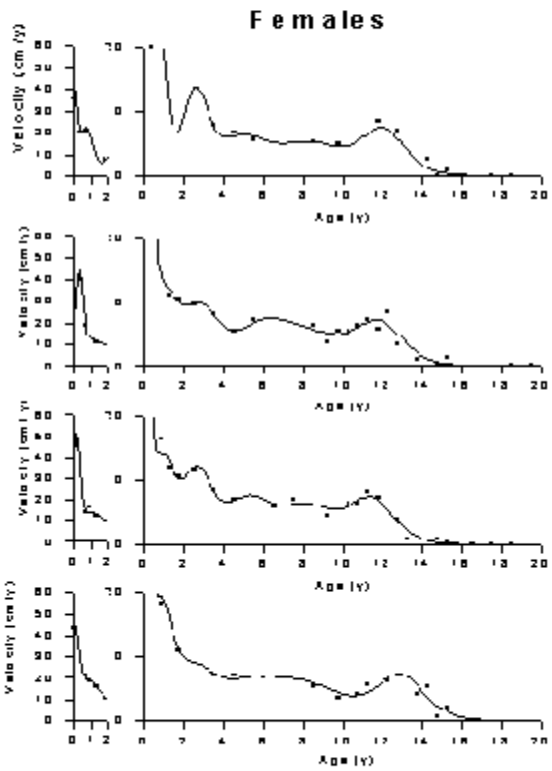
Height Displacement Curves of Eight Zurich Children--Slide #7



