Improving the Reliability of Exposure Tracking by Merging Exposure Models with Biomonitoring Data

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Overview

- **Public health tracking and biomarkers**
  - **Elements of exposure tracking**
  - **Biomarkers and biomonitoring**
  - **Value of biomarkers for exposure tracking**
- **Exposure models**
- **Case studies**
  - **Persistent compounds (radiation, dioxin)**
  - **Volatile organic compound (TCE)**
  - **Pesticides**
- **Exposure biomarkers discussion**
  - **Prospects**
  - **Limitations**

Public Health Tracking and Biomarkers

Public Health Tracking and Biomarkers

- **Exposure tracking and public health tracking**
- **Elements of exposure assessment**
  - **Exposure media (air, water, food, soil, etc)**
  - **Time/activity budgets**
  - **Exposure events**
- **Biomarkers**
  - **Exposure**
  - **Effects**
  - **Susceptibility**
- **Reliability of biological samples for characterizing exposure**
  - **Source**
  - **Magnitude**
  - **Variation of exposure (time and space)**

Framework for the Environmental Public Health Tracking Network

State & National Data Collection Systems

- Environmental Hazards
- Environmental Exposure
- Health Effects

Integrating Environmental Health Data

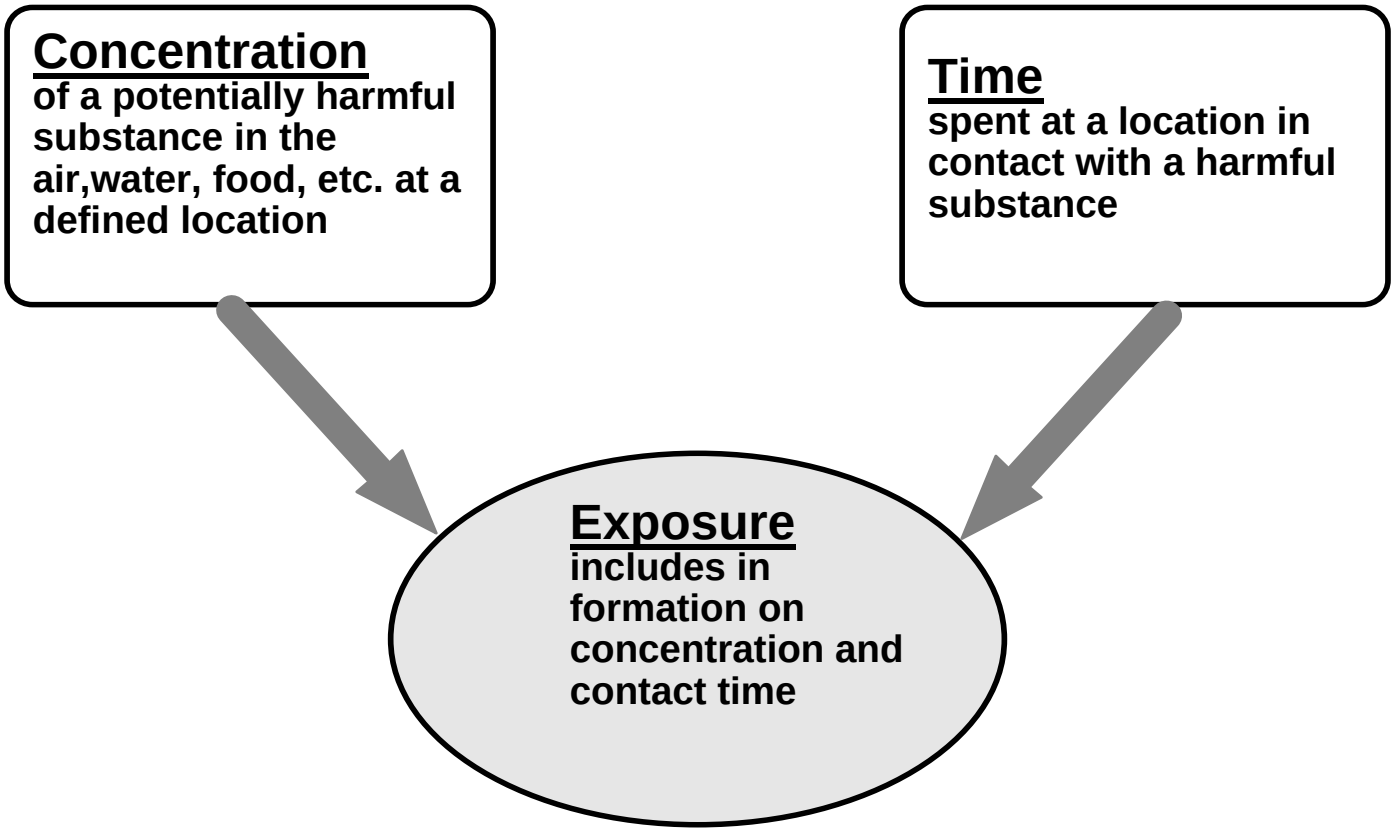
- Linkage
- Analysis
- Evaluation
- Dissemination

Public Health Actions

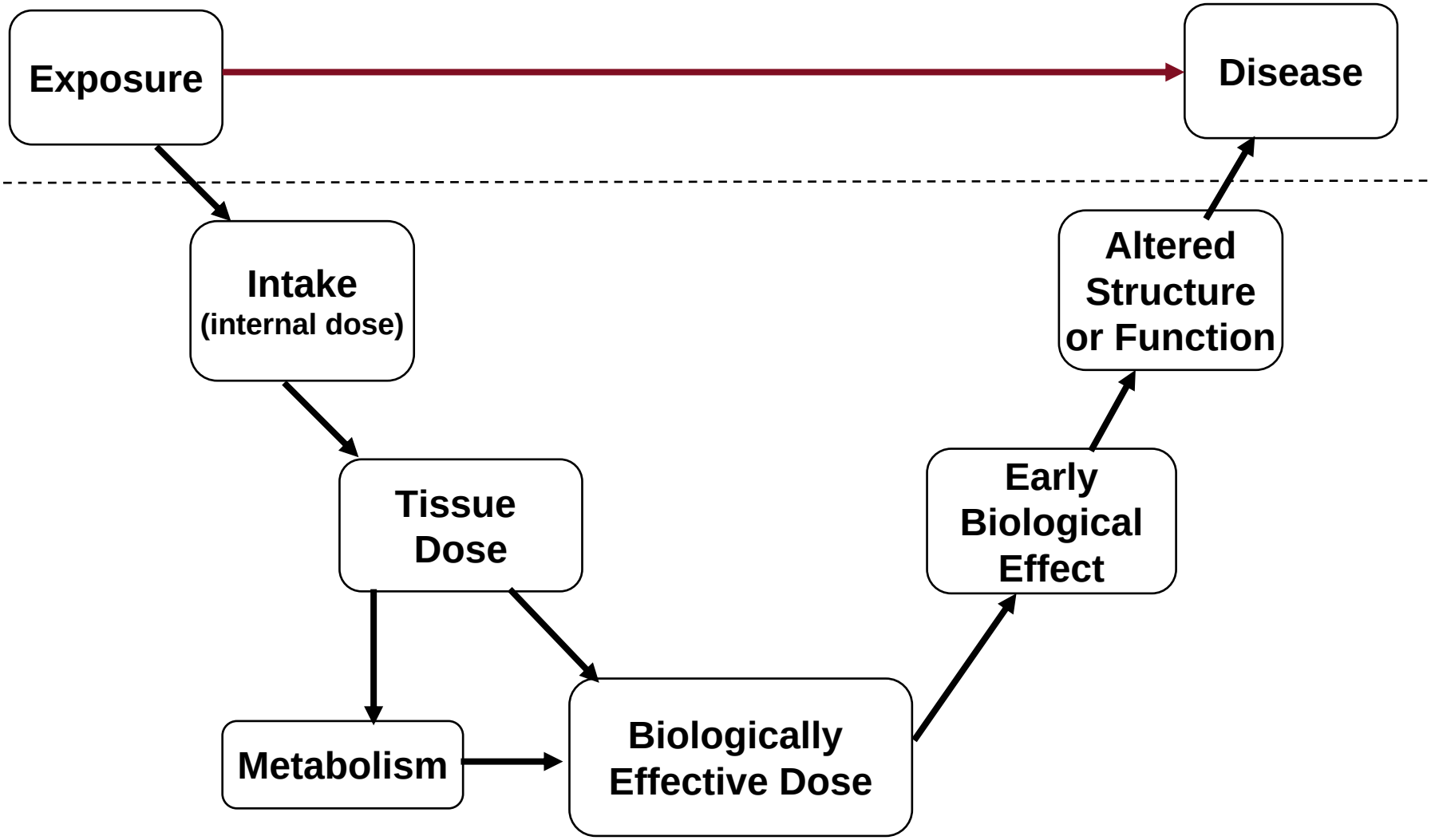
- Research
- Track health effects, exposures, and hazards
- Develop, implement, and evaluate interventions & policies
- Raise awareness

Exposure Tracking

- **Exposure refers to the physical contact of an organism with a substance present in a liquid, solid, or a gas.**

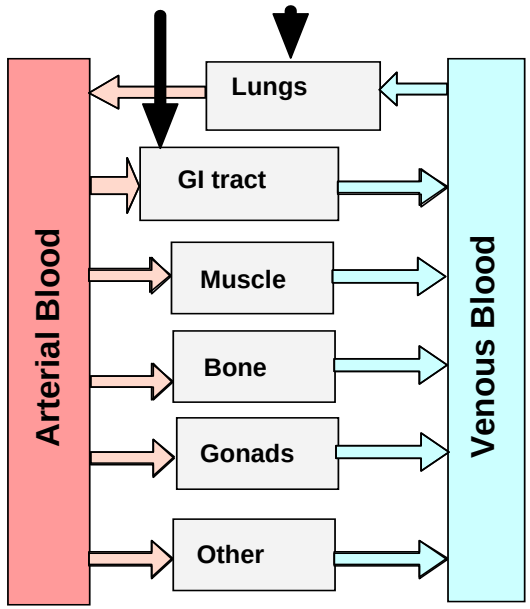


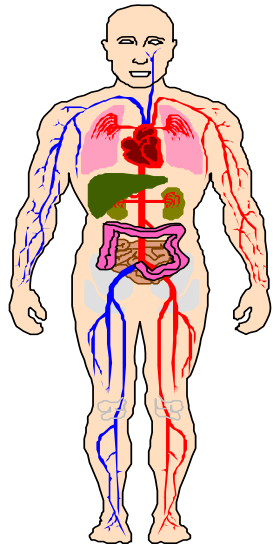
Markers on the path from exposure to disease



Biomarkers/Biomonitoring

- **Biomarkers**
  - Susceptibility
  - Exposure
  - Effect
- **Biological media**
  - Breath Saliva
  - Urine Blood
  - Other--lipid samples, biopsies
- **Biomonitoring**
  - Who is exposed?
  - How does exposure vary?
  - Does exposure correlate with disease?
  - Is exposure changing in time?





