Proposed Approach to Efficiently Develop Physiologically Based Pharmacokinetic (PBPK) & Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK-PD) Models for Pesticides

Introduction

The standard approach to extrapolating from animals to humans (inter-species) or across the human population (intra-species) in risk assessment is to apply 10X uncertainty factors. In *Science and Decisions: Advancing Risk Assessment* (NRC, 2009), the NAS recommends that the agency "…continue and expand use of the best, most current science to support and revise default assumptions." EPA published its document, "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation" (herein called, DDEF Guidance), in September of 2014[1], which provides a foundation for improving the scientific basis for inter- and intra-species extrapolation using data on pharmacokinetics (PK) and pharmacodynamics (PD).

The DDEF Guidance describes a hierarchal approach for using data and models with varying levels of sophistication to inform inter- and intra--species extrapolation. Recent advances in *in vitro* to *in vivo* extrapolation and computational modeling provide new opportunities to develop models for developing efficient and robust data-derived inter- and intra--species extrapolation factors.

As described here, to take advantages of these scientific advances, the Office of Pesticide Programs (OPP) is developing a tiered framework for extrapolation modeling. OPP is interested in beginning dialogue with interested stakeholders on this proposed tiered approach for developing efficient PBPK models using new technologies.

Physiologically Based Pharmacokinetic (PBPK) & PBPK-pharmacodynamic (PD) Models

There are two common types of PK models:

- empirical compartmental models; and
- physiologically based pharmacokinetic (PBPK) models.

Empirical models, also known as classical models, mathematically describe the temporal change in chemical concentration in blood, tissue, or excreta of the species in which the data were generated. The classical models often treat the body as a single homogenous or multi-compartment system with elimination of a compound occurring in a specific compartment; the characteristics of the compartments (e.g., number and volume) and transfer rates between compartments are hypothetical in that they are chosen for the purpose of describing the data rather than based *a priori* on the physiological characteristics of the organism or the biological attributes of the response. Due to these characteristics, classical models are used for interpolation [i.e., within the range of doses, dose route, and species in which the data were generated (Renwick, 1994)].

PBPK models differ from classical compartmental models in that they are composed of compartments with realistic tissue characteristics that are linked by blood flow. Other parameters used in these models account for chemical-specific characteristics that can be independently measured in both humans and laboratory animals

[1] http://www2.epa.gov/osa/guidance-applying-quantitative-data-develop-data-derived-extrapolation-factors-interspecies-and

(usually using *in vitro* techniques). These chemical-specific parameters may include absorption or permeability rates, tissue solubility (i.e., partition coefficients), binding, metabolism, and other clearance processes. These models are used to simulate the relationship between applied (administered) dose and internal dose at the target tissue. PBPK models require more data to develop compared to classical compartmental models, but they are advantageous because they can be used for extrapolation outside the ranges of dose and time course of available data (U.S. EPA, 2006; Krishnan and Andersen, 1994).

As described in detail in the EPA's 2006 document entitled, "*Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment*[2]*,"* "physiologically based pharmacokinetic (PBPK) modelling is a scientifically sound and robust approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessments." PBPK models consist of a series of mathematical representations of biological tissues and physiological processes in the body that simulate the absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body. PBPK models utilize known physiological and biochemical data to predict internal concentrations of chemical at target tissues or organs for a wide variety of exposure scenarios, and thus aid in many risk assessment applications.

Examples of PBPK model applications in risk assessments include:

- inter-species extrapolation,
- intra-species extrapolation,
- route-to-route extrapolation,
- high-to-low dose extrapolation, and
- estimation of response from varying exposure conditions and across life-stages.

PBPK models, with proper evaluation, can also be used in conjunction with exposure assessment to improve the quantitative characterization of the dose-response relationship and generate regulatory-relevant predictions of biological responses and adverse outcomes to inform the overall risk assessment decisions. These models can also be used to interpret biomonitoring data by estimating potential exposure doses.

PBPK models can also be linked to pharmacodynamic (PD) models to predict both dose-response and time course for the development of adverse effects, as well as for intermediate effects. Linked PBPK and PD (PBPK-PD) models can be developed when sufficient data exist to ascertain the mode of action (MOA), as well as to quantitatively estimate model parameters that represent rates and other quantities associated with key precursor events in the MOA. As such, a PBPK-PD model has the potential to describe chemical-specific ADME behaviors, as well as biological processes at the cellular and molecular levels in such a way as to link exposure concentrations to target tissue doses, and subsequent adverse effects.

Tiered Approach to Developing PBPK or PBPK-PD Models

The major determinant of the use of PBPK models in risk assessment is the availability of chemical-specific data for parameterizing the model, as well as time-course pharmacokinetic data for calibrating and evaluating the model for factors such as target organism and population/life-stage of interest, health endpoints, and exposure

[2] http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668#Download

pathways (dose ranges, routes, scenarios). The chlorpyrifos PBPK-PD model represents a case of highly refined model with chemical-specific parameters (e.g., tissue/blood partition coefficients, metabolic rates) measured for different life-stages, in both animals and humans.

