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

Course Description: 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 exposure 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.

Expected Course Duration: Approximately 1 hour

Terminal Learning Objective: Understand biomonitoring data (specifically NHANES) and how they can be used to quantify human exposure, and gain an understanding of how to use pharmacokinetic (PK) models and biomonitoring data for forward and backward analysis.

Enabling Learning Objectives:

- Understand key concepts and definitions pertaining to biomonitoring and PK models;
- Understand the NHANES database and its uses;
- Understand how biomonitoring data are used to construct PK models;
- Understand how to use forward and backward PK models;
- Understand what biomonitoring equivalents are.

Course Materials

- EXA 408 Reading Packet

Course Overview/List of Slides

TITLE SLIDE

What You Can Expect to Learn from this Course (Slide 1)

- Today we will talk about the main elements of biomonitoring and how it can be used in exposure assessments.
- We will talk about body burdens and biomarkers, which are types of biomonitoring data, and we will discuss the largest source of this type of data in the United States, the National Health and Nutritional Examination Survey (NHANES) database.
- Then we will discuss how biomonitoring data and pharmacokinetic, or PK, models are related, how PK models can be used for both forward and backward exposure analysis, and what biomonitoring equivalents are.

Source-to-Effect Continuum (Slide 2)

- As outlined throughout the EXA course series, exposure assessments evaluate the movement of a chemical from its source to a receptor.
- This approach relies on modeled or measured concentrations in external media. The concentration of a chemical in dust can be used with exposure factors data, like the incidental ingestion rate of dust, to predict or reconstruct dose.
- However, there are limitations to traditional exposure assessment methods.
    - For example, 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 also be difficult and subject to errors due to the assumptions made.
    - Additionally, exposure factor data rely on activity diaries, questionnaires, and participant's recollection about what they have done and where they have been, which is subjective and sometimes unreliable.
- Given these issues, traditional exposure assessments are subject to some uncertainties and can possibly result in misclassification of exposure.
- However, one thing to keep in mind about traditional exposure assessments is that they allow assessment exposure via just one pathway (consider personal sampling devices worn by individuals to monitor inhalation concentrations of a chemical). Biomonitoring alone does not often provide that level of specificity.
- Source: (Sexton, 2004)

Exposure Assessment Using Biomonitoring Data (Slide 3)

- 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 or overestimate exposure. Biomonitoring data can help us reconstruct the dose of a chemical a person received in a specific exposure scenario, thereby providing a biologically relevant measure of dose.
- However, it is difficult to use biomonitoring data to parse out the source or pathways of exposure, so using biomonitoring data can increase the uncertainty in this respect. (Hays et al., 2007)
- National Health and Nutritional Examination Surveys (pronounced n-hanes) includes the largest dataset of biomonitoring data currently available. This data set is used in many ways to characterize and study exposure. We'll talk more about NHANES after we discuss biomarkers and biomonitoring in more detail.
- Source: (Sexton, 2004)

BIOMONITORING, BIOMARKERS, AND BODY BURDENS (SLIDE 4)

- First we'll cover the definitions of biomonitoring, biomarkers, and body burdens, and then we'll discuss how they're used in exposure assessment.

Biomonitoring, Biomarkers, and Body Burdens (Slide 5)

- "Biomarker" is a general term for any biological indicator of exposure to a chemical. These can be the measured levels of chemicals, their metabolites, or byproducts produced through interactions between the chemical and the target tissue or cell. (NRC, 2006)
- A body burden measurement is a specific type of biomarker that describes the amount of the parent chemical–not its metabolites or byproducts–in the body.
- Biomarker and body burden data are collected via biomonitoring. Biomonitoring is 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. (Hays et al., 2007)
- Sources: (CDC, 2009; NRC, 2006; ATSDR, 2004; U.S. EPA, 1992a)

Biomonitoring Advantages and Limitations (Slide 6)

- So, what are some advantages and limitations to biomonitoring?
- One advantage is the ability to measure aggregate exposure to a given compound from all pathways. Body burden data includes 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, or biouptake, as well as the accumulation of the compound in the body, or bioaccumulation.

