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Interpreting Biomonitoring Data and Using Pharmacokinetic Modeling in Exposure Assessment



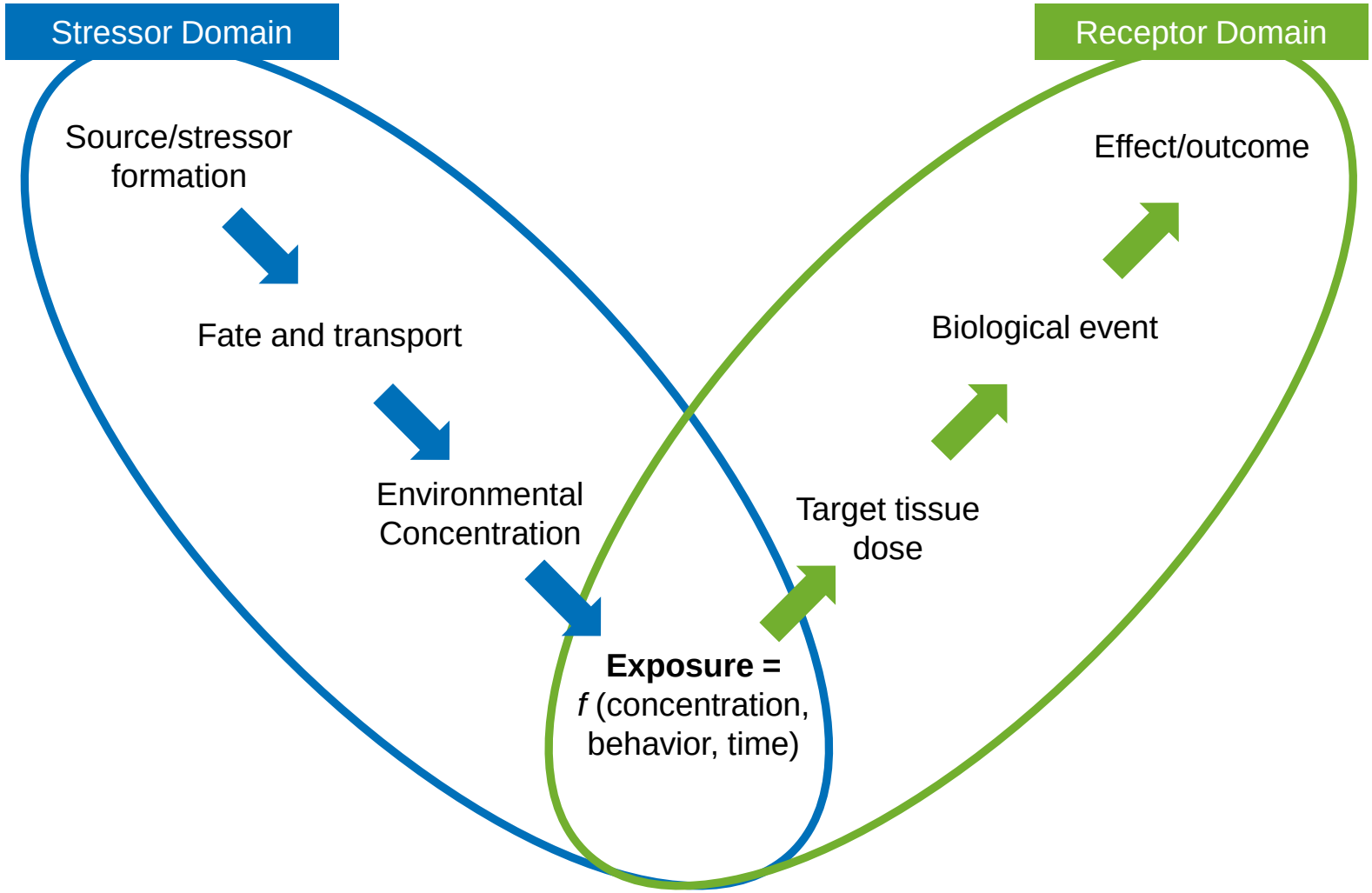
RISK ASSESSMENT TRAINING AND EXPERIENCE
Exposure Assessment Course Series – EXA 408

Office of Research and Development
National Center for Environmental Assessment

What You Can Expect to Learn from this Course

- Elements of biomonitoring
  - Body burdens and biomarkers
  - National Health and Nutrition Examination Survey (NHANES)
- How pharmacokinetic (PK) models are used in exposure assessment
  - Forward (predictive) analysis
  - Backward (reconstructive) analysis
  - Biomonitoring equivalents (BEs)

Source-to-Effect Continuum



Exposure Assessment Using Biomonitoring

- Biomonitoring data can be used to:

Measure total **internal** dose	Better estimate **intake** dose (in conjunction with PK models)	Reduce some types of **uncertainty**

- NHANES includes large dataset of biomonitoring data

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BIOMONITORING, BIOMARKERS, AND BODY BURDENS

Biomonitoring, Biomarkers, and Body Burdens

Biomarker:

Biologic **indicator** of exposure; used to measure chemical, metabolites, or product of **interaction** between chemical and target molecule or cell

Body burden:

Total **amount** of a **contaminant** in the body; a type of biomarker

Biomonitoring:

Method for **assessing** human exposure to **chemicals**, their **metabolites**, or their **byproducts**;
the **act** of **collecting** biomarker and body burden **data**

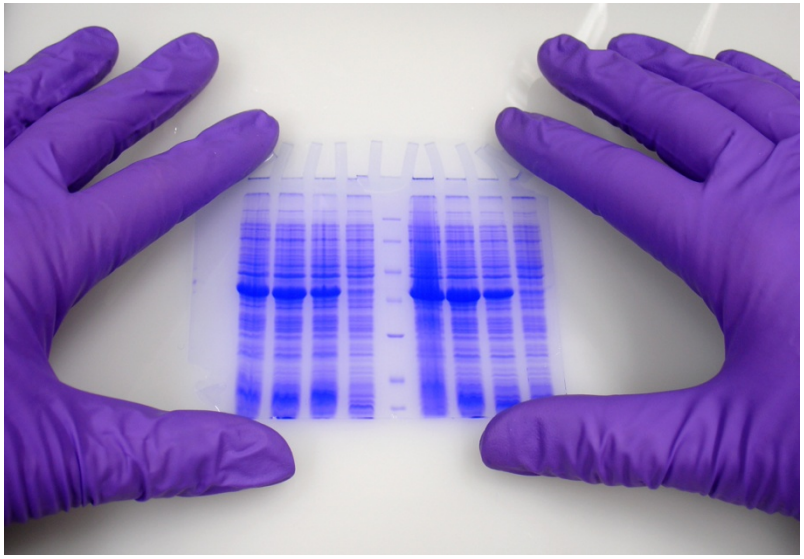
Biomonitoring Advantages and Limitations

Advantages	Limitations
Measures all aggregate exposure (all sources, all routes)	Not source- or pathway-specific
Reflects uptake and accumulation	Requires permissions for collection of human specimens
May be able to correlate internal dose with effects	Can be costly
	Difficult to interpret potential health risks

How Biomonitoring Measures Exposure

Biomarkers

- Used to measure:
  - Direct amount of a compound (i.e., body burden)
  - Biological interaction of the compound with the body
  - Physiological changes in an organism as a result of interaction with the compound



- Collected using biomonitoring methods
- Can be used to reconstruct past exposures
- Reflect internal dose but may not indicate risk

What is NHANES?

