In Silico Resources to Assist in the Development and Evaluation of Physiologically-Based Kinetic Models

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Abstract

Since their inception in pharmaceutical applications, physiologically-based kinetic (PBK) models are increasingly being used across a range of sectors, such as safety assessment of cosmetics, food additives, consumer goods, pesticides and other chemicals. Such models can be used to construct organ-level concentration-time profiles of xenobiotics. These models are essential in determining the overall internal exposure to a chemical and hence its ability to elicit a biological response. There are a multitude of *in silico* resources available to assist in the construction and evaluation of PBK models. An overview of these resources is presented herein, encompassing all attributes required for PBK modelling. These include predictive tools and databases for physico-chemical properties and absorption, distribution, metabolism and elimination (ADME) related properties. Data sources for existing PBK models, bespoke PBK software and generic software that can assist in model development are also identified. On-going efforts to harmonise approaches to PBK model construction, evaluation and reporting that would help increase the uptake and acceptance of these models are also discussed.

Keywords

PBK; PBPK; PBTK; *in silico* tools; ADME prediction

1. Introduction

The science of physiologically-based kinetic (PBK) modelling has been evolving in recent years, contemporaneously with developments in computational approaches across multiple sectors. Whilst, historically, data for models were obtained via time and resource intensive animal experimentation, there is now an array of *in silico* resources that can assist with the parameterisation, computational implementation and evaluation of these models. The role of internal exposure, in particular organ-level concentration-time profiles of xenobiotics, in determining true potential to elicit a biological response, is now recognised across multiple disciplines from drug development to chemical safety assessment of cosmetics, food additives, consumer goods, pesticides and other chemicals to which humans (and animals) are daily exposed. A recent report by Paini et al., 2017 [1] demonstrated the distinct upward trajectory in the use of PBK models over the last 30 years with respondents to a survey indicating a significant number of models being applied in chemical safety assessment. Other uses included experimental design, drug design, ecological health risk assessment, veterinary health, informing pharmaceutical dose selection for specific populations, clinical trial design and drug labelling. PBK models are being increasingly used to extrapolate from *in vitro* experimental data to *in vivo* scenarios (*in vitro* to *in vivo* extrapolation; IVIVE) in response to the ethical, societal and economical drivers to move away from *in vivo* animal experiments and towards new approach / next generation methodologies (NAM / NGM) [2], [3], [4]. Rowland et al., 2015 [5] discussed the increased number of submissions, containing PBK models, to regulatory agencies concerned with clinical drug development. Meetings organised by the US Food and Drug Administration (FDA; [6]) and the UK Medicines and Healthcare Products Regulatory (MHRA), in collaboration with the Association of British Pharmaceutical Industry (ABPI; [7]) centred on developing best practice in building and reporting PBK models and enhancing common understanding between regulators, academia and industry encouraging further use of PBK modelling. Recent US FDA guidance proposes appropriate format and content for submissions of physiologically based pharmacokinetic (PBPK) analyses for new drug / biologic license applications. Relevant publications were highlighted concerning key topics such as study design, specific populations (paediatrics, pregnancy, disease states) and potential drug-drug interactions [8].

Clearly, the use of PBK models across a range of disciplines is rapidly expanding. Laroche et al., 2018 [9] summarise recent developments and needs across multiple sectors i.e. pharmaceuticals, vaccines, cosmetics, fragrances, chemical, agrochemical and food industries. The aim of this paper is to present an overview of the *in silico* resources available to assist in PBK model construction and evaluation, that is relevant across the boundaries of the different sectors. It is recognised that such an overview can

never be truly complete as continual developments inevitably lead to changes in availability and capabilities of the software and databases recorded. However, at the time of writing, the information provided is as comprehensive as reasonably practicable and provides a "one stop shop" to signpost the various resources available. It is intended that this will not only provide a useful starting point for those relatively new to the field but also may identify additional, unexploited resources for experienced modellers.

2. Applications of PBK models

The foundations for PBK modelling were laid with the introduction of physiologically-based pharmacokinetic (PBPK) modelling which was used to describe the time course of pharmaceuticals within different organs or tissues of the body [10], [11]. This tool has also been applied to evaluate the health risks posed by environmental chemicals – referred to as physiologically-based toxicokinetic modelling (PBTK) defined by the World Health Organization as "a model that estimates the dose to target tissue by taking into account the rate of absorption into the body, distribution and storage in tissues, metabolism and excretion on the basis of interplay among critical physiological, physicochemical and biochemical determinants" (WHO, 2010,[12]). Being adaptable to individual physiology, these models enable internal exposure, hence potential therapeutic and adverse effects, to be predicted more accurately than models relying on external dose alone. For example, models can be parameterised for altered kidney or liver function as may be expressed by elderly or neonatal populations or pregnant women. The models can be extrapolated to take into account the effects that age, disease state or genetic variation may have on concentration-time profiles. Clinically, this enables appropriate dose adjustments to be more reliably predicted, optimising therapy for sensitive individuals, hence their increasing application in this area. Previously, in drug development many PBK models have focused on key organs having a significant effect on ADME properties of drugs, however, more recent applications specifically consider organs associated with toxicity and side effects in terms of safety assessment. For example, Pilari et al., 2017 [13] include organs of the reproductive and endocrine systems (testes and thyroid) in an extended PBK model more relevant to toxicity prediction. PBK models can also be applied to address issues of drug-drug (or drug-food; drug herbal product) interactions, where the presence of one drug (component of food or herb) may inhibit or induce metabolising enzymes or compete for transporters used by a co-administered compound. This can lead to a significant increase or decrease of circulating drug levels causing loss of therapeutic effect or induction of side effects. The application of such models also goes beyond predicting effects of pharmaceutical agents, similar considerations are important where excipients have been shown to exert undesirable biological effects. Valeur et al., 2018 [14] stipulate that increased knowledge is

required in terms of understanding the effects of excipients present in drug formulations, particularly with respect to potential toxicity in neonates who may, for example, show differences in metabolic capacity. PBK models, specifically adapted to the physiology of neonates, may provide important information to optimise treatment for these patients. PBK models are playing a pivotal role in several ongoing European Horizon 2020 projects that are exploiting the full potential of *in-silico* medical research to generate virtual patient/population libraries as well as data integration and data-driven *in-silico* models for enabling personalised medicine within a harmonised framework.

In addition to drugs, PBK models have been also been applied to the safety assessment of food, cosmetics and environmental chemicals. In the food industry, PBK models have been applied to assessing the health risks from exposure to pesticides, contaminants and food contact materials. The models enable multiple exposure scenarios, interspecies differences and intraspecies variation to be accounted for when predicting internal exposures. The scientific report of the European Food Safety Authority (EFSA) (2014) reviews many of these applications of PBK modelling in the food safety sector. For cosmetics and personal care products, the Notes of Guidance from the Scientific Committee on Consumer Safety (SCCS) (2016) explicitly recognise contributions from PBK models in safety assessment. Recently published Opinions of the SCCS (for example opinion on phenoxyethanol SCCS/1575/16) have incorporated data from PBK studies. Tan et al., 2018 [15] review the use of PBPK modelling in terms of public health decision making concerning environmental chemicals. Their report found that from 1977 – 2016, 65% of published models (identified using the PubMed database) related to environmental chemicals, and 31% related to drugs. While the potential of PBPK modelling has been recognised, barriers to uptake by public health agencies persist particularly because of a lack of expertise in the area - there is a limited number of people with sufficient expertise to build, evaluate and review models. These problems are exacerbated by a lack of consistency in the format of submissions. Additional issues identified in the report were problems of transferring models between platforms and lack of confidence in extrapolation. Several of these issues, and potential solutions, are discussed below. The application of PBK models to nanoparticles is another area of increasing interest. In 2010 Li et al discussed the factors to be considered when applying the models to nanoparticles, such as differences in metabolism, distribution and accumulation in the lymphatic system which can differ between nanoparticles and small molecules [16]. More recently Yuan et al reviewed the disposition properties of nanoparticles and how PBK models could take account of the unique characteristics of these particles [17]. A comprehensive review of PBK models for nanoparticles, and their acceptability for regulatory purposes was also recently published by Lamon et al [18]. The authors identified similar issues to those discussed by Tan et al [15] in relation to the problems that hindered regulatory acceptance: complexity of models; transferability across platforms and; lack of

confidence in models where tissue/plasma concentration data are lacking [18]. In regulatory toxicology, there is an ethical and economical desire to move away from animal experiments to alternative methods, such as *in vitro* testing. PBK modelling has an important role to play in extrapolating *in vitro* concentration-effect information to *in vivo* human dose-response relationships (IVIVE). This enables points of departure to be identified from *in vitro* studies for risk assessment purposes. Punt et al., 2011 [19] describe the successful application of this approach in terms of promoting alternatives to animals in risk assessment. Whilst the above demonstrates great variety in the types of chemicals investigated using PBK modelling, the model structures themselves are independent of the nature of the chemical.

