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Authors
Dr. Soubhagya Baddi¹
Assistant Professor, Department of Mathematics and Psychiatry, Dayananda Sagar College of Engineering, Bangalore – 560111,
Orcid id: 0009-0009-8711-9082
Email Id: soubhagya-maths@dayanandasagar.edu

Dr.R.Nagarajan²
Professor Department of Mathematics
Specialization in Fuzzy Mathematics J.J College of Engineering & Technology, (Sowdambikka Group of Institutions), Tiruchirappalli - 620009, Tamilnadu, India,
Orcid ID: 0000-0002-7333-8710,
Email: rajenagarajan1970@gmail.com,

C.Dilly Rani³
Assistant professor Department of Mathematics, J.J College of Engineering & Technology, (Sowdambikka Group of Institutions), Tiruchirappalli - 620009 Tamil Nadu,
Orcid: 0000-0002-9809-0889,
Email ID: kani21bala@gmail.com

Dr. Poonam⁴
Assistant Professor, Department of Applied Sciences, Specialization in Mathematics, Noida, Institute of Engineering & Technology, Gr. Noida, Uttar Pradesh, India ,
Orchid id-0009-0006-1321-3541,
Email id-poonamsachin83@gmail.com

Dr. Prabhat Bansal⁵
Assistant professor, Institute of Applied Sciences Mangalayatan University, Aligarh (UP), India
Orcid id -0000-0001-9380-8700,
Email id- prabhat.bansal@mangalayatan.edu.in

Dr sunil kumar Srivastava⁶
Associate professor, Department of Biostatistics, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, ORCID: <https://orcid.org/0000-0003-2473-399X>,
Email ID: Shyam.sunil32@gmail.com, sunils.pharmacy@tmu.ac.in

Sai Krishna⁷
Assistant Professor, Applied science Specialization in Mathematics College - Harlal Institute of management and technology Gr. Noida, Uttar Pradesh, India,
Orchid id- 0009-0002-7515-316X, Email id-krishnabhardwaj.65@gmail.com

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Mathematical Approaches to Pharmacokinetics and Toxicological Risk Assessment

Abstract

Mathematical modeling has become an essential component of modern pharmacokinetics and toxicological risk assessment, offering systematic tools to describe, predict, and interpret the behavior of chemical substances within biological systems. This study presents a comprehensive and integrative examination of mathematical approaches used to characterize exposure dynamics, biological responses, and adverse outcomes across pharmaceutical and toxicological contexts. The work synthesizes deterministic and probabilistic pharmacokinetic frameworks, population-based modeling strategies, and quantitative toxicological risk assessment methods, with particular emphasis on their integration through coupled pharmacokinetic–toxicodynamic modeling. By incorporating sensitivity analysis, uncertainty quantification, and structured model validation, the study highlights how mathematical rigor enhances the credibility, transparency, and predictive reliability of risk estimates. The analysis demonstrates that dynamic and uncertainty-aware models provide significant advantages over traditional static and deterministic approaches by explicitly addressing variability, nonlinear behavior, and time-dependent effects. These modeling frameworks support more informed decision-making in drug development, safety evaluation, and regulatory science. The study further underscores the importance of adopting fit-for-purpose modeling strategies and standardized validation practices to ensure robust application in real-world scenarios. Overall, the findings emphasize that integrated mathematical approaches represent a critical pathway toward more accurate, biologically meaningful, and defensible pharmacokinetic and toxicological risk assessments.

1. Introduction-

The fundamental component of the modern drug development and chemical safety assessment is the risk assessment in pharmacokinetics and toxicology. Pharmacokinetics tries to mathematically simulate absorption, distribution, metabolism and excretion of compounds in the body, and toxicological risk assessment tries to make estimations on the likelihood and severity of adverse effects of exposure to chemicals. During the past 20 years, the two disciplines have been growing in their connection to each other through the model-informed drug development (MIDD) paradigm, which concentrates on quantitative models to assist in decision-making during the drug lifecycle (Bhat et al., 2025). This shift reflects an appreciation of the growing inadequacy of conventional empirical approaches to deal with the complexity, uncertainty and variability of biological systems and human populations. The use of pharmacometric modeling has made a great contribution to regulatory science and research in pharmaceuticals. Simulation-based approaches have lately gained relevance in dose choice, trial optimization, benefit-risk evaluation, and post-marketing studies (Madabushi et al., 2022). The effectiveness of quantitative decision-making has also been enhanced through the collaborative structures involving the integration of mathematical models of industry, academia, and regulatory agencies (Anziano and Milligan, 2020). The current development indicates that pharmacometrics ceased to be a supportive analysis tool and became a key element of strategic drug development, with applications in the case of small molecules, biologics, and complex therapeutic modalities (Xiong et al., 2025).