- National Health and Nutrition Examination Survey
- Conducted by the Centers for Disease Control (CDC)
- Assesses the health and nutrition of adults and children in the United States
- Dataset consists of:
  - Physical examinations
  - Blood and urine samples
  - Health status information
  - Dietary information
  - Behavioral information
  - Demographic data

History of NHANES

Survey conducted

Survey conducted

Survey conducted

1960s

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

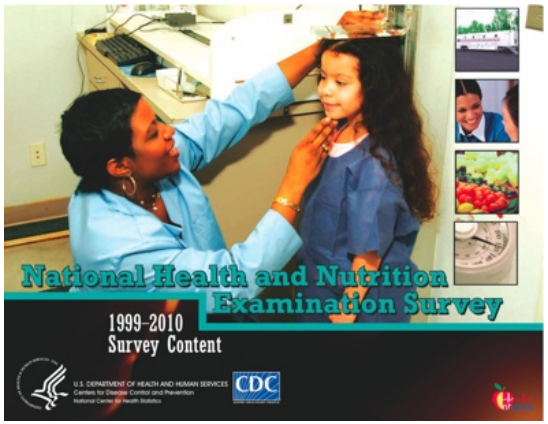
Beginning of NHANES

Survey modified and conducted

Survey conducted

Survey conducted

Survey being conducted



CDC Growth Charts

NHANES Biomonitoring Data

- Largest existing biomarker database
- Nationally representative
  - Sample weights individually assigned
- Blood, serum, and urine samples analyzed for concentrations of various compounds
  - Certain tests are only performed for certain age groups
- Survey population ranges from ages 1 to 60+
- Wide range (>200) of environmental chemicals and stressors measured
- Data publicly available and continually updated

Uses of NHANES Biomonitoring Data

- Characterize body burdens
- Determine populations with increased body burdens
- Identify exposure levels in populations of concern
- Establish reference or background values and identify unusually high exposures
- Assess efforts to reduce exposure and trends over time
- Direct research priorities
- Connect exposure to body burden

Other Sources of Biomonitoring Data

NHATS	National Human Adipose Tissue Survey	U.S. EPA	1970–1989
GerES	German Environmental Survey	Robert Koch Institute	1985–2006
TEAM	Total Exposure Assessment Methodology	U.S. EPA	1980s
NHEXAS	National Human Exposure Assessment Survey	U.S. EPA	1990s
NCS	The National Children's Study	NIH, NIEHS, CDC, U.S. EPA, and others	2000–ongoing
CHMS	Canadian Health Measures Survey	Statistics Canada, Health Canada, PHAC, and others	2007–ongoing

Using NHANES Data: Phthalates in Women

CHEMICAL CLASSES MEASURED IN BIOLOGICAL TISSUE OF PREGNANT WOMEN, NHANES 2003–2004

	No. of metabolites measured			
Chemical class	**Blood**	**Serum**	**Urine**	**Total**
Cotinine		1		1
Environmental phenols			4	4
Metals	4			4
Organochloride pesticides		13		13
Organophosphate insecticides			6	6
Perchlorate			1	1
Phthalates			13	13
PBDEs and other brominated flame retardants		11		11
PCBs and dioxin-like chemicals		55		55
PAHs			10	10
PCFs		12		12
VOCs	33			33

Source: Woodruff et al., 2011

Using NHANES Data: Phthalates in Women

Parent Compound	Metabolite	n	Reproductive Status	LOD	Percent >LOD	GM (GSE)	50th Percentile	95th Percentile
Benzylbutyl phthalate (BzBP)	Monobenzyl phthalate (MBzP)	91	Pregnant	0.1	100	15.12 (3.79)	17.8	86.8
		497	Nonpregnant		100	14.77 (0.79)	15.5	99.9
Dibutyl phthalate (DBP)	Monoisobutyl phthalate (MiBP)	91	Pregnant	0.3	99	3.47 (0.84)	4.4	19.5
		497	Nonpregnant		98	4.21 (0.27)	4.5	21.1
	Mono-*n*-butyl phthalate (MnBP)	91	Pregnant	0.4	99	18.83 (4.11)	17.1	143.8
		497	Nonpregnant		99	24.64 (1.16)	25.7	132.2
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)	91	Pregnant	0.4	100	226.53 (79.03)	265.7	2263.0
		497	Nonpregnant		100	246.06 (29.56)	234.5	2992.6

Source: Woodruff et al., 2011

Using NHANES Data: Dioxin Exposure

	Background daily exposure dose estimate	Body burden estimate
2003	EPA's 2003 "Reassessment" used mid-1990s measurements from air, soil, water, and food ingestion	Based on six blood surveys of 316 individuals
2009	2009 update based on measurements from food ingestion surveys from 2000 to 2004	Based on **NHANES** blood concentration recorded in 2000/2001

Using NHANES Data: Dioxin Exposure

AVERAGE CONCENTRATIONS (PG/G LIPID) OF INDIVIDUAL CONGENERS AND TEQS IN HUMAN BLOOD FROM THE DIOXIN REASSESSMENT (MID-1990S DATA) COMPARED TO NHANES 2001/2002 DATA

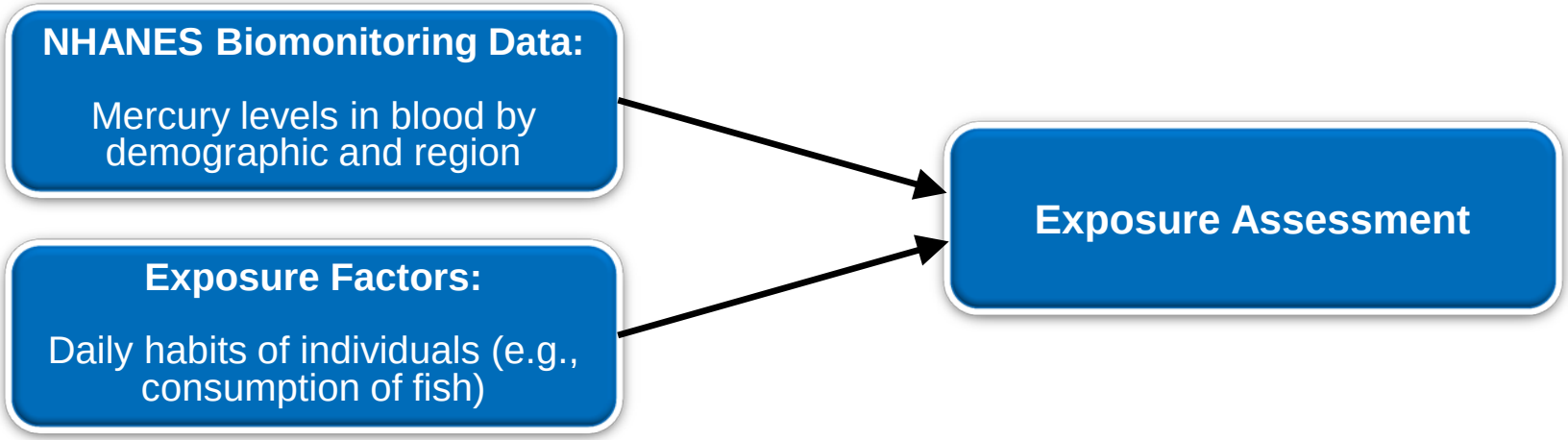
Congener	Mid-1990s, Mean concentrations ND = ½ LOD	NHANES 2001/2002 Mean concentrations ND = LOD/√(2)	NHANES 2001/2002 Mean concentrations ND = 0	Percent detected
2378-TCDD	2.1	2.5	0.7	13
12378-PCDD	5.2	4.6	3.7	35
123479-HxCDD	6.2	5.1	2.9	34
123678-HxCDD	73.1	47.1	46.9	93
123789-HxCDD	7.1	6.0	4.0	42
1234678-HpCDD	79.2	53.8	53.7	99
OCDD	664.0	452.1	419.2	82
1234789-HpCDF	1.2	2.4	ND	0
OCDF	2.1	7.4	ND	0
Total TEQ (PCDD/PCDF/cop PCB)	22.9	21.7	17.2	