3. Input parameters required for PBK model building

Figure 1 shows a characteristic representation of a PBK model structure in the centre of the image. Inputs typically required for modelling are shown on the right, and an example model output is shown on the left (the concentration-time curve for a specific chemical in a tissue or organ of interest). Within each compartment it is possible to incorporate more detailed model structures, for example the gastro-intestinal (GI) tract may be subdivided into individual compartments – stomach, duodenum, jejunum, ileum, caecum and colon with dissolved and undissolved chemical being considered separately. The predictive performance of a model can be evaluated by comparing experimentally-derived data (where available) with model-derived values.

[FIGURE 1 – HERE]

Development of PBK models requires both chemical specific parameters (e.g. metabolic rates, plasma protein binding fraction, dermal absorption rate) and chemical independent system information - physiological and anatomical values (e.g. blood flows and tissue volumes). Chemical specific factors may be derived from experimental measurements or predicted using an ever-increasing array of software available to predict these factors. Key properties relate to the ability to partition across biological membranes, hence the logarithm of the octanol: water partition coefficient (log P), aqueous water solubility and pKa (relating to potential for ionisation – in general unionised molecules cross biological membranes more readily) are commonly used to estimate those factors needed for a PBK model. In addition there are a multitude of *in silico* models that predict the absorption, distribution, metabolism and elimination (ADME) of chemicals. These include models for absorption through the gastro-intestinal tract (or surrogates thereof, such as PAMPA or CaCo-2 membranes), partitioning across the blood brain barrier, permeation through skin, plasma protein binding and extent of

distribution throughout the body (volume of distribution). A limited number of models also exist for more specific ADME properties, such as partitioning into milk or blood: testes concentration ratio. Patel et al., 2018 [20] have collated and reviewed over 80 of these ADME related models. One of the more difficult properties to predict using *in silico* methods is clearance; accurate estimation of clearance is essential as this determines the overall residence of a chemical in the body. For this reason, *in vitro* estimation of hepatic clearance is still the predominant method used to obtain such information using liver slices, or (sub) cellular fractions, however, total clearance (i.e. clearance by all routes including metabolism, biliary, renal clearance etc.) influences overall internal exposure. Similarly, although there are datasets for thousands of chemicals for which plasma protein binding has been measured and many *in silico* models derived from these data, measurement of plasma protein binding for new chemicals of interest is often undertaken as this parameter can have a significant effect on PBK model predictions. *In vitro* measurements, using human derived tissue, are clearly important sources of information for PBK model development, however, as the focus of this review is on *in silico* methods, information will be restricted to data sources for *in vitro* information rather than experimental details.

Multiple data sources are available providing system information i.e. the physiological and anatomical reference values on which PBK models are predicated. These include data for multiple species, life stages - from gestational development to the elderly, and disease-related adaptations to standard values. Much of this data has been empirically derived and collated over decades. In the next section each of the various types of input parameter for PBK models are considered individually and *in silico* resources for obtaining this information are identified. Whilst individual sources for the information are given, it is recognised that much of the collated information has been brought together in bespoke PBK modelling software that can provide, both key information for components of a model and an overall modelling platform; these are also identified below.

4. In silico resources available to assist in PBK model construction and evaluation

The following section illustrates the range of information, relevant to PBK model construction and evaluation, that is available from a wide variety of sources. These resources have been collated into eight tables, each relating to different components of PBK modelling or ancillary information. The contents of the tables are briefly summarised here; details on the availability and capabilities of the software, models and datasets are provided in tables 1-8. The resources have been collated here for information only. The authors have not evaluated each of these resources; their inclusion should not be considered an endorsement.

4.1 Resources for external exposure

Although not strictly associated with development of PBK models, Table 1 includes information on models for external exposure, as without an estimation of the amount to which the body is exposed externally there can be no estimation of internal exposure from a reliable PBK model. For drugs the precise amount and route of exposure are known making this a relatively simple "exposure" scenario. Dosing information for clinical applications across age groups can be obtained from resources such as Medicines Complete (refer to Table 1). For chemicals that humans (and animals) are exposed to via food, use of personal care or household cleaning products, or from the environment, the extent of exposure is more difficult to estimate. However, tools are available to provide estimates for these different scenarios. For example: EFSA provides estimates for dietary exposure; SCCS provides typical product usage for personal care products; the European Centre for Ecotoxicology and Ecotoxicity (ECETOC), the United States Environmental Protection Agency (US EPA) and the Dutch National Institute for Public Health and the Environment (RIVM), amongst others, provide models for predicting worker or consumer exposure to household products and environmental pollutants. A summary of these external exposure models is provided in Table 1.

4.2 Resources for obtaining physico-chemical properties

Knowledge of physico-chemical properties is important not only in terms of PBK modelling, for predicting uptake and distribution within the body (as indicated above), but also forms part of the fundamental characterisation data for chemicals. As such, there is a large number of databases reporting experimental values as well as predictive software both freely available and commercial from which to obtain these properties. Resources such as Chemspider (from the Royal Society of Chemistry), ACD / Percepta (from ACD laboratories) and EPISUITE (from the US EPA) provide estimates and/or measured values for log P, water solubility, vapour pressure, pKa etc. A number of these resources are indicated in Table 2. Several of these resources are also capable of predicting ADME-related properties, for example ADMET Predictor from Simulations Plus predicts log P, log D, solubility in intestinal fluid as well as permeability across skin, blood-brain barrier, interactions with proteins, transporters and other properties.

4.3 Resources for obtaining ADME-related information

Table 3 provides a compilation of predictive software, datasets and models for more than 50 ADME related endpoints. The amount of data and number of models available is highly variable depending

on the endpoint in question. Thousands of measured values are available for plasma protein binding data along with many predictive models, similarly there are many data and models for intestinal absorption, blood brain barrier partitioning, skin permeation, p-glycoprotein and transporter binding. Whilst there are many data for renal, hepatic and total clearance, there are fewer, accurate models for these endpoints, reflecting the difficulty of developing *in silico* models for such endpoints. This was highlighted in the report of Paini et al., 2019 [21] who identified hepatic clearance as a key input parameter for PBK models that was better derived from *in vitro* studies where possible. For highly specific information, for example tissue concentration-time profiles (that may be used to evaluate PBK model outputs), very few data are available. The on-line chemical modelling environment (oCHEM) provides some such data but provides much more extensive datasets for more standard endpoints such as inhibition of cytochrome P450 enzymes, CACO-2 permeability or fraction unbound (fraction unbound is of importance as it influences the extent to which a chemical distributed within the body). The paper of Przybylak et al., 2018 [22] is useful in this regard as it identifies over 140 ADME related datasets that can be used for development of new models; these models can be used to predict parameters for chemicals where experimental data are lacking. 31 of the datasets were considered as "benchmark" datasets, particularly suitable for modelling purposes (these were converted to Excel format and are available as supplementary information within the paper). Given the increasing focus on ADME properties in determining true potential to elicit a biological response, it is not surprising that the amount of software and data compilations in this area is expanding rapidly. Data are now available for multiple species and multiple ADME/PK endpoints ranging from computational ligand-protein interaction studies to clinical observations as illustrated by the diversity of resources in Table 3.

4.4 Resources for physiological and anatomical reference values

Whilst the focus of tables 2 and 3 is on the chemical-specific input parameters, Table 4 provides resources for the chemical independent physiological and anatomical reference values that are also required for PBK modelling. Resources, such as Brown et al., 1997 [23] and the Interspecies Database (from RIVM and the Dutch ministry of Health Welfare and Sports) (https://www.interspeciesinfo.com/) provide parameter values for organs (weights, volumes, composition, percentage of cardiac output, local blood flow etc.) for multiple species. The International Commission on Radiological Protection (ICRPP) provides age and gender-related values for humans and are commonly used for fundamental input values – other similar resources are also given in Table 4. Increasingly PBK frameworks for specific organ structures are being developed and published, as well as being incorporated into PBK modelling software (such as SimCYP from Certara).

Examples of these include: the models of Abduljali et al., 2018; 2012 [24], [25], [26] providing parameters for different stages of pregnancy and foetal development; the blood brain barrier/ brain compartment penetration models of Ball et al., 2013 [27], Gaohua et al., 2016 [28] and Zakaria et al., 2018 [29], the models for lung from Goahua et al., 2015 [30] and the testes and thyroid models from Pilari et al., 2017 [31]. Obviously, a major source of PBK modelling parameters are previously published PBK models, these models may serve as a template for deriving models for similar chemicals. In 2016, Lu et al., [32] published a Knowledgebase summarising 307 published PBK models along with a study demonstrating how information from these could be used to develop PBK models for other similar chemicals. Concepts relating to similarity and selection of chemicals, for which PBK models are available that can be used as templates for other chemicals, are discussed further below.

4.5 Physiologically-Based Kinetic modelling software

The number of bespoke PBK modelling packages available has been gradually increasing with freely available applications now making the area more accessible to a larger number of researchers; some of these are indicated in Table 5. The Simcyp Simulator software from Certara (https://www.certara.com/), in particular, is widely used by industry. The software incorporates a number of databases (physiological and anatomical data, genetic and epidemiological information) and model structures (e.g. those identified in Table 4) to enable organ-level predictions of concentration-time curves for specific human subpopulations, as well as modules for rats, dogs and knock-out mice. Cloe from Cyprotex (now part of Evotec AG) is another example of a complete PBK modelling package enabling organ concentration-time curves to be generated for humans, rats and mice. Freely available software includes: PK-Sim and MoBi (Bayer) – a PBK modelling tool with integrated databases for different species and capable of multiscale modelling; MEGen (Health and Safety Laboratory, UK) – a method to rapidly generate PBK model code; and more recently PLETHEM (Scitovation) which incorporates an 11 compartment PBK model and an IVIVE model relating *in vitro* points of departure to equivalent *in vivo* values.

