Bridging Components Along the Exposure-Dose-Response Continuum

Exposure Assessment Barriers and Bridges

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Topics

- Barriers
  - Barriers in current toxicological models
  - Barriers in exposure assessment
  - Institutional/financial/feasibility barriers
- Bridges
  - Computational toxicology
  - New exposure models
  - The exposure-PBPK Linkage
  - The role of the person in PRA
  - Bridges to Source and Ecological Modeling

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Barriers

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Toxicology and Variability and Uncertainty

- Historically regulatory models of toxicology provided a limited framework for quantitatively modeling uncertainty and variability in humans
  - Animal models
  - Safety/uncertainty factors

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Animal Models

- Animal models can tell us much about mechanism of action and the doses at which effects occur in the animal model
- They tell us little about how the probability of a response varies with the characteristics of the individual

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Uncertainty Factors

- What do they mean? How do they reflect:
  - Inter individual variability in humans?
  - Inter chemical variation in the ratio of the test animal to humans?
  - Uncertainty due to limitations in the toxicological data base?
  - Policy?
- Can they be objectively defined?
- Do the values for these factors have variability? uncertainty?
- Can they be quantitatively modeled in a PRA?

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PRA and Toxicology

….this has let to the ironic situation where the application of detailed, rigorous, probabilistic methods for uncertainty in an exposure assessment, whose results are then linked to a single point representation of dose-response, which is likely ignoring the lion's share of the overall uncertainty in the final risk estimate.

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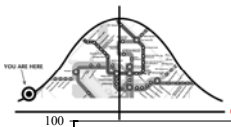
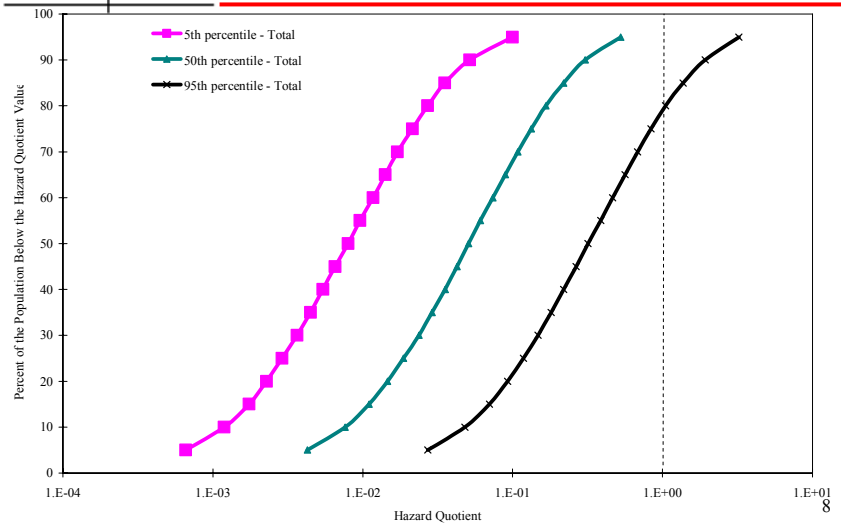


Clinch River Angler



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Barriers and Exposure Assessment

- While toxicity is universal
  - A chemical causes the same effect independent of when and who is testing
- Exposure is local
  - Exposure is dependent on human behavior there for exposure varies with the community

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A Divided Discipline

- The field of exposure assessment is a collection of independent communities: Health Physics, Industrial Hygiene, Consumer Products, Environmental, Food/Pesticides, and Drugs
- Each community has its own regulatory framework, policies, and traditions
- Each community is following an independent path in developing probabilistic tools

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Divisions are a Barrier

- Each community has to develop policies and procedures for PRA this slows and confuses the status of PRA
  - Not Invented Here
- The resources in any one community may not be sufficient to support the studies required by PRA again slowing the process of adopting this tool

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PRA and Economics

- Probabilistic Exposure Assessments are more expensive to perform than traditional approaches
- Probabilistic Exposure Assessments require detailed information on the variation and uncertainty in the factors that influence exposure
- The collection of such data are resource intensive

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Exposure Surveys

- Surveys of exposure related information can easily exceed several millions of dollars
  - Large numbers of participants required to evaluate the tails
  - Long term studies increase costs
  - Surveys must address heterogeneous populations

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Populations Differ

- Separate exposure assessments are required for each unique population
- Data from one population may not be applicable to another
  - Continuing Survey of Food Intakes by Individuals (CSFII) does not include Alaska and Hawaii
  - Studies of Tribal communities in Alaska cannot be predicted from CSFII
- Populations change over time and must be resurveyed

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Technical Challenges

- Surveys of longitudinal patterns of behaviors are difficult to perform.
  - Few individuals will participate in surveys for periods longer than a few days.
- People are not always conscious of their exposure related behaviors
  - How many times did you touch a counter top today
  - How many times did you place a non food object (pen) in your mouth?
- Parents cannot accurately report many behaviors that are critical for estimating children's exposures
  - Frequency of hand to mouth events
  - Frequency of contact with pets
  - Soil ingestion.
- Solutions
  - Videotaping of children
  - Diaper studies for soil ingestions
  - Automatic tracking of an individual's location in a home
  - Use of internet-based survey tools.

