Computational Toxicology 39 (2026) 100445

Contents lists available at ScienceDirect

Computational Toxicology

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

Full length article

PBPKO: an ontology for standardizing and harmonizing physiologically based pharmacokinetic (PBPK) models☆

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ARTICLE INFO

Editor name: Daniel Dietrich

Keywords:
Ontology
Physiologically based pharmacokinetic model (PBPK)
Semantics
FAIR
Pharmacokinetics
Mathematical modelling

ABSTRACT

Physiologically Based Pharmacokinetic (PBPK) Modelling have emerged as a critical method in pharmaceutical and environmental sciences. Despite its widespread adoption, inconsistent vocabulary used across models, software platforms, and literature remains a significant challenge. Such inconsistency limits the potential for data harmonization and model interoperability. This gap also hinders the adoption of machine-readable semantic technologies that could enhance PBPK model reporting, validation, and interoperability.

To address this gap, we developed PBPKO (Physiologically Based Pharmacokinetic Ontology), a dedicated ontology for the kinetic modelling community. PBPKO captures mechanisms and terminology commonly used in PBPK modelling, including concepts related to physiological parameters, biochemical parameters, biological processes, enzymes, transporters, and related concepts. As of release of v2026-07-15, the ontology comprises 858 classes and 7 object properties native to PBPKO. To support semantic interoperability within the broader biomedical ontology ecosystem, PBPKO is aligned with upper-level ontologies such as the Basic Formal Ontology (BFO) and the Relation Ontology (RO), and reuses terms from established resources including Gene Ontology (GO) and the Ontology for Biomedical Investigations (OBI).

In this work, we further applied PBPKO to the annotation of PFAS multi-compartment PBPK models as a case study, while also highlighting the parallel development effort of "FAIR PBPK Inspector", which leverages the ontology for model annotation. Together, these efforts support FAIR sharing of PBPK models and facilitate their regulatory acceptance through improved standardization. PBPK ontology is accessible with CC4 licences on https://github.com/InSilicoVida-Research-Lab/pbpko .

1. Introduction

The concept of Physiologically Based Pharmacokinetic (PBPK) modelling originated with Teorell's physiological models for drug distribution and elimination [42]. These models use compartments representing biological organs and tissues, interconnected by blood flow rates and governed by ADME (Absorption, Distribution, Metabolism, and Excretion) parameters, to describe compound kinetics.

Despite widespread adoption, PBPK modelling faces persistent challenges in model harmonization, data integration, and knowledge sharing [21,43]. A key issue is the lack of standardized terminology across modelling platforms and databases [39]. For instance, equivalent parameters may be labeled as "hepatic blood flow," "liver blood flow," or "blood flow to liver" in different tools, hindering automated model comparison and integration. Relevant data are further scattered across diverse sources, forcing modelers to manually search and harmonize

☆ 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.2026.100445
Received 11 May 2026; Received in revised form 16 July 2026; Accepted 11 August 2026
Available online 12 August 2026

information [45]. The adoption of FAIR (Findable, Accessible, Interoperable, and Reusable) principles is increasingly recognized as essential for enabling standardized, data-driven chemical risk assessment [32]. Regulatory agencies compound this challenge with varying expectations for model documentation, potentially causing miscommunication between developers and reviewers [16]. Several ontologies address aspects of this domain but fall short of comprehensive PBPK coverage. The PK Ontology [45] formalizes terminology for in vitro and in vivo clinical pharmacokinetic studies and their design methods to support text mining tasks. The pharmacodynamics ontology framework [18] captures dose-response relationships and mechanisms of action but does not extend to physiologically based modelling structures. The Drug Interaction Ontology [46] and DINTO [15] provide formal representations of drug-drug interactions and their mechanisms but are restricted to interaction phenomena rather than the broader physiological modelling framework. The BioAssay Ontology extension for PK/PD terms [36] supports bioassay annotation for electronic laboratory notebooks (ELNs) and data harmonization. Critically, none of these ontologies address the cross-domain integration needed to unify PK, toxicokinetic, and physiologically based modelling terminology under a single standardized framework.

Furthermore, among the aforementioned ontologies, only DINTO was developed in accordance with The Open Biological and Biomedical Ontologies (OBO) Foundry community guidelines (https://obofoundry.org/principles/fp-014-guidelines.html). However, its current status is deprecated. Adherence to such community standards is essential, as it enables interoperability with existing life sciences ontologies and supports knowledge sharing and reasoning across systems.

To address these gaps, we present PBPKO (Physiologically Based Pharmacokinetic Ontology), a comprehensive, machine-readable ontology covering the kinetic modelling domain, including pharmacokinetic (PK), toxicokinetic (TK), physiologically based pharmacokinetic (PBPK), physiologically based kinetic (PBK), physiologically based biokinetic (PBBK) and physiologically based toxicokinetic (PBTK) modelling. Developed following OBO Foundry best practices, PBPKO provides a formal vocabulary for describing tissue compartments, physiological parameters, ADME processes, model structures, and their interrelationships. By unifying terminology across these related but currently fragmented domains, PBPKO aims to facilitate model comparison, data integration, regulatory communication, and computational tool development within the modelling community.