Though these progresses have been made, there are still serious problems in pharmacokinetic modelling and toxicological risk evaluation. Biological systems are highly nonlinear, time-dependent, and inter-individual variable and are hard to describe in terms of simplified deterministic models. Traditional pharmacokinetic models usually use deterministic estimates of parameters and mean population dynamics, and are less able to capture uncertainty and heterogeneity. In a similar manner, the conventional toxicological risk evaluation often relies on the concept of static safety factors and threshold-related assumptions, which are not fully valid to reflect low dose effects, cumulative exposures and vulnerable subpopulations. Although preliminary surveys showed how model-based drug development affects the industrial decision-making process, they also revealed the lack of standardization, transparency, and predictive reliability (Stone et al., 2010).

To address these shortcomings, the need for more sophisticated mathematical and probabilistic models that are more effective in describing system behaviour and uncertainty is increasing. Compartmental and physiologically based models are mechanistic mathematical models that offer an organized mechanism of connecting biological processes with measured data. But unless these models are supported by good uncertainty quantification and uncertainty validation strategies, one can have overconfident or misleading predictions. Recent advances in physiologically based biopharmaceutics and pharmacokinetic modeling describe the need to have strict base model construction, validation procedures, and well-defined application scenarios to guarantee regulatory and scientific validity of application (Heimbach et al., 2024).

Modeling methods based on probabilistic and population models can provide useful extension of classical models, which explicitly consider variability and uncertainty. These methods can be used to make more realistic predictions of exposure and risk in different populations by modeling model parameters as random variables instead of constants. This opinion is consistent with the general objectives of MIDD, which are not only to improve predictive accuracy but also to increase transparency, reproducibility, and trust in quantitative measurements to be utilized in making high-stakes decisions (Bhat et al., 2025; Madabushi et al., 2022). It is also important to note that mathematical rigour with the use of pharmacokinetics and toxicology enables conversion of the deterministic safety margins to the probabilistic risk characterisation, with the result that scientific validity and regulatory relevance are increased.

Research on the development of pharmacokinetics and toxicological risk assessment founded on integrated mathematical models is significant. Under such integration, internal dose measures can be explicitly linked to the likelihood of adverse outcomes, and time-resolved and mechanism aware risk can be estimated. The increasing complexity of the exposure setting, including chronic dosing, combination therapy, and special populations, is also an indicator that they

should be able to have mathematically sound and flexible modeling approaches (Xiong et al., 2025; Heimbach et al., 2024).

Objectives of the study

1. To systematically examine and synthesize advanced mathematical and probabilistic approaches used in pharmacokinetic modeling and toxicological risk assessment within a unified quantitative framework
2. To demonstrate how integrated mathematical models can enhance uncertainty characterization, predictive reliability, and decision-making in model-informed drug development and safety assessment

2. Mathematical Frameworks for Pharmacokinetic Modeling

The quantitative framework of pharmacokinetics is based on mathematical modeling which allows systematic modeling of drug disposition in biological systems. The frameworks have over time developed into highly mechanistic, physiologically-based pharmacokinetic (PBPK) models due to regulatory requirements and computational developments. The current regulation considerations focus on transparency, biological plausibility, and context-based model use and show the increased role of mathematically rigorous pharmacokinetic models (European Medicines Agency, 2018; Guidance, FDA, 2020).

2.1 Compartmental and Physiologically Based Pharmacokinetic (PBPK) Models

Compartmental models model the body as a network of rate constants between kinetically homogeneous compartments, usually as a system of ordinary differential equations. These models are still popular as they are mathematically simplified, computationally simple and can be applied to sparse clinical data. Nevertheless, they have low physiological explainability, which limits their extrapolation across populations, species, and dosage conditions.

Conversely, PBPK models explicitly include anatomical structure and physiological processes, in the sense that they model individual organs and tissues as a network of compartments (interaction of blood flow, tissue partitioning, and biochemical transformation). PBPK modeling is becoming more acceptable in regulatory agencies to use in dose selection, biopharmaceutics, and assessment of formulation or manufacturing changes (Guidance, FDA, 2020). According to regulatory science updates, PBPK models can be used as decision-support tools in cases of sufficient validation and documentation (Grimstein et al., 2019).

Detailed methodological treatments of PBPK modeling explain how the equations of the mass balance are parameterized by physiological constants and properties of the compound to extrapolate between exposure routes and populations (Fisher et al., 2020). Historical insights also illustrate how PBPK models have evolved over time since the field of environmental toxicology to the mainstream pharmaceutical development (Lin and Fisher, 2020).

The following table (Table 1) provides a brief summary of major mathematical and conceptual variations between classical compartmental models and

PBPK models. The table points out that the greater the biological realism, the greater the extrapolative ability, but with more demands in terms of parameter and data.