ND = non-detect

Source: Lorber et al., 2009

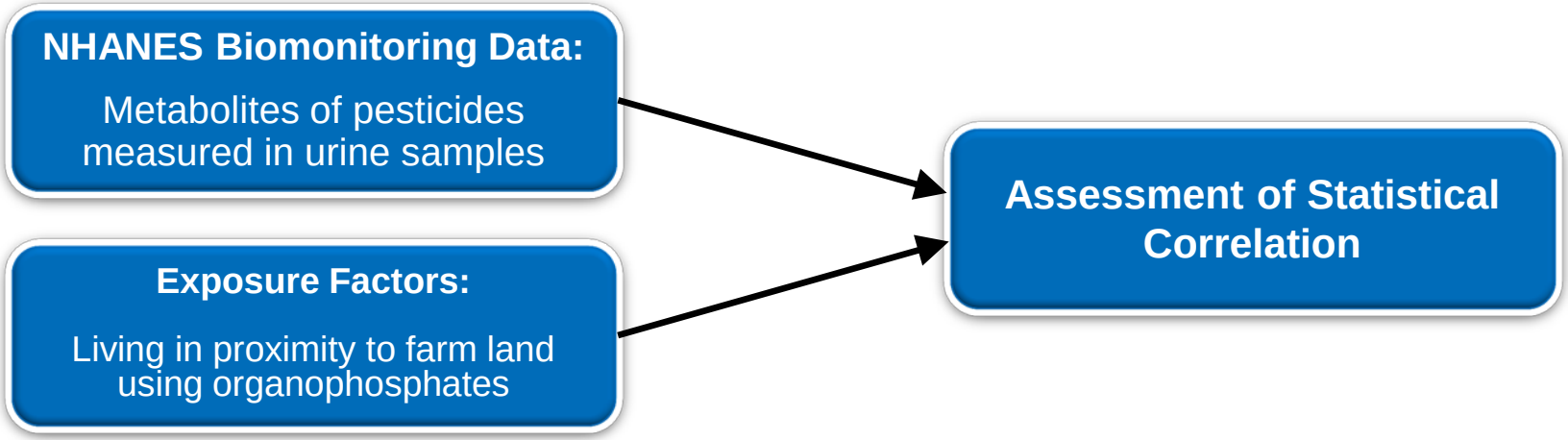
Using NHANES Data: MethylImercury and Fish Consumption

- NHANES data can be used to show association between measured exposure and exposure factors.
  - Example: association between blood mercury levels and fish consumption exposure factors



Using NHANES Data: Pesticides and ADHD

- Pesticide exposure and attention-deficit hyperactivity disorder (ADHD)
  - Association between levels of pesticides in urine samples and diagnosis of ADHD



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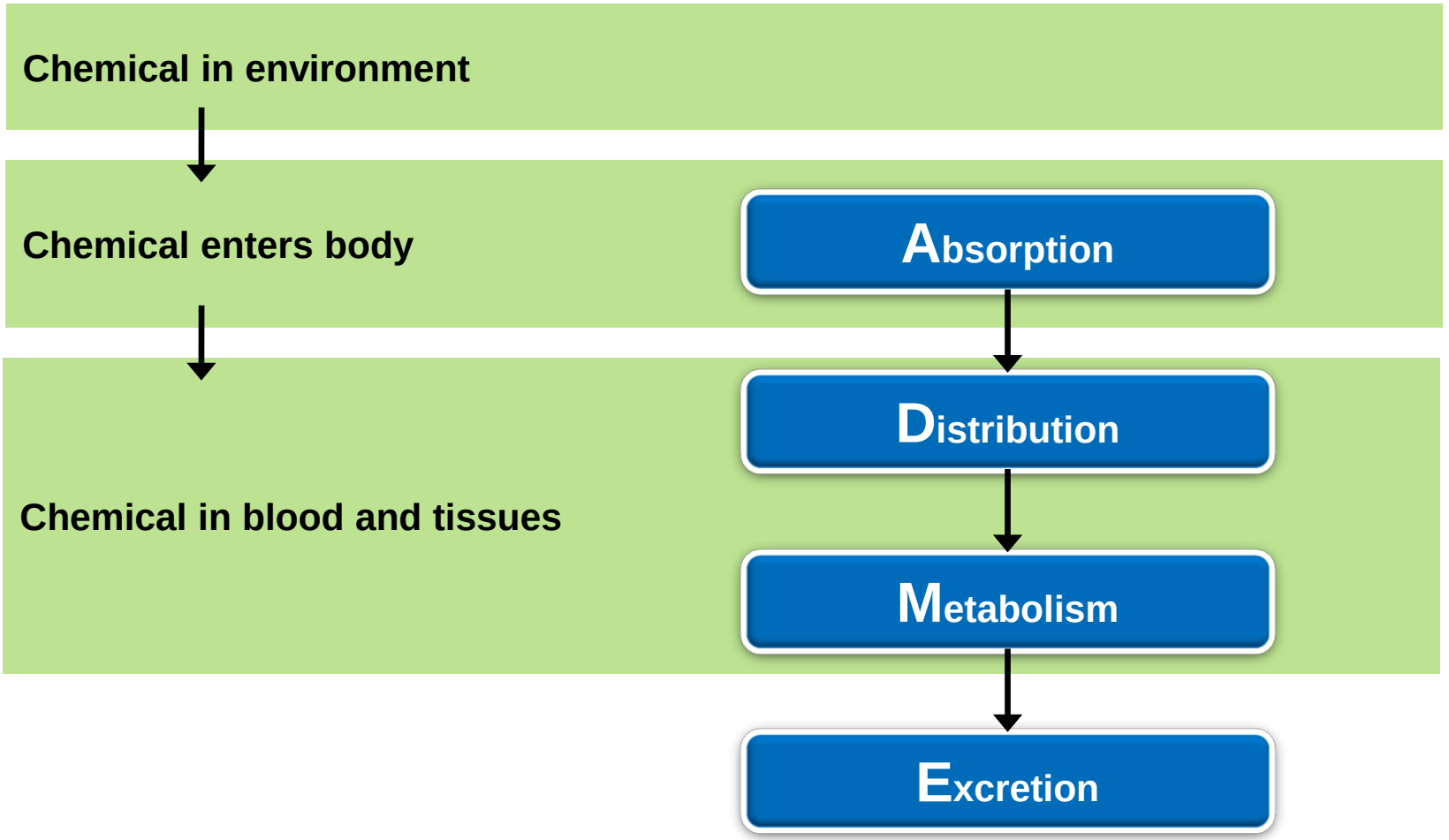
PHARMACOKINETIC MODELS