2. Methodology

2.1. Conceptualization

The first step of the workflow (Fig. 1) focused on identifying and defining the core concepts required to represent PBPK modelling knowledge. PBPK core concepts were compiled and refined through a systematic review and manual mapping process carried out in collaboration with PBPK domain experts and semantic experts. This collaborative effort produced an initial set of PBPKO terms and a corresponding PBPK conceptual model that served as the foundation for subsequent formalization.

To ensure interoperability and compliance with FAIR principles [44], PBPKO was not developed in isolation. Instead, it reuses and builds on established, high-quality biomedical ontologies from the OBO Foundry [41] and other relevant sources. This approach avoids the reinvention of core concepts and anchors PBPKO within the broader semantic biology ecosystem. Detailed workflow is presented in Fig. 1.

PBPKO formally imports two ontologies: the Ontology for Biomedical Investigations (OBI) [3] and the Relation Ontology (RO) (Index - OBO Relation Ontology), RO is aligned with the Basic Formal Ontology (BFO) [35] as a top-level ontology. Notably, both BFO and RO are recommended ontologies within the OBO Foundry community.

OBI provides a framework for describing scientific investigations,

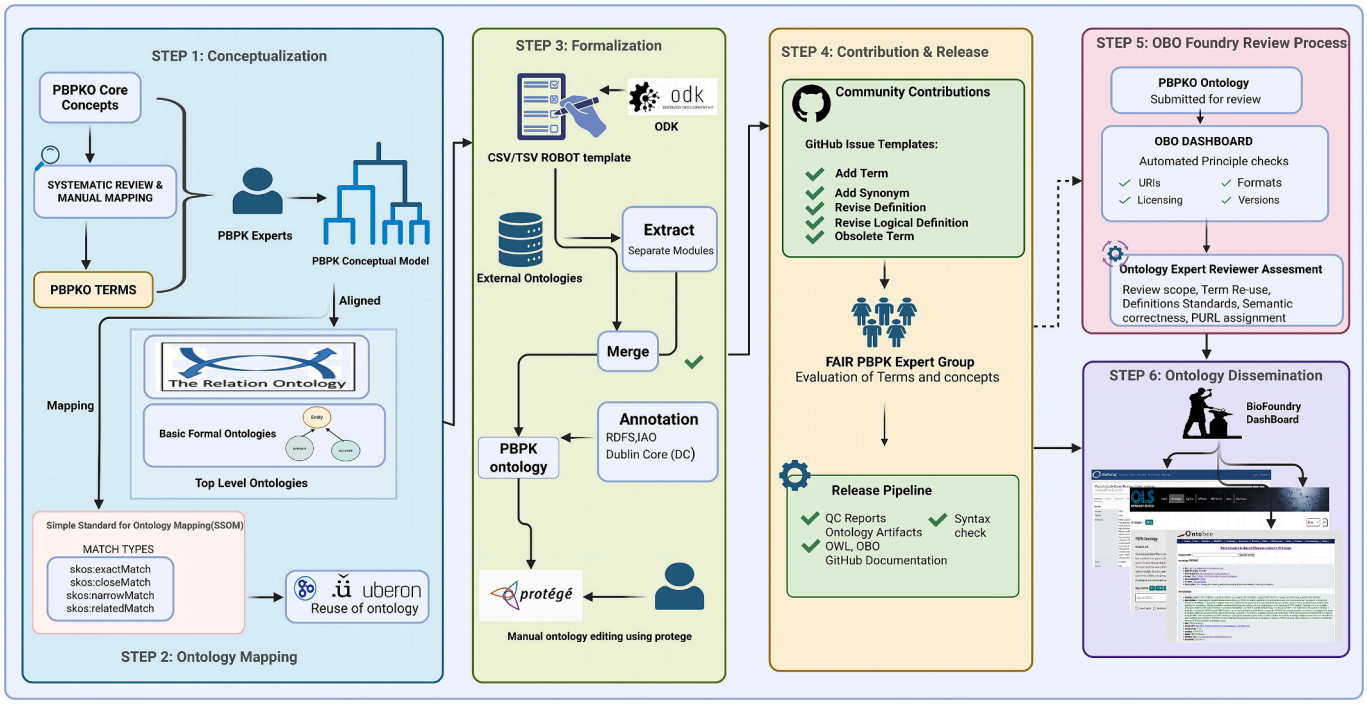

Fig. 1. Workflow for the development of PBPKO. **(1)** Domain experts first define the scope of the ontology and identify relevant PBPK modelling terminology through a systematic literature review. **(2)** The identified terms are aligned with top-level ontologies, including Basic Formal Ontology (BFO) and Relation Ontology (RO), and mapped to existing domain ontologies where appropriate. **(3)** The curated and mapped terms are formalized into ontological structures and reviewed by semantic experts to ensure logical consistency. **(4)** Community feedback is collected through structured GitHub issues. **(5)** Proposed changes are evaluated by domain and semantic experts before integration into the ontology. **(6)** The updated ontology is released periodically through ontology repositories and submitted for acceptance into the Open Biological and Biomedical Ontologies (OBO) Foundry.

including the models, data, and processes involved, and is leveraged by PBPKO for its upper-level structure (Fig. 2). RO provides a standardized set of relationships for use in biomedical ontologies and underpins PBPKO's custom object properties. This ensures that the relationships within PBPKO are logically consistent and can be interpreted by standard reasoners and semantic tools. Beyond these formal imports, PBPKO selectively incorporates terms from other domain-specific ontologies such as GO [2], UBERON [33].