Biomarker Issues

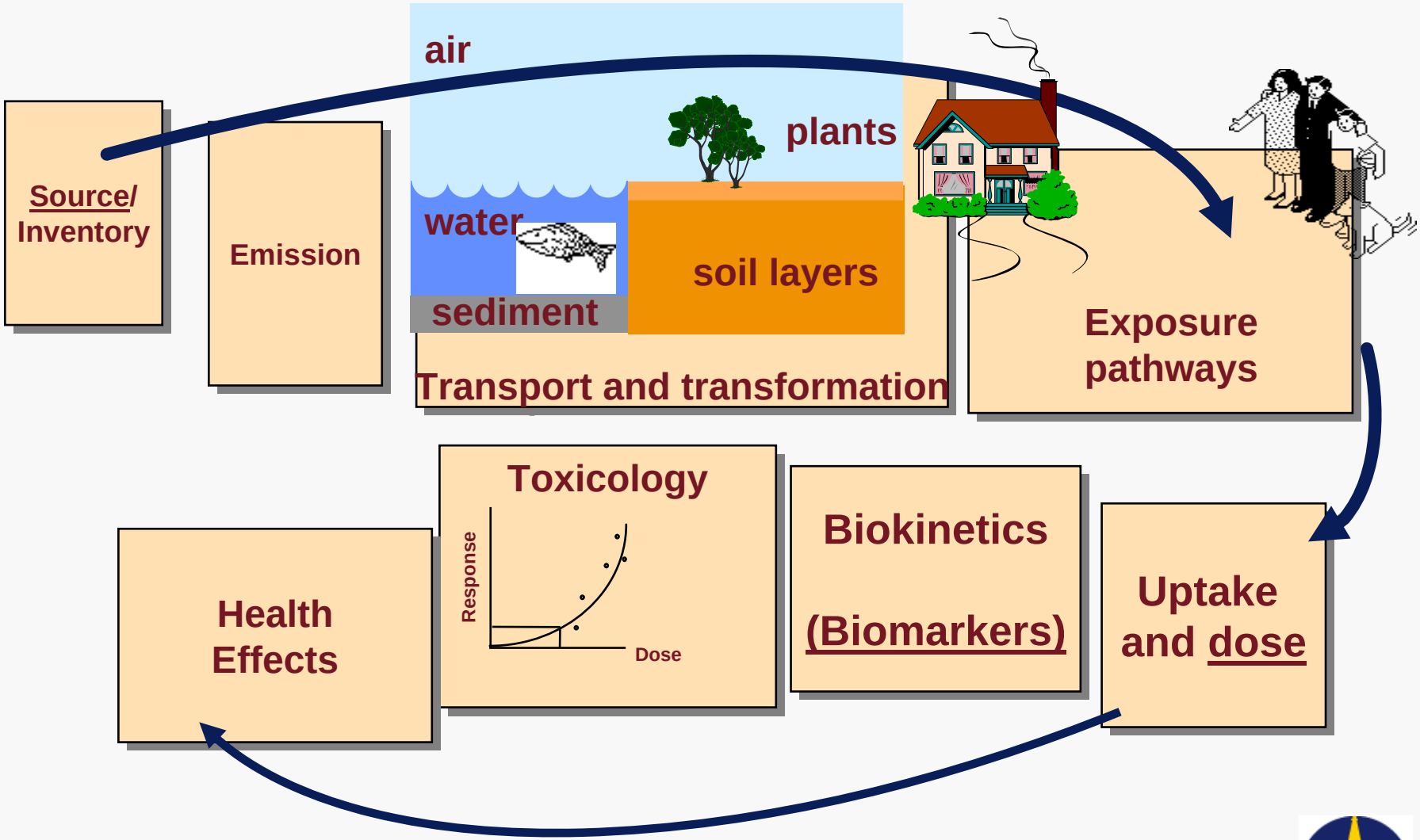
- **What is measured?**
  - Parent compound
  - Metabolites
  - Effect markers
- **Interpreting metabolites**
  - How efficient is transformation?
  - Are there competing sources for the same metabolite?
  - Relating metabolite concentration to intake
  - Variation in metabolism
- **Persistence**
  - Parent compound half life
  - Rates of transformation
  - Metabolite half life

Exposure Models

Exposure Models

- Source-exposure-intake-dose
- Concentration-time models
- Intake/uptake models

The Concept and Framework: Source-to-Dose in Health Tracking



Exposure (Concentration) Model

$$E = \frac{\sum_i C_i t_i}{\sum_i t_i}$$

E = average exposure in mg/m^3 over the period T = t_i

C_i = concentration in mg/m^3 in microenvironment i

t_i = time spent in microenvironment i

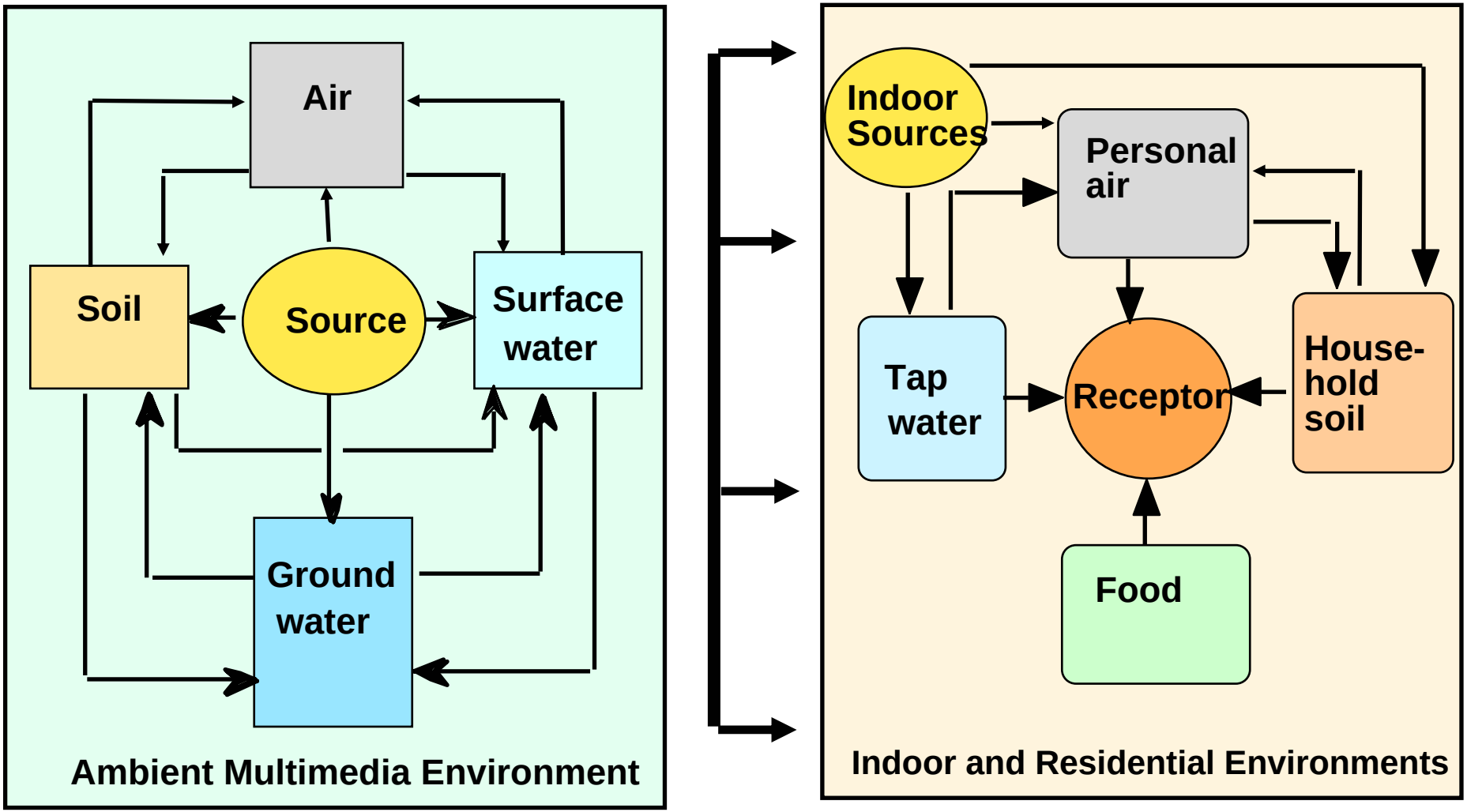
Basic Intake/Uptake Model

Unit Dose Factor (UDF)

$$ADD = \left[\frac{C_i}{C_k}\right] \times \left[\frac{IU_i}{BW}\right] \times \frac{EF \times ED}{AT} \times C_k$$

Average daily dose in mg/kg-d from exposure medium i and environmental medium k.	Inter-media transfer factor expressing the concentration ratio of the exposure medium i to the environmental medium k.	The intake or uptake factor per unit body weight associated with exposure medium i.	Exposure frequency, exposure duration and averaging time	Contaminant concentration in the environmental medium that provides a source to the exposure medium

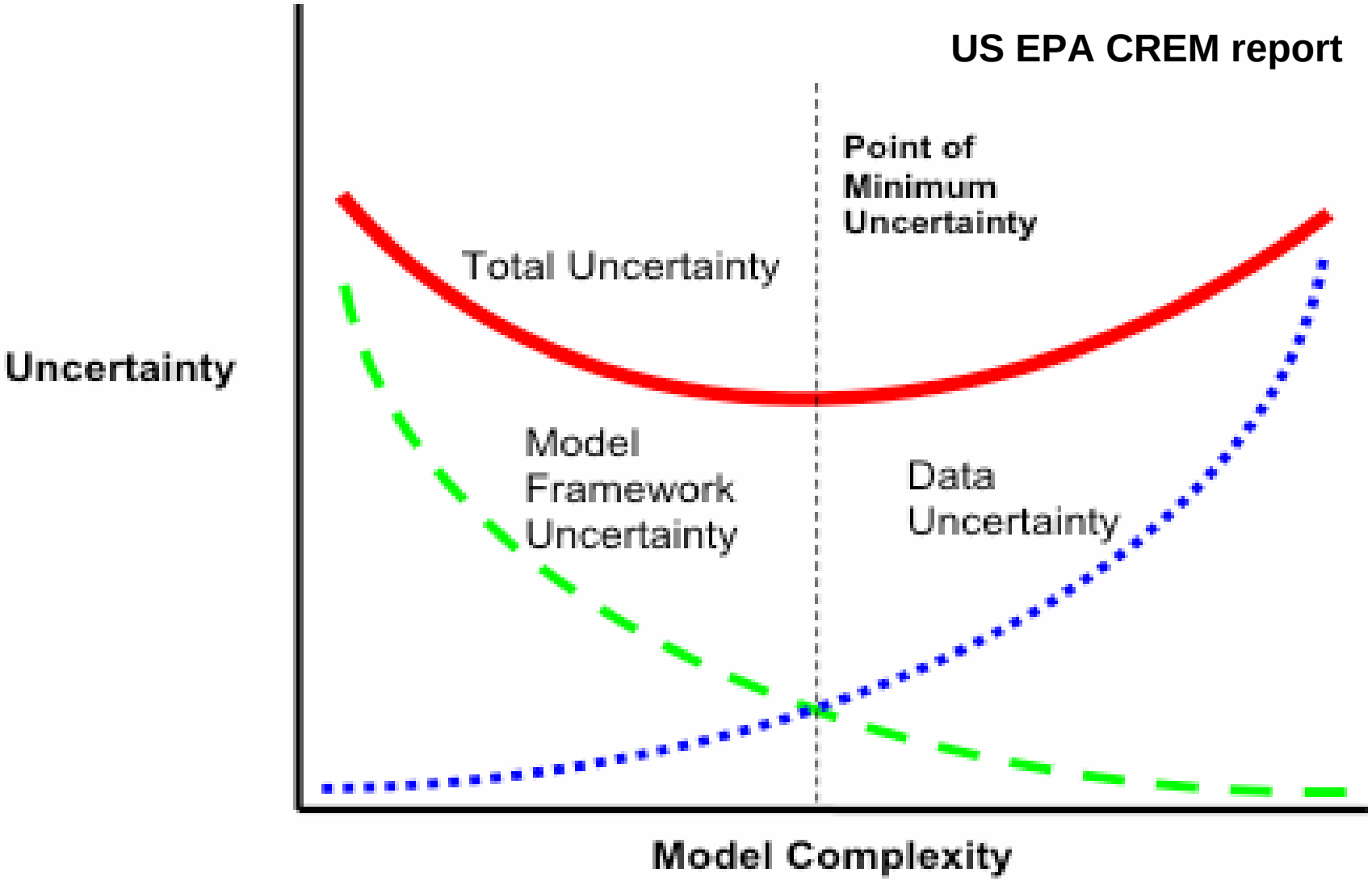
Multimedia to Multipathway Exposure and Intake



Confronting Model Limitations

- Relevance
- Transparency
- Complexity
- Uncertainty
- Can it be validated?
- Do people trust the model?

