EPA
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Exposure Assessment (EXA)
Course Series

Interpreting Biomonitoring Data and Using Pharmacokinetic Modeling in Exposure Assessment

Reading Packet

EXA 408



EPA's Risk Assessment Training and Experience (RATE) Program

EXA 408: Interpreting Biomonitoring Data and Using Pharmacokinetic Modeling in Exposure Assessment

READING PACKET

Exposure Assessment (EXA)
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EPA's Risk Assessment Training and Experience Program

EXA 408: Interpreting Biomonitoring Data and Using Pharmacokinetic Modeling in Exposure Assessment

Widespread acceptance and use of the CDC's National Health and Nutritional Examination Survey (NHANES) database, which, among other things, reports measured concentrations of environmental contaminants in blood and urine, has led to an expanded understanding of general population exposures in the United States. These biomonitoring data incorporate exposures from multiple pathways and sources and can help researchers characterize exposure and internal dose. This module will introduce the concept of biomonitoring and discuss the use of biomonitoring data with pharmacokinetic models to estimate dose.

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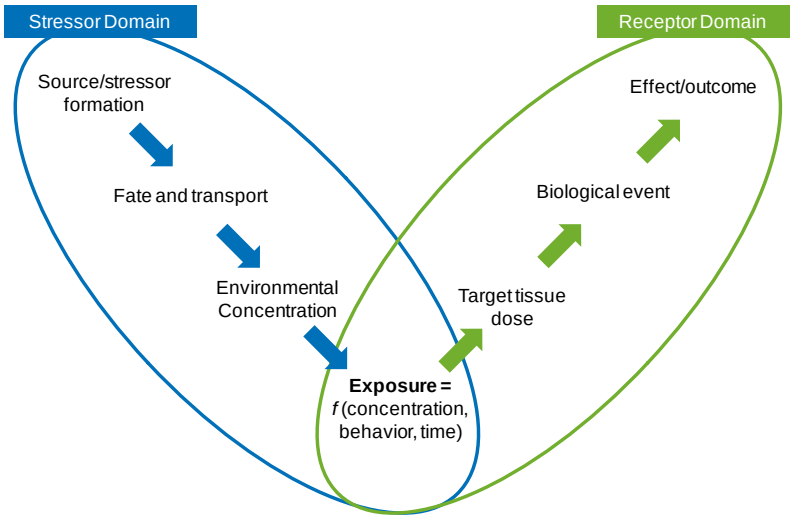
1. INTRODUCTION

This course covers the main elements of **biomonitoring** and how it can be used in exposure assessments. These elements include:

- Body burdens and biomarkers
- The National Health and Nutritional Examination Survey (NHANES) database
- Pharmacokinetic (PK) models, how they are related to biomonitoring, and how they can be used for both forward and backward exposure analysis
- Biomonitoring equivalents

Figure 1. Source-to-Effect Continuum



As outlined throughout the EXA course series, exposure assessments evaluate the movement of a chemical from its source to a receptor as shown in Figure 1. Traditional risk assessment has used a single-stressor approach because data are typically inadequate to quantify risks from multiple stressors, or the methodologies available for considering possible impacts from multiple exposures are limited. Traditional exposure assessments rely on modeled or measured concentrations in external media. For example, the concentration of a chemical in an environmental medium (e.g., soil) and exposure factors like ingestion rate, body weight, and exposure frequency/duration can be used to predict or reconstruct dose for potential receptors.

Some of the limitations to the methods used in traditional exposure assessment include the following.

- Monitoring at all possible exposure locations is difficult, costly, and might not accurately reflect the dose to the target population of the assessment.
- Modeling fate and transport of the chemical in the environment and in the human body can be difficult and subject to errors due to assumptions.
- Exposure factor data rely on activity diaries, questionnaires, and the recollection of participants about what they have done and where they have been, which is subjective and sometimes unreliable.

Given its limitations, traditional exposure assessment is subject to some uncertainties that can possibly result in a misrepresentation of exposure. **Using biomonitoring data in exposure assessment is an alternative to the traditional approach.** Biomonitoring data can be used to estimate the total internal dose of a chemical by measuring the actual levels of the chemical, its metabolites, or its byproducts in the body. These biomonitoring data can also be used in conjunction with PK models to estimate intake dose. Using biomonitoring data can potentially reduce the uncertainty associated with basing estimated dose on exposure factors and monitoring data, which might be unreliable and result in an overestimate or underestimate of exposure. It is difficult,

however, to parse out the source or pathways of exposure from biomonitoring data, and using biomonitoring data can increase the uncertainty in this respect (Hays et al., 2007). Biomonitoring data can help reconstruct the dose of chemical a person received in a specific exposure scenario, thereby providing a **biologically relevant measure of dose** (Sexton, 2004).

2. BIOMARKERS, BODY BURDENS, AND BIOMONITORING

This section provides some basic definitions related to biomonitoring, presents an overview of the National Health and Nutrition Examination Survey and describes how data included in this data set can be used in exposure assessment, and lists other sources of biomonitoring data.

2.1 Definitions

Biomarker: A general term for any biologic **indicator of exposure** to a chemical. These can be the measured levels of chemicals, their metabolites, or byproducts produced through interaction between the chemical and the target tissue or cell (NRC, 2006).

Biomarkers are collected using biomonitoring methods and measure one of the following:

- The amount of a compound in the body;
- The biological interaction of the compound with the body; or
- The changes in the physiology of the organism as a result of interaction with the compound.

Examples of biomarkers include protein and DNA adducts, changes in enzyme synthesis or activity, and chemical concentrations in urine. Depending on the contaminant and other factors, biomarkers can be useful in identifying source and timeframe of exposure. For instance, measuring the bioaccumulation of a substance or its metabolite can tell us how long the chemical has been in the body, and where the chemical is found in the body can tell us about the route of exposure. Biomarkers reflect internal dose and confirm that exposure to a chemical has occurred; however, the presence of a biomarker alone does not indicate that an effect has occurred or that a person is at risk for adverse effects (U.S. EPA, 1992a).

If the chemical being measured in the body is the parent compound, that measurement is considered a body burden, a specific type of biomarker.

NHANES is one source of biomarker data; this data source is covered in more detail in Section 2.2. Other sources of biomarker data include research studies conducted on smaller scales in the context of a specific research objective. An example would be a biomonitoring study conducted by a city health department to evaluate blood-lead levels in children.

