Physiologically based pharmacokinetic modeling as tool for the interpretation of biomonitoring data in the exposure assessment of environmental contaminants

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Scope of the lecture:
A huge variety of chemicals are constantly being introduced in the environment. The toxicological significance of exposure to these compounds and the consequences on human health are of increasing concern. Knowledge on **human exposures** and how they can affect health outcomes is mandatory in order to create healthy environments and improve health. Physiologically based toxicokinetic (PBTK) modeling can be a very useful tool to gain information on human exposure for different chemicals.

Learning objectives:
1. The importance of knowledge of toxicokinetics of chemical
2. What is physiologically based toxicokinetic modeling
3. How toxicokinetic modeling can help to interpret measured concentrations of pollutants

Extended abstract:

Regulators are faced with the enormous task of assessing the risk to human health related to exposure to more than hundreds of chemical contaminants of the environment. Among the hurdles, there is the prioritization of the chemicals to assess and to estimate adequately the human exposure to the chemicals of concern. The available resources do not always allow to obtain sufficient number of samples to capture time-concentration profiles of chemicals in people, or to adequately assess exposure in different subpopulations. Computational tools such as physiologically based pharmacokinetic (PBPK) modeling can be very useful in this context.

The aim of this presentation is to present the fundamentals of PBPK modeling and to demonstrate some of their applications in exposure assessment of environmental chemical contaminants, particularly those that relate to gaining information on exposure from biomonitoring data.

PBPK models are mechanistic mathematical representations of the processes of absorption, distribution, metabolism and excretion of chemicals. These models consist of tissue compartments that are linked by arterial and venous blood circulation. The accumulation of chemical in each compartment is described by mass balance differential equations. The equations are formulated with 3 types of parameters: species-specific parameters (physiology, anatomy, etc.), chemical-specific parameters (permeability, lipophilicity, volatility, pKa, etc.), and biochemical parameters (protein binding, membrane transport, biotransformation, etc.). All these parameters can be obtained independently from toxicokinetic data either from in silico, in vitro or in vivo methods. Once the parameter values are acquired, the model can be used to simulate different exposure scenarios to obtain information on internal concentrations over time in tissues of interest. When toxicokinetic data are available, these models can be validated and refined.

There are many reasons why PBPK models are of interest in toxicology and pharmacology. Because of their mechanistic underpinning, a great deal of confidence can be bestowed upon extrapolations performed with PBPK models compared to those made with empirical models. When determining guideline values for exposure to chemicals, toxicity data used to determine the point of departure (POD) such as No Observed Adverse Effect Levels (NOAEL) values are often obtained in conditions that differ from human exposure, and hence PBPK models can be used for different types of extrapolations (i.e., route-to-route, interspecies, high-to-low dose, interindividual, etc.) to minimize uncertainty in the calculated guideline values.

In addition, PBPK models can be of great utility for exposure assessment. As an integration tool for a number of sources of information (i.e., exposure, biology of the exposed person or population, lifestyle, and chemicals), PBPK modeling can allow estimations of internal or external exposure doses in individuals or populations, over a defined period or even for the duration of their life for past or future exposures. This can be done by combining PBPK modeling with techniques such as Monte-Carlo simulation, reverse dosimetry, bootstrapping and Monte Carlo Markov Chain simulations. In doing so, pertinent information on exposure can be obtained that could be difficult, even impossible, simply by environmental or biological monitoring.

In order to illustrate the utility of PBPK modeling in the interpretation of biomonitoring data, simulation results of recent or ongoing studies will be presented. First, in a study on persistent organic pollutants (POPs) exposure in an Inuit mother-infant cohort (Verner et al. 2009, 2010), infant blood concentrations-time profiles were reconstructed for a period of 6 months after birth based on gathered information on a single blood sample from the mother at delivery, the physiology of the child and the mother, and history of lactation. With this new information on internal exposure to POPs in infants, associations and windows of susceptibility for inattention and non-solicited activity in children could then be revealed for these chemicals.

In another study (Tohon et al. 2017), biomonitoring data of indoor volatile organic chemicals (VOCs) from the Canadian Health Measurement Survey (CHMS) were analyzed using a reverse dosimetry approach to determine the distribution of indoor exposure concentrations. Probabilistic PBPK modeling, performed by means of Monte Carlo simulations, were combined with probability calculations in order to convert distribution of blood measures into indoor air levels for the investigated subpopulations (12-19, 20-39, 40-59 and 60-79 years old).

Lastly, toxicokinetic interactions among chemicals are of concern in the interpretation of biomonitoring data because such phenomenon can skew estimations of external doses/concentrations if not adequately accounted for. Using PBPK modeling of mixtures of common VOCs, interactions among mixture components were modeled and validated in a controlled exposure study (Marchand et al. 2016) in volunteers and in the general population with data from the CHMS study (Tohon et al. 2017). Results show impact of interactions at VOC levels observed in the general population.

In conclusion, PBPK modeling can help in the interpretation of biomonitoring data for prioritization management efforts for the exposure assessment of environmental chemicals, to gather more exposure information on an individual basis (retrospectively or prospectively) in

order to relate health effects to chemical exposures, as well as to decipher critical windows of exposure to chemicals.

References:

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