- Biomonitoring can be used in epidemiology studies to analyze relationships between internal dose and health outcomes.
- However, biomonitoring data also have limitations. Using biomonitoring data might not help identify the particular sources or pathways 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 requirement 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.
- Source: (Sexton, 2004)

How Biomonitoring Measures Exposure (Slide 7)

- As illustrated here, biomonitoring captures exposure from multiple pathways and sources. Multiple external factors influence the exposure of a population as well as the population's response to exposure. These factors and stressors can include environmental pollutants, like from the factory shown here; diet, for instance if someone eats a lot of grilled meats or drinks tap water; access to health care; and other daily activities like smoking or exercise. Biomonitoring records the internal dose of a population, which is influenced by and captures the total effect of these outside factors.
- Sources: (NRC, 2006; Sexton, 2004)

Biomarkers (Slide 8)

- Biomarkers, which are collected using biomonitoring methods, measure 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 concentration in urine. Recall that if the chemical being measured in urine was the parent chemical and not a metabolite, that would be considered a body burden measurement.
- Depending on the contaminant and other factors, biomarkers can be useful in identifying source and time frame 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 doesn't indicate that an effect has occurred, or that a person is at risk for adverse effects.
- NHANES is one source of biomarker data. Other sources include research studies conducted on smaller scales in the context of a specific research projects. An example would be a

biomonitoring study conducted by a city health department to look at blood-lead levels in children.

- Now let's talk a little more about NHANES.
- Source: (U.S. EPA, 1992b)

What is NHANES? (Slide 9)

- The National Health and Nutrition Examination Survey, or NHANES, is a "program of studies designed to assess the health and nutritional status of adults and children in the United States." It collects data using a combination of interviews and physical examinations and 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 that the general population has been exposed to, body burdens of those chemicals, differences in body burdens according to demographics (such as age or race), and potential trends over time.
- Health status information has also been used along with the biomonitoring data to investigate potential relationships between chemical exposure and diseases.
- Biomonitoring data are collected through blood, urine, and sometimes hair, or oral samples. These biomonitoring samples are collected and analyzed for markers of disease like elevated blood sugar levels and for biomarkers of chemical exposure.
- Source: (CDC, 2009), CDC's web site (http://www.cdc.gov/nchs/nhanes.htm)

History of NHANES (Slide 10)

- NHANES began in the 1960s as a series of surveys for 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 U.S. The sample for the survey is selected to represent the U.S. population of all ages above age 1.
- Surveys are conducted every two years, asking new questions and collecting new data during each cycle.
- Source: (CDC, 2009), CDC's web site (http://www.cdc.gov/nchs/nhanes.htm)

NHANES Biomonitoring Data (Slide 11)

- The NHANES database is the largest existing database of biomarkers for the US population and is therefore a valuable resource for exposure assessors.
- NHANES data 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 civilian, non-institutionalized US 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 person is also assigned a numerical sample weight which measures the number of people in the population represented by that particular sampled person. These weights adjust for unequal selection probabilities or certain types of non-response to the surveys and must be used to obtain correct national estimates from the NHANES data.
- NHANES collects blood and urine samples from a population ranging in age from 1 to over 60. All lab tests are not performed on every age group; for example, urine samples are only collected from children over the age of 6. These samples are then analyzed for the presence of various compounds, including a variety of environmental chemicals of concern. Environmental chemicals are defined as compounds present in air, water, food, soil, dust, or other environmental media, such as consumer products.
- In 2000, the CDC compiled and published the *National Report on Human Exposure to Environmental Chemicals* based on the NHANES data. In 2009, the fourth edition of this report was published, presenting data for 212 environmental chemicals and their metabolites including disinfection by-products, volatile organic compounds, and perfluorinated compounds. Since NHANES is a dynamic survey conducted every two years, the list of monitored chemicals is continually updated to reflect emerging contaminants.
- Source: (Scott and Nguyen, 2011; CDC, 2009)

Uses of NHANES Biomonitoring Data (Slide 12)