4.6 Software to assist development of pharmacokinetic/pharmacodynamic models

Aside from the bespoke PBK modelling software indicated above, there are numerous applications that can assist in developing PBK or pharmacokinetic/pharmacodynamic (PK/PD) models. The website for Pharmacokinetic and Pharmacodynamic Resources (http://www.pharmpk.com/soft.html) lists over 100 such applications and the reader is referred to that resource for a more up-to-date and comprehensive listing. Examples of this type of application include routines for PK/PD simulations,

analysis tools, non-linear mixed effect modelling and simulation software. PopGen from Bayer enables virtual populations to be considered and ChemPK from Cyprotex can predict PK data including clearance, maximum concentration in tissue (C_{max}), time to reach the maximum concentration (T_{max},) and the area under the concentration-time curve (AUC) from oral and intravenous dosing. The RVis platform is currently under development at the Health and Safety Laboratory, UK, this can load, run and visualise outputs from models, with applications in IVIVE and sensitivity analysis, enabling the evaluation of PBK model structure and performance (Paini et al., 2017,[1]). These software and other examples are summarised in Table 6.

4.7 Generic mathematical and computational software that can be applied to issues in PBK modelling

Of the numerous research fields that exist at the interface of chemistry and biology, PBK modelling is more amenable than most to solutions from mathematical and computational sciences. Many of the issues relating to behaviour of chemicals within compartments, linked by vessels and showing definable increases and decreases over time - in part dependent on volumes and flow properties - are in many ways akin to engineering scenarios. Consequently, in terms of computational solutions there are many examples of software or simplistic programmes that can assist in coding and solving for differential equations in PBK models, although originally developed for other purposes. Berkley Madonna is one example of a platform commonly used for PBK modelling, it is in essence a differential equation solver that can also be used for other dynamical modelling problems. Other examples of mathematical modelling software that can assist in PBK modelling are GNU MCSIM, SigmaPlot, applications within Rstudio and Matlab (within which the SimBiology toolbox possesses customisable PK models and the ability to perform simulations for individuals or populations). Sensitivity analysis, important for determining the significance of individual model parameters, can be performed by PBK and PK/PD modelling-specific software (Tables 5 and 6) as well as more generic mathematically-based software. Examples of more generic resources that can be applied to issues in PBK modelling are given in Table 7.

4.8 Software to identify structurally similar chemicals

As discussed above, identifying a chemical, for which a PBK model has already been published (source chemical(s)) can provide key information for developing or evaluating a PBK model for a similar chemical of interest for which no model is available (target chemical). The concept of reading across information from source chemical(s) to a target chemical is well-established within regulatory toxicology. A great deal of guidance is available on how to select similar chemicals and report a read-

across prediction (Read Across Assessment Framework, ECHA (2015); [33]). This concept is now being increasingly applied to PBK model development. The key to the process is selecting the most appropriate source chemicals from which to read-across information and fully justifying the selection. One difficulty is that no chemical can be absolutely similar to another, they can only be similar in terms of given properties. In Table 8, several computational methods to identify structurally similar chemicals are given. However, the choice of similarity metrics used can have a significant effect on which chemicals are identified as most similar. In terms of selection based purely on structural similarity, a consensus from several similarity metrics may be more appropriate. Recent publications have addressed this issue specifically in terms of selecting source chemicals to develop or evaluate PBK models for target chemicals. Ellison, 2018 [34] selected source chemicals using structural properties (functional group, scaffold, metabolism, physico-chemical properties and chemical fingerprints) and functional similarity (i.e. in the same classes according to the Biopharmaceutics Disposition Classification System and Extended Clearance Classification System; the same likelihood of being a p-glycoprotein substrate; and similar volumes of distribution, bioavailability and systemic clearance). The results showed that the approach could be used to successfully predict the pharmacokinetic profile of target chemicals using appropriately selected source chemicals. Lester et al., 2018 [35] further explored the concepts of selecting source chemicals, emphasising the need to incorporate expert judgement as part of the process. The authors devised "rating rules" for selecting chemicals where expert judgement was included in a structured, less subjective approach. Table 8 includes examples of similarity approaches applied to the issue of PBK modelling including those of Lu et al., 2016 [32], Lester et al., 2018 [35] and Ellison, 2018 [34]. This issue of identifying "similar" chemicals is currently an area of intense research in many sectors both within European projects (e.g. the Innovative Medicines Initiative eTRANSAFE project (http://etransafe.eu/) for translational safety assessment of medicines) and at the global level through projects being developed via the Organisation for Economic Cooperation and Development (OECD). Hence, more guidance on selecting similar chemicals, and justifying the selection, is anticipated.

[TABLES 1-8 HERE]

5. Conclusions and outlook

A multitude of *in silico* resources have been presented herein to assist researchers in the development and evaluation of PBK models. This should provide a useful starting point to those new to the area as

well as signposting additional resources to more experienced researchers who may not be aware of developments in all of these resources. Bessems et al., 2015 [36] stipulated the need for "comprehensive 'one-stop' web-based kinetic modelling portals", ideally incorporating or linking to freely available kinetic modelling tools and databases, to facilitate kinetic modelling. This collation of resources serves as a single resource identifying tools and databases to assist in PBK model construction and evaluation.

Whilst many resources are available it is clear that there are several gaps not only in the underlying knowledge but also in the way in which the information is organised and stored. In terms of chemical-specific input parameters, large datasets of measured values and reasonable quality predictive models are available for certain endpoints. Some literature models may be reproduced readily and a range of software are available; predictions will be more reliable forforchemicals falling within the applicability domain of the model; predictions for chemicals outside of the applicability domain will have greater uncertainty. For other endpoints, notably renal and hepatic clearance, there are far fewer reliable *in silico* models and this, therefore, should be a focus for continuing modelling efforts, notwithstanding the improvements in *in vitro* techniques in this area. More experimental data are needed to develop these models, particularly differential enzyme and transporter expression / activity both across different tissues within a given animal and across different species. Scaling anatomical properties (such as organ weights) works reasonably well across species, however, other factors scale less well. For example scaling the number of hepatocytes from *in vitro* systems to that in an adult liver is possible but does not correspond to an accurate scaling of intrinsic clearance *in vitro* to human data [5]. Where improvements can be made on any aspect of the input parameters for PBK models, this leads to greater accuracy and reduced uncertainty of the model.

An important aspect to consider in developing and evaluating PBK models is the shift away from animal data to next generation physiologically-based kinetic (NG-PBK) models where data from *in vitro* and/or *in silico* studies replace *in vivo* data. Whilst there is some reluctance, particularly amongst regulatory organisations to accept such models in safety assessment, there are a number of ongoing activities to support this shift. More training and guidance, along with increased communication between the model developers and regulators have been proposed to increase acceptance of PBK models without animal data [21]. Whether or not a PBK model is considered acceptable depends on the intended purpose of the model; for example regulatory acceptance for safety assessment has more stringent criteria than models for in-house prioritisation. In accordance with Occam's Razor, the simplest model capable of describing chemical behaviour, with sufficient accuracy for the problem in question, should be employed.

Software developments, particularly the expansion of bespoke PBK modelling platforms available will be of great benefit to the area, particularly where freely available platforms increase accessibility for researchers. Community development of individual modules / subroutines that can be brought together in larger workflows or programming applications has shown to be a successful model for collaborative effort in both the R and KNIME environments. This is also a promising approach for continuing development of PBK models, where cross-sector collaboration between food, cosmetic, chemical and pharmaceutical industries can be used to resolve common problems.

Using data from source chemicals to make predictions for target chemicals is widely used for other applications (for example toxicity prediction in regulatory toxicology) and recent developments have demonstrated the utility of this approach for PBK modelling. Already, very useful methods to find similar chemicals have been published in the literature (such as Ellison 2018 [34]) and as more knowledge and tools become available to ascertain which chemicals are similar, this will advance this approach further. This highlights one outstanding issue that is, being able to rapidly identify chemicals for which PBK models have already been developed. The Knowledgebase developed by Lu et al., 2016 [32] is an excellent example of how existing models could be curated and made readily available for other researchers. Systematic reviews are now an established method to find, organise and extract information from literature studies. Data retrieved and search criteria being recorded in such a way as to enable subsequent researchers to readily update information in future. Ongoing systematic review of available PBK models is highly recommended to ensure maximum use can be made of published models. To this end a single repository for storing key information on published PBK models, would be highly beneficial, such a repository would benefit from consistency in the reporting of models. Following from an international workshop in this area, Loizou et al., 2008 [37] discussed the importance of developing good modelling practice (GMP) for PBPK modelling to assist model sharing, evaluation and consistency of application. Seven elements were proposed for a summary report with more detail being made available to specialists as necessary. The recommendations were for: an introduction including problem formulation/model applicability; a description of the model; metabolic information; relationship to mode of action; prediction of distribution accounting for human variability; an overview of uncertainty and sensitivity analysis; source of further information. More recently, the US Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER) [38] has published guidance for industry on the format and content for reporting results from PBPK analysis to the FDA. This sets out clear recommendations for what to include in each of six sections of the report. Briefly, reports should include: a succinct overview of the model; a summary of the drug's physico-chemical PK and PD properties; sufficient methodological information to allow model reproduction and evaluation (with appropriate workflows / decision trees); all system-specific and

drug specific parameters, their source, assumptions and uncertainties (as tables); a description of the simulation conditions; software name, version and parameterisation; model verification and application details; key conclusions; cross-referencing to other relevant reports and supplementary documentation as necessary. If consistent model reporting were more widely taken up by the modelling community this would again provide long term benefits to the field.