Models are Inherently Uncertain



How Can We Use Exposure Models?

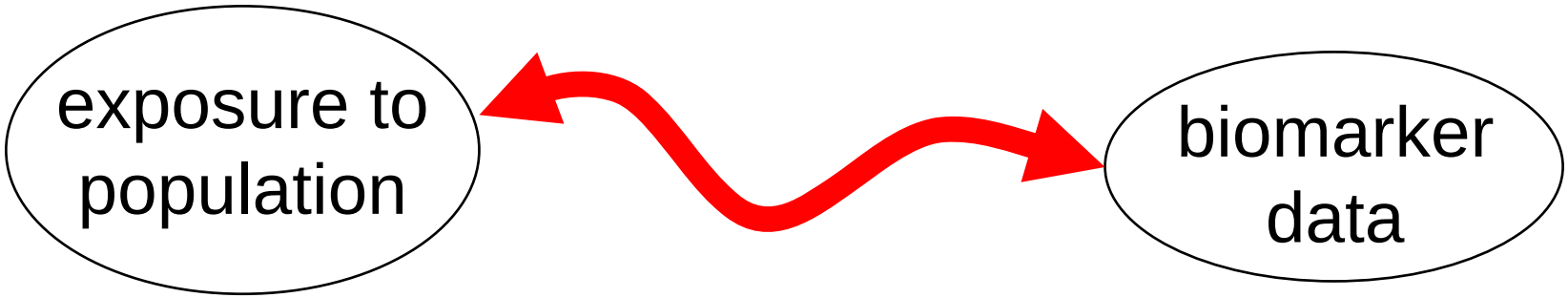
- **Insight**
- **Repositories of existing knowledge**
- **Exploring plausible exposure pathways**
- **Integrated metrics of source/dose relationships**
  - Intake fraction
  - Persistence
  - Proximity metrics
- **Accurate predictions of exposure???**

Case Studies

Case Studies

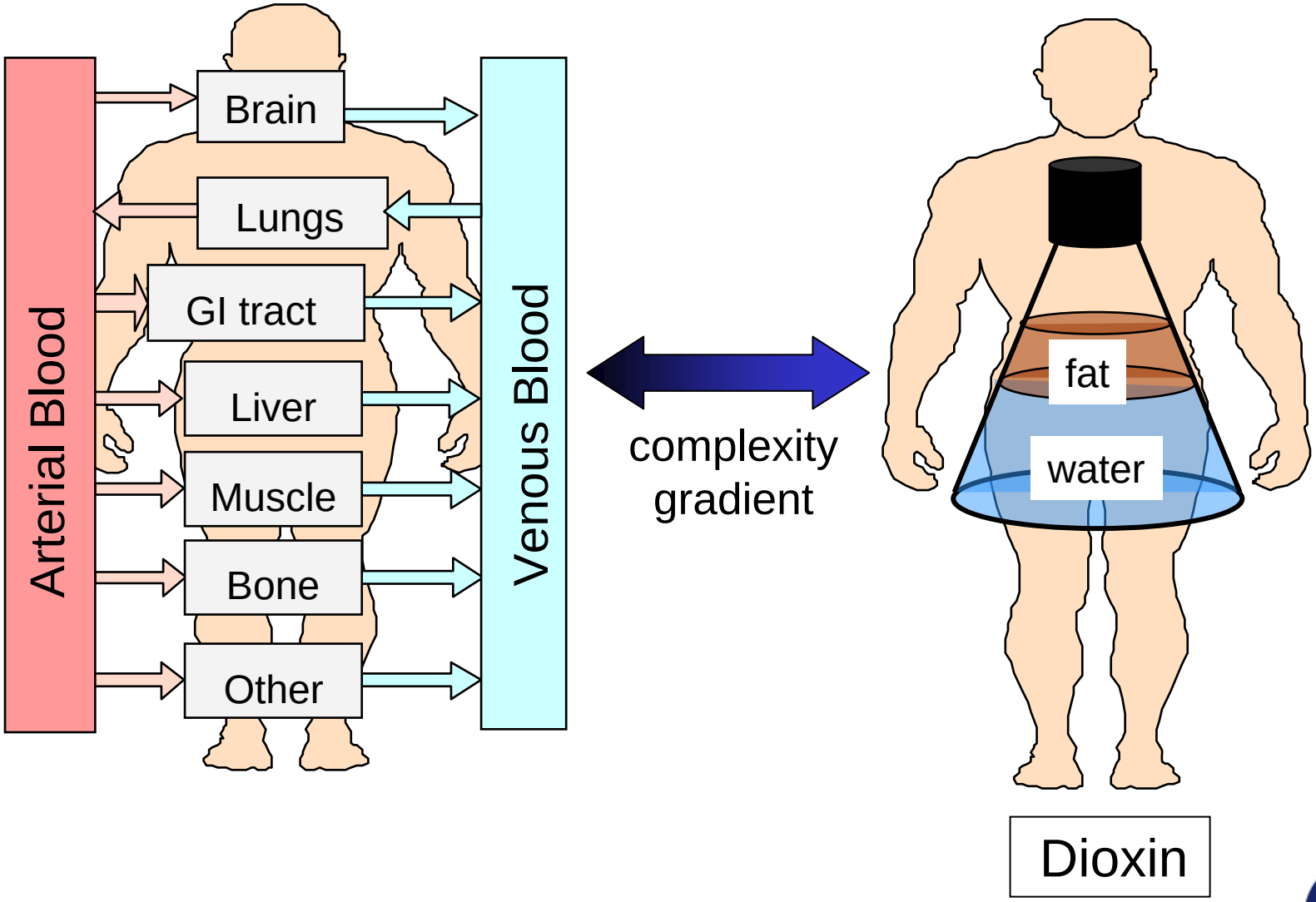
- **Persistent compounds**
  - Radiation
  - Dioxin-like compounds
- **Volatile organic compound (TCE)**
  - Data-Model Melding (Bayesian approaches)
  - Inverse modeling based on phisioligically-based pharmacokinetic (PBPK) models
- **Pesticides**
  - Comparing two populations
  - Testing model/biomarker premises

Ionizing Radiation

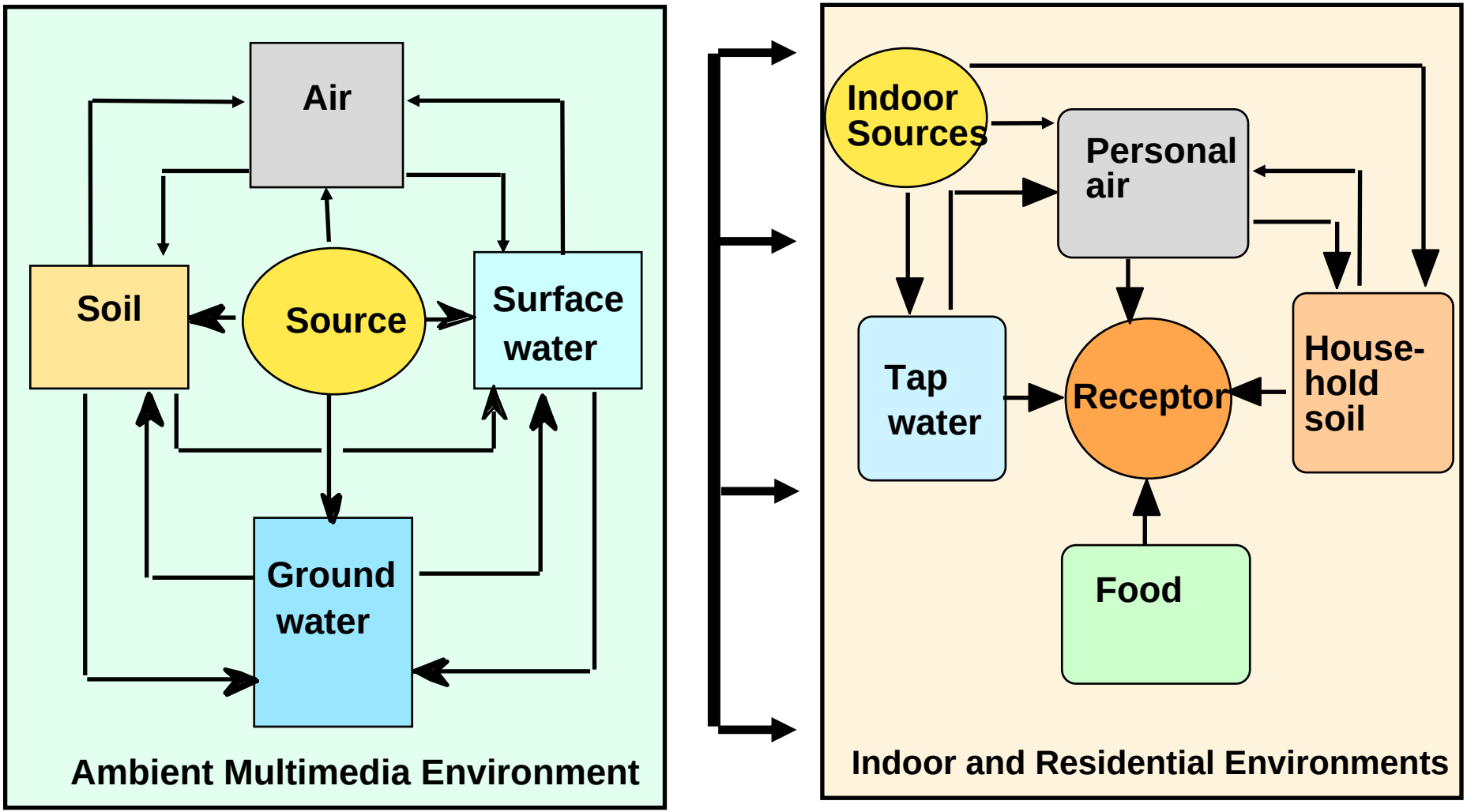


- **Heritable chromosome aberrations**
- **Number of aberrations correlates with lifetime cumulative dose**
- **Reliable biomarker of both dose and risk**
- **How many other substances have this property?**