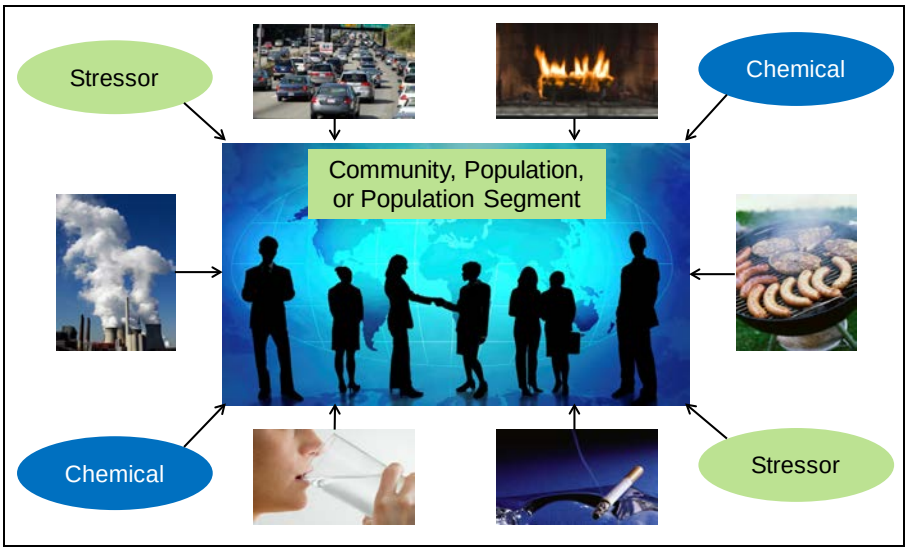
Body burden: A specific type of biomarker that describes the total amount of the **parent chemical**—not its metabolites or byproducts—in the body as measured through biomonitoring (ATSDR, 2004; U.S. EPA, 1992b).

Biomonitoring: The act of measuring the concentration of chemicals, their metabolites, or their byproducts in tissues or fluids such as blood, urine, breast milk, hair and other samples (CDC, 2009; Hays et al., 2007; ATSDR, 2004; U.S. EPA, 1992b). .

Biomonitoring can capture exposure from multiple pathways and sources, as is illustrated in the conceptual example presented in Figure 2. Biomonitoring data will provide measures of internal dose for particular chemicals of interest that also reflect effects from external factors, such as the following:

- Various environmental pollutants, like those emitted from the factory, automobiles, fireplace, and other sources depicted in the figure;
- Dietary habits—for example, if someone eats a lot of grilled meats or drinks water from a public or private source of drinking water;
- Access to health care and other social factors;
- Other daily activities, including smoking or exercise habits.

Figure 2. Biomonitoring Can Measure Various Exposures



A variety of external factors could influence the extent of exposure of individuals or a population as well as their response to exposure (NRC, 2006; Sexton, 2004).

There are advantages and limitations associated with biomonitoring, as summarized in the text box below. One advantage of biomonitoring is the ability to measure aggregate exposure to a given compound from all pathways; body burden data include total exposure to a single compound through multiple exposure sources and routes. Biomonitoring also reflects internal dose, which accounts for uptake of a compound into the body (biouptake) and the accumulation of the compound in the body (bioaccumulation). Biomonitoring can be used in epidemiology studies to analyze relationships between internal dose and health outcomes.

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

Biomonitoring data also have limitations. Using biomonitoring data might not help identify the particular source(s) or pathway(s) that are responsible for the bulk of the internal dose. Also, biomonitoring might involve the collection of human specimens such as blood, urine, breath, hair, or fat. Such collections can be particularly burdensome with regard to information collection requirements and permissions, and can also be cost prohibitive due to requirements of specialized equipment, training, preparation, testing, and storage. Finally, data from routine toxicity tests are not typically linked to an internal dose, so the interpretation of potential health risks from biomonitoring may be difficult in the absence of epidemiological studies (Sexton, 2004).

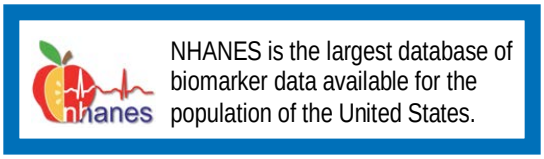
2.2 NHANES Biomonitoring Data

The National Health and Nutrition Examination Survey, or NHANES, is a program of studies conducted by the U.S. Centers for Disease Control and Prevention "designed to assess the health and nutritional status of adults and children in the United States" (http://www.cdc.gov/nchs/nhanes.htm). NHANES data are collected using a combination of interviews and physical examinations, and the program is designed to gather information and data on the health of the nation as a whole. NHANES findings are also the basis for national averages and distributions for measurements like height, weight, and blood pressure.

Biomonitoring data from NHANES have been used to identify:

- Chemicals to which the general population has been exposed
- Body burdens of chemicals
- Differences in body burdens according to demographics (such as age or race)
- Potential trends in body burdens over time

Health status information has also been used along with the biomonitoring data to investigate potential relationships between chemical exposure and diseases.



NHANES began in the 1960s as a series of surveys of different population groups and health topics. In 1999, the survey was modified to periodically examine a nationally representative sample of about 5,000 people in states across the United States. Surveys are conducted every two years, asking new questions and collecting new data during each cycle (CDC, 2009). The data included in NHANES are not collected using a simple random sample. Instead, survey participants are selected using a probability sampling design to ensure the data are representative of the noninstitutionalized, civilian U.S. population. People aged 60 and older, African Americans, and Hispanic people are oversampled to increase the reliability and precision of estimates for these groups. Each sampled individual is assigned a numerical sample weight that measures the number of people in the population represented by that particular sampled individual. These weights adjust for unequal selection probabilities or certain types of nonresponse to the surveys and must be used to obtain more accurate national estimates from the NHANES data.

Biomonitoring data are collected through blood, urine, and sometimes hair or oral samples from a population ranging in age from 1 to over 60. These samples are analyzed for markers of disease (like elevated blood sugar levels); the presence of various compounds, including a variety of environmental chemicals of concern; and biomarkers of chemical exposure (CDC, 2009). The full suite of lab tests is not performed on every age group; for example, urine samples are only collected from children over the age of 6.

In 2000, the CDC compiled and published the *National Report on Human Exposure to Environmental Chemicals* based on the 1999-2000 NHANES data. In 2009, the fourth edition of this report was published, presenting data for 212 environmental chemicals and their metabolites, including disinfection byproducts, volatile organic compounds, and perfluorinated compounds. Because NHANES is a dynamic survey conducted every two years, the list of monitored chemicals is continually updated to reflect emerging contaminants of concern (Scott and Nguyen, 2011; CDC, 2009).

NHANES surveys can be used to:

- Determine which chemicals of concern are present in U.S populations and at what concentrations the compounds are found
- Determine what proportion of the population has measured contaminant levels above the levels associated with adverse health effects
- Determine whether exposure is higher among minorities, children, women of childbearing age, or other populations of concern
- Establish reference or background values that can then be used by researchers and physicians to determine whether a person or group has an unusually high exposure to a particular chemical
- Track levels of chemicals in the body over time using historical data
- Prioritize research topics on human health effects due to exposure

In general, survey data on health status, family history, and behaviors like smoking and physical activity can be combined with data from blood and urine samples to draw conclusions about the connections between exposure, external factors, and resulting body burdens. Researchers can also use health and behavior data to determine which exposure pathways are most relevant for specific chemicals based on the types and amounts of chemicals that appear in biomonitoring samples (CDC, 2009).

To illustrate how NHANES data can be used to better understand exposures, two examples are provided as part of this course.

