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Review article

Chemical risk assessment in food animals via physiologically based pharmacokinetic modeling – Part I: Veterinary drugs on human food safety assessment

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ABSTRACT

Veterinary drugs and environmental pollutants can enter food animals and remain as residues in food chains threatening human food safety and health. Performing health risk and food safety assessments to derive safety levels of these xenobiotics can protect human health. Physiologically based pharmacokinetic (PBPK) modeling is a mathematical tool to quantitatively describe chemical disposition in humans and animals informing human food safety and health risk assessments. However, few reviews focus on the application of PBPK models in food animals and discuss their relationship to human food safety and health risk assessments in the last five years (2020–2024). In this series of reviews, we introduce the methodology, recent progress and challenges of PBPK modeling in food animals. The present review is Part I of this series of reviews and it focuses on applications of PBPK models of veterinary drugs in food animals, whereas Part II is a companion review focusing on environmental chemicals. Advanced strategies of PBPK modeling in risk and food safety assessment, including population PBPK, interactive PBPK web dashboard, and generic PBPK are also summarized in Part I. Additionally, we share our perspective on the existing challenges and future direction for PBPK modeling of veterinary medicines in food animals.

1. Introduction

Animals, humans, and the environment are closely linked and share a common global environment. Human daily, agricultural, and industrial production activities might disturb the balance in the "global ecosystem", where humans, animals, and the environment are interconnected and interdependent for survival, also termed "One Health" (Zinsstag et al. 2023). The misuse and overuse of veterinary drugs during animal husbandry and the excessive emission of industrial and/or agricultural chemicals into the environment have raised significant public health and food safety concerns. Veterinary drugs and environmental pollutants can remain as residues in food chains, such as eggs, meat, and milk, to pose a hazard to human health (Baynes et al. 2016; Canton et al. 2021; Margalida et al. 2014). According to World Health Organization (WHO) reports, 600 million people become ill after eating food contaminated with biological and chemical agents causing more than 400,000 people deaths every year (WHO 2022). Therefore, it is important to conduct chemical risk assessments, in the context of food safety, which aim to set safety levels and avoid the violative residues in animal-derived foods, thereby protecting human health (Dorne and Fink-Gremmels 2013; Wu et al. 2021).

Risk assessment is a process of estimating the probability of adverse effects on human health as well as protecting animals and the environment from chemical exposure. Chemical risk assessment includes four parts: hazard identification, dose–response assessment, exposure assessment, and risk characterization. In the current practice, epidemiologic approaches, laboratory experiments, and Quantitative Structure-Activity Relationship (QSAR) models are commonly used for hazard identification. No observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), and benchmark dose limit (BMDL) approaches are applied to derive the point of departure (POD) in dose–response assessment. Direct measurements in human biomonitoring studies and indirect estimation via computational models, such as population physiologically based pharmacokinetic (PBPK)

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models are common approaches for exposure assessment. Risk assessors integrate the qualitative and quantitative results to characterize the risk. To support chemical risk assessment, the U.S. Environmental Protection Agency (EPA) has developed guidelines, handbooks, frameworks, and general standard operating procedures (EPA 2025). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has also provided the guidelines for food safety assessment (JECFA 2020).

Traditionally, risk assessment is based on animal experiments to determine PODs. However, according to the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) database, thousands of chemicals are needed for risk assessment, which means numerous experimental animals will need to be used to build the required dose–response relationships for risk assessments of various chemicals. Additionally, other shortcomings, including the concordance between mammalian and rodent species, limitation of extrapolation from experimental animals to humans, and poor reproducibility, are challenging the traditional animal testing-based risk assessment framework (Schmeisser et al. 2023). Environmental chemical risk assessment policies, especially in the US and EU, are shifting away from animal-based experiments to high-throughput *in vitro* assays coupled with *in silico* modeling (Clerbaux et al. 2019; Lin et al. 2024). In the EU, the "3R" principle (Replacement, Reduction, and Refinement) has been continuously reinforced. In the US, the federal program of "Toxicology in the 21st Century" (Tox21) has had substantial progress in the development of *in vitro* and *in silico* models as alternative tools for toxicity testing (Thomas et al. 2018). The US Toxic Substances Control Act (TSCA) also encourages the development of new approach methodologies (NAMs) to support environmental chemical risk assessment (TSCA 2016). NAMs are technologies or approaches (*in vitro*, *in silico,* and *in chemico* methods) that can provide information on chemical risk assessment

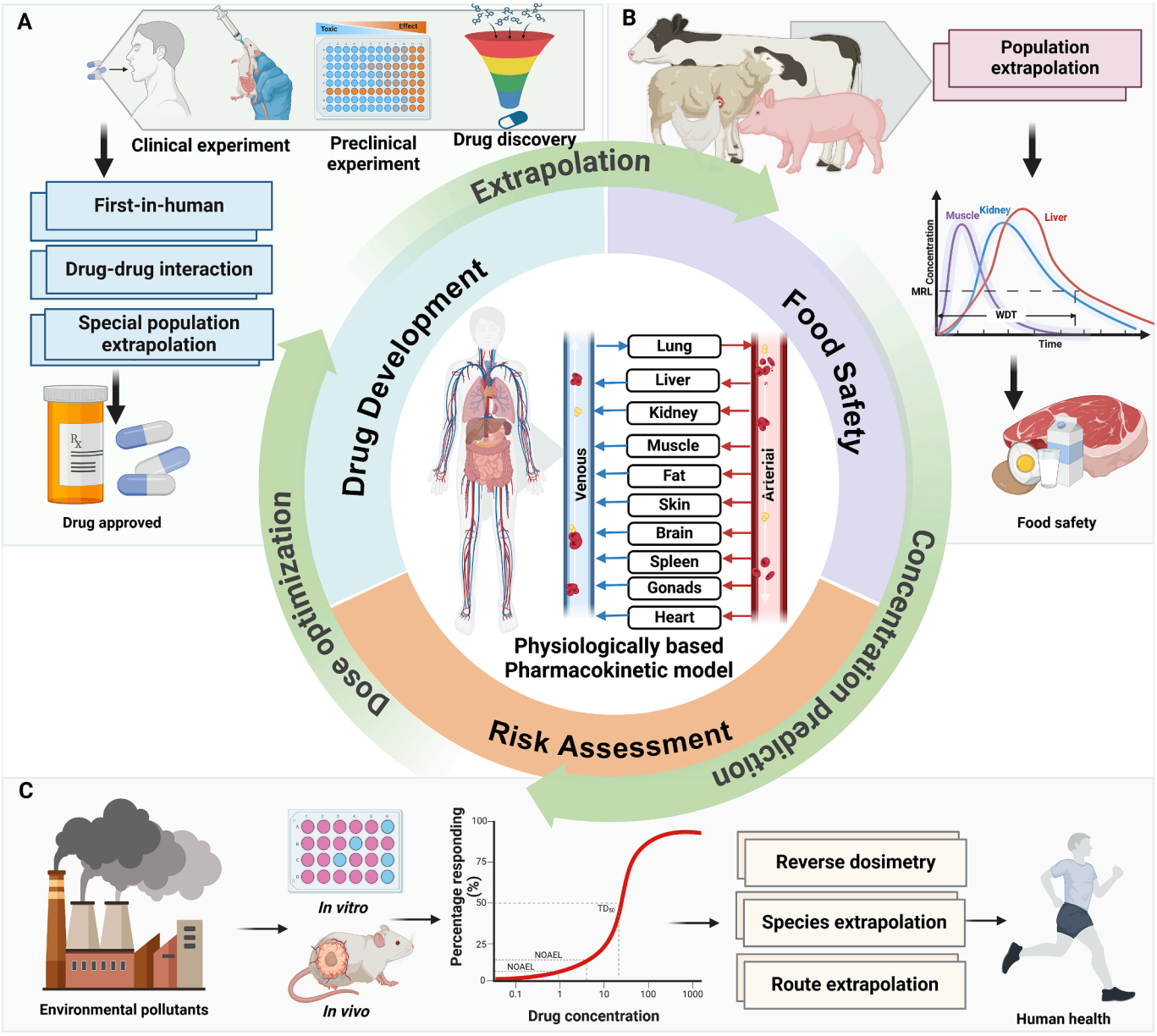

Fig. 1. Application of the PBPK model in drug development, food safety, and risk assessment. For the application in drug development (A), PBPK models can be used to optimize dose regimens for clinical experiments, predict drug-drug interactions, and extrapolate to special populations. For food safety assessment, PBPK models can predict drug concentrations in edible tissues and quantify variability in animal populations to determine withdrawal intervals (B). During risk assessment, PBPK models are applied for target organ dosimetry prediction, reverse dosimetry analysis, and extrapolations across species, exposure routes and from *in vitro* to *in vivo* (C). (This figure was created with BioRender.com).

without animals (Gonnabathula et al. 2024; Sewell et al. 2024; Stevanoska et al. 2024). In the past years, numerous NAMs, such as the *in vitro* high-throughput screening, omics technologies, organoids systems, and computational modeling, have been developed and applied in risk assessment, which shows great potential to be alternative methods for traditional animal methods (Chen et al. 2022a; Ni et al. 2024; Schmeisser et al. 2023).