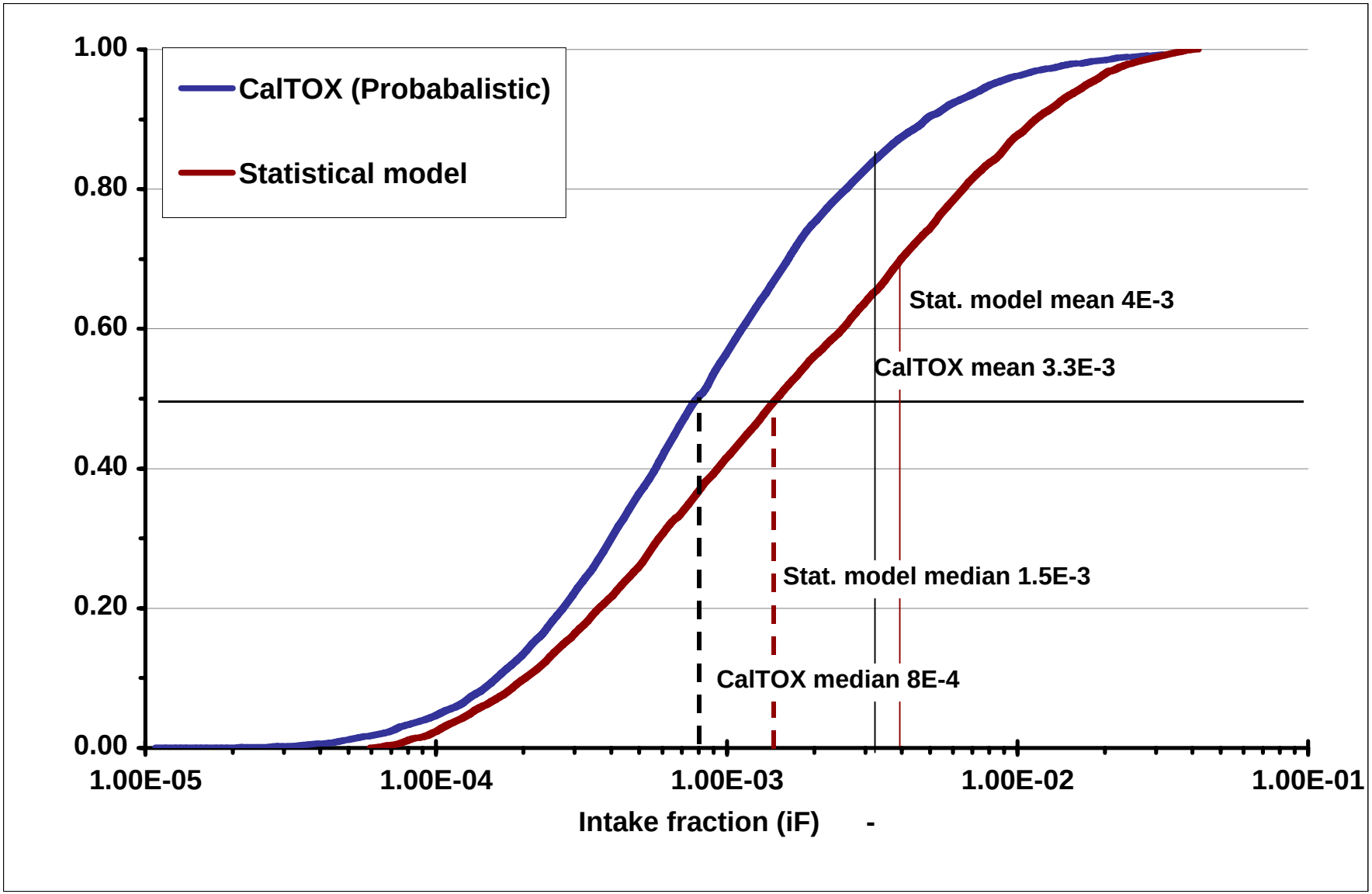
Pharmacokinetics: Dioxin-Like Compounds



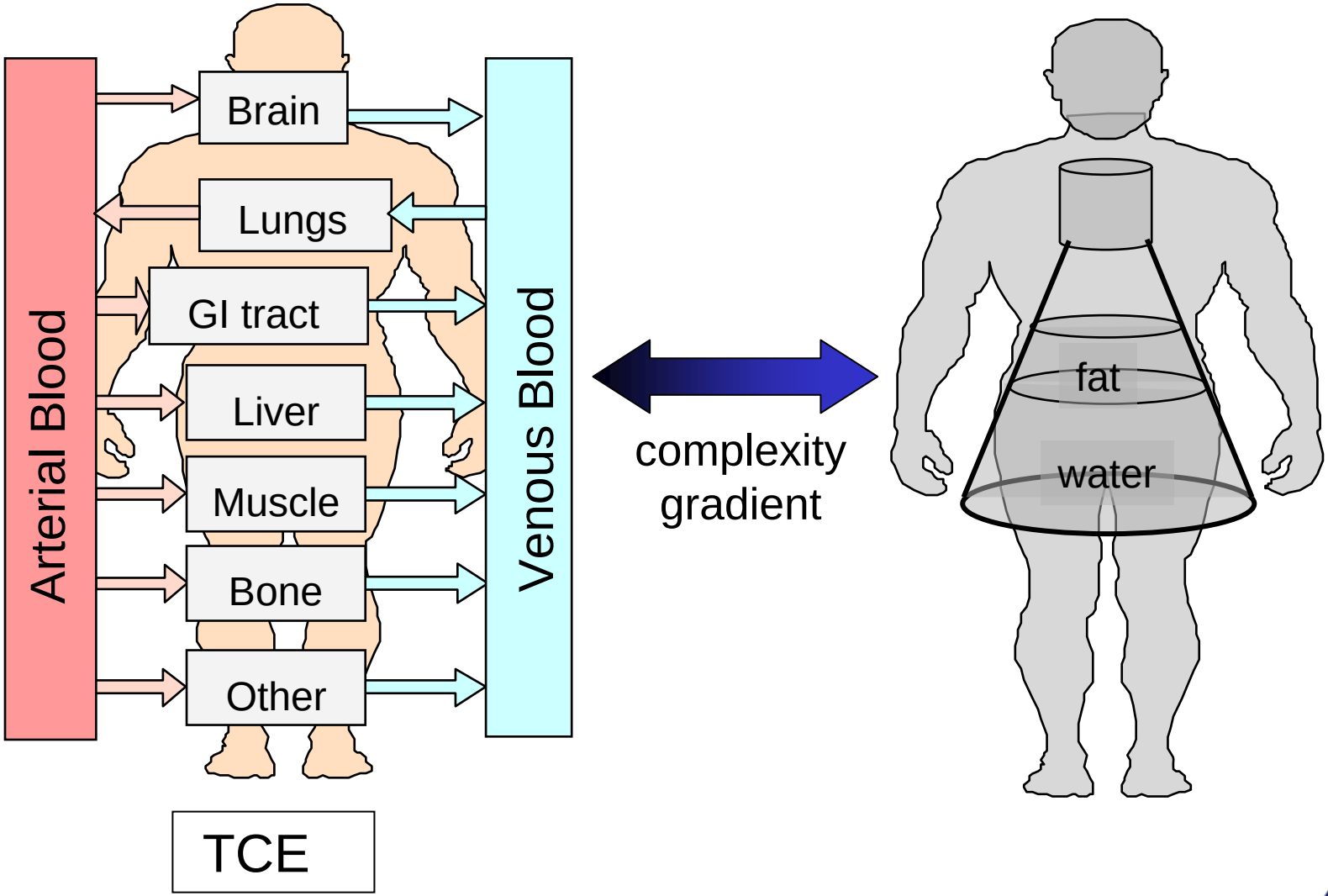
Multimedia to Multipathway Exposure and Intake



TCDD Intake/Emission ratio in the US:



Pharmacokinetics: Trichloroethelyene (TCE)



Data-Model Melding

- Bayes theorem
- Example of Bayesian logic
- Data-model melding as a model evaluation strategy
- TCE example

Bayes' Theorem

$$p(A/B) = \frac{p(A)\, p(B/A)}{p(B)}$$

Probability of A given B is equal the probability of A times the probability of observing B given A divided by the probability of B.

Rev. Thomas Bayes
1702-1761

Example of Bayesian Logic

A family has two children:

- What is the probability that they have two sons?

- What is the probability that they have two sons, given that one child is a boy?

Example of Bayesian Logic

Probability that they have two sons?

