Computational Toxicology 36 (2025) 100381

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.sciencedirect.com/journal/computational-toxicology

Full Length Article

Evaluation of PBK models using the OECD assessment framework taking PFAS as case study ☆

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A R T I C L E I N F O

Keywords:
PBK
OECD PBK guidance
PFAS
FAIR PBK
Rshiny application

A B S T R A C T

Physiologically based kinetic (PBK) models are becoming increasingly important in chemical risk assessment, helping in linking external and internal exposure concentrations, thereby supporting the development of regulatory health-based limits for chemicals with exposure from environmental, occupational, and consumer sources. To increase confidence in PBK models for regulatory purposes, the OECD published a guidance document in 2021 outlining the characterization, validation and reporting of PBK models. However, its use remains limited in chemical toxicology as reflected by the few publications that have applied it during model development. The aim of this study was to evaluate several published PBK models for Per- and polyfluoroalkyl substances (PFASs) as proof of concept to assess their validity and credibility for regulatory purposes, based on the OECD guidance. Out of 28 published PFASs human PBK models considered, 11 were selected for evaluation. The assessment used the OECD guidance document, encompassing two main areas: i) documentation (context/implementation, documentation, software implementation, verification, and peer engagement) and ii) assessment of model validity (biological basis, theoretical basis of model equations, input parameter's reliability, uncertainty and sensitivity analysis, goodness-of-fit and predictivity). To standardize this process, an online evaluation system based on the OECD guidance was developed and used for this model evaluation exercise. The collected data were analysed to assess the overall quality of published models and identify limitations in the current PFAS model landscape. Our analysis revealed opportunities for improvement in the biological representation within current PFAS models, particularly regarding the inclusion of diverse population groups. Currently, PFAS models primarily focus on only four compounds, highlighting an opportunity to extend coverage to other PFASs using read-across approaches for data-poor chemicals. Furthermore, our findings show that a harmonized approach for PBK model reporting is needed. To facilitate broader adoption of the OECD guidance, we developed and hosted an R Shiny

☆ This article is part of a special issue entitled: 'FAIR and PBK' published in Computational Toxicology.

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https://doi.org/10.1016/j.comtox.2025.100381
Received 22 May 2025; Received in revised form 28 August 2025; Accepted 13 September 2025
Available online 16 September 2025

template on our group's web server (https://app.shiny.insilicohub.org/Evaluation_PBPK/). This template can act as valuable tool for researchers evaluating PBK models according to the OECD guidance.
GitHub: PBPK-OECD-EVALUATION.

1. Introduction

Physiologically based kinetic (PBK) models are increasingly used in pharmaceuticals and toxicology to evaluate the safety and toxicity of compounds. Over the years, these models have become an integral part of drug development and chemical risk assessment [1,2]. In general, PBK modeling is applied in multiple contexts including inter- and intraspecies translation, in-vitro to in-vivo extrapolations (IVIVE), route-to-route extrapolation, target dose estimations, and daily intake calculations for both general and sensitive populations [3]. Despite the substantial increase in published PBK models over last 30 years with potential to predict kinetic of compounds (drugs and chemicals), their application in regulatory context remains limited (Fig. 1). The major reason for this limited regulatory acceptance includes a lack of modeling expertise within regulatory agencies to review submitted models, insufficient experimental kinetic data for model development, the absence of −user-friendly platforms for reviewers to test models, and variations in acceptance criteria across agencies and countries [4].

Regulatory bodies such as the OECD (Organisation for Economic Co-operation and Development), EMA (European Medicines Agency), USEPA (U.S. Environmental Protection Agency), and WHO (World Health Organization) have published multiple guidance documents to establish a harmonized approach for the characterization, validation and reporting of PBK models for regulatory use as well as to foster effective communication among key stakeholders [2,4–6]. Over time, these guidelines have been updated to include new approach methodologies (NAM), particularly those supporting the use of high-throughput in-vitro and in-silico data for PBK model development. In addition to model construction and validation, a complete reporting framework is also essential to aid modelers in reproducing results and building confidence in decision-making, and ultimately enabling the development of robust PBK models that can assist scientists and regulators in assessing and effectively regulating compound-specific toxicity [1,7,8]. Recently, Kirman et al. has evaluated PBK models for metal nanoparticles using OECD guidance document for inhalational exposure [9]. However, no such assessment using OECD framework has been conducted for PBK model developed for environmental chemicals.

The aim of this study was to apply the PBK OECD reporting template [2] to check whether published PBK models adhere to OECD criteria for model development and reporting, using perfluoroalkyl substances (PFAS) as a proof-of-concept case study. The template facilitated the identification of major limitations and challenges of such existing models, providing opportunities to improve them for regulatory use. PFAS are persistent man-made compounds regularly detected in the environment and in human biomonitoring samples, with the potential to bioaccumulate and cause adverse health effects [10]. They were selected as a case study because regulatory agencies regard them as a significant health concern. To predict the toxicokinetic profiles of PFAS in adult and vulnerable populations, multiple PBK models have been developed over the past decade for four PFAS compounds [11]. In this work, we evaluated models for PFOS (perfluorooctanesulfonic acid), PFOA (perfluorooctanoic acid), PFNA (perfluorononanoic acid) and PFHxS (perfluorohexanesulfonic acid) and identified key challenges that could help facilitate their use in improved risk assessment. The evaluation presented here can be extended to other chemicals to ensure the quality, reliability and robustness of PBK models.

