Review Article

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2025; 12(2):1692-1702

UDC: 615.015.4

doi:10.5937/hpimj2502692T

Physiologically Based Pharmacokinetic and Toxicokinetic Modeling: A Multidisciplinary Approach to Drug Development and Ecotoxicology

Nemanja B. Todorović[1], Aleksandra D. Ćoškov[1], Nebojša Lj. Andrić[2], Bojana Đ. Stanić[2], Boris Ž. Milijašević[3], Nataša P. Milošević[1], Slobodan M. Janković[4,5], Mladena N. Lalić-Popović[1,6]

[1] Department of Pharmacy, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia
[2] Department of Biology and Ecology, Faculty of Sciences, University of Novi Sad, Novi Sad, Serbia
[3] Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia
[4] University Clinical Center Kragujevac, Kragujevac, Serbia
[5] Faculty of medical Sciences, University of Kragujevac, Kragujevac, Serbia
[6] Centre for Medical and Pharmaceutical Investigations and Quality Control (CEMPhIC), Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia

SUMMARY

Introduction: Physiologically based pharmacokinetic (PBPK) modeling is a powerful tool in pharmaceutical research and drug development, offering accurate predictions of drug absorption, distribution, metabolism, and elimination (ADME). This method, when extended to xenobiotics, enables the study of toxins and other substances through physiologically based toxicokinetic (PBPT) models.

Methodology: This narrative review outlines recent applications of PBPK and PBTK modeling in drug development and ecotoxicology, based on literature retrieved from PubMed, Scopus, and Web of Science.

Topic: By incorporating physiological and biochemical data, PBPK models provide more precise simulations that closely resemble *in vivo* conditions. Advances in technology have improved the feasibility of these models, making them increasingly valuable for predicting drug behavior, as well as for cross-species and route-of-administration extrapolation. The mechanistic nature supports regulatory decision-making and reduces the need for extensive *in vivo* testing. Furthermore, PBPK models are instrumental in special population assessments, such as pediatrics or patients with organ impairment.

Conclusion: With continued integration of *in silico* tools and data obtained by other testing, PBPK modeling is poised to become a central platform in translational pharmacology and safety assessment. Regulatory agencies most commonly use PBPK models to support the assessment and prediction of drug-drug interactions.

Keywords: PBPK, PBTK, ADME, *In silico*, Risk Assessment, Xenobiotics, Environmental Toxicology

Corresponding author:
Full Professor Mladena Lalić-Popović, MPharm, PhD
Specialist in Pharmaceutical Technology
University of Novi Sad, Faculty of Medicine Novi Sad, Department of Pharmacy, Novi Sad, Serbia,
Hajduk Veljkova 3, 21000
E-mail: mladena.lalic-popovic@mf.uns.ac.rs

© The Serbian Medical Society 2014

INTRODUCTION

A broad spectrum of drug-related research methodologies is available today, ranging from experimental in vivo and in vitro studies to non-interventional designs such as pharmacoepidemiological and pharmacoeconomic analyses. These latter methods, which do not involve direct testing on animals or humans, can provide highly informative data on drug utilization, cost-effectiveness, and treatment outcomes in real-world settings. For example, pharmacoepidemiological assessments of chronic treatments like glaucoma therapy [1] exemplify how such methods guide clinical and policy decisions. Likewise, in silico methods such as physiologically based pharmacokinetic (PBPK) modeling provide valuable insights into drug performance by simulating absorption, distribution, metabolism, and excretion processes through computational frameworks. These approaches offer a mechanistic understanding that complements data from clinical, epidemiological, and preclinical research.

PBPK modeling is a mathematical modeling technique that has significant potential in pharmaceutical research and drug development. It enables the prediction of pharmacokinetic parameters - namely absorption, distribution, metabolism and elimination (ADME). The same principle can be applied to other xenobiotics, specifically to toxins within the context of physiologically based toxicokinetic (PBTK) modeling and simulations. This prediction seeks to consider all anatomical, physiological, biochemical, physical and chemical factors involved in ADME processes. By refining these techniques, models are produced that increasingly approximate the results observed in in vivo studies [2-4].

Modeling the fate of the drug/other xenobiotics within the body, considering all physiological characteristics, usually involves setting up multicompartment models in which individual compartments are actually models of different tissues and organs. The connections between them practically represent blood or lymph flows, and the concentrations (or quantities) in individual compartments are expressed by differential equations. The parameters of the system of differential equations are physiological parameters such as blood flow, lung ventilation, organ volumes, etc. A key challenge in this type of modeling lies in striking a balance between the inherent complexity of the investigated processes and the need for simplification, formulation and interpretation of the resulting outcomes derived from a system of differential equations. As technological advancements continue, this balance is becoming easier to achieve, allowing pharmacokinetic processes to be studied in ways that are more ethically and economically acceptable [2].

Therefore, in addition to its application in drug testing, this technique can be utilized to predict the behavior of all xenobiotics entering the human body, including food, toxins, and cosmetics. Additionally, there are models that focus on predicting other drug characteristics such as toxicology or pharmacodynamics. While the primary advantage of PBPK modeling lies in predicting pharmacokinetic parameters of drugs in humans, also enables cross-species extrapolation and translation between different routes of administration (e.g., from inhalation to oral) [4].

METHODOLOGY

This narrative review summarizes recent advances in the application of PBPK and PBTK modeling in drug development and ecotoxicology. Relevant literature was identified through a computerized search of PubMed, Scopus, and Web of Science databases using keywords including PBPK, PBTK, pharmacokinetics, toxicokinetics, drug development, and environmental risk assessment. Only articles in English, including original research and review papers, were included.

