

## **Physiologically Based Pharmacokinetic (PBPK) Modeling of Small Molecules: How Much Progress Have We Made?**

Nina Isoherranen

Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle,  
Washington

## Running Title Page

**Running title:** *Progress in PBPK models*

**Address correspondence to:** Nina Isoherranen, Department of Pharmaceutics, School of Pharmacy, University of Washington, Health Science Bldg., Box 357610, Seattle, Washington, USA 98195; phone: (206) 543-2517; email: [ni2@uw.edu](mailto:ni2@uw.edu)

Number of text pages: 30

Number of tables: 2

Number of figures: 2

Number of references: 94

Number of words in Abstract: 249

Number of words in Body of Manuscript: 7971

**Keywords:** in vitro to in vivo predictions, mechanistic models, physiologically based, pharmacokinetics, model verification

**Abbreviations:** CL, clearance; PBPK Physiologically based pharmacokinetic:

## **Abstract**

Physiologically based pharmacokinetic (PBPK) models of small molecules have become mainstream in drug development and in academic research. The use of PBPK models is continuously expanding with the majority of work now focusing on predictions of drug-drug interactions, drug-disease interactions, and changes in drug disposition across lifespan. Recently, publications that use PBPK modeling to predict drug disposition during pregnancy and in organ impairment have increased reflecting the advances in incorporating diverse physiological changes into the models. Due to the expanding computational power and diversity of modeling platforms available, the complexity of PBPK models has also increased. Academic efforts have provided clear advances in better capturing human physiology in PBPK models and incorporating more complex mathematical concepts into PBPK models. Examples of such advances include the segregated gut model with a series of gut compartments allowing modeling of physiological blood flow distribution within an organ and zonation of metabolic enzymes, and series compartment liver models allowing simulations of hepatic clearance for high extraction drugs. Despite these advances in academic research, the progress in assessing model quality and defining model acceptance criteria based on the intended use of the models has not kept pace. This review suggests that awareness of the need for predefined criteria for model acceptance has increased but many manuscripts still lack description of scientific justification and/or rationale for chosen acceptance criteria. As artificial intelligence and machine learning approaches become more broadly accepted, these tools offer promise for development of comprehensive assessment for existing observed data and analysis of model performance.

## **Significance Statement**

PBPK modeling has become a mainstream application in academic literature and is broadly used for predictions, analysis and evaluation of pharmacokinetic data. Many significant advances have been made in developing advanced PBPK models that better capture human physiology but oftentimes sufficient justification for the chosen model acceptance criterion and model structure is still missing. This review provides a summary of the current landscape of PBPK applications used and highlights the needs for advancing PBPK modeling science and training in academia.

## Introduction

Physiologically based pharmacokinetic (PBPK) modeling is a computational technique that uses physiological information together with biochemical and physicochemical characteristics of the drug to simulate plasma, tissue and excreta concentrations as a function of time for drugs and their metabolites. All PBPK models consist of system components and drug specific components that are independent of each other. PBPK models can incorporate various levels of physiological complexity and drug elimination and distribution processes depending on the intended use and the level of knowledge of the characteristics of the drug. For example, a full body PBPK model will typically include majority of the defined organs in the body such as large distribution organs (muscle, skin, adipose, bone), main drug eliminating organs (liver, kidney, intestine), possible sites of drug administration (intestine, lung) and other organs of interest for drug distribution or action (heart, brain, pancreas, spleen). These tissue compartments are connected through the lungs via blood flow that includes venous and arterial compartments (**Figure 1**). In contrast, minimal PBPK models lump together many major organs or include a nonspecific distribution compartment (Jeong *et al.*, 2022b; a), and typically incorporate only some, if any, organs of interest such as the liver, kidney or a target organ as individual organs (**Figure 1**). Depending on the research questions and intended use, the modeler can incorporate different types of organ models or levels of physiological information into the PBPK model leading to a great diversity and flexibility in the application of PBPK models. In addition, physiological models can be specific for a single organ and the relevant drug disposition processes in that organ, and used to only predict organ clearances. For example, a number of physiologically based models of the kidney have been developed (Neuhoff *et al.*, 2013; Scotcher, Jones, Rostami-Hodjegan, *et al.*, 2016; Huang and Isoherranen, 2018; Matsuzaki *et al.*, 2019) to simulate renal clearance, and numerous

models exist for advanced modeling of oral formulations and intestinal absorption (Ahmad *et al.*, 2020; Jamei *et al.*, 2020; Wu and Li, 2023).

The use of PBPK modeling has increased continuously over the past 20 years (Sager *et al.*, 2015; El-Khateeb *et al.*, 2021). PBPK modeling has been routinely included in regulatory submissions for over a decade (Zhao *et al.*, 2011; Christian Wagner, Pan, and Hsu, 2015; Christian Wagner, Pan, Hsu, *et al.*, 2015; C Wagner *et al.*, 2015; Luzon *et al.*, 2017; Grimstein *et al.*, 2019; Zhang *et al.*, 2020; Jean *et al.*, 2021), and is frequently reported in research applications published in scientific literature (Sager *et al.*, 2015; El-Khateeb *et al.*, 2021). PBPK modeling approaches have now become standard in assessment of drug-drug interaction risk (Shebley *et al.*, 2018; El-Khateeb *et al.*, 2021) and have been used extensively to predict absorption kinetics and formulation effects (Ahmad *et al.*, 2020; Jamei *et al.*, 2020; Wu and Li, 2023). They are also increasingly used to predict pharmacokinetic changes in specific populations (pregnant and lactating individuals, patients with renal or hepatic impairment) and across lifespan (pediatrics, geriatrics), and in exploring drug exposures at target site or specific organ pharmacokinetics-pharmacodynamics (PK-PD) (Sager *et al.*, 2015; El-Khateeb *et al.*, 2021). Numerous reviews have addressed the use of PBPK models in regulatory decision making (Zhao *et al.*, 2011; C Wagner *et al.*, 2015; Luzon *et al.*, 2017; Grimstein *et al.*, 2019; Zhang *et al.*, 2020; Jean *et al.*, 2021) and the reader is referred to these reviews and references therein for insight on how PBPK modeling is used in the context of model informed drug design (MIDD)(Madabushi *et al.*, 2022). For industry applications, the IQ group and several industry consortia have provided extensive reviews of the use and application of PBPK modeling in drug discovery and development (Shebley *et al.*, 2018; Hariparsad *et al.*, 2022). The current review is written from an academic perspective. It focuses on the progress made over the past decade in PBPK model development and use in research applications available in the

published literature, and summarizes the trends in model development, verification, and application workflows for different populations together with major advances made in developing more complex physiological models.

### **PBPK Modeling Platforms and Data Availability**

The PBPK modeler has a choice between the use of existing, user friendly PBPK software packages with graphical user interphases (SimCYP, GastroPlus, PK-Sim, GI-Sim, Simbiology) in which the model structure is typically *a priori* defined, or making their own custom models using various programming approaches (Matlab, R, Mobi within PK-Sim, ADAPT and others). The versatility in modeling platforms increases the need for advanced training in programming languages and techniques and in model assessment and evaluation in pharmaceutical sciences. While training expectations in population PK approaches and statistical analyses are fairly mature, the didactic training required for competency in PBPK modeling is less well defined and can still vary considerably from institution to institution. Due to the increasing availability of easy-to-use mathematical modeling software and the expanding computational power and speed, the use of PBPK modeling is continuously expanding to more complex model structures and applications. This increases the need for the modeler to possess in-depth mechanistic understanding of the underlying physiology and biochemistry of the developed PBPK models in addition to technical modeling expertise. Hence, academicians need to look into the future in terms of flexibility in curricula and training opportunities to prepare pharmaceutical sciences trainees to understand, use and advance PBPK modeling in a scientifically rigorous way. Similarly, funding agencies should assess whether the training currently provided across academic institutions is sufficient to ensure qualified workforce in this

area to address the needs of drug discovery and development and in clinical practice to improve patient outcomes.

The PBPK modeling packages include open and closed source applications, and there are variable levels of transparency between software applications to the underlying model code and mathematical assumptions made in model development (Aldibani *et al.*, 2023; Rajput *et al.*, 2023). Understanding the model structure and how different components in the model are connected is integral for assessing the validity of developed models for applications that expand the use of the model to predicting disposition in unstudied scenarios. Such understanding is also needed when comparing PBPK models developed for the same drug but using different software packages or when transferring models from one platform to another. For example, when simvastatin PBPK models developed using Simcyp or PK-Sim platforms were compared, the authors noted that the choice of the model development strategy was different for the two platforms resulting in different model input parameters but similar model performance (Prieto Garcia *et al.*, 2022). This highlighted the need for in-depth knowledge of the PBPK modeling platform and model structure (Prieto Garcia *et al.*, 2022).

There has been surprisingly little discussion in the scientific literature about the need for transparency in the underlying assumptions and construction of the models that are published regardless of whether the modeling platform is open or closed source. There is an increasing expectation that research become open (<https://www.unesco.org/en/open-science>) and the requirements for open science are increasing (McKiernan *et al.*, 2016) With general data availability statements becoming commonplace, the lack of specific guidance on transparency and open access of PBPK models remains. At present there is no clear description of standards for research publications on making PBPK models publicly available and how to “Publicly share



data and materials via a trusted repository” (McKiernan *et al.*, 2016). It has been recommended that “whenever it is feasible, the data, materials and analysis code used to generate the findings reported in one’s manuscript should be shared” (McKiernan *et al.*, 2016) At present no publicly available trusted repository or database that would serve the community at large exist for PBPK models beyond databases that provide physiological parameters (Chang *et al.*, 2021) or gene expression datasets (Cordes and Rapp, 2023). Most sharing of developed drug models occurs through proprietary databases of models developed for specific platforms and are restricted to user groups. As such the discussion and standards for reusability of models across platforms and users is still developing (Aldibani *et al.*, 2023; Rajput *et al.*, 2023).

A distinct gap in tools that would facilitate open science for PBPK modeling is the lack of converters available to export models from different closed source software applications to a common language or another software package that could be read and interpreted by broad community of users. Such applications are exemplary in the mass spectrometry and proteomics fields where it is a standard expectation that raw data generated by a commercial platform can be converted to a format generally readable by the scientific community who do not have access to the specific vendor software. The lack of open tools within PBPK community slows down science due to redundant model development and duplication of efforts, hinders progress in the field due to lack of open exchange of scientific solutions and limits collaborative efforts between users of different modeling platforms.

### **Model development, applications, and verification**

Reports of the use of PBPK models in scientific literature have increased rapidly over the past ten years (**Figure 2**). When the published literature was systematically reviewed in 2015 using

the search terms “PBPK” and “Physiologically based pharmacokinetic model” a total of 366 PBPK-related articles were identified that included PBPK modeling of pharmaceutical agents in humans (Sager *et al.*, 2015). A similar Pubmed search in July 2023 yielded 3,759 matches demonstrating the explosion in publications involving PBPK modeling. About 20% of these publications were identified as reviews or systematic reviews. **Figure 2** shows the increase in publications mentioning PBPK over the past three decades. The trend observed is very similar to that reported by others (El-Khateeb *et al.*, 2021).

The number of publications of PBPK models grew steadily between 2005 and 2018 but the number of publications per year has somewhat plateaued since 2018 regardless of the application of the PBPK model (**Figure 2**). It is possible that this plateau is related to the COVID-19 pandemic and does not reflect a longer-term trend. Future analyses will be needed to assess this trend. On the other hand, with PBPK modeling becoming a more mature field, it is also possible that the pace of advances in modeling has slowed, and some model development efforts have become standardized and no longer merit publication. As such, the number of publications should not be used as the sole indicator of how often PBPK modeling is used as part of a research program.

When the distribution of the applications of PBPK models in the published literature was evaluated in 2015 the most common application for PBPK models was drug-drug interaction predictions (Sager *et al.*, 2015). This trend continued throughout the decade following that review with drug interactions remaining the most common application of PBPK models with about 2-3-fold increase in the number of publications in this area each year (**Figure 2**). Use of PBPK modeling for predicting age dependent changes in drug disposition in different pediatric populations (neonates, infants, young children, adolescents) has also remained an important

application with about 3-4 fold increase in yearly publications in this area. This reflects the early acceptance of PBPK for this application already reported in 2015 (Sager *et al.*, 2015) and incorporation of PBPK modeling in drug development for pediatric populations (Freriksen *et al.*, 2023). In comparison, the use of PBPK modeling for organ impairment, pharmacogenetics or pregnancy saw about a 5-fold increase in the publications considering these areas (**Figure 2**) even though these areas of application remain a minority of PBPK modeling applications. The increase in the use of PBPK for specific populations reflects the advancements made over the past decade in understanding the diverse physiological processes and biochemical changes in these populations. This emerging understanding allows mechanistic modeling and prediction of drug disposition in these populations.

To provide guidance to sponsors, regulatory authorities such as the FDA and EMA as well as OECD have developed guidance documents for how to evaluate PBPK models and verify their performance for intended use (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product>, <https://www.fda.gov/files/drugs/published/Physiologically-Based-Pharmacokinetic-Analyses-%E2%80%94-Format-and-Content-Guidance-for-Industry.pdf> [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpbk-modelling-simulation\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpbk-modelling-simulation_en.pdf), <https://www.oecd.org/chemicalsafety/risk-assessment/guidance-document-on-the-characterisation-validation-and-reporting-of-physiologically-based-kinetic-models-for-regulatory-purposes.pdf>). While these guidance documents focus on regulatory applications and do not address how PBPK models should be considered in research applications, they provide a roadmap for most modelers considering PBPK modeling for drugs and therapeutics in humans.

In addition, they provide guidance on how to report PBPK models, and the recommendations from regulatory submissions can be adapted and refined for the scientific literature and research applications.

One of the recommended criteria for PBPK model use has been to report a predefined model acceptance criterion for the developed model (Jones *et al.*, 2015). When publications of PBPK models were reviewed in 2015, it was, however, noted that only about half of the published models specified a criterion for model verification *a priori* (Sager *et al.*, 2015). When these criteria were reported, most commonly a 2-fold range for an observed pharmacokinetic parameter in comparison to predicted was considered acceptable. Some papers also used a more stringent (25-30% range within observed mean parameter) criterion. For drug-drug interaction models a 2-fold criterion for predicted and observed DDI magnitude was often used with some authors opting for a more stringent 30% of the observed change. It was noted that the choice of these acceptance criteria was not clearly justified in the papers and did not match the types of drugs (narrow therapeutic index, P450 sensitive probes), and that overall criteria for model acceptance were inconsistent. Others have also shown that the 2-fold criterion may in some cases be too liberal and in some cases too stringent due to the observed variability in the drug disposition characteristics and due to the small study populations in the observed datasets (Abduljalil *et al.*, 2014). Yet, the theory and statistical analyses for PBPK model acceptance criteria have remained relatively rigid over the past decade.