The BioModels database [39], provided by the European Molecular Biology Laboratory – European Bioinformatics Institute EMBL-EBI; https://www.ebi.ac.uk/biomodels-main/) provides a repository of computational models of biological processes. Models are manually curated from the literature and made publicly available; if the model is reproducible it is listed as a curated model, if not then it is listed as a non-curated model. At time of writing very few PBK models are reported in this system, however, expansion of this resource could potentially make a useful repository for PBK models for other users to exploit. PBK-related software, such as GNU-MCSim and PK-Sim / MoBI are compatible with Systems Biology Markup Language (SBML; http://sbml.org/) which provides a machine-readable interchange format for computer models of biological processes. This enables key components of models to be shared in different software environments without the need to rewrite the models, so making them more accessible to other users, increasing model longevity and adaptability.

Capacity building in PBK model development and understanding amongst researchers from diverse fields has also been recognised as a clear need for future development. Jones and Rowland-Yeo (2013) [40] provide an excellent tutorial to explain the concepts of PBPK – components, parameters and applications in early stage and clinical drug development for those who are new to the area. More training material would help to move PBK model development from a niche to a more mainstream field of research, increasing the number of people able to review, interpret and use the models to make more accurate predictions of biological activity across life-stages, subpopulations and species. These developments give rise to boundless opportunities to apply PBK modelling to resolve many of the questions in *in vitro* to *in vivo* extrapolation, ecotoxicology (particularly bioaccumulation across species), veterinary science and human health.

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Table 1. Resources to predict external exposure

Resource	Available from	Brief summary of capability
Computational Toxicology Dashboard[F]	https://comptox.epa.gov/dashboard [41]	Provided by United States Environment Protection Agency (USEPA); the dashboard hosts a repository of data for 762,000 chemicals and includes links to exposure prediction and monitoring data
ConsExpo Web[F]	https://www.rivm.nl/en/consexpo	Mathematical model to assess exposure to chemicals from everyday consumer products (e.g. household cleaning products and personal care products (provided by the National Institute for Public Health and the Environment, Netherlands); considers inhalational, oral and dermal exposure
EC SCCS Notes of Guidance[F]	http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf [42]	European Commission Scientific Committee on Consumer Safety (EC SCCS) Notes of Guidance 9th revision: tables for exposure area, frequency of application, typical product usage etc. for personal care products
ECETOC TRA[F]	http://www.ecetoc.org/tools/targeted-risk-assessment-tra/	Targeted Risk Assessment (TRA) tool provided by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC); calculates risk of exposure from chemicals to workers, consumers and the environment
EPA ExpoBox[F]	https://www.epa.gov/expobox	This toolbox is a compilation of exposure assessment tools linking to guidance documents, databases, models etc. It is organised into six areas: approaches, media, routes, tiers and types, lifestages and populations and chemical classes
EPA ExpoCast[F]	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research	High Throughput exposure estimation for chemicals (complimentary to the EPA ToxCast program) for both environmental and consumer product exposure
FAIM / FEIM EFSA[F]	https://www.efsa.europa.eu/en/applications/foodingredients/tools	Food Additives / Enzyme Intake models (FAIM / FEIM) from the European Food Safety Authority (EFSA); estimates chronic dietary exposure to food additives / enzymes for different populations (based on collected food consumption data for different countries)

Medicines Complete[C]	https://about.medicinescomplete.com/	Dosing information for different uses and age groups
MerlinExpo[F]	https://merlin-expo.eu/	Modelling **E**xposure to chemicals for **R***i*sk assessment: a comprehensive **L**ibrary of multimedia and PBPK models for **i**ntegration, prediction, uncertainty and sensitivity analysis; library of models to assess human and environmental exposure
SHEDS (Stochastic Human Exposure and Dose Simulation (SHEDS)[F]	https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure	Probabilistic models to estimate total exposure of populations over time via inhalational, dermal, dietary and non-dietary routes.
Stoffenmanager[F] (substance manager)	https://stoffenmanager.nl/	Web-based quantitative exposure modelling tool for both respiratory and dermal exposure.

[F]Freely available; [C]Commercial

Additional sources of information:

- The report of the World Health Organisation (International programme on chemical safety, Environmental Health Criteria 242, Dermal Exposure, 2014, ISBN 978 92 4 157242 2) includes a review of several models for estimating (dermal) exposure including DREAM, DERM, Calendex, EASE, MEASE, ECETOC TRA, RISKOF DERM, BEAT, ConsExpo, SprayExpo, SHEDS-R etc.

Table 2. Resources for obtaining or predicting physico-chemical properties

Resource	Available from	Properties / Information	Additional Information
ACD /Percepta[C] (ACD Labs)	https://www.acdlabs.com/products/percepta/	Log P; log D; pKa; Abraham solvation parameters (relating to hydrogen bonding ability, polarizability, volume and partitioning)[P]	Platform comprising modules for prediction of physico-chemical properties, ADME and toxicity
ADME SARfari (EMBL-EBI)[F]	https://www.ebi.ac.uk/chembl/admesarfari/ [43]	Log P; log D (reports values from ACD); PSA; [M,P]	The European Bioinformatics Institute – part of the European Molecular Biology Laboratory provides a comprehensive range of molecular data resources for a range of research purposes
ADMETlab[F]	http://admet.scbdd.com/calcpre/index/ [44]	Log P; log D; log S	Application developed by the Computational Biology and Drug Design Group, Central South University, China
ADMET Predictor[C] (SimulationsPlus)	https://www.simulations-plus.com/software/admetpredictor/	Log P; log D; pKa; diffusion coefficient; air: water partition coefficient; pH dependent solubility; solubility in gastric/intestinal fluid (fed and fasted states)	Available as a standalone ADMET property predictor or within the GastroPlus modelling platform
ALOGPS 2.1[F] (Virtual Computational Chemistry Laboratory)	http://www.vcclab.org/lab/alogps/	Log P; log D; water solubility; pKa [P]	In addition to calculating the values the software requests predictions from additional sources (e.g. KOWWIN, Molinspiration, Dragon X etc.) and displays all predictions to enable comparison

Biobyte[C] (Bio-Loom)	http://www.biobyte.com/	Log P, log D, pKa[P,M]	Includes database of 60,000 measured log P and log D values (various solvents) and 14,000 pKa values
ChemIDPlus Advanced	https://chem.nlm.nih.gov/chemidplus/	Log P, pKa, solubility, vapour pressure, m.pt[M,P]	National Institute of Health, US National Library of Medicine database and predicted values
Chemspider[F] (Royal Society of Chemistry)	http://www.chemspider.com/ [45]	Log P; water solubility pKa, vapour pressure, Henry's law constant[M,P]	Comprehensive resource for over 60 million chemical structures; includes experimental data where available and links to predictions from EPISUITE, ACD/Labs and ChemAxon
ChemAxon[C]	https://chemaxon.com/	Log P; log D; hydrophilic:lipophilic balance; water solubility; hydrogen bond donor / acceptor; pKa[P]	Chemical property predictors are one component in a suite of chemoinformatics tools.
Corina Symphony[F] (MN-AM)	https://www.mn-am.com/ [46]	Log P; hydrogen bond donor / acceptor parameters[P]	A chemoinformatics application for generating multiple chemical descriptors
Computational Toxicology Dashboard[F]	https://comptox.epa.gov/dashboard [47]	Log P, m. pt, b. pt, vapour pressure, etc[M,P]	Provided by United States Environment Protection Agency (USEPA); The dashboard hosts a repository of data for 762,000 chemicals and links to other data sources; includes physico-chemical properties, activity, fate, hazard and other data.
Episuite[F] (US-EPA))	https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface	Log P; water solubility, vapour pressure, Henry's law constant[M,P]	Extensive database of measured values; atom/fragment contribution method to estimate log P; water solubility calculated using log P and appropriate correction factors
MOE (Molecular Modelling Environment)[F]	https://www.chemcomp.com/MOE-	Calculates >400 molecular descriptors including physico-chemical properties,	Chemical Computing Group, Canada (interfaces to other software such as Gaussian, GAMESS, MOPAC and ADF)