TOPIC

Elements of the pharmacokinetic/toxicokinetic model

A multidisciplinary approach integrates knowledge from various scientific disciplines, enabling an understanding of complex phenomena and develop the innovative solutions [5]. PBPK models integrate two key data sets – pharmacological data and physiological system data (human or other species) to generate necessary information for simulation the pharmacokinetics of the investigated drug in a living organism. The simplest models typically account for clearance via the liver and kidneys. The gastrointestinal tract is typically the most

complex system to characterize and is often represented through two sub-compartments: the lumen (where the drug resides as unabsorbed) and the enterocytes (absorbed drug molecules). In addition, parameters affecting the pharmacokinetic properties of the drug in the gastrointestinal tract are tissue volume, surface area of the gastrointestinal tract, gastric emptying / intestinal transport, time, pH value of different parts and all of them can be considered by modern pharmacokinetic modeling approaches based on physiological characteristics of the organism [2-4]. As our understanding of drug properties and gastrointestinal physiology advances, the limitations of early PBPK models are increasingly being overcome. Many of these limitations are also shared by in vitro methods—such as the PAMPA (parallel artificial membrane permeability assay) system—especially when predicting drug absorption involving active transport mechanisms.

System-specific (i.e., species-dependent) parameters, such as tissue volume or blood flow are available in the literature and continiously updated. Other critical parameters include the glomerular filtration rate, the amount of microsomal proteins, plasma proteins, enzymes, the number and type of transporters. Beyond simply defining the parameters of interest, it is important to consider the natural existence of their variability within the same species. This is particularly important when modeling special populations, such as healthy adults of different ethnic backgrounds (e.g., American, Chinese, Japanese), as well as individuals with hepatic or renal impairment, smokers, children, the elderly, pregnant women, obese individuals, and cancer patients [4].

Modeling strategies and their application

There are two basic approaches in pharmacokinetic / toxicokinetic modeling: the traditional top-down and the modern bottom-up approach, which implies the application of knowledge about the molecular structure and mechanisms of the organism in modeling the fate of the tested xenobiotic. Practically, in the ideal case, the second approach allows setting up the chemical structure of the xenobiotic, such that it satisfies all the required parameters. Successful application of this approach relies heavily on the precision of input data, which are typically derived from prior **in silico** and **in vitro** experiments. Accurate and reliable input is essential to achieving the highest possible concordance between predicted and observed pharmacokinetic or toxicokinetic values [2-4].

Regardless of the extent of available information that exists about a drug molecule, PBPK can be applied at all stages of drug testing, from early molecular development to the final stages of clinical drug trials. When it comes to application in preclinical research, this modeling finds a place in the prediction of animal or human pharmacokinetics, projection of dose efficiency and oral absorption. Well-developed models also provide opportunities for formulation design proposals and biopharmaceutical properties, while respecting the 3R principle (reduction, refinement and replacement of animal models) [4].

PBPK modeling of modified-release formulations

It is well recognized that the pharmacokinetic profile of a drug is significantly affected by its formulation characteristics [6,7]. Modified-release dosage forms are specifically designed to control both the timing and rate of active pharmaceutical ingredient (API) release. Modifying the release of active ingredients offers several therapeutic advantages, such as minimizing adverse drug reactions and reducing the frequency of administration. These formulations are particularly beneficial in the management of chronic diseases. The development of pharmaceutical formulations with modified release is more complex compared to conventional dosage forms, making the availability of various methods particularly important [8].

PBPK modeling has been successfully applied in the formulation development of various drugs, including: ropinirole [9], tofacitinib [10], sildenafil [11], hydrocortisone [12] etc. The goal of modified release modeling is to change the characteristics of the pharmaceutical form of the drug with immediate release in such a way as to reduce the difference between the maximum and the minimum of the function that describes the pharmacokinetics of the active pharmaceutical ingredient. Although absorption is a critical step in the development of modified-release formulations, all aspects of PBPK modeling can be applied.

One illustrative example from the lit-

erature involves the use of PBPK modeling to identify drug- and formulation-related factors influencing bioequivalence. Basu *et al.* developed and qualified PBPK model for modified--release metoprolol formulations [13]. Metoprolol, a commonly used beta-blocker for hypertension and heart failure, was selected due to its good solubility and permeability (BCS Class I), so these characteristics are not a limiting factor for dissolution and consequently bioequivalence. For drugs belonging to BCS I class, formulation factors dominantly affect the processes that are important for achieving bioequivalence. Dissolution profiles of bioequivalent test and reference metoprolol formulations in doses of 50 mg and 200 mg were analyzed. Authors stated release-controlling polymer as a critical factor for achieving adequate dissolution, absorption and pharmacokinetics.

According to another research, PBPK model was developed and used to determinate key factors influencing the absorption of furosemide from immediate release (IR) and modified-release (MR) formulations as well as to simulate and predict plasma concentrations of this component [14]. Furosemide, a potent loop diuretic, belongs to BCS Class IV, due to its low permeability and solubility [14-16]. In the case of MR formulations, few studies have applied PBPK modeling to identify key factors influencing the plasma concentration profile – such as release characteristics, gastrointestinal tract route, and drug permeability – and whether they could be exploited in formulation optimization [14]. Researchers have found that unit size of MR furosemide formulations can influence gastric emptying rates in the fasted state, and additionally, the model suggested that the release rate in the small intestine, alongside with gastric emptying and intestinal absorption rates, are key determinants of furosemide absorption from MR capsules.