Pharmacokinetics

The study of the time course of ADME of a substance in an organism's body

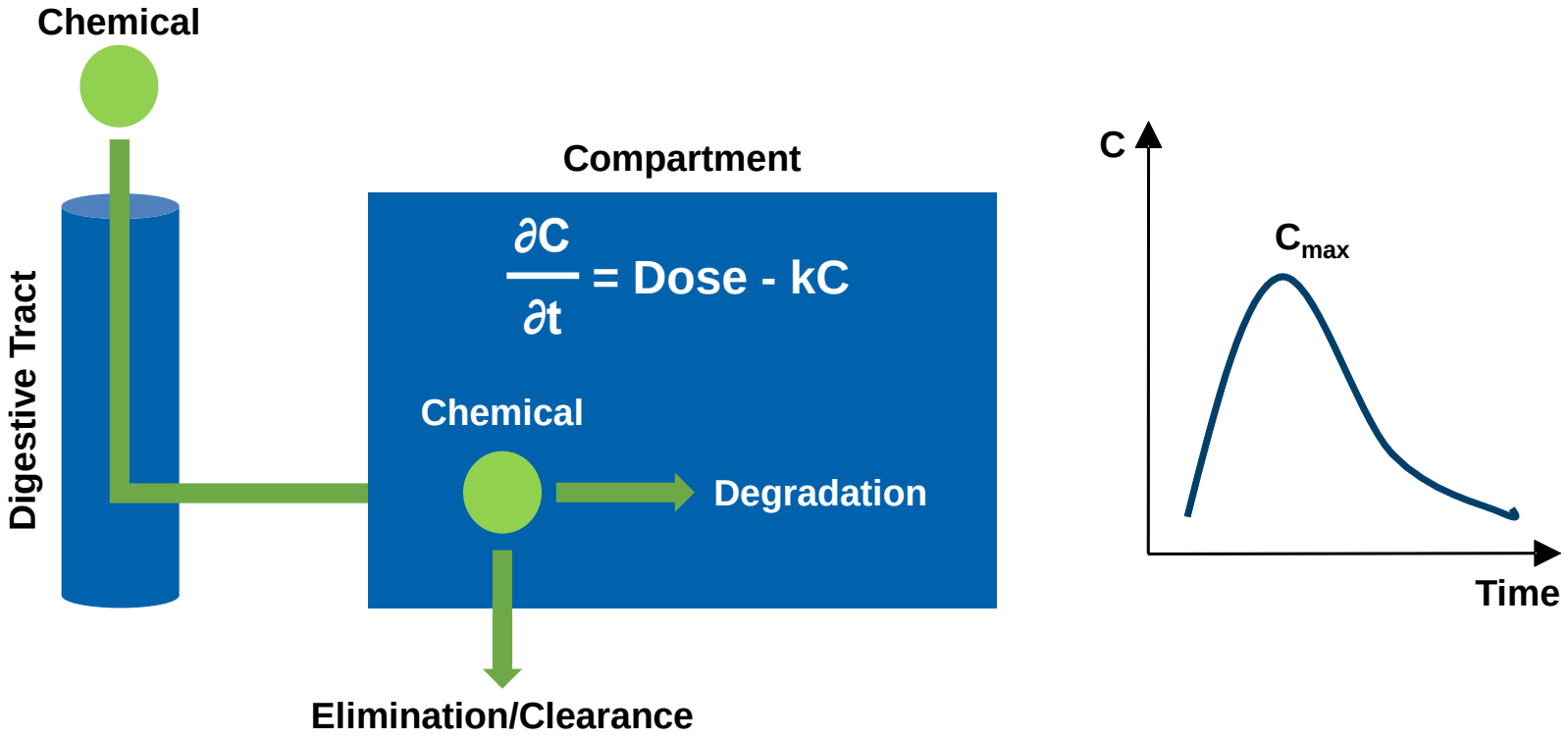


Pharmacokinetic Models

- Pharmacokinetic (PK) models evaluate the internal dose of a compound
  - Simple – one-compartment, first-order
    - First-order: Rate of elimination of chemical is dependent on the amount of chemical present
    - Steady state: Assuming no net change in amount of chemical
  - Complex – multi-compartment, physiologically-based pharmacokinetic

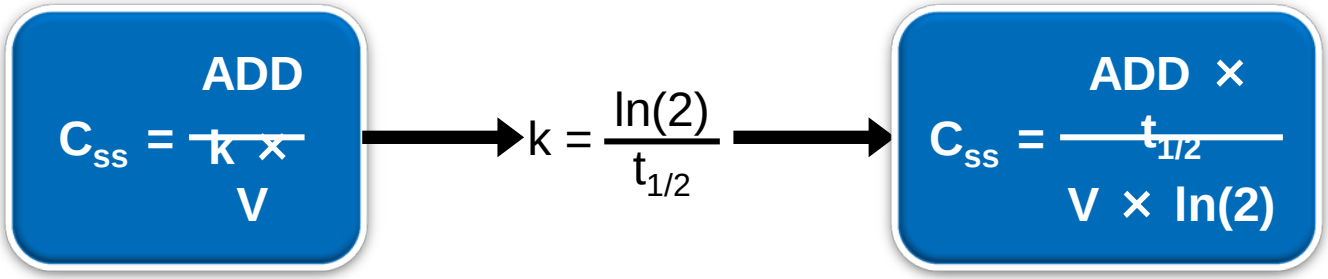
- How can PK models be used in exposure assessment?
  - Characterize internal dose
  - Route-to-route extrapolation of the internal dose
  - Exposure reconstruction from epidemiological studies

One-Compartment, First-Order PK Models



- C is the pollutant concentration (mass/volume)
- k is the first-order elimination rate constant ($time^{-1}$)

Steady-State One-Compartment, First-Order PK Model



Where:

- C_{ss} is the steady-state pollutant concentration (mg/L, ng/g-lipid weight)
- ADD is the average daily dose (mg/day, ng/day)
- k is the first-order elimination constant (day^{-1}, sec^{-1})
- V is the volume of distribution (L)
- $t_{1/2}$ is the half life for elimination (day, sec)

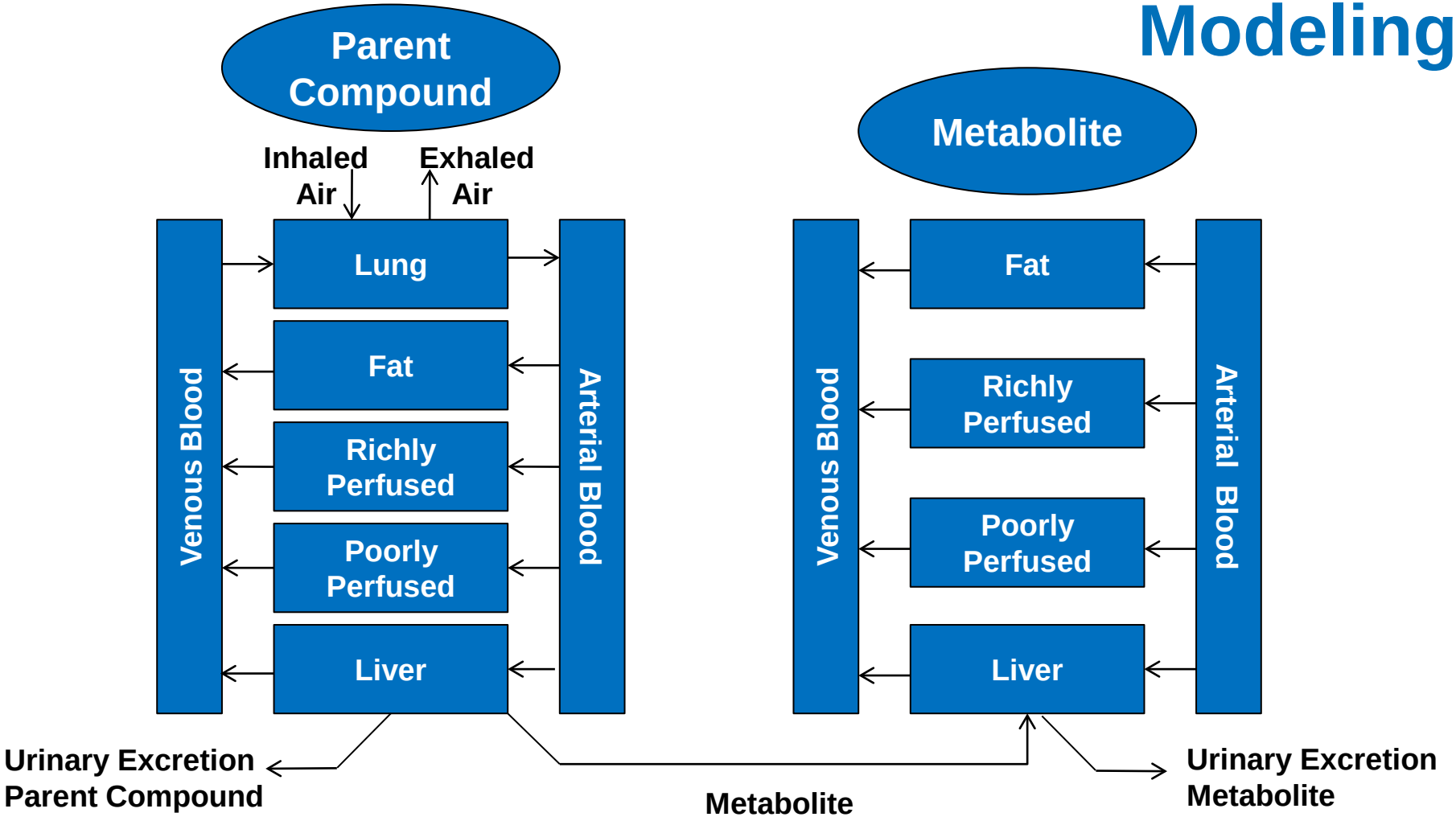
Non-Steady-State PK Model

$$C(t) = C(0)e^{-kt} + \left[\frac{ADD_t}{V_t} \times \frac{1 - e^{-kt}}{k}\right]$$