2.2. Ontology mapping using SSOM

The primary aim of developing PBPKO was to reuse relevant concepts from existing ontologies wherever possible, introducing new terms only when no suitable equivalent existed. Following the initial development of PBPKO, a systematic review of external ontologies was performed to identify equivalent or related concepts. Identified correspondences were recorded in the Simple Standard for Sharing Ontological Mappings (SSSOM) format [29,30], enabling consistent representation of relationships between PBPKO terms and terms from other ontologies (Table 1). For each candidate pair, four SKOS match types were considered skos:exactMatch (6), skos:closeMatch (102) 108 mappings in total, covering 89 PBPKO subjects and 20 target ontologies). All correspondences were curated manually (semapv:ManualMappingCuration) and are shared in GitHub repository.

This mapping process ensures that PBPKO remains interoperable with widely used biomedical ontologies, facilitating integration with external datasets and concepts.

2.3. Ontology formalization

The lightweight ontology was formalized using OWL (Web Ontology Language) [1]. OWL was developed for using ontologies over the World Wide Web and has emerged as a standard language for representing knowledge in the Semantic web. The initial version of the ontology was created using Protégé to define core classes and link them using object properties.

Manually formalizing an ontology using the OWL descriptive language and linking it to other ontologies can be a tedious process, as terms beyond those mapped also need to be imported. To automate this, the ROBOT [20] tool template method was leveraged. ROBOT enables the specification of vocabulary terms in CSV or TSV templates, where the first two rows are designated for annotations, and the subsequent rows define the terms to be incorporated into the ontology. The first annotation row is intended for human-readable content, while the second row contains terms for machine-readability, drawing on top-level ontology annotations.

The "template" command was used first to create the base PBPK ontology from CSV/TSV files containing PBPK terms. This was followed by the "extract" command to extract terms from external ontologies and create separate small modules using MIREOT [9], which preserves the hierarchy but not full logical entailments. Finally, the "merge" command was used to combine the base PBPKO ontology with the imported modules.

RDFS (Resource Description Framework Schema) [7], IAO (Information Artifact Ontology) [5], SKOS (Simple Knowledge Organization Schema) [14], and Dublin Core ontologies (DC) [22] were used to annotate properties such as IDs, labels, synonyms, and editors. Specifically, SKOS terms were used to reference closely related terms within the PBPKO. Additionally, terms from other ontologies were reused: for instance, the Uberon ontology provides terminology for various organ-related concepts. Furthermore, the Gene Ontology (GO) is referenced for the term "excretion," which pertains to biological processes. The SSOM mappings developed during the mapping stage were also used to annotate terms with close and related matches. Manual ontology editing and refinement were carried out using Protégé[34] throughout this stage.

The latest release(v2026-07-15) of the PBPK ontology has been migrated to the Ontology Development Kit (ODK)[29,30], a standardized framework widely used in the OBO Foundry community to streamline long-term ontology maintenance. ODK reorganizes the repository into a modular, reproducible layout in which all native PBPKO classes, object properties, labels, definitions, and logical axioms are authored in a single edit file (pbpko-edit.owl) using Protégé, while release artefacts (pbpko.owl, pbpko-base.owl, and related OBO exports) are generated automatically and are not edited by hand. This edit-file-only workflow replaces the earlier ROBOT template seed approach for native terms, although ROBOT remains central to the build pipeline.

ODK further automates import management through slim modular imports: only the foreign terms required for structural axioms are extracted from upstream ontologies (BFO, GO, OBI, RO, and IAO) into per-source import modules using seed term lists and MIREOT-based extraction, rather than importing entire external ontologies. Cross-ontology references that serve annotation purposes only such as mappings to UBERON, FMA, BTO, and SBO are maintained separately as SSSOM mappings, keeping the release ontology lean while preserving semantic links established during the earlier mapping stage. Build steps (import refresh, merge, reasoner checks, and release preparation) are orchestrated through standardized Make targets executed inside a Dockerized ODK environment, ensuring that all contributors and continuous integration (CI) pipelines produce identical outputs.