To evaluate whether model verification practices have changed since the review in 2015, a subset of published manuscripts describing PBPK models since 2015 were analyzed as a representative sample. To capture the most recent and up-to-date approaches the manuscripts published in 2022 were chosen for this evaluation. A Pubmed search of the PBPK models

published in humans for drugs during the year of 2022 yielded 382 published manuscripts. Of these, 71 were marked as reviews yielding a sample size of 316 manuscripts, a similar initial sample size as the 366 manuscripts identified overall for the 2015 analysis. These manuscripts were further reviewed for whether they specified the application of PBPK models reported and provided original PBPK model development yielding a dataset of 187 manuscripts. These manuscripts were then evaluated for the type of application, for the strategy of model development, model verification criteria and for the software used. As noted in the previous analysis as well, this sample size is likely an incomplete set of all the papers published for PBPK modeling in humans in 2022 but it is expected to represent adequately the use of PBPK models with the exception of absorption and formulation modeling which was not specifically searched for in the current review.

Approximately half of the models in 2022 were developed to simulate drug-drug interactions, a larger fraction than what was reported by others (El-Khateeb *et al.*, 2021). Of these reports half addressed PBPK modeling of metabolic drug-drug interactions involving inhibition and induction of predominantly cytochrome P450 enzymes but also other metabolic enzymes. About 20% of the published models considered drug-drug interactions involving drug transporters such as OATPs and kidney transporters such as OATs and MATEs. The remaining third of the drug-drug interaction studies included modeling pH dependent drug absorption interactions, mixed mechanisms of drug-drug interactions and drug interactions involving pharmacological activity.

Interestingly, use of PBPK modeling to simulate drug disposition in pediatric populations remained a common application with ~14% of the applications focusing on pediatric populations. The use of PBPK models to simulate the disposition of monoclonal antibodies

remained somewhat rare accounting for ~5% of overall of the published papers. Many PBPK models (~10%) incorporated simulations of pharmacogenetic variation in the modeling approach. Ten (~5%) manuscripts described the application of PBPK modeling to pregnant populations to either predict drug disposition in the pregnant mother or to evaluate the fetal exposure and potential toxicokinetics in the fetus for the therapeutic agents. A total of 15 manuscripts (8%) were identified that described PBPK modeling in renal or hepatic impairment populations. Of these, eight were for renal impairment/chronic kidney disease populations, four for hepatic impairment/liver disease and three that included both organ impairment populations. Overall the distribution of applications was relatively similar to that described in 2015.

The use of PBPK modeling to predict drug disposition in populations with organ impairment (hepatic or renal impairment) is of special interest as organ impairment studies are often challenging to conduct, and the patients with organ impairment may be at increased risk of adverse events making dosage adjustment critical. Due to the complexity of multiple drug disposition mechanisms affected by organ impairment (altered liver or kidney blood flow, changes in protein binding, altered enzyme/transporter expression) the changes in drug disposition in different organ impairment scenarios can be difficult to predict using traditional static methods. **Table 1** summarizes the 14 manuscripts published for organ impairment populations in 2022. These studies used a variety of simulation platforms/programs. For the renal impairment population three of the studies were conducted using PK-Sim platform (C Wu *et al.*, 2022; Dubinsky *et al.*, 2022; Alsmadi and Alzughoul, 2023), three were conducted using Simcyp population simulator (Miao *et al.*, 2022; Wang and Chan, 2022b; a) and one using Gastroplus (Y Xu *et al.*, 2022). For hepatic impairment populations three of the studies were conducted using Simcyp (Watanabe *et al.*, 2022; X Wu *et al.*, 2022; Ladumor *et al.*, 2023) and one using PK-Sim (L Xu *et al.*,

2022). For the studies that considered both RI and HI populations one used PK-Sim (Fan *et al.*, 2022), one used Simcyp (Itohara *et al.*, 2022) and one used Gastroplus (Zhao *et al.*, 2022). This distribution of software packages differs somewhat from what was reported in 2015, perhaps unsurprisingly as software development is highly dynamic with new options becoming available frequently. One may also speculate that depending on the specific purpose of use of the developed model (Organ impairment, drug-drug interactions etc) certain software packages may be uniquely suited for such applications due to work and development that has been put into developing population models.

In terms of model acceptance criteria all but two (Fan *et al.*, 2022; Miao *et al.*, 2022) of the manuscripts listed a predefined model acceptance criterion in the manuscript. The manuscript by (Miao *et al.*, 2022) was unique as this study tested prospective prediction of dorzagliatin disposition in renal impairment population using PBPK modeling and hence observed data was not available for the modeling exercise for the intended use. The frequency of reporting model acceptance criteria and defining these criteria prior to model development and verification shows a clear increase in the awareness on the importance of defining model acceptance criteria *a priori* when compared to the status of the field in 2015. However, the diversity of approaches adopted for model acceptance was somewhat surprising. In some cases a calculation of acceptance criterion based on observed variability in vivo was used, in some cases an AAFE, AFE or percent error cutoff was applied and some publications still used a 2-fold criterion (**Table 1**). As already noted in 2015 (Sager *et al.*, 2015) the acceptance criterion was not matched to the therapeutic index or sensitivity of a substrate and the 2-fold criterion was used for some drugs and scenarios where this is clinically likely too lenient (**Table 1**). A notable advancement with PBPK models of organ impairment is the inclusion of studies that combine drug interactions with organ

impairment scenarios. These applications provide an illustration of the flexibility of PBPK modeling to evaluate complex scenarios and provide guidance in situations where clinical trials may be very challenging. Similarly, the application of PBPK-PD in organ impairment populations is an important advancement in the field.

Another area of interest for PBPK modeling is the use of PBPK models to explore drug disposition during pregnancy (Gaohua *et al.*, 2012; Ke *et al.*, 2012; Jing *et al.*, 2017; Zhang and Unadkat, 2017; Zhang *et al.*, 2017; Shum *et al.*, 2021). There is a great need for reliable PBPK models to predict drug disposition during pregnancy as minority of the drugs given to pregnant women have ever been evaluated in pregnant women for PK or PD changes (Ke *et al.*, 2014a, 2018; Abduljalil and Badhan, 2020). Hence drugs are often given to pregnant women off-label despite the fact that the drug treatment may be critical for the survival of the mom and the health of the developing fetus. It is well established that pharmacokinetics of drugs changes during pregnancy due to multiple processes (change in blood flows and GFR, altered protein binding and albumin concentrations, increased or decreased CYP expression in the liver) and that these changes can be dependent on gestational age (Isoherranen and Thummel, 2013; Ke *et al.*, 2014b). As pregnant women are a sensitive population, studying all the drugs given to pregnant women and incorporating all the different gestational stages into clinical studies is practically and ethically impossible. PBPK modeling can provide much needed information on prioritizing specific studies in pregnant women and in directing dosage adjustments and selection of therapies based on predicted exposures. PBPK modeling also provides a unique opportunity to predict maternal-fetal disposition of drugs and fetal exposures to the drug of interest (Zhang and Unadkat, 2017; Zhang *et al.*, 2017; Shum *et al.*, 2021; Balhara *et al.*, 2022). This is especially important and significant as sampling of drug concentrations from the fetal compartment is not possible across



gestation and simulations of the fetal exposures can provide extremely valuable information about the risks and benefits of drug treatment to the fetus.

A decade ago about 2% of the publications describing PBPK models addressed pregnancy as the target application (Sager *et al.*, 2015). In the current analysis pregnancy modeling had increased. Of the 187 manuscripts published in 2022 that were reviewed ten (~5%) described the application of PBPK modeling to pregnant populations to either predict drug disposition in the pregnant mother or to evaluate the fetal exposure and potential toxicokinetics of the therapeutic agents in the fetus (**Table 2**). The majority (n=5) of the pregnancy PBPK models were constructed using Simcyp simulator (Abduljalil, Ning, *et al.*, 2022; Abduljalil, Pansari, *et al.*, 2022; Bukkems *et al.*, 2022; Peng *et al.*, 2022; Li and Xie, 2023), but other software packages such as R (n=2, (Chang *et al.*, 2022; Kapraun *et al.*, 2022)), PK-Sim (n=2, (Alsmadi, 2023; Liu *et al.*, 2023)) and Gastroplus or combination of software platforms (Coppola *et al.*, 2022) were also used. It is notable that R packages are particularly used for pregnancy modeling while none of the organ impairment applications used R. This is likely due to the toxicology applications and consideration within the pregnancy modeling and the broad use of R packages in the field of toxicokinetics. The review also revealed that all three major software packages, Simcyp, Gastroplus and PK-Sim include pregnancy models within the software package facilitating applications of PBPK modeling to predicting drug disposition during pregnancy, maternal-fetal distribution of drugs and potential toxicokinetics during pregnancy.

Within the pregnancy applications a variety of model acceptance criteria were used within and between the studies and majority of the studies defined model acceptance criteria in model development workflow (Table 2). Four studies stated that model performance was evaluated based on visual comparison of predicted and observed data (Abduljalil, Ning, *et al.*, 2022;

Chang *et al.*, 2022; Alsmadi, 2023; Liu *et al.*, 2023), while one study assessed the correlation between predicted and observed data (Kapuraun *et al.*, 2022). Two studies used the 90% predictive interval as the range that observed data needed to be within (Alsmadi, 2023; Li and Xie, 2023) and one specified a visual comparison of the observed mean plasma concentration-time curve and the predicted 5-95<sup>th</sup> percentile (Coppola *et al.*, 2022). Two of the papers (Abduljalil, Pansari, *et al.*, 2022; Peng *et al.*, 2022) specifically noted that the observed plasma concentration-time curve had to be within the 5<sup>th</sup> and 95<sup>th</sup> percentile of the simulated. Similarly two papers (Bukkems *et al.*, 2022; Peng *et al.*, 2022) established a stringent criteria for predicted pharmacokinetics parameters with 0.8-1.25 fold (bioequivalence) or 0.7-1.3-fold (narrow therapeutic index), respectively. The 2-fold range of pharmacokinetics parameters was also used in two studies (Li and Xie, 2023; Liu *et al.*, 2023).

The pregnancy PBPK models included a diversity of verification datasets to assess model performance. Many of the pregnancy applications were based on previously developed PBPK models that had been already assessed for model performance in nonpregnant population (Table 2). The pregnancy modeling was then undertaken to evaluate either maternal-fetal distribution in which case umbilical vein to maternal plasma ratios were often used for model verification, or to define the maternal PK during pregnancy. Most of these models followed the generally recommended workflow where the drug model was verified in nonpregnant population prior to applying it to pregnant population. Taken together these models show the increasing trust in PBPK modeling in evaluating drug disposition during pregnancy. A notable advancement was the incorporation of the mechanistic kidney model into pregnancy PBPK modeling for renally cleared drugs (Abduljalil, Ning, *et al.*, 2022; Abduljalil, Pansari, *et al.*, 2022; Coppola *et al.*, 2022; Li and Xie, 2023) although it was noted that limited information is available for physiological changes in

the kidney during pregnancy and for how transporter expression changes in the kidney during pregnancy. Several of the papers (Bukkems *et al.*, 2022; Peng *et al.*, 2022) also used either perfused placenta studies or mechanistic modeling of the placenta to better predict maternal-fetal distribution. Taken together this review shows significant advances over the past decade in the mechanistic PBPK modeling of drug disposition during pregnancy.

### **Different Model Structures and Approaches for Clearance Processes in PBPK models**

All PBPK models make some underlying assumptions regarding the physiological processes that govern drug elimination and distribution. All models also simplify the overall complexity of the human body. As usage of PBPK models has increased there has been a parallel increase in development of more complex models that attempt to better capture clearance processes, distribution characteristic, intestinal absorption, and drug administration via inhalation or transdermal routes. However, the models can only be as good as the underlying knowledge of the physiology and physiological parameters that are incorporated into the models. As model complexity increases it is becoming apparent that the knowledge of human physiology that governs drug disposition is a limiting factor for model development. The heterogeneity of many diseases and the corresponding heterogeneity in physiological changes is not yet well incorporated into current PBPK modeling frameworks. Some well-known deficiencies include the lack of knowledge of precise transporter expression in the human kidney tubular epithelial cells rather than whole kidney *in vivo*, the localization of the transporters at different subsections of the kidney, and the lack of knowledge on how pH gradients and tubular flows are altered in the different sections of the kidney when urine pH or flow is altered or in chronic kidney disease (Scotcher, Jones, Posada, Rostami-Hodjegan, *et al.*, 2016). Similarly, the physiological changes

associated with pregnancy such as changes in liver and kidney blood flow, intestinal mobility and transit time, gastric emptying and active uptake transport in the intestine have not been well characterize and limit further PBPK modeling in pregnancy. It is also noteworthy that the understanding of detailed physiological changes that occur in various cancers and different stages of cancer progression or during treatment is limited. Due to the challenges in conducting detailed pharmacokinetic studies in these patient populations coupled with the narrow therapeutic index of most treatments, PBPK modeling has the potential to greatly improve dosing regimen design and individualized therapy in cancer chemotherapy but better data is needed in the general physiology to advance the field.

Sensitivity analyses can be used to demonstrate that lack of such physiological knowledge has minimal impact on model performance in many cases. However, for drugs that have a high hepatic extraction ratio, such as THC or metoprolol for example, lack of knowledge about hepatic blood flow changes during pregnancy is a major challenge for modeling their disposition during pregnancy. Similarly, for drugs that have renal clearance that is sensitive to urine pH, the poor characterization on how pH gradients are established across the kidney during pregnancy or in disease states such as chronic kidney disease can confound model development. As such there is a continuous need for PBPK modelers to partner with scientists who can develop advanced tools of characterization of physiological processes and their alterations in disease states and apply these tools to practice in clinical research.

The incorporation of more complex PBPK models into commercial software platforms has lagged behind academic research advances. For example, at the time of this writing the segregated gut model (Pang *et al.*, 2017, 2020; Noh and Pang, 2019) has not been incorporated into commercial software packages despite the fact that it allows modeling the route dependent

metabolism of drugs that are subject to significant gut extraction. Typically, PBPK modeler can choose between approaching absorption kinetics using simple first order absorption model that incorporates the absorption constant  $k_a$  and the fraction absorbed as predefined parameters, or using a more complex model that is typically a further developed version of the original advanced compartmental absorption transit (ACAT) model (Yu and Amidon, 1999). The advanced absorption kinetic models include the advanced dissolution absorption metabolism (ADAM) model in Simcyp, the advanced compartmental absorption and transit (ACAT) model in GastroPlus and a series compartment model in GI-Sim. All of these allow predictions of oral bioavailability based on physicochemical drug characteristics and experimental permeability data of the drug (Sjögren *et al.*, 2016). These models provide advanced ability to model drug absorption from the intestine in a segmented fashion. They can account for the differences in gut wall permeability between different regions, differences in pH across different regions of the intestine and the heterogenous expression and localization of metabolic enzymes and drug transporters in the intestine. Although these models generally have similar structures, the predictive performance of the different gastrointestinal drug absorption models can be quite different (Sjögren *et al.*, 2016).