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Exposure Information has Financial Value

- Many of the factors that influence exposure are regarded as confidential business information
  - Who buys what, when, and how much is marketing data
  - Composition and characteristics are technical information
- Once a survey is performed it takes on financial value
  - Charging for use of exposure related data
  - Keeping raw data confidential
- As a result exposure information is often tightly controlled

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Bridges

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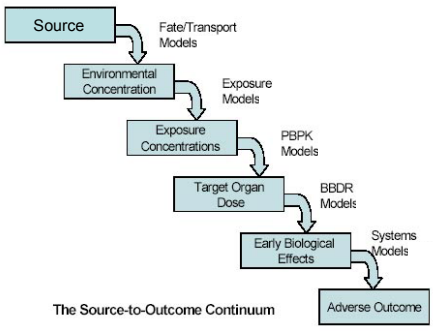
Computational Toxicology

- The traditional system of regulatory toxicology is being replaced with a new system of linked models
  - Quantitative
  - Objective
- These models are amenable to probabilistic techniques for variation and uncertainty



The Source-to-Outcome Continuum

Adapted from EPA, 2005

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New Exposure Models

- In the early 1990s Monte Carlo made a name for itself as an alternative to a “worst case” exposure assessments
- In the last 10 year a new concept of Monte Carlo exposure assessment as been developed
- Simulation of human behaviors over time

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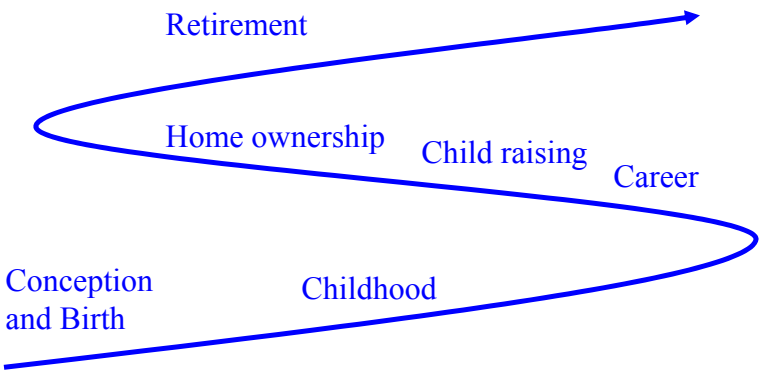
Modeling A Person’s Life



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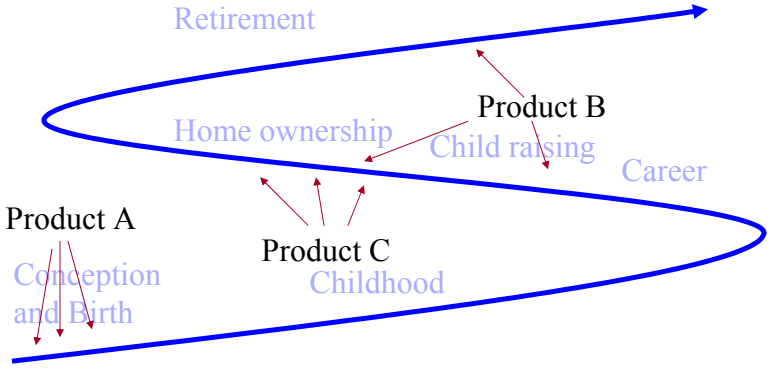
Exposures to One Chemical in Multiple Products



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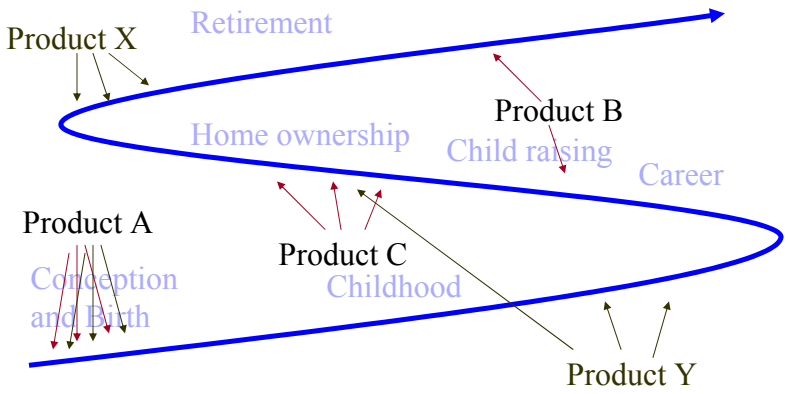
Two Chemicals in Multiple Products