	Molecular_Operating_Environment.htm	Topological Polar Surface Area (TPSA), log P, log D, pKa, electronic effects such as hydrogen bonding capacity, partial charges, dipole moment etc.	
Moka[C] Molecular Discovery	http://www.moldiscovery.com/software/moka/	pKa[P]	Calculates pKa using a method trained on more than 25,000 pKa values (algorithm uses descriptors derived from GRID molecular interaction fields)
Molinspiration[F]	http://www.molinspiration.com/	Log P; hydrogen bond donors / acceptors; TPSA; volume	Interactive web service to calculate molecular properties, visualise and manipulate structures
OECD QSAR toolbox[F]	https://www.qsartoolbox.org/	Multiple physico-chemical properties[M,P]	The Toolbox has been developed to help fill gaps in (eco) toxicity data. It includes a large compilation of donated databases (for both properties and biological activities)
PubChem Open Chemistry database[F]	https://pubchem.ncbi.nlm.nih.gov/search/	Multiple physico-chemical properties including log P, TPSA, water solubility, pKa, vapour pressure[M,P]	A comprehensive data resource including chemical and physical properties, uses, toxicity, safety information etc.
Schrodinger:[C] QikProp	https://www.schrodinger.com/	pKa; Log P; water solubility	Schrodinger software encompasses a range of molecular modelling packages for drug design includes prediction of physico-chemical and ADME properties
SwissADME[F]	http://www.swissadme.ch/ [48]	Multiple physico-chemical properties including log P (various methods of calculation), water solubility,	Webservice from the Swiss Institute of Bioinformatics

	TPSA; no. hydrogen bond donors / acceptors[P]

[F]Freely available; [C]Commercial; [P]Predicted value; [M]Measured value

Additional sources of information:

- The above is not an exhaustive list - many other resources are available. As part of the ANTARES project (Alternative Non-Testing methods Assessed for REACH Substances) extensive lists of software capable of predicting physico-chemical (and other properties) have been compiled; these lists of software are available at: http://www.antares-life.eu/index.php?sec=modellist
- The Computational Chemistry List (http://www.ccl.net/chemistry/links/software/index.shtml) is an extensive list of software for calculating a multitude of physico-chemical and ADME-related properties, quantum chemical and molecular mechanics based descriptors. The website provides a brief summary of the software and a link to the parent websites

Table 3. Resources for information on ADME properties (datasets, models and predictive software)

Resource	Available from	Properties / information	Additional information
ACD/Percepta[C]	ACD Labs https://www.acdlabs.com/products/percepta/	Estimates multiple ADME-PK related parameters including absoprtion, bioavailability, Cp (T), Tmax and Cp (max), AUC, Pgp substrate specificity, Vd, protein binding. Blood Brain Barrier (BBB) penetration etc.	Multiple modules available for predicting both physico-chemical and ADME related properties.
ADME database[C]; Fujitsu	http://www.fqs.pl/en/chemistry/products/adme-db [49]	Interactions of substances with Phase I and II metabolising enzymes and drug transporters; database of kinetic parameters – *in vitro* assay model (Km, V_{max}, K_i, Ks, efficiency, IC_{50}, EC_{50}, t½ etc.)	Data available for > 26,000 substances (72,000 entries for CYPs; 15,400 for other enzymes); 34,000 entries providing data on >400 transporters
ADMETlab[F]	http://admet.scbdd.com/calcpre/index/ [44]	Human intestinal absorption; Caco-2 permeability; P-gp / CYP substrates and inhibitors; bioavailability; plasma protein binding; BBB partitioning; volume of distribution; t½ , clearance	Developed by the Computational Biology and Drug Design Group, Central South university, China
ADMET Predictor[C] (SimulationsPlus)	https://www.simulations-plus.com/software/admetpredictor/ [50]	Permeability (skin, cornea, gastro-intestinal tract, BBB); interactions with OATP1B1 and P-gP; plasma protein binding; blood: plasma ratio, volume of distribution; fraction unbound in microsomes etc.)	Available as a standalone ADMET property predictor or within the GastroPlus modelling platform
admetSAR[F]	http://lmmd.ecust.edu.cn/admetsar2	Dataset for ADMET properties curated from literature; ADMET-Simulator also predicts approx. 50 relevant ADMET	Comprises both literature data (>210,000 data points for >96,000 compounds) and predictive software based on regression /

	[51]	endpoints. (Human intestinal absorption, bioavailability, volume of distribution, plasma protein binding, clearance, Ki IC50 etc.)	classification models to predict approximately 50 ADMET endpoints.
ADME SARfari (EMBL-EBI)[F]	https://www.ebi.ac.uk/chembl/admesarfari [43]	Identifies ADME targets; finds pharmacokinetic data for input chemical or similar compounds	EMBL-EBI provides a range of data sources including data for ADME relevant proteins responsible for metabolism / transport in humans and other species
The ADME databases[F]	http://modem.ucsd.edu/adme/databases/databases_extend.htm [52]	Data for log S, Caco-2 permeability, blood-brain permeability, P-gp inhibition, oral absorption and bioavailability	ADME relevant databases developed using data collected from literature.
ADMETNet[F]	http://bioinf.xmu.edu.cn/ADMETNet/index.html [53]	Depicts pharmacokinetic pathways for drugs; provides data such as half-life, free fraction in plasma bioavailability, volume of distribution etc.	Data for 1, 541 drugs; provides external links for additional searches on compound of interest (e.g. DrugBank, Drugs.com, ChemSpider, admetSAR etc.)
ADME-AP[F]	http://bidd.nus.edu.sg/group/admeap/admeap.asp [54]	A database of proteins associated with drug absorption, distribution, metabolism, and excretion	Provides information on ADME associated proteins e.g. functions, similarities, substrates, ligands, tissue distributions and other properties; 321 proteins and 964 substrates
BIOVIA Metabolite: Biovia (formerly Accelrys)[C]	http://accelrys.com/products/collaborative-science/databases/	Compilation of *in vitro* and *in vivo* metabolic data from literature, conference proceedings and New Drug Applications	Comprehensive database on biotransformations (predominantly for drugs)
Brenda[F]	http://www.brenda-enzymes.org/index.php [55]	Extensive database of V_{max}, K_m, K_{cat} and other parameters related to enzyme kinetics.	Enzyme function data from literature, text mining and external databases; >3 million data points, from over 135,000 references; links to literature reports
BBB[F]			

Computational Toxicology Dashboard[F]	https://comptox.epa.gov/dashboard [47]	ADME data to be included in this database (ongoing)	Provided by United States Environment Protection Agency (USEPA)
Cytochrome P450 Drug Interaction Table[F]	http://medicine.iupui.edu/clinpharm/ddis/clinical-table [56]	List of drugs acting as substrates, inhibitors (partial ranking as to weak, moderate or strong) and inducers of CYP enzymes - 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4,5,7	Developed as a drug-drug interaction table by Indiana University
DIDB - Metabolism and Transport Drug Interaction Database[C]	https://www.drugbankinteractioninfo.org/ [57]	*In vitro* and *in vivo* drug interaction data from literature and New Drug Applications (NDA)	Manually curated data relating to drug interactions, developed by the University of Washington
Drugbank[F]	https://www.drugbank.ca/ [58]	Key ADME properties for drugs e.g. % oral absorption, volume of distribution, protein binding, metabolic information, t ½, clearance etc.	Data entries for >11,000 drugs with >200 data fields per compound (note not all fields are complete for each drug). Includes predicted ADMET properties such as absorption, p-glycoprotein and metabolising enzyme interactions
e-PK gene[C]	https://www.drugbankinteractioninfo.org/ [59]	Information on the impact of genetic variation on parent compound pharmacokinetics (i.e. changes in AUC, Cl or Cmax for different populations)	Manually curated from pharmacogenetics literature and New Drug Applications; developed by the University of Washington
EDETOX database[F]	https://apps.ncl.ac.uk/edetox/ [60]	A database of *in vitro* and *in vivo* skin penetration data for many compounds, including information on skin type, area and vehicle	1,657 *in vitro* and 844 *in vivo* records (across all species and chemicals) compiled from published literature; developed by the University of Newcastle
Evolvus: Microsomal Stability Database[C]	http://www.evolvus.com/products/datab	Liver microsome stability assay data (Cl_{int} and t½) for drugs and drug-like compounds	Customisable, commercial database; includes assay specific data to assist *in silico* modelling

	ases/microsomalstability.html	curated from literature for rat, mouse, human and dog)	
Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th Edition	McGraw-Hill Publishers (2017) ISBN-13: 978-1259584732	Appendices provide key pharmacokinetic data for commonly used drugs e.g. oral bioavailability, urinary excretion, % bound in plasma, clearance, volume of distribution, half-life, Tmax and Cmax	Standard pharmacology text book providing references to original publications for the data
Hazard Evaluation Support System and Integrated Platform (HESS)[F]	http://www.nite.go.jp/en/chem/qsar/hess-e.html [61]	Metabolic maps and ADME data for humans and rats	National Institute of Technology and Evaluation, Japan; database incorporated within OECD QSAR Toolbox
IDAAPM[F]	http://idaapm.helsinki.fi/ [62]	Integrated database for ADMET and adverse effect predictive modelling	Comprises information on approved drugs, ADMET properties, adverse affects and target / affinity data
KinParDB[F] Joint Research Centre European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)	https://eurl-ecvam.jrc.ec.europa.eu/	Kinetic parameters (e.g. clearance, half-life, AUC) for 100 diverse chemicals	Includes experimental details for the generation of the data
Laboratory of Molecular Modeling and Design (LMMD) Datasets[F]	http://lmmd.ecust.edu.cn/	ADME databases curated from the literature with information on blood brain barrier (BBB) partitioning, human intestinal absorption, P450 inhibitors and non-inhibitors	BBB partitioning data for 1,593 compounds; HIA data for 578 compounds; inhibitor and non-inhibitor information for 27,000 compounds interacting with 5 CYPs isoforms – 1A2, 2C9, 2C19, 2D6 and 3A4 – extracted from PubChem