- The NHANES database has many uses. Some of the most important are presented here.
- NHANES surveys can be used to determine which chemicals of concern get into Americans' bodies and at what concentrations the compounds are present.
- The data can be used to determine what proportion of the population has measured contaminant levels above the levels associated with adverse health. It is also possible to determine whether exposure is higher among minorities, children, women of childbearing age, or other populations of concern.
- The large sample size means that the NHANES data can be used to 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.
- The historical data provided by NHANES allow for the tracking of levels of chemicals in the body over time. Analysis of these trends can be used to assess the effectiveness of public health efforts to reduce Americans' exposure to harmful compounds.
- All of this information is helpful for prioritizing 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 collections to draw conclusions about the connections between exposure and resulting body burdens. Researchers can also use the health and behavior data to determine which exposure pathways are most relevant for exposure to specific chemicals based on the types and amounts of chemicals that appear in biomonitoring samples.
- Source: (CDC, 2009)

Other Sources of Biomonitoring Data (Slide 13)

- There are other sources of biomonitoring data besides NHANES that record information on exposure and biomonitoring, such as those surveys and databases listed here.
- Two of the programs listed are currently in progress—the National Children's Study and the Canadian Health Measures Survey. Further details on these surveys, as well as additional sources of data, can be found in the reading packet.
- In addition to these sources, individual research studies are also used to collect biomonitoring data on a much smaller scale for specific populations or pollutants.

Using NHANES Data: Phthalates in Women (Slide 14)

- Here's an example of how NHANES data can be used to gain insight into exposure.
- 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.
- This table 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.
- Metabolites of phthalates are 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 may contaminate the samples. As shown on the slide, thirteen different chemical metabolites of phthalates were measured in urine.
- Source: (Woodruff et al., 2011)

Using NHANES Data: Phthalates in Women (Slide 15)

- Researchers calculated various statistics for urinary phthalate metabolite concentrations as seen here, including the geometric mean, geometric standard error (abbreviated on the slide as GM and GSE, respectively), and median (or 50^{th} percentile).
- Urinary measurements are useful because phthalates are often rapidly metabolized, have half-lives on the order of hours, and are primarily eliminated via the urine.
- As seen in the percent greater than level of detection, or LOD, column, phthalate metabolites are present in almost 100% of samples, for both pregnant and non-pregnant 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 means that women are exposed nearly every day of measurement.
- This determination is based entirely on biomonitoring data, and exemplifies how exposure assessors can draw conclusions about exposure based on body burden measurements.
- In general, however, body burden data alone cannot be used to draw conclusions about exposure beyond the fact that an individual was exposed. It must be combined with other

data like epidemiological data or questionnaires to elucidate potential exposure sources or pathways or potential effects of exposure.

- Source: (Woodruff et al., 2011)

Using NHANES Data: Dioxin Exposure (Slide 16)

- Here is another example of how NHANES data can be used to provide information on exposure.
- 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 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, but because more than 90% of exposures were determined to come from ingestion of animal products, EPA only used newer food survey information to update the daily exposure estimate in 2009.
- For reevaluating the body burden of dioxins, EPA used blood concentration data collected from NHANES from 2000 to 2001.
- Source: (Lorber et al., 2009)

Using NHANES Data: Dioxin Exposure (Slide 17)

- Let's look at some of the dioxin data in NHANES.
- Dioxin is measured in the blood instead of in the urine because dioxin is long-lived in the body. 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 can be used to track trends in exposure. Survey results have shown a consistent decline in dioxin exposure from a peak in the late 1960s to present day.
- Source: (Lorber et al., 2009)

Using NHANES Data: Methylmercury and Fish Consumption (Slide 18)

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

- Because NHANES collects data on mercury levels in the blood and information on daily habits of individuals (or exposure factors), scientists are able to explore potential relationships between mercury levels and daily habits 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; Mahaffey et al., 2008).

Using NHANES Data: Pesticides and ADHD (Slide 19)

- Researchers have also examined the statistical correlation between metabolites of organophosphate pesticides as measured in urine samples, and the diagnosis of attention-deficit hyperactivity disorder (ADHD) using data collected from NHANES monitoring.
- Researchers are concerned about this relationship in part because of widespread use of organophosphate pesticides 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. Source: (Bouchard, 2010)

PHARMACOKINETIC MODELS (SLIDE 20)

- So now we've discussed what biomonitoring data are and how we collect them. But once we have the data, how can they be used to characterize exposure?
- One way is through use of pharmacokinetic models.