An important application of PBPK modeling and simulation of drug absorption and food effects (Tistaert *et al.*, 2019; Riedmaier *et al.*, 2020; Al Shoyaib *et al.*, 2023). However, confidence in model predictions in this area is still moderate. A review of the literature and regulatory submissions suggested that PBPK modeling is typically used to attempt to predict food effects for BCS class II and IV drugs (Li *et al.*, 2018). The reasoning for this was that BCS class I drugs typically are not subject to food effects and BCS class III drugs often involve transporters for absorption, an area for which food effects have not been mechanistically characterized (Li *et al.*,

2018). The authors noted that in half of the PBPK modeling cases assessed, food effects were predicted within 1.25-fold and 75% of the simulations were within 2-fold. Yet, the authors concluded that caution should be exercised in determining the performance of PBPK models in this area (Li et al., 2018). In a separate case study assessment from several pharmaceutical companies, it was suggested that for immediate release formulations of BCS class I and II compounds, PBPK modeling can be used to predict lack of food effect and positive food effect (Tistaert *et al.*, 2019). However, it was noted that the absorption model for such applications should be well validated, fasted state PK should be available and the model should be validated for clinical data on a food effect before extrapolation to expanded food effect simulations. Surprisingly in a subsequent industry perspective publication (Riedmaier *et al.*, 2020) BCS classification did not appear to affect the level of confidence in PBPK predictions of food effects. Majority of the food effects considered were predicted with high to moderate confidence leading to a recommendation to leverage PBPK modeling in assessment of food effects (Riedmaier *et al.*, 2020). However, overall confidence in PBPK modeling of bioavailability, bioequivalence and food effects is still weaker than many other applications and subject to active research. In an FDA workshop regarding food effects and PBPK modeling, the topic of differences in input parameter values between software platforms was brought up and it was noted that there is a need for standardization on how data is generated in vitro to be used in PBPK modeling (Al Shoyaib *et al.*, 2023). Recently PBPK modeling has also been expanded to model the drug-drug interactions resulting from acid reducing agents causing changes in gastric pH (Dong *et al.*, 2020). This work suggested that such drug-drug interactions could be adequately predicted but further work is needed with modeling drugs which are affected significantly by changes in gastric pH.

The compartmental absorption models have been noted to result in many ordinary differential equations for which solutions are computationally facile (Nagar *et al.*, 2017). As an alternative continuous absorption models have been developed (Willmann *et al.*, 2004; Nagar *et al.*, 2017). In these models physiological values such as surface area, pH and experimental velocities were incorporated into the model together with specific cellular characteristics of the enterocyte across the length of the intestine. Physicochemical characteristics governing the absorption of oral solutions and solid dosage forms were also incorporated and the oral absorption of a series of model drugs was well predicted. However, these continuous models are yet to be incorporated into commonly used PBPK software platforms.

A weakness of the currently commonly used compartmental absorption models is that they do not adequately capture the impact of intestinal physiology on systemic clearance of drugs. In the segregated gut model the intestinal compartment includes the inert serosa and the active enterocyte regions as separate compartments and the blood flow to each of these compartments is segregated (Pang *et al.*, 2017). This is in contrast to the conventional models in which the serosa and enterocytes are considered a single well mixed compartment. Unlike traditional intestinal models where the entire intestinal blood flow perfuses the entire gut compartment, in the segregated flow model only a fraction (5-20%) of the intestinal blood flow perfuses the enterocytes (Pang *et al.*, 2017, 2020; Noh and Pang, 2019). Since the metabolically active and drug transporter expressing component of the intestine is the enterocyte compartment this segregation of the intestinal blood flow effectively reduces the contribution of the enterocytes to the systemic clearance of drugs while maintaining the contribution of the enterocyte metabolism in first pass metabolism during drug absorption. In other words, only a fraction of the drug in arterial circulation can access the enterocyte enzymes and transporters

allowing >80% of the drug to bypass enterocyte metabolism during systemic clearance (Pang *et al.*, 2020). This is important in particular for intermediate to high extraction substrates of CYP3A4 and UGTs for which both intestinal and hepatic metabolism are important, but the model has also been shown to provide improved data on drug-drug interactions when both the inhibitor and substrate are administered po (Pang *et al.*, 2020). In addition, a relatively comprehensive PBPK model of the intestine that combines the segmented gut concept allowing for simulation of enzyme and transporter expression patterns and the segregated flow concept has been developed (Pang *et al.*, 2020). PBPK modelers should consider the segregated gut model for drugs that have relatively high clearance and are substrates for CYP3A4 or UGT enzymes.

In recent years the modeling of hepatic clearance in PBPK models has received considerable attention. In addition to number of publications in the overall hepatic clearance models for static predictions and pharmacokinetic data analysis, attention has been paid to whether the well stirred model of the liver is the most appropriate model to use in PBPK models (Li and Jusko, 2022, 2023b; a). At present commercial PBPK modeling packages as well as majority of custom made PBPK models incorporate hepatic clearance according to the well stirred model. The incorporation of the dispersion model of hepatic clearance, the most physiologically sound model of hepatic clearance (Pang and Rowland, 2019), has been computationally complex and hence limited (Li and Jusko, 2022). Instead, a series compartment liver model was incorporated into PBPK models to allow better simulation of hepatic clearance especially for high extraction ratio drugs (Watanabe *et al.*, 2009; Li and Jusko, 2022). In the case of pravastatin, transporter contribution to the hepatic clearance was incorporated in the series compartment model and the preference for the series compartment model was justified due to the fact that dispersion model typically better captures hepatic clearance of high extraction drugs



(pravastatin has blood flow limited hepatic clearance in rats) (Watanabe *et al.*, 2009). The PBPK model incorporated 5 liver compartments to appropriately capture hepatic extraction of pravastatin. When the dispersion model and series compartment model results were systematically compared 1, 2 and 5 series compartments were evaluated with a goal to explore the impact of the number of series compartments in model performance (Li and Jusko, 2022). As may be expected due to added degrees of freedom in the model, adding compartments resulted in challenges in parameter identifiability and the authors concluded that it may not be trivial to define the optimal number of compartments to include (Li and Jusko, 2022). A unique advantage of the series compartment model is that it allows modeling of the zonation of enzymes within the liver. This will likely provide improvements in simulations of high extraction compounds and their metabolites. Again, PBPK modelers are encouraged to carefully consider what is the most appropriate liver model to use in model development to best capture the disposition characteristics of their drug of interest.

Renal clearance is one of the main elimination pathways for drugs and their metabolites but it has received much less attention than hepatic clearance in *in vitro* to *in vivo* predictions of drug clearance and in PBPK modeling. This is likely because renal clearance can often be well predicted via allometric scaling and/or using glomerular filtration rate (GFR) and plasma unbound fraction. Renal clearance is often included in PBPK models as simple clearance pathway without a complex physiological model of the kidney. However, allometric scaling can suffer from species differences in transporter expression, urine pH and differences in plasma protein binding (Scotcher, Jones, Posada, Galetin, *et al.*, 2016). On the other hand, using static mechanistic modeling of renal clearance, passive reabsorption was shown to have a major impact on the accuracy of renal clearance predictions (Scotcher, Jones, Rostami-Hodjegan, *et al.*, 2016). Of

the commercial PBPK modeling platforms Simcyp incorporates the option to use a physiologically based mechanistic kidney model (Neuhoff *et al.*, 2013; Abduljalil, Pansari, *et al.*, 2022) but how widely this option is used is unclear. Mechanistic modeling of the kidney in PBPK models can accurately incorporate reabsorption processes as well as active transport based on *in vitro* data (Huang and Isoherranen, 2018; Matsuzaki *et al.*, 2019). An open code mechanistic kidney model was developed (Huang and Isoherranen, 2018) and incorporated into full body PBPK model (Huang *et al.*, 2020) to predict renal clearance from *in vitro* data, to simulate pH dependent renal clearance and to assess urinary metabolic ratios in a parent-metabolite system. Similarly, the impact of urine flow and urine pH on renal clearance was simulated using the Simcyp mechanistic kidney model (Matsuzaki *et al.*, 2019).

For modeling chronic kidney disease, several studies have been published in which the intact nephron hypothesis has been applied to PBPK modeling and mechanistic models of the kidney. The creatinine-drug interactions occurring between OAT2 inhibitors in different stages of kidney disease were simulated using a minimal physiologically based mechanistic kidney model (Takita *et al.*, 2020). In a separate study a pyridoxic acid PBPK model was developed using Simcyp and the mechanistic kidney model adapted based on the intact nephron hypothesis for patients with chronic kidney disease (Tan *et al.*, 2023). In this model the number of proximal tubular cells was decreased proportionately with GFR according to intact nephron hypothesis while the expression of OAT1/3 was decreased by additional 16%-50% from what would be proportional to GFR (Tan *et al.*, 2023).

The assumption of intact nephron hypothesis and decrease in OAT1/3 activity in chronic kidney disease may not be appropriate in all circumstances and is likely not physiologically accurate when considered in context of tubular fluid flow (Huang and Isoherranen, 2020a).

During kidney disease the kidney undergoes adaptations to maintain the fluid balance resulting in smaller fraction reabsorbed for permeable drugs under kidney disease than in healthy kidneys (Huang and Isoherranen, 2020a). These alterations in urine and tubular flows were incorporated into a mechanistic kidney model in chronic kidney disease to predict renal clearance and the adaptation in tubular flows was shown to be necessary in modeling renal clearance changes for permeable drugs in chronic kidney disease (Huang and Isoherranen, 2020a). The decrease in OAT activity beyond what would be predicted by intact nephron hypothesis may be due to inhibition of these transporters by uremic solutes rather than additional downregulation of their expression (Chang *et al.*, 2023). The impact of uremic solutes on kidney OAT activity and renal clearance of tenofovir in patients with renal impairment was simulated using the mechanistic kidney model (Chang *et al.*, 2023). The importance of understanding the variability and individual changes in kidney blood flow, GFR, and transporter activity in progressive kidney disease was illustrated via use of the mechanistic kidney model to predicting drug clearance in chronic kidney disease in individual patients based on biomarker data of transporter activity in the kidney in the same individuals (Granda *et al.*, 2023). Finally, in an effort to test whether data collected from microphysiological systems could be incorporated into PBPK models, the data of morphine and morphine glucuronide permeability and transport obtained in kidney tubule-on-a-chip model was incorporated into the mechanistic kidney model and the disposition of morphine and morphine glucuronide in patients with declining kidney function was predicted (Imaoka *et al.*, 2021). Taken together these examples show the power of mechanistic PBPK modeling of renal clearance and the potential to translate complex *in vitro* data into clinical pharmacokinetic predictions and clinical pharmacology.

## Distribution kinetics, predictions of plasma concentration time curves and PBPK model design

Over the past decades PBPK modeling has focused extensively on clearance predictions and different organ clearance approaches. However, one of the distinct advantages of PBPK modeling is that it allows mechanistic predictions, simulations, and analyses of distribution kinetics. Hence the shape of the plasma concentration versus time curve in addition to the area under the plasma concentration versus time curve (AUC) can be simulated based on mechanistic and preclinical data. Such predictions cannot be accomplished using compartmental models or static PK calculations without existing *in vivo* data. The complexity of predicting distribution kinetics is often overlooked in predictions of human drug disposition (Huang and Isoherranen, 2020b), and the advantages of the use of PBPK models in distribution predictions and in predicting the half-life of new compounds have not been adequately recognized. Most PBPK approaches model distribution as a perfusion limited phenomenon. However, with the acknowledgment of transporter contribution to distribution and recognized permeability limitations in distribution, PBPK models are also incorporating more complex distribution assessment. For example, recently a new PBPK model termed ‘PermQ’ was developed that incorporates permeability considerations together with intracellular lipids (Korzekwa *et al.*, 2022). This model advances the consideration for the complexity of tissue composition and capillary permeability and the simulation of distribution phenomena in and out of physiological membranes.

A typical full body PBPK model will include blood flows to the individual organs and partition coefficients ( $K_p$ -values) to these organs (**Figure 1**). The  $K_p$  values refer to the tissue concentration ( $C_t$ ) to plasma concentration ( $C_p$ ) ratio at steady state (distribution equilibrium). In

other words, the  $K_p$  values are the concentration ratios for a specific organ or tissue that can be measured at steady state during an iv infusion. By use of the tissue specific blood flows and  $K_p$  values, the rate and extent of distribution to these organs can be simulated and together with clearance parameters this allows simulation of the overall plasma concentration time curve.

Many methods for predicting tissue specific  $K_p$  values *in silico* have been published and the reader is referred to the original publications (Rodgers and Rowland, 2006; Poulin and Theil, 2009; Poulin *et al.*, 2011) and some of the relevant reviews for more detailed analysis of this topic (Zou *et al.*, 2012; Holt *et al.*, 2019; Utsey *et al.*, 2020). One limitation for the *in silico* methods of  $K_p$  prediction is the lack of detailed information of the composition of human tissues and organs and the still rudimentary understanding of the distribution characteristics of drugs across different cell types within an organ. For example, current prediction methods do not generally consider heterogeneity of tissues/organs with multiple different cell types nor binding to intracellular proteins such as intracellular fatty acid binding proteins that are abundant across the body and bind numerous drugs (Yabut and Isoherranen, 2023). The assumed partitioning to specific subcellular lipids (acidic, and neutral phospholipids, neutral lipids) is also typically predicted from systems such as water:octanol or water:vegetable oil partitioning that may be an inadequate reflection of the specific lipid partitioning, in particular for drugs with ionizable groups. These values are also often obtained from other *in silico* prediction systems that may not fully capture lipid partitioning. A note of caution should be made against the common practice of using uniform scaling factors to adjust *in silico* predicted  $K_p$  values to obtain a  $V_{ss}$  value that matches an observed  $V_{ss}$  or results in an apparent  $V_\beta$  value that allows an appropriate capture of the half-life of a drug. There is no mechanistic or scientific basis to assume that the  $K_p$  prediction from the *in silico* methods would be equally incorrect for all organs. For example, in the “Rodgers and

Rowland” method the lipid composition and partitioning in each organ is considered to predict the  $K_{p,u}$  values, but the fraction of the tissue volume in the different lipid components is different and hence impacted differently for each organ (Rodgers *et al.*, 2005). Species differences in the specific lipid content have also been noted resulting in discrepant tissue  $K_{p,u}$  predictions between species (Rodgers *et al.*, 2012). How these differences impact extrapolation of  $K_{p,u}$  values from preclinical species to humans has not been fully elucidated and remains an area requiring further investigation. In the context of uniform scaling of  $K_p$  values, each organ has a unique and distinct effect on distribution kinetics, especially the rate of distribution, due to the different blood flows to the specific organs. It is important for the modeler to consider the scenario that a  $K_p$  error for the adipose or bone tissue will appear different in the simulation output than a similar magnitude of  $K_p$  error for the skin or muscle- two similarly sized organs.