Where:

- C(t) is the pollutant concentration at time, t (mg/L, ng/g-lipid weight)
- C(0) is the initial pollutant concentration at time, 0 (mg/L, ng/g-lipid weight)
- ADD is the average daily dose (mg/day, ng/day)
- k is the first-order elimination constant
- V is the volume of distribution (L)

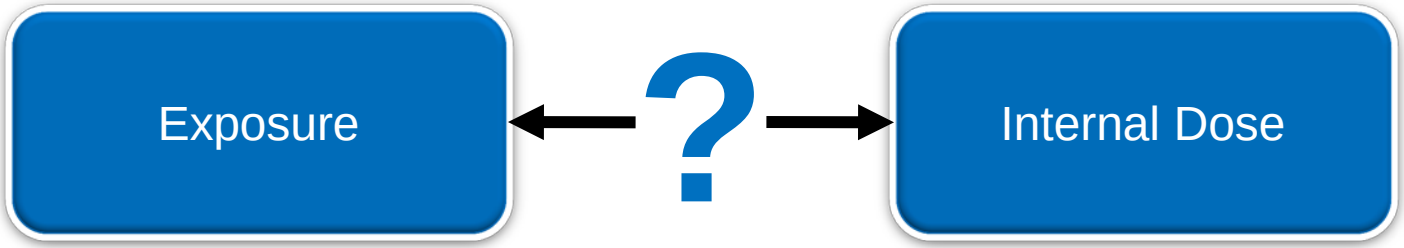
Multi-Compartment Physiologically-Based PK Modeling



Source: Hays 2007, Figure 6, p 9

PK Advantages & Limitations

Advantages	Limitations
Provides insight into the body burdens that result from specific exposures (forward-based) or to specific exposure patterns that cause a body burden (backward-based)	Requires specific knowledge of model parameters Must understand relationship between exposure and internal dose



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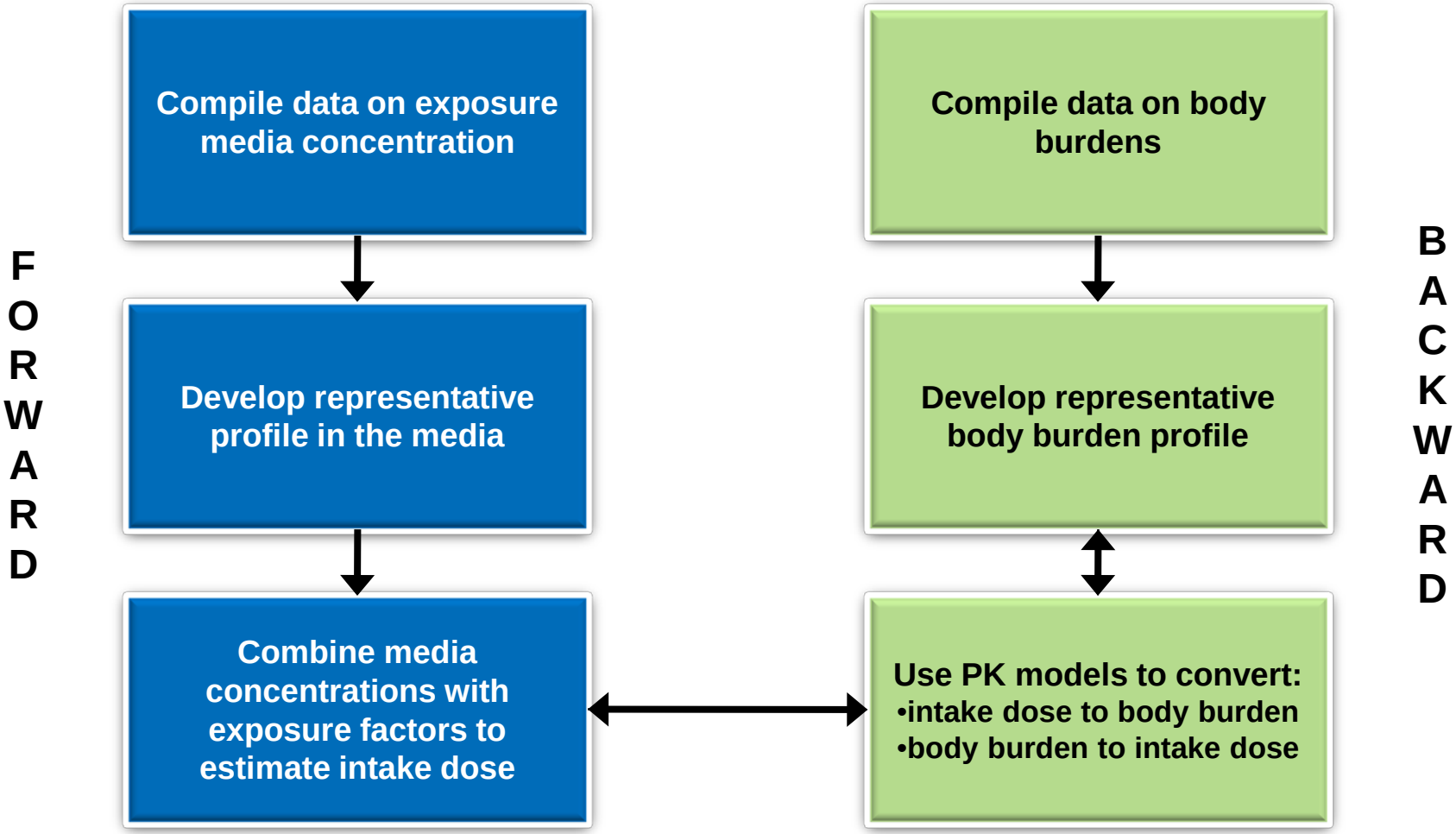
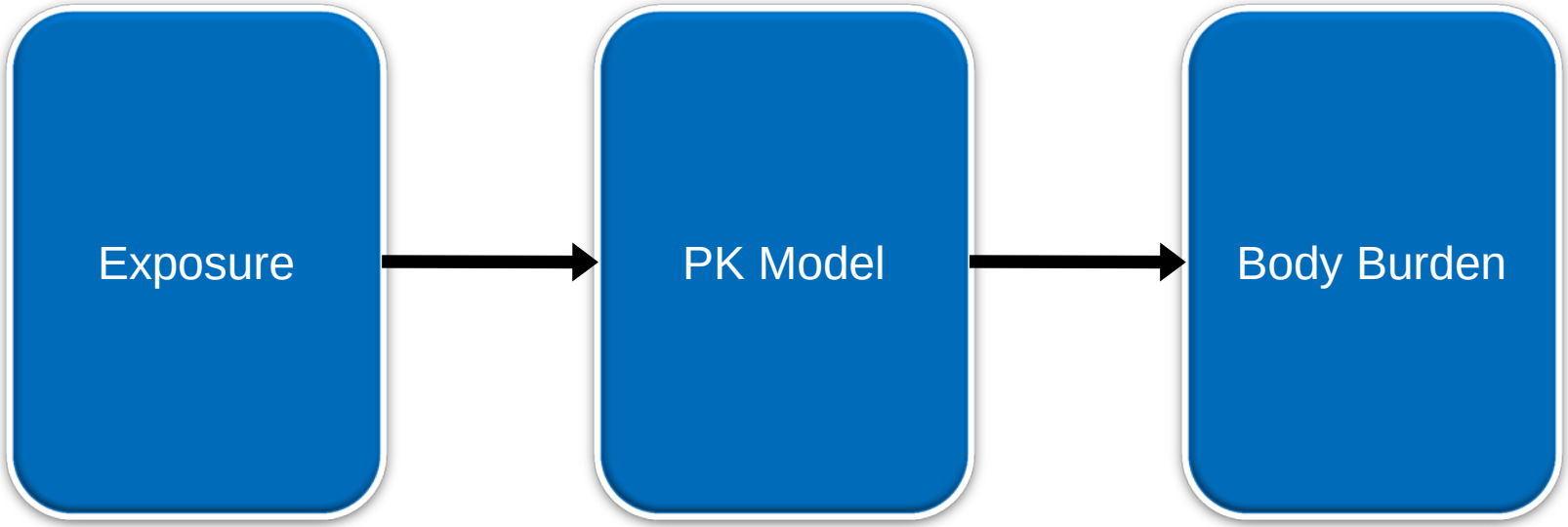
USING PHARMACOKINETIC MODELS