Quality control and release governance are also standardized. On every pull request and push to the main branch, GitHub Actions runs ROBOT validation reports and custom SPARQL checks (e.g., ID format, metadata completeness, and logical consistency) against the edit and base artefacts. Successfully builds automatically refresh committed release files at the repository root. Dated releases follow OBO Foundry versioning conventions (vYYYY-MM-DD), triggered by a release commit; the workflow then sets owl:versionIRI and related metadata, generates a changelog and ontology diff report, creates a GitHub Release with OBO/OWL assets, and archives the release on Zenodo for persistent citation. PURL configuration enables stable resolution of both the latest ontology (http://purl.obolibrary.org/obo/pbpko.owl) and version-specific snapshots. Contributor workflows, import policies, and release procedures are documented in a MkDocs [31] site and in repository guides, supporting transparent community curation through GitHub issue templates and pull-request review. Together, these ODK practices reduce manual merge errors, enforce OBO Foundry best practices, and provide a

Table 1
Ontologies cross-referenced for SSOM mapping with PBPKO.

Ontology	Abbreviation	Number of mappings
Uberon multi-species anatomy ontology	UBERON	48
BRENDA Tissue Ontology	BTO	10
Ontology of Biological Attributes	OBA	9
Foundational Model of Anatomy	FMA	9
Systems Biology Ontology	SBO	7
Medical Subject Headings	MeSH	3
Exposure Ontology	ExO	3
Gene Ontology	GO	2
SNOMED Clinical Terms	SNOMED CT	2
Experimental Factor Ontology	EFO	2
Chemical Entities of Biological Interest	ChEBI	2
Toxic Process Ontology	TXPO	2
Ontology of Genes and Genomes	OGG	2
Clinical Measurement Ontology	CMO	1
Phenotype And Trait Ontology	PATO	1
Semantic science Integrated Ontology	SIO	1
Gender, Sex, and Sexual Orientation Ontology	GSSO	1
Ontology of units of Measure	OM	1
Logical Observation Identifiers Names and Codes	LOINC	1
Vertebrate Trait Ontology	VT	1
Total		**108**

sustainable foundation for ongoing PBPKO extension and maintenance.

2.4. Community contribution

The PBPKO development supports community contribution management through structured GitHub issue templates. This standardized workflow enables contributors to request changes, additions, or report problems using predefined templates that ensure complete information capture (Table 2).

These templates automatically assign appropriate labels (e.g., "new term request") and can be configured to assign specific ontology maintainers to review requests. Submitted contributions are evaluated by the FAIR PBPK Expert Group, which assesses the proposed terms and concepts before they are incorporated into the ontology.

2.5. OBO foundry review process

PBPKO was developed following the principles (https://obofoundry.org/principles/fp-000-summary.html) of the OBO Foundry and underwent a rigorous process before acceptance. The initial submission of the ontology was processed through automated evaluation via the OBO dashboard, which implements programmatic checks to ensure adherence to OBO Foundry principles. The automated assessment evaluates compliance across multiple dimensions including licensing, format validation, URI conventions, versioning practices, and basic structural integrity. Following automated review, domain expert reviewers were assigned to evaluate the ontology based on scope, term reuse, collaboration, and textual definitions. The ontology went through a transparent iterative revision cycle ensuring higher quality standards, reusability and consistency with broader biomedical ontology ecosystem standards. The whole review process is documented in the following GitHub issue (https://github.com/OBOFoundry/OBOFoundry.github.io/issues/2563).

Following successful OBO Foundry review, PBPKO is disseminated through the OBO Dashboard, which propagates the developed artifact to other ontology portals such as BioPortal (https://bioportal.bioontology.org/ontologies/PBPKO), OLS (https://www.ebi.ac.uk/ols4/ontologies/pbpko) and OntoBee (https://ontobee.org/ontology/PBPKO). This ensures broad accessibility and supports adoption by the wider PBPK and biomedical modelling communities.

3. Results and discussion

3.1. Conceptualization of the PBPK ontology

PBPK models range from one-compartment to multi-compartment representations, with complexity depending on the compound structure and the available experimental data. Grouping these heterogeneous models into a coherent set of parent classes for a uniform ontology was therefore a major bottleneck during the conceptualization stage. Drawing on existing knowledge in the field and guided by expert input from the joint semantic and PBPK working group, the decision was made to organize the first version of PBPKO around five major parent classes (Table 3), i.e., physiologically based pharmacokinetic model, compartment, parameter, biological process, and transporter (Fig. 2). All other terms were grouped under these parent classes as subclasses based on their relevance..)

3.1.1. PBPK model

The first section mainly focused on different types of PBPK models which have been developed over the years to describe the compound PK using mathematical modelling techniques. It combines principal PBPK modelling approaches, model types, and subtypes. This class includes several miscellaneous models and approaches which in future can be further improved (Fig. 3 A).

3.1.2. Compartment

In the PBPK model, each biological organ or tissue is represented by its anatomical or physiological properties through compartments and further into sub-compartments which represent the lowest level of structural differentiation [25]. Some of the major compartments included are gut, brain, kidney, lungs, heart, intestine, blood, and rest-of-body compartments. Sub-compartments of the digestive system and excretion compartments (urine and feces) are also included. Generally, two blood compartments, arterial and venous blood, connect the organs in PBPK but these are often replaced by plasma. Sometimes, to reduce the complexity of models, poorly perfused and richly perfused tissues are included in the model where compounds can metabolize or stay depending on ADME.