Physiologically based pharmacokinetic (PBPK) modeling, also called physiologically-based toxicokinetic/kinetic (PBTK or PBK) modeling, is a computational tool that can quantitatively describe the absorption, distribution, metabolism, and excretion (ADME) of chemical substances and their metabolites in animals or humans based on physiological mechanisms of organisms and chemical-specific properties (Lin et al. 2016a; WHO 2010). PBPK modeling, a NAM, has been widely applied in human health risk and food safety assessment of chemicals and nanomaterials by simulating ADME processes of xenobiotics in the body, determining internal dosimetry, extrapolating data, reducing uncertainty factors, and estimating the safety levels (Chen et al. 2022b; Thompson 2022). Multiple regulatory agencies, such as the European Food Safety Authority (EFSA) (EFSA 2014b), the U.S. EPA (EPA 2006), the WHO (WHO 2010), and the Organization for Economic Co-operation and Development (OECD) (OECD 2021) have published guidance documents to guide the model development and recommend the adoption of PBPK models for environmental chemical risk assessment for both animal health and human health. Additionally, the U.S. Food and Drug Administration (FDA) (FDA 2018) and the European Medicines Agency (EMA) (EMA 2018) have published guidance documents to apply PBPK models for pharmaceutical applications.

As illustrated in Fig. 1, PBPK models are very useful in many scientific areas, including food safety, risk assessment, and drug discovery and development. In the field of drug discovery and development, PBPK models can be used to simulate drug concentrations in plasma and target organs, explore first-in-human doses, predict drug-drug interactions, and establish dose-exposure relationships in special populations (i.e., pregnant, pediatric, or diseased) (Sun et al. 2024). For food safety assessment, drug depletion kinetics in various edible tissues can be predicted by a PBPK model, thereby helping predict extra-label withdrawal times of drugs to ensure the safety of animal-derived food products, such as meat, milk, and eggs (Baier et al. 2022; Chou et al. 2023; Lautz et al. 2024b; Wu et al. 2025). PBPK models can also be used in environmental chemical risk assessment, such as reverse dosimetry analysis, extrapolation across species and exposure paradigms, and population variability characterization. Additionally, the next-generation PBPK models have gained widespread acceptance from regulatory agencies (Chang et al. 2022; Punt et al. 2022; Reale et al. 2024). Quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) via the PBPK model is a desired approach for the next-generation PBPK model, which makes the linkage between *in vitro* biological measurements and *in vivo* outcomes. PBPK-IVIVE can provide adequate predictions of *in vivo* kinetics (Chang et al. 2022; Punt et al. 2021).

Our lab previously reviewed the methodology and applications of PBPK models of veterinary drugs in food animals for food safety assessment (Lin et al. 2016a). Another group also reviewed the application of PBPK models for drugs and environmental chemicals in farm animals to support animal health assessment (Lautz et al. 2019). In recent years, the applications of PBPK models in food-producing animals to support human food safety and health risk assessments of veterinary drugs and environmental pollutants have steadily increased. Additionally, multiple novel technologies or advanced mathematical algorithms were combined with PBPK models, such as the machine learning or artificial intelligence (AI)-assisted PBPK models, the web interface of PBPK models (also termed interactive physiologically based pharmacokinetic [iPBPK] interface), IVIVE-PBPK, etc. However, many recent review articles have focused on introducing the application of PBPK in risk assessment for rodents and humans (Deepika and Kumar 2023; Gonnabathula et al. 2024; Stevanoska et al. 2024); none has introduced the updated application of PBPK models in food animals to support human health and food safety assessments. To introduce the advancements and discuss the challenges of PBPK models in food animals, we conduct a series of reviews to summarize the recent progress and existing challenges of PBPK models of veterinary medicines and environmental chemicals in food animals published from 2018 to 2024 in two companion reviews, Part I and Part II. The current review (Part I) primarily focuses on the applications of PBPK models of veterinary medicines for human food safety assessment. It outlines the procedures involved in developing PBPK models for food animals and introduces the role of PBPK models in food safety assessment. In addition, the existing challenges and the perspectives on developing PBPK models for veterinary medicines are introduced. Part II of this series of reviews focuses on PBPK models for environmental chemicals in food animals and is presented in a companion article (Mi and Lin 2025).

2. Development of PBPK models in food animals

Generally, there are six steps to develop a PBPK model, including (i) Model conceptualization: design the PBPK model structure based on the intended application and available data and mechanisms of ADME; (ii) Collection of PK data and relevant parameters including physiological and chemical-specific parameters; (iii) Model construction: convert the PBPK model to a series of mathematical equations using a selected software program; (iv) Model parameterization and calibration: incorporate known parameter values into the model and estimate unknown parameter values by fitting to calibration datasets; (v) Model evaluation: evaluate the model with independent datasets that have not been used in the model calibration process; and (vi) Model applications.

The general structure of a PBPK model for food animals is shown in Fig. 2A. The model structure is designed based on multiple factors, including research objectives, availability of data, and the mechanisms of ADME of the modeled substances. Typically, the liver and kidney are modeled as the individual compartments because they are the major metabolism and excretion tissues. Muscle and fat, the primary edible tissues of food animals, are also described as individual compartments. The remaining part of the body is assumed as a "rest of body" or "remaining" compartment. Note that care must be taken to ensure that the "rest of body" compartment does not serve as a "buffer" compartment containing an unreasonably high percentage of the mass balance throughout the simulation time. The remaining compartment can be further divided into rich-perfused tissue and slow-perfused tissue compartments based on flow rates. Partition coefficient (PC) for the rest (remaining) compartment can be calculated as the weighted mean of PCs of the lumped organs, accounting for poorly and richly perfused tissues either together or apart (Wiuff et al. 2002).

Specific individual compartments of interest can be added to the general structure. For the therapeutic application of a drug to treat respiratory tract diseases, the lung is commonly modeled as an individual compartment to capture the drug concentration in the target tissue. For monitoring drug residues in food products, such as eggs, the ovary is modeled as an individual compartment for laying hens (Fig. 2B), and for milk, the udder is modeled as a separate compartment for lactational cows, ewes, or goats (Fig. 2C). If the metabolite is the maker residue, a sub-model of the metabolite would be adopted (Fig. 2D). The parent drug is generally metabolized in the liver compartment and metabolites are generated in the liver and would be distributed throughout the body via blood circulation.