Table 1. Comparison of Compartmental and PBPK Pharmacokinetic Models

Feature	Compartmental Models	PBPK Models
Mathematical structure	Low-dimensional ODE systems	High-dimensional mechanistic ODE systems
Physiological realism	Limited	High
Parameter interpretation	Empirical	Physiological and biochemical
Regulatory application	Supportive	Increasingly decision-critical

2.2 Nonlinear Kinetics and Dynamic System Formulations

Saturable metabolism, capacity-limited transport and time-dependent physiological adaptation give many pharmacokinetic processes a nonlinear behavior. Such effects require non-linear rate models of dynamic systems. Michaelis-Menten metabolism, enzyme induction, and target-mediated drug disposition are usually described by the use of nonlinear differential equations as part of PBPK models (Fisher et al., 2020). Dynamic formulations can also be used to perform time-resolved exposure of different dosing programs and physiological conditions. The regulatory guidance indicates that nonlinear behavior has to be clearly justified, mathematically consistent and experimental data to prove the credibility of models (European Medicines Agency, 2018). The historical reviews of the development of PBPK also demonstrate the necessity of the nonlinear formulations to address the complex toxicological and pharmacological situations (Lin and Fisher, 2020).

2.3 Deterministic versus Stochastic Modeling Perspectives

Conventional pharmacokinetic frameworks are mostly deterministic models, which suppose constant parameter values and predictability of system behavior to a specific input. Deterministic models are not effective in modeling uncertainty and variability

associated with biological heterogeneity and data constraints although they are effective in describing average responses. Consequently, the regulatory assessments are becoming more and more dependent on the accompanying uncertainty analyses to put the model predictions into perspective (European Medicines Agency, 2018).

In stochastic perspectives, parameter values or system dynamics are given some randomness, commonly by use of Monte Carlo simulation and probabilistic sampling. These methods can be used to investigate variability of the population at the level of the population and confidence limits of exposure. The sensitivity and uncertainty analysis methods are highly developed in PBPK modeling and are regarded as a key to a strong interpretation and regulatory acceptance (Covington & Gearhart, 2020). These probabilistic extensions make pharmacokinetic models more than just descriptive models, and enable them to be predictive models that can be applied in risk-based decision-making.

Figure 1 is a conceptual representation of the development of deterministic compartmental models to stochastic PBPK models. The figure underlines the fact that the complexity of the model and the probabilistic approach to treatment make the model more biological and increase the predictive confidence, but more thorough validation is needed.

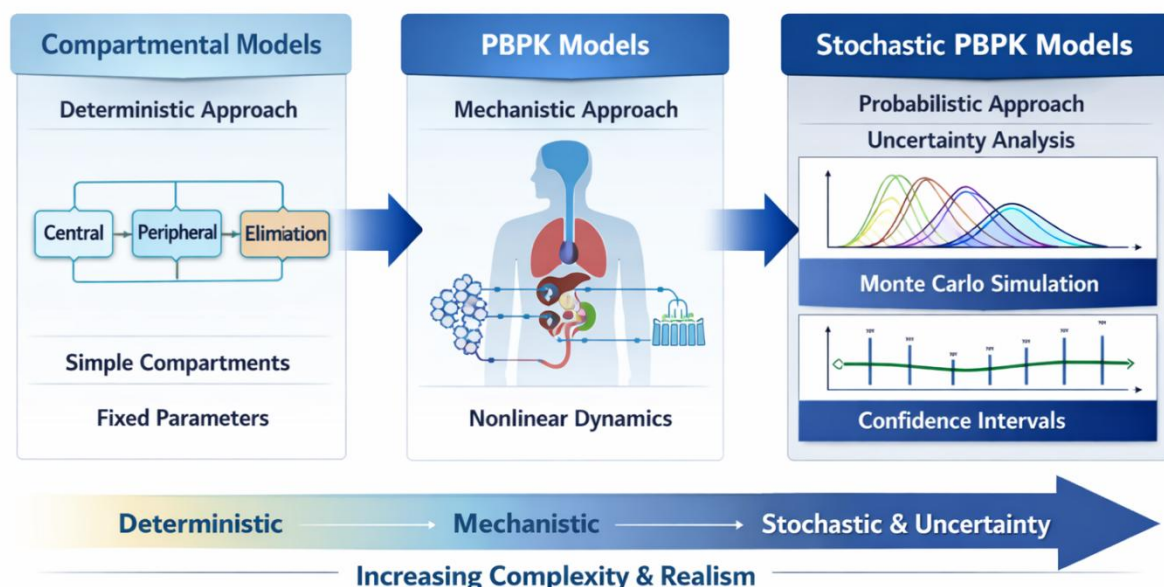


Figure 1. Conceptual evolution of pharmacokinetic modeling frameworks

The figure depicts the transition from simple deterministic compartmental models to mechanistic PBPK models augmented with stochastic and uncertainty analysis components, reflecting increasing regulatory and scientific expectations.

3. Probabilistic and Population-Based Modeling Approaches

Population-based and probabilistic modeling techniques are extensions of classical frameworks of pharmacokinetics that explicitly describe variability, uncertainty and heterogeneity between individuals and across populations. Modern pharmacometrics and toxicology are focused on these methods, which allow predicting drug exposure and risk in a more realistic way under a wide range of clinical and environmental conditions. Such models can enable precision dosing, risk assessment with a probability, and sound regulatory decision-making by replacing single-point estimates with distributions (Maertens et al., 2022).