2. Methodology

For evaluating the PFAS PBK model with OECD criteria (explained below, Fig. 2), the following strategy was adopted:

1) Selection of PFASs PBK models
2) Preparation of PBK model evaluation checklist template and assigning a categorial and scoring system
3) Formation of expert panel, including both developers and users
4) Model evaluation

2.1. Selection of the published PFAS PBK models

Initially to choose the existing PFAS PBK model, PubMed advanced

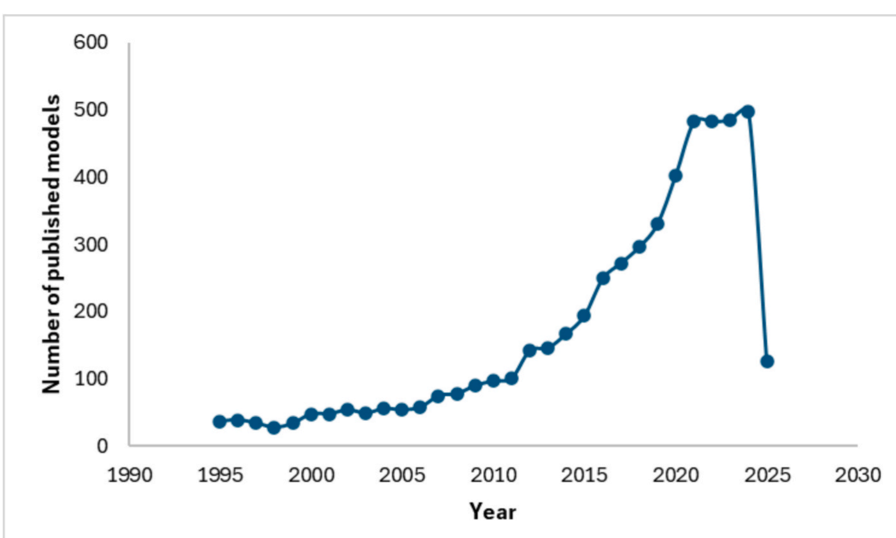

Fig. 1. Published PBK models over the last 30 years searched using PubMed advanced search (Keyword: PBPK (Physiologically based Pharmacokinetic) Model or PBK (Physiologically based Kinetic) Model or PBTK (Physiologically based Toxicokinetic) (Model search done on 05 March 2025).

search criteria were used with the following keywords: "PFAS" and "PBPK", "PBK" or "PBTK". A total of 28 articles were found (search made in April 2023). Exclusion criteria included articles not retrievable via PubMed, review, semi review, reports, and PBK models developed for species other than humans. In case if multiple PFAS PBK models were published from the same corresponding author then the most recent model was considered for the evaluation. PBK model for PFAS published by EFSA was not included since it is based on model from Locissano et al. which was already a part of the evaluation [12,13]. Also, the scientific opinion published by EFSA cannot be found through PubMed which was one of exclusion criteria. PBK models considering different life stages/ aspects were selected, e.g., pregnancy, age-dependent, sex-specific, gestational and lactational models. Out of 28 articles, 11 were further shortlisted for the evaluation based on these criteria (Table 1). All the selected articles were published between 2011 and 2023.

2.2. PBK model evaluation checklist with categorial and scoring system

We developed an online tool using a standardized questionnaire template to facilitate the harmonized evaluation of selected PFAS PBK models by the expert panel. The questionnaire was derived from the OECD guidance document checklist and reformatted into a structured template (Fig. 3). The evaluation template was organized into six major steps: Step 1) scope and purpose of the model (problem formulation), step 2) model conceptualization (model structure and mathematical representation), step 3) model parameterization (parameter estimation and analysis), step 4) computer implementation (solving the equations), step 5) model performance (validation, sensitivity, variability and uncertainty analysis) and step 6) model reporting and dissemination (Fig. 3). The checklist consisted of multiple-choice questions, each followed by a section where experts could provide justification for their responses. Questions concerning model characterization used a categorical system (Yes, No, Partially, I cannot answer, Not applicable), followed by a scoring system (1–5, plus I cannot answer) to rate the degree of confidence in each characteristic section. This structure enabled a more consistent and quantitative evaluation rather than relying solely on qualitative feedback. Further details on the checklist and its application are provided in Section 5 and the supplementary material.

2.3. Formation of expert panel and Assignment of PBK models

The expert panel consisted of PBK model developers and users with expertise in chemical risk assessment. A total of 12 experts were selected for the evaluation, representing institutions across Europe. The panel included members from academia (10 experts), and regulatory institutes (2 experts), with varying years of experience (Table S1). PBK models were randomly assigned to panel members regardless of their institutional affiliation; however, care was taken to avoid assigning models to experts with a conflict of interest (co-author of published model or coming from same lab). Each article was evaluated by at least two independent experts.

2.4. Model evaluation

The evaluation of PBK model was conducted by panel members using the checklist described in Section 2.2. Additional questions were incorporated to address model-specific aspects such as population age groups, geographical relevance, and biological mechanisms underlying the long half-life of PFAS. A scoring system was applied to facilitate a more quantitative assessment, while allowing evaluators discretion in assign scores. Confidence in a model was considered higher when it demonstrated a well-defined structure, strong parameterization, validation against toxicokinetic data, robust uncertainty and sensitivity analyses, and comprehensive documentation (Fig. 4). Experts were able to justify their responses after each question, ensuring transparency in the evaluation process. The finalized questionnaire was implemented on an RShiny platform, as described in Section 5. The complete checklist, including scoring responses, is provided in the supplementary material (Fig. S9).