By combining the physiology of food animals with drug-specific physicochemical properties to parameterize mathematical equations, a PBPK model can capture complex physiological processes and ADME characteristics of a drug. For *absorption*, chemical substances can enter into the body under various administration routes, and then flow throughout the body and be distributed into various tissues via blood circulation. There are four common drug exposure routes, including intravenous (IV), intramuscular (IM), subcutaneous (SC), and oral

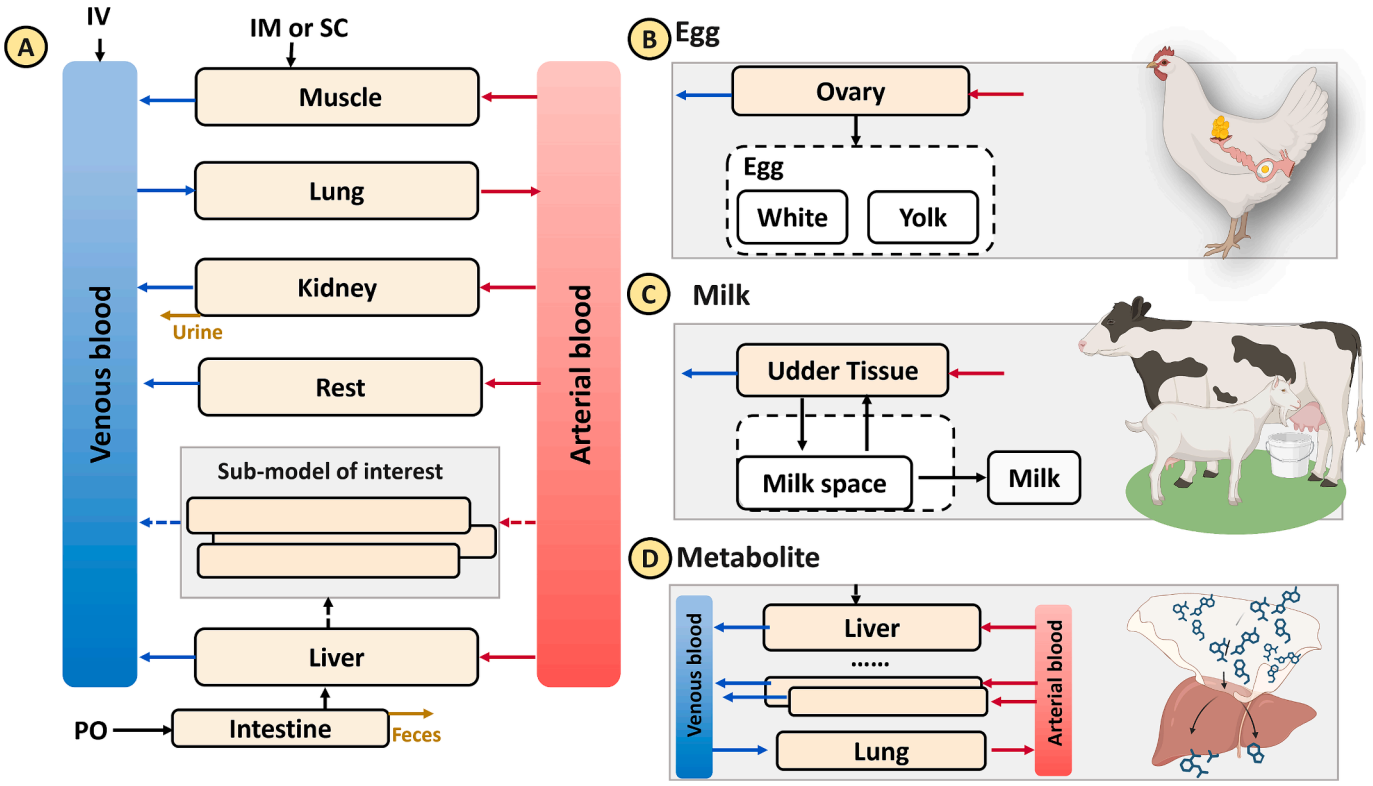

Fig. 2. A schematic of the structure of a physiologically based pharmacokinetic (PBPK) model in food animals. IV, IM, SC, and PO represent intravenous, intramuscular, subcutaneous, and oral administrations, respectively. Panel A represents the general structure of a PBPK model. Additional compartments or a sub-model of interest can be added based on research needs. If the model is developed to investigate the drug residue in eggs, the ovary compartment (B) would be added. The udder compartment is added as an individual compartment for predicting drug depletion in milk (C). If the research aims to investigate the PK profile of the metabolite, then a metabolite sub-model would need to be added (D). (This figure was created with BioRender.com).

administration. Under IV administration, the drug is assumed to be directly entered into venous blood (i.e., 100 % absorption), the reference route for PK and bioavailability studies (Toutain and Bousquet-Mélou 2004). The absorption of a drug after IM and SC administration can be modeled as a first-order rate process at the muscle compartment. A two-compartment mechanistic model consisting of a fast absorption fraction and a slow-release depot is frequently used to describe drug absorption after IM or SC injection in food animals (Leavens et al. 2012; Lin et al. 2015; Mi et al. 2023; Riad et al. 2021). Modeling residues at the injection site is challenging due to the formation of local drug depots, the erratic PK profiles at the injection site, and the inflammatory response after injection (Bettonte et al. 2024; Sanquer et al. 2006). For oral exposure, including oral gavage, dietary, and drinking water exposure, a two-compartment structure, consisting of the stomach and intestine is commonly used to model drug absorption (Chou et al. 2022b). Drug is transmitted from stomach to intestine with a gastric emptying rate and absorbed from the small intestine into the liver via a portal vein under the control of intestinal absorption rate. Viel et al. further developed a multi-compartment intestinal structure consisting of duodenum, proximal jejunum, distal jejunum, ileum, proximal colon, and distal colon to describe marbofloxacin concentration in various parts of colons and tissues of swine (Viel et al. 2023).

For *Distribution*, both physiological parameters and chemical-specific parameters impact drug distribution or accumulation in tissues. Physiological parameters, including cardiac output, blood flow rates and tissue volumes, have been summarized in several review articles, including swine and cattle (Lin et al., 2020), sheep and goats (Li et al. 2021), chickens, turkeys and mallards (Lautz et al. 2020c; Scanes et al. 2022; Wang et al. 2021), and fish (Rainbow trout, Zebrafish, Fathead minnow, Stickleback, Carp) (Grech et al. 2019; Xie et al. 2024). Tissue-to-plasma PCs are important chemical-specific parameters in PBPK models to simulate chemical kinetic properties. *In vivo* experiments can derive the PC values by comparing tissue and plasma concentrations at a steady state or by calculating the ratios of the area under the concentration–time curves (AUC) in tissues to the AUC in plasma (Huang et al. 2015; Yang et al. 2014). However, ethical and financial considerations arise with this approach. *In silico* methods are increasingly applied to calculate PCs by integrating tissue composition data (i.e., water content, protein content, neutral lipids, and pH) and physiochemical properties [i.e., lipophilicity (logP), acid dissociation (PKa) and unbound fraction in plasma] (Lautz et al. 2024a; Rodgers and Rowland 2006). Tissue composition data for food animals (swine, cattle, sheep, and chickens) have been summarized in the published literature (Chou et al. 2022b; Lautz et al. 2024a). Lautz et al. applied the commonly used mechanistic equations (Berezhkovskiy 2004; Rodgers and Rowland 2006; Schmitt 2008) and the tissue composition of rats and humans (Utsey et al. 2020) to predict PCs of chemicals in various food animals, and the results were highly correlated to the *in vivo*-derived values (Lautz et al. 2024a). Chou et al. used the average value of PCs from various mechanistic equations (Berezhkovskiy 2004; Poulin and Theil 2002; Rodgers and Rowland 2006; Schmitt 2008) as the initial values to develop a PBPK model for drugs in cattle and swine (Chou et al. 2022b). A public toolbox can also be directly used to calculate PCs and protein binding rates in rats and humans (Punt et al. 2021), which remains to be extrapolated to food animals. Describing biphasic or triphasic decay in the vascular compartment is difficult for PBPK models due to the gaps in understanding the underlying mechanisms. Deep compartments have been employed to model the complex PK behaviors, such as the biphasic PK of colistin in plasma (Viel et al. 2018) and oxytetracycline PK in milk (Tardiveau et al. 2022). However, the lack of datasets for the deep compartment continues to pose challenges.