3.1.3. Parameter

The parameter class is broad in PBPKO which includes all the biochemical, physicochemical, and physiological terms being used in building and optimizing the PBPK models (Fig. 3B). PBPK models require a variety of biochemical parameters like absorption rate

Table 2
Issue template for PBPKO.

Template Category	Purpose
Add Term Template	For new PBPK term requests, requiring preferred labels, synonyms, definitions with PubMed citations, parent term relationships, and contributor ORCID attribution.
Add Synonym Template	Suggesting new synonyms for existing PBPK terms.
Revise Textual Definition	Improving term definitions with proper citations.
Revised Subclass Relationship	Modifying hierarchical relationships between PBPK concepts.
Revise Logical Definition	Improving OWL-DL axiomatization.
Obsolete Term Template	For deprecating outdated or incorrect terms.
Typos/Bugs/Errors Template	For general quality control issues.

Table 3
Core classes of the PBPK ontology.

Classification	ID	Description
physiologically based pharmacokinetic model	PBPKO:00003	A data representation model that predicts the absorption, distribution, metabolism, and excretion (ADME) of chemical substances in biological species based on physiological principles using mathematical modelling techniques. It encompasses the various types of PBPK modelling approaches in use.
compartment	PBPKO:00446	A data representation model component representing a distinct physiological space (organ, tissue, fluid) where ADME processes occur. Refers to the various organs or locations in the body where a chemical or xenobiotic interacts.
parameter	PBPKO:00002	A data item involved in PBPK modelling. It comprises the various factors and corresponding values necessary to construct PBPK models.
biological process	GO:0008150	Comprises the various biological processes such as absorption, distribution, metabolism, and excretion.
transporter	PBPKO:00217	A material entity representing a protein responsible for the import or export of compounds across cell membranes.

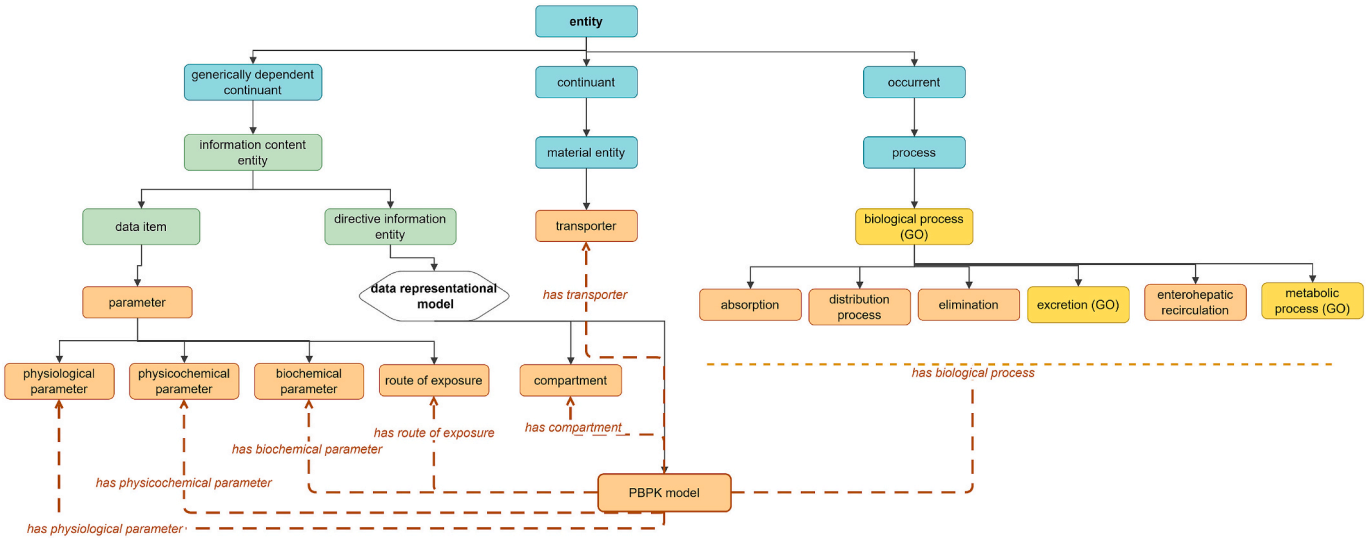

Fig. 2. High-level organization of PBPKO classes and their alignment with top-level and domain ontologies. PBPKO classes (orange) are anchored under the Basic Formal Ontology (BFO; blue), and reuse terms from the Information Artifact Ontology (IAO; green), the Ontology for Biomedical Investigations (OBI; white), and the Gene Ontology (GO; yellow). Solid arrows indicate subclass (is-a) relationships, while dashed arrows represent object properties, linking the central PBPK model class to its parameters, compartments, biological processes, routes of exposure, and transporters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

constant, partition coefficient, protein binding, unbound fraction, dissociation constant, rate of metabolic reaction among others to accurately predict the pharmacokinetics and tissue distribution of compounds. Physicochemical parameters are lipophilicity, water solubility, distribution coefficients, molecular weight, hydrogen-bond acceptor and donor counts, etc. primarily describing the structure of the compound. Physiological parameters refer to known physiology and correspond to blood flow and volume of different organs or tissues in the body. Additionally, demographic data like height, body weight, surface area etc. are also included to introduce the population variability in the model. A detailed description of the terms associated with these parameters can be found in the ontology file.