The Merck Index On-line[F]	https://www.rsc.org/merck-index	Provides links to original publications for individual drugs, including detailed reports for pharmacokinetics	The Merck Index Online, from the Royal Society of Chemistry; information on physical and biological properties and structure
METRABASE[F]	http://www-metrabase.ch.cam.ac.uk/ [63]	Data on interactions between chemicals and proteins relating to metabolism and transport; 20 transporters and 13 CYP enzymes; identifies substrates and non-substrates / inhibitors and inducers	Data extracted from literature and on-line resources for 3438 compounds; >11,000 interaction records from > 1,211 references; developed by the university of Cambridge
Microsomal stability[C]	http://www.evolvus.com/products/databases/microsomalstability.html	Database for parameters of liver microsomal stability assays like CL_{int} and $T_{1/2}$ for various drug and drug like compounds.	entries for liver microsomes from different organisms (rat, mouse, human, dog) are curated
Obach et al., 2008	http://dmd.aspetjournals.org/content/36/7/1385	Clinical IV data	Database for 670 drugs
OECD QSAR toolbox[F]	https://www.qsartoolbox.org/ [64]	Encompasses a collation of databases including data on plasma protein binding, absorption, rat and human metabolic data – skin and liver	Data can be accessed from the OECD QSAR Tool box ver 4.2; liver and skin metabolism simulators also incorporated
On-line chemical modelling environment - oCHEM [F]	https://ochem.eu/home/show.do [65]	Datasets for many ADME properties (e.g. absorption, BBB partitioning, Caco2 permeability, log P, log D, water solubility, plasma protein binding, IC50, CYP Inhibition, P-gp substrate activity; tissue:blood partition coefficients and time dependent tissue-drug concentrations	Provides an expanding database of experimental results with a predictive modelling framework. Users can upload their own data and models based on the wiki principle. Large datasets for some parameters but much more limited for others e.g. tissue-dug concentrations.

PharmaInformatic: PACT-F[C] / PPB-DB[C]	http://www.pharmainformatic.com/html/pact-f.html	PACT-F provides bioavailability data for humans (from clinical trials) and preclinical animal studies. PPB-DB provides protein binding information	Comprises 8,296 records for bioavailability and >17,000 data records for protein binding from 2,400 publications
Pharmapendium[C]: Elsevier	https://www.elsevier.com/solutions/pharmapendium-clinical-data	ADME information searchable by terms such as % absorption, bioavailability, cell / protein binding metabolic transformation, tissue distribution, volume of distribution, clearance, half-life; humans, birds, fish and mammals	Pharmacokinetic data for approved drugs extracted from drug approval packages.
pkCSM[F]	http://biosig.unimelb.edu.au/pkcsm/ [66]	Caco-2 / skin permeability, HIA, P-gp / CYP substrate / inhibitor; clearance, renal OCT2 substrate; volume of distribution, BBB permeability, fraction unbound in plasma	Uses graph-based signatures to predict a range of ADMET properties
QikProp[C]	https://www.schrodinger.com/products	Predicts ADME relevant properties (e.g. blood brain partitioning, protein binding Caco-2 and MDCK permeability)	Part of a suite of molecular modelling packages for drug design (see above)
SwissADME[F]	http://www.swissadme.ch/ [67]	Multiple ADME–related properties including GI absorption, BBB penetration, skin penetration, interactions with P-gp and CYPs, drug-likeness characteristics[P]	Webservice from the Swiss Institute of Bioinformatics.
TRANSFORMER[F]	http://bioinformatics.charite.de/transfomer/index.php?site=home [68]	Information on metabolism and transport of compounds in humans	Data for interactions with Phase I (4007 reactions) and Phase II (431 reactions) enzymes and drug transporters (1,158 interactions) for 2,800 drugs
TP-Search[F]	http://togodb.dbcls.jp/tpsearch [69]	Transporters database	Information on substrates and inhibitors for a wide range of transporters

US FDA drug database - drugs@fda[F] (Orange Book)	https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm	*In vitro* and *in vivo* ADME data	Clinical PK data also available
UCSF-FDA Transportal[F]	http://transportal.compbio.ucsf.edu/about/ [70]	Information on transporter expression, location, substrates, inhibitors and interactions	University of California, San Franciso-Food and Drug Administration resource developed as part of FDA-led Critical Path Initiative
VolSurf[F]	http://www.moldiscovery.com/software/vsplus/ [71]	Creates 128 molecular descriptors from 3D Molecular Interaction Fields (MIFs) related to ADME	Passive intestinal absorption, BBB, solubility, PPB, Vd, and metabolic stability models available.
VNN ADMET[F]	https://vnnadmet.bhsai.org/vnnadmet/login.xhtml [72]	Predicts ADMET properties and facilitates building of new models based on variable nearest neighbour (vNN) methodology	This platform comprises 15 models for ADMET prediction models

[F]Freely available; [C]Commercial

Additional sources of information:

- Many of the bespoke ADME / PBK modelling software packages are capable of predicting relevant physico-chemical or pharmacokinetic properties.
- Madden et al., 2017 [73]: Incorporates a review of data sources and software providing information relating to metabolism in skin and liver e.g. prediction of metabolites, CYP isoforms involved in biotransformation, predictive models for kinetic parameters etc.
- Mostrag-Szlichtyng and Worth, 2010 (http://publications.jrc.ec.europa.eu/repository/handle/JRC58570): An extensive review of QSAR models and software available to predict ADME properties, with an emphasis on methods to estimate oral bioavailability, human intestinal absorption, blood brain barrier penetration, plasma protein binding, metabolism and excretion. The review provides references for: 16 ADME related databases;15 datasets for ADME; 13 software tools for predicting input parameters; 41 software tools for ADME prediction (note that some of these data resources are no longer available); 8 rules of thumb for intestinal absorption / blood brain barrier partitioning; 37 models for human intestinal absorption; 13 models for bioavailability; 77 models for BBB partitioning; 28 models for plasma protein binding; 87 models relating to metabolism and 16 models relating to excretion.
- Patel et al., 2018 [20]: As part of an investigation into the reproducibility of QSAR models, Patel et al compiled a list of 80 different models for 31 ADME related endpoints and assessed these models against the OECD principles for validation of QSARs

- Przybylak et al., 2018 [22]: Over 140 ADME datasets were collated in this study and were assessed for their suitability for modelling purposes. Many of these datasets represent a compilation of previously published datasets that have been curated by various authors. 31 were considered to be “benchmark” datasets for 24 different ADME properties; each of these datasets is available in Excel spreadsheet format as Supplementary Information from the article.

Table 4. Resources for obtaining reference values for physiological/anatomical parameters and model structures for specific organs

Resource	Reference	Properties / Information	Additional Information
Abduljali et al., 2012	[26]	Key parameters for PBK modelling in pregnancy according to gestational age.	Integration of data from extensive literature review of changes in anatomical, physiological and metabolic parameter changes during normal pregnancy.
Abduljali et al., 2018	[24], [25]	Key biometric / morphological and compositional parameters to develop PBK models for a foetus at different gestational ages	Integration of data from extensive literature review providing data on size, height, weight, surface area, abdominal and head circumference, body composition.
Ball et al., 2013	[27]	PBK model structure for blood brain barrier (BBB) penetration based on literature review of existing PBK models for CNS	Includes evaluation of the applicability of *in-vitro-in vivo* extrapolation in PBK models for BBB penetration
Brown et al., 1997	[23]	Physiological and anatomical parameter reference values (and ranges for values) for mice, rats, dogs and humans. Organ weights, composition, regional blood flows, volumes, cardiac output, respiratory parameters etc.	A comprehensive, key reference source for physiological and anatomical reference values in multiple species, expanding upon previous data collations and providing information on potential variability of the parameters.
Chetty et al., 2018	[74]	PBPK considerations for geriatric population	Potential use of PBPK models to inform dose adjustments in elderly
Darwich et al ., 2014	[75]	Enterocyte turnover in humans, rabbits, guinea pigs, rats, hamsters and mice	Collation of enterocyte turnover values in different species; turnover influences level of metabolising enzymes in gut wall which can be particularly relevant in drug-drug interactions
Gentry et al., 2005	[76]	Physiological values for PBK modelling (organ weights / volumes, ventilation, food / water intake, blood flows, bile flow, creatinine clearance, glomerular filtration rate) in neonatal and young rats and mice	Physiological parameters collated from literature reports are available in database format upon request to the corresponding author.