While use of *in silico* methods to predict  $K_p$  values is efficient and easy, more labor intensive and detailed experimental assessment of  $K_p$  values is recommended if the prediction of terminal half-life and distribution characteristics is desired. The predicted  $V_{ss}$  if done based on *in silico* methods, also needs to be compared to some observed data. The modeler should be aware that the terminal half-life observed and simulated is dependent on CL and  $V_\beta$  rather than  $V_{ss}$  and hence accurate prediction of half-life using PBPK models requires appropriate identification of the main distribution organs that impact  $V_\beta$ . This may not be obvious from simple consideration of  $V_{ss}$ . In cases where active transporters are involved in distribution kinetics the permeability limited distribution processes may have a disproportionate impact on  $V_\beta$ . In an ideal case, intravenous dosing data are available in humans which allows calculation of central compartment volume ( $V_c$ ),  $V_{ss}$  and  $V_\beta$  but such data are rarely available to the modeler. Often iv dosing data are, however, available from preclinical species. If preclinical species data are available

following iv dosing the  $V_c$  and  $V_{ss}$  can be determined in preclinical species and  $V_c$  and  $V_{ss}$  in humans predicted using allometric scaling and the Øie-Tozer method (Øie and Tozer, 1979) that allows consideration of interspecies differences in unbound fraction in plasma. Notably, the distribution of the compound of interest to individual organs cannot be determined from plasma concentration-time curves. The determination of  $V_{ss}$  even after iv dosing in humans can only provide an average  $K_p$  value for all organs combined. The assignment of the  $K_p$  values to specific organs is always subject to an identifiability problem. Several feasible approaches can be used in practice to acknowledge this challenge and capitalize on the power of PBPK modeling while acknowledging the lack of confidence in specific tissue  $K_p$  values. As one approach, the average  $K_p$  value can be calculated from  $V_{ss}$  (either measured in humans or scaled from preclinical species) using the classic equation  $V_{ss} = V_p + K_p \times V_T$  and all organs can initially be assigned this  $K_p$ . The specific  $K_p$  -values for some of the large organs can then be optimized (proportionally increased and decreased) to capture the terminal half-life and early distribution phase of the drug of interest without altering  $V_{ss}$ . The modeler can use qualitative knowledge of the lipid composition and the physicochemical characteristics of the drug to consider the most likely organs for which distribution is less or more extensive than the overall total body  $K_p$  value. This approach does, however, assume that reliable clearance values are known. As an alternative approach, the  $K_p$  values can be predicted using *in silico* methods and, as noted above, then optimized specifically to the large organs that result in detectable difference in the  $V_{ss}$  prediction. In both cases it should be acknowledged that there are numerous combinations of tissue  $K_p$  values that will all yield equally good plasma concentration-time curves and these values are increasingly difficult to identify following non-iv dosing routes (Huang and Isoherranen, 2020b). Similarly the more organs that are included in the model the more degrees of freedom are present

in the model and hence the better the model fit is. As such the model generated specific tissue concentration curves should be interpreted with caution especially if the tissue concentrations are considered in light of pharmacological activity or toxicity.

Experimental measurements of  $K_p$  values are beneficial for establishing specific tissue distribution characteristics. In particular, experimental verification of  $K_p$  values using preclinical models is useful if a PD component is included in the model to provide additional confidence for distribution kinetics to the site of action. Additionally, if confidence is desired for the specific organs of distribution or for the rank order of  $K_p$  values between tissues, experimental verification is of value. An experimentally measured  $K_p$  value that is incorporated into a PBPK model should be the steady state equilibrium  $C_T/C_p$  ratio. However, experimental  $K_p$  values are often measured during elimination phase following iv bolus in preclinical species. The tissue to plasma concentration ratio is not the same during the elimination phase of drugs as it is at steady state (Jeong and Jusko, 2022a). This has been nicely shown via experimental studies in rats following dosing of ketamine (Edwards and Mather, 2001). The tissue to plasma concentration ratios were up to 10-fold greater during the terminal phase following iv-bolus than following iv infusion. This can be explained by arteriovenous differences in concentrations of ketamine and the clearance of ketamine during the elimination phase. The arterial concentrations perfusing the tissue are lower than the venous concentrations during the elimination phase and hence the tissue becomes a reservoir for the drug. The redistribution of the drug from the tissue may be much slower than the clearance leading to a higher concentration ratio between the tissue and plasma than what would be expected from a steady state  $K_p$  value. These  $K_p$  values measured during the terminal elimination phase can, however, be converted to the steady state  $K_p$  values for non-eliminating organs using the Chen and Gross method (Jeong and Jusko, 2022b). For eliminating



organs the clearance parameters also need to be considered and the choice of the liver model impacts the ultimate calculation of the  $K_p$  value (Jeong and Jusko, 2022b; Li and Jusko, 2023b; a). As such it is important to appreciate the theoretical basis of  $K_p$  values incorporated in the models and the limitations of experimentally determined concentration ratios.

Currently used criteria for model verification (AUC and  $C_{max}$  fold differences) likely do not adequately explore whether distribution kinetics is appropriately described by the model and whether the shape of the plasma concentration-time curve is accurately captured. The AUC depends only on the bioavailable dose and the systemic clearance of the drug ( $AUC=FD/CL$ ) and hence the  $AUC_{observed}/AUC_{predicted}$  reflects mainly the accuracy of simulations of oral and/or systemic clearance. This lack of sensitivity of AUC to the shape of the plasma concentration curve has been previously noted and a calculation of an exposure overlap coefficient (EOC) was proposed to compare the curve shapes between simulation and observed data (Holt *et al.*, 2019). The EOC is the calculated fraction of the observed AUC that overlaps with the predicted and hence is always a value  $<1$ . When the EOC was used to assess model performance for a series of drugs the EOC values ranged from 0.71 to 1 (Korzekwa *et al.*, 2022). At present no clear criterion has been proposed for acceptable range for EOC for fit for purpose modeling and further assessment of this approach is needed. For EOC one may also need to consider the model fit to the observed data to allow integrations of the C versus t data and comparison of the calculated areas for the simulated concentrations. In studies where noncompartmental modeling is typically used this may require further considerations of compartmental analysis of the observed data to accurately capture the observed area of the AUC that does not overlap with the simulation.

In addition to AUC,  $C_{max}$  is usually included as an additional measure to determine model performance and whether distribution and clearance parameters are defined appropriately.

$C_{max}$ , however, has several weaknesses as an observed parameter. First, the observed  $C_{max}$  value depends on the sampling schedule for the observed study and can be poorly defined value if sampling is too sparse missing the true  $C_{max}$  or if the absorption kinetics are relatively slow such as with controlled release formulations when multiple sampling points result values close to the  $C_{max}$  and  $t_{max}$ . Second,  $C_{max}$  depends on multiple PK parameters and does not directly measure error in a given parameter. As such  $C_{max}$  does not directly inform on any specific pharmacokinetic parameter and multiple parameter combinations exist to obtain  $C_{max}$  estimates that are within acceptable range of observed data. The observed  $C_{max}$  depends on the bioavailability (F), volume of distribution,  $t_{max}$  and elimination rate constant  $k$  of the parent drug all of which are defined by a combination of values inputted in a PBPK model. Of particular interest for PBPK modeling is the issue of  $C_{max}$  and the impact of  $V$  on  $C_{max}$ . In classic pharmacokinetics following one compartment model  $C_{max}$  is defined as  $C_{max} = \frac{k_a FD}{V(k_a - k)} [e^{-kt_{max}} - e^{-k_a t_{max}}]$  (Han *et al.*, 2018). However, explicit solutions for  $C_{max}$  do not exist for multicompartment models. Great majority of drugs display multicompartment behavior following iv administration and hence the interpretation of  $C_{max}$  and error in  $C_{max}$  simulations in PBPK models can be confounded in the absence of iv data. It should be emphasized that models of distribution kinetics can only be appropriately verified if iv data exists. In the absence of iv data PBPK models have a parameter identifiability problem; it is not possible to differentiate the effect of  $k_a$ , distribution rate ( $\alpha$  in compartmental kinetics) and flip-flop phenomena and multiple possible solutions can be obtained. Such confounding effects were illustrated when comparing simulated arterial and venous concentrations and observed arterial and venous concentrations of drugs (Huang and Isoherranen, 2020b). Using buccal fentanyl as a model it was shown that the erroneous assumptions regarding distribution kinetics (comparing

observed venous to simulated arterial concentrations) could be “corrected” to yield an acceptable  $C_{\max}$  value by altering absorption kinetics (Huang and Isoherranen, 2020b). It should be emphasized that arteriovenous differences are specifically a distribution phenomenon and do not impact clearance which as a pharmacokinetic parameter is independent of distribution as long as true sampling is done for sufficient duration to capture terminal elimination phase and  $AUC_{\infty}$ .

As models become more sophisticated the evaluation of model performance and transparency in confidence in model assumptions need to keep pace. For example, it is recommended that modelers assess the overall AAFE for plasma concentration time curves in addition to the accuracy of AUC predictions to establish how well distribution kinetics is captured as AAFE allows evaluation of the entire plasma concentration-time curve. Indeed such approaches are increasingly used in published PBPK models (Table 1 and 2).

### **Future Opportunities for PBPK modeling**

PBPK modeling has become a mature field within pharmaceutical sciences and the use of PBPK modeling applications has broadened to include prediction of drug disposition in variety of complex patient populations. However, incorporating the diversity of academic advances in structural model development and incorporation of more complex physiological concepts in PBPK models is becoming a challenge to commercial software platforms. It is likely that more versatility will need to be incorporated into the “closed source” or “closed code” software packages to allow modelers to explore the best structural model for the specific purpose. While software packages are moving to this direction it is still hard to predict whether the regulatory requirements of model compatibility and validation can be maintained with increased modeling

flexibility. The computational speed may also become limiting with some of these extended capabilities.

The expectations for model verification and validation have increased over the past decade and the use of independent model development datasets and model validation datasets have become well incorporated into the literature. In majority of the papers reviewed in detail for this analysis (Tables 1 and 2) the manuscripts stated a predefined acceptance criterion. Notably, many models used for specific populations were also based on previously developed models for the specific compounds in healthy volunteers. During the model development and verification process, the limitation in many cases is the ability of the modeler to identify and capture all the available clinical data for a compound of interest and to assess in a statistically rigorous way whether the model is fit for purpose in light of all available data. In addition, while the overall model may fit predefined acceptance criteria this does not mean the developed model is the best possible model for the given data. The modeler will typically go through a subjective parameter optimization process that will allow “fit-for-purpose” applications. However, in any scenario there are multiple combinations of values that will provide a model that fits the acceptance criteria. Choice of the final best fit and weight put on specific clinical and *in vitro* data used in model development can be subjective and yield biased data. Novel computational approaches may address this issue. Such computational approaches include artificial intelligence (AI), machine learning and artificial neural networks (ANN)(Chou and Lin, 2023). Proof of concept studies with ANNs have already been conducted and these studies have shown that ANN could predict patient plasma concentration-time curves when trained with PK data (Bräm *et al.*, 2022). Similarly, a deep learning approach based on neural ordinary differential equations was used to predict PK data in previously unstudied scenarios (Lu *et al.*, 2021).

For bottom-up PBPK model development most developed PBPK models already use some level of *in silico* predictions such as LopP values, pK<sub>a</sub> or K<sub>p</sub> values although clearance predictions and permeability values still typically rely on experimental data. Machine learning methods are, however, increasingly used to generate the parameters used for PBPK model development (Chou and Lin, 2023). Machine learning is already available for many pharmacokinetic parameter predictions that have previously relied on mechanistic predictive equations (Chou and Lin, 2023) and several recent studies have incorporated AI and machine learning into PBPK modeling with AI and machine learning being used to generate specific parameters in bottom-up modeling (Chou and Lin, 2023; Chou *et al.*, 2023; Habiballah and Reifeld, 2023). These AI assisted PBPK models at present typically use QSAR approaches that get incorporated into the PBPK model. For example a machine learning method was developed to predict K<sub>p</sub> values simply from physicochemical parameters of a drug (Chou and Lin, 2023) and the feasibility of use of machine learning methods to predict distribution characteristics was assessed in a pilot study of 12 drugs (Parrott *et al.*, 2022).

The model development process in PBPK applications that use so called “top down” or “middle out” approach could also benefit from artificial intelligence (AI) applications and machine learning. As such one can expect that AI will become incorporated into PBPK model development workflows to allow unbiased optimization of model parameters. AI can also likely in the future significantly improve the ability of the modeler to identify and summarize all available PK data in published literature and capture the reported pharmacokinetic data. Due to the expanding computational power, machine learning and AI methods will likely also assist in evaluating multiple different model structures and rapidly provide assessment of the various

organ models, level of complexity needed for distribution modeling and assessment of critical experimental data needed to provide confidence in PBPK estimates and predictions.

In the top down and middle out approaches the modeler typically manually optimizes some parameters in the PBPK model to achieve a model that fits observed data within defined acceptance criteria. Typical parameters that are optimized include individual tissue  $K_p$  values, specific enzyme intrinsic clearance values and in some cases unbound fractions, bioavailability or transporter clearance but any model parameter could theoretically be optimized. This approach is often referred to as “learn and confirm”. As noted above multiple combinations of parameters can be identified that all result in acceptable solutions that fit pre-defined acceptance criteria. A modeler often struggles in deciding how to weigh individual studies in optimization process and how to develop a model that provides the closest comprehensive match to the totality of observed clinical data. In addition, the optimization of parameters is time consuming and usually not automated relying on the knowledge and experience of the modeler to identify best parameters. It is conceivable that in the future this parameter optimization step could be done by an AI or a machine learning algorithm that samples a much greater space of possible combinations of optimized parameters and ultimately identifies the truly best model to fit to the collective clinical data available. AI applications can provide superior speed and power and enable consideration of large number of combinations of data for this purpose.

One may speculate that in the future more mechanistic models will get incorporated into the AI applications that will allow automatic optimization of the PBPK model parameters and unbiased model development and optimization within a mathematically defined framework. This will likely lead to a need to develop novel PBPK modeling platforms that interface with advanced machine learning and AI applications. It is expected that the role of the modeler will

change with these developments and there will be a need to further define how such AI generated models can be evaluated during regulatory reviews and in scientific literature.

**Data Availability Statement:**

The author declares that all the data supporting this review is available within the paper or through existing publications reviewed.

