Development and Application of Physiologically-Based Kinetic (PBK) Models

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Editorial

The true value of physiologically-based kinetic (PBK) models is their adaptability, capable of representing complete diversity both within, and between, species. PBK modelling is an area of science that draws upon knowledge and expertise across multiple disciplines, from mathematics and programming, to physiology and epidemiology. Once the preserve of pharmaceutical studies (devising physiologically-based pharmacokinetic (PBPK) models to understand spatio-temporal concentrations of drugs in humans) advances in computational methods have enabled the science to flourish, leading to many more applications. Physiologically-based toxicokinetic (PBTK) modelling can be used to inform research and development projects as well as safety assessment of foods, consumer products and chemicals in humans, veterinary/companion animals and environmental species. Celebrating the inherent diversity in PBK modelling, in both the underlying science and its multiple applications, this Special Issue is a collection of papers that explores the different facets of PBK modelling. Contributions have been incorporated on a variety of topics, ranging from optimisation of *in vitro* systems, to modelling *in vivo* kinetics in neonates. Beyond the more practical elements, strategies for prioritising testing and efforts at the global level to promote uptake of PBK models in the regulatory sector have also been included. Through presenting a broad outlook on current developments in PBK modelling, we hope to ensure that every reader, from whichever perspective they approach PBK modelling, finds something of interest. The aim of this Special Issue is to capture the breadth of current developments, create greater awareness of the power and applicability of PBK models and to motivate others to use and accept the approach.

In a physiologically-based kinetic (PBK) model, an organism may be considered as a series of compartments (representing key organs) connected by blood flow. Following uptake, the chemical may be stored, excreted, metabolised or remain unchanged in transiting the organ. More simplistic models possess fewer compartments (organ-types, such as poorly perfused or highly perfused may be grouped together) whereas for more complex models, additional compartments or sub-compartments may be incorporated. The purpose of the model is to predict the concentration-time curve of a chemical of interest in blood or plasma and/or specific tissue(s) of interest. This is important because it is the internal exposure of a chemical (i.e. the concentration-time profile at the target site) that determines the true potential of a chemical to elicit a biological response. Models require chemical-specific parameters (e.g. lipophilicity, potential to bind to proteins etc) and physiological/anatomical parameters (e.g. blood flows, organ volumes etc). Differential equations are used to determine the time course of the chemical in each tissue, with the models being fully adaptable for different exposure scenarios (e.g. oral, dermal or inhalatory routes) and for individuals within a population (accounting for developmental stages or disease states that may affect physiological processes). Whilst originally developed, and predominantly used, within the pharmaceutical industry, such models are increasingly applied to assess chemical safety across a range of sectors, including food, cosmetic, personal care product and environmental health. PBK models may be used for forward dosimetry (to predict internal exposure following a given dose) or reverse dosimetry/dose reconstruction (to predict the external dose responsible for an observed concentration *in vivo).* This observed concentration can either be on the basis of a biomarker concentration or an *in vitro* determined effect concentration. PBK modelling can be applied to quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) where concentrations in blood (or tissues) are simulated in order to determine the dose level that gives rise to a concentration in the target tissue, equivalent to the concentration at which an effect was observed *in vitro*.

Whilst PBK models have traditionally been developed, optimised and evaluated using animal data, the science is now moving towards a new paradigm where information from *in silico* and *in vitro* methods are used as New Approach Methodologies (NAMs) to reduce or replace animal use. This presents significant challenges, not only in constructing the models, but also in ensuring their validity, particularly for regulatory purposes. In this issue, the outcome of an expert workshop (hosted by the European Commission Joint Research Centre, European Union Reference Laboratory for Alternatives to Animal Testing) convened to investigate the use of next

generation physiologically-based kinetic (NG-PBK) models in regulatory decision making, is reported. An insight is also given into ongoing work at the Organisation for Economic Collaboration and Development (OECD) to develop guidance on characterising, validating and reporting PBK models with an emphasis on models constructed using non-animal data. Recognition of non-animal alternatives is important as generation of animal data (aside from ethical issues) is a slow process and more rapid assessment is necessary for the large number of new, and existing, chemicals for which safety-assessment is required. One solution to this is a tiered approach for screening and prioritizing chemicals, using data from high throughput methods to replace *in vivo* data, to parameterize PBK models, as discussed herein.

Development of model code, has been an area of expansion in recent years. In addition to industry-standard commercial packages, that have been available for a number of years, there are an increasing number of freely available tools for PBK model development and analysis. The Population Lifecourse Exposure to Health Effects Model (PLETHEM) PLETHEM is introduced here. Written in R code, PLETHEM provides workflows to support PBK modelling, along with a database of relevant parameters, equations and models with both the source code and a user guide to support those starting out with this system. As the number of software packages, databases and predictive models with relevance to PBK modelling increases, it can be difficult for those new to the area to know where to start, and for experienced practioners to keep pace with the latest developments. In response to this, we have incorporated an overview of *in silico* resources available for development and evaluation of PBK models; including databases for parameter values, predictive models for physico-chemical and pharmacokinetic properties, summaries of PBK–specific modelling software, as well as generic mathematical solvers.

PBK modelling is predicated on the need to predict kinetic profiles, as accurately as practicable, across relevant populations and sub-populations. Much of the research in this area arises from the need to establish safe levels of exposure for humans in chemical risk assessment, taking account of population variability. Use of default uncertainty factors, although historically a widely-used approach, has much scope for refinement, especially as more population data become available. Use of Bayesian models for meta-analysis of human population variability has been shown as an approach to generate uncertainty factors, with emphasis here on metabolic differences. Model code has been made available for other users to further develop this area. Arguably, the most significant factor to consider, in terms of safety assessment, is how the most sensitive individuals within a population may be affected. For this reason there has been an increased focus on developing models (or equations that may serve as building blocks for models) for pregnancy related changes, placental transfer and physiological difference in neonates (preterm and full term); examples of these are also included in this issue. Protection of sensitive individuals in a clinical setting is also explored in a paper describing a framework for predicting probability of liver injury following paracetamol ingestion, in healthy and high-risk sub populations.

Development of increasingly robust PBK models, relies on continual advancements in the underlying science, with current emphasis on *in vitro* and *in silico* methods. Novel applications in mathematical biology are helping to optimise modelling of *in vitro* systems to more accurately represent the *in vivo* situation. In this issue, *in silico* optimisation of oxygen gradients to improve design of experiments using hepatic spheroids is presented as one such application. Finally, as recognised in many areas of science, nanoparticles are known to have unique and distinctive properties. We end this issue with a detailed review of PBK models of nanomaterials that are available in the literature and their suitability for regulatory applications.

PBK modelling has truly moved from a niche academic discipline, predominantly relating to pharmaceutical studies, to a versatile and valuable tool increasingly used in a number of sectors. Application in new areas will no doubt drive further expansion of the science and may ultimately help to resolve some of the confounding factors in converting external exposure to true internal concentrations. Issues such as accounting for physiological changes occurring with chronic exposure or the influence of mixture or vehicle effects, particularly on the most sensitive individuals will provide ample opportunity for continuing research in this important area.

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