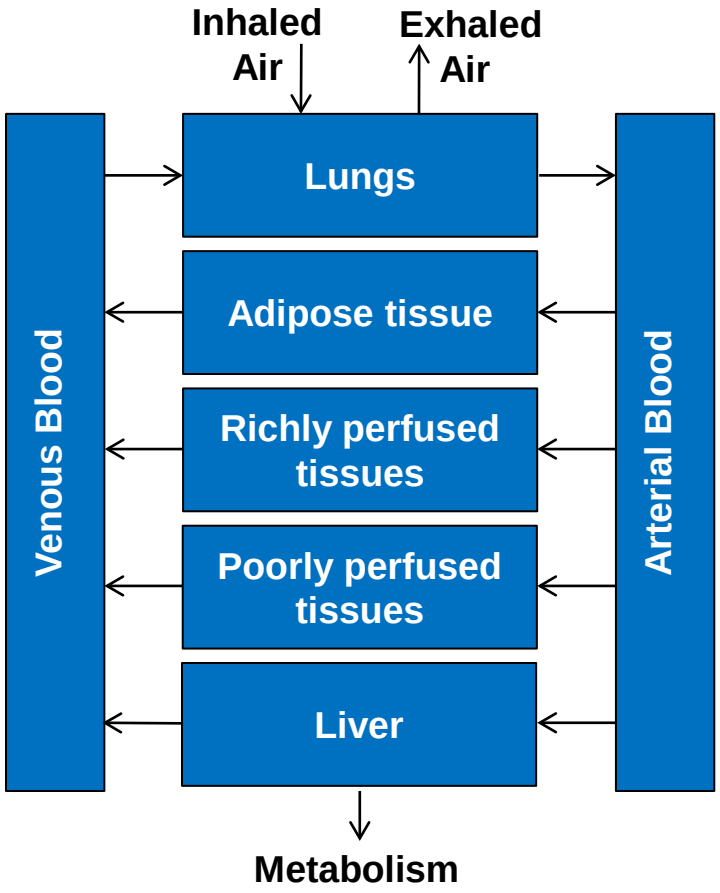
Forward & Backward Analysis



Forward Analysis

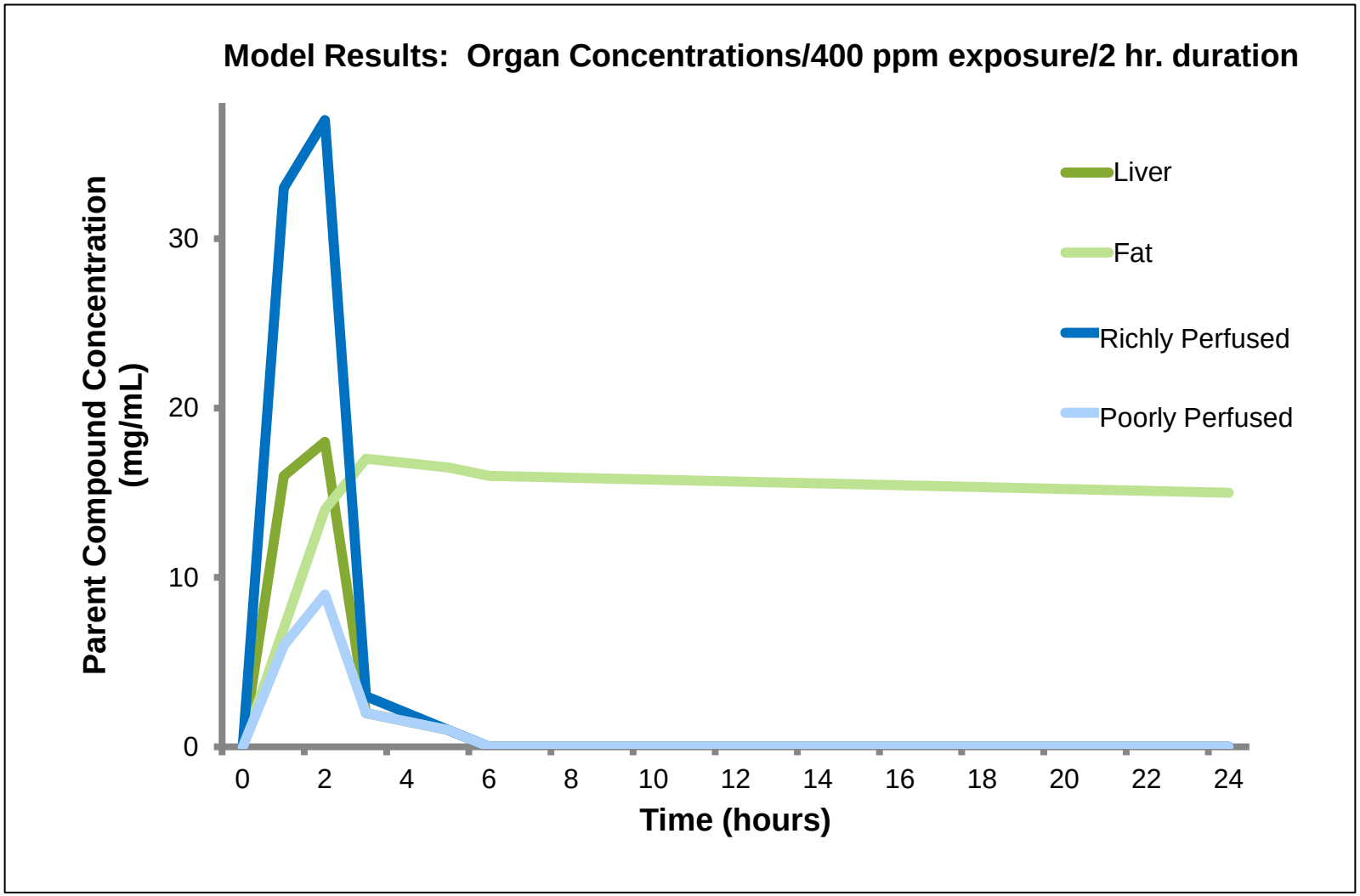


Forward Analysis Example: Inhalation of VOCs

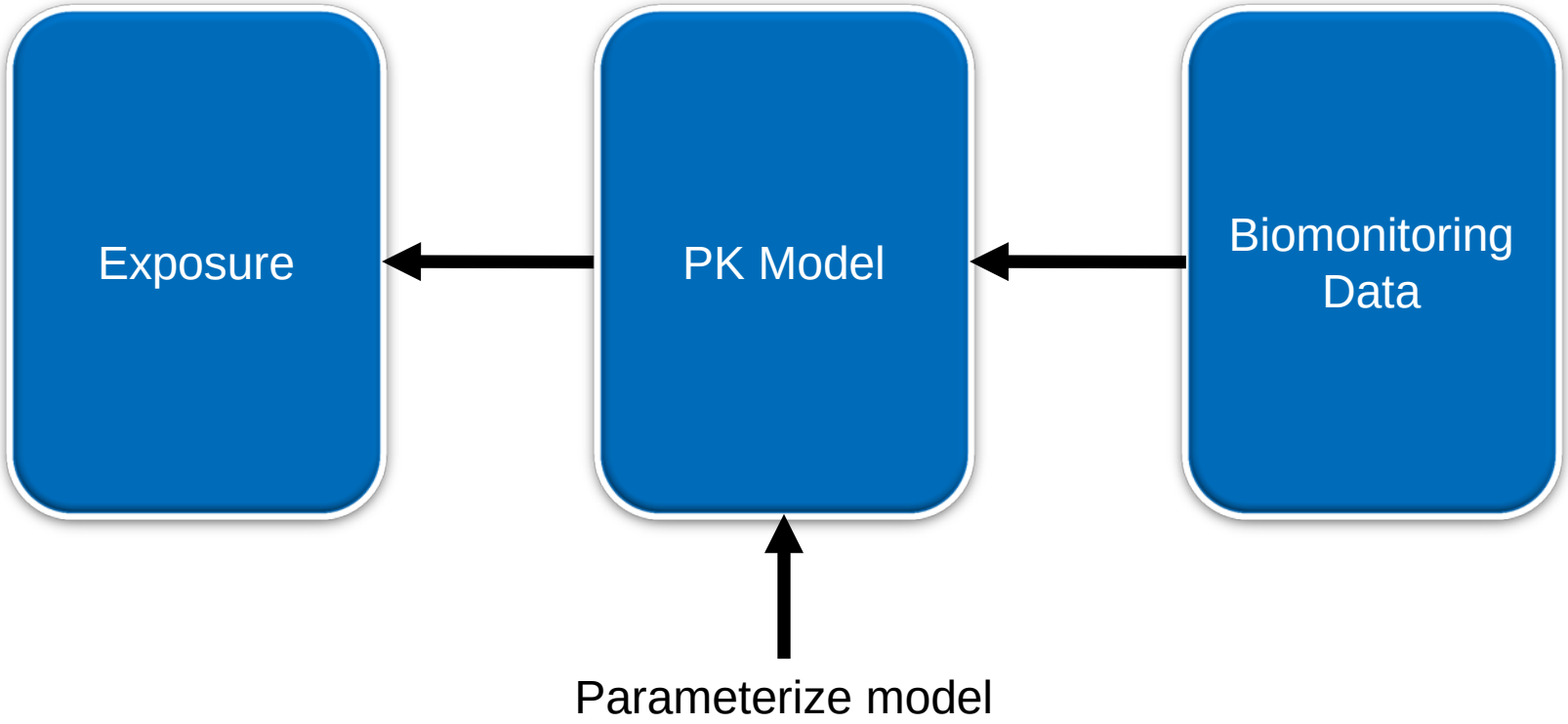


- Scenario: Inhalation exposure to a lipophilic volatile compound
- Concentration and duration of exposure: 400 ppm for 2 hours
- Simulations based on human physiological parameters

Forward Analysis Example: VOC Modeling Results



Backward Analysis

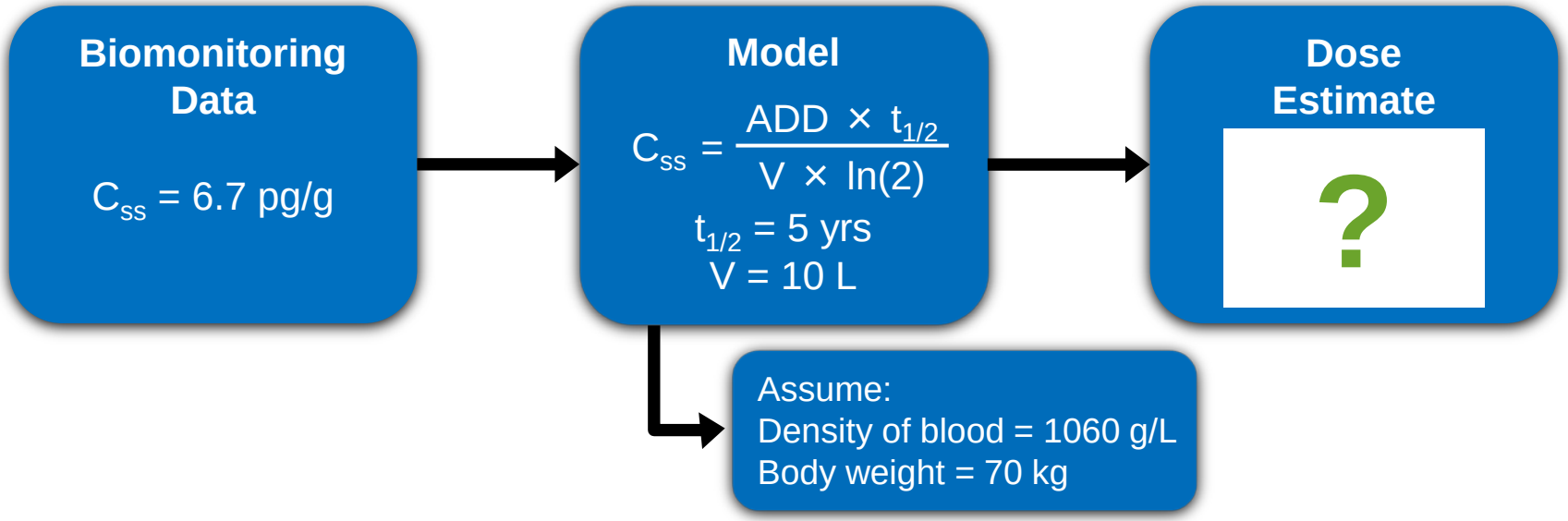


Steps for Conducting Backward Analysis

Step 1:	**Use biomonitoring data to establish contaminant level in body**
Step 2:	**Construct a PK model or select an existing one**
Step 3:	**Assign values to model parameters (e.g., kinetic constants, blood flows)**