Additionally, we have included the route of exposure, PBPK model simulation time and some output generated from the PBPK model in parameter class. This can be considered a little controversial but to reduce complexity and facilitate analysis of these terms, based on expert opinion it was considered as a part of "parameter". In general, there is a fixed value for exposure, like dermal, inhalation, intraarterial, intrathecal, intravenous bolus, intravenous infusion, nasal, ocular, oral, subcutaneous and transdermal exposure, so it was included in parameters. In PBPK, output mostly includes area under curve, maximum plasma or organ concentration (Cmax), mean residence time (MRT), and many more which are fixed values or value ranges and hence can be included in parameter.

3.1.4. Biological process

Biological process in PBPKO refers to the core PK processes like absorption, distribution, elimination, metabolism and excretion which are mostly compound-specific inputs (Fig. 3C). Some of these ADME processes are also included as biochemical parameters since they have specific values for a specific compound. Based on PBPK knowledge, the biological process can be included in biochemical parameters but since most of the terms here were defined in Gene Ontology as biological events, it was imported as such and considered a separate class.

3.1.5. Transporter

Transporter refers to membrane transport proteins which are mostly involved in compound disposition and distribution affecting the ADME profile [37]. There are hundreds of transporters involved in this phenomenon but here we include only three major transporters ABCC2, ABCC3 and OATP. This class will be further extended to include multiple transporters in the next version of PBPKO along with the mechanistic actions and associated equations.

3.2. Classes and relations

The release v2026-07-15 of the (PBPKO) includes over 858 classes and 7 relations native to PBPKO, supplemented by classes and relations imported from established ontologies such as the Ontology for Biomedical Investigations (OBI), the Relation Ontology (RO), and the Gene Ontology (GO). This structure allows PBPKO to focus on its domain while leveraging robust, community-accepted definitions for foundational concepts. The high-level organization of PBPKO is depicted in Fig. 3. The ontology is anchored by the central class "physiologically based pharmacokinetic model", which is defined as a type of data representation model from OBI. This core class is linked with the other essential components using a set of newly defined object properties (which form sub properties of object properties defined in Relation Ontology).

3.3. Application of PBPKO

3.3.1. Harmonizing PBPK models

To demonstrate the broader applicability of PBPKO in the toxicology domain, three previously published PBPK models (Table 4) were annotated: (i) a pregnancy BPA (Bisphenol A) model [38], (ii) a pediatric BPA model [12], and (iii) a dynamic, age-dependent PFOS (perfluorooctanesulfonic acid) model [11] (Table 4). All three models were originally implemented in R and were first converted to Antimony and subsequently to SBML (Systems Biology Markup Language) [17] format prior to annotation (Fig. 4).

The pregnancy BPA model comprised five compartments and 51 parameters, of which 49 (96.1%) were successfully annotated with PBPKO terms; only hematocrit (Hct) and the absorption rate constant (Kabs) lacked suitable matches. The pediatric BPA model similarly comprised five compartments and 41 parameters, of which 40 (97.6%) were annotated, with Kabs again remaining unmapped. The complete list of annotated terms for both models is provided in Supplementary Files . All the annotated model are available in supplementary.

For the PFOS model [11], 86 out of 99 model parameters such as

Fig. 3. Hierarchical classification of PBPK model types under the A) central class physiologically based pharmacokinetic model (PBPKO:00003). Subclasses include organ-specific models (gut, lung, kidney, brain), population and life-stage-specific models (population, pregnant, lactational), structural model types (whole body, one-compartment), mechanistic approaches (perfusion-limited, permeability-limited), and parameterization strategies (top-down, bottom-up). B) Parameter class (PBPKO:00139) in PBPKO consisting biochemical, physicochemical, physiological, and output parameters, as well as route of exposure, assigned race, and PBPK model simulation time, capturing the full range of quantitative inputs and outputs used in PBPK modelling. C) biological process class (GO:0008150) in PBPKO which is reused from the Gene Ontology (GO) and groups the core ADME-related processes absorption, distribution, metabolism, excretion, elimination, and enterohepatic recirculation relevant to PBPK modelling.

physiological, physicochemical, and biochemical were systematically mapped to the closest available PBPKO concepts, with 86 (86.9%) successfully annotated. Annotation of this model was performed directly on the SBML representation using tellurium [6], which provides SBML parsing through libSBML[4].

Annotation of PBPK models is not restricted to a single workflow. "sbmlutils"[23] for instance, supports bottom-up SBML model construction in Python and is ontology-agnostic, allowing annotation with any user-defined vocabulary. For interactive annotation, tools such as makesbml (https://sys-bio.github.io/makesbml/) (*Make SBML Models!*) provide a web-based, client-side solution for bidirectional conversion between Antimony and SBML. Because Antimony is a human-readable representation of SBML, annotations can be added conveniently at the Antimony level and then converted to SBML while preserving the embedded annotations .