Example: Using NHANES Data to Understand Exposure to Phthalates in Women

Phthalates are a class of chemicals added to plastics to increase their flexibility and durability. When plastics break down, phthalates are released into the environment. Exposure to phthalates has been shown to cause health problems, such as asthma, cancer, endocrine disruption, and obesity. The table below shows information from a study that analyzed NHANES 2003-2004 data for 163 chemicals, including phthalates, found in samples of blood, serum, and urine collected from pregnant women (Woodruff et al., 2011).

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

Metabolites of phthalates were measured instead of phthalates themselves because phthalates break down very rapidly in the body and little, if any, of the parent product is expected to remain in the body after exposure. Additionally, laboratory equipment is likely to contain phthalates, which can contaminate the samples. In this case, 13 different chemical metabolites of phthalates were measured in urine.

Researchers calculated various statistics for urinary phthalate metabolite concentrations, including the geometric mean, geometric standard error, and median (or 50th percentile), as shown in the table below (Woodruff et al., 2011). Urinary measurements are

useful because phthalates are often rapidly metabolized, with half lives on the order of hours, and therefore they are primarily eliminated via the urine. As seen in the percent greater than level of detection, or LOD, column in the table below, phthalate metabolites were present in nearly all of the samples for both pregnant and nonpregnant women. Because phthalates are rapidly metabolized and eliminated from the body within hours of exposure, the fact that almost 100% of women tested show phthalate metabolites in their urine indicates that women were exposed nearly every day that measurements were taken. This determination is based entirely on biomonitoring data and exemplifies how exposure assessors can draw conclusions about exposure (including timing) based on body burden measurements.

STATISTICS FOR URINARY PHTHALATE METABOLITE CONCENTRATIONS IN PREGNANT AND NONPREGNANT WOMEN, NHANES 2003–2004

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

In general, however, body burden data alone cannot be used to draw conclusions about exposure beyond the fact that an individual was exposed. These data must be combined with other information, such as epidemiological data or questionnaire responses, to elucidate potential exposure sources and pathways and potential effects of exposure.

Example: Using NHANES Data to Understand Exposure to Dioxins

Another example of how NHANES data can be used to provide information on exposure involves dioxins. Since 1991, U.S. EPA has been assessing the health risks of exposure to 2,3,7,8-TCDD and dioxin-like compounds, which are highly toxic byproducts of various industrial processes and are considered persistent organic pollutants. EPA originally produced background daily exposures and body burden estimates for dioxins using data collected in the 1990s. EPA has since updated the exposure assessment using new data collected from 2000 to 2004 and continues to update the assessment as needed.

The background daily exposure estimated in 1990 was based on measured concentrations of dioxins in air, soil, water, and food. Because more than 90% of exposures were determined to come from ingestion of animal products, EPA used only newer food survey information to update the daily exposure estimates in 2009. To reevaluate the body burden of dioxins, EPA used blood concentration data collected from NHANES during 2000–2001 (Lorber et al., 2009). The table below shows some of these dioxin data from NHANES.

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)	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

Dioxin was measured in blood instead of in the urine because dioxin is persistent in the body, and therefore blood measurements provide a more accurate representation of dioxin body burden. Dioxin has a long half life, and, because it is lipophilic, it accumulates in reservoirs like blood, serum, and lipids. Therefore, high levels of dioxins can persist in the body even if exposure does not occur on a daily or regular basis. NHANES data have been useful in tracking trends in dioxin exposure. Survey results have shown a consistent decline in dioxin exposure from a peak in the late 1960s to present day (Lorber et al., 2009).

Other Uses of NHANES

The NHANES program gathers data on other compounds of concern as well, such as blood measurements of methyl mercury. Methyl mercury is the form of mercury found in the body after dietary exposure through eating foods containing mercury, such as fish and shellfish. It is a chemical of concern because there is evidence that ingestion of methyl mercury can lead to impaired neurological development and function, especially in children and developing fetuses.

Because NHANES collects data on both mercury levels in the blood ***and*** information on daily habits of individuals (or exposure factors) related to fish consumption, scientists are able to explore potential relationships between mercury levels in blood and behaviors related to fish consumption. For example, scientists have used NHANES data to determine that blood mercury levels in women are associated with income, ethnicity, census region, and proximity to the coast. Groups that more commonly have elevated blood mercury levels include Asian women, women with higher incomes, women living in the northeast, and women living in coastal areas (CDC, 2009).

Using data collected from NHANES monitoring, researchers have also examined the statistical correlation between metabolites of organophosphate pesticides measured in urine samples and the diagnosis of attention-deficit hyperactivity disorder (ADHD). Researchers are concerned about this relationship in part because organophosphate pesticides are used widely in farming and residential landscaping. Previous studies have linked high organophosphate exposure to neurodevelopmental disorders in children. In addition, the dose of organophosphate pesticide is likely higher on a per kilogram body weight basis for children compared to adults (Bouchard, 2010).

2.3 Other Sources of Biomonitoring Data

In addition to NHANES, there are other sources of biomonitoring data that can be useful for exposure assessment. Some of these sources are listed in the table below. Two of the programs listed here, the National Children's Study and the Canadian Health Measures Survey, are currently ongoing. In addition to these

sources, individual research studies are conducted regularly to collect biomonitoring data on a much smaller scale for specific populations or pollutants.

Figure 3. Sources of Biomonitoring Data Other than NHANES

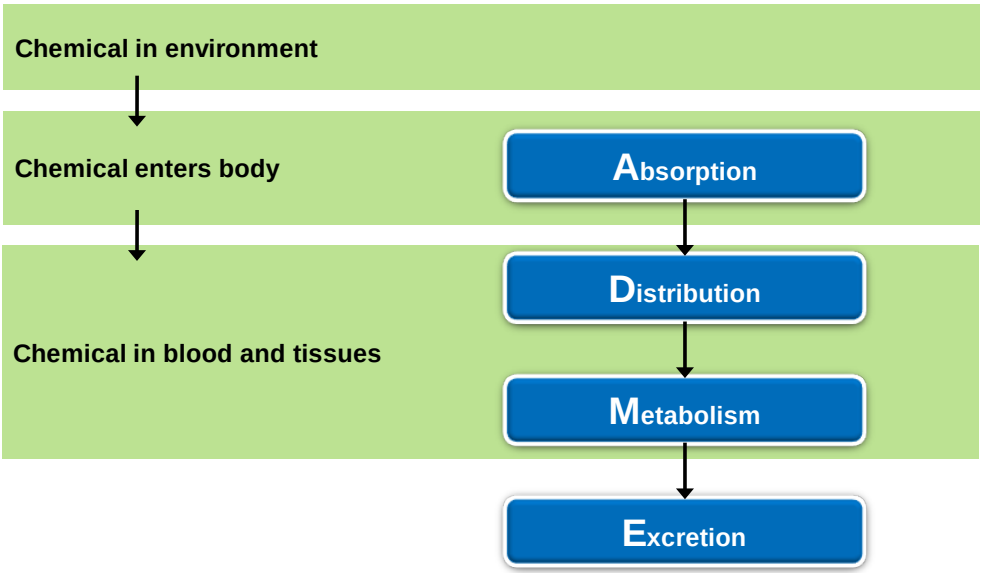
Program Name	Acronym	Supporting Organization	Description
National Human Adipose Tissue Survey	NHATS	U.S. EPA	Annual survey conducted from 1970 to 1989 to collect and chemically analyze human adipose tissue specimens for the presence of toxic chemicals (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55204)
National Human Exposure Assessment Survey	NHEXAS	U.S. EPA	Developed in the 1990s to provide critical information about multipathway, multimedia population exposure distribution to chemical classes, and included the collection of blood and urine from survey participants
Total Exposure Assessment Methodology	TEAM	U.S. EPA	Measured exposures to volatile organic compounds in the air, drinking water, and exhaled breath of participants in the late 1980s (http://exposurescience.org/pub/reports/TEAM_Study_book_1987.pdf)
The National Children's Study	NCS	NIH, NIEHS, CDC, U.S. EPA, and others	Examines the effects of the environment on the growth, development, and health of children across the United States; follows them from before birth until age 21 years; conducted since 2000; studies conducted as part of the NCS include biomonitoring data (http://www.nationalchildrensstudy.gov/Pages/default.aspx)
Canadian Health Measures Survey	CHMS	Statistics Canada, Health Canada, PHAC, and others	Begun in 2007, comprehensive set of data (including biomonitoring data) on the exposure of the Canadian population to environmental chemicals. (http://www.statcan.gc.ca/imdb-bmdi/document/5071_D2_T1_V1-eng.htm)
German Environmental Survey	GerES	Robert Koch Institute	Representative population study to determine the exposure of Germany's general population to environmental contaminants; collecting biomonitoring data since the mid 1980s (http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm)