Gaohua et al., 2015	[30]	Organ model structures, anatomical and physiological data for lung	Model developed to predict pharmacokinetics of anti-tuberculosis drugs in lung. Model embedded within Simcyp simulator.
Gaohua et al., 2016	[28]	Model structure and parameters for a four-compartment permeability-limited PBK model for brain.	Model performance investigated using paracetamol and phenytoin; Model embedded within Simcyp simulator.
Hall et al., 2011	[77]	Organ volumes, blood volumes and blood flow rates for mice, rats, rhesus monkeys, pigs and humans	The paper describes the development of a whole-body physiologically-based framework that uses novel physiological scaling laws to improve interspecies extrapolation.
Heikkinen et al., 2015	[78]	Quantified levels of cytochrome P450 and uridine diphosphate glucuronosyltransferase enzymes in Beagle dog liver and intestine	Enables comparison of enzyme levels between humans and dogs to assist interspecies scaling of pharmacokinetic properties
ICRPP	http://www.icrp.org/publication.asp?id=ICRP%20Publication%2089	Age and gender- specific anatomical and physiological reference values	A publication of the International Commission on Radiological Protection (ICRPP) to provide inputs for dosimetry calculations.
Interspecies database[F]	https://www.interspeciesinfo.com/	Anatomical, physiological and biochemical data for mouse, rat, rabbit, dog, monkey and pig	Developed by National Institute for Public Health and the Environment (RIVM) and the Dutch Ministry of Health, Welfare and Sports; provides physiological parameters for mouth, oesophagus, stomach, small and large intestine, liver, gallbladder, kidney and lung compiled from literature
Johnson et al., 2005	[79]	Models for liver volume from birth to adulthood	Meta-analysis of published data / models collated from 5,036 subjects including investigation of covariates (age, gender, ethnicity)
Lu et al., 2016	[32]	Corpus of information on PBK models for 307 chemicals published in literature	Enables identification of “similar” compounds that may serve as templates for PBK models; provides references for existing published models

PBK Knowledgebase			
National Center for Health Statistics[F]	https://www.cdc.gov/growthcharts/clinical_charts.htm	Growth charts for 0-2 yrs and over 2yrs (length, height, BMI, head circumference)	Links to World Health Organisation growth charts for 0-2yrs and United States Centers for Disease Control and Prevention growth charts for older than 2yrs
Pilari et al., 2017	[31]	Organ model structures, anatomical and physiological data for testes and thyroid	Model validated using data for fentanyl, alfentanil, omadacycline, amiodarone, desethylamiodarone, propylthiouracil
Price et al., (2003)	[80]	Volumes and blood flows for a range of organs and tissues, cardiac output and inhalation rate	Database with accompanying software for retrieving physiological parameters for PBK modelling accounting for inter-individual variation
Polak et al., 2012	[81]	Dermal absorption model	The effect of penetration enhancers, site of application, gender and ethnic variations incorporated
Thomson et al 2009	[82]	Age-specific organ volumes, blood flows, glomerular filtration rates for healthy and healthy-impaired elderly subjects.	Physiological parameter values collated from 155 publications available as a Microsoft ACCESS database.
Tylutki et al., 2015	[83]	Cardiac distribution of >200 drugs	Drug concentrations in cardiac tissue obtained from cardiac surgery and forensic study data.
Tylutki et al., 2017	[84]	4 compartmental heart model (epicardium, midmyocardium, endocardium, pericardial fluid)	Models account for CYP 450 metabolism in heart.

US EPA Physiological Information Database (PID)[F]	https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=202847&CFID=90333472&CFTOKEN=83385957	Physiological parameter values for humans and laboratory animals across life stages	Database (Microsoft ACCESS) created using data collated from extensive literature search and quality assured by independent contractor. Also available via HERO https://hero.epa.gov/hero/index.cfm website
Zakaria et al., 2018	[29]	Model structure and parameter values for a four-compartment PBK model for brain	A region specific PBK model for brain developed using compartments for frontal cortex, hippocampus, "rest-of-brain" and cerebrospinal fluid.

Additional sources of information:

- Note that PBK modelling software inherently includes physiological parameters for the generation of models, many of the model structures and parameters reported above have been incorporated into commercial software – refer to table 8 for example software and capabilities.
- Individual PBK models have been generated for hundreds of compounds (many of these have been collated within the publication of Lu et al - see above), however there are many other publications for existing PBK models that can also provide key information on models' structure and parameters that may be applied to the development of new models.

Table 5. Dedicated PBK modelling software

Software	Available from	Brief summary of capabilities
Cloe[C]	Cyprotex (Evotec AG) https://www.cyprotex.com/insilico/physiological_modelling/cloe-pk/	Predicts concentration-time profiles in plasma and 14 organs/tissues using *in vitro* ADME and physico-chemical data; models available for human, rat and mouse
Cosmos KNIME workflow[F]	http://www.cosmostox.eu/home/welcome/	Physiologically-Based Kinetic (PBK) models to simulate concentration-time profiles and internal dose metrics for dermal or oral exposure scenarios
High Throughput Toxicokinetics (Httk)[F]	https://cran.r-project.org/web/packages/httk/index.html	Provides data tables and functions for simulation; facilities to parameterise PBK and one-compartment TK models for multiple chemicals and species; *in vitro-in vivo* extrapolation of HTS data; models can be exported for use with other simulation software
GastroPlus[C]	Simulations Plus, Lancaster, CA https://www.simulations-plus.com/software/overview/	Comprises 10 modules including: PBPKPlus – enables PBPK modelling and IVIVE, can be parameterised for different disease states and age groups. ADMET Predictor – predicts physico-chemical and ADME properties. Additional Dosage Routes – simulates oral cavity, dermal, pulmonary ocular and intramuscular administration. PKPlus – estimates PK parameters
IndusChemFate[F] (CEFIC LRI)	http://cefic-lri.org/toolbox/induschemfate/ (Microsoft Excel spreadsheet files)	Generic PBK model (first tier or screening level tool); estimates tissue body fluid concentrations following oral, dermal or inhalational exposure to volatile or semi-volatile chemicals
MEGen[F]	http://xnet.hsl.gov.uk/megen	Web application to generate PBK model equations; parameters may be retrieved from the integrated database or obtained from literature; output available in MATLAB, ACSL or other format
PBPK Model	https://www.trentu.ca/academic/aminss/envmodel/models/PBPK.html [85]	The Canadian Centre for Environmental Modelling and Chemistry; Excel-based PBPK spreadsheet, parameterised for human male

Simcyp Simulator[C]	Certara, Princeton New Jersey https://www.certara.com/software/physiologically-based-pharmacokinetic-modeling-and-simulation/simcyp-simulator/?ap%5B0%5D=PBPK	PBK modelling and simulation platform; links *in vitro* data to *in vivo* ADME to predict PK/PD interactions for small molecules and biologics. Incorporates databases of genetic, physiological and epidemiological information to enable simulation of different populations (includes modules for paediatrics and rat, dog and knock-out mouse). Incorporates an automated sensitivity analysis tool that can be used to assess influence of changing specific parameters. Predicts ADME parameters such as oral, dermal, pulmonary absorption, clearance. Includes: ADAM (advanced dissolution, absorption and metabolism) model – predicts variability in bioavailability using physico-chemical properties and *in vitro* data; dissolution (from various dosage forms) for oral absorption; models also available for skin and pulmonary absorption; BBB partitioning, metabolism, clearance etc.
PK-Sim and MoBi[F]	Open Systems Pharmacology Suite (Bayer) http://www.systems-biology.com/products/PK-Sim.html	PK-Sim: PBK modelling tool with integrated database of anatomical and physiological parameters for humans, mouse, rat, dog and monkey. Uses interchangeable building blocks to enable alternative scenarios to be considered e.g. changing from animal model to human population or i.v. dose to controlled release. Mobi: Software for multiscale physiological modelling and simulation. A range of biological models can be imported (e.g. PBK model imported from PK-Sim) or developed *de novo;* Software is compatible with Matlab and R.
PLETHEM (Population Lifecourse Exposure-To-Health-Effects Model)[F]	ScitoVation http://scitovation.com/plethem.html	Open source R package incorporating: a generic 11 compartment diffusion limited PBPK model; a high-throughput IVIVE model to extrapolate *in-vitro* measured point of departure to equivalent exposures; an *in-vitro* to *in-vivo* model to extrapolate in-vitro measured metabolism values to predicted *in-vivo* values; population variability modelling; databases of age-dependent physiological and metabolic parameters; QSAR models to estimate partition coefficient
Simulo[F]	https://exprimo.com/simulo	It is a PK-PD Disease model simulator. It provides ability to perform Monte Carlo simulations and evaluations of study designs and dosing strategies.