PBPK in population simulation

Pharmacokinetics can vary significantly across different populations. Some contributing factors include gender, body mass index (BMI), polypharmacy, hypertension, diabetes, pregnancy, or combinations of these factors [17-19]. Therefore, identifying appropriate methods capable of efficiently assessing pharmacokinetic variability without the need to include a large number of population subgroups is of great importance. Recent advances in scientific research have extended the use of PBPK modeling into clinical trial design, particularly for populations with limited available data, such as pediatrics [4,20-27], pregnant women [27-31], and the elderly [32-35]. In addition, this type of modeling can also be used to predict the pharmacokinetics of a drug in the individuals with impaired organ function (e.g. liver, kidney), as well as obese populations [33,34,36,37]. Considering the physiological changes that occur during disease progression, commercially available PBPK modeling platforms are capable of distinguishing between various disease types and stages. For example, they enable simulations of pharmacokinetics in conditions such as the three stages of liver cirrhosis, simple steatosis, nonalcoholic steatohepatitis (NASH), and four levels of renal impairment, among others. There are also studies that include models on diabetic patients [22,39,40]. Moreover, certain models offer the prediction of drug properties across diverse ethnic groups, including European, Chinese, Japanese, who may exhibit physiological differences that influence the ADME characteristics of the active substance [4,32,41,42].

An example of PBPK modeling for cross-population translation can be seen with the CYP substrate montelukast. The model was developed using basic physicochemical parameters, preclinical data and clinical data obtained from intravenous and oral administration of the drug to the adult population. This model was then used to predict pharmacokinetics in various pediatric subgroups by accounting for anatomical and physiological differences between adults and children. One key parameter was the absorbed fraction of the dose, which ranged from 0.25 in the youngest examined group (one month to two years old) to between 0.7 and 0.9 in children older than two years [4].

A new study from 2025 indicated that PBPK modeling, alongside virtual clinical approach, can be used to assess how obesity affects imatinib pharmacokinetics in cancer patients and to evaluate the effectiveness of TDM-guided dose adjustments in optimizing drug exposure [43]. Research so far shows that imatinib, a drug used to treat myeloid leukemia, is less effective when used in obese people. Using clinical data from lean, overweight, and obese cancer patients, scien-

tists validated the PBKP model. This analysis revealed significant physiological differences among the selected populations (liver weight, enzyme activity, cardiac output, and hematocrit) which contributed to variations in therapeutic response. It is shown that obese patients have much lower maxmimum concentration Cmax and area-under-the-curve (AUC) values of imatinib. As a result from this research, it is evident that PBPK modeling can be used to optimize dosing strategies for imatinib in obese cancer patients, supporting more precise and individualized treatment approaches in oncology.

PBPK and PBTK in ecotoxicology

In addition to investigating drug behavior and prediction within the human body, there is growing interest in studying environmental toxins. This is particularly important given the increasing exposure to complex mixtures of chemicals through food, water, air, and consumer products. Understanding the toxicokinetic profiles of these substances is crucial for risk assessment, public health protection, and the development of regulatory guidelines [44-46]. Since the mid-20th century, ecotoxicology, as a multidisciplinary science, has studied the impact of various chemicals on both organisms and the environment, with the goal of protecting the health and integrity of ecosystems [47,48]. As previously mentioned, by using the PBPK and PBTK models, through understanding and connecting sciences such as physiology, anatomy and biochemistry, it is possible to successfully predict the behavior of xenobiotics in organisms, as well as their concentration in physiologically inaccessible compartments. The use of **PBTK models** has significantly increased in the context of **toxicological research** and risk assessment [49]. This significantly minimizes costs, time, and the use of animals to obtain experimental results [49,50]. In addition, by combining PBTK models with other methods, such as toxicodynamics (TD), certain toxic effects of the contaminant itself, such as mortality, can be predicted [51]. Numerous **PBTK models** have already been developed for a wide range of species, including fish, birds, and mammals [49-55]. On the other hand, the existence of a large number of animal species, along with their morphological and physiological differences, can make the application of these models challenging, as it requires special parameterization, and often extrapolation between species, especially when it comes to endangered or focal ones [56-60]. Also, toxicity tests are often conducted using standard laboratory species rather than the focal species, yet the same dose can cause markedly different effects across species [59].

Among aquatic species, zebrafish (Danio rerio) are widely used in ecotoxicological studies due to their rapid development, small size, and cost-effectiveness [51,61,62]. An example of such a study, the PBTK-TD model was used to simulate the uptake and distribution of cadmium and lead in the organs of zebrafish (brain, liver, blood, gills, intestines, reproductive organs, carcass) [51]. The study showed that the developed PBTK-TD model accurately predicted the uptake, distribution, and toxicity of cadmium and lead in zebrafish, but also that accumulation and toxicity differed from organ to organ, with the greatest accumulation of cadmium in the liver, while the greatest accumulation of lead in the gills.

Another study, involving zebrafish, specifically their eleutheroembryos, is based on the development of an appropriate PBPK model for the precise prediction of real-world exposure levels to endocrine disruptors, bisphenol A (BPA) and its analogues (BPAF, BPF and BPS) [62]. The model demonstrated strong predictive accuracy, thereby enhancing the reliability of toxicity assessments for these compounds in early developmental stages.