**Authorship Contributions:**

Participated in data collection: Isoherranen

Performed data analysis: Isoherranen

Wrote or contributed to the writing of the manuscript: Isoherranen



- Abduljalil K, and Badhan RKS (2020) Drug dosing during pregnancy-opportunities for physiologically based pharmacokinetic models. *J Pharmacokinet Pharmacodyn* **47**:319–340.
- Abduljalil K, Cain T, Humphries H, and Rostami-Hodjegan A (2014) Deciding on success criteria for predictability of pharmacokinetic parameters from in vitro studies: an analysis based on in vivo observations. *Drug Metab Dispos* **42**:1478–84.
- Abduljalil K, Ning J, Pansari A, Pan X, and Jamei M (2022) Prediction of Maternal and Fetoplacental Concentrations of Cefazolin, Cefuroxime, and Amoxicillin during Pregnancy Using Bottom-Up Physiologically Based Pharmacokinetic Models. *Drug Metab Dispos* **50**:386–400.
- Abduljalil K, Pansari A, Ning J, and Jamei M (2022) Prediction of Maternal and Fetal Acyclovir, Emtricitabine, Lamivudine, and Metformin Concentrations during Pregnancy Using a Physiologically Based Pharmacokinetic Modeling Approach. *Clin Pharmacokinet* **61**:725–748.
- Ahmad A, Pepin X, Aarons L, Wang Y, Darwich AS, Wood JM, Tannergren C, Karlsson E, Patterson C, Thörn H, Ruston L, Mattinson A, Carlert S, Berg S, Murphy D, Engman H, Laru J, Barker R, Flanagan T, Abrahamsson B, Budhdeo S, Franek F, Moir A, Hanisch G, Pathak SM, Turner D, Jamei M, Brown J, Good D, Vaidhyanathan S, Jackson C, Nicolas O, Beilles S, Nguefack J-F, Louit G, Henrion L, Ollier C, Boulu L, Xu C, Heimbach T, Ren X, Lin W, Nguyen-Trung A-T, Zhang J, He H, Wu F, Bolger MB, Mullin JM, van Osdol B, Szeto K, Korjamo T, Pappinen S, Tuunainen J, Zhu W, Xia B, Daublain P, Wong S, Varma MVS, Modi S, Schäfer KJ, Schmid K, Lloyd R, Patel A, Tistaert C, Bevernage J, Nguyen MA, Lindley D, Carr R, and Rostami-Hodjegan A (2020) IMI - Oral biopharmaceutics tools project - Evaluation of bottom-up PBPK prediction success part 4: Prediction accuracy and software comparisons with improved data and modelling strategies. *Eur J Pharm Biopharm* **156**:50–63.
- Aldibani HKA, Rajput AJ, and Rostami-Hodjegan A (2023) In-depth analysis of patterns in selection of different physiologically-based pharmacokinetic modeling tools: Part II - Assessment of model reusability and comparison between open and non-open source-code software. *Biopharm Drug Dispos* **44**:292–300.

- Al Shoyaib A, Riedmaier AE, Kumar A, Roy P, Parrott NJ, Fang L, Tampal N, Yang Y, Jereb R, Zhao L, and Wu F (2023) Regulatory utility of physiologically based pharmacokinetic modeling for assessing food impact in bioequivalence studies: A workshop summary report. *CPT Pharmacometrics Syst Pharmacol* **12**:610–618.
- Alsmadi MM (2023) The investigation of the complex population-drug-drug interaction between ritonavir-boosted lopinavir and chloroquine or ivermectin using physiologically-based pharmacokinetic modeling. *Drug Metab Pers Ther* **38**:87–105.
- Alsmadi MM, and Alzughoul SB (2023) In vitro-in vivo extrapolation of bexarotene metabolism in the presence of chronic kidney disease and acute kidney injury in rat using physiologically based pharmacokinetic modeling and extrapolation to human. *Biopharm Drug Dispos* **44**:221–244.
- Balhara A, Kumar AR, and Unadkat JD (2022) Predicting Human Fetal Drug Exposure Through Maternal-Fetal PBPK Modeling and In Vitro or Ex Vivo Studies. *J Clin Pharmacol* **62 Suppl 1**:S94–S114.
- Bräm DS, Parrott N, Hutchinson L, and Steiert B (2022) Introduction of an artificial neural network–based method for concentration-time predictions. *CPT Pharmacometrics Syst Pharmacol* **11**:745–754.
- Bukkems VE, van Hove H, Roelofsen D, Freriksen JJM, van Ewijk-Beneken Kolmer EWJ, Burger DM, van Drongelen J, Svensson EM, Greupink R, and Colbers A (2022) Prediction of Maternal and Fetal Doravirine Exposure by Integrating Physiologically Based Pharmacokinetic Modeling and Human Placenta Perfusion Experiments. *Clin Pharmacokinet* **61**:1129–1141.
- Chang HP, Kim SJ, Wu D, Shah K, and Shah DK (2021) Age-Related Changes in Pediatric Physiology: Quantitative Analysis of Organ Weights and Blood Flows : Age-Related Changes in Pediatric Physiology. *AAPS J* **23**:50.
- Chang S-Y, Huang W, Chapron A, Quiñones AJL, Wang J, Isoherranen N, Shen DD, Kelly EJ, Himmelfarb J, and Yeung CK (2023) Incorporating Uremic Solute-mediated Inhibition of OAT1/3 Improves PBPK Prediction of Tenofovir Renal and Systemic Disposition in Patients with Severe Kidney Disease. *Pharm Res*, doi: 10.1007/s11095-023-03594-x.
- Chang X, Palmer J, Lumen A, Lee UJ, Ceger P, Mansouri K, Sprankle C, Donley E, Bell S, Knudsen TB, Wambaugh J, Cook B, Allen D, and Kleinstreuer N (2022) Quantitative in

- vitro to in vivo extrapolation for developmental toxicity potency of valproic acid analogues. *Birth Defects Res* **114**:1037–1055.
- Chou W-C, Chen Q, Yuan L, Cheng Y-H, He C, Monteiro-Riviere NA, Riviere JE, and Lin Z (2023) An artificial intelligence-assisted physiologically-based pharmacokinetic model to predict nanoparticle delivery to tumors in mice. *J Control Release* **361**:53–63.
- Chou W-C, and Lin Z (2023) Machine learning and artificial intelligence in physiologically based pharmacokinetic modeling. *Toxicol Sci* **191**:1–14.
- Coppola P, Kerwash E, and Cole S (2022) The Use of Pregnancy Physiologically Based Pharmacokinetic Modeling for Renally Cleared Drugs. *J Clin Pharmacol* **62 Suppl 1**:S129–S139.
- Cordes H, and Rapp H (2023) Gene expression databases for physiologically based pharmacokinetic modeling of humans and animal species. *CPT Pharmacometrics Syst Pharmacol* **12**:311–319.
- Dong Z, Li J, Wu F, Zhao P, Lee S-C, Zhang Lillian, Seo P, and Zhang Lei (2020) Application of Physiologically-Based Pharmacokinetic Modeling to Predict Gastric pH-Dependent Drug-Drug Interactions for Weak Base Drugs. *CPT Pharmacometrics Syst Pharmacol* **9**:456–465.
- Dubinsky S, Malik P, Hajducek DM, and Edginton A (2022) Determining the Effects of Chronic Kidney Disease on Organic Anion Transporter1/3 Activity Through Physiologically Based Pharmacokinetic Modeling. *Clin Pharmacokinet* **61**:997–1012.
- Edwards SR, and Mather LE (2001) Tissue uptake of ketamine and norketamine enantiomers in the rat: indirect evidence for extrahepatic metabolic inversion. *Life Sci* **69**:2051–66.
- El-Khateeb E, Burkhill S, Murby S, Amirat H, Rostami-Hodjegan A, and Ahmad A (2021) Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms. *Biopharm Drug Dispos* **42**:107–117.
- Fan J, Yang Y, Grimstein M, Zhang X, Kitabi E, Earp JC, Arya V, Reynolds KS, Zhu H, and Wang Y (2022) Whole Body PBPK Modeling of Remdesivir and Its Metabolites to Aid in Estimating Active Metabolite Exposure in the Lung and Liver in Patients With Organ Dysfunction. *Clin Pharmacol Ther* **111**:624–634.
- Freriksen JJM, van der Heijden JEM, de Hoop-Sommen MA, Greupink R, and de Wildt SN (2023) Physiologically Based Pharmacokinetic (PBPK) Model-Informed Dosing Guidelines

- for Pediatric Clinical Care: A Pragmatic Approach for a Special Population. *Pediatric Drugs* **25**:5–11.
- Gaohua L, Abduljalil K, Jamei M, Johnson TN, and Rostami-Hodjegan A (2012) A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. *Br J Clin Pharmacol* **74**:873–885.
- Granda M, Huang W, Yeung C, Isoherranen N, and Kestenbaum B (2023) PREDICTING COMPLEX KIDNEY DRUG HANDLING USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL INFORMED BY BIOMARKER-ESTIMATED SECRETORY CLEARANCE AND BLOOD FLOW. *Clinical Translational Science*.
- Grimstein M, Yang Y, Zhang X, Grillo J, Huang S-M, Zineh I, and Wang Y (2019) Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration’s Office of Clinical Pharmacology. *J Pharm Sci* **108**:21–25.
- Habiballah S, and Reisfeld B (2023) Adapting physiologically-based pharmacokinetic models for machine learning applications. *Sci Rep* **13**:14934.
- Han YR, Lee PI, and Pang KS (2018) Finding T<sub>max</sub> and C<sub>max</sub> in Multicompartmental Models. *Drug Metab Dispos* **46**:1796–1804.
- Hariparsad N, Ramsden D, Taskar K, Badée J, Venkatakrishnan K, Reddy MB, Cabalu T, Mukherjee D, Rehmel J, Bolleddula J, Emami Riedmaier A, Prakash C, Chanteux H, Mao J, Umehara K, Shah K, De Zwart L, Dowty M, Kotsuma M, Li M, Pilla Reddy V, McGinnity DF, and Parrott N (2022) Current Practices, Gap Analysis, and Proposed Workflows for PBPK Modeling of Cytochrome P450 Induction: An Industry Perspective. *Clin Pharmacol Ther* **112**:770–781.
- Holt K, Nagar S, and Korzekwa K (2019) Methods to Predict Volume of Distribution. *Curr Pharmacol Rep* **5**:391–399.
- Huang W, Czuba LC, and Isoherranen N (2020) Mechanistic PBPK modeling of urine pH effect on renal and systemic disposition of methamphetamine and amphetamines. *Journal of Pharmacology and Experimental Therapeutics* **373**:488–501, American Society for Pharmacology and Experimental Therapy.

- Huang W, and Isoherranen N (2018) Development of a Dynamic Physiologically Based Mechanistic Kidney Model to Predict Renal Clearance. *CPT Pharmacometrics Syst Pharmacol*, doi: 10.1002/psp4.12321.
- Huang W, and Isoherranen N (2020a) Novel Mechanistic PBPK Model to Predict Renal Clearance in Varying Stages of CKD by Incorporating Tubular Adaptation and Dynamic Passive Reabsorption. *CPT Pharmacometrics Syst Pharmacol* **9**:571–583, American Society for Clinical Pharmacology and Therapeutics.
- Huang W, and Isoherranen N (2020b) Sampling site has a critical impact on physiologically based pharmacokinetic modelings. *Journal of Pharmacology and Experimental Therapeutics* **372**:30–45, American Society for Pharmacology and Experimental Therapy.
- Imaoka T, Huang W, Shum S, Hailey DW, Chang SY, Chapron A, Yeung CK, Himmelfarb J, Isoherranen N, and Kelly EJ (2021) Bridging the gap between in silico and in vivo by modeling opioid disposition in a kidney proximal tubule microphysiological system. *Sci Rep* **11**, Nature Research.
- Isoherranen N, and Thummel KE (2013) Drug metabolism and transport during pregnancy: How does drug disposition change during pregnancy and what are the mechanisms that cause such changes? *Drug Metabolism and Disposition* **41**:256–262.
- Itohara K, Yano I, Nakagawa S, Yonezawa A, Omura T, Imai S, Nakagawa T, Sawada A, Kobayashi T, Tochio A, Sakai K, Taura K, Ogawa O, and Matsubara K (2022) Extrapolation of physiologically based pharmacokinetic model for tacrolimus from renal to liver transplant patients. *Drug Metab Pharmacokinet* **42**:100423.
- Jamei M, Abrahamsson B, Brown J, Bevernage J, Bolger MB, Heimbach T, Karlsson E, Kotzagiorgis E, Lindahl A, McAllister M, Mullin JM, Pepin X, Tistaert C, Turner DB, and Kesisoglou F (2020) Current status and future opportunities for incorporation of dissolution data in PBPK modeling for pharmaceutical development and regulatory applications: OrBiTo consortium commentary. *Eur J Pharm Biopharm* **155**:55–68.
- Jean D, Naik K, Milligan L, Hall S, Mei Huang S, Isoherranen N, Kuemmel C, Seo P, Tegenge MA, Wang Y, Yang Y, Zhang X, Zhao L, Zhao P, Benjamin J, Bergman K, Grillo J, Madabushi R, Wu F, Zhu H, and Zineh I (2021) Development of best practices in physiologically based pharmacokinetic modeling to support clinical pharmacology

- regulatory decision-making—A workshop summary. *CPT Pharmacometrics Syst Pharmacol* **10**:1271–1275.
- Jeong Y-S, and Jusko WJ (2022a) Consideration of Fractional Distribution Parameter  $f_d$  in the Chen and Gross Method for Tissue-to-Plasma Partition Coefficients: Comparison of Several Methods. *Pharm Res* **39**:463–479.
- Jeong Y-S, and Jusko WJ (2022b) Consideration of Fractional Distribution Parameter  $f_d$  in the Chen and Gross Method for Tissue-to-Plasma Partition Coefficients: Comparison of Several Methods. *Pharm Res* **39**:463–479.
- Jeong Y-S, Kim M-S, and Chung S-J (2022a) Determination of the Number of Tissue Groups of Kinetically Distinct Transit Time in Whole-Body Physiologically Based Pharmacokinetic (PBPK) Models I: Theoretical Consideration of Bottom-Up Approach of Lumping Tissues in Whole-Body PBPK. *AAPS J* **24**:90.
- Jeong Y-S, Kim M-S, and Chung S-J (2022b) Determination of the Number of Tissue Groups of Kinetically Distinct Transit Time in Whole-Body Physiologically Based Pharmacokinetic (PBPK) Models II: Practical Application of Tissue Lumping Theories for Pharmacokinetics of Various Compounds. *AAPS J* **24**:91.
- Jing J, Petroff R, Shum S, Crouthamel B, Topletz AR, Grant KS, Burbacher TM, and Isoherranen N (2017) Toxicokinetics and Physiologically Based Pharmacokinetic Modeling of the Shellfish Toxin Domoic Acid in Nonhuman Primates. *Drug Metabolism and Disposition* **dmd.117.078485**.
- Jones HM, Chen Y, Gibson C, Heimbach T, Parrott N, Peters SA, Snoeys J, Upreti V V., Zheng M, and Hall SD (2015) Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. *Clin Pharmacol Ther* **97**:247–262.
- Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, and Wambaugh JF (2022) Evaluation of a rapid, generic human gestational dose model. *Reprod Toxicol* **113**:172–188.
- Ke a B, Nallani SC, Zhao P, Rostami-Hodjegan a, and Unadkat JD (2012) A PBPK Model to Predict Disposition of CYP3A-Metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction. *CPT Pharmacometrics Syst Pharmacol* **1**:e3.