Step 4:	**Run model to obtain exposure estimates**

Backward Analysis Example: Reconstruction of Dioxin Dose

One compartment, first-order, steady state model:



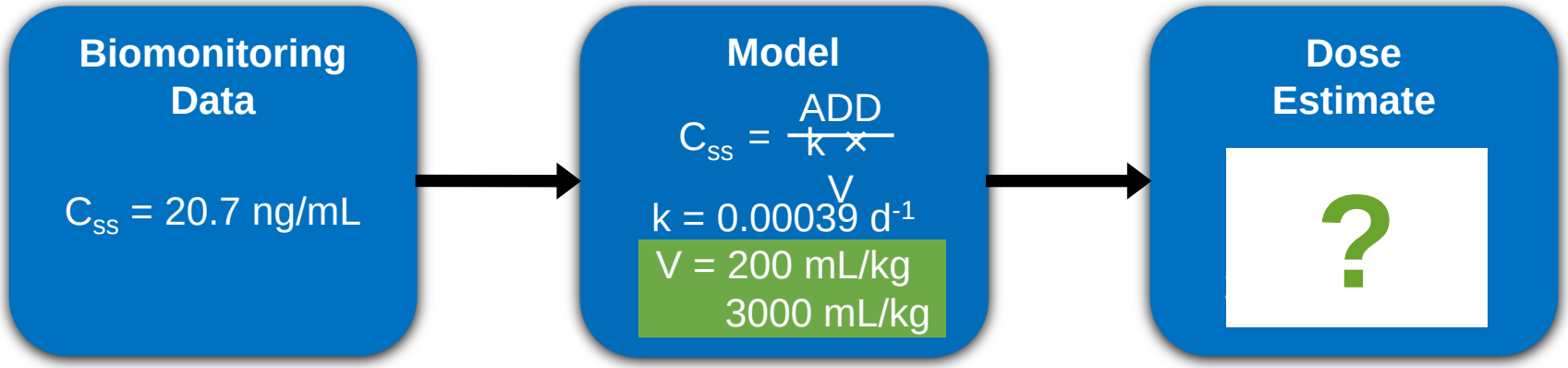
$$C_{ss} = \frac{ADD \times t_{1/2}}{V \times \ln(2)} \rightarrow ADD = \frac{C_{ss} \times V \times \ln(2)}{t_{1/2}} \rightarrow ADD = \frac{(6.7 \frac{\text{pg-dioxin}}{\text{g-blood}})(10 \text{ L-blood})\ln(2)}{5 \text{ years}}$$

$$ADD = \frac{(6.7 \frac{\text{pg-dioxin}}{\text{g-blood}})(1060 \frac{\text{g-blood}}{\text{L-blood}})(10 \text{ L-blood})\ln(2)}{5 \text{ years}(365 \frac{\text{days}}{\text{year}})(70 \text{ kg-bw})} \rightarrow ADD = 0.385 \frac{\text{pg-dioxin}}{\text{kg-bw-day}}$$