For *Metabolism,* the parent drug is primarily metabolized following

first-order or saturable kinetics depending on the metabolic pathway of the drug and its dose. In a PBPK model, the sub-model structure of a metabolite could be the same as the parent drug and connect with the parent drug model through metabolism. For a typical veterinary drug, because of the relatively low drug exposure, the first-order kinetics is often sufficient to describe the metabolism of a veterinary drug (Chou et al. 2022b; Lin et al. 2016b). For environmental pollutants, when the chemical *in vivo* exposure is high to saturate the metabolism, the Michaelis-Menten equation is adopted to capture this metabolism. For example, Mit et al. implemented the Michaelis-Menten equation into a PBPK model of zebrafish and rainbow trout to simulate the metabolism of bisphenol A (BPA) and the metabolites (BPA-monoglucuronide and BPA-monosulfate) and their concentrations in fish (Mit et al. 2022). Liu et al. also used the Michaelis-Menten equation to describe the metabolism process of 4-nonylphenol (4-NP) and triclosan (TCS) in the PBPK model to predict parent and metabolite concentrations in fish (Liu et al. 2022). Usually, data on the metabolite are limited compared to the parent drug, and if needed, the PC values for the metabolite can be assumed to be the same as the parent drug based on structural similarity (Zeng et al. 2017). The traditional interspecies extrapolation method, i.e., allometric scaling, highly relies on animal body weight and body surface area, ignoring the metabolism difference among animal species. A PBPK model is characterized by animal physiology and describes the metabolic process for a specific chemical, thereby avoiding the uncertainty of allometric scaling associated with traditional interspecies extrapolation (Sweeney et al. 2010; Zhang et al. 2024). The *in vitro* intrinsic clearance determined by microsomes or hepatocytes can be extrapolated to *in vivo,* informing PBPK model development and reducing animal experiments (Lautz et al. 2022).

For *Excretion*, the excretion process can be described as a first-order linear equation (Xu et al. 2020) or a saturable process (Chou and Lin 2019) via urine and/or feces. Enterohepatic circulation can be modeled by a biliary excretion rate and a re-absorption rate. To mimic the renal excretion and reabsorption process, the kidney is divided into sub-compartments including proximal tubule lumen/filtrate, proximal tubule cells (PTCs), and the rest of kidney (Chou and Lin 2019). For fish, the chemicals can be eliminated via expiration by gills, and the excretion rate is influenced by gill ventilation (Wang et al. 2022).

In our earlier review, the model development methodology was introduced in detail (Lin et al. 2016a). Additional information about PBPK model development, calibration, and evaluation guidelines for risk assessment can also be found in the official guidance documents (EPA 2006; OECD 2021; WHO 2010). The following sections focus on the applications, challenges, and future perspectives of PBPK models for drugs in food animals to support human food safety and health risk assessments.

3. Risk assessment of veterinary drugs for food safety assessment

3.1. Procedure to determine health-protection values for veterinary drugs

Veterinary medicines, including antibacterial, anticoccidial, and anti-inflammation drugs, are used to treat clinical diseases and protect animal health. However, irrational use of veterinary medicines, such as abuse, misuse, and inobservance of the withdrawal time (WDT), and cross-contamination of animal feeding stuffs can cause violative residues in animal-derived food products (KuKanich et al. 2005). Drug residues would accumulate in the edible tissues and migrate into food products (e.g., milk and eggs). Violative residues within animal-derived food products could be the cause of numerous health concerns for humans, such as the transformation of antimicrobial resistance from animals to humans (Sagar et al. 2023), the impact on human intestinal microbial flora (e.g., aminoglycosides) (Baynes et al. 2016), allergic reaction (e.g., penicillin) (Wu et al. 2023), carcinogenicity (e.g., sulfamethazine) (Littlefield et al. 1989), nephropathy (e.g., gentamicin) (Baynes et al. 2016), hepatotoxicity (e.g., cotrimoxazole) (Choquet-Kastylevsky et al. 2002), and bone marrow toxicity (e.g., chloramphenicol) (Eliakim-Raz et al. 2015).

WDT is a recommended interval when the drug concentration in the target tissue is depleted to be below the maximum residue limit (MRL) after the last administration. MRL, also termed tolerance in the US, is the maximum allowable concentration of a specific substance in animal-derived food products. MRL is a management tool for risk assessment to ensure drug residues in animal-derived food products are kept at a safe level for consumers (Chicoine et al. 2020). The determination of MRL relies on acceptable daily intake (ADI). There are two types of ADI, including toxicological ADI (tADI) and microbiological ADI (mADI). tADI is calculated from POD divided by uncertainty factors. NOAEL and BMDL are commonly used PODs that are determined from the dose–response relationship curve of a specific toxic effect (JECFA 2020). The default uncertainty factors are set as 100 accounting for inter-species and inter-individual variability (JECFA 2020). PBPK models can be used to determine chemical-specific adjustment factors (CSAFs), quantify interspecies TK variability, and replace default uncertainty factors, thereby supporting risk assessment (WHO 2005).

Veterinary drug residues in animal-derived food products can disrupt the human intestinal microbiome and promote the emergency of antimicrobial resistance. mADI can describe the impact of antibiotics on the intestinal gut by observing microbiological endpoints including disruption of the colonization barrier and increase of resistant bacteria by *in vivo* or *in vitro* experiments (VICH 2019). The minimum inhibitory concentration, mass of colon content, and the available concentration in the colon are used to determine mADI from *in vitro* studies. For the *in vivo* test, the determination of mADI is the same as tADI by animal toxicological experiments (Cerniglia et al. 2016). Compared with tADI and mADI, the minimum is defined as the final ADI (Boobis et al. 2017). The ADI is further adjusted with standard food basket values (300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 mL milk, 100 g eggs, and 20 g honey), which are assumed for a 60 kg person daily food consumption to obtain MRLs for each tissue (JECFA 2020). There is a potential for veterinary drug residues to cause adverse effects on humans for a single meal. Acute reference dose (ARfD), based on the acute effects, is the appropriate value for estimating the veterinary drug residues in food during short-term exposure and assessing the risks to customers. The guideline document on how to derive the ARfD is available from Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA 2017). ARfD would assist with the MRL establishment; when the ARfD value is below the ADI value, the ADI should be reconsidered and normally set at the same numerical value as ARfD (JECFA 2017).

3.2. The role of PBPK models in food safety assessment

Determining WDT is a rigorous process, including the definite MRLs in each tissue, an accurate and sensitive analytical detection method, identification of the marker residue, and plasma PK and tissue depletion profiles of the marker residue from animal experiments, and a statistical calculation method (VICH 2015). Additionally, regulatory agencies, such as EMA and FDA, have different requirements for the final WDT, particularly regarding marker residue types and statistical methods. Drug residues in tissues are determined by the marker residue whose concentrations are in relationship to the total residue (Rychen et al. 2017). The marker residue could be either the parent drug, its metabolites (usually the main metabolite), or their combination. In the case of florfenicol (FF), EMA recommends using the combination of concentrations of FF and its metabolites, florfenicol amine (FFA), to determine the WDT, whereas the FDA just uses FFA to determine its WDT. Additionally, they have different requirements for statistical methods. In the US, the 99th percentile tolerance limit with 95 % confidence is used to determine WDT (FDA 2016). In the EU, the upper one-sided 95 % tolerance limit for the drug residue below the MRL with 95 % confidence is adopted (EMA 2016). Thus, it is complex, expensive, and time-

consuming to determine WDT. PBPK models are a flexible tool to quantitatively estimate the WDT. For example, Yang et al. successfully developed a PBPK model for FF and its metabolite, florfenicol amine (FFA) which can capture the kinetics of FF and FFA in edible tissues in cattle. This PBPK model was integrated with Monte Carlo simulation and was used to estimate WDT as 46 days and 44 days based on the EMA and FDA requirements, respectively (Yang et al. 2019). With the assistance of PBPK models, unnecessary animal PK and tissue residue depletion experiments can be avoided when determining the WDT for drugs in food animals.

FDA and EMA have approved that veterinarians can use the approved human and animal drug in an extra-label manner, also known as extra-label drug use (ELDU) or off-label use, to treat animal disease provided that certain stipulations are met. In the US, the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) is the guidance document of ELDU of drugs in food animals. Following ELDU in food

Table 1
Published PBPK models of veterinary drugs in food animals from 2018 to 2024.