Addressing the previously mentioned challenge of limited models for many animal species, a team of scientists proposed a workflow to develop models tailored for new animal species [59]. The study conducted a cross-species sensitivity analysis to identify the most sensitive parameters in existing mammalian PBTK models. Starting with a validated rabbit model, the analysis was extended to six additional mammalian species. It is revealed that only a few parameters are sensitive in each model. Similarity across species were non-gastrointestinal parameters, while gastrointestinal (GIT) parameters exhibited increased variation. Furthermore, for the same substance, changes within a species were typically more noticeable than differences between species. The scientists believe that the proposed workflow will support the development of new models in the future.

Application of PBPK and PBTK in industry and recognition by regulatory bodies

Regulatory bodies increasingly recognize the importance of this approach in defining drug-drug interactions, assessing damage to individual organs and developing age-appropriate pharmaceutical forms of drugs intended for different pediatric populations. Physiologically based pharmacokinetic modeling and simulation have so far been recommended by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the Ministry of Health, Labour and Welfare of Japan (MHLW) primarily to assess the existence of drug-drug interactions [3,4,63]. The EMA has issued guidelines for the use of these methods for monitoring hepatotoxicity depending on the dose and duration of treatment with the investigational drug [64]. The FDA, in particular, supports the use of this methodology for development in pediatric populations [65]. Between 2008 and 2012, a total of 33 drug registration applications were submitted to the FDA that included data based on a physiologically based pharmacokinetic modeling approach. The largest part of that data (61%) was related to the evaluation of drug-drug interactions. An example of the mentioned interaction can be seen on the drug ibrutinib, where the interaction at the level of the CYP3A enzyme with a strong inhibitor - ketoconazole and an inducer - rifampicin was examined. Based on the data from this study, a special dosage was created for patients who, in addition to ibrutinib, need to use another drug that by its nature is an inhibitor or inducer of the CYP3A enzyme [66]. Ibrutinib is also approved by the Agency for Medicines and Medical Devices of Serbia (Serbian: *Agencija za lekove i medicinska sredstva Srbije*, ALIMS) and in its SmPC, chapter 4.5 (Interactions with other drugs and other types of interactions) states data based on the described simulations [67]. In parallel with PBPK modeling, physiologically based toxicokinetic (PBTK) modeling is gaining increased attention from regulatory agencies for its utility in predicting the ADME properties of environmental xenobiotics. Agencies are beginning to incorporate PBTK models into risk assessment procedures to enhance the efficiency of safety evaluations and improve strategies for protecting public and environmental health.

Limitations of PBPK/PBTK modeling

Although physiologically based pharmacokinetic (PBPK) and toxicokinetic (PBTK) modeling are increasingly recognized as valuable tools in drug research, development, and regulatory assessment, they remain relatively novel approacheswith several inherent challenges and limitations.

One of the main challenges is the shortage of qualified experts in the field. This gap is largely attributed to the **absence of formal education programs** that include PBPK/PBTK modeling in their curricula. Currently, short training courses and professional development programs are being offered by software companies. Such training is usually not available to undergraduate students, which delays both interest and progress in this field. Moreover, investment in scientific research related to PBPK/PBTK modeling is still considered insufficient. The shortage of highly trained personnel leads to difficulties in the review process of documentation submitted to regulatory agencies, as well as challenges in standardizing and reporting this type of scientific research [68].

Even when expertise is available, the development of PBPK models remains challenging due togaps or inconsistencies in both in vitro and in vivo data required for model development. This issue is particularly evident in the modeling of toxic compounds such as **bisphenols** or **perfluorooctanoic acid (PFOA)**, for which human concentration–time data are often unavailable. While **animal data** may be used for extrapolation, this approach carries the risk of **under- or overestimating internal exposure** in humans [68,69]. Even when a model is successfully validated in a general population, it is often not feasible to achieve the same level of validation for specific populations such as pregnant women, children, and patients with certain conditions, due to the lack of appropriate clinical studies. Modeling substances with complex chemical structures, such as proteins and nucleic acids, which are increasingly used in modern pharmacotherapy, remains a highly demanding task. Their physicochemical complexity often exceeds the current capabilities of standard PBPK modeling approaches, which are still in the early stages of development for such molecules [69].

Transferability is recognized as a critical need among researchers working in

the field of PBPK modeling, yet it remains largely unmet. Investigators often specialize in a single software tool, where data generated in one program may not be compatible or readable in another. It is important to emphasize that the investigation of xenobiotic behavior in the human body is primarily of professional interest to healthcare practitioners, who are not trained as programmers. For this reason, user-friendliness of PBPK modeling platforms is especially important, as complex or non-intuitive interfaces may hinder broader adoption and practical use in clinical and regulatory settings. Substantial efforts are needed to overcome this limitation in the future and to facilitate broader usability, particularly when it comes to the critical evaluation of published results [68]. On the other hand, due to insufficient development of programming skills, the full potential of in silico methods for the development of more mechanistically based models remains underutilized [69].

Given the inherent complexity of PBPK modeling, its development and application require active involvement of clinical practitioners, especially clinical pharmacologists, toxicologists, physiologists, pediatricians, and other specialists interested in drug pharmacokinetics and xenobiotic behavior in the human body. Pharmacists, responsible for dosage form development, extensively use PBPK models to simulate bioavailability and support formulation strategies. Furthermore, there is a growing need for the inclusion of regulatory scientists to guide and evaluate model applications within regulatory frameworks. Finally, computational scientists and modeling experts, whose skills in software use and mechanistic model building are indispensable for advancing and ensuring the reliability of the models, contribute significantly to model development. Thus, a multidisciplinary and collaborative approach among all these professionals is essential to fully realize PBPK/PBTK modeling potential.