3.1 Population Pharmacokinetics and Mixed-Effects Models

Population pharmacokinetics offers a statistical model of the analysis of drug concentration data versus time

on a population basis (a group of people at once). Mixed-effects models are used to break down pharmacokinetic parameters into fixed effects which models the typical population behavior, and random effects which models the inter-individual variability. This hierarchical form enables the analysis of sparse and unbalanced clinical data to be efficiently analysed and maintain biological interpretability.

Nonlinear mixed-effects modeling is now a common method of population pharmacokinetic analysis, with open-source and commercial software platforms. Such models are developed and simulated, which allows exploring covariate effects, dose-exposure relationships, and optimizing the trial design (Fidler et al., 2019). The best modeling practices focus on open documentation, reproducibility, and defining modeling goals to promote the scientific and regulatory credibility (EFPIA MID3 Workgroup et al., 2016).

Table 2 is a summary of important elements of population pharmacokinetic mixed-effects models. These effects are explained in the table which shows that fixed effects, random effects, and residual variability are all used to explain the observed concentration time data at the population level.

Table 2. Core Components of Population Pharmacokinetic Mixed-Effects Models

Model Component	Description
Fixed effects	Typical population parameter values
Random effects	Inter-individual variability
Residual error	Measurement and model noise
Covariates	Demographic or physiological predictors

3.2 Stochastic Differential Equation Formulations

Although mixed-effects models are used to model variability using statistical distributions, stochastic differential equation (SDE) formulations inject randomness into the equations of the dynamic system. Pharmacokinetic processes (absorption, or clearance) in this framework are modeled as stochastic processes, which also permit a representation of temporal variability and unobserved variability.

The models of SDE are especially effective when the deterministic formulations cannot reflect the observed variability or the system noise is a major factor affecting the exposure dynamics. Probabilistic modeling views emphasize the fact that the addition of stochasticity makes pharmacokinetic modeling more realistic and consistent with more general probabilistic risk assessment concepts (Maertens et al., 2022). Simulation exploration of the time-propagation of uncertainty is also possible using these formulations.

3.3 Bayesian Inference and Uncertainty Quantification

Bayesian inference It offers a consistent and probabilistic model of parameter estimation and uncertainty quantification in pharmacokinetic modeling. Bayesian techniques can obtain posterior distributions of parameters by integrating prior knowledge with observed data and contributes to the result with both evidence provided by data and prior

knowledge. This method is especially beneficial when there is a data limitation or when prior physiological data is provided.

Precision dosing based on model informed via pharmacokinetic modeling is shown to be useful in model guided Bayesian guided pharmacokinetic modeling, where individualized therapy is applied through constant revision of parameter estimates as new data becomes available (Aljutayli et al., 2022). In terms of risk assessment, the quantification of uncertainty in Bayesian is in favor of probabilistic decision making in that it deals with credible intervals and not single-point prediction.

3.4 Modeling Inter-Individual Variability

Inter-individual variability is caused by the differences in physiology, genetic, age, and disease condition, and environment. It is important to correctly describe this variability, both in pharmacokinetic prediction and toxicological risk assessment. The quantification of variability through population-based methods enables the use of variability in exposure and risk estimations and lessens the importance of the conservative default assumptions.

The integration of toxicokinetic variability into probabilistic models allows the narrowing of the uncertainty and safety factors which were common in risk assessment (Dorne & Renwick, 2005). This type of integration brings together pharmacometrics and

toxicology, which strengthens the use of population-based modeling as a common method of quantitative risk assessment. According to the best-practice guidelines, the explicit modeling of variability is a factor that improves transparency and scientific defensibility in the context of drug development and safety assessment (EFPIA MID3 Workgroup et al., 2016).

4. Mathematical Models for Toxicological Risk Assessment

Mathematical modeling has been at the heart of toxicological risk assessment to offer quantitative methods to correlate the chemical exposure with the likelihood and severity of adverse health effects. In contrast to pharmacokinetics which considers the dynamics of internal dose, toxicological modeling aims at translating the exposure into risk-relevant endpoints which are used in regulatory decision-making. Modern risk assessment is progressively becoming based on mechanistic and probabilistic mathematical methods to abandon conservative default assumptions in favor of transparent, data-driven, and reproducible judgments (Haber et al., 2018).

4.1 Dose–Response and Exposure–Response Relationships

Dose-response modeling forms the basis of the toxicological risk assessment process, determining the functional relationship between the administered or internal dose and the biological effect seen. Simple linear and threshold models have been used as mathematical forms representing saturation, hormesis, or adaptive responses. Exposure-response models take the framework further by actually considering the duration, frequency and route of exposure and thus more explicitly connects the toxicological effects to real life exposure situations.