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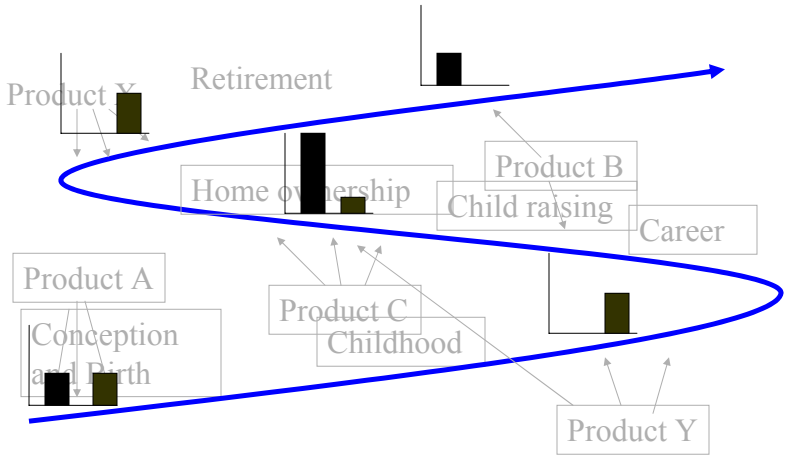
Two Chemicals in Multiple Products



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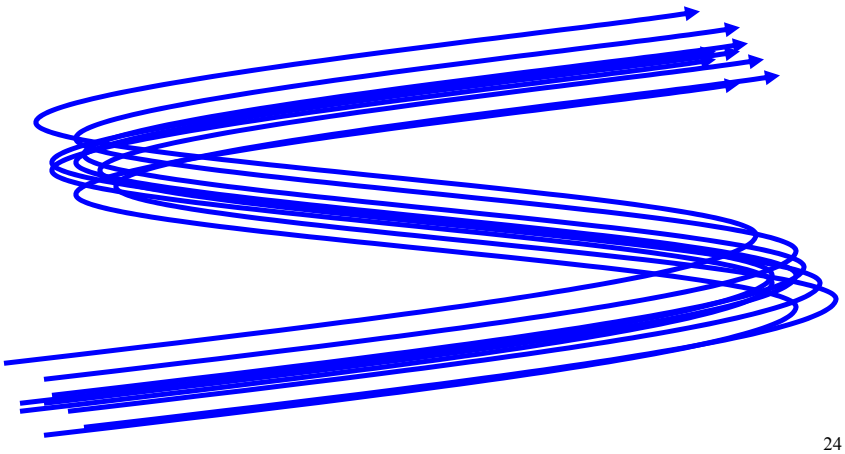
Modeling an Exposed Population



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Examples

- A number of software programs have been built
  - LifeLine
  - SHEDS
  - CARES
  - APEX

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Person Oriented Modeling

- All of the models are characterized by a focus on the person
- The characteristic's of the person(s) being modeled defines:
  - The potential for an exposure to occur or not occur
  - The magnitude of the exposure
  - The temporal pattern of the exposure
  - The magnitude of the dose

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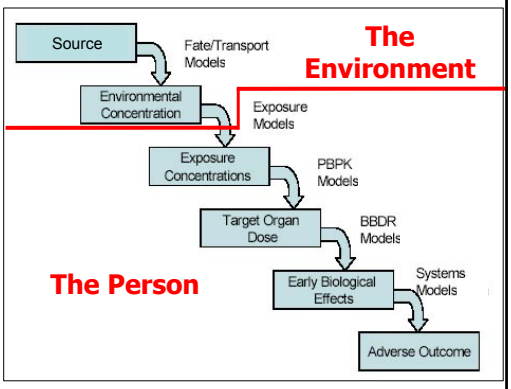
World to Person transition

- The scope of models in the "Source to Outcome Continuum" changes from the environment to the body at exposure assessment
- The definition of the person established in the exposure assessment provides the framework for PBPK, BBDR, and System Modeling



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Defining A Coherent Person

- The characteristics of a person influence:
  - Exposure assessment, PBPK, BBDR, System Modeling
- The characteristics must be kept consistent through out the various models of the source to outcome continuum.
  - Same values for each model
  - Internally consistent values

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Bridging Exposure-PBPK Modeling

- PBPK models require three types of data
  - Route specific exposures over time (exposure per time step)
  - Physiological characteristics of the person
  - Compound-specific data on the absorption, distribution, metabolism, and excretion kinetics of the individual substances and how they vary across individuals in the population of interest