3. PHARMACOKINETIC MODELS

Once data have been gathered, how can they be used to characterize exposure? One way is through use of **pharmacokinetic (PK) models**. Pharmacokinetics is the study of the fate of foreign substances in living organisms. It characterizes the **absorption**, **distribution**, **metabolism**, and **excretion** (**ADME**) of a substance in an organism's body. Figure 4 is a conceptual overview of the processes encompassed by pharmacokinetics. Pollutants can enter the body through a variety of pathways; for example, chemicals can be absorbed through the lungs via inhalation, the gut via ingestion, or the skin via dermal exposure.

Once a chemical is absorbed into the body, it is distributed throughout the body primarily via the blood. It can sometimes be sequestered in bone or other tissues. For many chemicals, the body begins to metabolize the pollutant in order to facilitate elimination. Excretion of a chemical can occur via the skin, feces, breath, urine, or other bodily fluids such as breast milk (US EPA, 2011).

Figure 4. Overview of Pharmacokinetics



For exposure analysis, PK models use data and mathematical equations to evaluate the fate of pollutants in the body after exposure has occurred. PK models vary in complexity. The simplest PK model is a one-compartment, first order model that assumes immediate distribution within a single "compartment" such as blood or body lipids. More complex PK models account for an organism's physiology in their equations and are called physiologically-based pharmacokinetic (PBPK) models.

In order to link the body burden of a chemical to the exposures that led to these levels, PK or PBPK models require various model parameters that reflect how much of the chemical is cleared over time, including volume of distribution, metabolic rates, and clearance rates. Most of the model parameters for PK models are derived from clinical or laboratory exposure studies on humans or animals.

In exposure assessment, PK models can be used to characterize the internal dose by identifying and evaluating the relationship between an applied dose and biomonitoring data. These models can be used to enable route-to-route extrapolation of the internal dose. That is, if the exposure route to a compound was ingestion, PK models could be used to extrapolate that to an internal dose for an inhalation exposure. PK models can also be used to reconstruct exposure when used in combination with data from epidemiological studies (U.S. EPA, 2006, pg 2-11–2-12).

The remainder of this section focuses on how PK models correlate internal doses with exposure. For reference, course HSR 306 reviews PK modeling in more detail.

3.1 One-Compartment Models

At its most basic, a simple **one-compartment, first-order PK model** estimates the change in concentration in one compartment over time given a specified exposure regime. It takes what comes in, or dose; subtracts what goes out via an elimination rate constant, *k*; and calculates the change in concentration of a chemical over time. This is shown conceptually by the figure and equation in Figure 5, accompanied by a hypothetical plot of chemical concentration versus time that illustrates the increase and subsequent elimination or degradation of chemical mass.

Figure 5. One-Compartment Model

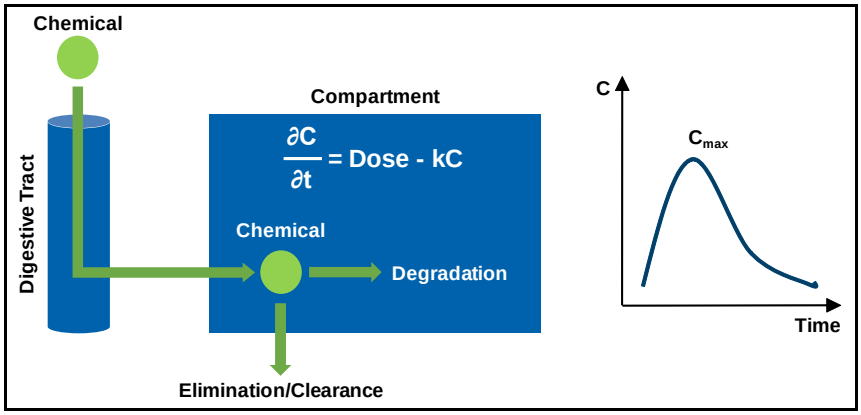
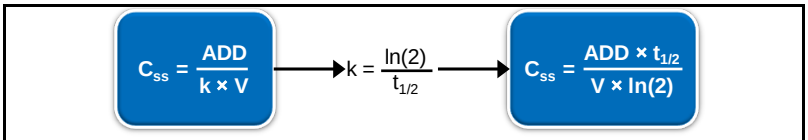


Figure 6. One-Compartment Steady-State Model



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)

Assuming steady state conditions, the differential equation in Figure 5 for a constant dose and elimination rate—meaning no net change of concentration of the chemical compound—can be solved as shown in Figure 6.

In this steady-state model, the average daily dose, or ADD, of a chemical is assumed to be constant. The chemical is assumed to dissipate from the volume of distribution (or the compartment) by a first-order process, defined by the elimination constant *k*. The half life ($t_{1/2}$) of elimination, which is the time it takes to reduce the concentration of the pollutant by 50 percent, is related to *k* according to the equation depicted in the middle of Figure 6. (Lorber, 2008). This figure shows two versions of the same equation for estimating the concentration at steady state—one with the first order elimination constant, *k*, and the other where the components of *k* are shown.

Actual exposures and human body physiology are more complicated than what is captured in this one-compartment, first-order steady-state model. Adding a level of complexity, the relationship presented in Figure 7 shows how the one-compartment, first-order model can be adapted to a temporal (unsteady-state) framework. The dose, rate constant, and even the volume through which the chemical is distributed can change over time. Like the previous model, this equation models the chemical in only one compartment of the body and assumes first-order kinetics, but it also assumes that the concentration of the chemical changes over time.