The international guidance focuses on the need to choose dose-response models, which are biologically plausible, statistically robust, and fit available data (OECD, 2020). The uncertainty of model selection is identified as a crucial factor since mathematical representations may produce significantly varying risk estimates at low dosage. As a result, dose-response modeling requires transparency of reporting and sensitivity analysis as key elements in the framework of regulatory settings (EFSA Scientific Committee et al., 2022).

4.2 Time-Dependent and Cumulative Toxicity Models

Most toxicological effects are not only a matter of dosage magnitude but also of the duration and the time trends of exposure. Toxicity models Time-dependent Toxicity models also include dynamic processes, including accumulation, delayed effect onset, and recovery, and are frequently represented by systems of differential or difference equations. The models are especially applicable in chronic exposure situations, repeated dose, and long biological half-life contaminants of the environment.

Cumulative toxicity models are mathematical models that combine exposure with time to determine the total toxic burden, which can be used to determine risk at long-term exposure conditions. These practices are consistent with regulatory requirements that risk assessment needs to consider repeated and lifetime exposures as opposed to one-dose exposures (OECD, 2020). Combining time-resolved exposure measures and toxicological endpoint increases the usefulness of risk estimates in protecting human health.

4.3 Benchmark Dose Modeling and Low-Dose Extrapolation

Benchmark dose (BMD) modeling has become a quantitative technique of choice when obtaining points of departure in toxicological risk assessment. Instead of using no-observed-adverse-effect levels, BMD modeling uses mathematical dose-response curves to experimental data, and approximates the dose needed to produce a specified change in response. This method utilizes available information more efficiently and gives a statistically specified confidence limit on regulatory decision-making (Haber et al., 2018).

Regulatory advice emphasizes that BMD modeling must pay special attention to model choice, data quality, and uncertainty characterization especially in cases where the model is to be extrapolated to low dose areas that may be of interest to human exposure (EFSA Scientific Committee et al., 2022). Mathematical issues are model averaging, background response, thinly veiled or heterogeneous data. Through these obstacles, BMD modeling is now seen as an advanced scientific method in place of conventional threshold models.

Table 3 highlights major differences between the conventional threshold-based methods and benchmark dose modeling. The table shows that the BMD approaches enhance the statistical efficiency and uncertainty characterization and add complexity of modeling.

Table 3. Comparison of Traditional Threshold Approaches and Benchmark Dose Modeling

Aspect	Threshold-Based Methods	Benchmark Dose Modeling
Use of data	Limited to single dose	Uses full dose–response curve
Uncertainty quantification	Implicit	Explicit confidence bounds
Regulatory acceptance	Established	Increasingly preferred
Mathematical complexity	Low	Moderate to high

4.4 Quantitative Probabilistic Risk Metrics

The quantitative risk metrics convert dose response relationships that have been modeled into direct actions that guide regulatory decisions, e.g. probability of

adverse effect, margin of exposure, or population-level distributions of risks. Probabilistic models explicitly model uncertainty and variability and risk can be

represented as a distribution instead of a deterministic value.

Recent efforts focus on the fact that probabilistic risk assessment offers a more realistic and informative foundation of regulatory criteria development, especially in situations of variability across populations, and uncertainty in model inputs (Flinders et al., 2025). Probabilistic metrics combined with physiologically relevant kinetic modeling also improves the internal dose estimation and the connection between exposure and adverse effects (OECD, 2021). There is a growing regulatory support of such integrated frameworks, as long as models have been properly validated and reported.

On the whole, mathematical risk assessment models of toxicology are being changed to less conservative, deterministic paradigms to mechanistic and probabilistic models. It is an indication of an increasing regulatory and scientific agreement that uncertainty, variability, and biological complexity are to be explicitly considered so that credible and protective risk estimates could be obtained (Haber et al., 2018; EFSA Scientific Committee et al., 2022).

5. Integrated Pharmacokinetic–Toxicodynamic (PK–TD) Modeling

Integrated pharmacokinetic–toxicodynamic (PK–TD) modeling provides a quantitative framework for linking internal exposure to subsequent biological responses and adverse outcomes. By coupling pharmacokinetics with toxicodynamics, these models enable mechanistic interpretation of how time-varying internal concentrations translate into toxic effects. Such integration is increasingly recognized as essential for addressing complex exposure scenarios and improving the predictive power of toxicological risk assessment across pharmaceutical and environmental contexts (Vaidya et al., 2021).

5.1 Coupling Pharmacokinetics with Toxicodynamic Responses

PK-TD models are mathematical equations that relate concentration time profiles obtained using pharmacokinetic models with toxicodynamic functions used to describe the relationship between internal dose and biological effect. This connection supports explicit modeling of effect-site dynamics, latencies between exposure and effect and cumulative damage mechanisms. Pharmaceutical PK PK-TD models have been applied to determine organ-specific toxicity as well as aid in translating preclinical systems to human toxicity (Zou et al., 2020).