- Ke AB, Greupink R, and Abduljalil K (2018) Drug Dosing in Pregnant Women: Challenges and Opportunities in Using Physiologically Based Pharmacokinetic Modeling and Simulations. *CPT Pharmacometrics Syst Pharmacol* **7**:103–110.
- Ke AB, Rostami-Hodjegan A, Zhao P, and Unadkat JD (2014a) Pharmacometrics in pregnancy: An unmet need. *Annu Rev Pharmacol Toxicol* **54**:53–69.
- Ke AB, Rostami-Hodjegan A, Zhao P, and Unadkat JD (2014b) Pharmacometrics in pregnancy: An unmet need. *Annu Rev Pharmacol Toxicol* **54**:53–69.
- Korzekwa K, Radice C, and Nagar S (2022) A permeability- and perfusion-based PBPK model for improved prediction of concentration-time profiles. *Clin Transl Sci* **15**:2035–2052.
- Ladumor MK, Storelli F, Liang X, Lai Y, Enogieru OJ, Chothe PP, Evers R, and Unadkat JD (2023) Predicting changes in the pharmacokinetics of CYP3A-metabolized drugs in hepatic impairment and insights into factors driving these changes. *CPT Pharmacometrics Syst Pharmacol* **12**:261–273.
- Li M, Zhao P, Pan Y, and Wagner C (2018) Predictive Performance of Physiologically Based Pharmacokinetic Models for the Effect of Food on Oral Drug Absorption: Current Status. *CPT Pharmacometrics Syst Pharmacol* **7**:82–89.
- Li S, and Xie F (2023) Foetal and neonatal exposure prediction and dosing evaluation for ampicillin using a physiologically-based pharmacokinetic modelling approach. *Br J Clin Pharmacol* **89**:1402–1412.
- Li X, and Jusko WJ (2022) Assessing Liver-to-Plasma Partition Coefficients and In Silico Calculation Methods: When Does the Hepatic Model Matter in PBPK? *Drug Metab Dispos*, doi: 10.1124/dmd.122.000994.
- Li X, and Jusko WJ (2023a) Exploring the Pharmacokinetic Mysteries of the Liver: Application of Series Compartment Models of Hepatic Elimination. *Drug Metab Dispos* **51**:618–628.
- Li X, and Jusko WJ (2023b) Utility of Minimal Physiologically Based Pharmacokinetic Models for Assessing Fractional Distribution, Oral Absorption, and Series-Compartment Models of Hepatic Clearance. *Drug Metab Dispos* **51**:1403–1418.
- Liu XI, Dallmann A, Brooks K, Best BM, Clarke DF, Mirochnick M, van den Anker JN, Capparelli E V, and Momper JD (2023) Physiologically-based pharmacokinetic modeling of remdesivir and its metabolites in pregnant women with COVID-19. *CPT Pharmacometrics Syst Pharmacol* **12**:148–153.

- Lu J, Deng K, Zhang X, Liu G, and Guan Y (2021) Neural-ODE for pharmacokinetics modeling and its advantage to alternative machine learning models in predicting new dosing regimens. *iScience* **24**:102804.
- Luzon E, Blake K, Cole S, Nordmark A, Versantvoort C, and Berglund EG (2017) Physiologically based pharmacokinetic modeling in regulatory decision-making at the European Medicines Agency. *Clin Pharmacol Ther* **102**:98–105.
- Madabushi R, Seo P, Zhao L, Tegenge M, and Zhu H (2022) Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making. *Pharm Res* **39**:1669–1680.
- Matsuzaki T, Scotcher D, Darwich AS, Galetin A, and Rostami-Hodjegan A (2019) Towards further verification of physiologically-based kidney models: Predictability of the effects of urine-flow and urine-pH on renal clearance. *Journal of Pharmacology and Experimental Therapeutics* **368**:157–168.
- McKiernan EC, Bourne PE, Brown CT, Buck S, Kenall A, Lin J, McDougall D, Nosek BA, Ram K, Soderberg CK, Spies JR, Thaney K, Updegrove A, Woo KH, and Yarkoni T (2016) How open science helps researchers succeed. *Elife* **5**.
- Miao J, Fu P, Ren S, Hu C, Wang Ying, Jiao C, Li P, Zhao Y, Tang C, Qian Y, Yang R, Dong Y, Rong J, Wang Yaohui, Jin X, Sun Y, and Chen L (2022) Effect of renal impairment on the pharmacokinetics and safety of dorzagliatin, a novel dual-acting glucokinase activator. *Clin Transl Sci* **15**:548–557.
- Nagar S, Korzekwa RC, and Korzekwa K (2017) Continuous Intestinal Absorption Model Based on the Convection-Diffusion Equation. *Mol Pharm* **14**:3069–3086.
- Neuhoff S, Lu G, Burt H, Jamei M, Li L, Tucker GT, and Rodtami-Hodjegan A (2013) Accounting for transporters in renal clearance: towards a mechanistic kidney model (Mech Kim), in *Transporters in Drug Development* (Sugiyama Y, and Steffansen B eds) pp 155–177, Springer, New York.
- Noh K, and Pang KS (2019) Theoretical consideration of the properties of intestinal flow models on route-dependent drug removal: Segregated Flow (SFM) vs. Traditional (TM). *Biopharm Drug Dispos* **40**:195–213.
- Øie S, and Tozer TN (1979) Effect of Altered Plasma Protein Binding on Apparent Volume of Distribution. *J Pharm Sci* **68**:1203–1205.



- Pang KS, Peng HB, and Noh K (2020) The Segregated Intestinal Flow Model (SFM) for Drug Absorption and Drug Metabolism: Implications on Intestinal and Liver Metabolism and Drug-Drug Interactions. *Pharmaceutics* **12**.
- Pang KS, Yang QJ, and Noh K (2017) Unequivocal evidence supporting the segregated flow intestinal model that discriminates intestine versus liver first-pass removal with PBPK modeling. *Biopharm Drug Dispos* **38**:231–250.
- Parrott N, Manevski N, and Olivares-Morales A (2022) Can We Predict Clinical Pharmacokinetics of Highly Lipophilic Compounds by Integration of Machine Learning or In Vitro Data into Physiologically Based Models? A Feasibility Study Based on 12 Development Compounds. *Mol Pharm* **19**:3858–3868.
- Peng J, Ladumor MK, and Unadkat JD (2022) Estimation of Fetal-to-Maternal Unbound Steady-State Plasma Concentration Ratio of P-Glycoprotein and/or Breast Cancer Resistance Protein Substrate Drugs Using a Maternal-Fetal Physiologically Based Pharmacokinetic Model. *Drug Metab Dispos* **50**:613–623.
- Poulin P, Ekins S, and Theil F-P (2011) A hybrid approach to advancing quantitative prediction of tissue distribution of basic drugs in human. *Toxicol Appl Pharmacol* **250**:194–212.
- Poulin P, and Theil F-P (2009) Development of a novel method for predicting human volume of distribution at steady-state of basic drugs and comparative assessment with existing methods. *J Pharm Sci* **98**:4941–61.
- Prieto Garcia L, Lundahl A, Ahlström C, Vildhede A, Lennernäs H, and Sjögren E (2022) Does the choice of applied physiologically-based pharmacokinetics platform matter? A case study on simvastatin disposition and drug–drug interaction. *CPT Pharmacometrics Syst Pharmacol* **11**:1194–1209.
- Rajput AJ, Aldibani HKA, and Rostami-Hodjegan A (2023) In-depth analysis of patterns in selection of different physiologically based pharmacokinetic modeling tools: Part I - Applications and rationale behind the use of open source-code software. *Biopharm Drug Dispos* **44**:274–285.
- Riedmaier AE, DeMent K, Huckle J, Bransford P, Stillhart C, Lloyd R, Alluri R, Basu S, Chen Y, Dhamankar V, Dodd S, Kulkarni P, Olivares-Morales A, Peng C-C, Pepin X, Ren X, Tran T, Tistaert C, Heimbach T, Kesisoglou F, Wagner C, and Parrott N (2020) Use of

- Physiologically Based Pharmacokinetic (PBPK) Modeling for Predicting Drug-Food Interactions: an Industry Perspective. *AAPS J* **22**:123.
- Rodgers T, Jones HM, and Rowland M (2012) Tissue lipids and drug distribution: dog versus rat. *J Pharm Sci* **101**:4615–26.
- Rodgers T, Leahy D, and Rowland M (2005) Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci* **94**:1259–76.
- Rodgers T, and Rowland M (2006) Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J Pharm Sci* **95**:1238–1257.
- Sager JE, Yu J, Ragueneau-Majlessi I, and Isoherranen N (2015) Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification. *Drug Metabolism and Disposition* **43**:1823–1837.
- Scotcher D, Jones C, Posada M, Galetin A, and Rostami-Hodjegan A (2016) Key to Opening Kidney for In Vitro-In Vivo Extrapolation Entrance in Health and Disease: Part II: Mechanistic Models and In Vitro-In Vivo Extrapolation. *AAPS J* **18**:1082–1094.
- Scotcher D, Jones C, Posada M, Rostami-Hodjegan A, and Galetin A (2016) Key to Opening Kidney for In Vitro-In Vivo Extrapolation Entrance in Health and Disease: Part I: In Vitro Systems and Physiological Data. *AAPS J* **18**:1067–1081.
- Scotcher D, Jones C, Rostami-Hodjegan A, and Galetin A (2016) Novel minimal physiologically-based model for the prediction of passive tubular reabsorption and renal excretion clearance. *European Journal of Pharmaceutical Sciences* **94**:59–71, Elsevier B.V.
- Shebley M, Sandhu P, Emami Riedmaier A, Jamei M, Narayanan R, Patel A, Peters SA, Reddy VP, Zheng M, de Zwart L, Beneton M, Bouzom F, Chen J, Chen Y, Cleary Y, Collins C, Dickinson GL, Djebli N, Einolf HJ, Gardner I, Huth F, Kazmi F, Khalil F, Lin J, Odinecs A, Patel C, Rong H, Schuck E, Sharma P, Wu S-P, Xu Y, Yamazaki S, Yoshida K, and Rowland M (2018) Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective. *Clin Pharmacol Ther* **104**:88–110.

- Shum S, Shen DD, and Isoherranen N (2021) Predicting Maternal-Fetal Disposition of Fentanyl Following Intravenous and Epidural Administration Using Physiologically Based Pharmacokinetic Modeling. *Drug Metabolism and Disposition* **49**:1003–1015.
- Sjögren E, Thörn H, and Tannergren C (2016) *In Silico* Modeling of Gastrointestinal Drug Absorption: Predictive Performance of Three Physiologically Based Absorption Models. *Mol Pharm* **13**:1763–1778.
- Takita H, Scotcher D, Chinnadurai R, Kalra PA, and Galetin A (2020) Physiologically-Based Pharmacokinetic Modelling of Creatinine-Drug Interactions in the Chronic Kidney Disease Population. *CPT Pharmacometrics Syst Pharmacol* **9**:695–706.
- Tan SPF, Willemin M-E, Snoeys J, Shen H, Rostami-Hodjegan A, Scotcher D, and Galetin A (2023) Development of 4-Pyridoxic Acid PBPK Model to Support Biomarker-Informed Evaluation of OAT1/3 Inhibition and Effect of Chronic Kidney Disease. *Clin Pharmacol Ther* **114**:1243–1253.
- Tistaert C, Heimbach T, Xia B, Parrott N, Samant TS, and Kesisoglou F (2019) Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies. *J Pharm Sci* **108**:592–602.
- Utsey K, Gastonguay MS, Russell S, Freling R, Riggs MM, and Elmokadem A (2020) Quantification of the Impact of Partition Coefficient Prediction Methods on Physiologically Based Pharmacokinetic Model Output Using a Standardized Tissue Composition. *Drug Metab Dispos* **48**:903–916.
- Wagner Christian, Pan Y, and Hsu V (2015) Predicting the Effect of Cytochrome P450 Inhibitors on Substrate Drugs : Analysis of Physiologically Based Pharmacokinetic Modeling Submissions to the US Food and Drug Administration. 117–127.
- Wagner Christian, Pan Y, Hsu V, Sinha V, and Zhao P (2015) Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic ( PBPK ) Modeling : An Analysis of PBPK Submissions to the US. *Clin Pharmacokinet* **450**, Springer International Publishing.
- Wagner C, Zhao P, Pan Y, Hsu V, Grillo J, Huang SM, and Sinha V (2015) Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK. *CPT Pharmacometrics Syst Pharmacol* **4**:226–30.

- Wang Z, and Chan ECY (2022a) Physiologically-Based Pharmacokinetic Modeling-Guided Dose Management of Oral Anticoagulants when Initiating Nirmatrelvir/Ritonavir (Paxlovid) for COVID-19 Treatment. *Clin Pharmacol Ther* **112**:803–807.
- Wang Z, and Chan ECY (2022b) Physiologically-Based Pharmacokinetic Modelling to Investigate Baricitinib and Tofacitinib Dosing Recommendations for COVID-19 in Geriatrics. *Clin Pharmacol Ther* **112**:291–296.
- Watanabe A, Ishizuka T, Yamada M, Igawa Y, Shimizu T, and Ishizuka H (2022) Physiologically based pharmacokinetic modelling to predict the clinical effect of CYP3A inhibitors/inducers on esaxerenone pharmacokinetics in healthy subjects and subjects with hepatic impairment. *Eur J Clin Pharmacol* **78**:65–73.
- Watanabe T, Kusuhara H, Maeda K, Shitara Y, and Sugiyama Y (2009) Physiologically based pharmacokinetic modeling to predict transporter-mediated clearance and distribution of pravastatin in humans. *J Pharmacol Exp Ther* **328**:652–62.
- Willmann S, Schmitt W, Keldenich J, Lippert J, and Dressman JB (2004) A physiological model for the estimation of the fraction dose absorbed in humans. *J Med Chem* **47**:4022–31.
- Wu C, Liu H, Yu S, Ren C, Zhang J, Wang G, Li B, and Liu Y (2022) Prediction of pharmacokinetics and pharmacodynamics of trelagliptin and omarigliptin in healthy humans and in patients with renal impairment using physiologically based pharmacokinetic combined DPP-4 occupancy modeling. *Biomed Pharmacother* **153**:113509.
- Wu D, and Li M (2023) Current State and Challenges of Physiologically Based Biopharmaceutics Modeling (PBBM) in Oral Drug Product Development. *Pharm Res* **40**:321–336.
- Wu X, Zhang X, Xu R, Shaik IH, and Venkataramanan R (2022) Physiologically based pharmacokinetic modelling of treprostinil after intravenous injection and extended-release oral tablet administration in healthy volunteers: An extrapolation to other patient populations including patients with hepatic impairment. *Br J Clin Pharmacol* **88**:587–599.
- Xu L, Yu S, Liu H, Yi B, Wang G, and Liu Y (2022) Physiologically based pharmacokinetic combined BTK occupancy modeling for optimal dosing regimen prediction of acalabrutinib in patients alone, with different CYP3A4 variants, co-administered with CYP3A4 modulators and with hepatic impairment. *Eur J Clin Pharmacol* **78**:1435–1446.