Pharmacokinetics (Slide 21)

- Pharmacokinetics is the study of the fate of foreign substances in living organisms and characterizes the absorption, distribution, metabolism, and excretion (ADME) of a substance in the organism's body.
- This figure is a conceptual overview of what processes are encompassed by pharmacokinetics. As depicted, pollutants enter the body through multiple pathways. 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 to various tissues and possibly sequestered in bone or other tissue. Distribution of the chemical occurs mainly via the blood.
- 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.
- Source: (US EPA, 2011)

Pharmacokinetic Models (Slide 22)

- In exposure analysis, PK models use data and mathematical equations to evaluate the fate of pollutants in the body after exposure has taken place. These models vary in complexity.
    - The simplest PK model is a one-compartment, first order model that assumes immediate distribution into 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 or PBPK models.
- To link the body burden of a chemical seen in organisms to the exposures that led to these levels, PK or PBPK models require model parameters such as volume of distribution, metabolic rates, and clearance rates, which reflect how much of the chemical is cleared over time. Most of the model parameters for PK models are derived from clinical or laboratory work from human or animal exposure studies.
- 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.
    - They can be used to enable route-to-route extrapolation of the internal dose. That is, if the exposure route to a compound were ingestion, PK models could be used to extrapolate the internal dose after an inhalation exposure.
    - They can also be used to reconstruct exposure when used in combination with data from epidemiological studies.
- 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.
- Source: (U.S. EPA, 2006, pg 2-11–2-12)

One-Compartment, First Order PK Models (Slide 23)

- 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, the dose; subtracts what goes out via an elimination rate constant, *k*; and calculates the change in concentration of a chemical over time.

Steady-State One-Compartment, First Order PK Model (Slide 24)

- The simplest PK model is a one-compartment, first order, steady state model. This model is created by solving the previous differential equation assuming a constant dose and elimination rate, meaning no net change of concentration of the chemical compound.
- In this type of modeling, 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*, equal to ln(2) divided by $t_{1/2}$.
- The half life of elimination is the time it takes to reduce the concentration of the chemical by 50%.
- This slide shows two versions of the same equation—one with the first order elimination constant, *k*, and the other where the components of *k* are shown.

- Source: (Lorber, 2008)

Non-Steady-State PK Model (Slide 25)

- The human body and actual exposure is, in reality, more complicated than is captured in a one-compartment, first order, steady state model. This slide shows how the one-compartment, first order model can be realized in a temporal framework. The dose, first order elimination rate constant, and even the volume through which the chemical is distributed can change over time. Like the previous model, this equation is still modeling the chemical in only one compartment of the body and assuming first order kinetics, but it does not assume that the concentration of the chemical is constant.
- Non-steady-state PK models such as these can be used to show the effects of different dosing patterns. This can be useful when analyzing past exposure events or unusual dosing patterns.
- These models also reflect changes in the volume of distribution and metabolic rates caused by changing human physiology as an individual ages.
- Source: (Lorber, 2008)

Multi-Compartment Physiologically-Based PK Modeling (Slide 26)

- Multiple-compartment models are more complex and include the organs and tissues relevant for the specific chemical distribution, metabolism, or toxicity. These models may 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 may 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 the chemicals distribute in various tissues. For many chemicals, the data may not be available to build these more complex models.
- The diagram on this slide shows a PBPK model for a chemical that is inhaled. The chemical enters the body via inhalation through the lungs, then moves through tissues and organs that are both richly perfused with blood (e.g., heart, lungs, liver) and those that are poorly perfused (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 may 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.
- Source: (Hays et al., 2007)

PK Advantages & Limitations (Slide 27)

- 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 pharmacokinetic models 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.

