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# Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications

Alicia Paini [a, *], Jeremy A. Leonard [b], Tomas Kliment [c], Yu-Mei Tan [d], Andrew Worth [a]

[a] European Commission, Joint Research Centre, Directorate Health, Consumers and Reference Materials, Via E Fermi 2749, 21027 Ispra, Italy
[b] Oak Ridge Institute for Science and Education, Oak Ridge, TN 37831, USA
[c] Klimeto, Juzna 4, Roznava, Slovakia
[d] U.S. Environmental Protection Agency, National Research Laboratory, Research Triangle Park, NC 27709, USA

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ABSTRACT

Physiologically based kinetic (PBK) models are used widely throughout a number of working sectors, including academia and industry, to provide insight into the dosimetry related to observed adverse health effects in humans and other species. Use of these models has increased over the last several decades, especially in conjunction with emerging alternative methods to animal testing, such as *in vitro* studies and data-driven *in silico* quantitative-structure-activity-relationship (QSAR) predictions. Experimental information derived from these new approach methods can be used as input for model parameters and allows for increased confidence in models for chemicals that did not have *in vivo* data for model calibration. Despite significant advancements in good modelling practice (GMP) for model development and evaluation, there remains some reluctance among regulatory agencies to use such models during the risk assessment process. Here, the results of a survey disseminated to the modelling community are presented in order to inform the frequency of use and applications of PBK models in science and regulatory submission. Additionally, the survey was designed to identify a network of investigators involved in PBK modelling and knowledgeable of GMP so that they might be contacted in the future for peer review of PBK models, especially in regards to vetting the models to such a degree as to gain a greater acceptance for regulatory purposes.



## 1. Introduction

Physiologically based kinetic (PBK[1]) models describe the body as a set of interconnected compartments that represent plasma and various organs, and characterize a chemical's fate within the body in regards to pharmacokinetic properties including absorption, distribution, metabolism and elimination (ADME). The development and use of PBK models have significantly increased over the last two decades, as is reflected in the rise of published literature referencing PBK models (Fig. 1). A wide variety of institutions have expressed a high degree of interest in PBK model applications, including academia, regulatory agencies, pharmaceutical and chemical industries (Schuck et al., 2015). PBK models have been deemed an effective means to aid in *in vitro* to *in vivo* extrapolation (IVIVE) (Blaauboer, 2010; Kramer et al., 2015), route to route extrapolation (Bessems et al., 2017), high to low dose, and inter- and intra-species extrapolations (Punt et al., 2016).

The European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), which is part of the European Commission, published its Toxicokinetic Strategy (2015)[2] outlining a plan for identifying opportunities to apply new approach methods (NAM) to generate and more effectively use toxicokinetic

* Corresponding author. European Commission, Joint Research Centre, Directorate Health, Consumers and Reference Materials, Chemical Safety and Alternative Methods Unit, Via E. Fermi 2749, TP 126, I-21027 Ispra, VA, Italy.
*E-mail address:* alicia.paini@ec.europa.eu (A. Paini).

[1] The term PBK model is synonymous with physiologically based pharmacokinetic (PBPK), physiologically based biokinetic (PBBK), and physiologically based toxicokinetic (PBTK) models.

[2] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC96418/eurl%20ecvam%20toxicokinetics%20strategy.pdf.

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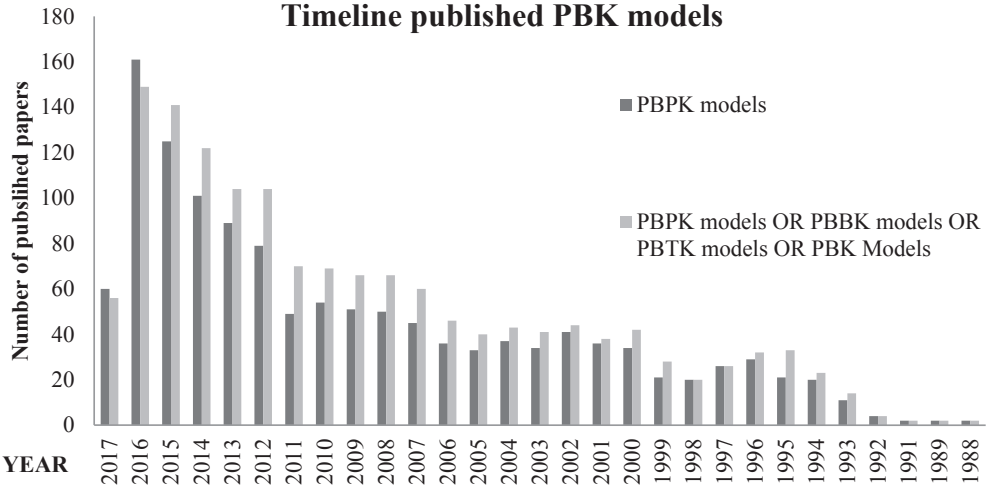