Also, time-course and dose-response data for multiple tissues were measured for different exposure routes. As demonstrated in the example of chlorpyrifos model, which took over a decade to develop and refine, developing PBPK or PBPK-PD models can be resource-intensive and time-consuming.

The Agency is interested in developing a tiered approach (Figure 1) for efficiently developing PBPK (or PBPK-PD) models using contemporary approaches such as read across and *in vitro* to *in vivo* extrapolation (IVIVE, see review by Yoon et al, 2012), with each tier using different amounts/types of data and thus providing different levels of refinement to developing data-derived extrapolation factors.

In the continuum of types of such models, at one extreme would be the chlorpyrifos PBPK-PD model that was originally developed by Timchalk and coworkers in 2002 (Timchalk et al., 2002a, b) and has been refined over more than a decade as more PK and PD data have become available (Busby-Hjerpe et al., 2010; Cole et al., 2005; Garabrant et al., 2009; Lee et al., 2009; Lowe et al., 2009; Lu et al., 2010; Marty et al., 2007; Timchalk and Poet, 2008; Timchalk et al., 2005; Timchalk et al., 2006; Poet et al, 2014).

At the other extreme from the chlorpyrifos PBPK-PD model would be generic PBPK models developed without any data for either parameterization or evaluation. The chemical-specific parameters of these models are estimated based on the chemical structures using molecular modeling tools such as quantitative structure-activity relationship (QSAR) model. Many software packages (e.g., QiKProp[3], MOE[4]) exist whereby one can develop or utilize QSAR models for parameters such as dermal permeation rates, fraction unbound, and volume of distribution. In addition, several commercial PBPK modeling and simulation software programs (e.g., Simcyp[5], GastroPlus™[6]) are available for rapid PBPK model development. In these software packages, the model structure is generic, yet modifiable; and values of chemical-specific parameters are estimated using built-in QSAR models. While these software packages allow a detailed PBPK model to be built with little data, the application of this type of PBPK models in risk assessment is limited to screening and prioritization purpose.

In addition, cheminformatics tools can be applied to explore the chemical space that contains most ADME data to more effectively identify molecular properties of pesticides that can be predictive of ADME behaviors of chemicals with sparse data. These tools and computational molecular modeling also have the potential to explain the underlying molecular processes of chemical interactions and transformations in the biological system, and thus inform both PK and PD processes. Provisional estimates of parameter values derived from computational molecular models may then be tested, such as *in vitro* measurements of metabolic rates based on specific CYPs.

Unlike the QSAR models implemented in the generic PBPK platform (e.g., GastroPlus), QSAR models built with a training set that focuses mainly on a group of chemicals with some degree of shared characteristics should have a more relevant domain of applicability, and thus reducing the uncertainty in the prediction since these chemicals should have similar structures as those used to build the QSAR model. Regardless of the methods used to

[3] http://www.schrodinger.com/QikProp/
[4] https://www.chemcomp.com/MOE-Molecular_Operating_Environment.htm
[5] http://www.simcyp.com/
[6] http://www.simulations-plus.com/Products.aspx?pID=11

estimate values of model parameters or the approach taken to build the model structure, it is preferred to have some PK or PD data available to evaluate the performance of a model.

For intra-species extrapolation, the PBPK model needs to have the capability to capture human variability, ideally including the life-stage of concern, in physiology (e.g., BW, fat percentage, ventilation rates) and biology (e.g., metabolism rate, enzyme inhibition rate). Several open-source (e.g., PopGen[7], P3M[8]) or commercial packages (e.g., Simcyp, GastroPlus) are available for estimating anatomical, physiological, and several metabolic variation in human populations and in various life-stages. Variation of other parameters only need to focus on the sensitive model parameters that likely may be measured using *in vitro* assays.

For most pesticides, major data gaps exist that preclude construction of well-parameterized PBPK or PBPK-PD models (e.g., chlorpyrifos PBPK-PD model), but some animal or human *in vitro* or *in vivo* data may be available or can be rapidly collected either to build a PBPK model with some, but limited predictive ability (e.g., acceptable plasma concentration predictions) or to evaluate a provisional PBPK model parameterized using QSAR models. In other words, PBPK model development for most pesticides is likely to lie between the two extreme tiers. In these cases, previously published PBPK models for chemicals can be used as a starting point to guide the model structure design, parameter optimization, and experimental validation of a *de novo* model for a structurally-similar chemical. Such an approach is common practice in the PBPK modeling field. As stated above, OPP is interested in beginning dialogue with interested stakeholders on this proposed tiered approach for developing efficient PBPK models using new technologies.

[7] McNally et al., (2014) PopGen: A virtual human population generator, Toxicology 315:70-85.
[8] Price et al., (2003) Modeling interindividual variation in physiological factors used in PBPK models of humans. Crit Rev Toxicol 33(5):469-503.

Figure 1. Tiered Approaches in PBPK modeling