USING PHARMACOKINETIC MODELS (SLIDE 28)

Forward & Backward Analysis (Slide 29)

- The framework for use of PK models in exposure assessment is shown here.
- PK models relate intake dose of a compound with the body burden of that compound and can be run either forwards or backwards.
- Forward analysis of 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" and uses measured body burdens to reconstruct past exposures by calculating intake doses.

Forward Analysis (Slide 30)

- 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.

Forward Analysis Example: Inhalation of VOCs (Slide 31)

- Let's consider the example of inhalation exposure to a lipophilic volatile compound, such as toluene, that we created for this module.
- Using predictive PK analysis, we can look at the toxicokinetics and internal dose related to an exposure to 400 ppm of the compound for 2 hours.
- For many chemicals, a one-compartment, first order model and the assumption of constant exposure rates do not accurately capture what happens to the chemical. Instead, we need a more complex model like the one shown here; it is a non-steady state, multicompartment PBPK model and shows the distribution to multiple organs.
- Exposure to this compound occurs via inhalation, shown at the top of this figure 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 that have lots of blood (like the stomach), poorly perfused tissues with less blood (like 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.

Forward Analysis Example: VOC Modeling Results (Slide 32)

- This graph shows how the concentration of the compound in the model could change over time in the liver, fat, and both richly and poorly perfused tissues. Remember that for this scenario we said exposure occurred over two hours.
- Richly perfused tissues (shown in dark blue), and the liver (shown in dark green), which is also a richly perfused tissue, 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.
- Similarly, the rate of distribution to the fat (shown in light green) is less rapid than to the liver. We can also see that the compound is much slower to decay in the fat due to its lipophilic nature.

Backward Analysis (Slide 33)

- 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, we need not only biomonitoring data, but also other data 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 research. In some cases where measured data are not available for a parameter, we can use surrogate or substitute values 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.

Steps for Conducting Backward Analysis (Slide 34)

- A backward analysis is often of more interest to exposure assessors because it provides a way to reconstruct exposures from biomonitoring data.
- To conduct a reconstructive analysis, we must begin by gathering biomonitoring data on a specific chemical or contaminant in the body.
- Based on the available data, we can either construct a PK model or select an existing one to parameterize.
- Often, the model needs to be able to handle internal dose metrics resulting from a variety of dosing patterns. For example, we may need to model low-level, intermittent occupational

exposure over 8 hours per day, 5 days per week or, alternatively, a one-time accidental exposure to a high concentration of a chemical.

- After the PK model is selected, modeling parameters specific to the chemical under investigation should be determined 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 which can be used to parameterize the model with regard to absorption, distribution, metabolism, and excretion of a chemical in the body. Human dosing studies can provide the data necessary to calibrate the model, but this is rarely the case.
- With this information, the PK model can be run and used to back-calculate the exposure that resulted in the measured body burden.

Backward Analysis Example: Reconstruction of Dioxin Dose (Slide 35)

- Let's walk through an example of modeling dioxin exposure through a one-compartment, first order, steady state model.

  (advance slide)
- Biomonitoring has produced a measured dioxin level of 6.7 picograms per gram in the tissue of interest.
  (advance slide)
- The model equation requires the half life of dioxin and a volume of distribution. Here, we assume 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.
  (advance slide)
- We will use the model equation to solve for a dose estimate.
  (advance slide)
- Here we have solved the equation for the adjusted daily dose, and have plugged in the available data. However, we need more information in order to solve for the correct units.

  ? What other information is required to calculate the daily dose in picograms per kilogram per day?

  (advance slide)
- We also need density of blood and body weight.
  (advance slide)
- When we have all of the required information, we can solve the equation and estimate that the average daily dose of dioxin was 0.385 pg/kg-day.

Backward Analysis Example: PFOS (Slide 36)

- Now let's consider the case of PFOS, or perfluorooctanoic sulfonate.
- 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 non-stick products.

- In part due to 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.