CONCLUSION

This review examines the emerging role of PBPK/PBTK in areas such as modified-release drugs, population simulation, ecotoxicology implementations, as well as the regulatory aspect of its application. As modern science shifts towards reducing animal testing to the lowest possible level, minimizing costs and increasing the use of *in silico* methods for research purposes, it is anticipated that the application of PBPK and PBTK models will continue to rise and extend into additional scientific fields in the near future.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ACKNOWLEDGEMENT

This research was supported by the Science Fund of the Republic of Serbia, #7010, Integration of Biological Responses and PBTK Modeling in Chemical Toxicity Assessment: A Case Study of Perfluorooctanoic Acid (PFOA) – ToxIN.

REFERENCES

1. Ćoškov AD, Savanović DR, Todorović NB, Lalić-Popovic MN, Tomić NZ, Milijašević BŽ. Drug Consumption And Treatment Costs of The Glaucoma Therapy in The Republic of Serbia. Hosp. Pharmacol. Int. Multidiscip. J. 2024;11(3):1499-508.

2. Zhuang X, Lu C. PBPK modeling and simulation in drug research and development. Acta Pharm. Sin. B. 2016;6(5):430-40.

3. Jamei M. Recent advances in development and application of physiologically-based pharmacokinetic (PBPK) models: a transition from academic curiosity to regulatory acceptance. Curr. Pharmacol. Rep. 2016;2(3):161-9.

4. Tsamandouras N, Rostami-Hodjegan A, Aarons L. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. Br J Clin Pharmacol. 2015;79(1):48-55.

5. Janković SM, Nikolić LI, Marković SZ, Kastratović DA. Multidisciplinary teams in healthcare. Hosp. Pharmacol. Int. Multidiscip. 2024;11(1):1370-6.

6. Todorović N, Panić JČ, Pavlić B, Popović S, Ristić I, Rakić S, Rajšić I, Vukmirović S, Čonić BS, Milijašević B, Milošević N. Supercritical fluid technology as a strategy for nifedipine solid dispersions formulation: In vitro and in vivo evaluation. Int. J. Pharm. 2024;649:123634.

7. Lalic M, Pilipovic A, Golocorbin-Kon S, Gebauer-Bukurov K, Bozic K, Mikov M, Cvejic J. Comparison of dissolution profiles and serum concentrations of two Lamotrigine tablet formulations. Drugs in R D. 2011;11(1):53-60.

8. Subhani S, Kim C, Muniz P, Rodriguez M, van Os S, Suarez E, Cristofoletti R, Schmidt S, Vozmediano V. Application of physiologically based absorption and pharmacokinetic modeling in the development pro-

cess of oral modified release generic products. Eur. J. Pharm. Biopharm. 2022;176:87-94.

9. Shuklinova O, Dorożyński P, Kulinowski P, Polak S. Quality control dissolution data is biopredictive for a modified release ropinirole formulation: Virtual experiment with the use of re-developed and verified PBPK model. Pharm. 2022;14(7):1514.

10. Purohit V, Sagawa K, Hsu HJ, Kushner J, Dowty ME, Tse S, Lin J, Blanchard A, Mukherjee A, Le V, Chang C. Integrating Clinical Variability into PBPK Models for Virtual Bioequivalence of Single and Multiple Doses of Tofacitinib Modified-Release Dosage Form. Clin. Pharmacol. Ther. 2024;116(4):996-1004.

11. Arafat M, Sarfraz M, AbuRuz S. Development and in vitro evaluation of controlled release viagra® containing poloxamer-188 using gastroplus™ pbpk modeling software for in vivo predictions and pharmacokinetic assessments. Pharm. 2021;14(5):479.

12. Bonner JJ, Burt H, Johnson TN, Whitaker MJ, Porter J, Ross RJ. Development and verification of an endogenous PBPK model to inform hydrocortisone replacement dosing in children and adults with cortisol deficiency. Eur. J. Pharm. Sci. 2021;165:105913.

13. Basu S, Yang H, Fang L, Gonzalez-Sales M, Zhao L, Trame MN, Lesko L, Schmidt S. Physiologically based pharmacokinetic modeling to evaluate formulation factors influencing bioequivalence of metoprolol extended-release products. J. Clin. Pharmacol. 2019;59(9):1252-63.

14. Otsuka K, Wagner C, Selen A, Dressman J. Prediction of in-vivo pharmacokinetic profile for immediate and modified release oral dosage forms of furosemide using an in-vitro-in-silico-in-vivo approach. J. Pharm. Pharmacol. 2015;67(5):651-65.

15. Diniz LF, Carvalho Jr PS, Pena SA, Gonçalves JE, Souza MA, de Souza Filho JD, Bomfim Filho LF, Franco CH, Diniz R, Fernandes C. Enhancing the solubility and permeability of the diuretic drug furosemide via multicomponent crystal forms. Int. J. Pharm. 2020;587:119694.

16. Markovic M, Zur M, Ragatsky I, Cvijić S, Dahan A. BCS Class IV oral drugs and absorption windows: Regional-dependent intestinal permeability of furosemide. Pharm. 2020;12(12):1175.