**Fig. 1.** Number of papers published per year in the last 30 years. The search was conducted using PubMed on the 08th of April 2017, with key words including "PBPK model" only, or a set of keywords including the string "PBPK models OR PBBK models OR PBTK models OR PBK Models". The year 2017 represents only papers published in the first 3 months.

data. The central feature of this strategy is using PBK models to integrate ADME data and to predict whole-body toxicokinetic behaviours. To facilitate the acceptance of PBK models for which development is based solely on non-animal data, good modelling practice (GMP) focusing on this new generation of PBK models is required for further development and recognition at an international level. As a starting point, GMP should include relevant information from existing guidance documents (WHO/IPCS, 2010; US EPA, 2006; EMA, 2016; US FDA, 2016). For example, development of PBK models can be accomplished through a six-step approach (Rietjens et al., 2011), regardless of the use of conventional methods or NAM to parameterize models. Briefly, these steps include (i) defining a simplified representation of the biological system for which model compartments can be included (i.e., a conceptual model); (ii) translating the conceptual model into a mathematical model by formulating a differential equation for each compartment; (iii) defining equation parameters as values derived either from literature or from experiments; (iv) solving the equations by calculating the concentrations of relevant compounds and their metabolites in the specific compartments, or the extent of their adverse reactions with the toxicological receptor; (v) evaluating model performance, with adjustments and improvements to the model when necessary; and (vi) using simulations to make predictions (Rietjens et al., 2011). The process involving each of these six steps should be transparent and documented. In addition, GMP may involve the development of standard reporting formats, which is equivalent in purpose to the QSAR Model Reporting Format (QMRF) and QSAR Prediction Reporting Format (QPRF), for presenting sufficient details of model construction and application. Such detailed reporting will aid kinetic modellers in accounting for all the necessary components that constitute a proper model and is expected to facilitate acceptance of kinetic modelling approaches by decision makers. Finally, the formation of a panel comprised of international PBK modelling experts and a knowledgeable group of peer-reviewers would not only expedite the drafting of GMP, but also promote future applications of PBK models in regulatory risk assessment.

As toxicity testing and risk assessment shift more towards approaches involving NAMs such as *in vitro* techniques, PBK models are being used more frequently to convert *in vitro* points of departure (PoDs) to *in vivo* exposure (i.e., reverse dosimetry) for risk screening. Several examples are outlined in the review by Punt et al. (2011), including those for neurotoxicity (DeJongh et al., 1999; Forsby and Blaauboer, 2007), acute and repeated dose toxicity (Gubbels-van Hal et al., 2005; Rotroff et al., 2010; Pery et al., 2013; Gajewska et al., 2015), developmental toxicity (Verwei et al., 2006; Louisse et al., 2010), and genotoxicity (Paini et al., 2010). Among these examples, Paini et al. (2010) converted a threshold for a molecular initiating event (e.g., DNA binding) to an external exposure; Pery et al. (2013) and Gajewska et al. (2015) linked *in vitro* cell viability to an external dose; Wetmore et al. (2012a,b) incorporated *in vitro* metabolism measurements in IVIVE and reverse dosimetry to estimate external doses that are relevant to *in vitro* PoDs.

One of the major limitations for a broader application of PBK models highlighted by Punt et al. (2011) is that development of new PBK models can be labour intensive processes that require generation of a large range of data through *in vitro*, *in silico*, or *in vivo* analyses to construct and parameterize a model. A more efficient approach is starting with the structure of a previously developed, well-parameterized, and thoroughly-vetted model for a close analogue; and adjusting chemical-specific parameters based on *in vitro* or *in silico* data (e.g., metabolism rates, absorption rates, partition coefficients between blood and tissues) (Lu et al., 2016). Such approach also directs the modellers to obtain necessary *in vitro* or *in silico* data that are relevant to a specific chemical.

In order to facilitate acceptance and use of the new generation of PBK models, which rely on non-animal data, in the regulatory domain, experts were invited by EURL ECVAM to participate in a workshop on "Physiologically-based kinetic modelling in risk assessment – reaching a whole new level in regulatory decision-making" (Ispra, Italy, November 16–17, 2016) to identify challenges in (i) applying PBK modelling to support regulatory decision making; (ii) constructing PBK models without the use of *in vivo* kinetic and dynamic data, instead, relying solely on *in vitro* or *in silico* methods; and (iii) assessing model credibility and validity. The workshop participants concluded that an updated GMP requires inclusion of strengths and limitations encountered when parameterizing PBK models using *in vitro* measurements and *in silico* predictions, as well as processes for evaluating these types of PBK models to support regulatory decision-making. Other outcomes of the workshop and recommendations of the workshop participants are summarized by Paini et al. (2017). Prior to the workshop, in October 2016, the organizers sent invited experts a questionnaire containing 11 questions, to understand the use of PBK models from these experts (Paini et al., 2017). Due to the agreement among the