Backward Analysis Example: Reconstruction of PFOS Dose (Slide 37)

- The body burden concentration of PFOS obtained from NHANES is 20.7 ng/mL *(advance slide)*
- To calculate the steady state average daily dose from the model equation, the volume of distribution for PFOS and the PFOS elimination constant are also needed. For this information, we turn to the results of other modeling studies. *(advance slide)*
- A half life of PFOS can be found by calculating the median of the half life used in occupational studies. Recall that *k* is a function of the half life and the natural log of 2, meaning that we can find *k* in this instance. In this example, the study authors selected two serum volumes of distribution normalized to bodyweight of 200 and 3,000 milliliters per kilogram to encompass the volumes used in other analyses (Egeghy and Lorber, 2011). *(advance slide)*

? Assuming a steady-state model and using the body burden, elimination constant, which volume will lead to a higher adjusted daily dose?

PFOS PK Model Results (Slide 38)

- Using a volume of 200 mL/kg, the modeled intake rate is 1.6 ng/kg-body weight-day, shown in the middle bar on the graph. But if PFOS is distributed through a larger volume, the modeled intake is estimated to be 24.2 ng/kg-body weight-day, shown on the right (Egeghy and Lorber, 2011).
- The bar on the left side of the graph shows the intake rate calculated using traditional exposure pathways and exposure factors. Depending on the volume of distribution, the PK model predicts either higher or lower values than the conventional exposure pathway analysis.
- Thus, this example shows that the model is highly sensitive to the volume of distribution and highlights the importance of making sure your inputs are correct and justified.

BIOMONITORING EQUIVALENTS (SLIDE 39)

- Now that we've discussed PK modeling, we're going to briefly talk about biomonitoring equivalents.

What Are Biomonitoring Equivalents? (Slide 40)

- Body burden measurements represent the current level of the chemical in the body, not the intake dose. However, human health reference values for acceptable 'safe' 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, we cannot directly compare biomonitoring concentrations 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.
- Source: (Hays et al., 2007)

Use of Biomonitoring Equivalents (Slide 41)

- 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 may be more easily understood by the general public than values such as reference doses or concentrations.
- As you can see here, some international agencies have begun using BEs, while EPA and IRIS use dose-based reference values like RfDs.
- Source: (Hays et al., 2007)

BE Use Example: Lead (Slide 42)

- An example of a biomonitoring equivalent used in the United States is the one defined for lead.
- 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 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.
- 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.
- At the recommendation of its Advisory Committee on Childhood Lead Poisoning Prevention, the agency adopted a value of 5 µg/dL in 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.
- Separate from the action level for children is the Biological Exposure Index (BEI), which is a guidance value for assessing biomonitoring results relating 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.
- Both of these values are types of biomonitoring equivalents. They are biomarker levels that indicate that exposure that could potentially lead to adverse effects has occurred.
- **Sources:** (ATSDR, 2007), EPA Basic Information on Lead in Paint, Dust, and Soil (http://www.epa.gov/lead/pubs/leadinfo.htm#health), ATSDR Lead Toxicity – What Are the U.S. Standards for Lead Levels? (http://www.atsdr.cdc.gov/csem/csem.asp?csem=7&po=8)(Betts, 2012; ACGIH, 2005)

CONCLUSION (SLIDE 43)

Conclusion (Slide 44)

- This concludes the presentation on interpreting biomonitoring data and their use in exposure assessment. Let's review the main points.
- 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 us to evaluate aggregate exposure to a given compound from multiple exposure sources and routes.
- NHANES is an important source of biomonitoring data for the population of the United States. NHANES sample population is designed to ensure the data represent the entire population, and data are updated every two years. Because data are gathered periodically and across large population segments, we have the ability to analyze trends in body burdens of chemicals for specific subpopulations (for example, blood lead levels in children over time, phthalates in pregnant and non-pregnant women).
- Body burden and other biomarker data, gathered through biomonitoring, can be used to strengthen exposure assessment.
- 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 PK model selection is justified and that appropriate model inputs are used so that the estimated internal dose or exposure represents the most biologically plausible estimate.

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.

Mahaffey, K. R.; Clickner, R. P.; Jeffries, R. A. (2008) Adult women's blood mercury concentrations vary regionally in the United States: Association with patterns of fish consumption (NHANES 1999–2004). Environ Health Perspect 117: 47-53. http://dx.doi.org/10.1289/ehp.11674.

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. 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: 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). (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.