ScitoVation
PIONEERS IN CHEMICAL SAFETY ASSESSMENT

ScitoVation Insight | Issue 4

PBPK Modeling in Regulatory Safety Decisions

Key message: Recent EPA and FDA activity highlights the growing role of pharmacokinetic and mechanistic modeling in regulatory safety assessment. Considering PBPK early in a tiered assessment strategy can help identify when internal dosimetry and human-relevant evidence can strengthen a safety decision.

Safety assessments often begin with an administered dose or an estimate of external exposure. However, the quantity most relevant to the safety decision may be different: how much of the chemical or its active metabolite reaches the relevant tissue, and for how long. Physiologically based pharmacokinetic (PBPK) modeling connects these quantities using information about the chemical and the organism. This connection can be especially useful when available toxicity data do not directly match the exposure route, population, or question a reviewer needs to address.

Recent regulatory examples show how internal-dose modeling is being used to evaluate specific chemicals and point to a wider role for PBPK and related approaches in regulatory safety assessment[1,2]. For sponsors, the opportunity is not simply to wait until PBPK modeling is requested, but to consider early in a tiered assessment whether PBPK modeling, quantitative in vitro-to-in vivo extrapolation (qIVIVE), or targeted pharmacokinetic data could improve the human relevance of the available evidence.

In this article, we explore recent examples of PBPK and related pharmacokinetic approaches that inform regulatory assessments and consider how these tools can add value in a tiered safety assessment.

How PBPK is becoming important in regulatory safety assessment: recent EPA examples

1. Two chemicals with explicit PBPK applications

The Environmental Protection Agency (EPA) notice dated June 22, 2026, identifies two PBPK applications submitted for scientific peer review. For 1,1,2-trichloroethane, EPA sought input on PBPK parameters and the model's use to derive an inhalation point of departure through route-to-route extrapolation. For ethylene dibromide, EPA sought input on a PBPK model with an in silico dermal component used to derive dermal human-equivalent doses[1].

These examples demonstrate how internal dosimetry can be used in EPA's assessment process to evaluate exposure routes that differ from those examined in the available toxicity studies[1]. They reinforce the value of considering human relevance when interpreting evidence from both in vitro and animal studies and of generating the pharmacokinetic data needed to support that interpretation.

2. Cypermethrin links modeling to a final decision

In an August 20, 2026, final pesticide-tolerance rule for the pyrethroid cypermethrin, EPA cited human PBPK models alongside in vivo and in vitro evidence on protein binding, enzyme development, and metabolic clearance when discussing age-related sensitivity to pyrethroids[2]. This example shows modeling contributing to the evidence supporting a regulatory decision, rather than a new instruction to commission a model. Table 1 summarizes these examples and the specific role PBPK modeling played in each regulatory context.

Table 1. Examples of PBPK applications in recent EPA assessments and regulatory decisions.

Compound	PBPK application	Regulatory status
1,1,2-Trichloroethane	Derive an inhalation point of departure across exposure routes	EPA application under peer review; June 22
Ethylene dibromide	Derive dermal human-equivalent doses with a dermal sub-model	EPA application under peer review; June 22
Cypermethrin	Inform the evidence on age-related pharmacokinetic differences	PBPK evidence cited in a final tolerance rule; August 20

Building the evidence behind age-related differences: ScitoVation's pyrethroid research, including cypermethrin

ScitoVation worked with the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) to investigate age-related pharmacokinetic differences across the pyrethroid class, including cypermethrin. In our related published work by Mallick et al., 2020, life-stage PBPK modeling supported by IVIVE was used to translate external exposure into predicted target-tissue concentrations in children and adults across multiple pyrethroids[3].

Recent guidance from FDA encourages the use of PBPK models early to assess hepatic function

On September 2, 2026, the Food and Drug Administration (FDA) released draft guidance on pharmacokinetics in patients with impaired hepatic function. The guidance encourages early characterization of the effects of hepatic impairment and, where feasible, the use of modeling and simulation to support the inclusion of these patients in clinical trials. It also connects dosage recommendations to hepatic function, drug exposure, and exposure-response relationships[4,5].

This draft guidance does not explicitly name PBPK, but it highlights the opportunity to consider PBPK early when evaluating how changes in hepatic function may affect drug exposure. A well-supported PBPK approach can integrate changes in metabolism, transport, protein binding, and physiology to explore their potential impact on internal exposure across patient populations.

Toxicokinetic data requests are a related opportunity

EPA's July 23 proposal identifies toxicokinetic testing as potentially useful for P-24-192, a paints, coatings, and inks ingredient with CAS 478549-43-8. The notice explicitly states that the order does not require those tests. This entry is separate from the sulfonium photolithography chemicals discussed in the same notice (also discussed in ScitoVation Insight Issue 3)[6].