To assess the scalability and coverage of the ontology beyond

Table 4
Number and proportion of model parameters annotated with PBPKO terms across four PBPK models.

Model	Elements	Annotated	Coverage	Gap	source
Pregnancy BPA	51	49	96.1%	2	[38]
Pediatric BPA	41	40	97.6%	1	[12]
Multi compartment PFOS	99	86	86.9%	13	[11]
Glimepiride	153	105	68.6%	48	[13]

environmental chemicals, a pharmaceutical PBPK model was also annotated (Table 4). A glimepiride PBPK model [13] was annotated with PBPKO, with 105 of 153 terms (68.6%) successfully mapped a lower coverage than the environmental-chemical models, reflecting the more specialized pharmacokinetic and formulation-related parameters typical of drug models that PBPKO does not yet cover. PBPKO will be extended over time to incorporate pharmaceutics-specific terms.

3.3.2. *Interactive harmonization using FAIR PBK inspector*

PBPKO is being used to annotate existing PBPK models across different domains in order to harmonize them and make them FAIR (Findable, Accessible, Interoperable, and Reusable). In this context, a tool named FAIR PBK Inspector was developed within the EU-PARC project [28] to validate and annotate PBPK models for compliance with "The FAIR PBK standard" [24]. The FAIR PBK Inspector is a web-based application that enables users to inspect models for annotations of different elements of the model (such as compartments and parameters) using PBPKO and several other biomedical ontologies. It also provides a platform for FAIR exchange format in the form of an SBML file along with a CSV file containing annotation of terms and units. Within PARC, FAIR PBK Inspector was used to harmonize PBK models developed for different absorption routes including ingestion, inhalation, and dermal absorption demonstrating the applicability of PBPKO in harmonization of existing PBK models.

3.4. *Regulatory perspective*

The regulatory landscape for PBPK models has evolved considerably over the past two decades, transitioning from skepticism towards cautious acceptance, yet full integration into routine regulatory decision-making remains elusive. PBPK models are increasingly recognized by regulatory authorities for predicting organ concentration-time profiles, pharmacokinetics, and exposure levels in pharmaceutical development [39,40] and environmental risk assessment [8,10].

However, the core bottleneck preventing full integration into routine regulatory decision-making is the lack of harmonized regulatory frameworks and limited reusability of models, both of which stem from inconsistent terminology across institutions. Regulatory agencies such as the OECD, EFSA, FDA, and EPA have developed distinct evaluation criteria and documentation requirements using varying nomenclatures to describe identical model components. This creates semantic ambiguity that undermines systematic comparison, prevents automated quality checks, and forces manual review for each submission.

Published models remain trapped in heterogeneous software platforms and documentation styles that hinder adaptation to different regulatory contexts, despite shared physiological principles, resulting in massive underutilization of thousands of models documented in literature [47,48]. PBPKO directly addresses this fragmentation by establishing a standardized ontology that enables cross-institutional communication and machine-readable reporting format, allowing automated validation and enhance reusability of the models.

4. Conclusions and future perspectives

PBPKO serves as an application ontology developed following the basic principles of semantic definitions and foundational ontologies. While dedicated to the pharmacokinetic and toxicokinetic domain, its scope is not limited to it. The current vocabulary encompasses more than 858 terms used across different modelling areas, linked through object properties. The refinement of PBPKO through the OBO Foundry review process provides a strong basis for the use of this ontology in standardizing the definitions of the terms and resources used in PBPK modelling. PBPKO offers a framework for making the resources used in