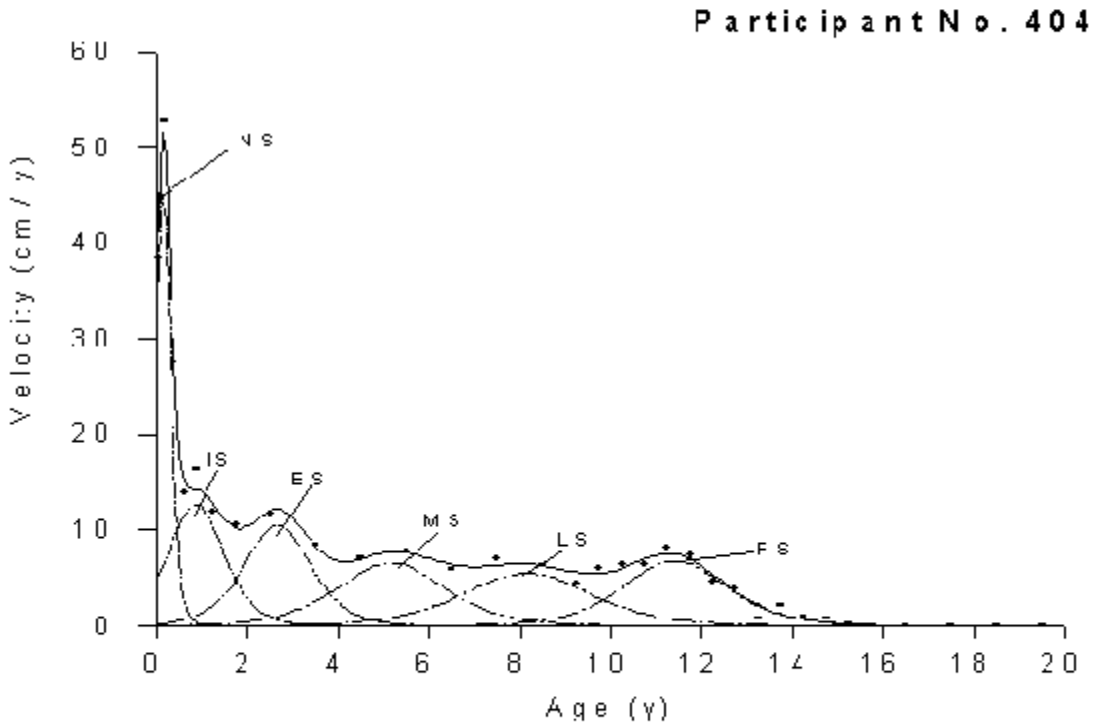


Height Velocity Curves of Eight Zurich Children--Slide #8





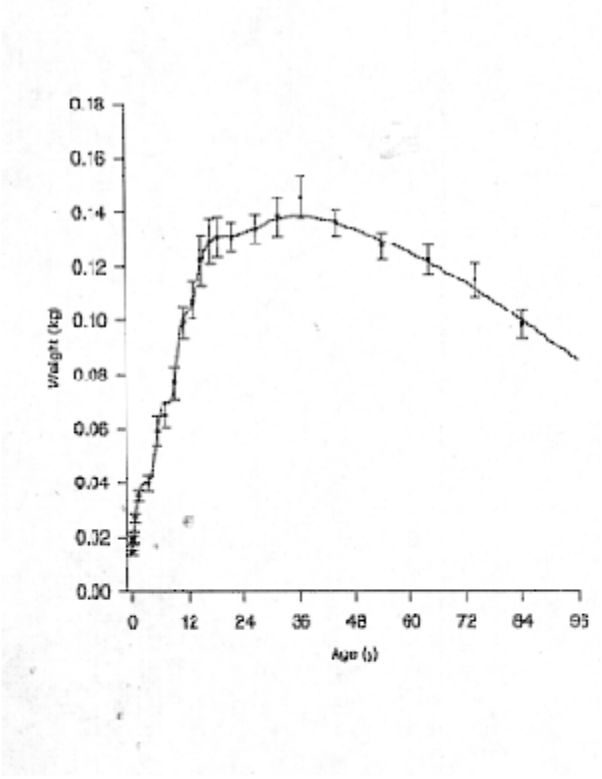
Individual Growth Spurts Identified from the Growth Curve of Zurich Participant No. 404--Slide #9

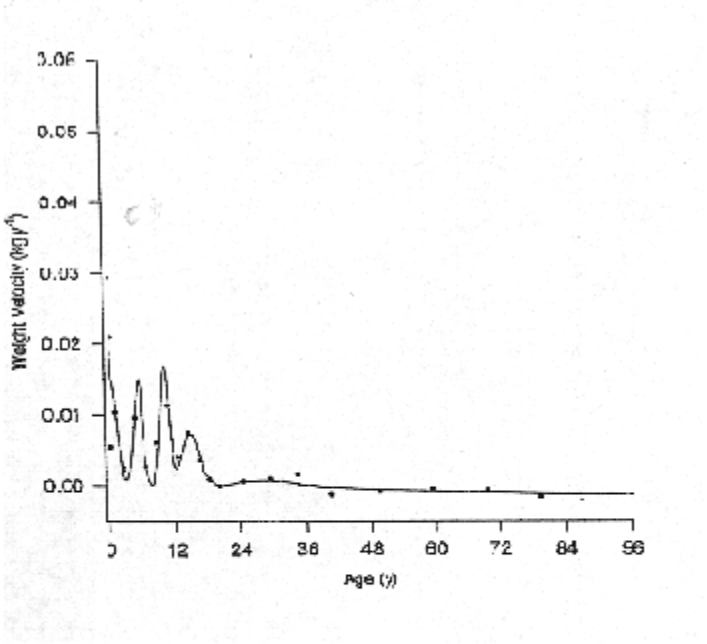


Critical Developmental Periods from Fitting Growth Curves of Eight Zurich Children--Slide #10

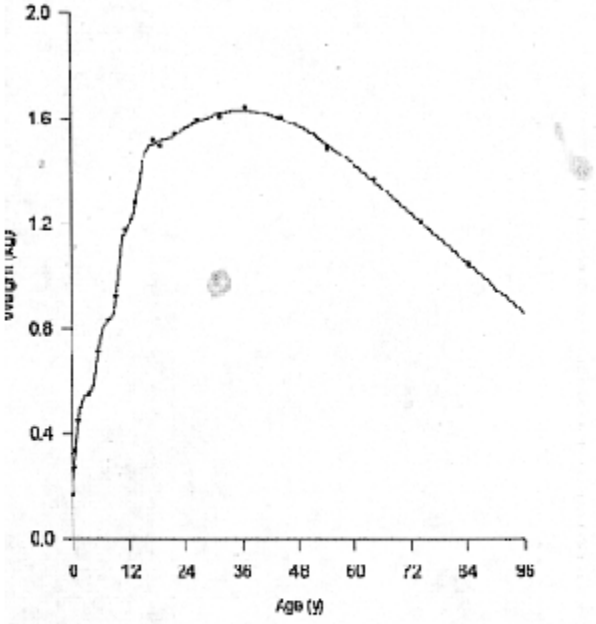
	Females		Males	
Critical Periods	Mean Age at PHV (y)	Std. Error	Mean Age at PHV (y)	Std. Error
Neonatal	0.0949	0.0662	0.0817	0.0621
Infantile	0.8210	0.0454	0.6680	0.3251
Early-Childhood	2.6025	0.0849	2.7250	0.2723
Middle-Childhood	5.2837	0.2241	6.1198	0.3453
Late-Childhood	8.2145	0.0609	10.127	0.3571
Pubertal	12.027	0.3075	14.472	0.3691