[F]Freely available; [C]Commercial

Table 6. Additional software / applications to assist in PBK or PK/PD modelling

Software	Available from	Brief summary of capabilities
A4S[F] (Accelera for Sandwich)	Reported in publication of Germani et al., 2013 [86]	Mat-lab based PK/PD simulator (incorporates 10 PK models; generates plasma concentration-time profiles, AUC, Cmax, t½ etc.)
ADAPTS[F]	Biomedical Simulations Resource, University of Southern California, [87] https://bmsr.usc.edu/software/adapt/	Individual and population PK/PD modelling application
Biokmod[F]	http://diarium.usal.es/guillermo/biokmod/	Mathematica-based packages for modelling linear and non-linear biokinetics; differential equation solver
ChemPK™ V.2[C]	Cyprotex, Cheshire, UK https://www.cyprotex.com/insilico/physiological_modelling/chempk	Predicts oral and i.v pharmacokinetic data from structure, using a KNIME workflow; calculates 10 tissue partition coefficients, absorption, renal clearance and metabolism; predicts clearance, t½ volume of distribution AUC, Cmax, Tmax etc.
GastroPlus[C]	Simulations Plus, Lancaster, CA https://www.simulations-plus.com/software/overview/ [88]	PKPlus module – estimates PK parameters for 1, 2 3-compartment or non-compartmental models; fitted parameters include 1st order absorption rate, lag time and bioavailability (can be linked back to GastroPlus model)
INTELLIPHARM[C]	Intellipharm, LLC, Niantic, USA https://www.intellipharm.com/physiologically-based-pharmacokinetic-modeling.htm	Combines simulation of drug dissolution, precipitation, absorption and gastric motility with bioavailability, clearance, and volume of distribution as coupled differential equations; provides open source code for PBK models.

Maxsim2[C]	http://www.maxsim2.com/ [89]	Interactive PK/PD modelling software enabling investigation of consequences of varying physico-chemical, physiological or anatomical features; incorporates common PK and PD models.
MetStabOn[F]	http://skandal.if-pan.krakow.pl/met_stab_pred/ [90]	*in silico* qualitative evaluation of metabolic stability ($T_{1/2}$, CL)
Magnolia[F]	https://www.magnoliasci.com/	Magnolia provides the tools for developing models using an equation-based modeling language, scripting the execution of simulations using either the Python programming language.
NONMEM (including PREDPP)[C]	ICON, Dublin https://www.iconplc.com/innovation/nonmem/ [91]	NONMEM – generic package for simulating / fitting data; PREDPP provides subroutines for predicting PK/PD data.
Pheonix WinNonlin and Pheonix NLME[C]	Certara, Princeton, New Jersey https://www.certara.com/wp-content/uploads/Resources/Brochures/BR_PhoenixWinNonlin.pdf	WinNonLin - Industry standard integrated tool for non-compartmental analysis, PK/PD modelling; NLME – non-linear mixed effect modelling and simulation software
PKfit for R[F]	https://cran.r-project.org/src/contrib/Archive/PKfit/	Pharmacokinetic tool for data analysis in R
PKPD Tools for Excel[F]	Add on for Microsoft Excel http://pkpdtools.com/excel/downloads/	Add-on to assist PK/PD simulation and modelling within Microsoft Excel[C].
PopGen[F]	Bayer http://xnet.hsl.gov.uk/popgen/ [92]	Virtual human population generator to predict realistic variation in anatomical and physiological parameters across populations.
PDx-Pop[C]	https://www.iconplc.com/	Requires NONMEM to run

RVIS[F]	http://cefic-lri.org/projects/aimt7-rvis-open-access-pbpk-modelling-platform/	Open source syntax R or C++ for the analysis of structure and performance of PBPK models
SAAM-II (Simulation and Analysis Modelling) Version 2.3[C]	TEG, The Epsilon Group, Virginia https://tegvirginia.com/software/saam-ii/ [93]	Development and statistical calibration of compartmental models; population kinetics; automatic generation of equations from model structure

[F]*Freely available;* [C]*Commercial*

Additional sources of information:

- The website for Pharmacokinetic and Pharmacodynamic Resources (Boomer.org) https://www.pharmpk.com/soft.html provides a summary of more than 100 software applications relevant to pharmacokinetic modelling. The software listed includes a range of applications from bespoke PBK modelling packages, such as SimCYP, to general differential equation solvers frequently used in PBK modelling, such as Berkeley Madonna. The resources given in table 6 include (amongst others) some of the packages identified by Boomer.org.

Table 7. Examples of mathematical modelling software used for PBK model building or PK/PD analysis

Resource	Available from	Brief summary of capabilities
Berkley Madonna[C]	Berkeley, CA https://berkeley-madonna.myshopify.com/ [94]	Generic differential equation solver capable of constructing complex models; automatic graphing of results; parameter estimation from curve fitting; sliders can investigate influence of changing different parameters
Cossan-X	https://cossan.co.uk/	Generic package for quantifying uncertainty; sensitivity and reliability analysis
GNU MCSIM[F]	GNU project https://www.gnu.org/software/mcsim/mcsim.html	Generic modelling and simulation program; solves user specified linear and nonlinear equations
Matlab[C] (SimBiology)[C]	MathWorks, Inc., Natick, MA https://www.mathworks.com/products/matlab.html [95]	Modelling and simulation tools focussed on PK/PD and systems biology; library of common, customisable PK models; simulates time course of chemicals; model parameters estimated by fitting to experimental data; individual or population models; can perform sensitivity analysis
Perl-speaks-NONMEM (PsN)[F]	https://uupharmacometrics.github.io/PsN/ [96]	A collection of Perl modules and programs for developing non-linear mixed effect models using NONMEM
R[F] (RStudio)[F]	The R Project from the R foundation https://www.r-project.org/about.html RStudio – integrated development environment for R https://www.rstudio.com/products/rpackages/	Freely available software with a network of users continually adding new applications for use by the community; statistical analysis (linear and nonlinear); graphing techniques; for examples httk and PKfit for R
SigmaPlot Transforms[F]	http://www.sigmaplot.co.uk/products/sigmaplot/transforms.php	Resource for manipulating data within a worksheet; plotting, transforming and fitting data

[F]*Freely available;* [C]*Commercial*

Table 8. Example methods for identifying similar chemicals

Resource	Available from	Brief summary of capability
Ambit 2[F]	http://cefic-lri.org/toolbox/ambit/	Includes database of >450,000 chemical structures, identifies similar chemicals based on Tanimoto similarity; identifies common substructures
ChemAxon[C]	https://chemaxon.com/products/ [97]	Extended-connectivity fingerprints; maximum common substructure searching
CheS-Mapper[F]	http://ches-mapper.org/ [98]	Enables clustering of molecules based on similar properties; a range of descriptors can be calculated (Java application)
ChemMine Tools[F]	http://chemmine.ucr.edu/ [99]	Performs clustering based on structural / physico-chemical similarity or user defined criteria; search against PubChem Compound Database using fingerprints
Ellison (2018)	[34]	A method to select source chemicals with existing PBK-related information that are similar to target chemicals where data are lacking using structural and functional similarity
Leadscope Toxicity Db[C]	https://www.leadscope.com/toxicity_database/ [100]	Database contains over 180,000 chemicals; capability for similarity and common substructure searching
Lester et al., (2018)	[35]	Rating rules for selecting source chemicals with existing PBK-related information that are similar to target chemicals where data are lacking
Lu et al., PBK Knowledgebase[F]	[32]	Incorporates facility to identify similar chemicals from the Knowledgebase based on physico-chemical properties
MOE (Molecular Modelling Environment)[C]	https://www.chemcomp.com/MOE-Molecular_Operating_Environment.htm [101]	Performs similarity searches using various fingerprint methods in 2D and 3D; MACCS and shape fingerprints

OECD QSAR Toolbox[F]	https://www.qsartoolbox.org/ [102]	Assists grouping of chemicals based on similarity (using physico-chemical, structural or mechanistic properties)
PubChem Open Chemistry database[F]	https://pubchem.ncbi.nlm.nih.gov/search/search.cgi [103]	2D and 3D similarity searching; clustering of similar molecules using dendrogams
RDKit / KNIME[F]	http://www.rdkit.org/docs/Overview.html [104]	Incorporates multiple methods to identify similar chemicals using both 2D and 3D methods (Daylight-like atom pairs, topological torsions, Morgan algorithm, "MACCS keys", extended reduced graphs, shape-based similarity, etc.)
Therapeutic Target DB (TTD)[F]	https://db.idrblab.org/ttd/ttd-search/drug-similarity [105]	Structural similarity search for drugs using Tanimoto index
Toxmatch[F]	https://sourceforge.net/p/toxmatch/code/ci/master/tree/ [106]	Open-source software encoding a range of structural and descriptor-based similarity indices enabling grouping of chemicals. Results can be viewed as scatter plots, pair wise or composite similarity histograms; similarity matrices can be exported
ToxRead (VEGA)[F]	http://www.toxread.eu/ [107]	Identifies most similar compounds from database using similarity metric developed within VEGA

[F]Freely available; [C]Commercial

Additional sources of information:

- Many databases of chemicals (e.g. Chemspider) and packages for retrieving / predicting ADMET information (as identified above) also provide the facility to search for similar molecules e.g. admetSAR [108], ADME SARfari, ChemSpider[45], ChEMBL (EMBL-EBI)[109], oCHEM etc.

Figure 1. Conceptual framework of a physiologically-based kinetic model showing necessary inputs of chemical-specific and system-specific properties and a typical output concentration-time curve for an individual organ