Drug	Species	Route	Model type	Vali.	WDT	Sens.	Varia.	Code	Software	Reference
Penicillin G	Dairy cows	IM and IMM	Mixed	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Li et al. (2018)
Colistin	Swine	IM	Mixed	Yes	Yes	LS	Yes	NA	NONMEM	Viel et al. (2018)
Flunixin	Cattle and swine	IV, IM, and SC	Flow-limited	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Li et al. (2019a)
Florfenicol	Cattle	IV, IM, SC, and PO	Flow-limited	Yes	Yes	LS	Yes	Yes	AcslXtreme	Yang et al. (2019)
Penicillin G	Heavy sows	IM	Flow-limited	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Li et al. (2019b)
Cefuroxime, Cephapirin, Penicillin	Dairy cows	IMM	Mixed	No	NA	LS	NA	NA	MATLAB	Woodward and Whittem (2019)
Oxytetracycline	Rainbow trout	PO	Flow-limited	Yes	NA	GS	NA	Yes	R language	Grech et al.(2019)
Pirlimycin	Dairy cows	IV and IMM	Mixed	No	NA	NA	Yes	NA	MATLAB	Woodward et al. (2020)
Doxycycline	Grass carp	IV and PO	Flow-limited	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Xu et al. (2020)
Enrofloxacin	Rainbow trout	IV, IB and PO	Flow-limited	Yes	Yes	LS	Yes	Yes	AcslXtreme	Yang et al. (2020)
Melamine, Oxytetracycline	Cattle, sheep and swine	IV and PO	Flow-limited	Yes	NA	GS	NA	Yes	R language	Lautz et al. (2020b)
Florfenicol, Monensin, Salinomycin	Chickens	PO	Flow-limited	Yes	NA	GS	NA	Yes	R language	Lautz et al. (2020c)
Enrofloxacin	Swine	PO	Flow-limited	No	Yes	LS	Yes	Yes	AcslXtreme	Zhou et al. (2021)
Oxytetracycline	Sheep and goats	IV and IM	Flow-limited	Yes	Yes	LS	Yes	Yes	R language	Riad et al. (2021)
Florfenicol	Tilapia	PO	Flow-limited	Yes	Yes	NA	Yes	Yes	R language	Lin and Chen (2021)
Oxytetracycline	Diary cows and goats	IV and IM	Mixed	Yes	Yes	GS	Yes	Yes	Monolix	Tardiveau et al. (2022)
Oxytetracycline	Cattle	IV	Flow-limited	Yes	NA	NA	Yes	NA	Multisim	Hekman et al. (2021)
Meloxicam	Chickens	IV and PO	Flow-limited	Yes	Yes	LS	Yes	Yes	R language	Yuan et al. (2022)
Orbifloxacin	Crucian carp	IV and IM	Flow-limited	Yes	NA	LS	NA	NA	AcslXtreme	Yang et al. (2022)
Florfenicol, Chloramphenicol, Ivermectin, Monensin, Salinomycin	Chickens	IV and PO	Flow-limited	Yes	NA	LS	NA	Yes	PK-sim	Baier et al. (2022)
Flunixin, Florfenicol, Penicillin G	Cattle and swine	IV, SC, IM, and PO	Flow-limited	Yes	Yes	LS	Yes	Yes	R language	Chou et al. (2022b)
Marbofloxacin	Swine	IV and IM	Mixed	Yes	Yes	GS	Yes	Yes	Monolix	Viel et al. (2023)
Cefquinome	Swine	IV and IM	Mixed	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Mi et al. (2023)
Diclazuril	Chickens	PO	Flow-limited	Yes	Yes	LS	Yes	Yes	AcslXtreme	Yang et al. (2023)
Aditoprim	Swine	IM	Flow-limited	Yes	Yes	LS	Yes	Yes	Berkeley Madonna	Mi et al. (2024)
Ractopamine	Goats	PO	Flow-limited	No	Yes	LS	Yes	Yes	AcslXtreme	Ai et al. (2024)
Carprofen, Flunixin, Ibuprofen, Ketoprofen, Meloxicam, Paracetamol, Salicylic acid	Cattle	IV, IM, SC, and PO	Flow-limited	Yes	NA	NA	NA	Yes	R language	Lautz et al. (2024b)
Flunixin	Cattle and swine	IV, IM, SC, and Dermal	Mixed	Yes	Yes	LS	Yes	Yes	R language	Wu et al. (2025)

Note: IV, IM, SC, and PO represent intravenous, intramuscular, subcutaneous, and oral administrations. IB represents immersion bath. IMM represents intramammary administration. Mixed means some compartments are flow-limited and others are membrane-limited. Vali., Sens., and Varia. represent validation, sensitivity analysis, and variability analysis, respectively. WDT means withdrawal times or withdrawal intervals. "Yes" for the validation indicates the PBPK model was validated by independent dataset(s), while "No" indicates no validation. A "Yes" for the variability analysis indicates that the PBPK model incorporates Monte Carlo simulations to account for population variability. Code means authors publish and share the model code. Yes indicates that the raw data for model development are available in the manuscript. NA indicates not available. "LS" and "GS" stand for local sensitivity analysis and global sensitivity analysis, respectively. Software represents the computer software for model development. The earlier PBPK models for drugs in food animals have been summarized in the two earlier reviews by Lin et al. (2016a) and Lautz et al. (2019).

animals, a scientifically-based extended WDT is necessary for food safety. PBPK models are a mechanistic model that can extrapolate to predict drug concentrations under ELDU, thereby helping estimate the extended WDT following ELDU. In the case of flunixin, it is labeled in cattle for IV administration of 2.2 mg/kg once a day or divided into 2 daily doses for up to 3 days, and in swine for IM administration of 2.2 mg/kg for 1 day. However, the common ELDU practice is IM injection in cattle and swine for consecutive 3 days. Li et al. have developed a population PBPK model of flunixin in cattle and swine to determine WDT as 7 days for cattle and 16 days for swine after IM administration at 2.2 mg/kg for consecutive 3 days (Li et al. 2019a), which can provide the recommended WDT for ELDU of flunixin in cattle and swine.

Overall, PBPK models can predict drug-depleted kinetics and monitor drug residues in edible tissues. It is a robust tool to meet different regulatory requirements for the determination of WDTs of different drugs in different species after different therapeutic regimens, which is cost-saving and consistent with "3R" and TOX21 principles.

3.3. PBPK models of veterinary drugs in food animals

Recent PBPK models of veterinary medicines in food animals are presented in Table 1. There are 56 models of 28 pharmacological compounds in various food-animal species. A large proportion of PBPK models focus on predicting drug residues in the edible tissues of cattle or swine and determining the WDT of label or extra-label doses. Seven PBPK models are developed for predicting drug depletion kinetics in the milk of lactating animals. Ten PBPK models can be used to predict drug residues in chickens and five models among them can predict residues in eggs. Five PBPK models focus on simulating the drug concentration in fish. The available information on the published PBPK models, including the model structure, model evaluation, WDT estimation, and modeling software, is presented in Table 1. ACSLXtreme, R language, Berkeley Madonna, and Monolix are popular software for PBPK model development. Model codes for most of these published PBPK models are publicly available, which are helpful for users to employ these PBPK models. Lin et al. have introduced the characterization of PBPK software, the syntax of modeling languages, and the conversion between different software that can help researchers without modeling experience to learn PBPK model development (Lin et al. 2017).