Although a request for toxicokinetic information is not itself a request for PBPK modeling, pharmacokinetic measurements can provide important inputs for understanding internal exposure and developing or refining a PBPK model. This creates an opportunity to consider the broader human-relevance question early: what pharmacokinetic information is needed to understand the relationship between external exposure and internal dose, and could PBPK help integrate those data into the safety assessment?

How ScitoVation approaches PBPK strategy

Considering PBPK early in a tiered safety assessment helps shape the evidence plan before key pharmacokinetic data gaps become limiting. ScitoVation scientists start with the safety question and available evidence to determine whether internal dosimetry could materially improve the assessment (Figure 1).

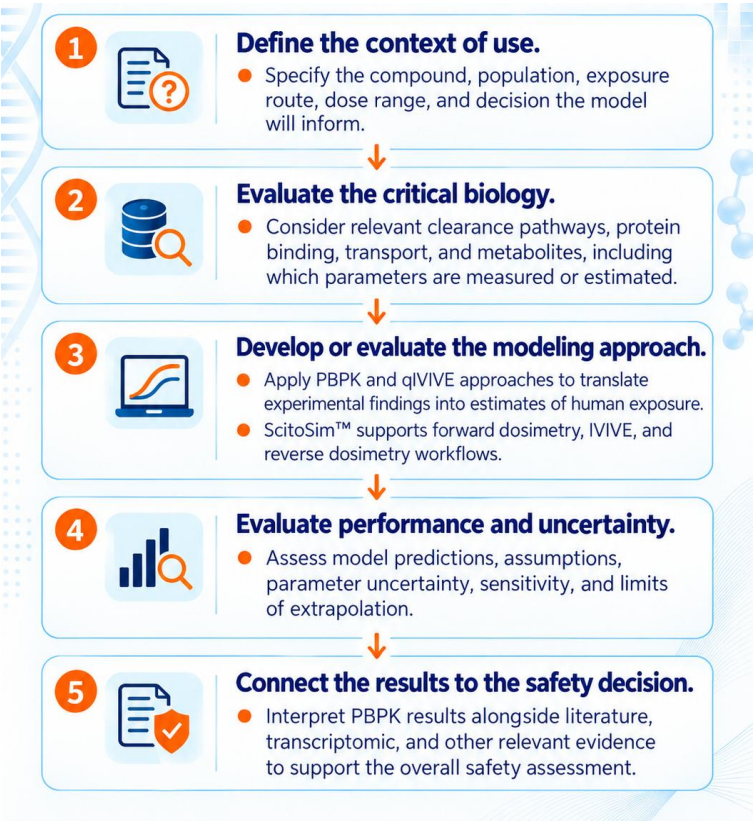


Figure 1. How ScitoVation supports a PBPK strategy.

The approach is then tailored to the specific decision. Route-to-route extrapolation, hepatic impairment, and comparison of child and adult exposures, for example, may each require

different data, assumptions, and demonstrations of model performance. This may involve identifying data gaps, designing targeted pharmacokinetic studies, evaluating an existing model, or developing a fit-for-purpose PBPK or qIVIVE approach.

ScitoSim™ enables this workflow with PBPK capabilities including forward dosimetry, IVIVE, reverse dosimetry, sensitivity analysis, and evaluation of variability in predicted exposures. ScitoVation scientists interpret the resulting outputs in the context of the safety question and, where appropriate, integrate them with the literature, transcriptomic data, and other relevant evidence.

The aim is to use PBPK where internal-dose information can meaningfully reduce uncertainty or improve the human relevance of the evidence, while identifying early what biological and pharmacokinetic data are needed to support a credible analysis.

The takeaway: Consider internal dosimetry before it becomes a data gap

Recent regulatory examples show that PBPK and related pharmacokinetic approaches are increasingly being used to answer questions that external exposure alone cannot resolve, including route-to-route extrapolation, age-related differences, and impaired hepatic function.

For sponsors, the practical opportunity is to consider PBPK earlier in a tiered safety assessment rather than waiting until modeling is requested. Doing so can identify the necessary pharmacokinetic information, clarify whether existing in vitro or animal evidence addresses the human safety question, and determine whether internal dosimetry could reduce uncertainty.

Facing a route-to-route extrapolation, a sensitive-population question, or a request for pharmacokinetic information? Share the compound and the decision you need to support, and we can help you determine whether PBPK would add useful evidence and what a credible modeling plan would require.

Discuss a PBPK strategy with a ScitoVation scientist

References

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