Figure 7. One-Compartment Unsteady-State 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)

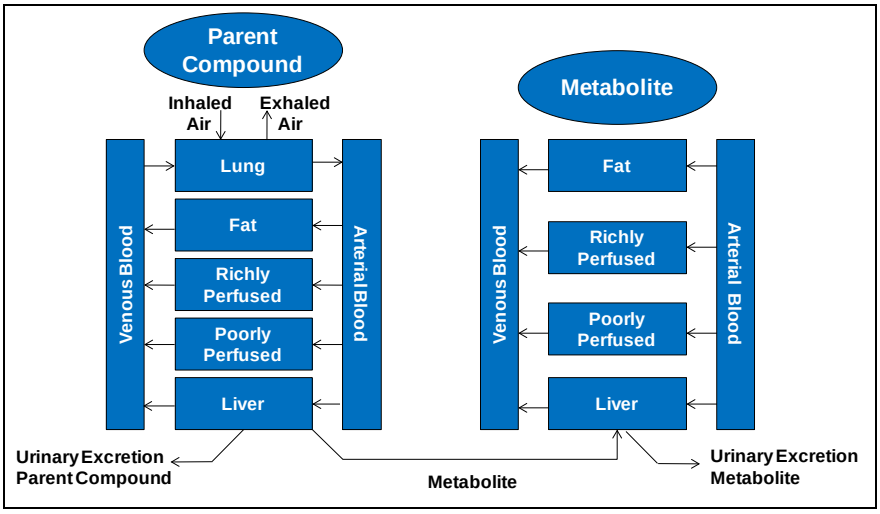
An unsteady-state PK model such as this can be used to show the effects of different dosing regimes. It can be useful when analyzing past exposure events or unusual dosing patterns. This type of model can also be modified to reflect changes in the volume of distribution and metabolic rates caused by changing human physiology as an individual ages (Lorber, 2008).

3.2 Multi-Compartment Models

Multiple-compartment models are more complex and typically include the organs and tissues relevant for the specific chemical distribution, metabolism, or toxicity. These models might specify venous movement of blood (away from organs and back to the heart and lungs) and arterial movement of blood (away from the heart and lungs to the rest of the body). More complex models can also describe the formation and transport of metabolites. Creating these mathematical models requires specific physiological data, such as blood flow rate to individual compartments, rate of metabolism, knowledge of whether processes are saturable, and partition coefficients (which describe how chemicals distribute in various tissues). For many chemicals, such data might not be available to build these more complex models.

The diagram in Figure 8 shows a PBPK model for a chemical that is inhaled. The chemical enters the body via inhalation through the lungs, and then moves through tissues and organs that are both richly perfused with blood (e.g., heart, lungs, liver) and poorly perfused with blood (e.g., muscle, skin). The fat tissue compartment is also explicitly defined, suggesting that the chemical may be sequestered in the fat. The parent compound might be exhaled or metabolized in the liver. This PBPK model also describes the distribution of the metabolite formed in the liver. Both the parent compound and metabolite are excreted in the urine (Hays et al., 2007).

Figure 8. Example of a Multi-Compartment PBPK Model



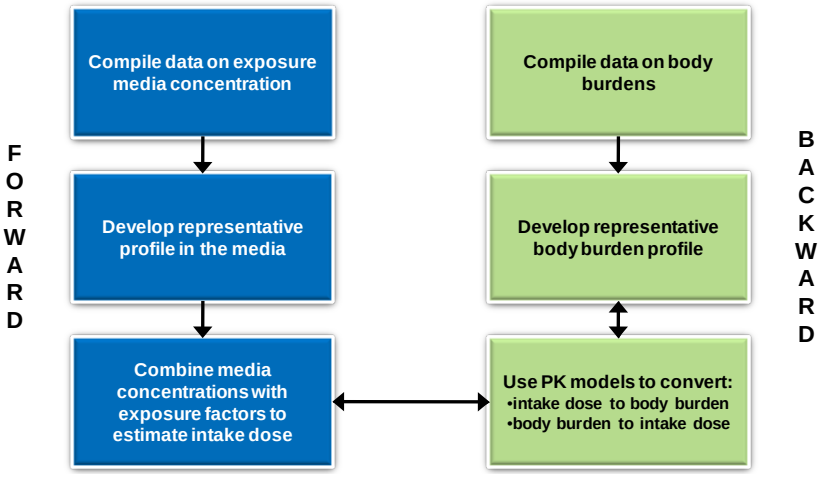
3.3 Using Pharmacokinetic Models

There are **advantages and limitations to using PK models**. After studying what happens to a chemical once it is absorbed, a PK model can be used to back-calculate the level of exposure based on biomonitoring data. Using PK models in this way for exposure reconstruction is potentially a very powerful application; however, detailed input parameters for the PK model must be known in order for the model to be reliable. Most importantly, the relationship between exposure and dose, including bioavailability, needs to be well understood, which is not always the case.

The framework for use of PK models in exposure assessment is shown in Figure 9. PK models relate intake dose of a compound with the body burden of that compound and can be run either forward or backward.

- **Forward analysis** using a PK model can be thought of as "**predictive**" because it uses measured or modeled intake doses to predict body burdens.
- **Backward analysis** using a PK model can be thought of as "**reconstructive**" because it uses measured body burdens to reconstruct past exposures by calculating intake doses.

Figure 9. Using PK Models in Exposure Assessment: Forward and Backward Assessment

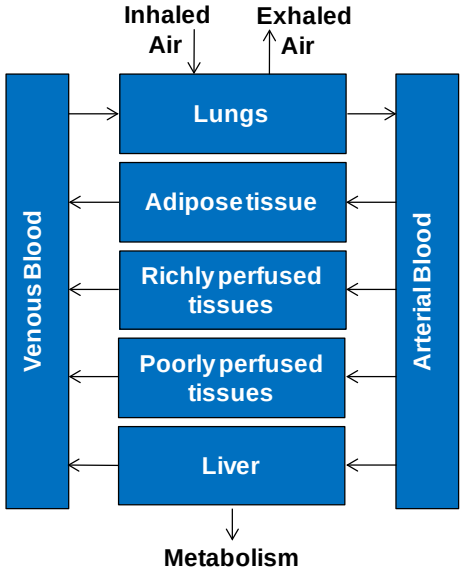


Forward Analysis

Forward analysis uses exposure concentration and duration of exposure to calculate biologically meaningful measures, such as body burdens or internal dose. The analysis begins with a known exposure scenario and determines fate of the chemical in the body.

Consider the example of inhalation exposure to a lipophilic volatile compound such as toluene. Using predictive PK analysis, the toxicokinetics and internal dose related to an exposure to 400 ppm of the compound for 2 hours can be examined. For many chemicals, a one-compartment, first-order model and the assumption of constant exposure rates do not accurately capture what happens after chemical exposure. Instead, a more complex model like the one shown in Figure 10 is needed. This figure depicts a model that is an unsteady-state, multicompartment PBPK model and models chemical distribution to multiple organs.