17. Lalic M, Cvejic J, Popovic J, Bozic K, Golocorbin-Kon S, Al-Salami H, Mikov M. Lamotrigine and valproate pharmacokinetics interactions in epileptic patients. Eur. J. Drug Metab. Pharmacokinet. 2009;34(2):93-9.

18. Lalic-Popovic M, Paunkovic J, Grujic Z, Golocorbin-Kon S, Vasovic V, Al-Salami H, Mikov M. The effect of diabetes and hypertension on the placental permeation of the hydrophilic drug, Ranitidine. Placenta. 2016;48:144-50.

19. Lalic-Popovic M, Paunkovic J, Grujic Z, Golocorbin-Kon S, Al-Salami H, Mikov M. Diabetes and hypertension increase the placental and transcellular permeation of the lipophilic drug diazepam in pregnant women. BMC Pregnancy Childbirth. 2013;13(1):188.

20. Krstevska A, Đuriš J, Ibrić S, Cvijić S. In-depth analysis of physiologically based pharmacokinetic (PBPK) modeling utilization in different application fields using text mining tools. Pharm. 2023;15(1):107.

21. Michelet R, Bocxlaer JV, Vermeulen A. PBPK in preterm and term neonates: a review. Curr. Pharm. des. 2017;23(38):5943-54.

22. Zhou J, Xu B, Zheng Y, Huang H, Wei Z, Chen S, Huang W, Liu M, Zhang Y, Wu X. Optimization of oral isavuconazole dose for population in special physiological or pathological state: a physiologically based pharmacokinetics model-informed precision dosing. J. Antimicrob. Chemother. 2024;79(9), pp.2379-2389.

23. Deepika D, Sharma RP, Schuhmacher M, Sakhi AK, Thomsen C, Chatzi L, Vafeiadi M, Quentin J, Slama R, Grazuleviciene R, Andrušaitytė S. Unravelling sex-specific BPA toxicokinetics in children using a pediatric PBPK model. Environ. res. 2022;215:114074.

24. T'jollyn H, Vermeulen A, Van Bocxlaer J. PBPK and its virtual populations: the impact of physiology on pediatric pharmacokinetic predictions of tramadol. AAPS J. 2019;21:1-2.

25. Freriksen JJ, van der Heijden JE, de Hoop-Sommen MA, Greupink R, de Wildt SN. Physiologically based pharmacokinetic (PBPK) model-informed dosing guidelines for pediatric clinical care: a pragmatic approach for a special population. Paediatr. Drugs. 2023;25(1):5-11.

26. Wu F, Tsakalozou E, Burckart GJ, Žakelj R, Gaohua L, Sagawa K, Lukacova V, Vaithiyalingam S, Fan J, Fotaki N, Patel N. PBPK Modeling to Support Bioavailability and Bioequivalence Assessment in Pediatric Populations. Pharm. Res. 2025;42(5):847-55.

27. Gill KL, Jones HM. Opportunities and challenges for PBPK model of mAbs in paediatrics and pregnancy. AAPS J. 2022;24(4):72.

28. Liu XI, Green DJ, van den Anker J, Ahmadzia HK, Calderon J, Burckart GJ, Dallmann A. Physiologically based Pharmacokinetic/Pharmacodynamic Modeling (PBPK/PD) of Famotidine in Pregnancy. J. Clin. Pharm. 2025;65(5):564-74.

29. Liu X, Wang W, Zhu J, Chen J, Wang X, Chen D, Ouyang D. Determining the Optimal Dosing of Methyldopa in Pregnancy-Induced Hypertension Using PBPK-PD Modeling. Clin. Pharmacokinet. 2025:1-4.

30. Atoyebi S, Bunglawala F, Cottura N, Grañana-Castillo S, Montanha MC, Olagunju A, Siccardi M, Waitt C. Physiologically-based pharmacokinetic modelling of long-acting injectable cabotegravir and rilpivirine in pregnancy. Br J Clin Pharmacol. 2025;91(4):989-1002.

31. Qian Y, Wu W, Ke C, Liu S, Chen J, Chen Y, Guo X, Lin W. Toward Precision Dosing of Lamotrigine During Pregnancy: Physiologically Based Pharmacokinetic Modeling and Simulation. CPT:PSP. 2025;14(5):929-40.

32. Wu X, Wang Z, Liu S, Wang H. Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population. Drug Des. Devel. Ther. 2025:3077-101.

33. Zhang M, Lei Z, Yao X, Zhang L, Yan P, Wu N, Chen M, Zhang F, Liu D. Model informed drug development: HSK21542 PBPK model supporting dose decisions in specific populations. Eur. J. Pharm. Sci. 2024;196:106763.

34. Li Y, Shao W, Wang X, Geng K, Wang W, Liu Z, Chen Y, Shen C, Xie H. Physiologically based pharmacokinetic model of brivaracetam to predict the exposure and dose exploration in hepatic impairment and elderly populations. J. Pharm. Sci. 2024;113(11):3286-96.

35. Thompson CM, Johns DO, Sonawane B, Barton HA, Hattis D, Tardif R, Krishnan K. Database for physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and health-impaired elderly. J. Toxicol. Environ. Health B Crit. Rev. 2009;12(1):1-24.

36. Krstevska A, Đuriš J, Ibrić S, Cvijić S. In-depth analysis of physiologically based pharmacokinetic (PBPK) modeling utilization in different application fields using text mining tools. Pharm. 2023;15(1):107.