In environmental and regulatory toxicology, toxicokinetic toxicodynamic modeling is an extension of this idea to a population level of risk assessment, which is the association of outside exposure patterns with sublethal and chronic endpoints. It has been shown that PK–TD models are capable of modeling the impact of varying exposure histories and shifting time

windows on measured toxicity which cannot be sufficiently described with a fixed dose measure (Romali et al., 2024). Such coupled models are thus more biologically realistic in their risk characterization.

5.2 Nonlinear Feedback Mechanisms and Adaptive Biological Processes

Biological systems are commonly non-linear in their feedback and adaptive reactions, which change toxicity with time. Such mechanisms are included in PKTD models by nonlinear toxicodynamic functions, feedback loops and state-dependent parameters. These characteristics enable the models to indicate processes like tolerance formation, repair processes and compensatory physiological adaptations.

Quantitative systems toxicology methods emphasize the significance of adding feedback-based dynamics in terms of predicting long-term or cumulative toxicity in an accurate manner (Vaidya et al., 2021). The adaptive and life-history processes have been demonstrated to play a significant role in defining the toxicodynamic outcomes and risk interpretation in ecological and reproductive toxicology (Jager et al., 2021). The nonlinear and adaptive processes not included in the failure to account might result in biased risk estimates or overly conservative risk estimates.

5.3 Multiscale and Hybrid Mathematical Frameworks

Multiscale PKtD models are models that combine processes at various levels of biological activity, such as the molecular interaction and cellular damage processes, tissue-level dysfunction and organism-level outcomes. Hybrid mathematical models An example of these hybrid mathematical models is a deterministic pharmacokinetic model (with uncertainty and variability) that propagates uncertainty and variability across scales via stochastic or probabilistic toxicodynamic components.

This multiscale integration has been especially useful in translational toxicology, which requires a connection between mechanistic cellular outcomes and clinically relevant outcomes (Vaidya et al., 2021). Hybrid toxicokinetic-toxicodynamic models used in environmental risk assessment help to extrapolate species and exposure conditions by integrating biological realism into mathematically amenable frameworks (Romali et al., 2024). These strategies support the purpose of integrated PK -TD modeling as a harmonizing model between pharmacometrics and toxicological risk assessment.

Figure 2 conceptually depicts how an integrated PK model and TD model should be structured and how externally exposing an organism will drive to internal concentration, effect-site dynamics, and adverse outcomes. The figure underscores the fact that feedback mechanisms and multiscale interactions are incorporated in the coupled modeling framework in order to aid realistic prediction of toxicity.

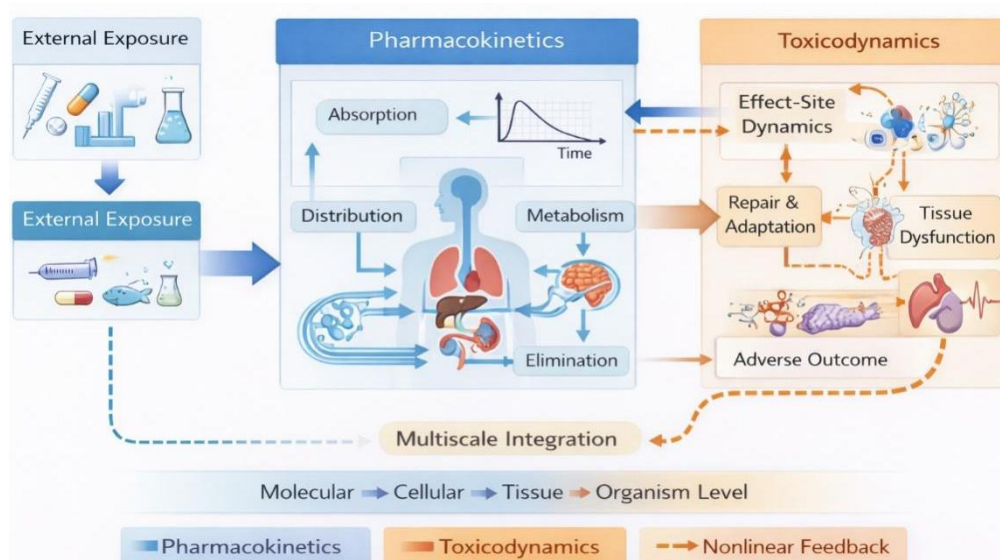


Figure 2. Conceptual structure of an integrated pharmacokinetic–toxicodynamic (PK–TD) modeling framework

The figure depicts the linkage between pharmacokinetic exposure dynamics and toxicodynamic response pathways, incorporating nonlinear feedback and multiscale biological processes.