Figure 10. Forward Analysis Example: Inhalation of Toluene

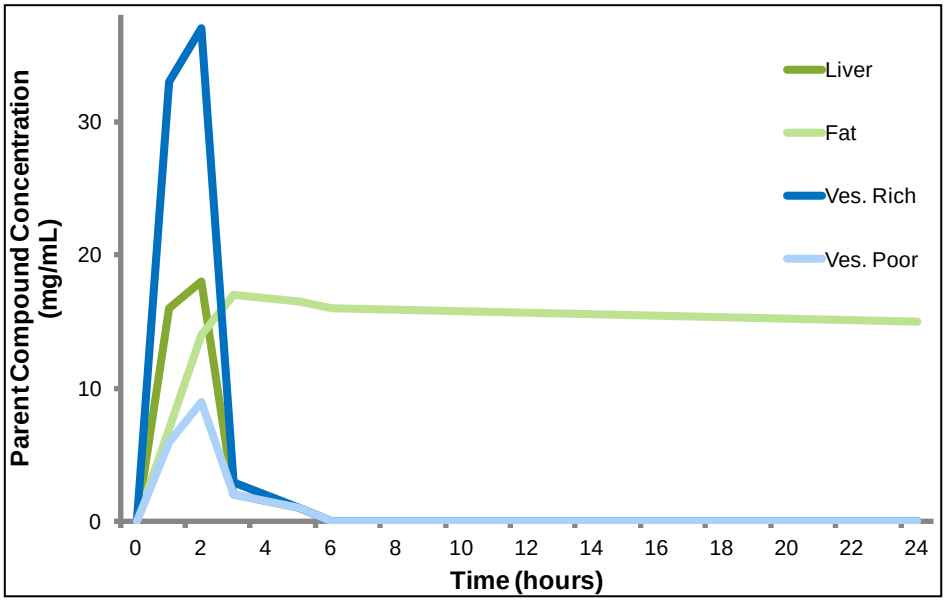


In this example, exposure to toluene occurs via inhalation, as shown at the top of Figure 10 by the arrow labeled "inhaled air" pointing down into the lungs. The compound enters the lungs and is transported throughout the body quickly via arterial blood. The chemical enters adipose tissue (fat), richly perfused tissues (such as the stomach), poorly perfused tissues (such as the skin), and the liver.

Compartments in the model are separated like this to represent the compartments that are important for metabolism of the compound of interest. From these four compartments in the model, venous blood continues to distribute the compound and transport it back to the lungs. The arrow pointing out of the liver indicates that this compound is metabolized in the liver.

Figure 11 shows how the concentration of the compound in the model changes over time in the liver, fat, and the richly and poorly perfused tissues. Recall that exposure in this example occurred over 2 hours.

Figure 11. Inhalation of Toluene Model Results



Concentration trends in richly perfused tissues (shown in dark blue) and the liver (shown in dark green) show a rapid spike in the parent compound concentration between 0 and 2 hours. Poorly perfused tissues (shown in light blue) exhibit a smaller spike in the parent compound due to the slower distribution of the compound to the venous blood supply. The rate of distribution to the fat (shown in light green) is slightly lower compared with the liver. It is also clear that the compound is much slower to decay in the fat, which in this case is due in part to its lipophilic nature.

Backward Analysis

Backward, or reconstructive, analysis uses PK modeling to infer total dose from measured contaminant levels in tissues or body fluids. In order to apply reconstructive modeling, biomonitoring data and other data are needed to parameterize and calibrate the model. Because many of the parameter inputs for PK modeling are dependent on empirical results from laboratory research, modeling is limited by the available data. In some cases where measured data are not available for a parameter, surrogate or substitute values can be used with justification.

As the name implies, backward modeling is not used to predict future exposures, and it is not applicable to all chemicals. Also, the exact sources and pathways of exposure resulting in body burden of the chemical cannot be determined by this method. A backward analysis is often useful to exposure assessors because it provides a way to reconstruct exposures from biomonitoring data.

To conduct a reconstructive analysis, one must follow these four steps.

1.) **Collect biomonitoring data on a specific chemical or contaminant in the body.**

2.) **Based on the available data, develop a PK model or select an existing PK model.**

Often, the model needs to be able to handle internal dose metrics resulting from a variety of dosing patterns. For example, low-level, intermittent occupational exposures over 8 hours per day, 5 days per week or, alternatively, a one-time accidental exposure to a high concentration of a chemical might need to be modeled.

3.) **Determine modeling parameters specific to the chemical under investigation based on existing data to give the most accurate estimate of dose.**

Ideally, laboratory studies on animals or selected human biomonitoring studies will provide data that can be used to parameterize the model with regard to absorption, distribution, metabolism, and excretion of a chemical in the body. Human dosing studies have sometimes provided the data necessary to calibrate a model, but this is rarely the case.

4.) **Run the PK model and use the results to back-calculate the exposure that resulted in the measured body burden.**

Presented in Figure 12 is an example reconstructive analysis for dioxin, using a one-compartment, first-order, steady-state model. In this example, biomonitoring has indicated a measured dioxin level of 6.7 picograms (pg)/g in the tissue of interest. The model equation requires the half life of dioxin and a volume of distribution. Here, it is assumed that the half life is 5 years, and the volume of distribution in adipose tissue is 10 liters. These values are all based on collected data. The model equation is used to solve for a dose estimate. In the figure, the equation has been solved for the adjusted daily dose, and the available data have been plugged in. However, more information is needed in order to solve for the correct units: density of blood and body weight. With all of the required information, the equation can be solved and the average daily dose of dioxin can be estimated at 0.385 pg/kg-day.

A second example uses perfluorooctanoic sulfonate (PFOS) (see Figure 13). PFOS is one compound in a class of chemicals called PFCs, or perfluorinated compounds. PFOS is extremely stable and both hydrophobic and lipophobic, which accounts for its widespread application in stain-resistant and nonstick products. Reflecting its high stability, PFOS has been shown to be persistent and bioaccumulative, with primary exposure pathways believed to be dietary ingestion and ingestion of house dust. NHANES provides biomonitoring data that can be used to characterize PFOS body burden.