Boy	Boy
Boy	Girl
Girl	Boy
Girl	Girl

= 1/4

Example of Bayesian Logic

Probability that they have two sons, <u>given</u> that one child is a boy

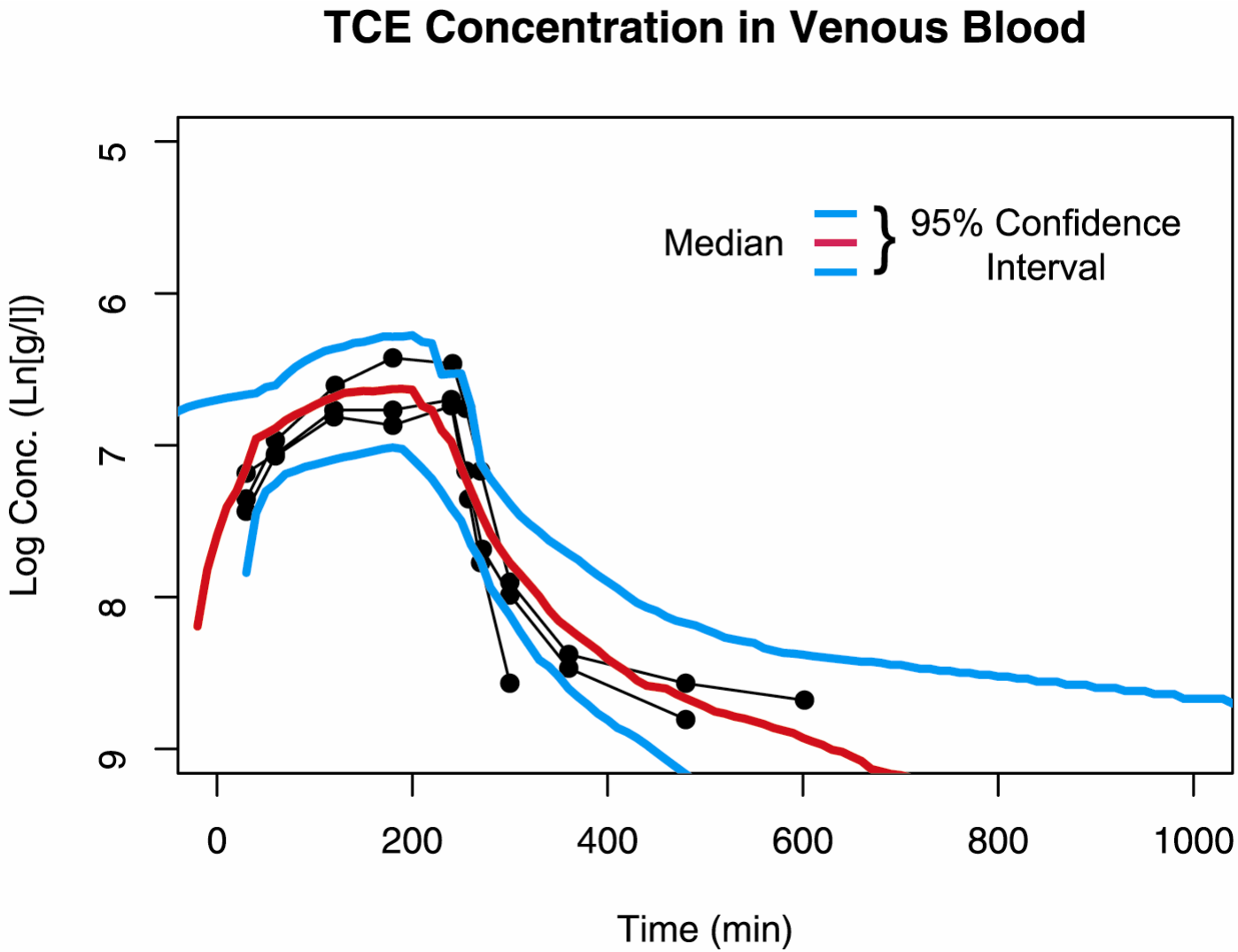
Boy Boy
Boy Girl
Girl Boy
~~Girl Girl~~

= 1/3

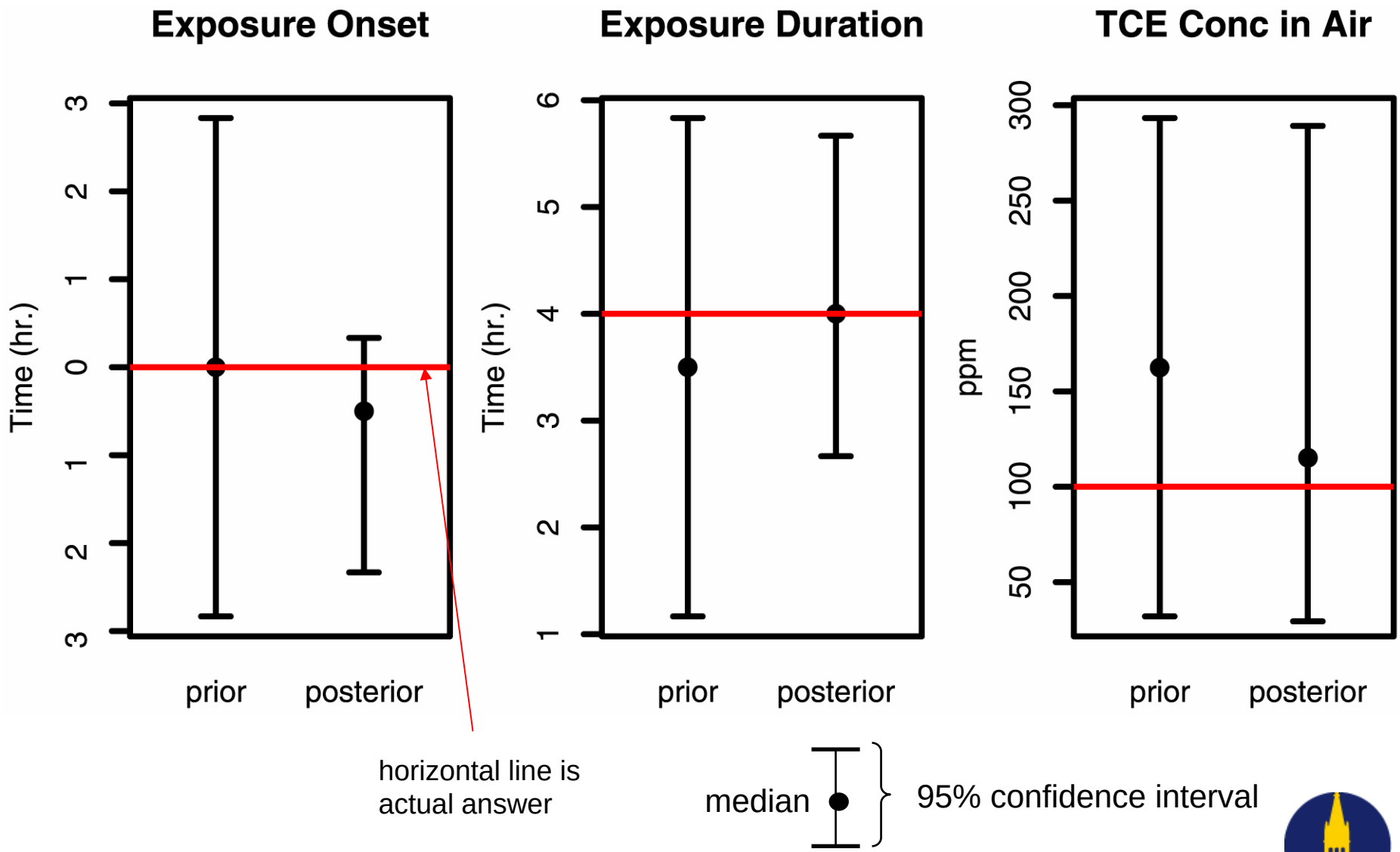
Bayesian Methods Applied to TCE Exposure

- **Can we use a PBPK model, biomarkers, Bayesian methods to reconstruct a know TCE exposure?**
- **Exposure conditions (ten male volunteers)**
  - **Duration: 4 hours**
  - **Onset: 0 hours**
  - **Air concentration: 100 ppm**
- **Pharmacokinetics**
  - **Cardiac output, Metabolism**
  - **Tissue/blood, air/blood partitioning**
  - **Compartment/Organ volumes**
- **Exposure priors**
  - **Duration: 1 to 6 hours**
  - **Onset: -3 to 3 hours**
  - **Air concentration: 50 to 200 ppm**

Predicted Concentration Range from Dataset 1

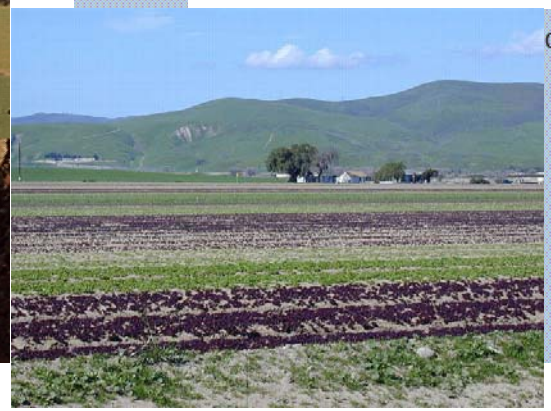


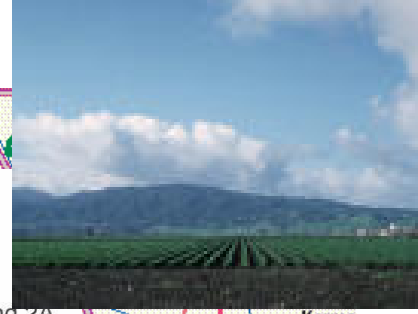
Exposure Reconstruction from Dataset 1

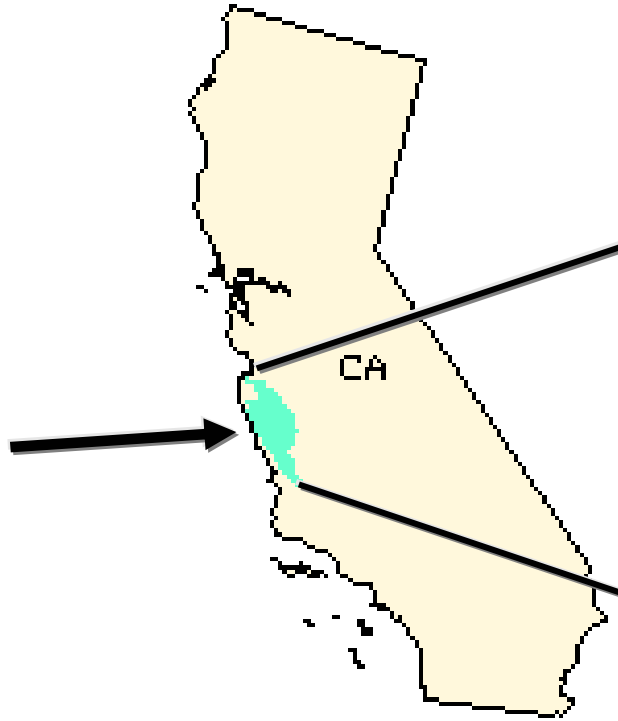


Merging Models and Data

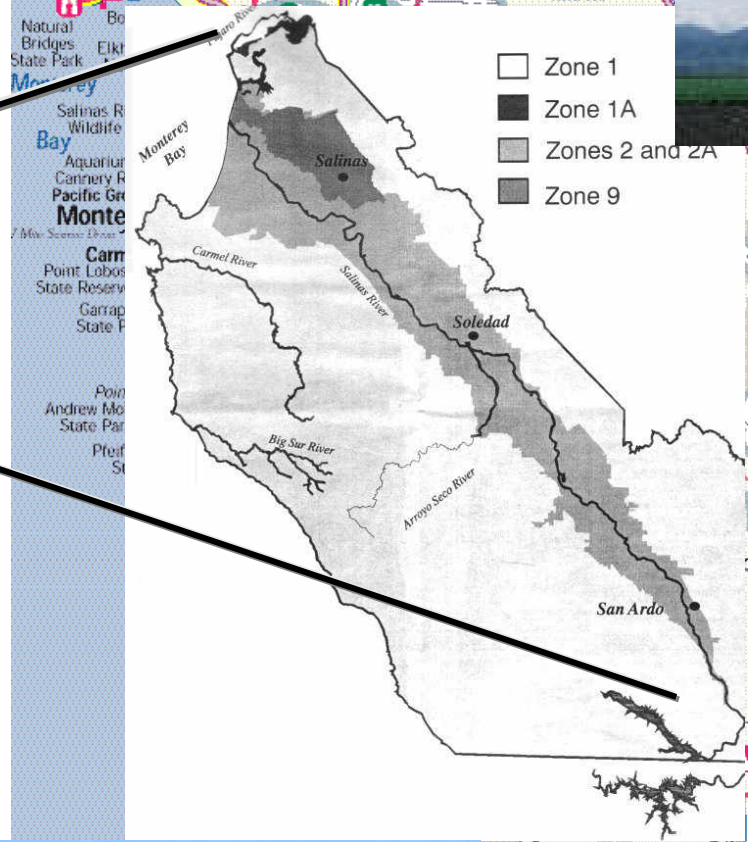
- **Organophosphate (OP) pesticide use in the Salinas Valley as a case study**
  - **Source magnitude**
  - **Human exposure**
- **Multipathway exposure model**
  - **Model application**
  - **Model evaluation with biomonitoring data**
- **What we learn from melding biomarker data with models?**