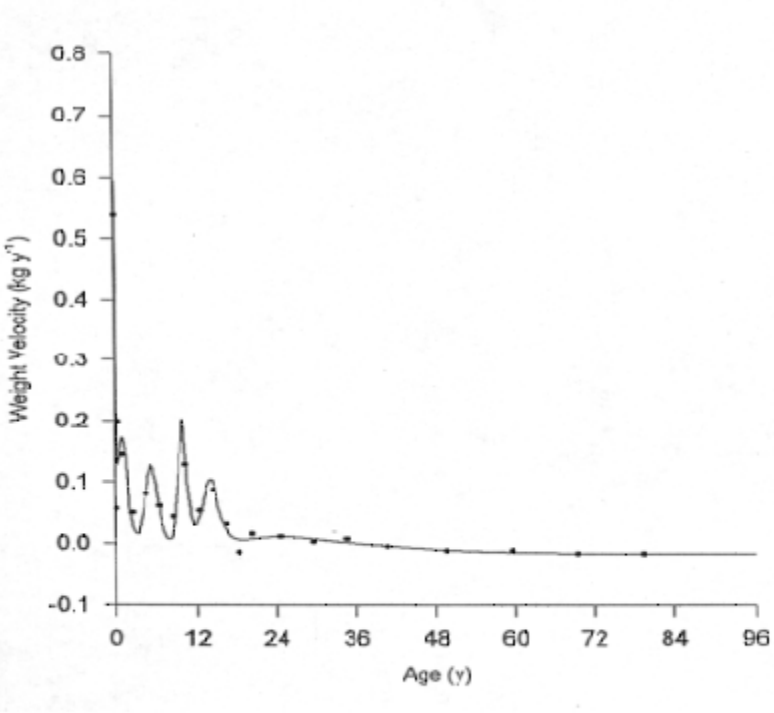
Growth and Aging of the Human Kidney
Slide #11





Growth and Aging of the Human Liver
Slide #12





Slide #13

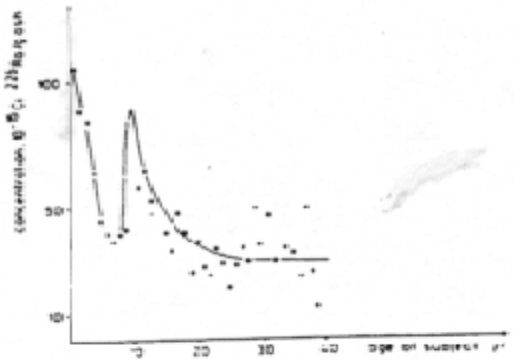


Figure 1. The radium concentration in bone ash as a function of age.

Slide #14

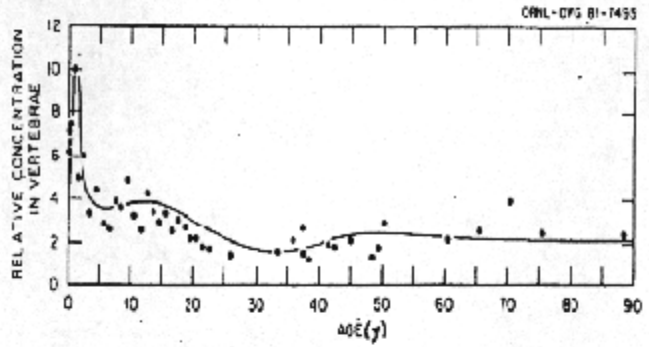


Figure 2. Differences with age in the strontium-90 concentrations in vertebrae for a New York population in 1964, a year with relatively high environmental levels.

References

Ref #1. - **Walker,J.T. and Walker, O.A. "A Multiphasic Approach for Describing Serial Height Data of Fels Children: A Hexaphasic-Logistic-Additive Growth Model", In Press.**

Ref #2.-**Ramsay, J.O., Bock, R.D. & Gasser ,T. 1995. Comparison of height acceleration curves in the Fels, Zurich, and Berkeley growth data.** *Ann. Hum. Biol.*, **22(5), 413-426.**

Ref#3.-**Falkner, F., 1960, Child Development. An International Method of Study. Modern Problems in Pediatircs: (Basel:Karger**