Several recent studies have extended PBPK models from beef cattle and meat goats to lactational cows or goats. In dairy cows, three different model designs of udder are commonly adopted to predict the drug concentration in milk, as Fig. 3 shows. Li et al. employed a one-compartment model, in which the milk space was assumed as a homogeneous tissue, to simulate penicillin G concentration in milk and determine WDTs under various dose regimens after IM or intramammary (IMM) administration (Li et al. 2018). A non-linear mixed effect (NLME) model of pirlimycin was developed using a PBPK

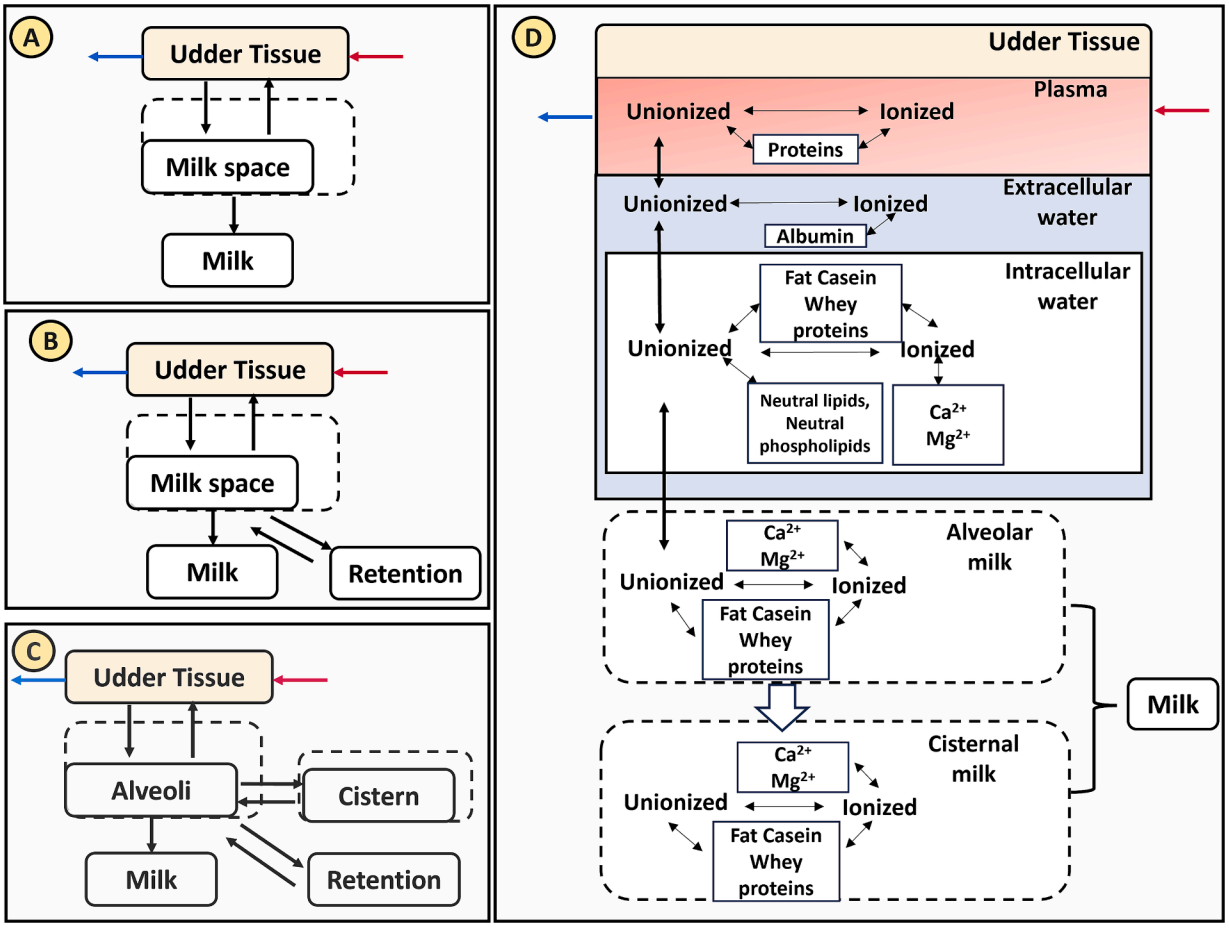

Fig. 3. Model structure of udder tissues. Panel A is the 1-compartment udder model. Milk space represents the completed udder structure including cistern and alveoli (Li et al. 2018). Panel B is the 2-compartment udder model. The retention compartment represents a volume-independent mechanism for drug disposition during the milking interval, such as the process of drug adsorption to the alveolar epithelium (Woodward et al. 2020). Panel C is the 3-compartment udder model consisting with a cistern and alveoli, and a retention compartment (Woodward and Whittem 2019). Panel D is the mechanistic udder model, consisting of vascular space, interstitial space (extracellular water and intracellular water), and the milk which is produced within the epithelial secretory cells (alveolar milk) and stored in the cistern (cisternal milk) through ducts. It is assumed that only the unbound and unionized form of the drug can diffuse between these sub-compartments (Tardiveau et al. 2022). The dashed line for the udder sub-model represents the volume changes in the milking process.

structure to identify the factor (healthy versus diseased) associated with concentrations in milk (Woodward et al. 2020). In this study, a two-compartment structure, containing a milk compartment and a retention compartment, was selected to describe the mammary gland quarters (Woodward et al. 2020). Three-compartment structure, containing the cistern, alveolus, and retention compartment, was adopted to represent the mammary gland of cattle in another study (Woodward and Whittem 2019), where drug residues (penicillin G, cefuroxime, and cephapirin) in milk can be accurately simulated, and clinical therapeutic strategies were proposed. A mechanistic PBPK model with the permeability-limited udder compartment was developed to describe the transfer of oxytetracycline into milk in lactating cows and goats. WDTs were predicted to be 5 days (in cow milk) and 4 days (in goat milk), respectively, after IM administration of 10 mg/kg for 4 consecutive days (Tardiveau et al. 2022). There is a review article on lactational PBPK models that further introduces the common structures of the udder and drug kinetics in milk both for humans and food animals (Dubbelboer et al. 2023).

Chemical residues in eggs are crucial food safety concerns. The model structures of reproductive tissue and egg compartments are shown in Fig. 4. Lautz et al. developed a generic PBPK model for three veterinary drugs and four environmental containments in laying hens and broilers (Lautz et al. 2020c). In their model, the egg was assumed as a single compartment and drug residue kinetics in eggs were simulated by considering reproductive tissue physiological parameters, including blood flow rate and tissue volume, as well as egg production rate (Lautz et al. 2020c). The accuracy of the model-predicted concentrations across all chemicals in eggs was 97 % within a 3-fold change of measured data (Lautz et al. 2020c). Considering that chemical-related parameters such as lipid solubility, PKa, and protein binding rate, would impact drug distribution in egg yolk and white, Yuan et al. modeled the egg yolk and white formation process to develop a PBPK model simulating meloxicam concentrations in edible tissues and eggs using R language (Yuan et al. 2022). In this model, the ovary was modeled as an individual compartment. Eggs were modeled as a sub-compartment of ovary for simulating the formation of white and yolk. The WDT was determined as 22 days in the egg yolk, 4 days in egg white, and 50 days in the liver at 1 mg/kg/day for 14 consecutive days of oral administration of meloxicam (Yuan et al. 2022). This PBPK model for meloxicam in broilers and layers was converted from the R language to a module-based software program PK-Sim, and the models from the two software programs had comparable simulation results (Zhang et al. 2025). Baier et al. adopted PK-Sim to develop a generic PBPK model of five veterinary medicines and four environmental chemicals in poultry. They adopted the method described by Hekman and Schefferlie (2011), which separates the yolk connected to the ovary from the white connected to the oviduct, and incorporated the ovulation-egg-laying process into the PBPK model to capture the PK profiles of florfenicol, chloramphenicol, ivermectin, monensin, and salinomycin in laying hens and to predict drug residues in eggs (Baier et al. 2022).

In recent years, PBPK modeling has been steadily applied to various edible fish species, such as rainbow trout, grass carp, and crucian carp. Yang et al. developed a PBPK model of enrofloxacin (ENR) and its metabolite ciprofloxacin (CIP) in rainbow trout after oral or immersion bath (IB) administration (Yang et al. 2020). In this model, IB refers to the progression of drug absorption through the gill. The sum concentration of ENR and CIP is the marker residue; thus, a sub-model of CIP is developed. Water temperatures heavily impact the PK profiles of ENR and CIP in fish. In this model, cardiac output is directly proportional to the water temperature, and blood flow rates of tissues are also scaled. Yang et al. fully utilized the flexibility of the PBPK model to determine the WDTs in rainbow trout under various scenarios including administration methods (oral or IB), dosage regimens, and water temperatures (5, 10, or 16 °C). The WDTs were determined ranging from 80 to 272 days, with longer WDTs observed at low water temperatures compared to high water temperatures (Yang et al. 2020). Yang et al. developed a temperature-related PBPK model of orbifloxacin in crucian carp (Yang et al. 2022). Cardiac output was adjusted with the water temperature changing. This model can predict the orbifloxacin concentrations in liver, kidney, muscle, and skin after IM administration at 25 °C, which is useful for determining the WDT of orbifloxacin under the extra-label use (Yang et al. 2022). A PBPK model was developed for doxycycline in grass carp (Xu et al. 2020). In this model, the intestinal gut of grass carp was divided into foregut, midgut, and hindgut. The enterohepatic circulation after oral administration was incorporated into the model. The WDT was determined 74 days after the label dose (20 mg/kg daily for three days) by oral gavage (Xu et al. 2020).