6. Sensitivity Analysis, Uncertainty, and Model Validation

Mathematically driven pharmacokinetic and toxicological risk assessment frameworks include such critical elements as sensitivity analysis, quantification of uncertainties, and model validation. This has led to the need to prove the credibility, robustness and predictive reliability of models as they become more informative of high-impact regulatory and clinical decisions. The regulatory guidance and best-practice frameworks underline the fact that the model outputs should be viewed within the frame of uncertainty in terms of parameters, structural assumptions, and data constraints (European Medicines Agency, 2018; Kuemmel et al., 2020).

6.1 Local and Global Sensitivity Analysis Techniques

Sensitivity analysis is used to study the effects that the changes of model parameters have on outputs of interest, which may be internal dose measures or risk

measures. Local sensitivity analysis determines the impact of small changes about nominal parameter values and gives the behavior of models around calibrated solutions. Although local methods are computationally efficient, they might not be able to represent nonlinear interactions and parameter interdependencies.

Global sensitivity analysis mitigates these drawbacks through the exploration of the entire parameter space and the analysis of the relative significance of parameters within their plausible ranges. It has been shown that systematic reviews can be misleading when the sensitivity analysis is done inappropriately or incompletely, which is why it is necessary to use global methods on complex models in a rigorous and transparent manner (Saltelli et al., 2019). The regulatory-oriented modeling is then more inclined towards global sensitivity modeling to facilitate defensible decision making (European Medicines Agency, 2018).

Table 4 provides a summary of the conceptual difference between local and global sensitivity analysis methods. The table shows that global methods offer a more detailed view of model behavior because it comes at a higher computational cost.

Table 4. Comparison of Local and Global Sensitivity Analysis Approaches

Aspect	Local Sensitivity Analysis	Global Sensitivity Analysis
Parameter variation	Small perturbations	Full parameter space
Nonlinearity capture	Limited	Explicit
Interaction effects	Not captured	Captured
Regulatory relevance	Supportive	Increasingly preferred

6.2 Parameter Identifiability and Model Robustness

The identifiability of parameters is the capacity to estimate model parameters using the data available. Unidentifiability may lead to the occurrence of many combinations of parameters that give the same model outputs thus compromising the belief on prediction. It is necessary to use identifiability analysis to

differentiate well-informed parameters and weakly constrained or redundant parameters.

Model robustness is further than identifiability to determine how sensitive predictions of the model to model structure, assumptions, and parameter uncertainty. Model credibility frameworks highlight that robustness is to be assessed on the basis of systematic stress testing, scenario testing, and the clear

description of assumptions (Courcelles et al., 2024). These practices facilitate the confidence of model based findings, especially in the regulation.

6.3 Uncertainty Propagation and Confidence in Risk Predictions

Uncertainty propagation is a measure of the sensitivity of uncertainty in the inputs, parameters and model structure, which is then transferred to model outputs. Instead of making single deterministic predictions, uncertainty-aware models can make distributions of predictions, and the risk can be interpreted probabilistically. This methodology corresponds to the current regulatory requirements of the clear communication of confidence and uncertainty in quantitative measurements (European Medicines Agency, 2018).

The practice of modeling practice review has highlighted that overconfidence or misleading risk estimates may occur due to the inability to propagate the uncertainty as per the need (Saltelli et al., 2019). As a result, uncertainty analysis has become an essential part of a plausible pharmacokinetic and toxicological modeling, and not an incidental additional activity.

6.4 Application and Model Validation

Model validation determines how well a model is suited to the purpose for which it is developed. The validation can be done either by comparing it to external data, by assessing its predictive ability, or by qualitative agreement with established biological behavior. Notably, validation is context-specific and ought to be apt to the particular question of regulations or science under consideration (Kuemmel et al., 2020). Credibility assessment frameworks emphasize the fact that validation is not a dichotomous concept, and a graded process, but it incorporates evidence produced in the framework of model development, sensitivity analysis, quantifying uncertainty, and predicting performance (Courcelles et al., 2024). The conceptual model of the development of the model, sensitivity analysis, uncertainty evaluation and validation is shown in Figure 3. The number highlights that model credibility is developed through the combination of these elements and not through any of the steps of evaluations.

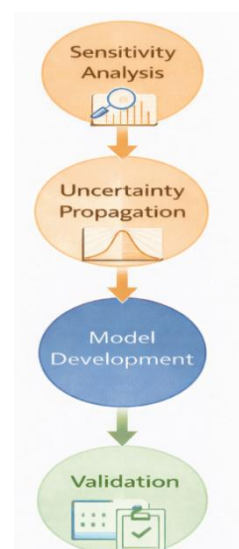


Figure 3. Conceptual workflow for model credibility, uncertainty analysis, and validation

The figure depicts an iterative modeling cycle linking sensitivity analysis, uncertainty propagation, and validation to support credible and fit-for-purpose model application.

7. Discussion

The current research paper provides a synthesis of mathematical methods in pharmacokinetic and toxicological risk assessment with a focus on the paradigms of probabilistic, mechanistic and integrative models. The above mentioned frameworks show together the role of mathematical rigor to improve understanding of exposure-response relationships by explicitly representing time dependence, variability and uncertainty. Specifically, integrated PK -TD models can be used to provide a direct connection between the internal dose dynamics and the adverse biological outcomes, which enhances the biological relevance and interpretability of risk estimates in both pharmaceutical and environmental settings (Romali et al., 2024).