Figure 12. Reconstruction of Dioxin Dose

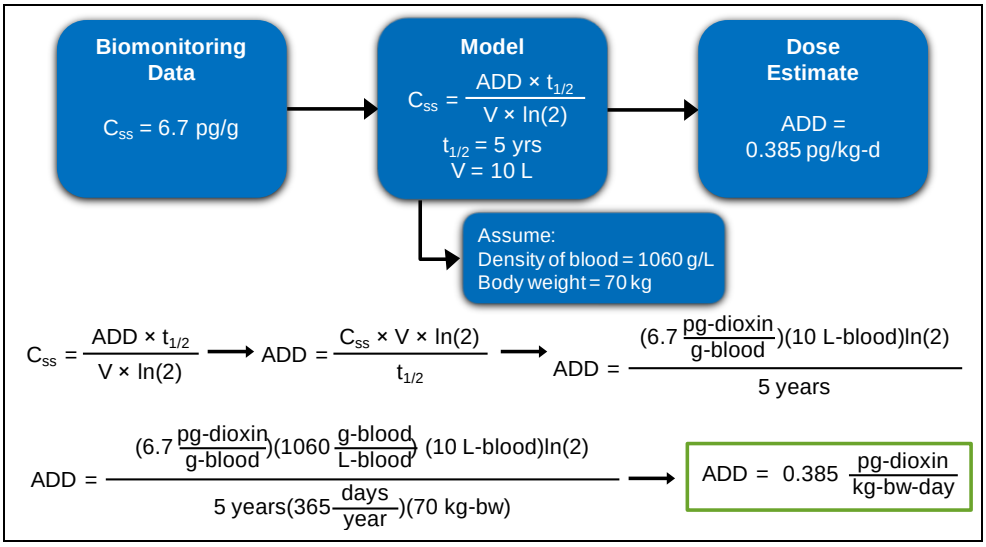
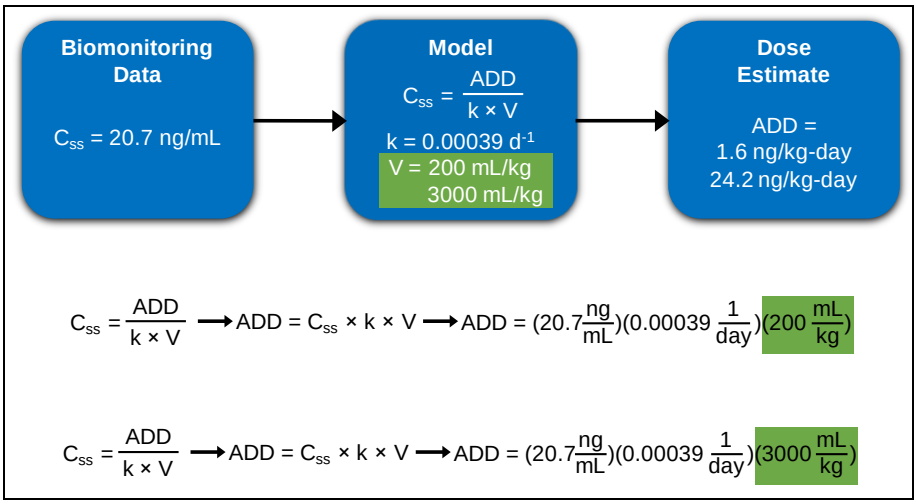


Figure 13. Reconstruction of PFOS Dose



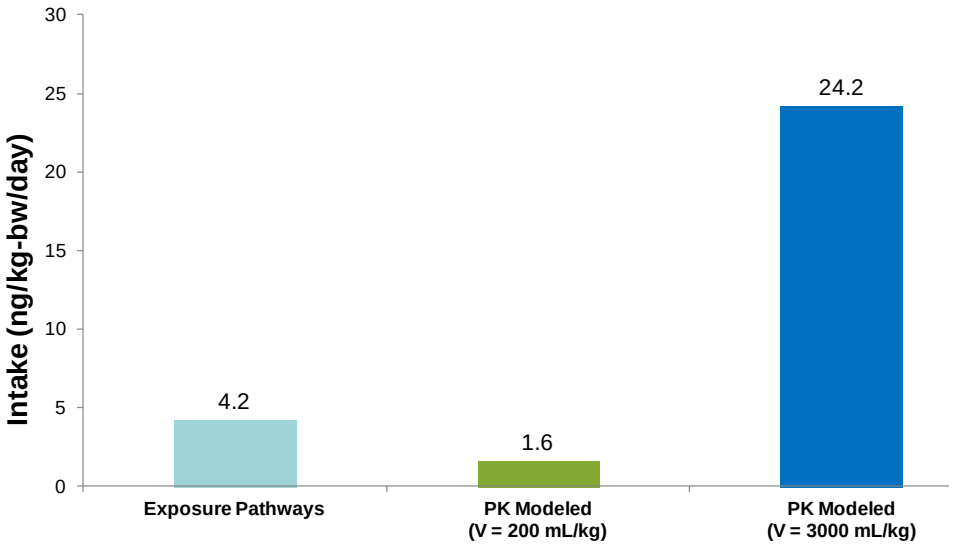
For this example, the body burden concentration of PFOS obtained from NHANES is 20.7 ng/mL. To calculate the steady-state average daily dose from the model equation, the volume of distribution for PFOS and the PFOS elimination constant (*k*) are needed. To obtain this information, results of other modeling studies were examined by Egeghy and Lorber (2011). Recall that *k* is a function of the half life and the natural log of 2. Egeghy and Lorber (2011) estimated a half life of PFOS by calculating the median of the half lives used in several occupational studies. In this example, the study authors then selected two serum volumes of distribution (normalized to bodyweight) of 200 and 3,000 mL/kg to encompass the volumes used in other analyses (Egeghy and Lorber, 2011).

This example can be used to illustrate the impact of serum volume, a physiological parameter, on dose. If we assume a steady-state model and use the same values for body burden and elimination constant, these two serum volumes will lead to different adjusted daily doses. Specifically, as illustrated in Figure 14, using a volume of 200 mL/kg, the modeled intake rate is 1.6 ng/kg-day. If PFOS is distributed through the larger volume of 3,000 mL/kg, the modeled intake is estimated to be 24.2 ng/kg-day (Egeghy and Lorber, 2011). For

comparison, the first bar in Figure 14 shows the intake rate of 4.2 ng/kg-day calculated using exposure pathway and exposure factor data gathered by Egeghy and Lorber (2011).

Depending on the volume of distribution used, the PK model predicts either higher or lower values than the screening level exposure intake assessment performed by Egeghy and Lorber (2011). Thus, this example shows that the PK model used was highly sensitive to the volume of distribution for PFOS and highlights the importance of making sure model inputs are correct and justified.

Figure 14. PFOS Modeling Results Compared with Results of Conventional Exposure Pathway Analysis



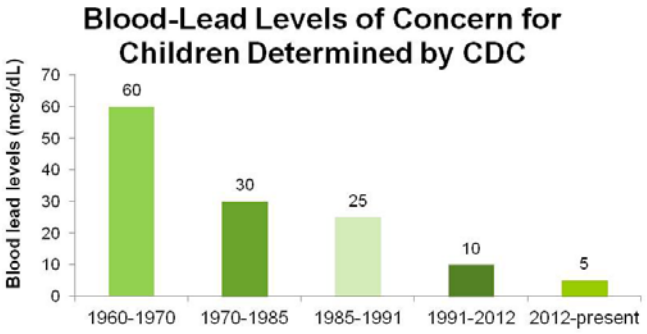
4. BIOMONITORING EQUIVALENTS

This section briefly discusses biomonitoring equivalents. Body burden measurements represent the current level of the chemical in the body, not the intake dose. However, human health reference values for acceptable levels of chemicals, such as reference doses, tolerable daily intakes, or minimal risk levels, are based on intake doses. Very few chemicals have health-based screening levels for body burden measurements. This means that for most chemicals, biomonitoring concentrations cannot be directly compared to human health reference values. This is where biomonitoring equivalents come into play.