3. Results and discussion

The OECD guidelines outline an assessment framework for the evaluation of PBK models based on biological basis, uncertainty and sensitivity analysis, and model prediction. The OECD assessment is not quantitative but purely qualitative, intended to provide assessors and regulators with an overview of the evidence presented by model developers. In addition, the guidelines are broadly applicable to all compounds including nanoforms, biologicals, macromolecules and peptides with the aim of building relative confidence in the model. For this study, PFAS were selected as the case study chemical due to their widespread occurrence, persistence, accumulation potential, and toxicity. As a consequence of the health threat posed by PFAS, regulators at the European level have reduced the tolerable weekly intake (TWI) of PFAS from microgram to nanogram per kg body weight, incorporating new

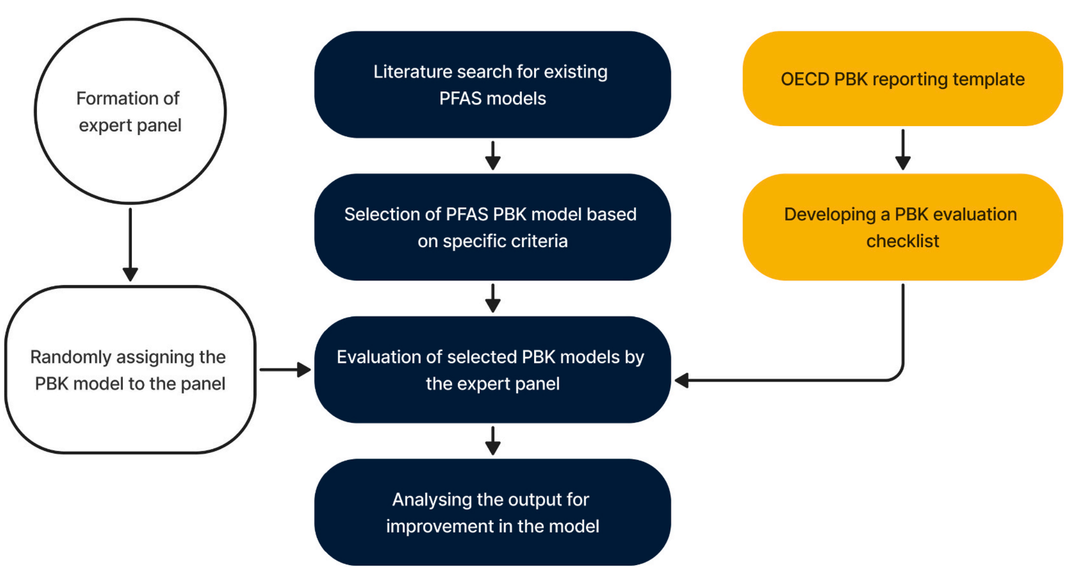

Fig. 2. Framework for evaluating the existing PFAS PBK model using OECD published PBK guidance document.

Table 1
Details of the models considered for evaluation.

S. No.	Title of the article	Year	Reference (DOI)
1	Evaluation and prediction of pharmacokinetics in the monkey and human using a PBPK model.	2011	https://doi.org/10.1016/j.yrtph.2010.12.004
2	Development of PBPK Models for PFOA and PFOS for Human Pregnancy and Lactation Life Stages.	2013	https://doi.org/10.1080/15287394.2012.722523
3	Sex-specific risk assessment of PFHxS using a physiologically based pharmacokinetic model.	2018	https://doi.org/10.1007/s00204-017–2116-5
4	Prediction of maternal and foetal exposures to perfluoroalkyl compounds in a Spanish birth cohort using toxicokinetic modelling.	2019	https://doi.org/10.1016/j.taap.2019.114640
5	Prenatal exposure to PFOS and PFOA in a pregnant women cohort of Catalonia, Spain.	2019	https://doi.org/10.1016/j.envres.2019.05.040
6	Bayesian evaluation of a physiologically based pharmacokinetic (PBPK) model for perfluorooctane sulfonate (PFOS) to characterize the interspecies uncertainty between mice, rats, monkeys, and humans: Development and performance verification.	2019	https://doi.org/10.1016/j.envint.2019.03.058
7	Exploring sex differences in human health risk assessment for PFNA and PFDA using a PBPK model.	2019	https://doi.org/10.1007/s00204-018–2365-y
8	Development of a Gestational and Lactational Physiologically Based Pharmacokinetic (PBPK) Model for Perfluorooctane Sulfonate (PFOS) in Rats and Humans and Its Implications in the Derivation of Health-Based Toxicity Values.	2021	https://doi.org/10.1289/EHP7671
9	Risk Assessment of Perfluorooctane Sulfonate (PFOS) using Dynamic Age Dependent Physiologically based Pharmacokinetic Model (PBPK) across Human Lifetime.	2021	https://doi.org/10.1016/j.envres.2021.111287
10	Physiologically based pharmacokinetic (PBPK) modeling of perfluorohexane sulfonate (PFHxS) in humans	2022	https://doi.org/10.1016/j.yrtph.2021.105099
	Comparison of aggregated exposure to perfluorooctanoic acid (PFOA) from diet and personal care products with concentrations in blood using a PBPK model – Results from the Norwegian biomonitoring study in EuroMix.	2023	https://doi.org/10.1016/j.envres.2023.117341

scientific evidence. The most recent TWI values for four PFAS (PFOS, PFOA, PFNA and PFHxS) were derived using PBK model predictions, which accounted for infants as a sensitive population and immunotoxicity as the critical end point. Hence, PFAS PBK models were considered for our case study with the goal of guiding modelers and developers in improving existing models by addressing current limitations and challenges. We adapted the evaluation framework to make it quantitative, facilitating the weighing of overall evidence and providing a structured framework for model development.

Standardization of PBK modeling plays a crucial role in improving model transparency, reproducibility, and regulatory acceptance. In this study, we evaluated aspects related to implementation and model validity to support the harmonization of PBK models across regulatory contexts. Satisfying these criteria can enhance confidence in the model, particularly regarding its applicability and predictive performance. We also emphasized the refinement of the evaluation checklist as a means to support regulatory acceptance of PBK model submissions. Alignment of the model structure and parameters with the biological basis, evaluation of predictive performance using biokinetic data in the species of interest and the use of sensitivity analysis to determine the uncertainty of the predicted dose metrics can strengthen confidence in PBK models. Our findings highlight the importance of following the framework proposed by the OECD during PBK model development to enhance scientific and regulatory validity. Furthermore, we proposed that the model evaluations should be quantitative rather than purely qualitative and stress the importance of considering case-specific contexts when developing or evaluating PBK models for chemical risk assessment and drug development. The implications of these findings are explored in detail below.