- Xu Y, Chen J, Ruan Z, Jiang B, Yang D, Hu Y, and Lou H (2022) Simulation of febuxostat pharmacokinetics in healthy subjects and patients with impaired kidney function using physiologically based pharmacokinetic modeling. *Biopharm Drug Dispos* **43**:140–151.
- Yabut KCB, and Isoherranen N (2023) Impact of Intracellular Lipid Binding Proteins on Endogenous and Xenobiotic Ligand Metabolism and Disposition, NLM (Medline).
- Yu LX, and Amidon GL (1999) A compartmental absorption and transit model for estimating oral drug absorption. *Int J Pharm* **186**:119–25.
- Zhang X, Yang Y, Grimstein M, Fan J, Grillo JA, Huang S-M, Zhu H, and Wang Y (2020) Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology. *J Clin Pharmacol* **60 Suppl 1**:S160–S178.
- Zhang Z, Imperial MZ, Patilea-Vrana GI, Wedagedera J, Gaohua L, and Unadkat JD (2017) Development of a Novel Maternal-Fetal Physiologically Based Pharmacokinetic Model I: Insights into Factors that Determine Fetal Drug Exposure through Simulations and Sensitivity Analyses. *Drug Metabolism and Disposition* **45**:920–938.
- Zhang Z, and Unadkat JD (2017) Development of a Novel Maternal-Fetal Physiologically Based Pharmacokinetic Model II: Verification of the model for passive placental permeability drugs. *Drug Metabolism and Disposition* **45**:939–946.
- Zhao H, Wei Y, He K, Zhao X, Mu H, and Wen Q (2022) Prediction of janagliflozin pharmacokinetics in type 2 diabetes mellitus patients with liver cirrhosis or renal impairment using a physiologically based pharmacokinetic model. *Eur J Pharm Sci* **179**:106298.
- Zhao P, Zhang L, Grillo JA, Liu Q, Bullock JM, Moon YJ, Song P, Brar SS, Madabushi R, Wu TC, Booth BP, Rahman NA, Reynolds KS, Gil Berglund E, Lesko LJ, and Huang S-M (2011) Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther* **89**:259–67.
- Zou P, Zheng N, Yang Y, Yu LX, and Sun D (2012) Prediction of volume of distribution at steady state in humans: comparison of different approaches. *Expert Opin Drug Metab Toxicol* **8**:855–72.

## Footnotes

The author has no actual or perceived conflict of interest with the contents of this article. This work was supported in part by a grant from the National Institutes of Health [Grant P01 DA032507].

## Figure captions

**Figure 1:** Representative structures of a full body PBPK model (A) and a simplified lumped compartment PBPK model (B).

**Figure 2:** Number of publications reported with PBPK modeling found in PubMed searches for the time window from 2015 to 2022. The total number of PBPK papers is shown as bar chart and the numbers of PBPK papers for select specific applications (drug-drug interactions, pediatrics, pharmacogenetics, pregnancy, and organ impairment) are shown in individual panels. The year a publication is listed is based on when the manuscript first appeared in PubMed (if ahead of print).

**Tables**

Table 1. Summary of PBPK models published in 2022 for organ impairment applications. N/A not available

Drug	Application	Model structure	CL prediction	V prediction	Population description	Verification/validation	Acceptance criterion	Software	PMID
Acalabrutinib and metabolite ACP-5862	BTK occupancy PD (PBPK-BO)	Full PBPK	Bottom up	Rodgers & Rowland	Healthy, HI	Independent studies, DDI	Fold error	PK-Sim	(L Xu <i>et al.</i> , 2022)
Alprazolam, sirolimus, nifedipine, midazolam, felodipine, buspirone, ibrutinib	Hepatic impairment and CYP3A4 activity	Minimal and full PBPK	SimCYP library files with adjustment	SimCYP library files with adjustment	Matched to observed, HI	SimCYP library files with adjustment, iv and po data	2-fold for PK parameters	SimCYP	(Ladumor <i>et al.</i> , 2023)
Baricitinib, Tofacitinib	Covid19, geriatric, RI	Minimal PBPK	Published models, SimCYP library	Published models, SimCYP library	Similar to observed	Previous studies, multiple populations	1.84-fold AUCR	SimCYP	(Wang and Chan, 2022b)
Bexarotene	Prospective prediction of PK in AKI and different stages of CKD	Full PBPK	Middle out, scaling and in vivo PK	Scaled to humans from rats	Demographics consistent with observed data, cancer population	Sensitivity analysis,	AFE within 2 or 3 fold, 95% predictive intervals	PK-Sim	(Alsmadi and Alzughoul, 2023)
Ciprofloxacin, furosemide, meropenem, acyclovir	OAT expression in CKD	Full PBPK	Bottom up (OATs, MATE, MRP, CYP, UGT)	Rodgers & Rowland	Healthy RI	Independent studies, DDI	AFE 07-1,3, AAFE <2, 85-95% of observed within 90 <sup>th</sup> pred interval	PK-Sim	(Dubinsky <i>et al.</i> , 2022)
Dorzagliatin	Prospective prediction of RI	N/A	IVIVE	Allometric scaling	Healthy, T2DM	Independent studies, DDI	N/A	SimCYP	(Miao <i>et al.</i> , 2022)
Esaxerenone	Hepatic impairment	Minimal PBPK	In vivo PK	In vivo	Matched to clinical	Independent studies, DDI	DDI ratio	SimCYP	(Watanabe <i>et al.</i> , 2022)
Febuxostat	Renal impairment	Full PBPK	In vivo	Rodgers-Single	Healthy, gout patients	Independent studies, gout patients	% error	GastroPlus	(Y Xu <i>et al.</i> , 2022)
Janaglifozin	Renal impairment, Hepatic impair	Full PBPK	PBPK from rat and dog and enzyme	PBPK from rat and dog	Similar to observed, renal and hepatic impairment	Healthy individuals, T2DM HI and RI studies	2-fold for fold change	GastroPlus	(Zhao <i>et al.</i> , 2022)



	ment		levels in humans						
Remdesivir and metabolites	Predict hepatic and renal impairment, tissue PK of remdesivir	Full PBPK	Middle out	Rodgers and Rowland	Similar to observed	Compared to healthy	N/A	PK-Sim	(Fan <i>et al.</i> , 2022)
Rivaroxaban or Warfarin with ritonavir	Disease-drug interaction, PD (INR)	Minimal PBPK	Library	Library	Prospective healthy, white Geriatric CKD, moderate impairment	Independent validation for alternate substrate and dosing	0.67-1.5 0.7-1.43	SimCYP	(Wang and Chan, 2022a)
Tacrolimus	Renal and hepatic impairment	Minimal PBPK	Bottom-up with ISEF	In vivo data	CYP3A5 genotyped similar populations	Genotyped studies, healthy	N/A	SimCYP	(Itohara <i>et al.</i> , 2022)
Trelagliptin Oarigliptin	DPP4 occupancy, RI	Full PBPK	GFR	Rodgers and Rowland, $K_p$ scale	Japanese, European	Independent studies	AAFE 2-fold	PK-Sim-MoBi	(C Wu <i>et al.</i> , 2022)
Treprostinil	Extended release in Hepatic impairment	Full PBPK	In vivo, top down retrograde	Rodgers and Rowland, In vivo	Matched to clinical	Independent studies (iv, po)	% error <50%	SimCYP	(X Wu <i>et al.</i> , 2022)

Table 2. Summary of PBPK models published in 2022 for simulating drug disposition during pregnancy

Drug	Application	Model structure	CL prediction	V prediction	Population description	Verification/validation	Acceptance criterion	Software	PMID
Cefazolin, Cefuroxime, Amoxicillin	Maternal-fetal concentrations. PK in pregnancy, placental and fetal exposure	fullPBPK with fetoplacental model	Mechanistic kidney model	Full PBPK model, Rodgers and Rowland method for Kp	Pregnant and nonpregnant matched demographics or default	Prior models and data for nonpregnant. Multiple studies and populations	N/A	Simcyp	(Abduljali, Ning, <i>et al.</i> , 2022)
Acyclovir, Emtricitabine, Lamivudine, Metformin	Maternal-fetal concentrations. PK in pregnancy, placental and fetal exposure	fullPBPK with fetoplacental model	Mechanistic kidney model	Full PBPK model, Rodgers and Rowland method for Kp with scaling	N/A	Prior models for nonpregnant used except lamivudine. Predicted compared to observed	observed within the 95th and 5th percentiles of predicted; predicted within twofold of the observed	Simcyp	(Abduljali, Pansari, <i>et al.</i> , 2022)
Ampicillin	Fetal and neonatal ampicillin concentrations for Streptococcus infection treatment	fullPBPK with fetoplacental model	Top down (retrograde) for liver and biliary Mechanistic kidney model for CLr	Full PBPK model, Rodgers and Rowland method for Kp	Matched to observed	FDA guidance workflow for healthy adults and pediatrics	Observed within 90% prediction interval of the simulated curve. Two-fold criterion for aggregate data	Simcyp	(Li and Xie, 2023)
Ritonavir boosted lopinavir, chloroquine, ivermectin	Population drug-drug interactions for COVID including special populations	fullPBPK	Previously published and middle out, enzyme kinetics	Additional protein binding prediction for special populations. Poulin and Theil or Rodgers and Rowland prediction of Kp	Similar to observed, 1:1 male to female. The original PK-Sim pregnancy population was customized to include enzyme changes	Historical PPK data in nonpregnant populations	At least 85% of the observed data within the 90% predictive interval, Sensitivity analysis	PK-Sim	(Alsmadi, 2023)
Doravirine	Predict maternal and fetal	Full PBPK	Previously developed	Optimized from prior model.	Nonpregnant individuals	Independent data following iv and po	predicted/observed ratios for	Simcyp	(Bukkems <i>et al.</i> , 2022)

	exposure			Placental perfusion studies for fetal distribution		dosing to nonpregnant individuals	AUC, $C_{max}$ , and $C_{trough}$ between 0.7 and 1.3		
General (859 chemicals with human toxicokinetic data)	Predict fetal exposure for toxicokinetics	7 maternal and fetals tissue and placenta	From prior work	Measured partition coefficient when available. Prior models	N/A	Maternal-to-fetal plasma ratio at birth	N/A	R	(Kupraun <i>et al.</i> , 2022)
Remdesivir and its GS-704277 and GS-441524 metabolites	Translate prior nonpregnant model to pregnancy	Full PBPK with adjustments for enzymes and GFR	From prior model	From prior non-pregnant model	Matched to observed	Previously published nonpregnant model, observed data in pregnancy	AUC, $C_{max}$ and $C_{24}$ within 2-fold	PK-Sim with MoBi	(Liu <i>et al.</i> , 2023)
Ceftazidime, cefuroxime, metformin, oseltamivir, amoxicillin	Assessment of PBPK for renally cleared drugs during pregnancy	Full PBPK. With ADAM or ACAT	From prior models available in software libraries	From prior models available in software libraries	Matched to observed	Independent nonpregnant iv and po data, pregnant population; visual comparison	N/A	Gastroplus, Simcyp, PKSim	(Coppola <i>et al.</i> , 2022)
P-gp and BCRP transported drugs, nelfinavir, efavirenz, imatinib	Fetal-to-maternal unbound steady state plasma concentration ratio	Full PBPK, ADAM model for absorption (N)	Middle out back calculated CYP mediate clearance (N)	Full PBPK with $K_p$ predicted using Poulin and Theil method (N)	Similar to observed	Independently validated in nonpregnant subjects. Iv and po dosing data. Efavirenz and imatinib previously developed and validated for nonpregnant	Observed PK profile was within the 5 <sup>th</sup> and 95 <sup>th</sup> percentile of predicted and simulated data was within 0.8-1.25 of observed	Simcyp	(Peng <i>et al.</i> , 2022)
Valproic acid	Predict developmental toxicity of valproic acid	Full PBPK	Bottom up, IVIVE	From literature	N/A	Simulated concentrations compared to toxicologically relevant concentrations	N/A	R, Gastroplus	(Chang <i>et al.</i> , 2022)