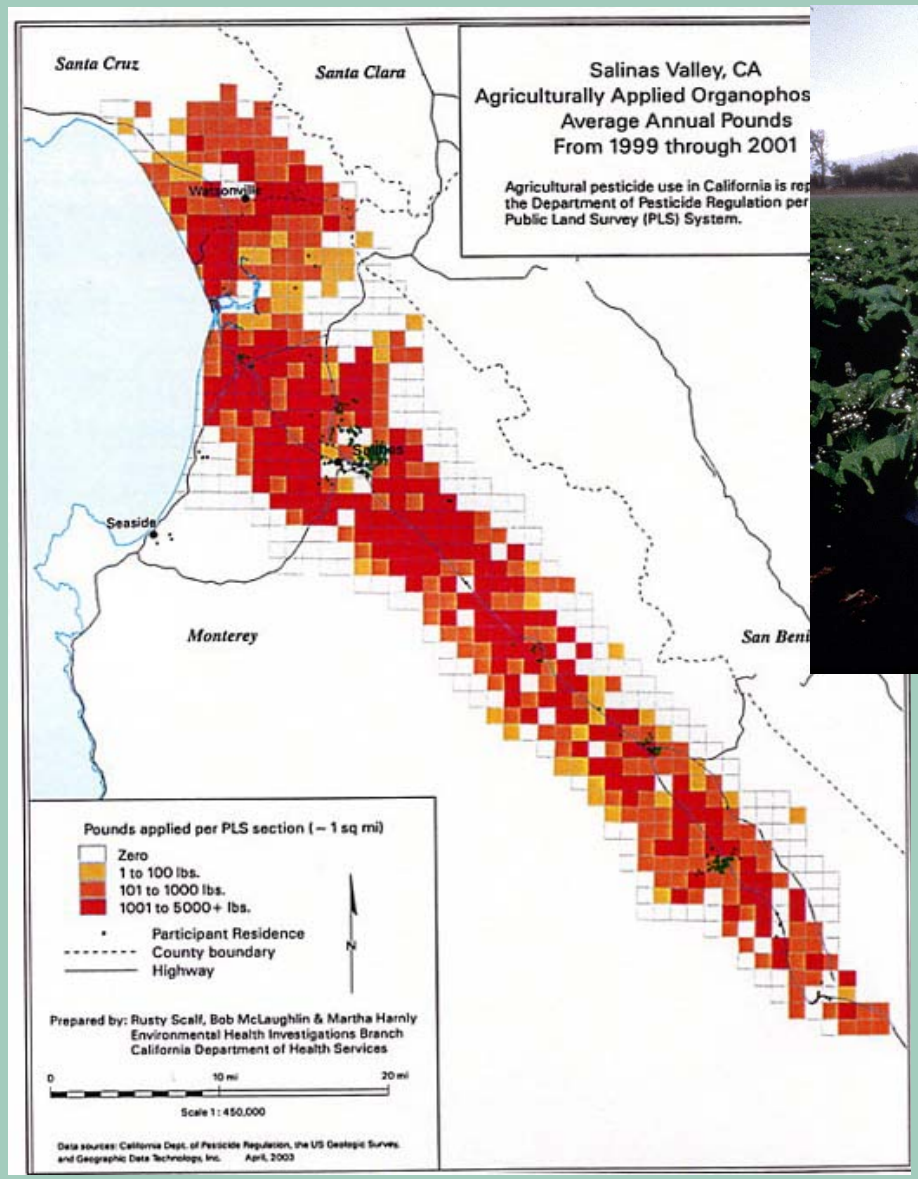

CA


Santa Cruz
Mission
17
Santa Cruz
Aptos
152
Watsonville
101
Gilroy
152
San Luis Reservoir


Zone 1
Zone 1A
Zones 2 and 2A
Zone 9
Monterey Bay
Salinas
Carmel River
Salinas River
Soledad
Big Sur River
Arroyo Seco River
San Ardo


Kerma
San Joaquin
33
Canterbury
Aqueduct
145
Coalinga
198
33
Avenal
COAST
Mission San Miguel Arcangel
46
Shandon
41
Templeton
RANGE
Cambria
46
Atascadero
229
Point Estero
41
Cayucos
Morro Bay
Santa Lucia Wilderness
Santa Margarita
Santa Margarita Lake
Morro Bay State Park
Los Osos
Montaña de Oro State Park
Valencia Peak Tr
San Luis Obispo
Point Buchon
Mission San Luis Obispo
Avila Beach
Lopez Lake
227
SAN LUIS OBISPO
Point San Luis
Arroyo Grande
Pismo Beach
Nipomo
Grover Beach
Oceano

Organophosphate Pesticide Use



The Salinas Valley is a region of intense pesticide use

CHAMACOS: The Salinas Valley

Steinbeck called it "The Long Valley" in his 1938 book that created a narrative portrait of the region and its people.

CHAMACOS

CENTER FOR THE HEALTH ASSESSMENT OF MOTHERS AND CHILDREN OF SALINAS

CHAMACOS works to develop a narrative description of pesticide exposures and health for its farmworker population

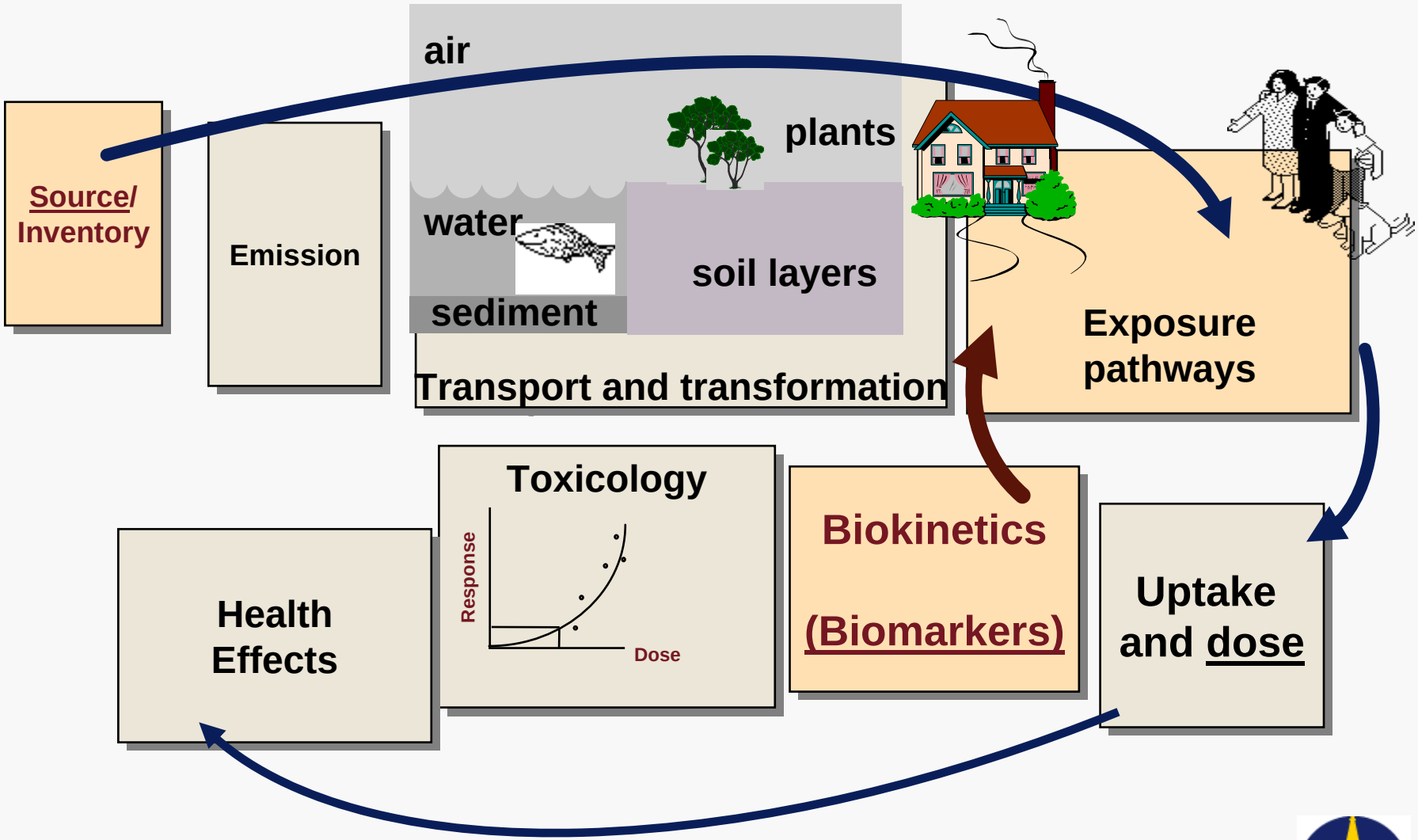
Evaluation Opportunities

- **CHAMACOS provides monitoring data on chemical concentrations in**
  - **Urine**
  - **Blood**
  - **Environmental media**
- **CHAMACOS provides an important opportunity to study the fate and impact of pesticides**

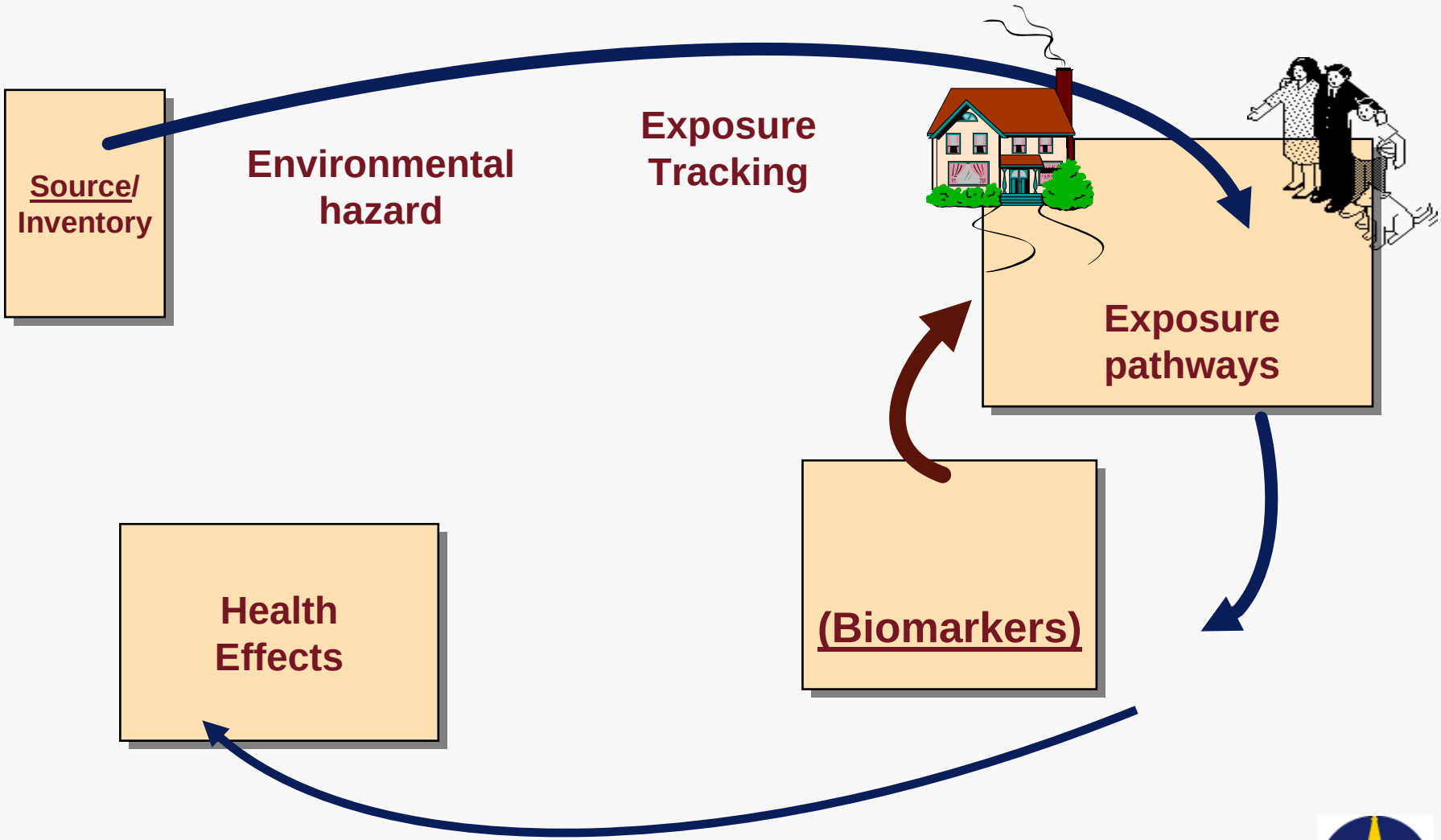
Evaluation Opportunities

- **National biomonitoring in the US reveals that many chemicals in the environment are absorbed into our bodies**
- **The US Centers for disease control *National Health and Nutrition Evaluation Survey (NHANES)* provides monitoring of pesticide metabolites in blood and urine**
- **Only provides a *national* NOT a *regional* picture**