3.1. Implementation and documentation of the model

This section covers the general documentation of the PFAS PBK models.

3.1.1. Consideration of different age groups

Consideration of age groups plays a critical role in PBK modeling since different age groups show variation in physiological and biochemical processes affecting tissue dosimetry of compounds [14]. The current PFAS PBK models mostly focus on human adults, pregnant females, and fetus, predicting adult, maternal and pre- and postnatal exposure contributions to body burden. These vulnerable populations are at potential health risk due to exposure to environmental toxins. Almost 40 % of the models do not include teenagers and other pediatric populations, thus limiting their applicability to specific age groups (Fig. S1). However, since most PFAS are long-acting chemicals with half-lives of several years [15] predicting lifetime exposure provides insights into PFAS toxicokinetics, especially in the first years of life. To date, adult PBK models can be considered the gold standard for PFAS, since PFASs are stable chemicals and PBK models can be extended relatively by using a classical body weight and ontogeny based scaling approach to predict concentrations for other age groups such as pediatric and geriatric populations [16] However, significant uncertainty may arise due to variation in fraction unbound and renal resorption over time across different age groups [17–19]. EFSA has highlighted these uncertainties when extrapolating adult toxicokinetics to children, due to age-specific physiological differences, exposure variability, and potential underestimation of health risks. The EFSA assessment on PFASs illustrates these challenges, emphasizing the need for refined models incorporating child-specific parameters, long-term accumulation data, and developmental toxicokinetics to improve regulatory decision-making and risk assessment accuracy. With these considerations, a TWI of 4.4 ng/Kg BW/week was established for the sum of all four PFASs (PFOA, PFNA, PFHxS and PFOS) with no additional uncertainty factor applied to it [20]. Additionally, in its scientific opinion document, EFSA highlighted that PFAS exposure to toddlers and 'other children' was approximately twice that of adolescents and adult age groups due to higher food intake relative to their body weight. Through model extrapolation, it has been deduced that maternal exposure of 1.16 ng/day resulted in a serum level of 31.9 ng/ml in one-year old children. Lower bound exposure estimates and measured serum PFAS levels suggest that some segments of the European population exceed the TWI [12].

3.1.2. Consideration of geography demographics

The inclusion of geographic demographics in any PBK model incorporates the parameters influenced by ethnicity, such as the prevalence of genetic variants and hepatic characteristics. Studies have highlighted the effect of geography and demographic variability on serum PFAS concentration, which helps the regulatory bodies in exposure mapping [21]. Almost 44.4 % of the evaluated models have covered more than one continental population, with 27.8 % including the European population, but PBK models have less representation in terms of Asian population (Fig. S1). This may be due to fewer epidemiological studies conducted for PFAS analysis in humans in Asia. However recently high PFAS levels have been detected in China, Japan and South Korea [22]. For instance, Chou and Lin., 2021 used toxicokinetic data

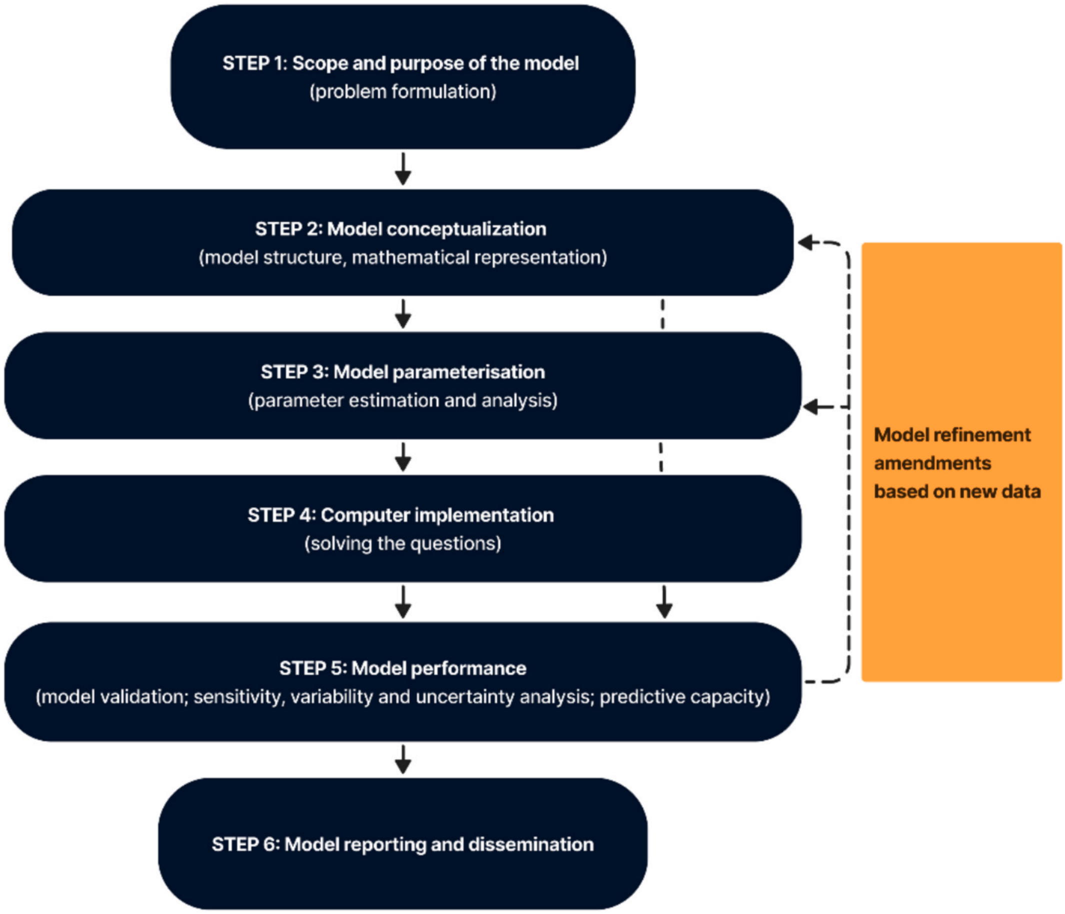

Fig. 3. Assessment of PBK model building, evaluation and validation as per OECD guidance ([]
adapted from OECD guidelines) 2.