Backward Analysis Example: PFOS

- Perfluorooctanoic sulfonate (PFOS)
- Type of perfluorinated compound (PFC)
- Extremely stable, hydrophobic, lipophobic
- Found in stain-resistant and non-stick products
- Persistent and bioaccumulative
- Dietary ingestion and ingestion of house dust believed to be primary exposure pathways

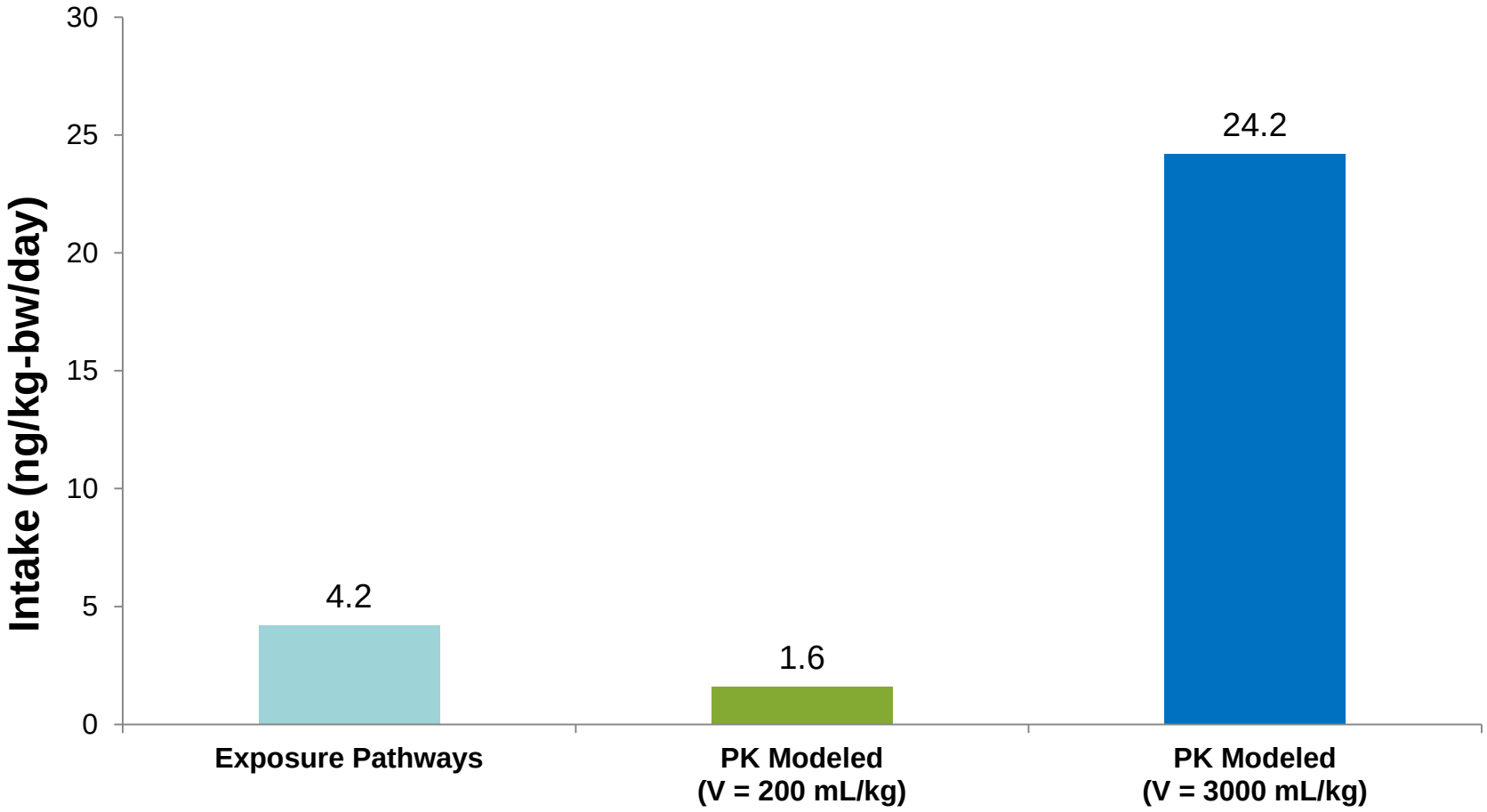
Backward Analysis Example: Reconstruction of PFOS Dose



$$C_{ss} = \frac{ADD}{k \times V} \rightarrow ADD = C_{ss} \times k \times V \rightarrow ADD = (20.7\frac{ng}{mL})(0.00039\ \frac{1}{day})(200\frac{mL}{kg})$$

$$C_{ss} = \frac{ADD}{k \times V} \rightarrow ADD = C_{ss} \times k \times V \rightarrow ADD = (20.7\frac{ng}{mL})(0.00039\ \frac{1}{day})(3000\frac{mL}{kg})$$

PFOS PK Model Results



Source: Egeghy and Lorber, 2011

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BIOMONITORING EQUIVALENTS

What are Biomonitoring Equivalents?

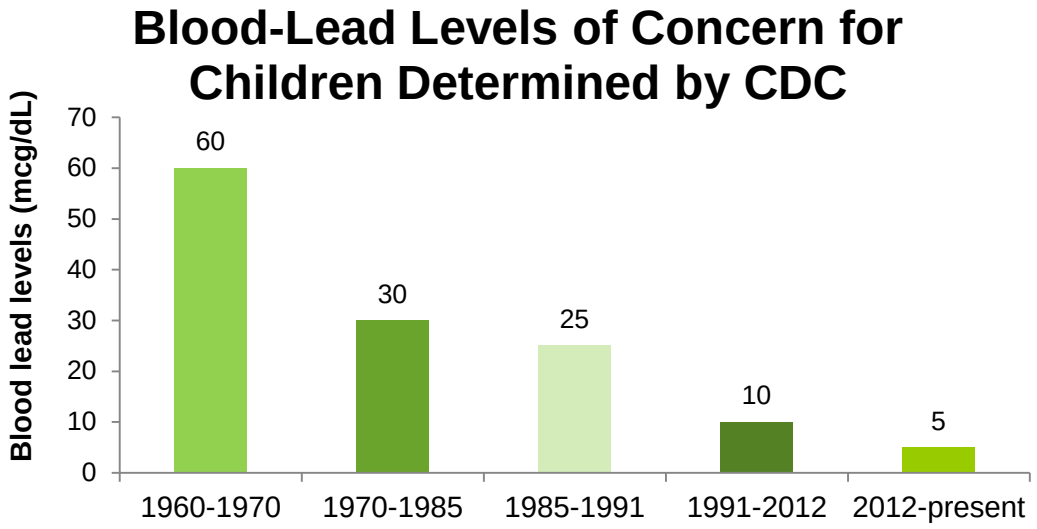
- The levels of specific chemicals in blood, urine, or other human biological media or tissues, gathered using biomonitoring methods, that are consistent with existing exposure guidance values

Use of Biomonitoring Equivalents

- Possible to link biomonitoring data and health effects using BEs and epidemiological studies, but there are limitations
- USA:
  - Does not currently use BEs for regulatory requirements
  - Some support for using BEs because they are more easily understood by general public
- Abroad:
  - HealthCanada and some European nations have begun using BEs

BE Use Example: Lead

- Effects from lead exposure are varied and numerous
- Children more vulnerable and sensitive to lead exposure
- CDC adopted a Level of Concern for children of 5 µg/dL
- Biological Exposure Index (BEI) for adults = 30 µg/dL
  - Relates to occupational exposure



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CONCLUSION

Conclusion

- Biomonitoring measures the actual levels of chemicals in the body.
- NHANES is an important source of biomonitoring data.
- Body burden and other biomarker data, gathered through biomonitoring, can strengthen exposure assessment.
- Pharmacokinetic modeling can be used to relate exposure to dose using reconstructive or predictive methods.