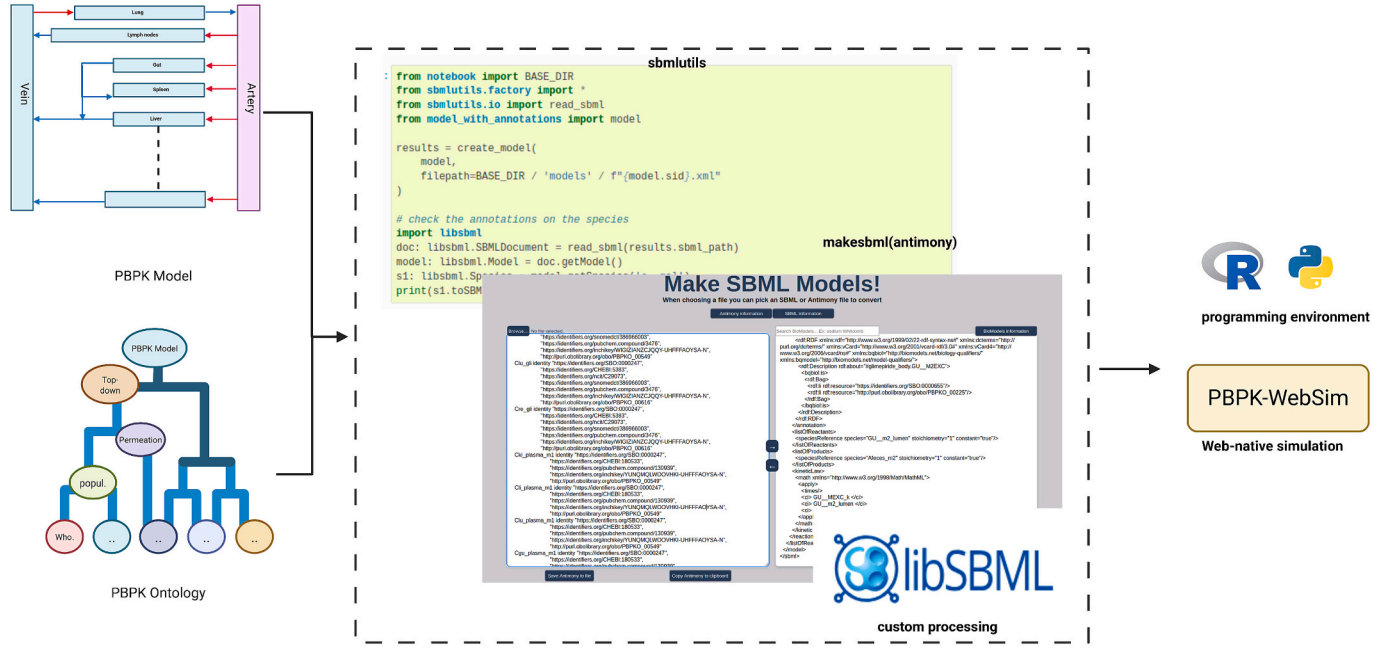

Fig. 4. Ontology-guided PBPK modelling pipeline. Three complementary approaches are used to annotate PBPK models in SBML format: (i) model construction and annotation using sbmlutils, (ii) Antimony-to-SBML conversion followed by annotation, and (iii) custom SBML processing using libSBML. The resulting annotated SBML models can be used for simulation and analysis in R, Python, or native web-based simulation platforms such as PBPK-WebSim [26].

pharmacokinetic and toxicokinetic modelling FAIR, by annotating them with persistent identifiers and exporting models in a harmonized data exchange format (SBML) across different platforms. Integration with "FAIR PBK Inspector" helps harmonize existing models and lays the foundation for development of new models, enabling the seamless exchange of information across different platforms and programming languages.

Future releases of PBPKO will integrate additional terms related to multi-species, metabolites, binary, ternary and complex mixtures and the various equations and parameters used in the field, informed by ongoing discussions with experts and their wider community. One such community effort is currently underway within the EU-PARC project in which "The FAIR PBK standard" is being built around this ontology. This standard will allow developers to assess the FAIRification level of their models at different stages and harmonize them according to the standards, providing a seamless exchange of information across platforms. In parallel, future development will extend PBPKO to support emerging contaminants such as microplastics, nanoplastics, and engineered nanoparticles, whose unique particle-specific kinetics and biological interactions are not adequately captured by conventional ADME-based models. This will require new ontology classes and relations, expanding PBPKO for next-generation PBPK modelling and regulatory risk assessment.

Beyond extending domain coverage, PBPKO is well positioned to support the growing use of artificial intelligence (AI) and machine learning (ML) in PBPK model development, including parameter estimation, automated model generation, and database mining. As AI-assisted and machine-generated PBPK models become more common, PBPKO provides a shared, machine-readable vocabulary that promotes semantic consistency, interoperability, and interpretability across platforms. Furthermore, integrating PBPKO with AI-assisted annotation pipelines (e.g., automated term suggestion and SBML tagging) could substantially reduce the manual effort required for large-scale model annotation and harmonization.

CRediT authorship contribution statement

Saurav Kumar: Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shubh Sharma:** Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. **Panče Panov:** Writing – review & editing, Validation, Investigation. **Johannes W. Kruisselbrink:** Writing – review & editing. **Antonio Moreno Ribas:** Writing – review & editing. **Deepika Deepika:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Vikas Kumar:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Conceptualization.

Disclaimer

The position and views expressed in this paper are the views of the authors and not necessarily the positions of the institutions they are affiliated with.

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.

Acknowledgement

This work was supported by the Partnership for the Assessment of Risk from Chemicals (PARC) funding by the European Union's Horizon Europe research and innovation Programme under Grant Agreement No. 101057014 and the Environmental Health and Exposome (ENVESOME) funding by the European Union's Horizon Europe under Grant Agreement No. 101157269.

We also sincerely acknowledge the OBO Foundry review team for their valuable efforts and constructive feedback, which helped us refine the ontology and align it with community standards to facilitate seamless integration with other biomedical ontologies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comtox.2026.100445.

Data availability

PBPKO is publicly available on the GitHub repository (https://github.com/InSilicoVida-Research-Lab/pbpko), together with its documentation and maintenance information, ensuring transparency and facilitating community engagement. The ontology is released under the Creative Commons Attribution 4.0 International (CC BY 4.0) license, permitting reuse, modification, and redistribution with appropriate attribution.

Supplementary files with annotated terms from the model used for case study are shared.

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