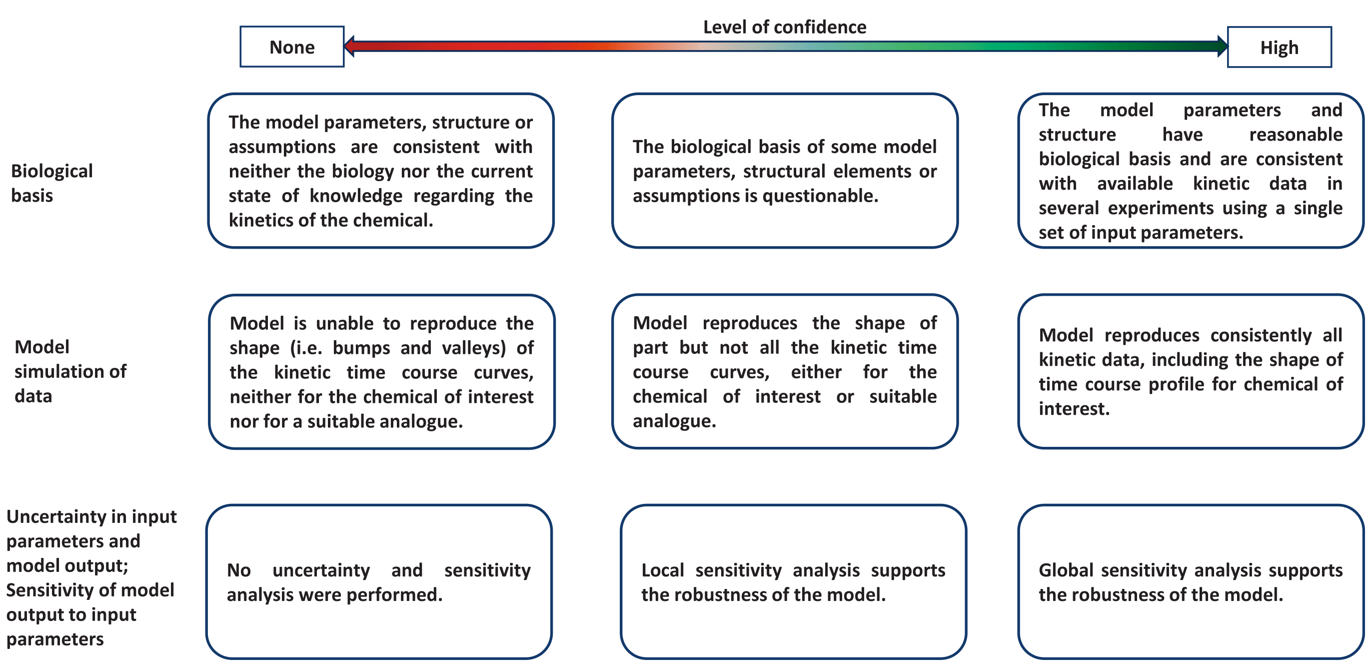

Fig. 4. None to high confidence level for PBK Model depending on multiple attributes like biological basis, model simulation and uncertainty and sensitivity for different input and output parameters ([]
adapted from OECD guidance document) 2.

from multiple populations, including Japanese, Danish, American, Chinese, Swedish, German, Norwegian, South Korean, and French populations [23]. However, Sweeney et al., 2022 considered only the general American population [11]. Deepika et al., 2021 included the Chinese and Australian and Norwegian population [24]. Loccisano et al., 2013 used referenced data from Denmark, Germany, Canada, Korea, Japan and South Africa [13]. This factor is important since inclusion of populations from different geographies further strengthens the model. In the future, with more data available, physiological parameters such as organ blood flow, organ volume, body weight and height of different populations can be incorporated [22].

3.2. PBK model structure

The structure of the PBK model is very important and depends on the use-case scenario and data availability and can vary from being simplistic to complex. Most PFAS PBK models (82.4 %) currently consider the renal resorption (RR) process to explain the long half-life of PFAS. However, models including both RR and enterohepatic recirculation (EHR) are limited (17.6 %) even though EHR is a common disposition mechanism for PFAS and can help in strengthening the biological basis of the model (Fig. S1) [24,25]. Adding EHR has the additional advantage of reducing dependency on animal data since its parameterization can be achieved using in-vitro data through in-vitro to in-vivo extrapolation (IVIVE). However, it is worth noting that EHR may not be a sensitive parameter and can increase the complexity of the model, but this is something which can be analyzed only after its incorporation in the model.

3.3. Documentation of the model

In terms of documentation, 90 % of the models have provided a clear indication of the chemical for which they were being developed. For instance, Husoy et al. 2023 has clearly stated that the model is specifically for PFOA [25]. In some models, explanations of the equations are lacking, with only equations given for uptake, elimination and transport in the kidney compartment [26]. Rovira et al., 2019 has mentioned a few important equations related to exposure assessment in pregnant women through different routes and adapted other standard equations from a pre-published article [27,28]. Currently PFAS models are limited to 4 compounds *viz.* PFOA, PFOS, PFNA and PFHxS due to limitation of data availability. Eighty percent of the models developed are for similar scientific purposes while 20 % are repurposed for other chemicals. A clear mention of the plausibility of the model assumptions is very crucial for building a robust model. For instance, consideration of a filtrate subcompartment in the kidney or inclusion of a delay compartment for PFAS provided by Loccisano et al. (2011) provided justification to explain the longer half-life of the chemical [29]. In 55 % of the selected papers the model assumptions were clearly described (Fig. S2).