The Concept and Framework: Source-to-Dose in Health Tracking



The Concept and Framework: Source-to-Dose in Health Tracking

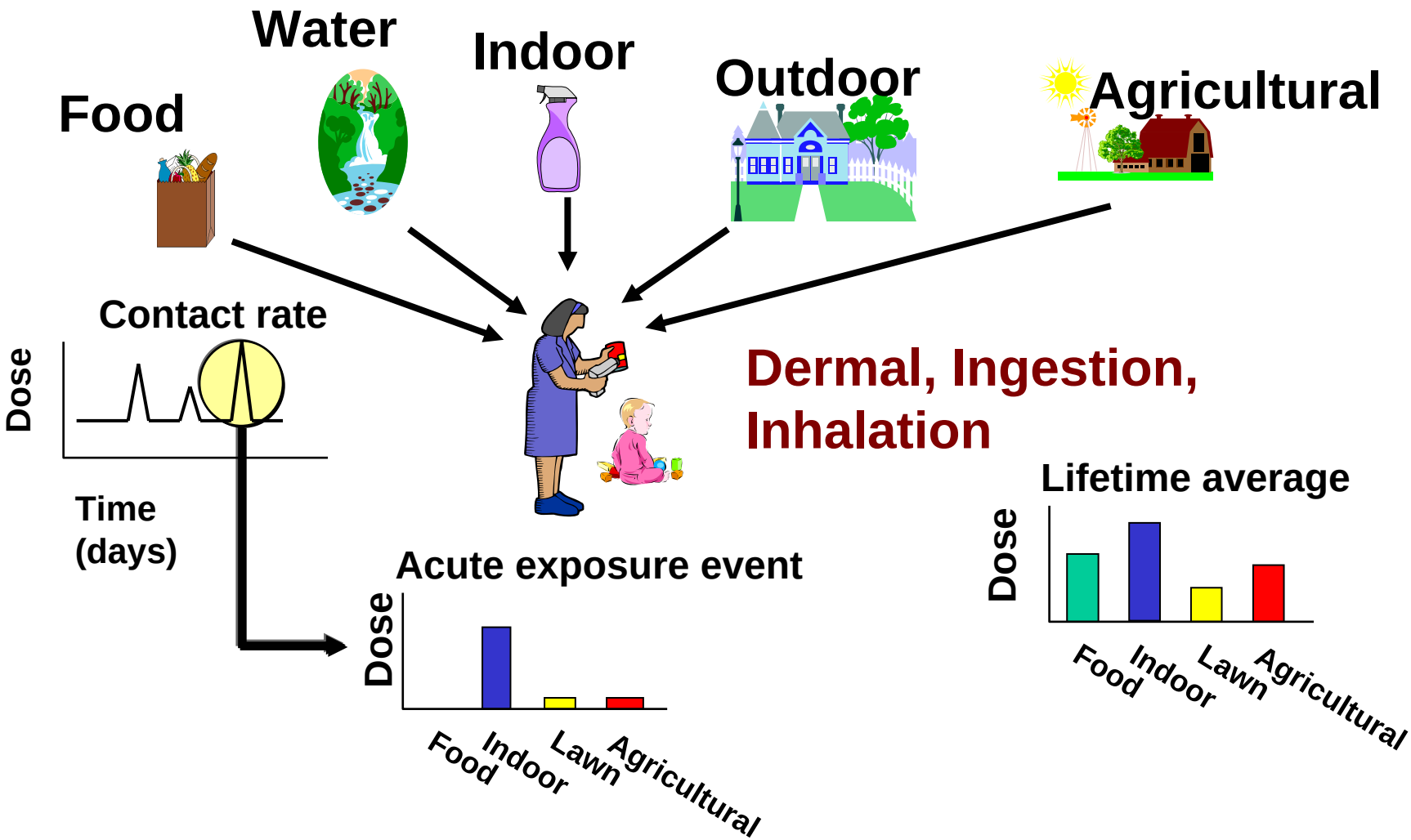


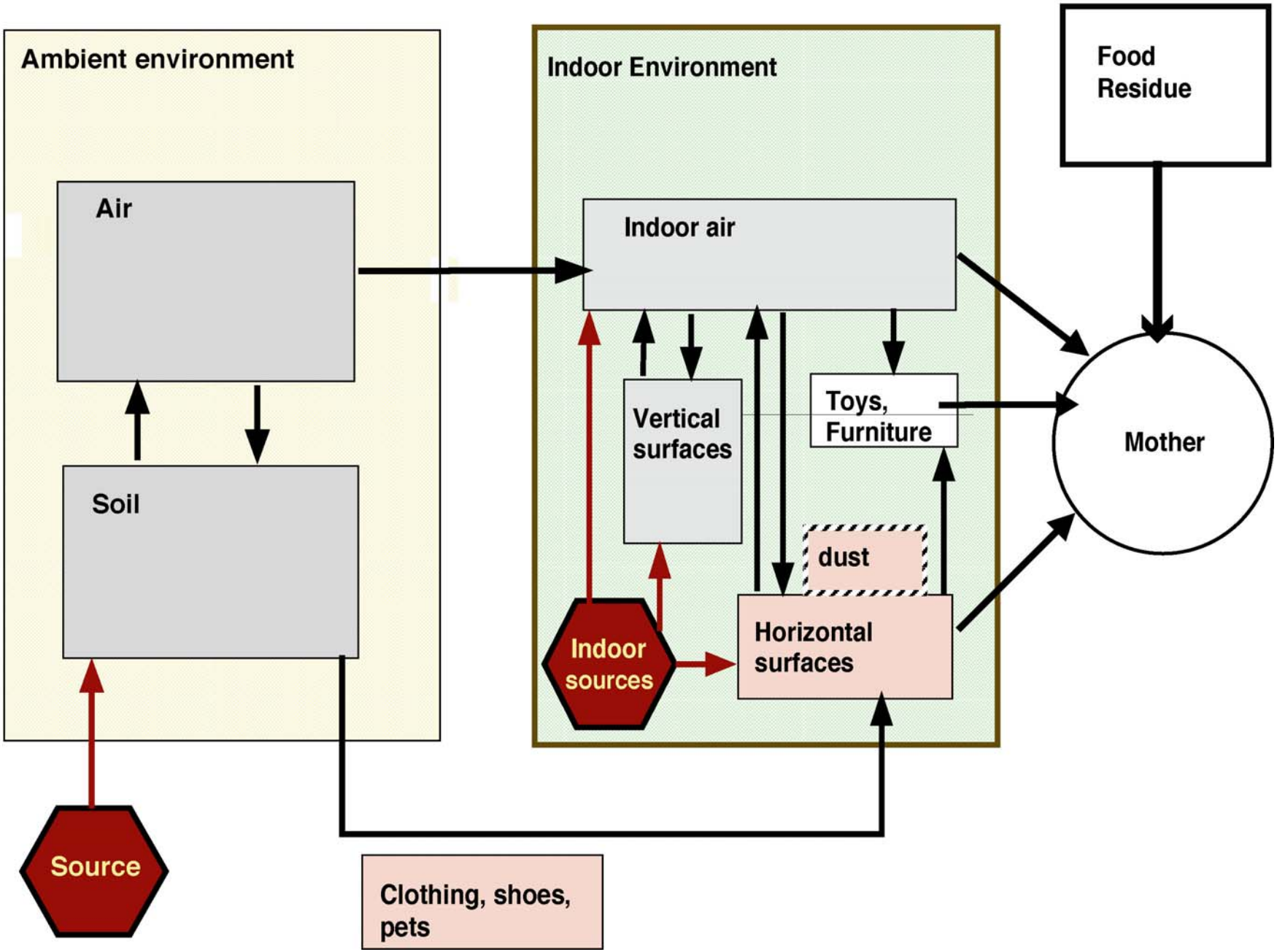
Pesticide Use: Salinas Valley

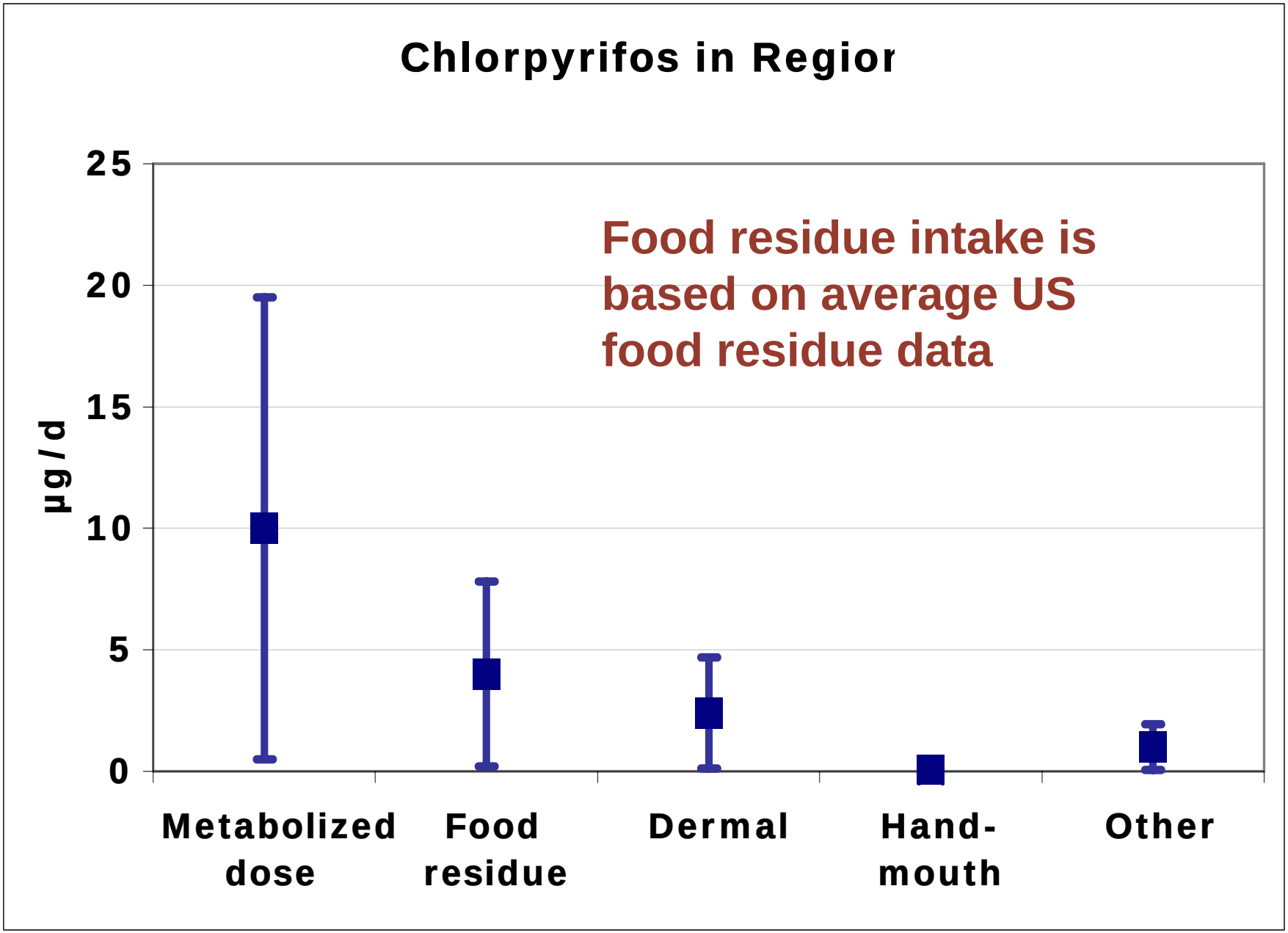
OP Pesticide	kg Applied (2001)
Diazinon	60,699 (DM)
Malathion	43,873 (DE)
Acephate	32,602
Oxydemeton-methyl	26,300 (DE)
Chlorpyrifos	24,975 (DM)
Dimethoate	15,556 (DE)
Bensulide	14,850
Naled	7,748 (DE)
Methidathion	6,464 (DE)
Disulfoton	4,644 (DM)

