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PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELS

Scientific Models to Help Evaluate Health Effects of Chemicals

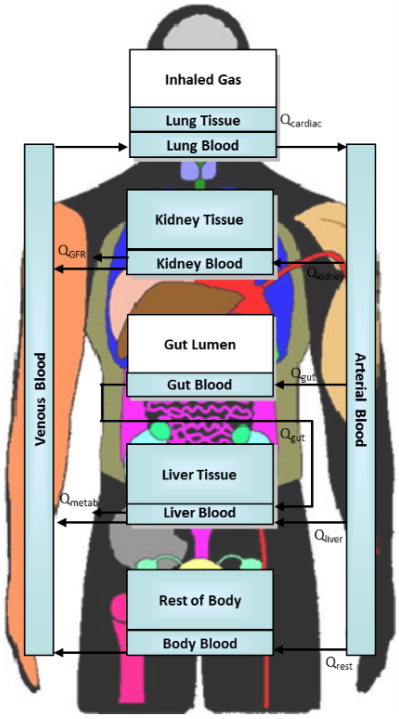
Background

To evaluate chemicals for potential health effects, the U.S. Environmental Protection Agency (EPA) uses both chemical toxicity and exposure information. Toxicity information includes what effects a chemical can have as well as the amount of chemical needed to cause those effects. Chemical exposure describes how (breathing, eating, skin contact, etc.) and how much of a chemical one may be exposed to.

One scientific approach used to better understand the health effects of chemicals is known as Physiologically-Based Pharmacokinetic (PBPK) modeling. A PBPK model is used to relate the amount of chemical exposure to the amount of chemical found in the blood and organs at different points in time. For example, PBPK models can be used to help identify whether a toxic level of a chemical would be found in blood or an organ of a person following exposure to a certain amount of a chemical through drinking water. Since PBPK models can be useful tools in toxicology and risk assessment, it is important to understand what these models are and how they can be used.

PBPK Models Overview

PBPK models are mathematical descriptions of how a chemical enters the body (e.g., breathing, drinking, eating etc.), the amount of chemical that gets into the blood, how the chemical moves between body tissues and the blood, and how the body alters (i.e., metabolizes) and eliminates the chemical. PBPK models incorporate information about the body's anatomical and



physiological structure as well as biochemical processes into the model structure. PBPK models can be simplistic, with a small number of features that are important for describing the movement of a chemical in the body, or complex with a large number of features that dictate chemical fate and movement. Whether researchers develop and use a simplistic or complex PBPK model depends on what health question is being answered and how much information is available to inform the development of a model.

Simplistic PBPK models are often used to get a quick snapshot of a chemical's fate and movement in the body. EPA researchers use simplistic PBPK models to link possible chemical concentrations in the environment to blood concentrations for a large number of chemicals. For example, simplistic PBPK models can be used to rapidly link the amount of chemical exposure to specific blood concentrations that have the potential to disrupt the hormone systems of the body. Combining PBPK predictions of concentration with toxicity data helps EPA researchers prioritize which chemicals used in daily life may have the highest likelihood of leading to health effects.

In other instances, more complex PBPK models are used if the health question being answered requires precise details on how the chemical distributes to multiple tissues and organs. For example, the Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) has been used to inform predictions about the health effects of lead, which is known to interfere with a variety of body processes and is toxic to organs and tissues including the heart and nervous system.

Developing PBPK Models

PBPK models are developed using mathematical values (called "parameters") and equations that describe characteristics and processes of the body, such as body weight, blood flow rate, and metabolism rate. As the number of model parameters and equations increases, the complexity of the model increases. PBPK model parameters include both generic and chemical-specific. Generic parameters describe physiological processes that do not typically vary from one chemical to another such as the size and connectedness of tissues/organs, breathing rates, and blood flow rates. These generic

parameters are often species-specific and allow the model to describe humans or specific animals. Chemical-specific parameters include biochemical processes such as how much a chemical concentrates into specific tissues (for example, more chemical in fat than muscle) or how quickly the chemical is metabolized.

The tissues described by a PBPK model are selected based on the researcher's question, the amount of data available, and how the researcher decides to segment target organs and tissues in the body. Because different researchers have different needs for a PBPK model, different decisions may be reached about which tissues to include in their model. This means that there may be more than one PBPK model for a given chemical.

Traditional pharmacokinetic studies expose laboratory animals to controlled doses of a chemical and then gather biological samples from the animal over time. The samples gathered help researchers determine how much and how quickly a chemical is absorbed into the blood, distributed to different tissues, metabolized and excreted or removed from the body.

As an alternative, many PBPK models are now developed based on pharmacokinetic principles and "test tube" experiments using tissues, cells (such as liver cells), subcellular fractions (e.g., microsomes), or specific proteins. "High-throughput PBPK" models are constructed using these approaches.

All PBPK models use computer programming languages that solve the mathematical equations with the parameters supplied by the user. The mathematical equations describe the amount of chemical in the different compartments over time. There are many different programming languages, and some require payment for licenses or subscriptions while others are open and freely available.

EPA's Usage of PBPK Models

One reason EPA uses PBPK models is to try to understand what animal toxicity data means for a human. This process is known as extrapolation. A PBPK model that describes a chemical in a laboratory animal species can be used for humans by changing the physiological parameters. Using human physiology allows for more human-relevant predictions. PBPK models can also be used for "route-to-route extrapolation" to change how chemical exposure occurs. For example, if laboratory data was generated for the oral route and used to develop a PBPK model, adjustments may be made to the model to estimate the disposition of a chemical following inhalation if that is more relevant to humans.

EPA researchers recently expanded existing PBPK models to better describe specific groups of people, such as children, senior citizens, and individuals with diseases (e.g., obesity and diabetes). Since different groups have different physiologies, the estimates for tissue concentrations of chemicals will be different. For example, one EPA research effort uses height and weight data from a Centers for Disease Control and Prevention survey of Americans to develop PBPK physiological parameters for different ethnic groups. Additional efforts have investigated using PBPK models to better understand effects on specific life stages and populations by developing tools to predict chemical concentrations and distribution in pregnant women and fetuses during gestation and critical windows of development.

The PBPK models that EPA researchers develop and use are publically available. The models undergo peer review in scientific journals and through scientific advisory panels. EPA's website provides papers, data, and in some cases, the code used in the models. EPA has created freely available computer software that contains peer-reviewed data, models, and tools, along with companion databases that include additional chemical property and bioactivity information that can be brought together for integrated analyses. Ongoing efforts will add more chemicals, models, and data to each of these platforms in the future.

PBPK models provide a critical link between chemical toxicity and exposure information, as well as an important tool for using animal, in vitro, and computer-based experiments to inform chemical evaluations.

More Information:

http://www.epa.gov/comptox/expocast
https://cran.r-project.org/web/packages/httk/index.html

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