3.3.1. *Population PBPK models*

Considering the uncertainty of physiological parameters and chemical-specific parameters among individuals, a population PBPK model can be developed by combining Monte Carlo simulation. Monte Carlo simulation can be conducted for 1000 iterations and parameters can be randomly sampled from a specific distribution for every iteration. Generally, the physiological parameters are assumed to follow the normal distribution, and chemical-specific parameters are assumed to follow the log-normal distribution. The probabilistic distribution is described by the mean value and coefficient of variation (CV). CVs of common physiological parameters for several food animal species in various life stages have been summarized, including swine and cattle (Lin et al., 2020), sheep and goats (Li et al. 2021), chickens, turkeys and mallards (Lautz et al. 2020c; Scanes et al. 2022; Wang et al. 2021), and fish (Grech et al. 2019). For other physiological parameters, the defaults of CV are usually defined as 30 %. For chemical-specific parameters, CVs for tissue-to-plasma PCs and the rates of absorption, excretion, and metabolism were assumed as 20 % and 30 %, respectively (Li et al. 2017; Riad et al. 2021; Xu et al. 2020). The lower bound (2.5th percentile) and upper bound (97.5th percentile) of the distribution were set to constrain the range of random selection to ensure the resampled parameter values are physiologically plausible. The concentration–time curves of 1000 virtual individuals in various tissues can be derived by the population PBPK model. As Table 1 shows, PBPK models (n =30) implemented with Monte Carlo simulation are increasingly developed to account for population variability and 28 population PBPK models have been developed to determine WDTs of drugs.

Another more advanced population analysis approach is the Bayesian Markov chain Monte Carlo (MCMC) simulation. Bayesian

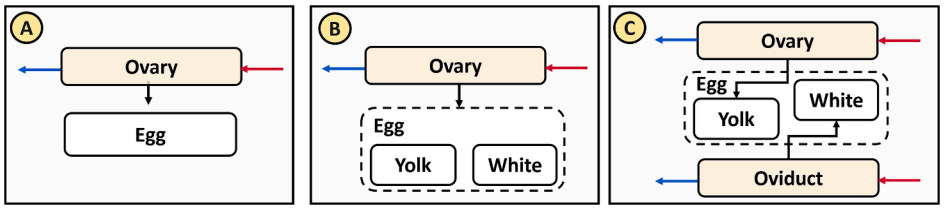

Fig. 4. Model structure of reproductive tissues for chickens and the egg compartment. Panel A represents a single-compartment model for the egg where drug residues are uniformly distributed throughout the whole egg (Lautz et al. 2020c); Panel B represents a two-compartment model of the egg, consisting of the yolk and the white, with drug residues derived from the ovary (Yuan et al. 2022). Panel C also represents an extended two-compartment model of the egg, incorporating the oviduct, where residues in the yolk from the ovary and in the white from the oviduct (Baier et al. 2022).

MCMC can characterize the uncertainty and variability of parameters and optimize the simulation to improve the predicted precision of the PBPK model (Chiu et al. 2009; Chou et al. 2022a). Lin and Chen developed a Bayesian population PBPK model to assess the WDT of FF in tilapia (Lin and Chen 2021). Two posterior sets were generated and applied to simulate drug concentrations in edible tissues of tilapia with different body weights. The optimal Bayesian population PBPK model estimated WDT of FF to be 14–18 days at 22 °C and 11–14 days at 28 °C, respectively (Lin and Chen 2021). When NLME modeling is applied to population PBPK models, fixed effects and inter-individual variability are incorporated, and the residual error(s) are excluded (Tardiveau et al. 2022). Currently, the limitation of population PBPK models is that they disregard the intrinsic correlations that may exist between certain physiological parameters (Tsamandouras et al. 2015).

3.3.2. Interactive PBPK web dashboard

One barrier to the application and extension of PBPK models is the need for users to understand and use computer programming. To address this issue, user-friendly web-based PBPK model dashboards have been developed (Table 2), which make it convenient for researchers and regulators to predict drug residue and determine the WDT using PBPK models. Population PBPK models can be converted to interactive PBPK (iPBPK) interfaces using the R package "Shiny" (Chou et al. 2023; Li et al. 2019a; Riad et al. 2021). Users can input the information of dosage (dose or interval) and animal (species and body weight) into the interface and run a Monte Carlo simulation with 1000 iterations to simulate drug depletion in various tissues. The reported iPBPK interfaces and the web links are summarized in Table 2. A web-based toolbox named QIVIVE tools was developed by Punt and collaborators (Punt et al. 2021). This toolbox combined QIVIVE with QSAR models. By applying QIVIVE tools, plasma binding rate and PCs can be determined based on physicochemical properties; *in vivo* metabolic rate can be extrapolated from *in vitro* experiments; and the drug concentration in various tissues can be simulated (Punt et al. 2021). EFSA has developed an open-source platform, TKplate, which integrates PBPK and TK-TD models for human health, animal health, and environmental risk assessments. Currently, this platform supports the prediction of drug residues for 12 chemicals, including four veterinary drugs, across four food animal species, including cattle, sheep, swine, and chickens (Dorne et al. 2023). These web tools have the potential to fill the professional knowledge gap and help regulatory agencies and veterinarians easily apply PBPK models.

Table 2
Applications of interactive PBPK models in food animals.

Drug	Animals	Route	Weblink	Reference
Flunixin	Cattle and swine	IV, SC, and IM	https://pengpbpk.shinyapps.io/Flunixin/	Li et al. (2019a)
Penicillin G	Cattle and market-age swine	IM	https://pengpbpk.shinyapps.io/pen_g/	Lin et al. (2020a)
Oxytetracycline	Sheep and goats	IV and IM	https://pbpk.shinyapps.io/OTC_App/	Riad et al. (2021)
Meloxicam	Broiler and laying chickens	IV and PO	https://pbpk.shinyapps.io/Meloxicam/	Yuan et al. (2022)
Flunixin, Florfenicol, Penicillin G	Cattle and swine	IV, SC, IM, and PO	https://pbpk.shinyapps.io/igPBPKApp/	Chou et al. (2022b)
Florfenicol, Monensin, Oxytetracycline, Salinomycin	Swine, cattle, sheep, and chickens	–	https://r4eu.efsa.europa.eu/app/tktd	Dorne et al. (2023)

Note: IV, IM, SC, and PO represent intravenous, intramuscular, subcutaneous, and oral administrations, respectively. All the links were assessed on 22 January 2025.

3.3.3. Generic PBPK models

Most existing PBPK models have been developed for a specific drug in one animal species. Due to the large number of drugs and many food animal species, it is time-consuming, expensive, and unrealistic to develop PBPK models for each medicine in each species (Chou et al. 2022b). A generic PBPK model is designed for providing a framework applicable to a wide range of substances with similar physicochemical and kinetic properties. It can integrate with *in silico/in vitro* data generated by NAMs, such as QSAR and the read-across approach, to predict drug concentrations and support quantitative risk assessment while minimizing the requirement of *in vivo* data (Chou et al. 2022b; EFSA 2014a; Lautz et al. 2020c) A generic PBPK model was developed to predict concentrations of melamine and oxytetracycline in edible tissues for cattle, swine, and goats, and in milk for lactating cows and goats (Lautz et al. 2020b). In this model, the chemical-specific parameters were calculated by a QSAR model (Hendriks et al. 2005). A generic PBPK model was developed to predict flunixin, florfenicol, and penicillin G residues and WDTs following various administration routes in swine and cattle (Chou et al. 2022b). The partition coefficients were calculated by mechanistic models based on physicochemical properties (e.g., logP and PKa) and tissue composition (Chou et al. 2022b). Lautz et al. developed a generic PBPK model for chickens aimed at predicting the drug residues of 7 compounds in tissues and eggs and also adopted a QSAR model to derive PCs (Hendriks et al. 2005; Lautz et al. 2020c). Baier et al. applied PK-Sim and MoBi in Open Systems Pharmacology Suite (OSPS) to develop a generic PBPK model for 9 compounds in 3 avian species (chicken, duck, and quail) (Baier et al. 2022). The parameter clearance was scaled up using *in vitro* to *in vivo* extrapolation approach in the OSPS. A QSAR model (Utsey et al. 2020) was applied to calculate PCs for the 9 compounds in the 3 avian species (Baier et al. 2022).