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Exposure Data from POM

- POM provides a estimate of exposure for each time step of the exposure history

Table 3a. Time Dependent Data (Part 1)

Time Step		Measure of Inhalation Exposure (mg)	Measure of Oral Exposure (mg)	Concentration in Shower Water (mg/l)	Measure of Dermal Exposure (mg)	Area of Dermal Exposure (cm2)
Begin. Time	End. Time					
0:00	0:10					
0:10	0:20					
23:50	24:00:00					

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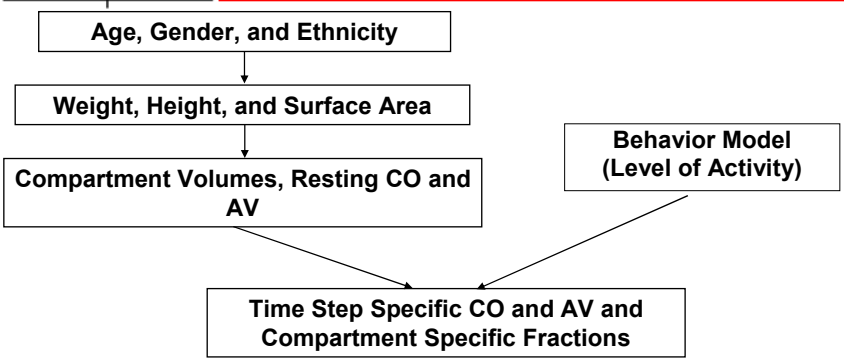
Coherent Physiology



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Defining Physiology

- Total well perfused tissues
- Red marrow
- Lungs (tissue volume)
- Brain
- Kidneys
- Liver
- Pancreas
- Thyroid
- Spleen
- GI organs (total tissue volume for stomach and small and large intestines)
- Blood
- Plasma
- Blood cells
- Total poorly perfused tissues
- Dermis
- Epidermis
- Skeletal muscle
- Heart (Tissue volume)
- Tongue
- Total fatty tissues
- Adipose issue
- Yellow marrow
- Bone tissue

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Defining the Physiology

Table 2. Time Independent Data								
Demographic Information				Volumes of Selected Compartments of PBPK/PD Model				
Age	Gender	Race	Ethnicity	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5

Table 3b. Time Dependent Data (Part 2)								
Time Step				Fraction of Cardiac Output for Each Compartment				
Begin. Time	End. Time	Cardiac Output	Alveolar Ventilation Rate	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5
0:00	0:10							
0:10	0:20							
23:50	24:00							

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Interface Issues

	EXPOSURE MODEL	PBPK/PD MODEL
Overlap	Includes algorithms for dermal absorption Calculates absorbed dose	Includes algorithms for dermal absorption Calculates absorbed dose
Gap	Does not include algorithms for dermal absorption Calculates exposure on skin surface.	Does not include algorithms for dermal absorption
Seamless	Includes algorithms for dermal absorption Calculates absorbed dose	Does not include algorithms for dermal absorption

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BBDR and Systems Modeling

- Defining the person provides a basis for modeling:
  - Genetic variability in kinetic factors or metabolism
  - The capacity of the individual as a function of
    - Behaviors: Smoking, dieting, or exercise
    - Health Status: Gravidity or nursing
  - Occurrence of transient effects such as illness

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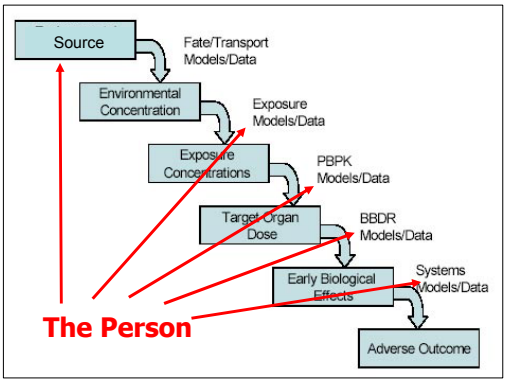
Modeling Source Terms

- In many instances the behavior of individuals influences the source of exposure
- Thus the definition of the person affects the source as well



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Bridges to Ecological

- Defining the person and creating longitudinal models of exposure also facilitates building bridges to ecological modeling
- The POM approach has been used to evaluate risks to other species.
- Creation of a temporal/spatial framework for a population of individuals will also allow a concurrent assessment of populations of other species

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Summary

- The field of probabilistic exposure assessment is has made considerable advances over the last 10 years
- Probabilistic exposure models are able to support PBPK modeling
- Defining the person, their characteristics, behaviors, and environments is essential to a successful PRA

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