Publishing PBK model code is still not widely practiced within the modeler community which leads to difficulties in reproducing models by other developers and regulators. Only 60 % of the papers have published their model codes [11,23,25,26,29,30]. The PBK community should consider publishing their code on GitHub, Zenodo, FAIRDOM or other open access repositories to make the model findable, accessible, interoperable and reusable (FAIR). The unavailability or partial availability of code in 40 % of the models is a major limitation, often making it difficult to evaluate the assumptions.

Representation of the mode of action for any PBK model is a very important step that helps in exposure predictions and increasing the confidence among regulators and the scientific community [31]. Only 15 % of the models have graphical representation of the proposed mode of action [26,29,30]. Sometimes for PBK models, the model structure itself represents the mode of action, hence a separate graphical representation may not be necessary [32]. Graphical representation of the conceptual model has been demonstrated by 80 % of the models showing the general structure of the model. Most of the models include gut, liver, kidney, adipose, plasma and the rest of the body as compartments. Some models have included the brain compartment as well [24,27,30,33]. Models focusing on sex specific risk assessment have considered the loss of menstrual blood in the model structure [33,34]. The models where the objective was to predict the maternal and fetal exposure of PFAS included the placenta, mammary gland and a separate fetal compartment [13,23,27,30]. Compartments like lung, bone, adrenal, thyroid, skin and bone marrow were also considered depending on the model requirements [24,27,30].

An important aspect of PBK model documentation is the tabulation of parameters with their relevance and reliability clearly described. Currently, almost 60 % of the papers have presented the parameters in a proper structured way [13,23–27,29,30,34]. However, the method of presentation varies from paper to paper necessitating the need for a structured format to do so. For instance, some authors did not provide the standard deviation or range considered for the parameters [24,25] while others did not consider the variability and uncertainty of the parameters [30]. Some authors presented the mean value along with posterior distributions for mean and variance. Relevance and reliability in the reported parameters were found to be a little less with 45 % of the papers having partial reliability (including some parameters but not all) while 35 % of the papers having properly mentioned the parameters [11,23,24,26,29].

Uncertainty and sensitivity analysis are important pillars for building confidence in PBK model especially to take into account variation in experimental data [35]. Approximately 55 % of the selected papers reported conducting uncertainty and sensitivity analysis. Among these, local sensitivity analysis (LSA) was the most commonly used approach, performed in 65 % of the papers [13,23,25,26,29,33,34], while global sensitivity analysis was performed in 25 % of the papers [11,24,25]. For instance, Deepika et al., 2021 performed a global sensitivity analysis (GSA) using the pksensi R-package [24], whereas other studies implemented LSA. A summary of the responses given by the expert panel can be seen in figure S2.

3.4. Software implementation and verification

The code availability is one of the contextual factors which influence the degree of confidence in the model. In general, providing model code ensures correctness of syntax, parameter values, unit consistency, mass and blood flow balance, and the absence of numerical errors. If code is provided, it can be reviewed by the model developer and regulators to check the accuracy of the computational implementation [2]. Almost 55 % of the model codes express the mathematical model [11,23,25,26,30] while almost 40 % of model codes were free from syntactic and mathematical errors [11,23,25,26,29,30]. This question remains a limitation since many times the code is not provided or is present in a format that cannot be replicated and reapplied. About 45 % of PBK models have units of both input and output parameters correctly reported [11,23,25–27,30] (Fig. S3). Often, the mass balance was not clearly mentioned while reporting the model by the authors. Similarly, for physiological parameters, mass balance for blood flow and tissue volume was not reported properly. However, in general, almost all models achieve mass balance but reporting it can improve confidence in the model.

All models use well established algorithms for solving ordinary differential equations (ODE) ranging from deSolve to other solvers, which converge on the solution without numerical errors. A detailed list of PBK modelling software, applications and mathematical modeling software was provided by Madden et al. 2019 [36] which is also recommended in the OECD guidelines [2].

3.5. Peer engagement (input/review)

65 % of the models have not been used for regulatory purposes with

only 10 % contributing to regulatory relevance [29]. 50 % of the models require additional review, with the major limitation being the lack of code or understanding of the code. Additional review by reviewers in terms of replication of code can sometime be important for building confidence in the model which is currently a limitation for the existing papers published on modeling. In the future, an option could be included to provide executable files for the model which reviewers can run to check the output. Overall, 5 % of the models have the highest degree of confidence in peer engagement of the model, followed by 20 % having the second highest and 40 % having moderate confidence in peer engagement (Fig. S4).

3.6. Assessment of model validity

3.6.1. Biological basis of model (model structure and parameters)

Almost 80 % of the models have implemented biological mechanisms including reabsorption [29] and relevant compartments. However, PFAS models mostly included a hypothetical delay compartment, which needs to be modified in the future to increase the biological relevance of the model. The addition of a “delay compartment” was introduced initially by Loccisano et al., 2011 to get a better fit for the urine data since the rate of appearance of PFOA in urine was slower than its rate of disappearance from the plasma [29]. Over time, more data have become available for PFAS kidney transporters, and hence this delay compartment can be removed by including permeability limited transporters. About 45 % of the models have shown sufficient complexity of the model structure, making them relevant for regulatory application (Fig. S5). However, the OECD guidelines suggest that model parsimony should be followed in the context of regulatory application, while the proposed model should still be able to represent the complexity of the human body [2]. The model should have the number of compartments which are required to mimic the condition of the target population. For instance, Rovira et al., 2019 added the fetal compartment since the target population was pregnant women [27]. The point worth mentioning is that most of the models lack organs needed to capture developmental and reproductive toxicity and immune system effects. Since immunotoxicity is considered as a major toxicity for PFAS exposure [37,38], adding compartments related to this can further help link PBK model with toxicodynamic models for predicting PFAS effects over time.