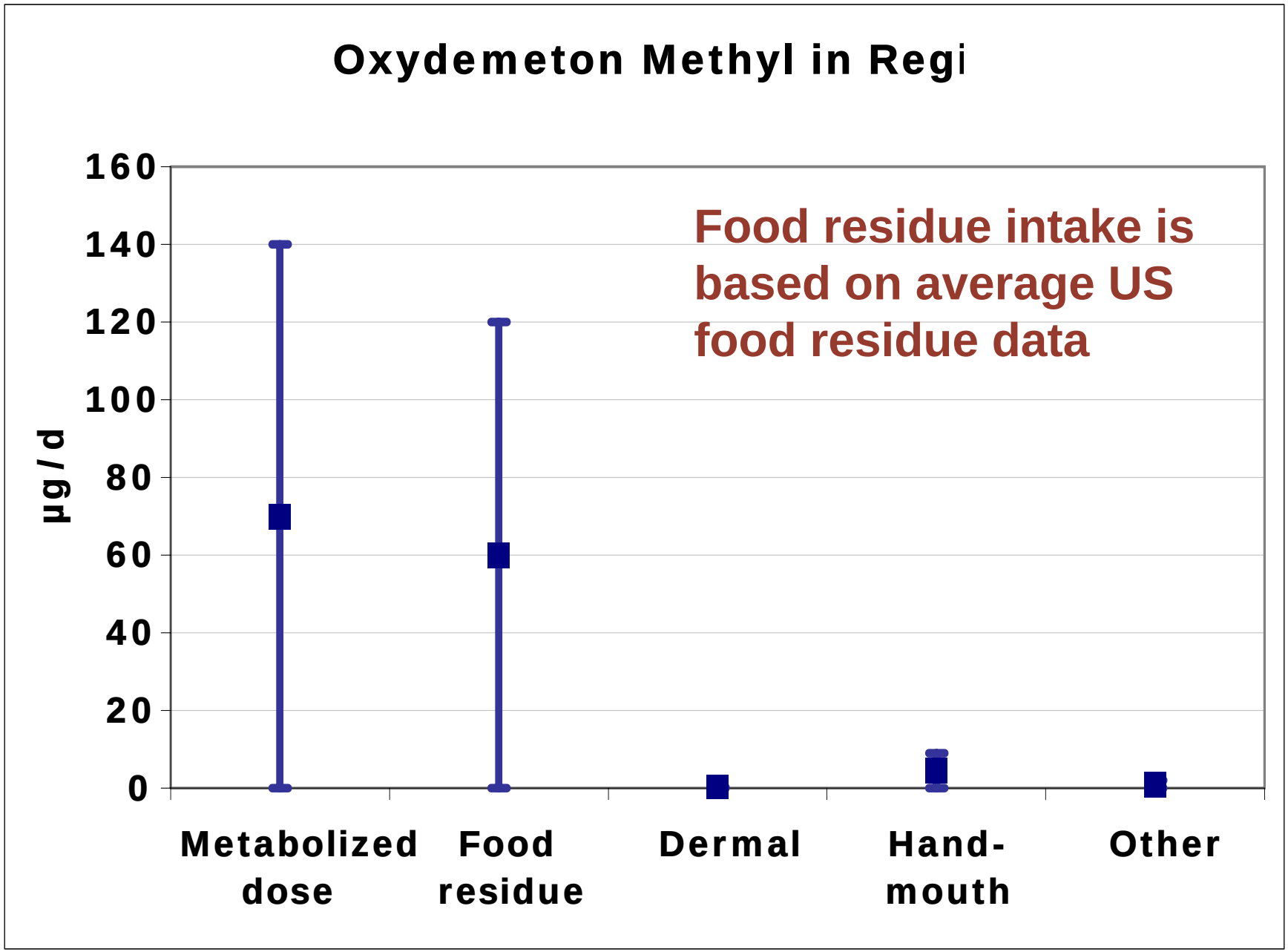
Total OP Pesticide Use: 240,000 kg

Pesticide intake depends on release location, transport and fate, and human intake through competing exposure pathways




Ambient environment
Air
Soil
Source
Indoor Environment
Indoor air
Vertical surfaces
Toys, Furniture
dust
Indoor sources
Horizontal surfaces
Food Residue
Mother
Clothing, shoes, pets


Chlorpyrifos in Regior
25
20
15
10
5
0
µg/d
Food residue intake is based on average US food residue data
Metabolized dose
Food residue
Dermal
Hand-mouth
Other


Oxydemeton Methyl in Regi
160
140
120
100
80
60
40
20
0
µg/d
Food residue intake is based on average US food residue data
Metabolized dose
Food residue
Dermal
Hand-mouth
Other

Biomarker Populations

CHAMACOS Mothers (N=585, all pregnant)

- **Mean age: 25 years**
- **92% Spanish-speaking**
- **44% worked in agriculture**
- **84% other agricultural workers in household**
- ***Biological samples: Urine, Blood***

NHANES (N=1985 total, 996 female)

- **Stratified probability-based sample of the entire US population**
- ***Biological samples: Urine, Blood***

Biomarkers of Pesticide Exposure

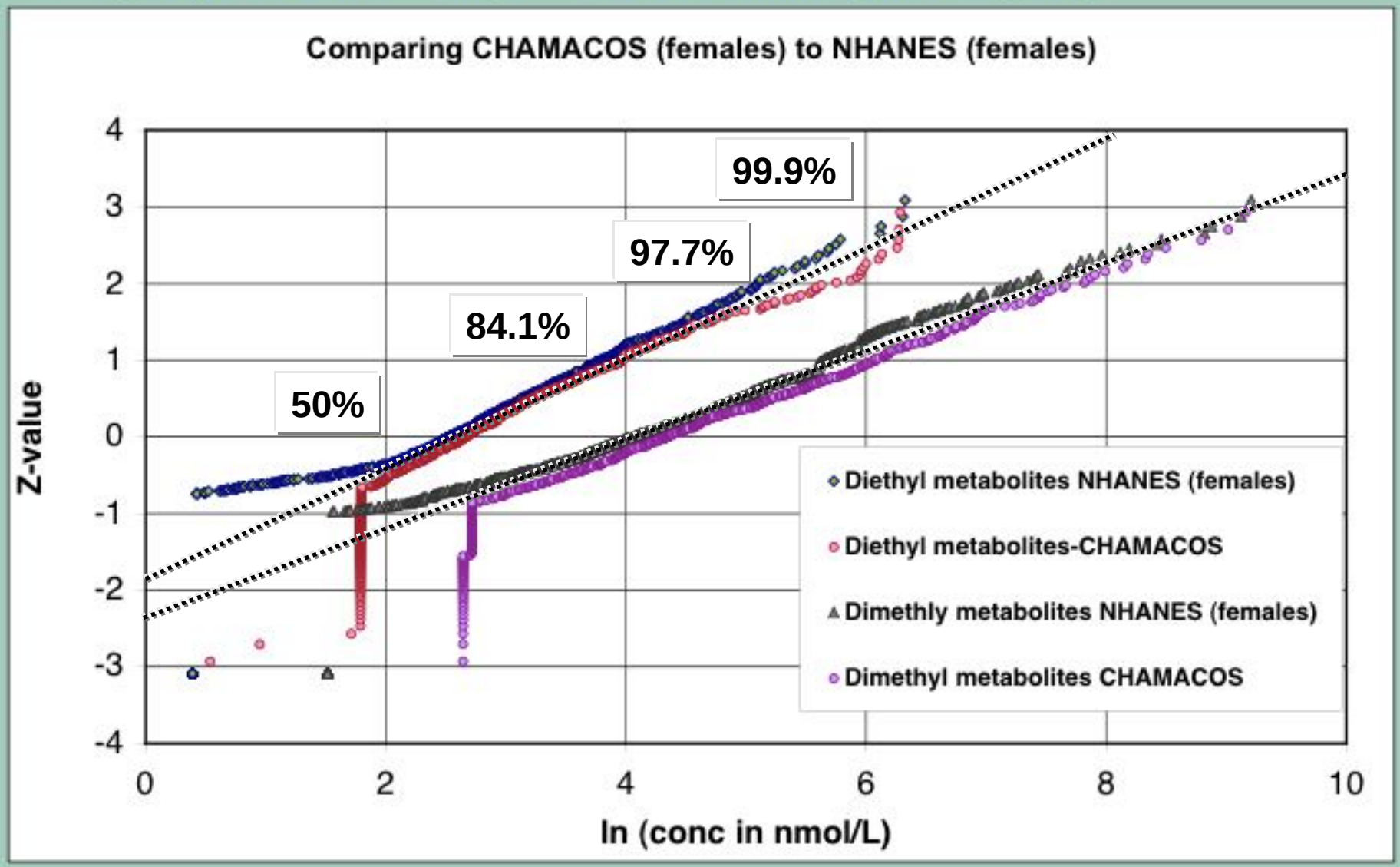
- **Dialkyl phosphate metabolites in spot urines are the primary measure of OP exposure (capture 80% of pesticides):**
  - **Dimethyl phosphate (DMP)**
  - **Dimethyl thiophosphate (DMTP)**
  - **Dimethyl dithiophosphate (DMDTP)**

  ~ 70 µg/day

  - **Diethyl phosphate (DEP)**
  - **Diethyl thiophosphate (DETP)**
  - **Diethyl dithiophosphate (DEDTP)**

  ~ 10 µg/day

Probability plot for the distributions of total **diethyl** and **dimethyl** phosphate concentrations the CHAMCOS mothers at baseline visit to the clinic (**585** samples) and NHANES subjects who are female (**996** samples)



Summary Points, Discussion

Summary Points

- **Health tracking requires reliable exposure classification**
- **Exposure models are uncertain and lack "ground-truthing"**
- **Biomarkers can be valuable but fail to reveal source, duration, and variation of exposure**
- **Case studies reveal the value of melding models and biomarker data**
  - **Prospects**
  - **Limitations**

Future Directions

- **Other pollutants**
  - **Brominated flame retardants**
  - **Other persistent bioaccumulative pollutants**
- **Better understand uncertainty and variability in**
  - **Biomarker surveys**
  - **PBPK Modeling**
- **Incorporate “value-of-information” analyses before conducting exposure tracking surveys**
  - **How much biomarker data?**
  - **Could other biomarkers help?**
  - **Could other environmental or behavior data help?**
  - **Could longitudinal data information help?**