Biomonitoring equivalents, or BEs, are values that correlate a body burden measurement with intake doses that are considered safe and acceptable (Hays et al., 2007). By developing BEs, biomonitoring data could be linked with health effects using epidemiological studies. However, due to relatively small sample sizes and complicated relationships between chemical detection and manifestation of a health effect, the use of BEs is unlikely to occur on a large scale in the near future. BEs are not currently used for setting regulatory requirements in the United States, but this could change. Some risk assessors argue that a strength of the BE approach is that they can be more easily understood by the general public than values such as reference doses or reference concentrations. Health Canada and some European nations have begun using BEs for characterizing exposure and risk. EPA continues to uses dose-based reference values like the RfD (Hays et al., 2007).

One example of a BE used in the United States is the one defined for lead in blood. Lead can cause toxicity through multiple modes of action operating in multiple systems. As a result, effects from lead exposure are varied and numerous. Children, however, are not only more vulnerable to lead exposure, but are also more sensitive. Their bodies absorb more lead than adults, and their brains and nervous systems are more sensitive to the damaging effects of lead.

Figure 15. CDC Blood-Lead Levels of Concern Identified for Children since 1960



As recently as the 1960s, the blood lead level of concern for children was 60 µg/dL. As new information has emerged about the neurological, reproductive, and possible hypertensive toxicity of lead, and as more sensitive parameters are developed, the blood-lead levels of concern for lead exposure in children have been progressively lowered by CDC. As shown in Figure 15, a level of 10 µg/dL was adopted by CDC in 1991 as a level of concern for children based on the correlation between this blood lead level and adverse health effects. This is an advisory level for environmental and educational intervention. At the recommendation of its Advisory Committee on Childhood Lead Poisoning Prevention, the agency adopted a value of 5 µg/dL in 2012 (Betts, 2012). This value is based on the 97.5th percentile of blood lead levels in U.S. children aged 1-5 years, as measured by NHANES. This reference value will be updated every four years based on the two most recent iterations of NHANES.

A Biological Exposure Index (BEI) for lead has been developed by the American Conference of Governmental Industrial Hygienists (ACGIH) as a guidance value for assessing biomonitoring results related to occupational

exposure in adults. The BEI for blood lead is 30 µg/dL (ACGIH, 2005). This level indicates exposure to lead has occurred at the Threshold Limit Value (TLV) of 50 µg/m^3 in air. Blood-lead level is a type of biomonitoring equivalent. It is a biomarker level that indicates that exposure to lead has occurred that could potentially lead to adverse effects (ATSDR, 2007).

5. CONCLUSION

This EXA course provides an overview of biomonitoring data and how these data might be used in exposure assessment. Some important points of this course are summarized below.

- Biomonitoring measures the actual levels of chemicals in the body reflecting internal dose, which can be used in a variety of ways to inform exposure assessments. Biomonitoring data allow evaluation of aggregate exposure to a given compound from multiple exposure sources and routes.
- NHANES is an important source of biomonitoring data for people in the United States. NHANES sampling is designed to ensure the data represent the entire population, and data are updated every 2 years. Because data are gathered periodically and across large population segments, trends in body burdens of chemicals for specific subpopulations can be analyzed.
- Body burden and other biomarker data gathered through biomonitoring can be used to strengthen exposure assessments.
- Pharmacokinetic modeling can be used in conjunction with biomonitoring data to relate exposure to internal dose using predictive analysis, or internal dose to exposure in a reconstructive analysis. It is important to ensure that the appropriate PK model is selected and that appropriate model inputs are used so that the estimated internal dose or exposure represents the most biologically plausible estimate.

6. REFERENCES

ACGIH. (American Conference of Governmental Industrial Hygienists). (2005) TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR. (Agency for Toxic Substances and Disease Registry). (2004). ATSDR glossary of terms Retrieved August 23, 2010, from http://www.atsdr.cdc.gov/glossary.html

ATSDR. (Agency for Toxic Substances and Disease Registry). (2007) Toxicological profile for lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Betts, K. S. (2012) CDC updates guidelines for children's lead exposure. Environ Health Perspect 120: a268. http://dx.doi.org/10.1289/ehp.120-a268.

Bouchard, M. F., Bellinger, D.C., Wright, R.O., Weisskopf, M.G. (2010) Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics 125: e1270-1278.

CDC. (Centers for Disease Control and Prevention). (2009) Fourth national report on human exposure to environmental chemicals. Atlanta, GA. http://www.cdc.gov/exposurereport/.

Egeghy, P. P. and Lorber, M. (2011) An assessment of the exposure of Americans to perfluorooctane sulfonate: A comparison of estimated intake with values inferred from NHANES data. J Expo Sci Environ Epidemiol 21: 150-168. http://dx.doi.org/10.1038/jes.2009.73.

Hays, S.; Becker, R.; Leung, H.; Aylward, L.; Pyatt, D. (2007) Biomonitoring equivalents: A screening approach for interpreting biomonitoring results from a public health risk perspective. Regul Toxicol Pharmacol 47: 96-109. http://dx.doi.org/10.1016/j.yrtph.2006.08.004.

Lorber, M. (2008) Exposure of Americans to polybrominated diphenyl ethers. J Expo Sci Environ Epidemiol 18: 2-19. http://dx.doi.org/10.1038/sj.jes.7500572.

Lorber, M.; Patterson, D.; Huwe, J.; Kahn, H. (2009) Evaluation of background exposures of Americans to dioxin-like compounds in the 1990s and the 2000s. Chemosphere 77: 640-651. http://dx.doi.org/10.1016/j.chemosphere.2009.08.016.

NRC. (National Research Council). (2006) Human biomonitoring for environmental chemicals. Washington, D.C.: The National Academies Press.

Scott, L. L. F. and Nguyen, L. M. (2011) Geographic region of residence and blood lead levels in U.S. children: Results of the National Health and Nutrition Examination Survey. Int Arch Occup Environ Health 84: 513-522. http://dx.doi.org/10.1007/s00420-011-0624-9.

Sexton, K., Needham, L, Pirkle, J. . (2004) Human Biomonitoring of Environmental Chemicals. American Scientist 92: 38-45. http://www.cdc.gov/biomonitoring/pdf/AS_article_biomonitoring.pdf.

U.S. EPA. (U.S. Environmental Protection Agency). (1992a) Guidelines for exposure assessment. (EPA/600/Z-92/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=15263.

U.S. EPA. (U.S. Environmental Protection Agency). (1992b) Guidelines for exposure assessment. (EPA/600/Z-92/001). Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=15263.

U.S. EPA. (U.S. Environmental Protection Agency). (2006) Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (final report). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development.

US EPA. (2011). Pharmacokinetic and Pharmacodynamic Modeling Retrieved May 17, 2011, from http://www.epa.gov/hhrp/quick_finder/modeling.html

Woodruff, T. J.; Zota, A. R.; Schwartz, J. M. (2011) Environmental Chemicals in Pregnant Women in the United States: NHANES 2003-2004. Environ Health Perspect 119: 878-885. http://dx.doi.org/10.1289/ehp.1002727.