37. Berton M, Bettonte S, Stader F, Battegay M, Marzolini C. Physiologically based pharmacokinetic modelling to identify physiological and drug parameters driving pharmacokinetics in obese individuals. Clin. Pharmacokinet. 2023;62(2):277-95.

38. Zhou, J., Xu, B., Zheng, Y., Huang, H., Wei, Z., Chen, S., Huang, W., Liu, M., Zhang, Y. and Wu, X., 2024. Optimization of oral isavuconazole dose for population in special physiological or pathological state: a physiologically based pharmacokinetics model-informed precision dosing. Antimicrob. Chemother. , 79(9), pp.2379-2389.

39. Li J, Guo HF, Liu C, Zhong Z, Liu L, Liu XD. Prediction of drug disposition in diabetic patients by means of a physiologically based pharmacokinetic model. Clin. Pharmacokinet. 2015;54:179-93.

40. Guo G, Ke M, Xu J, Wu W, Chen J, Ke C, Huang P, Lin C. Physiologically based pharmacokinetic model of sodium-glucose cotransporter 2 inhibitors predicted pharmacokinetics and pharmacodynamics to explore dosage regimen for patients with type 2 diabetes mellitus and renal insufficiency. Front. Pharmacol. 2025;16:1520268.

41. Wedagedera, J.R., Afuape, A., Chirumamilla, S.K., Momiji, H., Leary, R., Dunlavey, M., Matthews, R., Abduljalil, K., Jamei, M. and Bois, F.Y., 2022. Population PBPK modeling using parametric and nonparametric methods of the Simcyp Simulator, and Bayesian samplers. CPT: PSP. , 11(6), pp.755-765.

42. Adiwidjaja J, Gross AS, Boddy AV, McLachlan AJ. Physiologically-based pharmacokinetic model predictions of inter-ethnic differences in imatinib pharmacokinetics and dosing regimens. Br J Clin Pharmacol. 2022;88(4):1735-50.

43. Burhanuddin K, Mohammed A, Burhanuddin NA, Badhan RK. Precision Medicine in Oncology: Imatinib Dosing in the Obese Cancer Population Using Virtual Clinical Trials. CPT:PSP. 2025.

44. Milosevic N, Janjic N, Milic N, Milanovic M, Popovic J, Antonovic D. Pharmacokinetics and toxicity predictors of new s-triazines, herbicide candidates, in correlation with chromatogrpahic retention constants. J. Agric. Food Chem. 2014;62(34):8579-85.

45. Đurić L, Milanović M, Drljača Lero J, Milošević N, Milić N. In silico analysis of endocrine-disrupting potential of triclosan, bisphenol A, and their analogs and derivatives. J. Appl. Toxicol. 2024;44(12):1897-913.

46. Opacic M, Todorovic N, Lalic-Popovic M, Stanic B, Andric N. Advancing probabilistic risk assessment of perfluorooctanoic acid through integration of in vitro data and physiologically based toxicokinetic modeling coupled with population-specific analysis. J. Hazard. Mater. 2025:139402.

47. Vasseur P, Masfaraud JF, Blaise C. Ecotoxicology, revisiting its pioneers. Environ. Sci. Pollut. Res. Int. 2021;28:3852-7.

48. Fernández-Marcos ML. Current Developments in Soil Ecotoxicology. Toxics. 2024;12(10):734.

49. Krishnan K, Peyret T. Physiologically based toxicokinetic (PBTK) modeling in ecotoxicology. Ecotoxicology modeling. 2009:145-75.

50. Grech A, Brochot C, Dorne JL, Quignot N, Bois FY, Beaudouin R. Toxicokinetic models and related tools in environmental risk assessment of chemicals. Sci. Total Environ. 2017;578:1-5.

51. Zhang Y, Feng J, Gao Y, Liu X, Qu L, Zhu L. Physiologically based toxicokinetic and toxicodynamic (PBTK-TD) modelling of Cd and Pb exposure in adult zebrafish Danio rerio: Accumulation and toxicity. Environ. Pollut. 2019;249:959-68.

52. PM, Dedrick RL, Guarino AM. Pharmacokinetic modeling of the dogfish shark (Squalus acanthias): distribution and urinary and biliary excretion of phenol red and its glucuronide. J Pharmacokinet Biopharm. 1976;4:377-88.

53. Zaharko DS, Dedrick RL, Oliverio VT. Prediction of the distribution of methotrexate in the sting rays Dasyatidae sabina and sayi by use of a model developed in mice. Comparative Biochemistry and Physiology Part A: Physiology. 1972;42(1):183-94.

54. Law FC, Abedini S, Kennedy CJ. A biologically based toxicokinetic model for pyrene in rainbow

trout. Toxicol. Appl. Pharmacol. 1991;110(3):390-402.

55. Ling MP, Liao CM, Tsai JW, Chen BC. A PBTK/TD modeling-based approach can assess arsenic bioaccumulation in farmed tilapia (Oreochromis mossambicus) and human health risks. IEAM. 2005;1(1):40-54.

56. Nichols JW, Bennett RS, Rossmann R, French JB, Sappington KG. A physiologically based toxicokinetic model for methylmercury in female American kestrels. Environ. Toxicol. Chem. 2010;29(8):1854-67.

57. Yang F, Yang YR, Wang L, Huang XH, Qiao G, Zeng ZL. Estimating marbofloxacin withdrawal time in broiler chickens using a population physiologically based pharmacokinetics model. J. Vet. Pharmacol. Ther. 2014;37(6):579-88.