Almost 80 % of the models provided full or partial details about model structure and physiological parameters. More than 65 % of the models also accounted for absorption, distribution, metabolism, and excretion (ADME) specific parameters, but some articles did not provide all parameters in the text. Almost all models accounted for saturable transport in the kidney compartment, thus supporting almost 45 % of models with a high degree of confidence in their structural basis.

3.6.2. Theoretical basis of model equations

For model equations like Michaelis-Menten kinetics, 70 % of models have provided enough information to increase confidence in the model. For PFAS, Michaelis-Menten kinetics was applied to describe reabsorption from the filtrate compartment to the kidney, for which enough explanation was provided with 55 % of models having a higher degree of confidence (Fig. S6).

3.6.3. Reliability of input parameters

The uncertainty in input parameters, especially individual variability, reproducibility and reliability was missing in 50 % of the models, with only 10 % of models accounting for uncertainty in input parameters (Fig. S6). For instance, in Chou and Lin (2021), several biomonitoring studies have been used to calibrate and evaluate the models by applying coefficients of variation to the model parameters. However, there was a lack of data on individual exposures levels [23]. The sensitive parameters were estimated using the Levenberg–Marquardt algorithm based on available in-vivo calibration datasets for each species. Another model used Bayesian PBK analysis by updating the prior distribution of estimated parameters with experimental data to generate the posterior distribution using Markov chain Monte Carlo (MCMC) simulations [26]. However, in Deepika et al., 2021, the standard deviation of parameter values was missing with some models lacking data on individual exposures [24]. In Kim et al. 2019, uncertainty factors were included for risk assessment purposes and not for PBK model parameters [34]. Overall, 20 % of the models got a higher rating for confidence in reliability of input parameters with 25 % having a medium rating. Multiple models lack uncertainty and variability range in input parameters [13,27,29].

3.6.4. Uncertainty and sensitivity analysis

Sensitivity analysis helps to identify the key sources of uncertainty or variability or both when there is simultaneous variation in multiple input variables [39]. 30 % of the models accounted for uncertainty and sensitivity while 35 % lacked the analysis. For sensitivity analysis, LSA was performed in 65 % of models with 25 % models not performing any LSA. Most of the authors varied parameters by 1 % to evaluate the variation in output. For instance, Chou and Lin., 2019 performed LSA on a total of 68 posterior parameters for the model development [26]. GSA to identify multiple important contributing factors was not performed in 70 % of the models, with 25 % conducting of the models doing GSA by multiple approaches. For instance, Deepika et al., 2021 included 33 anthropometric, physiological and biochemical parameters to determine the most influential parameters for concentration of PFOS in plasma, fat, liver, kidney and bone marrow [24].

40 % of the models included uncertainty and sensitivity for input parameters that were reasonable for the intended application, with multiple models showing physiological parameters like free fraction, blood flow, biliary elimination rate constant, partition coefficient of liver and transporter related parameters to be highly sensitive. Overall, the lack of appropriate uncertainty and sensitivity analyses leads to 15 % of models receiving a lower rating, followed by 35 % with a medium rating and only 5 % with a high degree of confidence (Fig. S7) [40,4].

3.6.5. Goodness of fit and predictivity

The goodness of fit and predictivity of a PBK model are key criteria for determining the suitability of the model. The goodness of fit metric assesses how closely a PBK model’s predictions align with observed experimental data [5]. Assessment of model predictive capacity using a read-across approach or other methods with PFASs analogues was not applicable for our case study since the model parameters and data were available for the chosen chemicals in 99 % of the cases. Questions related to defining the goodness of fit and predictivity of a source chemical based on read-across and other approaches were not relevant here. Quantitative comparison was reported in 70 % of cases for model predictions along with estimated data with two models providing only qualitative comparisons [27,30]. 40 % of models also reported a goodness of fit metric, with 20 % providing partial descriptions. For instance, Sweeney et al., 2022 included average fold error (AFE) and average absolute fold error (AAFE) numerically while others presented results only graphically lacking numerical estimation [11]. 15 % of models received a high degree of confidence [11,24,25] for goodness of fit and predictivity for specified chemical, followed by 25 % [13,23,26,30] and 30 % [24–26,29,33] with a moderate degree of confidence (Fig. S8) [11,27,30,33].

4. Discussion on improving PBK reporting

OECD reporting for PBK guidelines focuses on the assessment of toxicity testing with emphasis on harmonized approaches to facilitate and promote the usage of PBK in regulatory applications. Efforts to create a unified reporting template exist, but they have yet to be fully adopted. The main challenge is that PBK model suitability is assessed case-by-case; hence a recommendation for one chemical might not be suitable for another. While developing the questionnaire for PBK evaluation checklist, we observed that OECD template is merely qualitative which becomes the limitation for selecting good model for regulatory usage. As a result, quantitative assessment was included in the checklist to improve the reporting framework. Taking this quantitative framework into account, a revised OECD template has been created in a user-friendly interface (described in detail in section 5).

Another important consideration should be the validation of the model. There is often confusion between modelers and regulators or risk evaluators about which data was used for optimization, calibration and validation of the model. When modeling multiple chemicals, experimental data are often limited. In such cases, a clear guideline is required where even semi-validation can provide enough confidence for the scientific validity of the model and its predictions. The WHO PBK reporting guideline states that for validation, the ratio between simulated and observed data is acceptable within a factor of 2. If this ratio is not within a factor of 2 then the model needs further refinement and updating based on the available ADME data [41]. As different chemicals behave differently from a toxicity perspective, a generic acceptable limit may not apply.