The methods discussed in this paper have a better description of system behavior in a realistic exposure condition compared to the traditional deterministic pharmacokinetic and toxicological models. Traditional models usually use hard-coded parameters and hard-coded thresholds, which may hide significant nonlinearities and adaptive biological behaviors. By contrast, PK -TD and probabilistic models support the use of changing exposures, delayed toxicity, and feedback processes, which more closely align with the observed biological processes (Jager et al., 2021). The same benefits have been emphasized in drug delivery system pharmacokinetic-pharmacodynamic modeling where integrated models can provide better predictive power even with greater mathematical and computational complexity (Zou et al., 2020).

Regulatory and clinical-wise, sensitivity analysis, uncertainty quantification, and model validation should be integrated to make sure that conclusions made through models are credible and fit-for-purpose. Regulatory authorities are placing more focus on open

documentation, rationale of assumptions and objective assessment of uncertainty on physiologically based and pharmacometric models (European Medicines Agency, 2018; US Food and Drug Administration, 2018). Credibility assessment frameworks offer systematic instructions in the assessment of the appropriateness of models used in particular decision scenarios, which enhances the trust in model-driven drug development and risk assessment (Kuemmel et al., 2020; Courcelles et al., 2024).

The results mentioned here also point to the increasing significance of the probabilistic interpretation of risk. Instead of using only conservative point estimates, probabilistic risk measures enable the regulators and clinicians to assess the probability and the extent of adverse outcomes in each population. This change is beneficial to make more delicate decisions, especially to deal with inter-individual variability, vulnerable subpopulation, or complicated dosing schedules (Xiong et al., 2025). The use of the environment also shows that time-variable exposure modeling can significantly change the characterization of risks in contrast to fixed methods, highlighting the importance of dynamic mathematical models (Romoli et al., 2024). Despite these benefits, numerous weaknesses and practical concerns are to be considered. The modern mathematical models are very parameterized and require a lot of data to be parameterized and validated, which is not always the case. The lack of confidence in predictions and identifiability issues may occur due to ill-posed parameters. Besides, the absence of appropriate sensitivity analysis implementation can result in an incorrect conclusion, which is underlined by the systematic criticism of the current modeling practice (Saltelli et al., 2019). These problems emphasize the need of methodological rigor, transparency and adherence to best-practice.

massive adoption would also be hampered by computational complexity and expertise requirements, particularly in resource-limited regulatory settings. However, these obstacles are being slowly diminished through an additional development of standard operating procedures, open source software and regulatory policies. As pharmacometrics and systems modeling mature, the likelihood of applying mathematical practices in drug development and toxicological risk assessment increases, and their ability to achieve significant success increases (Xiong et al., 2025).

Generally, the discussion highlights that mathematical methods in their rightful implementation, verification, and interpretation have significant benefits over traditional ones. These models increase scientific credibility and relevance of decision by explicitly considering uncertainty, variability and dynamic biological processes. Additional consistency between methodological innovation and regulatory requirements will be required to see the full potential of mathematical modeling in the pharmacokinetics and toxicological risk assessment (European Medicines Agency, 2018; Courcelles et al., 2024).

8. Conclusions

The study has provided a detailed overview of mathematical methods of pharmacokinetics and toxicological risk assessment, with a specific focus on the key modeling frameworks of mechanistic, probabilistic, and integrative models to deal with the biological complexity and uncertainty. The work has demonstrated how mathematical rigor can help, in a better way to interpret the relationship between exposure and response and predict risk, by the same way using biological relevance, through systematic review of pharmacokinetic models, probabilistic and population-based models, toxicological risk assessment paradigms and integrated pharmacokinetic-toxicodynamic models. Both a sensitivity analysis and quantifying the uncertainties and formal validation of the model further support the credibility and transparency of model-based assessment and can be applied in regulatory and clinical decision-making. All these additions lead to the conclusion that the present risk estimation should no longer be based on deterministic and stable paradigms; it needs to be a dynamic and uncertainty-aware model capable of considering individual variations among individuals, and time-dependent effects. This is valuable since the research can be used to bridge pharmacokinetics versus toxicology in a single mathematical model so as to make better decisions concerning doses, safety evaluation, and risk management policies. The next round of future research should focus on larger measures of data integration on the biological level, better identifiability of parameters with new and advanced experimental designs, and greater use of adaptive and real-time models. To achieve effective and responsible use of mathematical models in drug development and toxicological risk assessment, more standardization of procedures, computer programs, and regulatory principles will be necessary. Lastly, these quantitative methods used systematically can contribute to the safety of the population's health, encourage the personal assessment of risks, and advance the scientific foundation of pharmacokinetics and toxicology.

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