4. Challenges and perspectives

PBPK models for drugs in food animals are increasingly applied. Multiple advanced strategies are proposed to assist model development, expand the model application areas, and facilitate model applications. However, there are still some challenges in PBPK model development for veterinary medicines in food animals. We present our viewpoints on challenges and the future direction as follows.

A large amount of veterinary medicine. There are hundreds of veterinary medicines; however, only a small proportion of veterinary medicines have been simulated in PBPK models. Limited PK data, time and labor consumption, and the high demands for modeling techniques are the main reasons for the slow progress. Most existing PBPK models focus on a specific substance in a particular species. To improve practical application, the development of generic PBPK models is recommended. Integrating QSAR to estimate model parameters can further inform the development of these generic PBPK models Additionally, advanced technologies such as machine learning, read-across approach, and IVIVE show significant potential for promoting the development of PBPK models (Chen et al. 2021; Wu et al. 2024). There remain challenges in applications of these NAMs to veterinary medicine, including the commercial availability of subcellular fractions and primary hepatocytes for hepatic metabolism for various food animal species, the development of species-specific cell models for permeability studies (such as IPEC-1 for pigs) (Ye et al. 2024), and the need of extensive datasets to develop QSAR models that predict specific parameters for each species (such as blood-to-plasma (B/P) ratios).

Species and breeding variation. The physiological characteristics are quite different among different animal species and even among different breeds of the same animal species, such as tissue volumes, blood flow rates, enzyme activities, and metabolism pathways. Among the common mammalian food animal species, their gastrointestinal tract systems are

quite different. Cattle, goats, and sheep have a complex digestive system consisting of four-compartment stomachs, whereas swine have a monogastric stomach. Existing PBPK models for food animals often apply a simplified model structure assuming a monogastric stomach to simulate oral absorption of xenobiotics in food animal species. PBPK models that simulate the complex oral absorption processes throughout the entire 4-stomach system in ruminants remain to be developed. The variability in microbiota across species and breeds can influence PK. Quantifying microbiota's contributions to drug disposition, such as the incorporating microbiome drug-metabolizing activity in intestinal compartments (Zimmermann-Kogadeeva et al. 2020), will improve the development and accuracy of PBPK models and facilitate interspecies extrapolation. Additionally, the different life stages for food animals, including growing, lactating, and pregnant, could alter the excretion method, metabolism rate, and drug distribution. The diversity of species and the variability in breeding status among food animals can significantly affect model performance. The development of PBPK models for veterinary drugs usually focuses on specific life stages due to their relatively short half-lives compared to those of certain environmental chemicals, such as per- and polyfluoroalkyl substances (PFAS). As such, it is not always a need to describe physiological events with longer intervals, such as time between molts in laying hens or intervals between calvings in dairy cows, because these physiological events are not in the same time scale as the half-lives of common veterinary drugs. Several reviews have summarized the physiological parameters for food animals (Grech et al. 2019; Lautz et al. 2020a; Li et al. 2021; Lin et al., 2020; Scanes et al. 2022; Wang et al. 2021), however, some of them did not consider the differences between different breeding statuses and life stages, in part due to lack of data from the primary literature. This may be why the values of physiological parameters are different among the published reviews. It is important for PBPK researchers to identify and adopt the 'physiologically correct' parameters for model development.

Data source and quality. PBPK models of veterinary medicine in food animals are mechanism-based and data-driven models. Drug concentration data in plasma and tissues are essential for model calibration and evaluation. It is an inevitable and time-consuming step to search publications and collect the relevant data in the public database. A professional database is helpful for PBPK model development, in which animal information, analytical techniques, and dosage regimens should be listed. Numerous publications report PK data in food animals. PK data often need to be extracted from the plots in the publications. There are many data digitizer tools, such as WebPlotDigitizer and Graphreader; however, human operations and software performances would influence data values. It would be helpful to apply automatic digitizer tools or AI algorithms to extract data (Dagdelen et al. 2024; Polak and Morgan 2024). Publishing concentration–time raw data in accessible formats, such as CSV or XLS, is encouraged to facilitate the development of PBPK models. It is also recommended to curate a database for PK data of drugs and environmental chemicals in food animals, similar to existing databases for drugs and environmental chemicals in humans (Sayre et al. 2020). Such databases should be accessible by other researchers to apply existing data and also upload their new data.

The demand of modeling expertise. Commercial software, such as Gastroplus and Simcyp, is a module-based platform in which users easily build PBPK models of human or laboratory animals. However, the application of the module-based software in PBPK modeling of food animals remains limited, in part, due to a lack of physiological parameters, such as tissue compositions (Lautz et al. 2024a) and drug-metabolizing enzymes/transporters (Elmorsi et al. 2020) in food animals. The main platform of PBPK modeling for food animals is the general programming software, such as the R program. For beginners, it is difficult to learn, develop, and use the PBPK models in the R program. Researchers need to have a basic understanding of mathematics, computer programming skills, physiology, pharmacology and toxicology knowledge in order to build a PBPK model for drugs in food animals. A mature commercial software designed for food animals is highly desired. Additionally, it is recommended that the model code with detailed annotations be published to help researchers learn, reproduce, and apply the PBPK model. To facilitate the application of the PBPK model for users without programming experience, the web-based platform of PBPK models, such as the iPBPK model (Chou et al. 2022b), is advocated. However, the web-based iPBPK platform still has some limitations. For example, it does not contact calibration modules for other drugs. Ideally, web-based PBPK platforms should be modular at several levels with the following considerations: (1) flexible model structures (e.g., whether or not to include an individual organ and the option to design the rest of body compartment either as a lumped compartment or divide it into slowly and richly perfused compartments); (2) be able to incorporate or exclude specific ADME mechanisms, such as enterohepatic circulation, as needed; (3) capable of including or excluding or converting input parameters, such as adding metabolism or transporters in different organs as needed or converting parameters with different units or from *in vitro* to *in vivo* (e.g., *in vitro* intrinsic clearance vs. *in vivo* determined clearance); and (4) the output prediction must account for species-specific features, such as mixing urine and faces in bird droppings in comparison to mammals and whether or not to separate the white and yolk of eggs.

5. Conclusion

In this review, we introduce the development procedure of PBPK models for drugs in food animals and their applications in human food safety assessment. A list of recently published PBPK models for drugs in food animals from 2018 to 2024 are summarized and discussed. Several advanced PBPK approaches, such as population PBPK, interactive PBPK web dashboard, and generic PBPK are discussed. We also share our perspectives on current challenges and future directions in this area. All of this information will improve researchers' understanding of the progress and challenges in PBPK modeling for food animals. In addition, there are some recommendations (Najjar et al. 2022) to enhance the regulatory acceptance of PBPK modeling in risk assessment, including: (1) defining the context and implementation; (2) harmonizing PBPK report template (Tan et al. 2020); (3) applying Good Modelling Practices (GMP) for transparency and designing a stepwise approach for PBPK model development; (4) using alternatives to *in vivo* data proofing the predictivity power; (5) conducting case studies to facilitate discussions between modelers and regulators. Future PBPK modeling efforts should adhere to the existing PBPK model development guidelines, promote open platforms and data sharing, and integrate advanced technologies and computational algorithms to enhance the robustness, reliability, and applicability of PBPK models, as well as reinforce their role in human food safety assessments.

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CRediT authorship contribution statement

Kun Mi: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Conceptualization. **Xue Wu:** Writing – review & editing, Visualization, Investigation, Data curation. **Zhoumeng Lin:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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.

Data availability

No data was used for the research described in the article.

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