Uncertainty in the model parameters should be clearly stated when reporting results, distinguishing between epistemic and aleatoric uncertainty. Often these terms are not clear to modelers, which leads to confusion while reporting. Epistemic uncertainty, which arises mainly from experimentation, can be reduced, while aleatoric uncertainty, which is often called variability, is inherent, i.e., physiological differences among individuals in a population cannot be eliminated, and therefore need to be included in the model. Uncertainty is a very important aspect of model building and validation and goes hand in hand with sensitivity. Most models developed to date lack sensitivity analysis, a crucial component for understanding the contribution of a particular input parameter to the output [2]. This was also the case with PFAS, where multiple models were lacking SA.

Current PBK reporting guidelines lack a concise structure for input and output parameter reporting, which was also observed in this case study. Researchers often report some parameters but not all. For instance, some publications include all the biochemical parameters used for building the model, while others report only a few. In addition, units and parameter naming conventions need to be harmonized and accordingly an appropriate table reporting framework is needed which includes parameter values along with included uncertainty (mean, SD, average etc.). Additionally, important output parameters like C_{max} (maximum concentration), AUC (area under the curve), T_{max} (time at which C_{max} was observed), or C_{ss} (steady state concentration) for persistent chemicals need to be included as a step of model validation. We observed that some publications reported output parameters like steady state concentration for PFAS in a table format while others showed it in a figure format. A harmonized Excel, XML or JSON file format needs to be provided that includes concentration–time results to help regulators with the evaluation of the models.

Additionally, researchers use different abbreviations for similar terminology, thus making reproducibility and application of the model challenging. For instance, some publications on PFAS PBK models mention fraction unbound as “fu”, while others use the terminology “free” for the same parameter. The same situation applies for other parameters like partition coefficient or elimination rate constants. To overcome this limitation, a PBK ontology has been developed recently (https://github.com/InSilicoVida-Research-Lab/pbpko) which can be used for PBK harmonization as well as building machine-readable models. Additionally, it is recommended to provide all models in a uniform format, for instance systems biology models are often provided in a SBML format, developed in the 1990 s which makes them easy to understand and reproduce. A very similar format can be applied for PBK reporting to make models FAIR.

While this study provides valuable insights into the implementation, validity, and current gaps of PBK models based on expert panel evaluation, there are certain limitations which need to be acknowledged. The panel size was relatively small (12 members) including both developers and users, however, the findings may not fully capture the diversity of perspectives within the broader PBK modeling community. Limited participation from industry and regulatory bodies was another constraint of this case study. Consequently, although the results obtained from this study highlight key strengths, weaknesses, and opportunities for PBK harmonization, caution should be exercised in extrapolating these conclusions to all PBK models as our study was limited to four PFAS compounds only. Future work involving broader stakeholder participation, and inclusion of a wider range of case studies will help strengthen the robustness and general applicability of such assessments.

5. A PBK OECD template

Based on this evaluation, we have developed a user-friendly webapp that incorporates all OECD evaluation criteria as a template. This template was designed to make it easier for the PBK community to evaluate models and assess overall model strength by generating graphs that visualize ratings and confidence in the evaluation. RShiny template is hosted on a public web server (https://app.shiny.insilicohub.org/Evaluation_PBPK/) and is open access for all users. The evaluation template includes all the questions from the OECD model evaluation checklist along with additional fields to capture information about the model developer, evaluator, and study-specific details such as the chemical assessed, population age group, and geographic context. Each question provides multiple-choice options enabling evaluators to select the most appropriate response. Some questions follow a categorical system requiring a simple “Yes,” “No,” or “Partially” answer, while others evaluate confidence levels across different aspects of modeling. For confidence-based questions, responses are scored on a scale of 1 to 5, where 1—2 indicate poor, 3–4 indicate moderate, and 5 represents high confidence. To ensure impartiality, every question included an additional option, “I cannot answer”, allowing evaluators to skip questions they are uncertain about. A “Not applicable” option is also available for the checklist items irrelevant to the chemical under evaluation. Furthermore, each response can be accompanied by a written justification to increase transparency.

This template can serve as a shared platform for the researchers to record the results of their evaluations and improve data availability of different environmental chemicals. A demonstration of the webapp user-interface has been provided in the supplementary file (Fig. S9) to give readers an overview of the application. The code for creating Rshiny template is openly available on GitHub. The PBK model evaluation checklist has been prepared using RShiny using the Shiny package (version 1.10.0) in RStudio (version 4.1.2).

6. Conclusion

The PBK model evaluation checklist used in this case study aids in application of OECD reporting template, thereby contributing to the harmonization of PBK model development and enhancing their use for regulatory purposes. This was also the first attempt to evaluate PBK models for PFAS family of compounds based on OECD reporting guidelines. Overall, this case study allowed us to identify several challenges in existing models, including the need to account for enterohepatic recirculation, to replace the delay compartment with a more biologically relevant one and many other harmonizing needs in the model development. From a model reporting prospective, there is a need to harmonize parameter names, abbreviations, and units in the reporting guidelines as well as reporting of output predictions. Such an evaluation provides direction for future research aimed at both harmonizing future PBK model reporting practices and improving existing models. Additionally, this case study shows the relevance of translating OECD guidance into a practical tool, as was also done with OECD guidance 211, which was translated into Tox Temp [42]. Finally, this evaluation can serve as a valuable reference for the PBK community including both developers and regulators and can be extended to a broader class of chemicals.

Funding Statement

This research was funded by the European Union co-funded project European Partnership for the assessment of Risk from chemicals (PARC) under grant agreement no. 101057014.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This study was financially supported by the European Union co-funded project European Partnership for the assessment of Risk from chemicals (PARC) under grant agreement no. 101057014. We also acknowledge contributions of all experts in the model evaluation.

Credit Author Statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comtox.2025.100381.

Data availability

Data will be made available on request.

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