58. Zeng D, Lin Z, Zeng Z, Fang B, Li M, Cheng YH, Sun Y. Assessing global human exposure to T-2 toxin via poultry meat consumption using a lifetime physiologically based pharmacokinetic model. J. Agric. Food Chem. 2019;67(5):1563-71.

59. Schneckener S, Preuss TG, Kuepfer L, Witt J. A workflow to build PBTK models for novel species. Arch. Toxicol. 2020;94:3847-60.

60. Scanes CG, Witt J, Ebeling M, Schaller S, Baier V, Bone AJ, Preuss TG, Heckmann D. Quantitative comparison of avian and mammalian physiologies for parameterization of physiologically based kinetic models. Front. Physiol. 2022;13:858386.

61. Renieri EA, Sfakianakis DG, Alegakis AA, Safenkova IV, Buha A, Matović V, Tzardi M, Dzantiev BB, Divanach P, Kentouri M, Tsatsakis AM. Nonlinear responses to waterborne cadmium exposure in zebrafish. An in vivo study. Environ. Res. 2017;157:173-81.

62. Billat PA, Brochot C, Brion F, Beaudouin R. A PBPK model to evaluate zebrafish eleutheroembryos' actual exposure: bisphenol A and analogs'(AF, F, and S) case studies. Environ. Sci. Pollut. Res. Int. 2023;30(3):7640-53.

63. Cvijić S, Ignjatović J, Parojčić J, Ibrić S. The emerging role of physiologically-based pharmacokinetic/biopharmaceutics modeling in formulation development. Arhiv za farmaciju. 2021;71(4):318-35.

64. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. European Medicines Agency. 2005.

65. Center for Drug Evaluation and Research, Summary minutes of the advisory committee for pharmaceutical science and clinical pharmacology. National Harbor, MD: Food and Drug Administration. 2012.

66. U.S. Food and Drug Administration. Drug Approvals and Databases: Imbruvica. [Online]. [2014, cited 03. 06. 2019]. Dostupno na: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.

67. Agencija za lekove i medicinska sredstva Srbije. Pretraživanje humanih lekova: ibrutinib. [Online]. [2015, ažurirano 03. 06. 2019, citirano 03. 06. 2019.]. Dostupno na: https://www.alims.gov.rs/ciril/lekovi/pretrazivanje-humanih-lekova/?a=p.

68. Tan YM, Worley RR, Leonard JA, Fisher JW. Challenges associated with applying physiologically based pharmacokinetic modeling for public health decision-making. Toxicol. Sci. 2018;162(2):341-8.

69. Wang W, Ouyang D. Opportunities and challenges of physiologically based pharmacokinetic modeling in drug delivery. Drug Discov. Today. 2022;27(8):2100-20.

Fiziološki zasnovano farmakokinetičko i toksikokinetičko modelovanje: multidisciplinarni pristup u razvoju lekova i ekotoksikologiji

Nemanja B. Todorović[1], Aleksandra D. Ćoškov[1], Nebojša Lj. Andrić[2], Bojana Đ. Stanić[2], Boris Ž. Milijašević[3], Nataša P. Milošević[1], Slobodan M. Janković[4,5], Mladena N. Lalić-Popović[1,6]

[1] Katedra za farmaciju, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[2] Departman za biologiju i ekologiju, Prirodno-matematički fakultet, Univerzitet u Novom Sadu, Novi Sad, Srbija
[3] Zavod za farmakologiju, toksikologiju i kliničku farmakologiju, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[4] Univerzitetski Klinički centar Kragujevac, Kragujevac, Srbija
[5] Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija
[6] Centar za medicinsko-farmaceutska istraživanja i kontrolu kvaliteta (CEMFIK), Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija

KRATAK SADRŽAJ

Uvod: Fiziološki zasnovano farmakokinetsko (PBPK) modelovanje je moćan alat u farmaceutskim istraživanjima i razvoju lekova, nudeći tačna predviđanja apsorpcije, distribucije, metabolizma i eliminacije lekova (ADME). Ova metoda, kada se proširi na ksenobiotike, omogućava proučavanje toksina i drugih supstanci putem fiziološki zasnovanih toksikokinetičkih (PBPT) modela.
Metodologija: Ovaj narativni pregled sumira nedavne primene PBPK i PBTK modelovanja u razvoju lekova i ekotoksikologiji.
Tema: Uključivanjem fizioloških i biohemijskih podataka, PBPK modeli pružaju preciznije simulacije koje veoma podsećaju na *in vivo* uslove. Napredak u tehnologiji je poboljšao izvodljivost ovih modela, čineći ih sve vrednijim za predviđanje ponašanja lekova, kao i za ekstrapolaciju između vrsta i načina primene. Mehanistička priroda podržava donošenje regulatornih odluka i smanjuje potrebu za obimnim ispitivanjima na živim organizmima. Pored toga, PBPK modeli su od ključnog značaja za procenu u posebnim populacijama, kao što su pedijatrijski pacijenti ili osobe sa oštećenjem organa.
Zaključak: Uz kontinuiranu integraciju *in silico* alata i podataka dobijenim drugim ispitivanjima, PBPK modelovanje postaje centralna platforma u translacionoj farmakologiji i proceni bezbednosti. Regulatorne agencije najčešće koriste PBPK modele za podršku proceni i predviđanju interakcija između lekova.

Ključne reči: PBPK, PBTK, ADME, *in silico*, procena rizika, ksenobiotici, toksikologija životne sredine

Received: July 25, 2025
Accepted: August 7, 2025