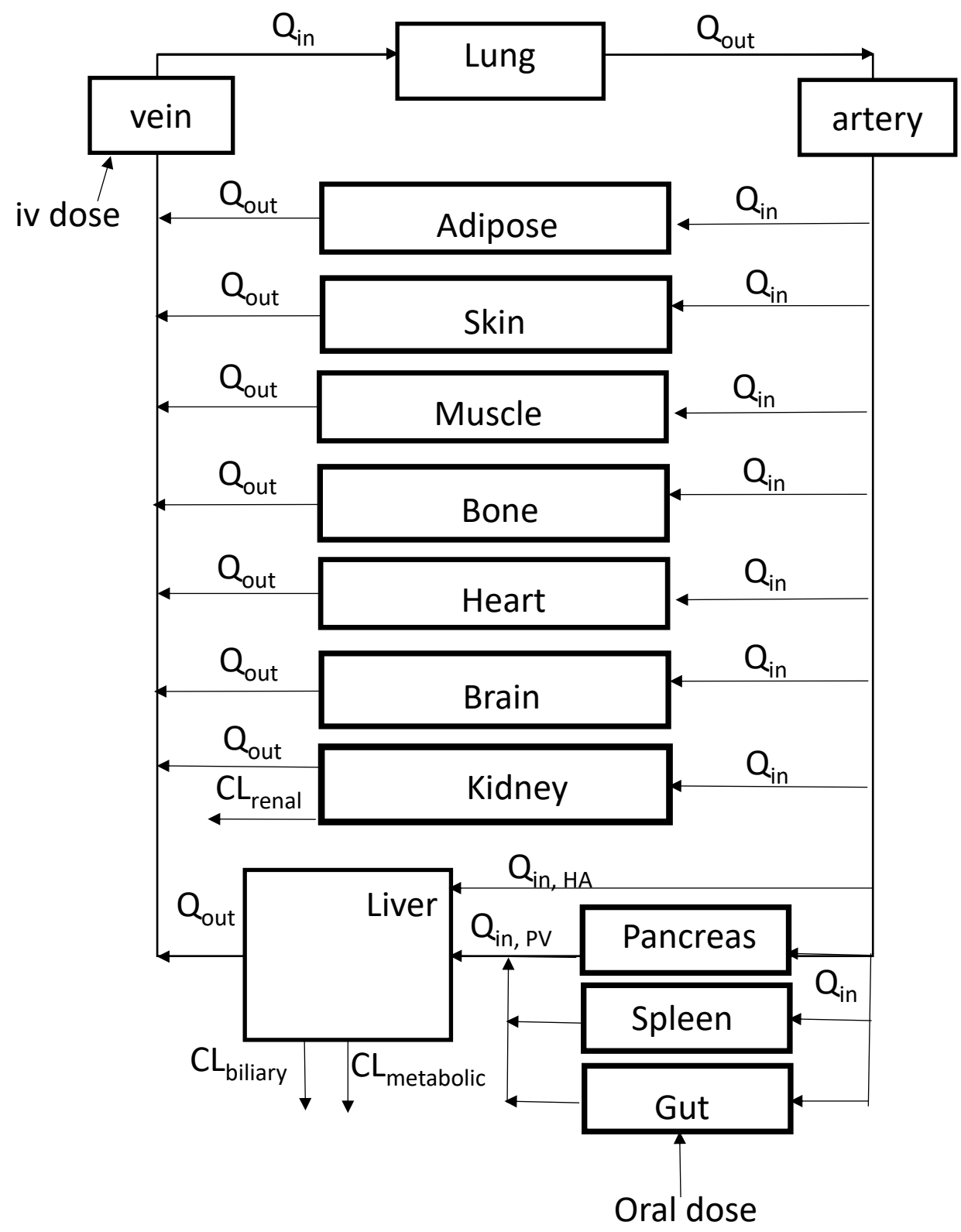
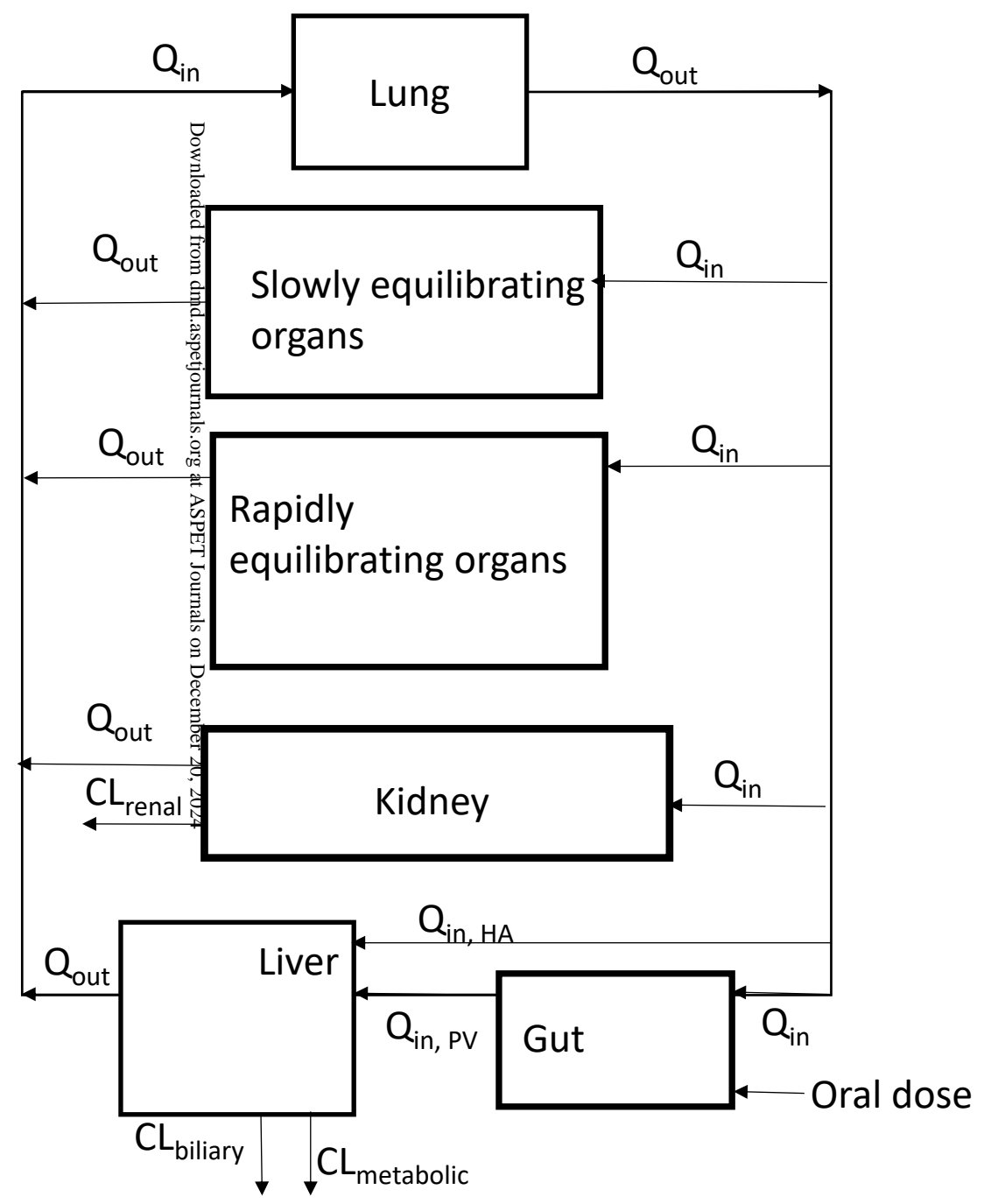
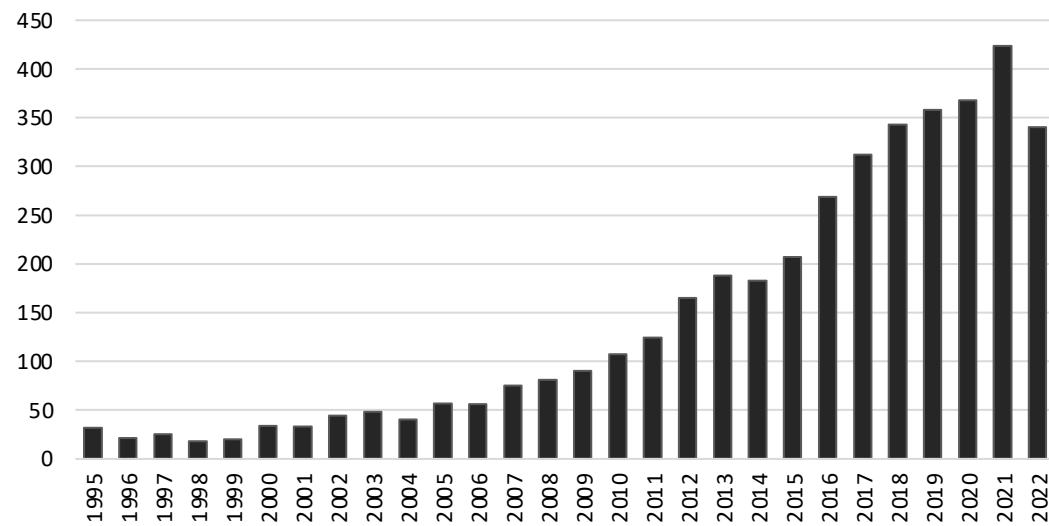
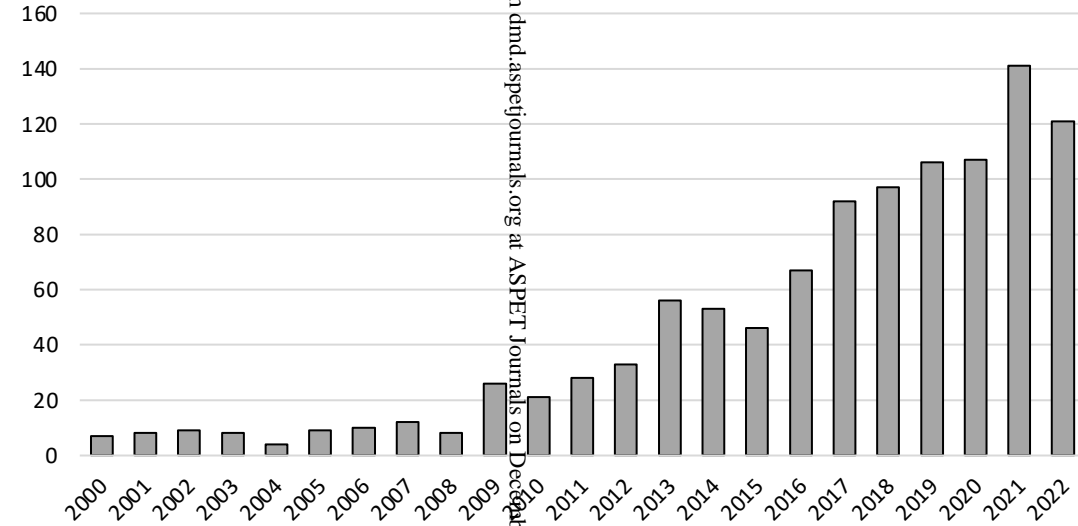
**A.****B.**

Figure 1

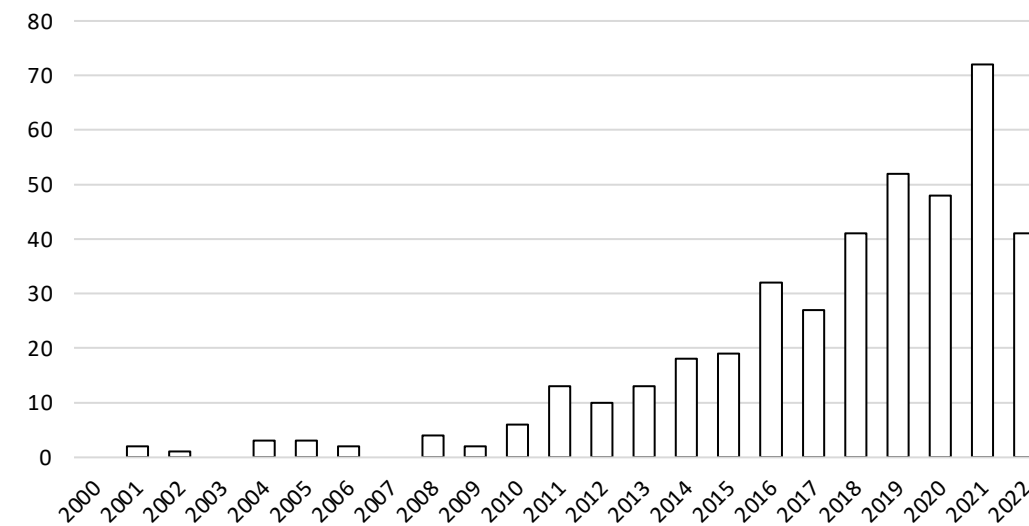
All PBPK publications



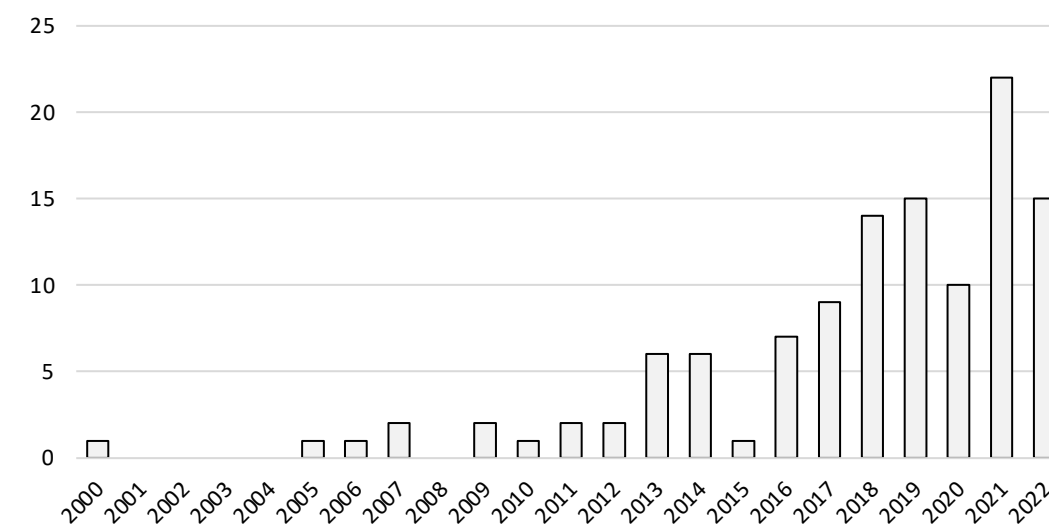
Drug Interactions



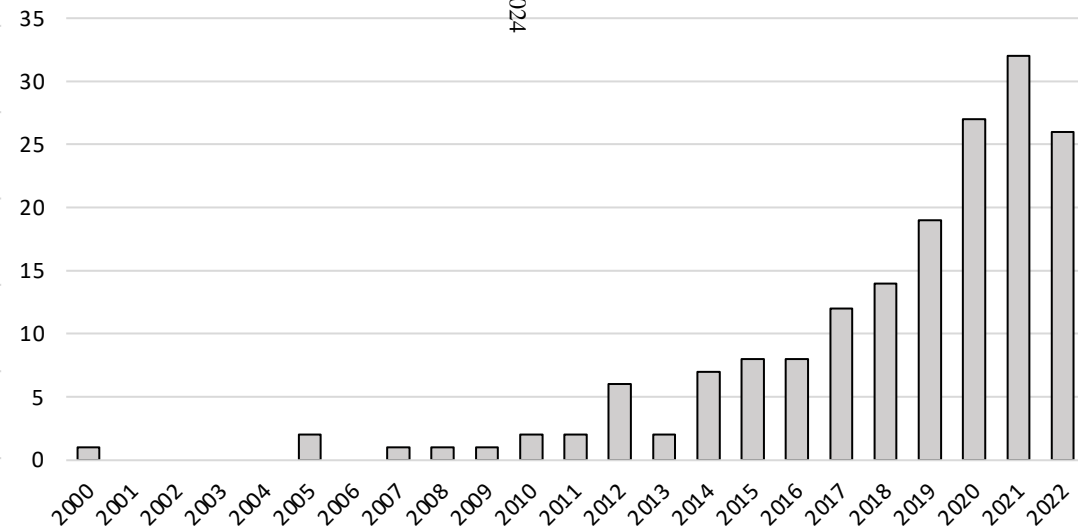
Pediatrics



Pharmacogenetics



Organ Impairment



Pregnancy

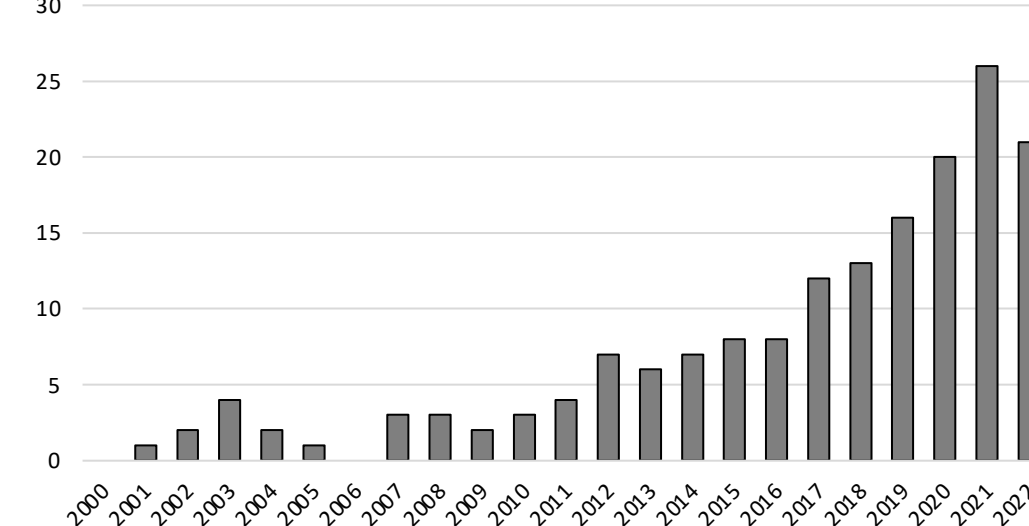


Figure 2